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(54) Titre : MODULATEURS DE CALPAIN ET LEURS UTILISATIONS THERAPEUTIQUES
(54) Title: CALPAIN MODULATORS AND THERAPEUTIC USES THEREOF

(57) Abrégé/Abstract:
Disclosed herein are small molecule calpain modulator compositions, pharmaceutical compositions, the use and preparation thereof.

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(54) Title: CALPAIN MODULATORS AND THERAPEUTIC USES THEREOF

(57) Abstract: Disclosed herein are small molecule calpain modulator compositions, pharmaceutical compositions, the use and preparation thereof.

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LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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CONTENANT LES PAGES 1 À 413

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

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CALPAIN MODULATORS AND THERAPEUTIC USES THEREOF

BACKGROUND

Field of the Invention

[0001] The present invention relates to the fields of chemistry and medicine. More particularly, the present invention relates to non-macrocyclic α-keto amide compounds as small molecule calpain modulators, compositions, their preparation, and their use as therapeutic agents.

Description of the Related Art

[0002] Fibrotic disease accounts for an estimated 45% of deaths in the developed world but the development of therapies for such diseases is still in its infancy. The current treatments for fibrotic diseases, such as for idiopathic lung fibrosis, renal fibrosis, systemic sclerosis, and liver cirrhosis, are few in number and only alleviate some of the symptoms of fibrosis while failing to treat the underlying cause.

[0003] Despite the current limited understanding of the diverse etiologies responsible for these conditions, similarities in the phenotype of the affected organs, across fibrotic diseases, strongly support the existence of common pathogenic pathways. At present, it is recognized that a primary driver of fibrotic disease is a high transforming growth factor-beta (TGFβ) signaling pathway which can promote the transformation of normally functioning cells into fibrosis-promoting cells. Termed "myofibroblasts," these transformed cells can secrete large amounts of extracellular matrix proteins and matrix degrading enzymes, resulting in the formation of scar tissue and eventual organ failure. This cellular process is transformative and termed "myofibroblast differentiation" (which includes Epithelial-to-Mesenchymal Transition (EpMT) and its variations like Endothelial-to-Mesenchymal Transition (EnMT) and Fibroblast-to-Myofibroblast Transition (FMT)). This process is a major target for the treatment of fibrotic diseases. Myofibroblast differentiation has also been shown to occur within cancer cells that have been chronically exposed to high TGFβ, causing stationary epithelial cells to become motile, invasive, and metastasize. Thus, within the context of cancer, the signaling has been documented to associate with the acquisition of drug resistance, immune system evasion, and development of stem cell properties.

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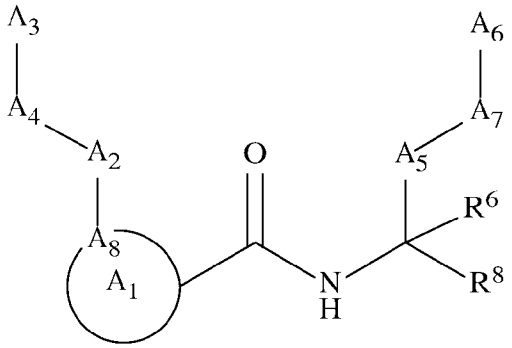
[0004] Despite the tremendous potential of myofibroblast differentiation-inhibiting drugs, and the numerous attempts to develop a working treatment, the data gathered thus far has yet to translate into practical therapy. This is partly due to the lack of an ideal target protein. Initial strategies to target the myofibroblast differentiation process focused on proximal inhibition of the TGFβ signaling pathway by various methods, including targeting ligand activators (e.g. alpha-v integrins), ligand-receptor interactions (e.g., using neutralizing antibodies) or TGFβ receptor kinase activity (e.g., small molecule chemical compound drugs to block signal transduction). Unfortunately, TGFβ is a pleiotropic cytokine with many physiological functions such that global suppression of TGFβ signaling was also associated with severe side effects. Additionally, current data suggests that such proximal inhibition may be vulnerable to pathologic workaround strategies (i.e., due to redundancy or compensation), that would limit the utility of such drugs. Further complicating matters is that, in cancer, TGFβ signaling early on functions as an anti-tumorigenic growth inhibitor but later becomes tumor promoting and is another reason why selective inhibition of pathogenic elements of signaling is so strongly desired. In light of these inherent limitations, current treatment strategies have refocused on identification and inhibition of critical distal events in TGFβ signaling, which in theory would preferentially target the pathologic, but not physiological functions of TGFβ signaling.

Summary

[0005] A compound having the structure of the formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

A_1 is selected from the group consisting of optionally substituted 5-10 membered heterocyclyl provided the 5-10 membered heterocyclyl is not substituted with oxo, optionally substituted 5-, 8-, or 9- membered heteroaryl, and optionally substituted C_{3-10} carbocyclyl;

A_2 is selected from the group consisting of optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted C_{3-10} carbocyclyl, -CR_2-, -S-, -S(=O)-, -SO_2-, -O-, -C(=S)-, -C(=O)-, -NR-, -CH=CH-, -C≡C-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(O)-, -NHC(S)NH-, -NHC(S)O-, -NHC(S)-, and single bond;

A_4 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-4} alkyl, -$(CR_2)_n$-S-$(CR_2)_n$-, -$(CR_2)_n$-S(=O)-$(CR_2)_n$-, -$(CR_2)_n$-SO_2-$(CR_2)_n$-, -$(CR_2)_n$-O-$(CR_2)_n$-, -$(CR_2)_n$-C(=S)-$(CR_2)_n$-, -$(CR_2)_n$-C(=O)-$(CR_2)_n$-, -$(CR_2)_n$-NR-$(CR_2)_n$-, -$(CR_2)_n$-CH=CH-$(CR_2)_n$-, -$(CR_2)_n$-OC(O)NH-$(CR_2)_n$-, -$(CR_2)_n$-NHC(O)NH-$(CR_2)_n$-, -$(CR_2)_n$-NHC(O)O-$(CR_2)_n$-, -$(CR_2)_n$-NHC(O)-$(CR_2)_n$-, -$(CR_2)_n$-NHC(S)NH-$(CR_2)_n$-, -$(CR_2)_n$-NHC(S)O-$(CR_2)_n$-, -$(CR_2)_n$-NHC(S)-$(CR_2)_n$-, and single bond;

when A_2 and A_4 are single bond, A_3 is directly attached to A_8;

A_3 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, and optionally substituted C_{3-10} carbocyclyl, or if A_2 is selected from optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted C_{3-10} carbocyclyl, then A_3 is selected from the group consisting of hydrogen, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl,-C≡CH, and optionally substituted 2- to 5-membered polyethylene glycol;

A_5 is selected from the group consisting of optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-8} alkyl, -S-, -S(=O)-, -SO_2-, -O-, -C(=S)-, -C(=O)-, -NR-, -CH=CH-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(O)-, -NHC(S)NH-, -NHC(S)O-, -NHC(S)-, and single bond;

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A_6 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, and optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted –O-C_{1-6} alkyl, optionally substituted –O C_{2-6} alkenyl, -OSO_2CF_3, and any natural or non-natural amino acid side chain;

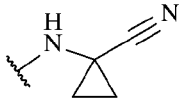
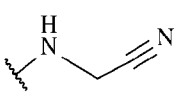
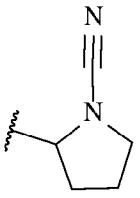
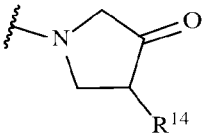
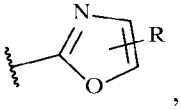
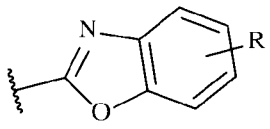
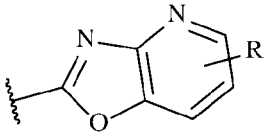
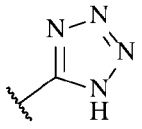
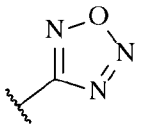
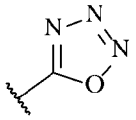
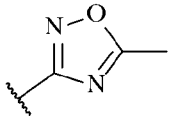
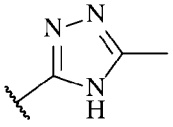
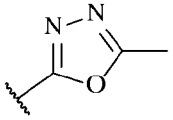
A_7 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-8} alkyl, -S-, S(=O)-, -SO_2-, -O-, -C(=S)-, -C(=O)-, -NR-, -CH=CH-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(O)-, -NHC(S)NH-, -NHC(S)O-, -NHC(S)-, and single bond;

when A_5 and A_7 are single bond, A_6 is directly attached to the carbon to which R^8 is attached;

A_8 is a ring member of A_1 and selected from the group consisting of C, CH, and N;

R^8 is selected from the group consisting of -COR^1, -CN, -CH=$CHSO_2R$, and -CH_2NO_2;

R^1 is selected from the group consisting of H, -OH, C_{1-4} haloalkyl, -COOH, -CH_2NO_2, -C(=O)NOR, -NH_2, -$CONR^2R^3$, -$CH(CH_3)$=CH_2, -$CH(CF_3)NR^2R^3$,

-C(F)=$CHCH_2CH_3$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ;

R^{14} is halo;

each R, R^2, and R^3 are independently selected from –H, optionally substituted C_{1-4} alkyl, optionally substituted C_{1-8} alkoxyalkyl, optionally substituted 2- to 5-membered polyethylene glycol, optionally substituted C_{3-7} carbocyclyl, optionally substituted 5-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, and optionally substituted 5-10 membered heteroaryl; and

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R^6 is independently selected from –H and optionally substituted C_{1-4} alkyl.

[0006] Other embodiments disclosed herein include a pharmaceutical composition comprising a therapeutically effective amount of a compound disclosed herein and a pharmaceutically acceptable excipient.

[0007] Other embodiments disclosed herein include a method of treating diseases and conditions mediated at least in part by the physiologic effects of CAPN1, CAPN2, or CAP9, or combinations thereof, comprising administering to a subject in need thereof a compound disclosed herein.

[0008] In some embodiments, compounds disclosed herein are specific inhibitors of one of: CAPN1, CAPN2 or CAPN9.

[0009] In some embodiments, compounds disclosed herein are selective inhibitors of one of: CAPN1, CAPN2 or CAPN9.

[0010] In some embodiments, compounds disclosed herein are selective inhibitors of: CAPN1 and CAPN2, or CAPN1 and CAPN9, or CAPN2 and CAPN9.

[0011] In some embodiments, compounds disclosed herein are effective inhibitors of CAPN1, CAPN2 and/or CAPN9.

[0012] In some embodiments, the non-macrocyclic α-keto amide compounds disclosed herein are broadly effective in treating a host of conditions arising from fibrosis or inflammation, and specifically including those associated with myofibroblast differentiation. Accordingly, compounds disclosed herein are active therapeutics for a diverse set of diseases or disorders that include or that produces a symptom which include, but are not limited to: liver fibrosis, renal fibrosis, lung fibrosis, hypersensitivity pneumonitis, interstitial fibrosis, systemic scleroderma, macular degeneration, pancreatic fibrosis, fibrosis of the spleen, cardiac fibrosis, mediastinal fibrosis, myelofibrosis, endomyocardial fibrosis, retroperitoneal fibrosis, progressive massive fibrosis, nephrogenic systemic fibrosis, fibrotic complications of surgery, chronic allograft vasculopathy and/or chronic rejection in transplanted organs, ischemic-reperfusion injury associated fibrosis, injection fibrosis, cirrhosis, diffuse parenchymal lung disease, post-vasectomy pain syndrome, and rheumatoid arthritis diseases or disorders. In other embodiments, the compounds disclosed herein can be used can be used in metabolic and reaction kinetic studies, detection and imaging techniques and radioactive treatments.

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[0013] In some embodiments, the compounds disclosed herein are used to treat diseases or conditions or that produces a symptom in a subject which include, but not limited to: liver fibrosis, renal fibrosis, lung fibrosis, hypersensitivity pneumonitis, interstitial fibrosis, systemic scleroderma, macular degeneration, pancreatic fibrosis, fibrosis of the spleen, cardiac fibrosis, mediastinal fibrosis, myelofibrosis, endomyocardial fibrosis, retroperitoneal fibrosis, progressive massive fibrosis, nephrogenic systemic fibrosis, fibrotic complications of surgery, chronic allograft vasculopathy and/or chronic rejection in transplanted organs, ischemic-reperfusion injury associated fibrosis, injection fibrosis, cirrhosis, diffuse parenchymal lung disease, post-vasectomy pain syndrome, and rheumatoid arthritis diseases.

[0014] In certain embodiments methods are provided for alleviating or ameliorating a condition or disorder, affected at least in part by the enzymatic activity of calpain 1 (CAPN1), calpain 2 (CAPN2), and/or calpain 9 (CAPN9), or mediated at least in part by the enzymatic activity of CAPN1, CAPN2, and/or CAPN9 wherein the condition includes or produces a symptom which includes: liver fibrosis, renal fibrosis, lung fibrosis, hypersensitivity pneumonitis, interstitial fibrosis, systemic scleroderma, macular degeneration, pancreatic fibrosis, fibrosis of the spleen, cardiac fibrosis, mediastinal fibrosis, myelofibrosis, endomyocardial fibrosis, retroperitoneal fibrosis, progressive massive fibrosis, nephrogenic systemic fibrosis, fibrotic complications of surgery, chronic allograft vasculopathy and/or chronic rejection in transplanted organs, ischemic-reperfusion injury associated fibrosis, injection fibrosis, cirrhosis, diffuse parenchymal lung disease, post-vasectomy pain syndrome, and/or rheumatoid arthritis.

[0015] In some embodiments, the methods, compounds, and/or compositions of the present invention are used for prophylactic therapy.

[0016] In some embodiments, the CAPN1, CAPN2, and/or CAPN9 inhibiting compounds demonstrate efficacy in animal models of human disease. Specifically, in-vivo treatment of mice, rabbits, and other mammalian subjects with compounds disclosed herein establish the utility of these compounds as therapeutic agents to modulate CAPN1, CAPN2, and/or CAPN9 activities in humans and thereby ameliorate corresponding medical conditions.

[0017] Some embodiments provide compounds, pharmaceutical compositions, and methods of use to inhibit myofibroblast differentiation. Some embodiments provide compounds,

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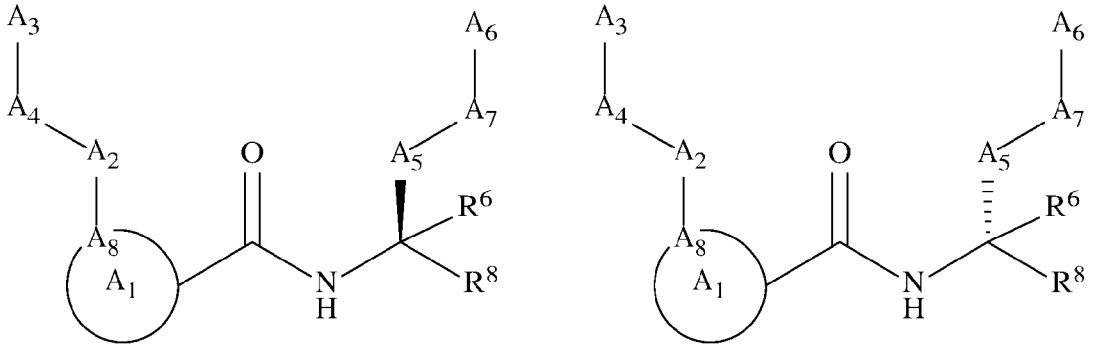
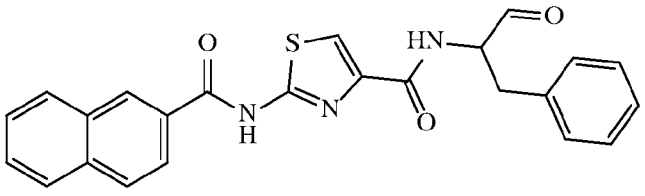
pharmaceutical compositions, and methods of use for inhibiting CAPN1, CAPN2, and/or CAPN9 or combinations of these enzyme activities such as CAPN1 and CAPN2, or CAPN1 and CAPN9, or CAPN2 and CAPN9. Some embodiments provide methods for treatment of diseases and disorders by inhibiting CAPN1, CAPN2, and/or CAPN9 or combinations of these enzymatic activities.

DETAILED DESCRIPTION

[0018] In some embodiments, compounds that are non-macrocyclic α-keto amides are provided that act as calpain modulators. Various embodiments of these compounds include compounds having the structures of Formula **I** as described above or pharmaceutically acceptable salts thereof. The structure of Formula **I** encompasses all stereoisomers and racemic mixtures, including the following structures and mixtures thereof:



[0019] In some embodiments of compounds of Formula (I), the compound is not selected from the group consisting of:



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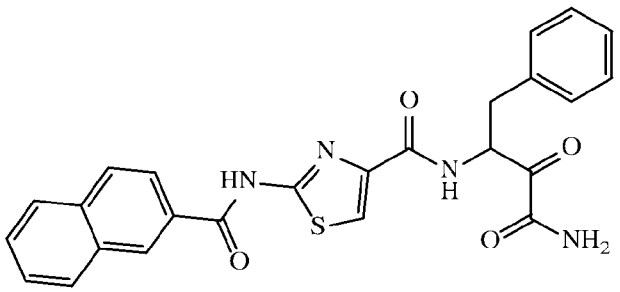

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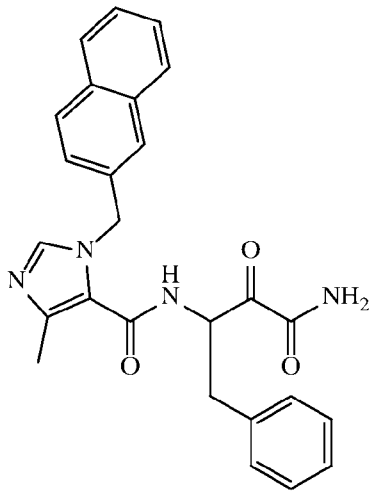
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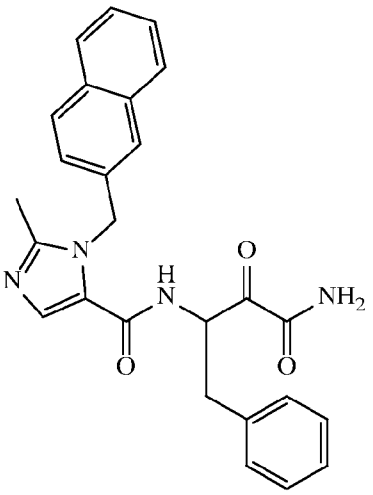
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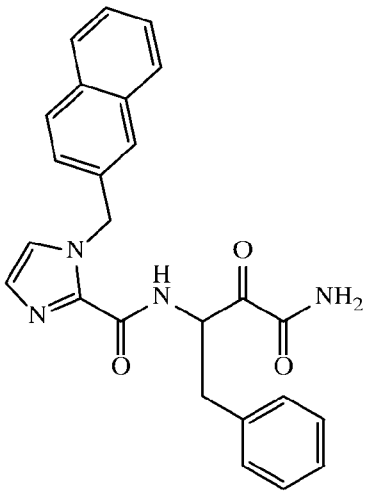
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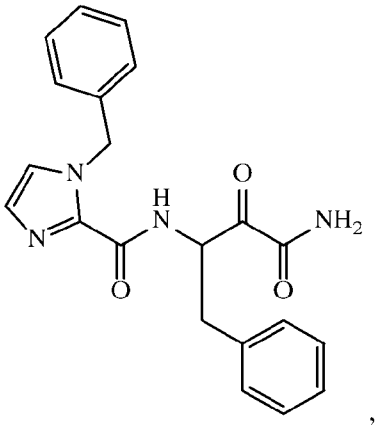
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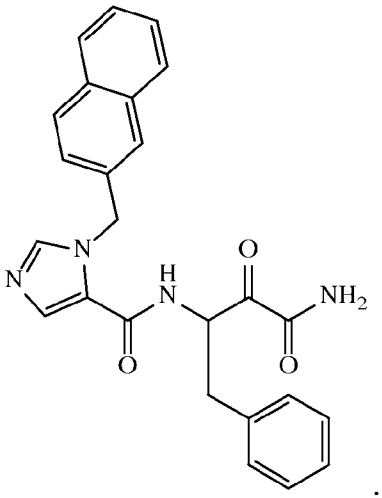
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[0020] In some embodiments of compounds of Formula (I):

A_1 is selected from the group consisting of optionally substituted 6-10 membered heterocyclyl provided the 6-10-membered heterocyclyl is not substituted with oxo; optionally substituted 5-, 8-, or 9- membered heteroaryl; and optionally substituted C_{3-10} carbocyclyl;

A_2 is selected from the group consisting of optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted C_{3-10} carbocyclyl, -CR_2-, -S-, -S(=O)-, -SO_2-, -O-, -C(=S)-, -C(=O)-, -NR-, -CH=CH-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(O)-, -NHC(S)NH-, -NHC(S)O-, -NHC(S)-, and single bond;

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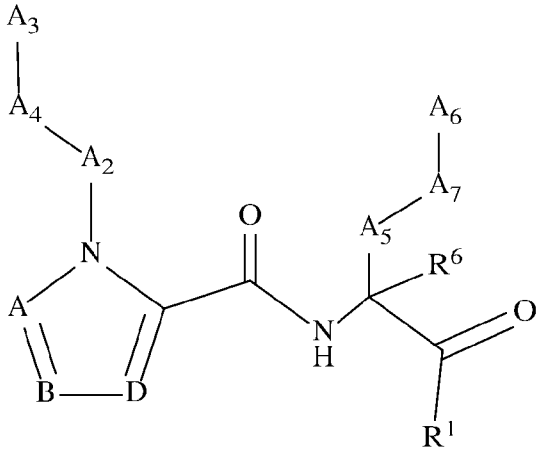
A_4 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-4} alkyl, -S-, S(=O)-, $-SO_2-$, -O-, -C(=S)-, -C(=O)-, -NR-, -CH=CH-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(O)-, -NHC(S)NH-, -NHC(S)O-, -NHC(S)-, and single bond;

A_3 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, and optionally substituted C_{3-10} carbocyclyl;

A_6 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-8} alkyl, optionally substituted $-O-C_{1-6}$ alkyl, optionally substituted $-O$ C_{2-6} alkenyl, and any natural or non-natural amino acid side chain; and

each R, R^2, and R^3 are independently selected from –H, optionally substituted C_{1-4} alkyl, optionally substituted C_{3-7} carbocyclyl, optionally substituted 5-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, and optionally substituted 5-10 membered heteroaryl.

[0021] Some embodiments of compounds of Formula (**I**) include compounds having the structure of Formula (**I-a**):



I-a

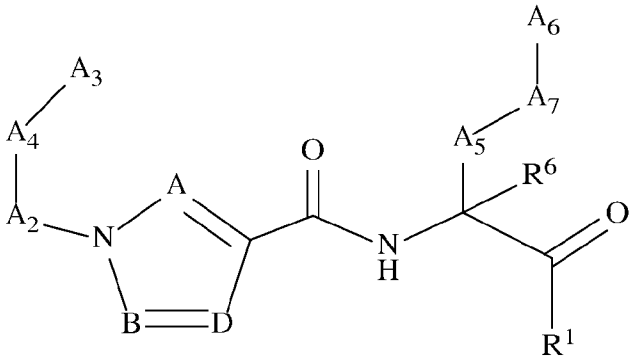
or a pharmaceutically acceptable salt thereof, wherein:

A, B, and D are each independently selected from the group consisting of $C(R^4)$ and N; and each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7}

carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy.

[0022] In some embodiments of compounds of Formula (**I-a**) or their pharmaceutically acceptable salts; A, B, and D are independently selected from the group consisting of CH and N. In some embodiments, A is N, B is CH, and D is CH. In some embodiments, A is CH, B is N, and D is CH.

[0023] Some embodiments of compounds of Formula (**I**) include compounds having the structure of Formula (**I-b**):



I-b

or a pharmaceutically acceptable salt thereof, wherein:

A, B, and D are each independently selected from the group consisting of C(R^4) and N; and each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy.

[0024] In some embodiments of compounds of Formula (**I-b**) or their pharmaceutically acceptable salts; A, B, and D are independently selected from the group consisting of CH and N.

[0025] Some embodiments of compounds of Formula (**I**) include compounds having the structure of Formula (**I-c**):

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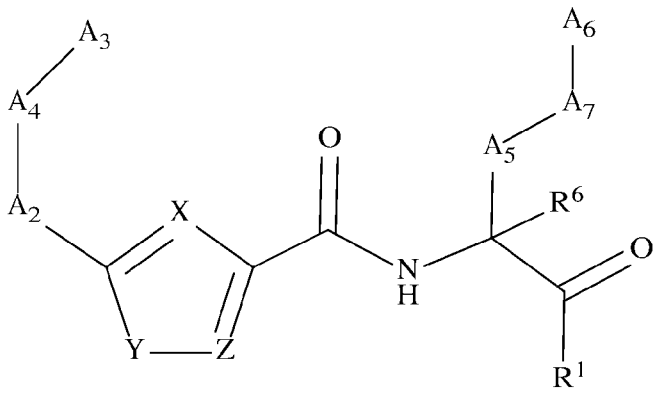


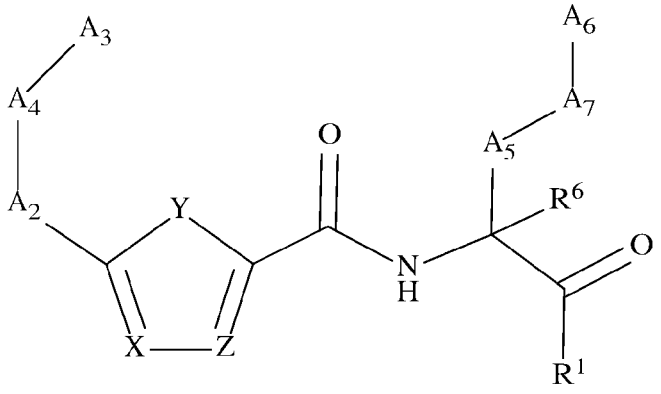
I-c

or a pharmaceutically acceptable salt thereof, wherein:

Y is selected from the group consisting of NR^5, O, S, and SO_2; X and Z are each independently selected from the group consisting of $C(R^4)$ and N; each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy; and R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} carbocyclyl.

[0026] In some embodiments of compounds of Formula (**I-c**) or their pharmaceutically acceptable salts; X and Z are independently selected from the group consisting of CH and N.

[0027] Some embodiments of compounds of Formula (**I**) include compounds having the structure of Formula (**I-d**):



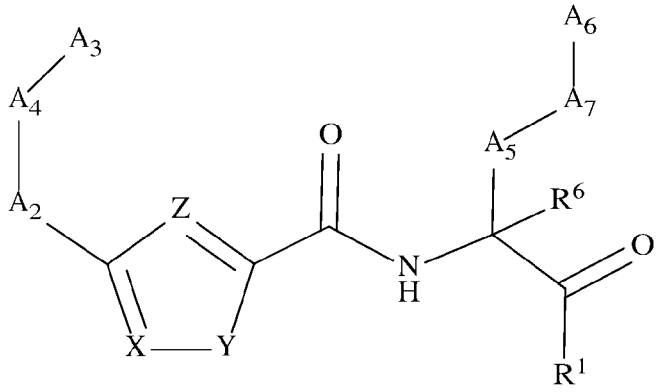
I-d

or a pharmaceutically acceptable salt thereof, wherein:

Y is selected from the group consisting of NR^5, O, S, and SO_2; X and Z are each independently selected from the group consisting of $C(R^4)$ and N; each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy; and R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} carbocyclyl.

[0028] In some embodiments of compounds of Formula (**I-d**) or their pharmaceutically acceptable salts; X and Z are independently selected from the group consisting of CH and N.

[0029] Some embodiments of compounds of Formula (**I**) include compounds having the structure of Formula (**I-e**):



I-e

or a pharmaceutically acceptable salt thereof, wherein:

Y is selected from the group consisting of NR^5, O, S, and SO_2; X and Z are each independently selected from the group consisting of $C(R^4)$ and N; each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy; and R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} carbocyclyl.

[0030] In some embodiments of compounds of Formula (**I-e**) or their pharmaceutically acceptable salts; X and Z are independently selected from the group consisting of CH and N.

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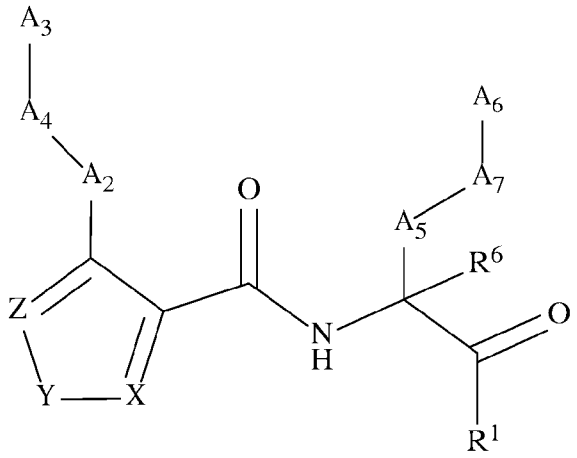
[0031] Some embodiments of compounds of Formula (**I**) include compounds having the structure of Formula (**I-f**):



I-f

or a pharmaceutically acceptable salt thereof, wherein:

Y is selected from the group consisting of NR^5, O, S, and SO_2; X and Z are each independently selected from the group consisting of $C(R^4)$ and N; each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy; and R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} carbocyclyl.

[0032] In some embodiments of compounds of Formula (**I-f**), Z is N, Y is NR^5, and X is CH.

[0033] In some embodiments of compounds of Formula (**I-f**), R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_1-C_4 haloalkyl, and cyclopropyl.

[0034] In some embodiments of compounds of Formula (**I-f**), Z is N, Y is O, and X is $C(R^4)$. In some embodiments of compounds of Formula (**I-f**), Z is N, Y is S, and X is $C(R^4)$. In some embodiments of compounds of Formula (**I-f**), Z is $C(R^4)$, Y is S, and X is $C(R^4)$.

[0035] In some embodiments of compounds of Formula (**I-f**), Z is $C(R^4)$, Y is O, and X is $C(R^4)$.

[0036] In some embodiments of compounds of Formula (**I-f**), Z is N, Y is S, and X is N. In some embodiments of compounds of Formula (**I-f**), Z is N, Y is O, and X is N.

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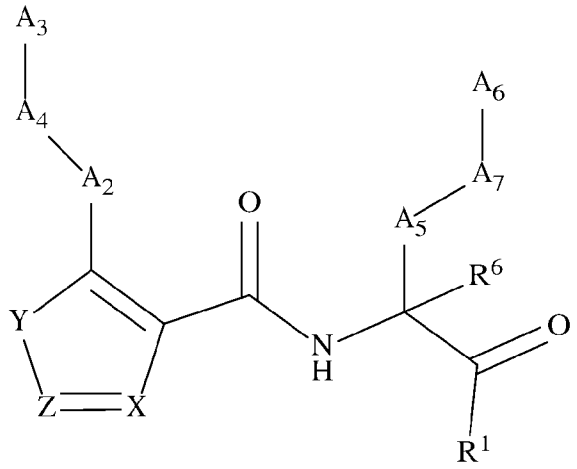
[0037] Some embodiments of compounds of Formula (**I**) include compounds having the structure of formula (**I-g**):



I-g

or a pharmaceutically acceptable salt thereof, wherein:

Y is selected from the group consisting of NR^5, O, S, and SO_2; X and Z are each independently selected from the group consisting of $C(R^4)$ and N; each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy; and R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy).

[0038] In some embodiments of compounds of Formula (**I-g**) or their pharmaceutically acceptable salts; X and Z are independently selected from the group consisting of CH and N. In some embodiments of compounds of Formula (**I-g**), Y is NR^5, Z is N, and X is CH.

[0039] Some embodiments of compounds of Formula (**I**) include compounds having the structure of Formula (**I-h**):

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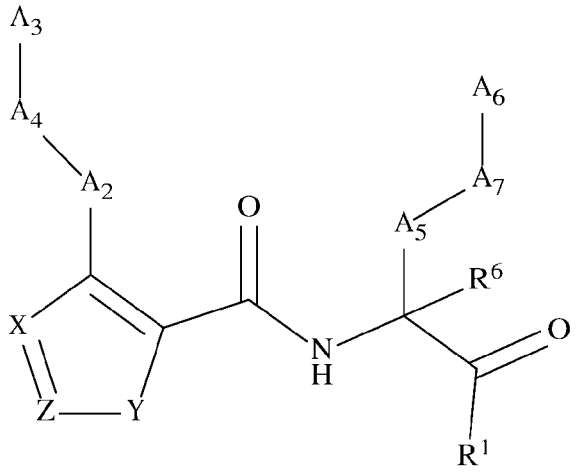

I-h

or a pharmaceutically acceptable salt thereof, wherein:

Y is selected from the group consisting of NR^5, O, S, and SO_2; X and Z are each independently selected from the group consisting of $C(R^4)$ and N; each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy; and R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy).

[0040] In some embodiments of compounds of Formula (**I-h**) or their pharmaceutically acceptable salts; X and Z are independently selected from the group consisting of CH and N. In some embodiments of compounds of Formula (**I-h**), X is CH, Z is N, and Y is NR^5.

[0041] In some embodiments of compounds of Formula (**I-h**), X is CH, Z is N, and Y is NR^5. In some embodiments of compounds of Formula (**I-h**), X is N, Z is $C(R^4)$, and Y is O.

[0042] In some embodiments of compounds of Formula (**I-h**), wherein R^4 is selected from –H and C_{1-4} alkyl.

[0043] In some embodiments of compounds of Formula (**I-h**), X is N, Z is $C(R^4)$, and Y is S. In some embodiments of compounds of Formula (**I-h**), X is N, Z is N, and Y is S.

[0044] Some embodiments of compounds of Formula (**I**) include compounds having the structure of formula (**I-j**):

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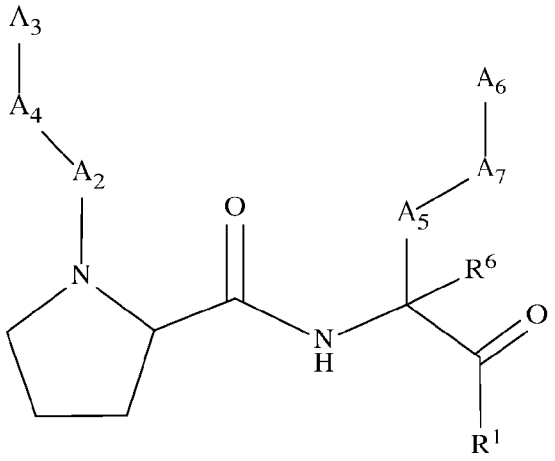
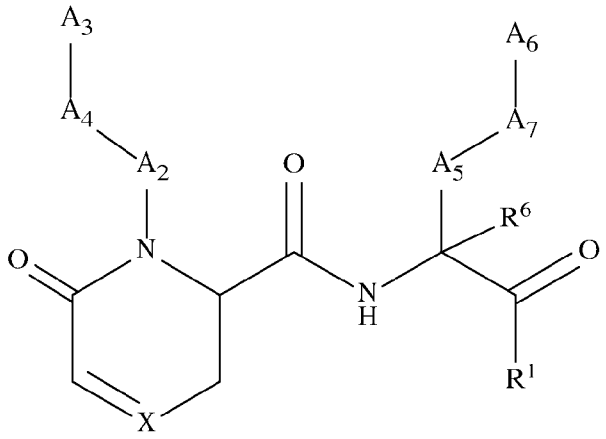


I-j

or a pharmaceutically acceptable salt thereof.

[0045] Some embodiments of compounds of Formula (**I**) include compounds having the structure of Formula (**I-k**):



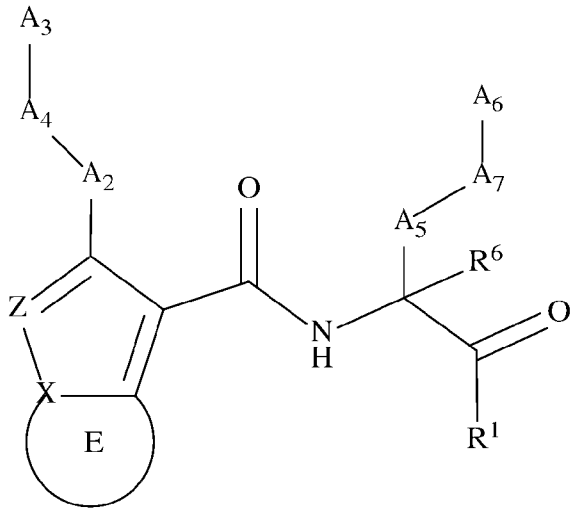
I-k

or a pharmaceutically acceptable salt thereof, wherein:

X is selected from the group consisting of C(OR^5), -C(R^4), and N; R^4 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy; and R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy).

[0046] In some embodiments of compounds of Formula (**I-k**) or their pharmaceutically acceptable salts; X and Z are independently selected from the group consisting of CH and N.

[0047] Some embodiments of compounds of Formula (**I**) include compounds having the structure of Formula (**I-m**):



I-m

or a pharmaceutically acceptable salt thereof, wherein:

X and Z are independently selected from the group consisting of C(R^4) and N; E is selected from the group consisting of an optionally substituted C_{5-6} carbocyclyl and an optionally substituted 5- to 6-membered heterocyclyl; and each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy.

[0048] Some embodiments of compounds of Formula (**I**) include compounds having the structure of Formula (**I-n**):

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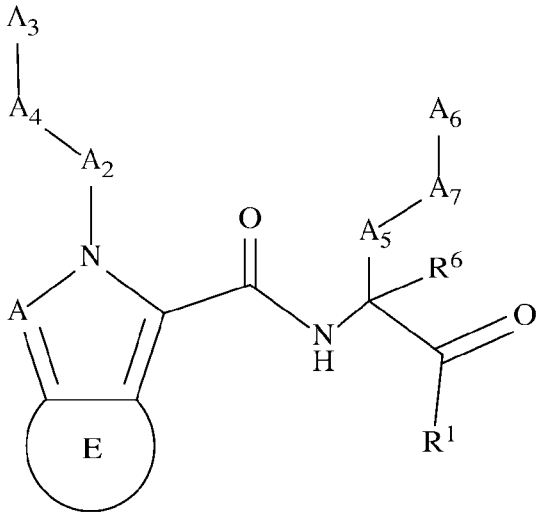
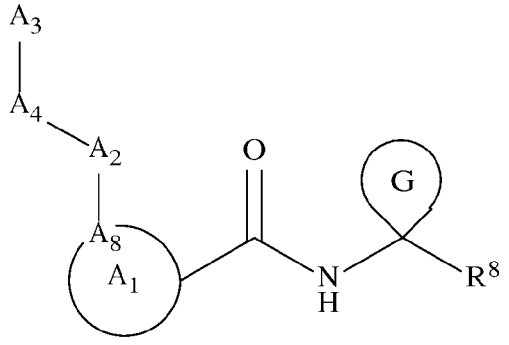


I-n

or a pharmaceutically acceptable salt thereof, wherein:

A is selected from the group consisting of C(R^4) and N; E is selected from the group consisting of an optionally substituted C_{5-6} carbocyclyl, an optionally substituted 5- to 6-membered heterocyclyl, an optionally substituted 5- to 6- membered heteroaryl, and an optionally substituted phenyl; and each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy.

[0049] Some embodiments include compounds of Formula (**III**)



III

or a pharmaceutically acceptable salt thereof, wherein:

A_1 is selected from the group consisting of optionally substituted 5-10 membered heterocyclyl provided the 6-10-membered heterocyclyl is not substituted with oxo; optionally substituted 5-, 8-, or 9- membered heteroaryl; and optionally substituted C_{3-10} carbocyclyl;

A_2 is selected from the group consisting of optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted C_{3-10} carbocyclyl, $-CR_2-$, -S-, -S(=O)-, $-SO_2-$, -O-, -C(=S)-, -C(=O)-, -NR-, -CH=CH-, -C≡C-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(O)-, -NHC(S)NH-, -NHC(S)O-, -NHC(S)-, and single bond;

A_4 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-4} alkyl, $-(CR_2)_n-S-(CR_2)_n-$, $-(CR_2)_n-S(=O)-(CR_2)_n-$, $-(CR_2)_n-SO_2-(CR_2)_n-$, $-(CR_2)_n-O-(CR_2)_n-$, $-(CR_2)_n-C(=S)-(CR_2)_n-$, $-(CR_2)_n-C(=O)-(CR_2)_n-$, $-(CR_2)_n-NR-(CR_2)_n-$, $-(CR_2)_n-CH=CH-(CR_2)_n-$, $-(CR_2)_n-OC(O)NH-(CR_2)_n-$, $-(CR_2)_n-NHC(O)NH-(CR_2)_n-$, $-(CR_2)_n-NHC(O)O-(CR_2)_n-$, $-(CR_2)_n-NHC(O)-(CR_2)_n-$, $-(CR_2)_n-NHC(S)NH-(CR_2)_n-$, $-(CR_2)_n-NHC(S)O-(CR_2)_n-$, $-(CR_2)_n-NHC(S)-(CR_2)_n-$, and single bond;

when A_2 and A_4 are single bond, A_3 is directly attached to A_8;

A_3 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, and optionally substituted C_{3-10} carbocyclyl, or if A_2 is selected from optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted C_{3-10} carbocyclyl, then A_3 is selected from the group consisting of hydrogen, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, -C≡CH, and optionally substituted 2- to 5-membered polyethylene glycol;

G is an optionally substituted C_3 to C_7 carbocyclyl or an optionally substituted 4- to 7-membered heterocyclyl;

A_8 is a ring member of A_1 and is selected from the group consisting of C and N;

R^8 is selected from the group consisting of $-COR^1$, -CN, $-CH=CHSO_2R$, $-CH_2NO_2$;

R^1 is selected from the group consisting of H, -OH, C_{1-4} haloalkyl, -COOH, $-CH_2NO_2$, -C(=O)NOR, $-NH_2$, $-CONR^2R^3$, $-CH(CH_3)=CH_2$, $-CH(CF_3)NR^2R^3$,

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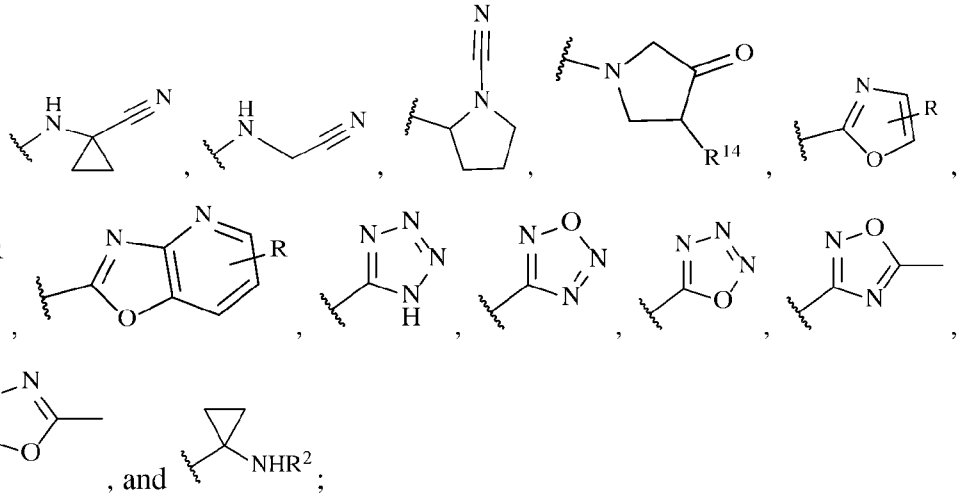
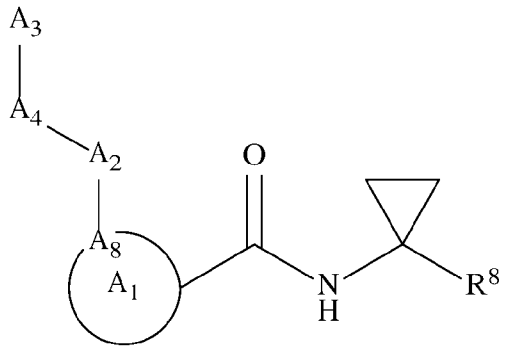
-C(F)=CHCH$_2$CH$_3$, 

, and ;

R^{14} is halo; and

each R, R^2, and R^3 are independently selected from –H, optionally substituted C_{1-4} alkyl, optionally substituted C_{1-8} alkoxyalkyl, optionally substituted 2- to 5-membered polyethylene glycol, optionally substituted C_{3-7} carbocyclyl, optionally substituted 5-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted C_{6-10} aryl(C_1-C_6)alkyl, and optionally substituted 5-10 membered heteroaryl; R^6 is independently selected from –H and optionally substituted C_{1-4} alkyl; and each n is independently selected to be an integer from 0 to 3.

[0050] Some embodiments of compounds of Formulas (**III**) include compounds having the structure of Formula (**III-a**):



III-a

or a pharmaceutically acceptable salt thereof.

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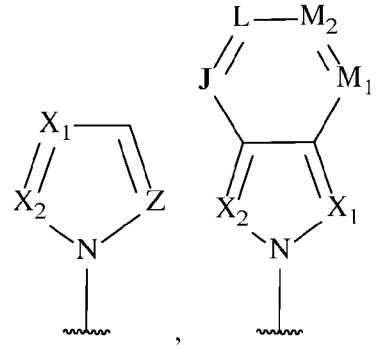
[0051] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), at least one of the optionally substituted moieties of A_2, A_4, and A_3 is substituted with ^{18}F.

[0052] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), at least one of the optionally substituted moieties of A_2, A_4, and A_3 is substituted with C_1-C_6 alkyl containing one or more ^{11}C.

[0053] In some embodiments of compounds of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**) or their pharmaceutically acceptable salts; A_3 is selected from the group consisting of



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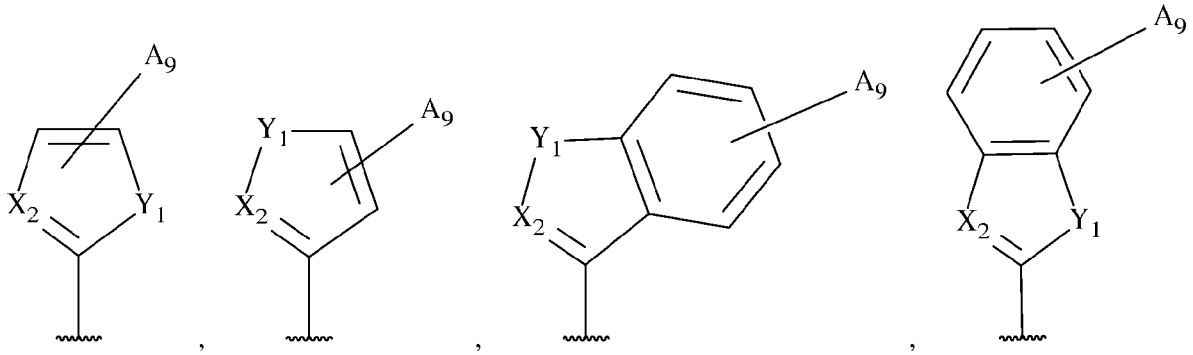

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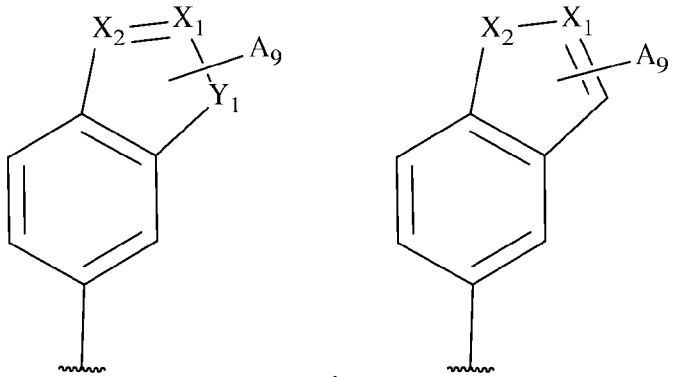
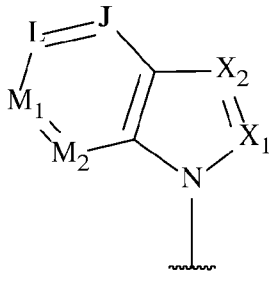


, and



; and A_9 is selected from the group consisting of H, C_{6-10} aryl, 5-10 membered heteroaryl, 3-10 membered heterocyclyl, and C_{3-10} carbocyclyl, C_{1-4} alkyl; X_2, X_1, and Z are each independently selected from the group consisting of $C(R^4)$ and N; Y_1 is selected from the group consisting of NR^5, O, and S; J, L, M_1 and M_2 are each independently selected from the group consisting of $C(R^4)$ and N; R^4 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl, halo, hydroxy, and C_1-C_6 alkoxy; R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} carbocyclyl.

[0054] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), A_2 is $–CH_2-$.

[0055] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), A_2 is –CH=CH-.

[0056] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), A_2 is –O-.

[0057] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), A_2 is S.

[0058] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), A_2 is single bond.

[0059] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), A_2 is phenyl.

[0060] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), A_3 is optionally substituted C_{6-10} aryl.

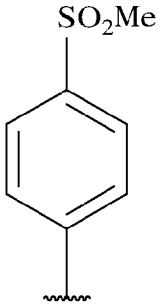
[0061] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), A_2 is selected from the group consisting of optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5- or 7-10 membered heteroaryl, optionally substituted C_{3-10} carbocyclyl, -S-, -S(=O)-,

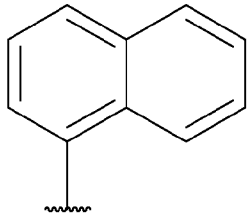
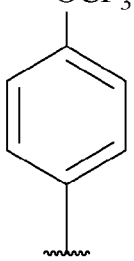
-SO_2-, -C(=S)-, -C(=O)-, -NR-, -CH=CH-, -C≡C-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(S)NH-, -NHC(S)O-, and -NHC(S)-.

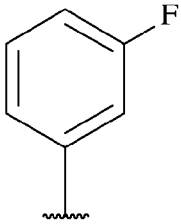
[0062] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), A_2 is selected from the group consisting of optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted C_{3-10} carbocyclyl, and -C≡C-,

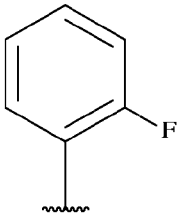
[0063] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), A_2 is selected from the group consisting of optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted C_{3-10} carbocyclyl.

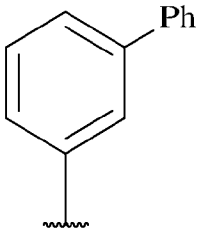
[0064] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), A_4 is single bond.

[0065] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), A_3 is selected from the group consisting of phenyl, 

, 
, 

, 

, 

, and 

.

[0066] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), A_3 is optionally substituted 5-10 membered heteroaryl.

[0067] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), A_3 is selected from the group consisting

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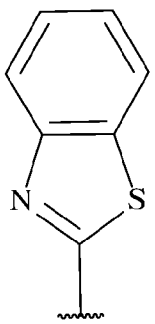
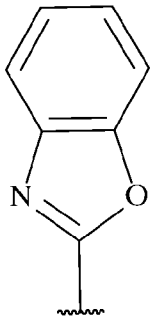
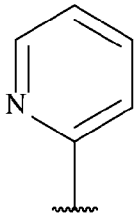
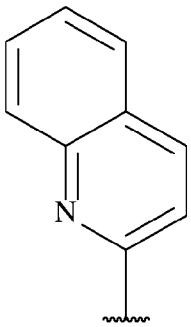
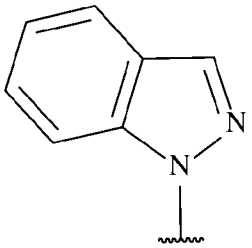
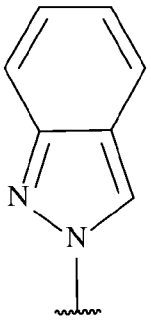
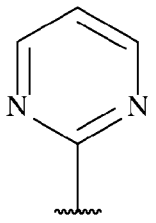
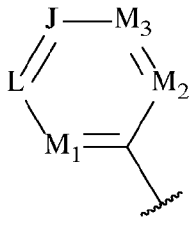
of  ,  ,  ,  ,  ,  ,  and .

[0068] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), wherein A_2 is a single bond, A_4 is a single bond, and A_3 is an optionally substituted C_{6-10} aryl or an optionally substituted 5-10 membered heteroaryl.

[0069] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), wherein A_3 has the structure:

 , wherein J, L, M_1, M_2, and M_3 are each independently selected from the group consisting of $C(R^4)$ and N; and each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy.

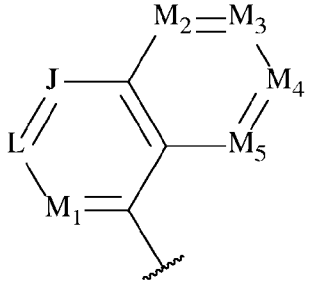
[0070] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), wherein each of J, L, M_1, M_2, and M_3 are $C(R^4)$

[0071] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), wherein each R^4 is independently selected from –H and halo.

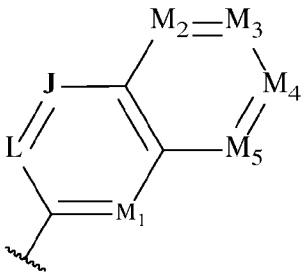
[0072] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), wherein M_1 is halo and each of J, L, M_2, and M_3 are CH.

[0073] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), wherein L is halo and each of J, M_1, M_2, and M_3 are CH.

[0074] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), wherein A_3 has a structure selected from the group consisting of:

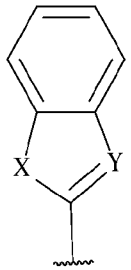


and



, wherein **J**, L, M_1, M_2, M_3, M_4, and M_5 are each independently selected from the group consisting of $C(R^4)$ and N; and each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy.

[0075] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), or (**I-p**), wherein A_3 has the structure:



, wherein X is selected from the group consisting of $C(R^4)$ and N; Y is selected from O and S; and R^4 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy.

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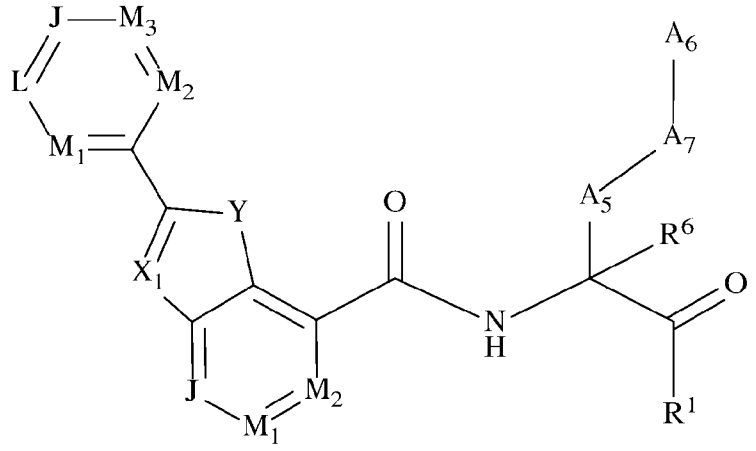
[0076] Some embodiments of compounds of Formula (**I**) include compounds having the structure of Formula (**I-o**):



I-o

or a pharmaceutically acceptable salt thereof, wherein:

Y is selected from the group consisting of NR^5, O, S, and SO_2; X_1 is selected from the group consisting of $C(R^4)$ and N; J, L, M_1, M_2, and M_3 are each independently selected from the group consisting of $C(R^4)$ and N; R^4 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl, halo, hydroxy, and C_1-C_6 alkoxy; R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy).

[0077] In some embodiments of compounds of Formula (**I-o**) or their pharmaceutically acceptable salts; J, L, M_1, M_2, and M_3 are independently selected from the group consisting of CH and N.

[0078] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), wherein at least one of the optionally substituted moieties of A_5, A_7, and A_6 is substituted with ^{18}F.

[0079] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), wherein at least one of the optionally substituted moieties of A_5, A_7, and A_6 is substituted with C_1-C_6 alkyl containing one or more ^{11}C.

[0080] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), A_6 is phenyl.

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[0081] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), A_6 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-8} alkyl, optionally substituted –O-C_{1-6} alkyl, and optionally substituted –O C_{2-6} alkenyl.

[0082] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), A_7 is -CH_2-.

[0083] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), A_7 is –CH=CH-.

[0084] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), A_7 is –O-.

[0085] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), A_7 is S.

[0086] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), A_7 is single bond.

[0087] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), A_7 is optionally substituted C_{6-10} aryl.

[0088] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), A_7 is phenyl.

[0089] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), A_5 is -CH_2-.

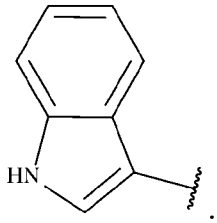
[0090] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), wherein A_5 is -CH_2- or -CH_2CH_2-; A_7 is a single bond; and A_6 is selected from the group consisting of C_1-C_4 alkyl, optionally substituted phenyl, optionally substituted 5-10 membered heteroaryl.

[0091] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), A_6 is optionally substituted phenyl.

[0092] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), wherein A_6 is unsubstituted phenyl.

[0093] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), wherein A_6 is phenyl optionally substituted with one or more C_{1-4} alkyl, C_{3-7} carbocyclyl, halo, hydroxy, and C_1-C_6 alkoxy.

[0094] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), A_6 has the structure:



[0095] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), wherein A_5 is a single bond, A_7 is a single bond; and A_6 is C_1-C_5 alkyl.

[0096] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), A_6 is selected from the group consisting of ethyl, n-propyl, isopropyl, isobutyl, 2,2-dimethylpropyl, and 1,2-dimethylpropyl.

[0097] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-o**), or (**I-p**) R^1 is $CONR^2R^3$.

[0098] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-o**), or (**I-p**) R^2 is –H and R^3 is optionally substituted C_{1-4} alkyl.

[0099] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-o**), or (**I-p**) wherein R^2 is –H and R^3 is selected from the group consisting of –H, C_1-C_4 alkyl optionally substituted with C-amido, and C_3-C_6 cycloalkyl.

[0100] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-o**), or (**I-p**) R^3 is selected from ethyl or cyclopropyl.

[0101] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-o**), or (**I-p**) R^3 is methyl substituted with C-amido.

[0102] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-o**), or (**I-p**) R^3 is H.

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[0103] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-o**), or (**I-p**) R^3 is optionally substituted C_{1-4} alkyl.

[0104] In some embodiments of Formulas (**I**), (**III**), (**III-a**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-o**), or (**I-p**) R^3 is benzyl.

[0105] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), R^6 is –H and optionally substituted C_{1-4} alkyl.

[0106] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), R^6 is optionally substituted C_{1-4} alkyl.

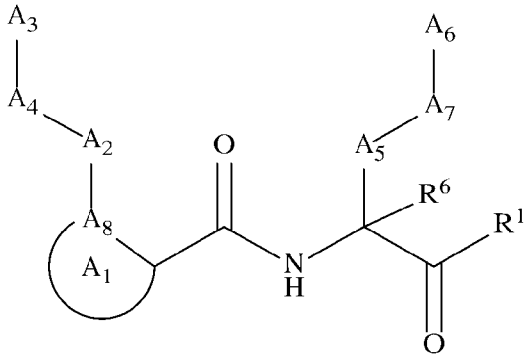
[0107] In some embodiments of Formulas (**I**), (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-j**), (**I-k**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**), R^6 is methyl.

[0108] In some embodiments of Formula (**I**), A_1 is selected from the group consisting of optionally substituted 6-10 membered heterocyclyl; 5-membered heterocyclyl optionally substituted with one or more C_{1-4} alkyl, C_{3-7} carbocyclyl, halo, hydroxy, or C_1-C_6 alkoxy; optionally substituted 5-, 8-, or 9- membered heteroaryl; and optionally substituted C_{3-10} carbocyclyl.

[0109] In some embodiments of Formula (**I**), A_1 is selected from the group consisting of 5-membered heterocyclyl optionally substituted with one or more C_{1-4} alkyl, C_{3-7} carbocyclyl, halo, hydroxy, or C_1-C_6 alkoxy and optionally substituted 5-membered heteroaryl.

[0110] In some embodiments of Formula (**I**), A_1 is optionally substituted 5-membered heteroaryl.

[0111] Some embodiments of compounds of Formula (**I**) include compounds having the structure of Formula (**I-p**):



I-p

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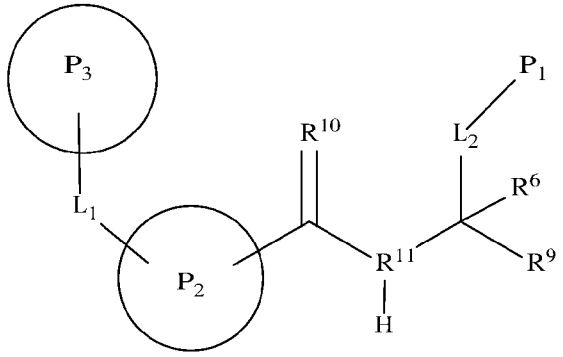
or a pharmaceutically acceptable salt thereof.

[0112] Some embodiments provide a compound of Formula (**II**):



II

or a pharmaceutically acceptable salt thereof, wherein:

[0113] P_2 is an optionally substituted cyclic moiety having a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 9 P2 pocket moiety selected from the group consisting of Gly190, Phe233, Gly253, His254, and Ala255;

[0114] L_1 is a bond or a moiety consisting of from 1 to 25 atoms selected from the group consisting of carbon, oxygen, nitrogen, hydrogen, and sulfur;

[0115] P_3 is an optionally substituted cyclic moiety positioned by L_1 and having a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_3 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 9 P3 pocket moiety selected from the group consisting of Gly189, Gly190, Ser191, Thr236, and Gly253;

[0116] R^{10} is oxo and is positioned by P_2 such that, upon binding of the compound to calpain 9, R^{10} forms a polar interaction with, and is within 4 Å or less of, calpain 9 Gly190 amide;

[0117] R^{11} is nitrogen and is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 9, R^{11} forms a polar interaction with, and is within 4 Å or less of, calpain 9 Gly253 carbonyl;

[0118] L_2 is a bond or a moiety consisting of from 1 to 25 atoms selected from the group consisting of carbon, oxygen, nitrogen, hydrogen, and sulfur;

[0119] P_1 is a moiety positioned by L_2 and having a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_1 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 9 P1 pocket moiety selected from the group consisting of Gly95, Lys188, Gly189, and Ser242;

[0120] R^9 is a moiety positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 9, at least one atom of R^9 forms a polar interaction with, and is within 4 Å or less of, at least one calpain 9 moiety selected from the group consisting of Gln91, Cys97, and His254; and

[0121] R^6 is selected from –H and optionally substituted C_{1-4} alkyl.

[0122] Some embodiments of compounds of Formula (**II**) include compounds wherein; R^9 is $-(C=R^{12})(C=R^{13})NR^2R^3$;

[0123] R^{12} is oxo and is positioned such that, upon binding of the compound to calpain 9, R^{12} forms a polar interaction with, and is within 4 Å or less of, calpain 9 His254 imidazole;

[0124] R^{13} is oxo and is positioned such that, upon binding of the compound to calpain 9, R^{13} forms a polar interaction with, and is within 4 Å or less of, at least one calpain 9 moiety selected from the group consisting of Gln91 side chain carboxamide and Cys97 backbone amide; and

[0125] R^2 and R^3 are independently selected from –H, optionally substituted C_{1-4} alkyl, optionally substituted C_{3-7} carbocyclyl, optionally substituted 5-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted C_{6-10}aryl(C_1-C_6)alkyl, and optionally substituted 5-10 membered heteroaryl.

[0126] Some embodiments of compounds of Formula (**II**) include compound wherein R^{12} is positioned such that, upon binding of the compound to calpain 9, R^{12} is within 2.6 to 3.2 Å or less of, calpain 9 His254 imidazole.

[0127] Some embodiments of compounds of Formula (**II**) include compound wherein R^{12} is positioned such that, upon binding of the compound to calpain 9, R^{12} is within 2.6 to 3.0 Å or less of, calpain 9 His254 imidazole.

[0128] Some embodiments of compounds of Formula (**II**) include compound wherein R^{13} is positioned such that, upon binding of the compound to calpain 9, R^{13} is within 2.6 to 3.5 Å to the calpain 9 moieties including both Gln91 side chain carboxamide and Cys97 backbone amide.

[0129] Some embodiments of compounds of Formula (**II**) include compound wherein R^{13} is positioned such that, upon binding of the compound to calpain 9, R^{13} is within 2.6 to 3.2 Å to the calpain 9 moieties including both Gln91 side chain carboxamide and Cys97 backbone amide.

[0130] Some embodiments of compounds of Formula (**II**) include compound wherein R^9 is positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 9, at least one atom of R^9 forms a polar interaction with, and is within 3.6 Å or less of, at least one calpain 9 moiety selected from the group consisting of Gln91, Cys97, and His254.

[0131] Some embodiments of compounds of Formula (**II**) include compound wherein R^9 is positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 9, at least one atom of R^9 is within 2.6 to 3.6 Å to the calpain 9 moieties including both Gln91 side chain carboxamide and Cys97 backbone amide.

[0132] Some embodiments of compounds of Formula (**II**) include compound wherein R^9 is positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 9, at least one atom of R^9 is within 2.9 to 3.2 Å to the calpain 9 moieties including both Gln91 side chain carboxamide and Cys97 backbone amide.

[0133] Some embodiments of compounds of Formula (**II**) include compound wherein a carbon atom in R^9 at its point of attachment forms a covalent bond with Cys97

[0134] Some embodiments of compounds of Formula (**II**) include compound wherein the covalent bond length is between 1.7 and 1.9 Å.

[0135] Some embodiments of compounds of Formula (**II**) include compound wherein P_2 is an optionally substituted 5-membered heteroaryl.

[0136] Some embodiments of compounds of Formula (**II**) include compound wherein R^{11} is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 9, R^{11} forms a polar interaction with, and is within 3.6 Å or less of, calpain 9 Gly253 carbonyl.

[0137] Some embodiments of compounds of Formula (**II**) include compound wherein, P_2 has a size and configuration such that, upon binding of the compound to calpain 1, at

least one atom of P_2 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 1 P2 pocket moiety selected from the group consisting of Gly208, Ser251, Gly271, His272, and Ala273;

[0138] P_3 is positioned by L_1 and has a size and configuration such that, upon binding of the compound to calpain 1, at least one atom of P_3 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 1 P3 pocket moiety selected from the group consisting of Gly207, Gly208, Ser209, Ile254, and Gly271;

[0139] R^{10} is positioned by P_2 such that, upon binding of the compound to calpain 1, R^{10} forms a polar interaction with, and is within 4 Å or less of, calpain 1 Gly208 amide;

[0140] R^{11} is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 1, R^{11} forms a polar interaction with, and is within 4 Å or less of, calpain 1 Gly271 carbonyl;

[0141] P_1 is positioned by L_2 and has a size and configuration such that, upon binding of the compound to calpain 1, at least one atom of P_1 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 1 P1 pocket moiety selected from the group consisting of Gly113, Ser206, Gly207, and Met260; and

[0142] R^9 is positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 1, at least one atom of R^9 forms a polar interaction with, and is within 4 Å or less of, at least one calpain 1 moiety selected from the group consisting of Gln109, Cys115, and His272.

[0143] Some embodiments of compounds of Formula (**II**) include compoundwherein:

[0144] P_2 has a size and configuration such that, upon binding of the compound to calpain 2, at least one atom of P_2 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 2 P2 pocket moiety selected from the group consisting of Gly198, Ser241, Gly261, His262, and Ala263;

[0145] P_3 is positioned by L_1 and has a size and configuration such that, upon binding of the compound to calpain 2, at least one atom of P_3 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 2 P3 pocket moiety selected from the group consisting of Gly197, Gly198, Ala199, Ile244, and Gly261;

[0146] R^{10} is positioned by P_2 such that, upon binding of the compound to calpain 2, R^{10} forms a polar interaction with, and is within 4 Å or less of, calpain 2 Gly198 amide;

[0147] R^{11} is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 2, R^{11} forms a polar interaction with, and is within 4 Å or less of, calpain 2 Gly261 carbonyl;

[0148] P_1 is positioned by L_2 and has a size and configuration such that, upon binding of the compound to calpain 2, at least one atom of P_1 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 2 P1 pocket moiety selected from the group consisting of Gly103, Ser196, Gly197, and Ser250; and

[0149] R^9 is positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 2, at least one atom of R^9 forms a polar interaction with, and is within 4 Å or less of, at least one calpain 2 moiety selected from the group consisting of Gln99, Cys105, and His262.

[0150] Some embodiments of compounds of Formula (**II**) include compound wherein P_2 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 is within 2.6 to 3.6 Å of Gly190 carbonyl oxygen.

[0151] Some embodiments of compounds of Formula (**II**) include compound wherein P_2 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 is within 2.9 to 3.3 Å of Gly190 carbonyl oxygen.

[0152] Some embodiments of compounds of Formula (**II**) include compound wherein P_2 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 is within 2.8 to 4.8 Å of a carbon atom in Phe233.

[0153] Some embodiments of compounds of Formula (**II**) include compound wherein P_2 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 is within 2.9 to 3.3 Å of a carbon atom in Phe233.

[0154] Some embodiments of compounds of Formula (**II**) include compound wherein P_2 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 is within 2.6 to 3.7 Å of Gly253 carbonyl oxygen.

[0155] Some embodiments of compounds of Formula (**II**) include compound wherein P_2 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 is within 2.9 to 3.3 Å of Gly253 carbonyl oxygen.

[0156] Some embodiments of compounds of Formula (**II**) include compound wherein P_2 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 is within 2.9 to 4.8 Å of Ala255 nitrogen.

[0157] Some embodiments of compounds of Formula (**II**) include compound wherein P_2 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 is within 3.2 to 4.0 Å of Ala255 nitrogen.

[0158] Some embodiments of compounds of Formula (**II**) include compound wherein P_3 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_3 is within 3.1 to 4.3 Å of Gly189 C-alpha.

[0159] Some embodiments of compounds of Formula (**II**) include compound wherein P_3 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_3 is within 3.2 to 4.0 Å of Gly189 C-alpha.

[0160] Some embodiments of compounds of Formula (**II**) include compound wherein P_3 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_3 is within 3.0 to 4.3 Å of Gly190 carbonyl oxygen.

[0161] Some embodiments of compounds of Formula (**II**) include compound wherein P_3 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_3 is within 3.2 to 4.0 Å of Gly190 carbonyl oxygen.

[0162] Some embodiments of compounds of Formula (**II**) include compound wherein P_3 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_3 is within 3.2 to 4.8 Å of Ser191 nitrogen.

[0163] Some embodiments of compounds of Formula (**II**) include compound wherein P_3 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_3 is within 3.2 to 4.0 Å of Ser191 nitrogen.

[0164] Some embodiments of compounds of Formula (**II**) include compound wherein R^{10} is positioned by P_2 such that, upon binding of the compound to calpain 9, R^{10} is within 2.6 to 3.5 Å of, calpain 9 Gly190 amide.

[0165] Some embodiments of compounds of Formula (**II**) include compound wherein R^{10} is positioned by P_2 such that, upon binding of the compound to calpain 9, R^{10} is within 2.9 to 3.3 Å of, calpain 9 Gly190 amide.

[0166] Some embodiments of compounds of Formula (**II**) include compound wherein R^{11} is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 9, R^{11} is within 2.6 to 3.6 Å or less of, calpain 9 Gly253 carbonyl.

[0167] Some embodiments of compounds of Formula (**II**) include compound wherein R^{11} is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 9, R^{11} is within 2.9 to 3.3 Å or less of, calpain 9 Gly253 carbonyl.

[0168] Some embodiments of compounds of Formula (**II**) include compound wherein P_1 is positioned by L_2 and has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_1 is within 3.2 to 4.4 Å Gly95 carbonyl oxygen.

[0169] Some embodiments of compounds of Formula (**II**) include compound wherein P_1 is positioned by L_2 and has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_1 is within 3.2 to 4.0 Å Gly95 carbonyl oxygen.

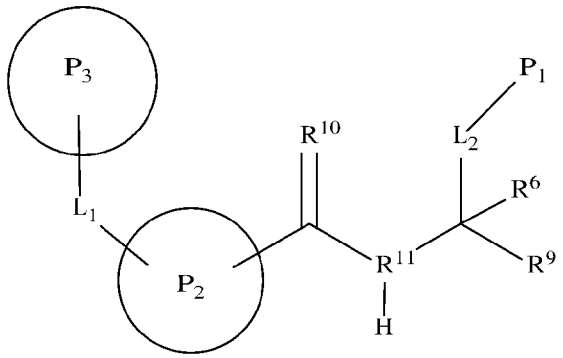
[0170] Some embodiments of compounds of Formula (**II**) include compound wherein P_1 is positioned by L_2 and has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_1 is within 3.2 to 4.7 Å of Lys188 carbonyl carbon.

[0171] Some embodiments of compounds of Formula (**II**) include compound wherein P_1 is positioned by L_2 and has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_1 is within 2.6 to 4.0 Å of Lys188 carbonyl carbon.

[0172] Some embodiments of compounds of Formula (**II**) include compound wherein P_1 is positioned by L_2 and has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_1 is within 3.0 to 4.1 Å of Gly189 C-alpha.

[0173] Some embodiments of compounds of Formula (**II**) include compound wherein P_1 is positioned by L_2 and has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_1 is within 3.2 to 4.0 Å of Gly189 C-alpha.

[0174] Some embodiments provide a compound of Formula (**II**):



II

or a pharmaceutically acceptable salt thereof, wherein:

[0175] P_2 is an optionally substituted cyclic moiety having a size and configuration such that, upon binding of the compound to calpain 1, at least one atom of P_2 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 1 P2 pocket moiety selected from the group consisting of Gly208, Ser251, Gly271, His272, and Ala273;

[0176] L_1 is a bond or a moiety consisting of from 1 to 25 atoms selected from the group consisting of carbon, oxygen, nitrogen, hydrogen, and sulfur;

[0177] P_3 is an optionally substituted cyclic moiety positioned by L_1 and having a size and configuration such that, upon binding of the compound to calpain 1, at least one atom of P_3 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 1 P3 pocket moiety selected from the group consisting of Gly207, Gly208, Ser209, Ile254, and Gly271;

[0178] R^{10} is oxo and is positioned by P_2 such that, upon binding of the compound to calpain 1, R^{10} forms a polar interaction with, and is within 4 Å or less of, calpain 1 Gly208 amide;

[0179] R^{11} is nitrogen and is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 1, R^{11} forms a polar interaction with, and is within 4 Å or less of, calpain 1 Gly271 carbonyl;

[0180] L_2 is a bond or a moiety consisting of from 1 to 25 atoms selected from the group consisting of carbon, oxygen, nitrogen, hydrogen, and sulfur;

[0181] P_1 is a moiety positioned by L_2 and having a size and configuration such that, upon binding of the compound to calpain 1, at least one atom of P_1 forms a non-polar interaction

with, and is within 5 Å or less of, at least one calpain 1 P1 pocket moiety selected from the group consisting of Gly113, Ser206, Gly207, and Met260;

[0182] R^9 is a moiety positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 1, at least one atom of R^9 forms a polar interaction with, and is within 4 Å or less of, at least one calpain 1 moiety selected from the group consisting of Gln109, Cys115, and His272; and R^6 is selected from –H and optionally substituted C_{1-4} alkyl.

[0183] Some embodiments of compounds of Formula (**II**) include compound wherein R^9 is $–(C=R^{12})(C=R^{13})NR^2R^3$;

[0184] R^{12} is oxo and is positioned such that, upon binding of the compound to calpain 1, R^{12} forms a polar interaction with, and is within 4 Å or less of, calpain 1 His272 imidazole;

[0185] R^{13} is oxo and is positioned such that, upon binding of the compound to calpain 1, R^{13} forms a polar interaction with, and is within 4 Å or less of, at least one calpain 1 moiety selected from the group consisting of Gln109 side chain carboxamide and Cys115 backbone amide; and

[0186] R^2 and R^3 are independently selected from –H, optionally substituted C_{1-4} alkyl, optionally substituted C_{3-7} carbocyclyl, optionally substituted 5-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted C_{6-10}aryl(C_1-C_6)alkyl, and optionally substituted 5-10 membered heteroaryl.

[0187] Some embodiments of compounds of Formula (**II**) include compound wherein R^9 is positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 1, at least one atom of R^9 forms a polar interaction with, and is within 3.5 Å or less of, at least one calpain 1 moiety selected from the group consisting of Gln109, Cys115, and His272.

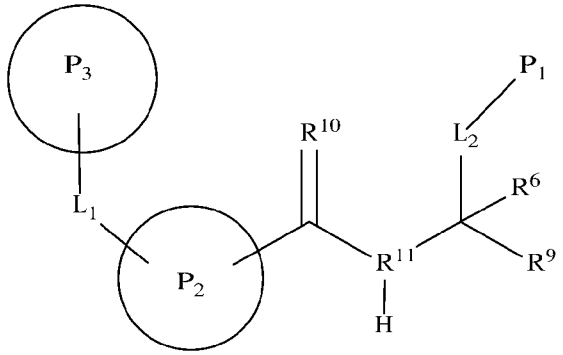
[0188] Some embodiments of compounds of Formula (**II**) include compound wherein a carbon atom in R^9 at its point of attachment forms a covalent bond with Cys115.

[0189] Some embodiments of compounds of Formula (**II**) include compound wherein the covalent bond length is between 1.7 and 1.9 Å.

[0190] Some embodiments of compounds of Formula (**II**) include compound wherein P_2 is an optionally substituted 5-membered heteroaryl.

[0191] Some embodiments of compounds of Formula (**II**) include compound wherein R^{11} is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 1, R^{11} forms a polar interaction with, and is within 3.5 Å or less of, calpain 1 Gly271 carbonyl.

[0192] Some embodiments provide a compound of Formula (**II**):



II

or a pharmaceutically acceptable salt thereof, wherein

[0193] P_2 is an optionally substituted cyclic moiety having a size and configuration such that, upon binding of the compound to calpain 2, at least one atom of P_2 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 2 P2 pocket moiety selected from the group consisting of Gly198, Ser241, Gly261, His262, and Ala263;

[0194] L_1 is a bond or a moiety consisting of from 1 to 25 atoms selected from the group consisting of carbon, oxygen, nitrogen, hydrogen, and sulfur;

[0195] P_3 is an optionally substituted cyclic moiety positioned by L_1 and having a size and configuration such that, upon binding of the compound to calpain 2, at least one atom of P_3 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 2 P3 pocket moiety selected from the group consisting of Gly197, Gly198, Ala199, Ile244, and Gly261;

[0196] R^{10} is oxo and is positioned by P_2 such that, upon binding of the compound to calpain 2, R^{10} forms a polar interaction with, and is within 4 Å or less of, calpain 2 Gly198 amide;

[0197] R^{11} is nitrogen and is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 2, R^{11} forms a polar interaction with, and is within 4 Å or less of, calpain 2 Gly261 carbonyl;

[0198] L_2 is a bond or a moiety consisting of from 1 to 25 atoms selected from the group consisting of carbon, oxygen, nitrogen, hydrogen, and sulfur;

[0199] P_1 is a moiety positioned by L_2 and having a size and configuration such that, upon binding of the compound to calpain 2, at least one atom of P_1 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 2 P1 pocket moiety selected from the group consisting of Gly103, Ser196, Gly197, and Ser250;

[0200] R^9 is a moiety positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 2, at least one atom of R^9 forms a polar interaction with, and is within 4 Å or less of, at least one calpain 2 moiety selected from the group consisting of Gln99, Cys105, and His262; and R^6 is selected from –H and optionally substituted C_{1-4} alkyl.

[0201] Some embodiments of compounds of Formula (**II**) include compound wherein R^9 is $-(C=R^{12})(C=R^{13})NR^2R^3$;

[0202] R^{12} is oxo and is positioned such that, upon binding of the compound to calpain 2, R^{12} forms a polar interaction with, and is within 4 Å or less of, calpain 2 His262 imidazole;

[0203] R^{13} is oxo and is positioned such that, upon binding of the compound to calpain 2, R^{13} forms a polar interaction with, and is within 4 Å or less of, at least one calpain 2 moiety selected from the group consisting of Gln99 side chain carboxamide and Cys105 backbone amide; and

[0204] R^2 and R^3 are independently selected from –H, optionally substituted C_{1-4} alkyl, optionally substituted C_{3-7} carbocyclyl, optionally substituted 5-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted C_{6-10}aryl(C_1-C_6)alkyl, and optionally substituted 5-10 membered heteroaryl.

[0205] Some embodiments of compounds of Formula (**II**) include compound wherein R^9 is positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 2, at least one atom of R^9 forms a polar interaction with, and is within 3.5 Å or less of, at least one calpain 2 moiety selected from the group consisting of Gln99, Cys105, and His262.

[0206] Some embodiments of compounds of Formula (**II**) include compound wherein a carbon atom in R^9 at its point of attachment forms a covalent bond with Cys195.

[0207] Some embodiments of compounds of Formula (**II**) include compound wherein the covalent bond length is between 1.7 and 1.9 Å.

[0208] Some embodiments of compounds of Formula (**II**) include compound wherein P_2 is an optionally substituted 5-membered heteroaryl.

[0209] Some embodiments of compounds of Formula (**II**) include compound wherein R^{11} is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 2, R^{11} forms a polar interaction with, and is within 3.5 Å or less of, calpain 2 Gly261 carbonyl.

[0210] Some embodiments include a compound selected from the group consisting of compounds 1 to 90, compounds 92-94, compound 195, compounds 197 to 235, compounds 238 to 273, compounds 276 to 281, compounds 283 to 299, compounds 303 to 309, compounds 313 to 363, compound 365, compounds 367-410, compounds 413-424, compounds 428-445, compounds 447-448, compounds 454-532, compound 540, compounds 546-588, compounds 591-605, compounds 607-611, compounds 613-630, and pharmaceutically acceptable salts thereof, as such compounds are described herein.

[0211] Some embodiments include a compound selected from the group consisting of compounds 91, 196, 274, 282, 310 to 312, 364, 366, 411, 536, 541, and pharmaceutically acceptable salts thereof, as such compounds are described herein.

[0212] Some embodiments include a compound selected from the group consisting of:

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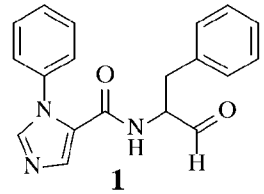

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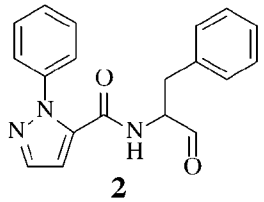

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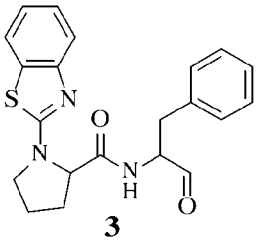

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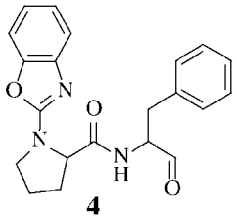

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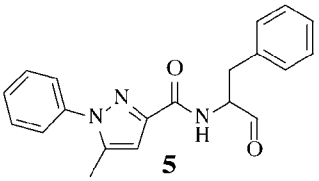

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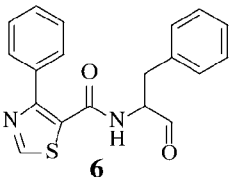

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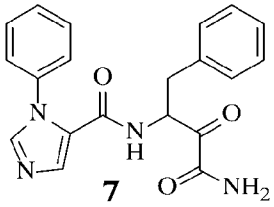

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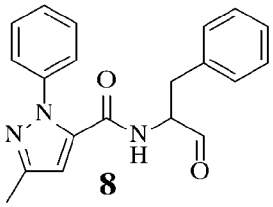

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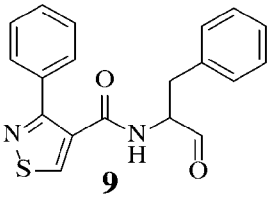

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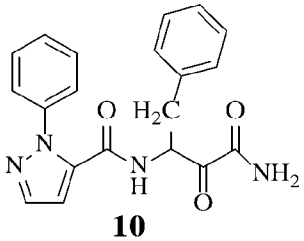

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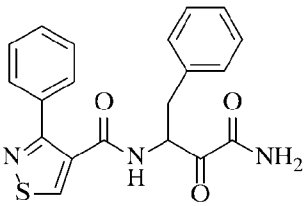

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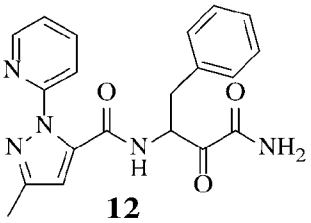

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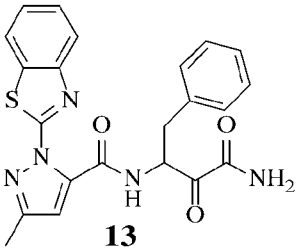

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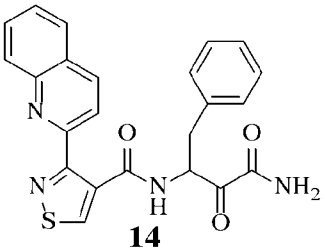

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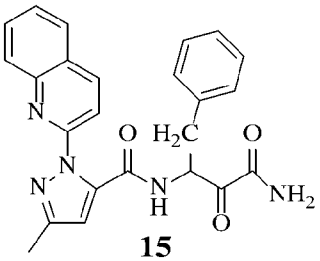

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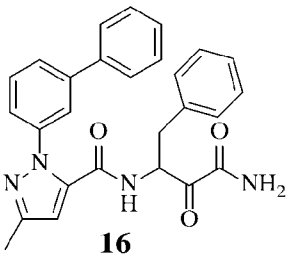

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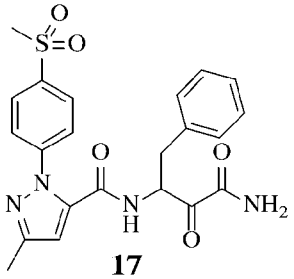

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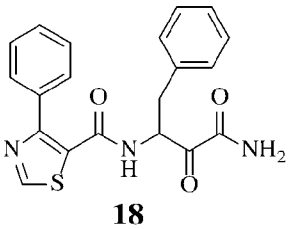

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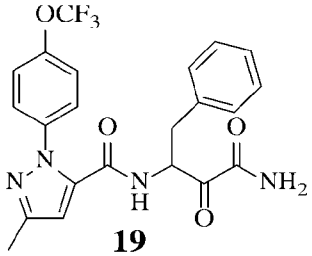

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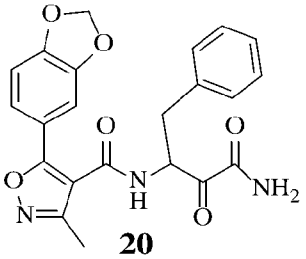

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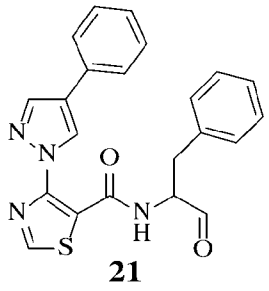

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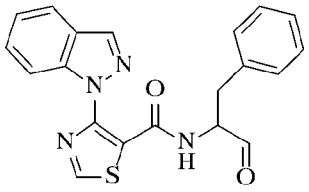

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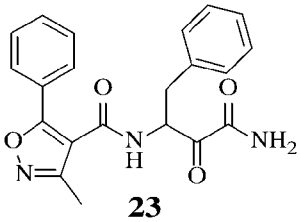

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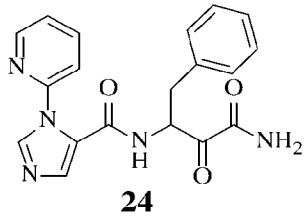

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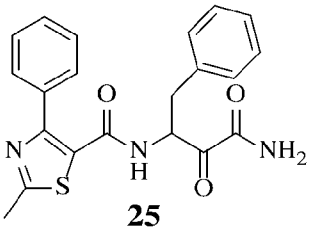

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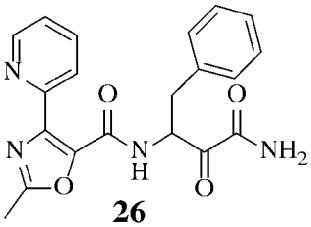

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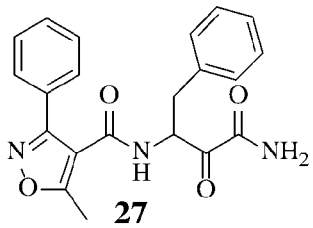

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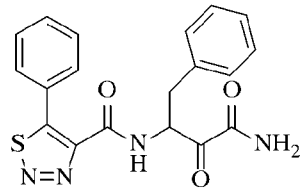

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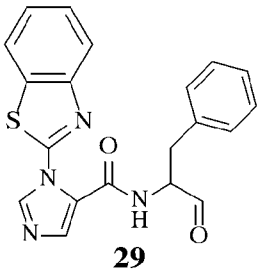

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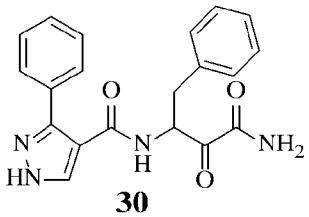

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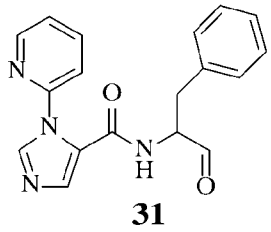

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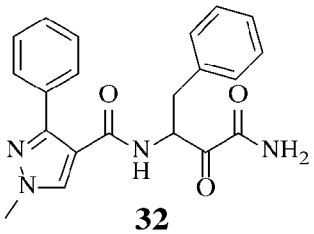

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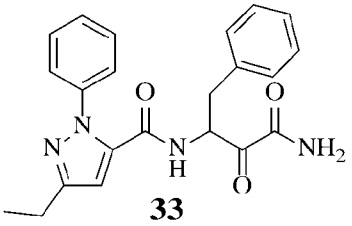

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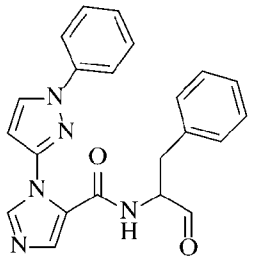

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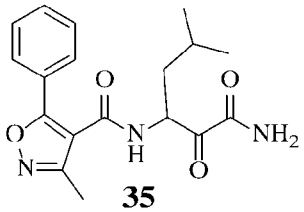

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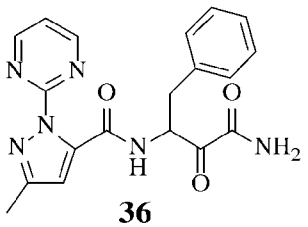

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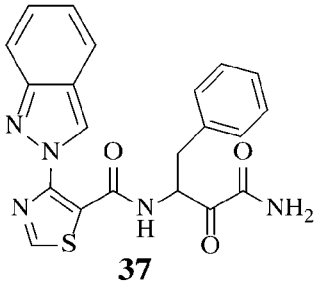

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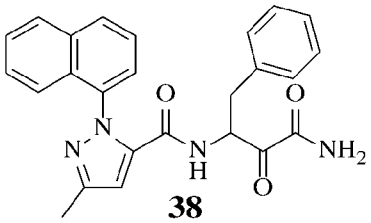

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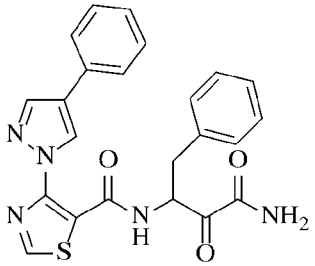

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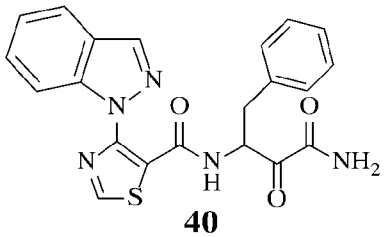

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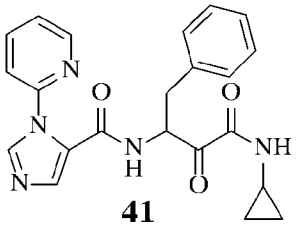

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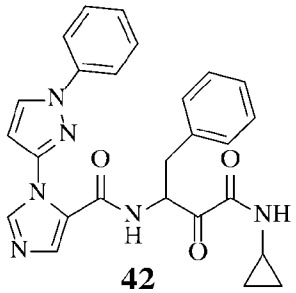

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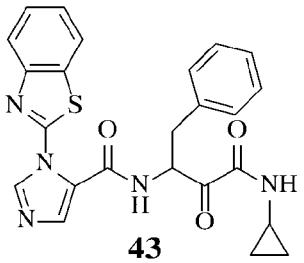

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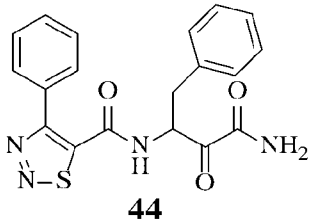

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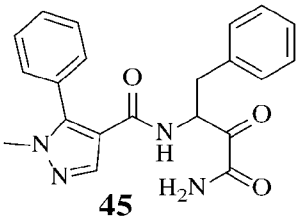

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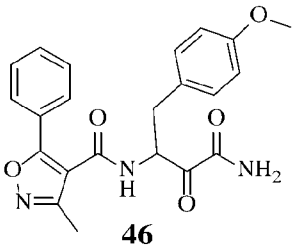

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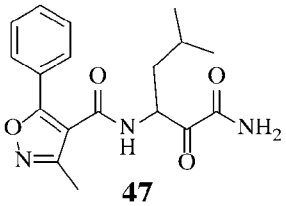

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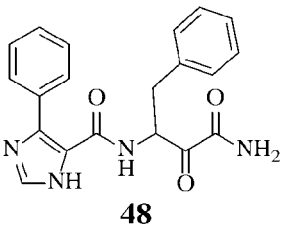

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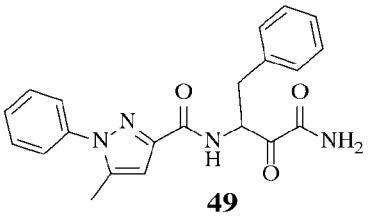

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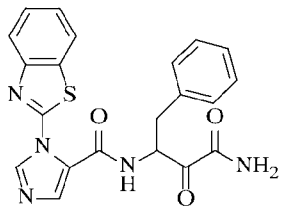

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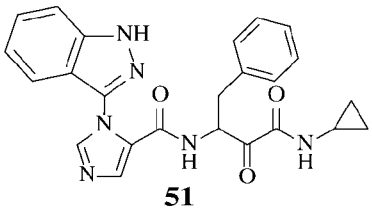

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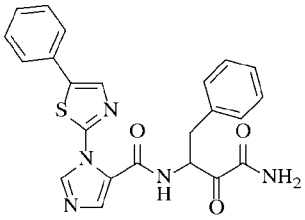

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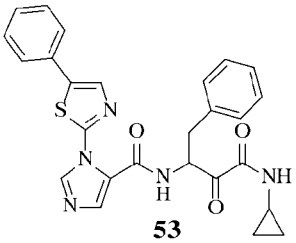

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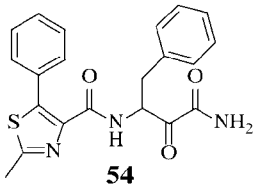

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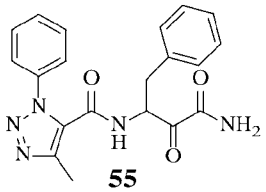

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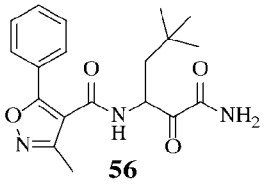

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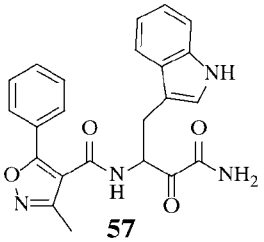

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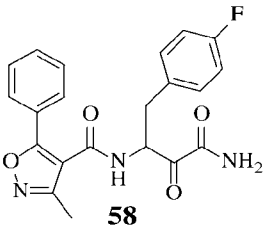

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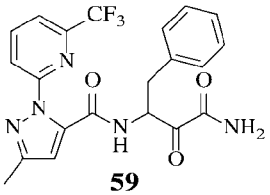

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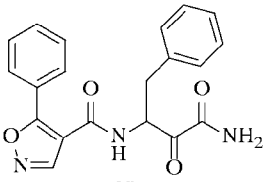

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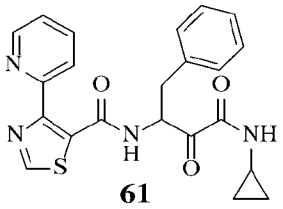

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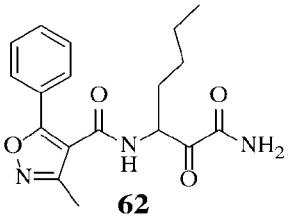

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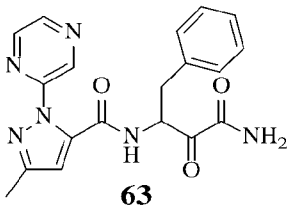

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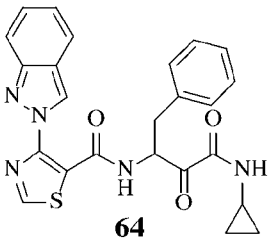

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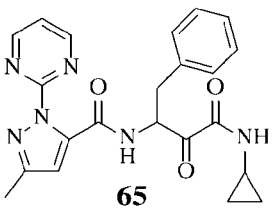

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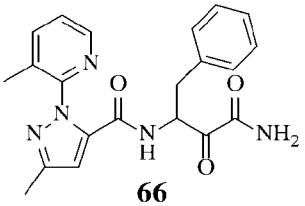

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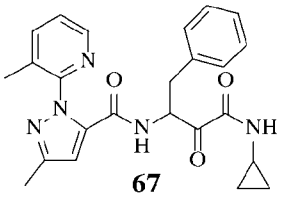

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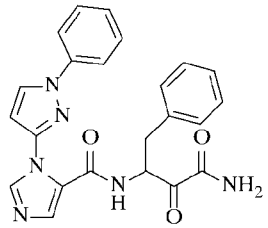

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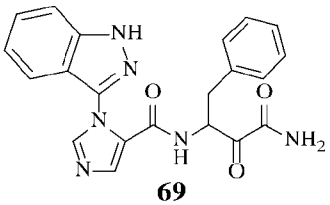

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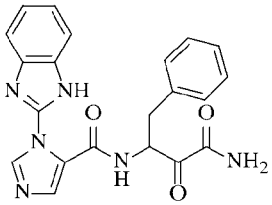

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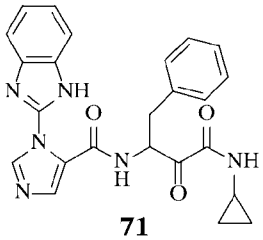

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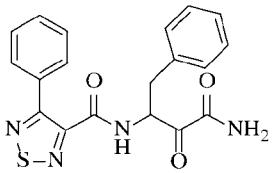

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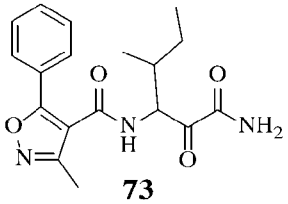

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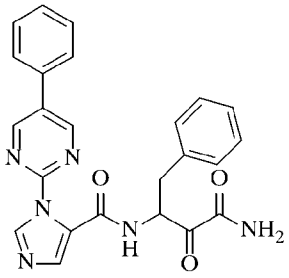

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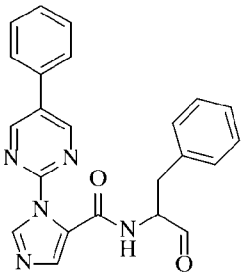

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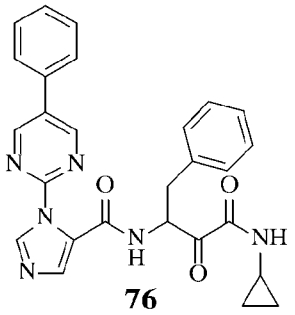

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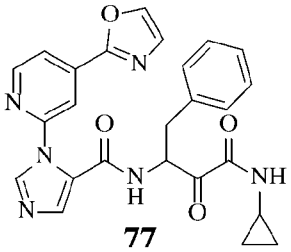

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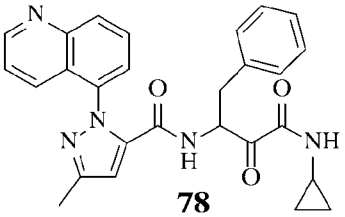

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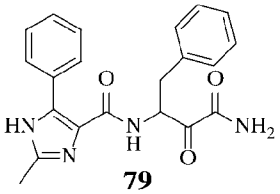

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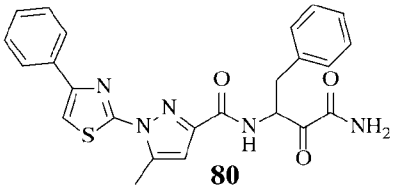

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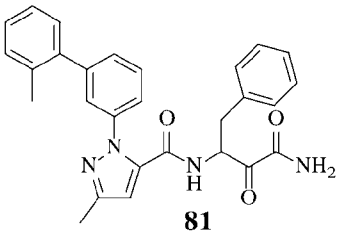

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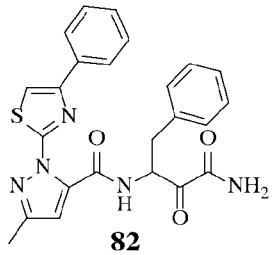

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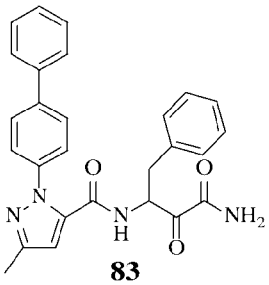

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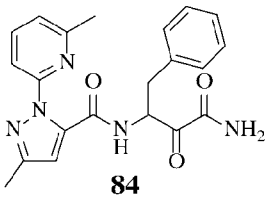

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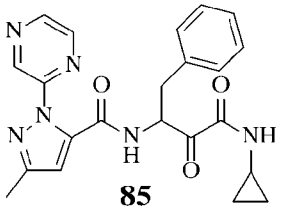

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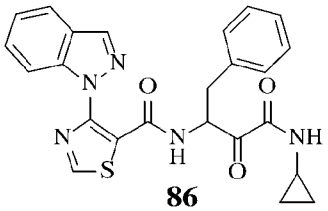

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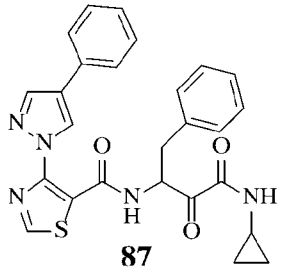

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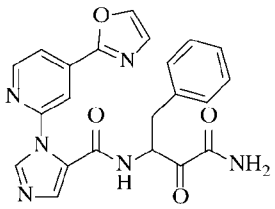

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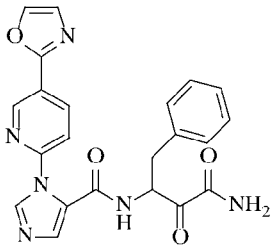

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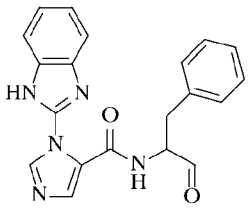

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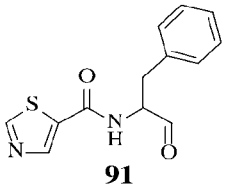

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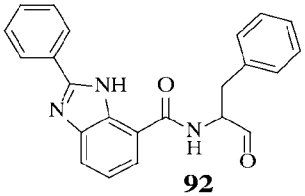

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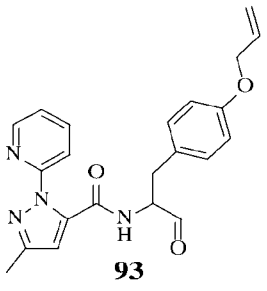

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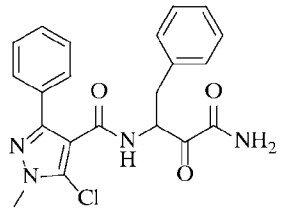

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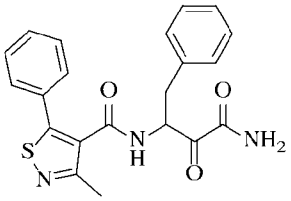

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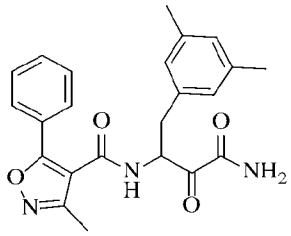

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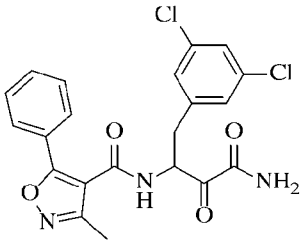

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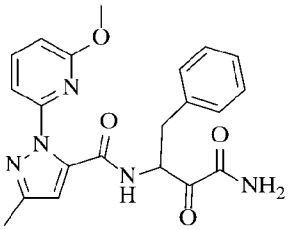

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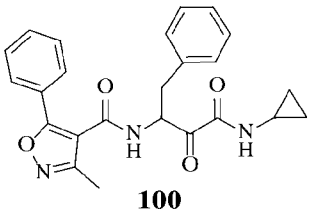

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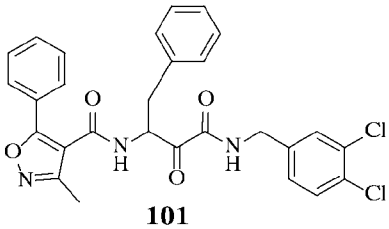

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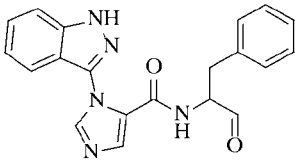

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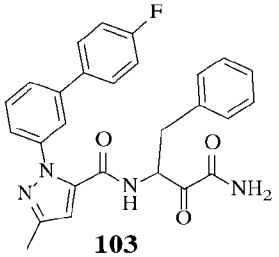

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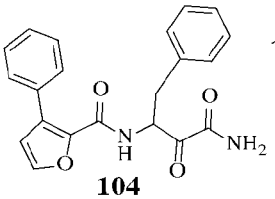

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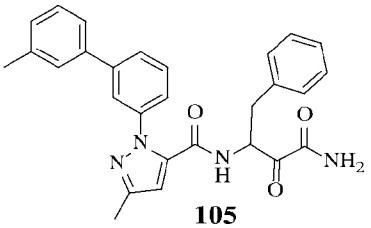

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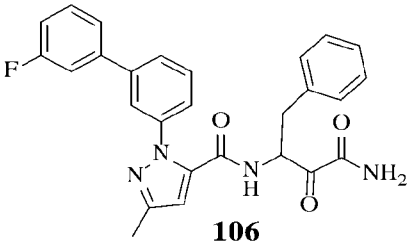

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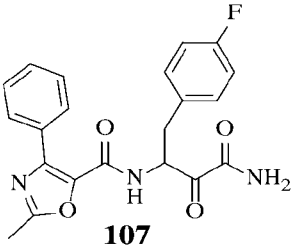

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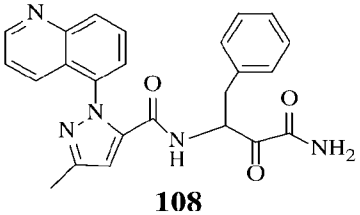

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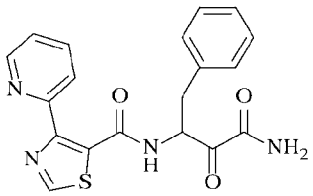

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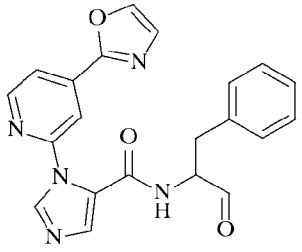

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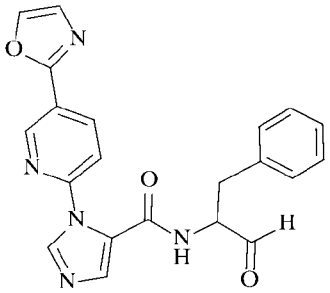

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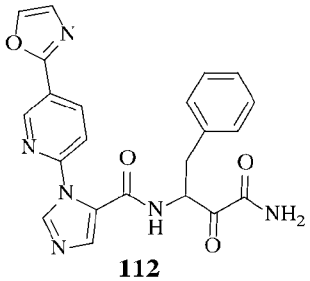

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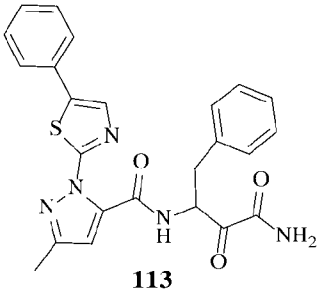

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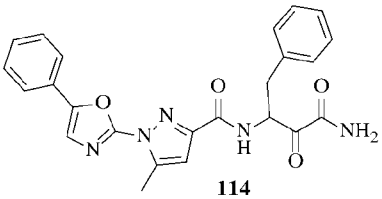

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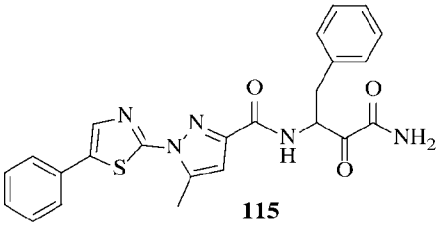

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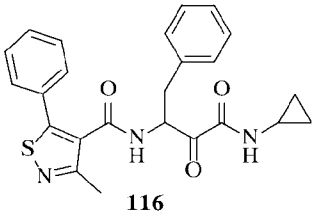

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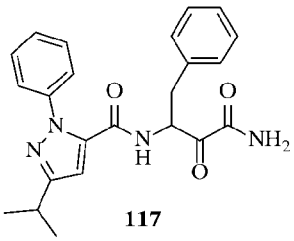

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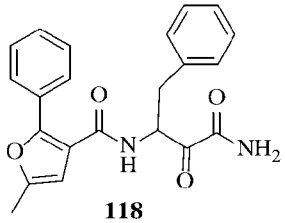

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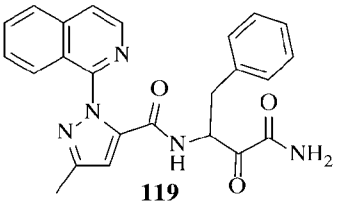

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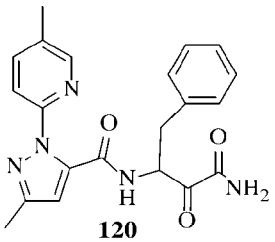

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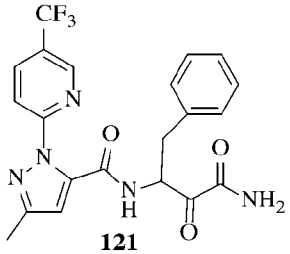

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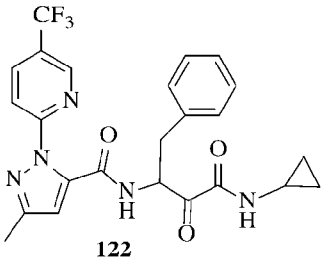

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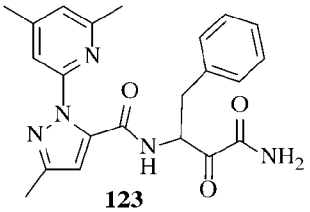

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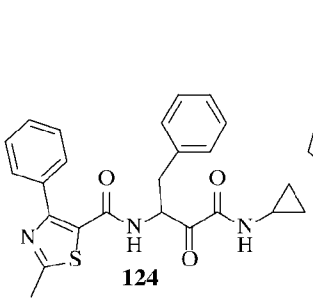

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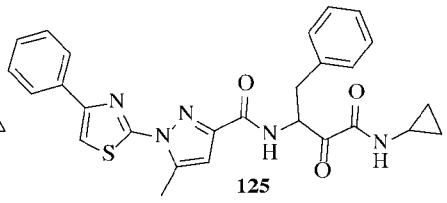

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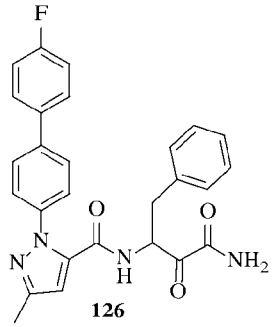

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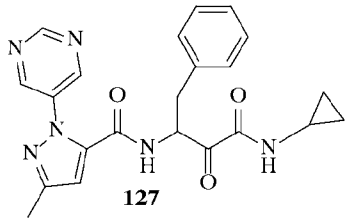

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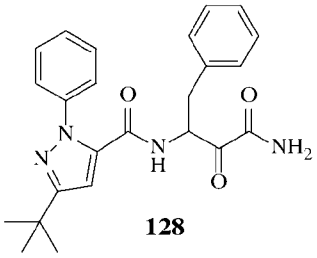

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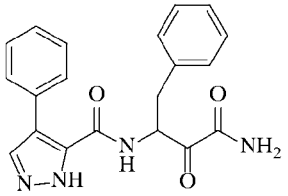

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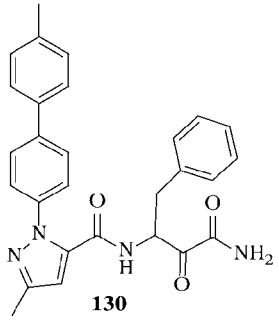

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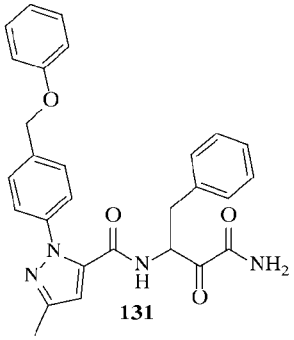

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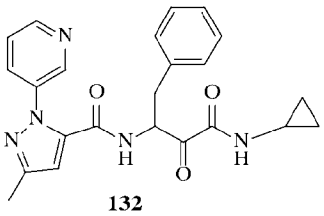

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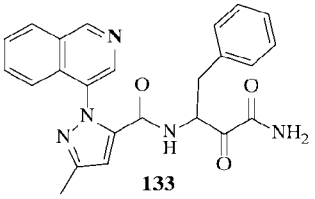

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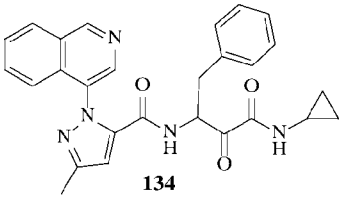

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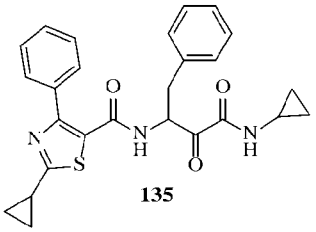

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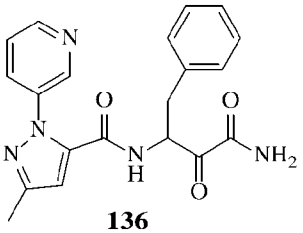

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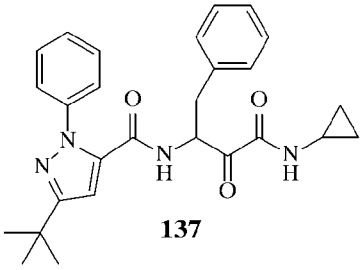

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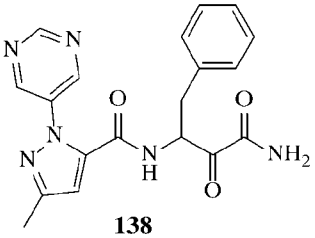

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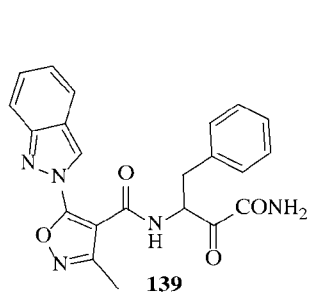

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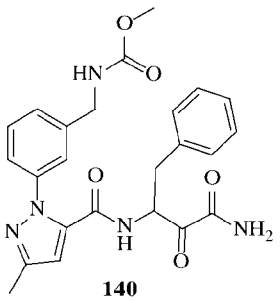

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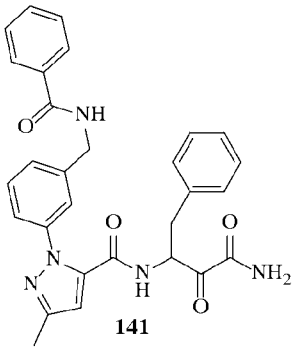

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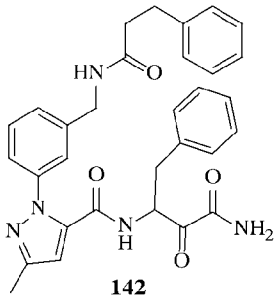

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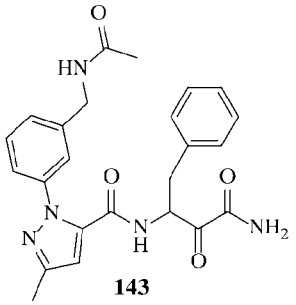

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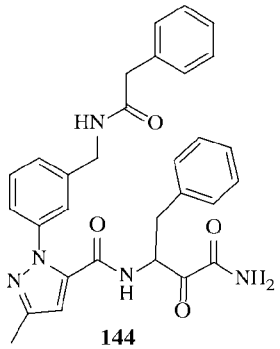

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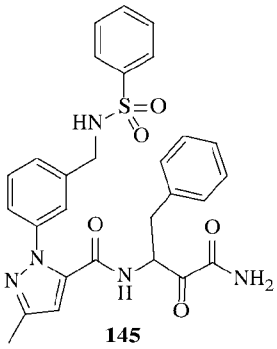

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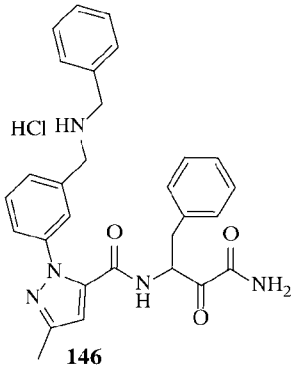

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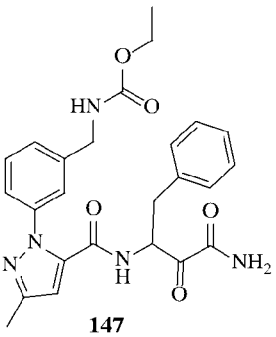

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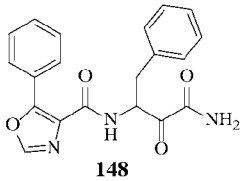

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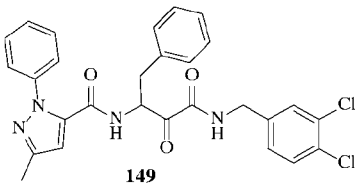

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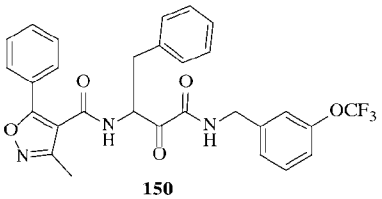

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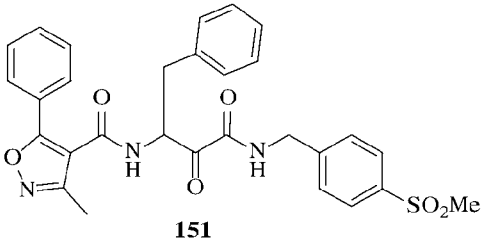

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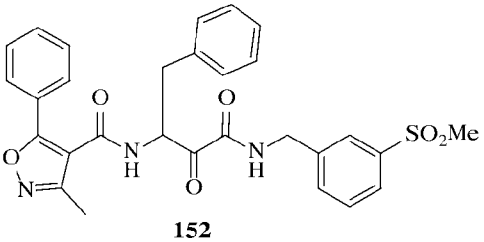

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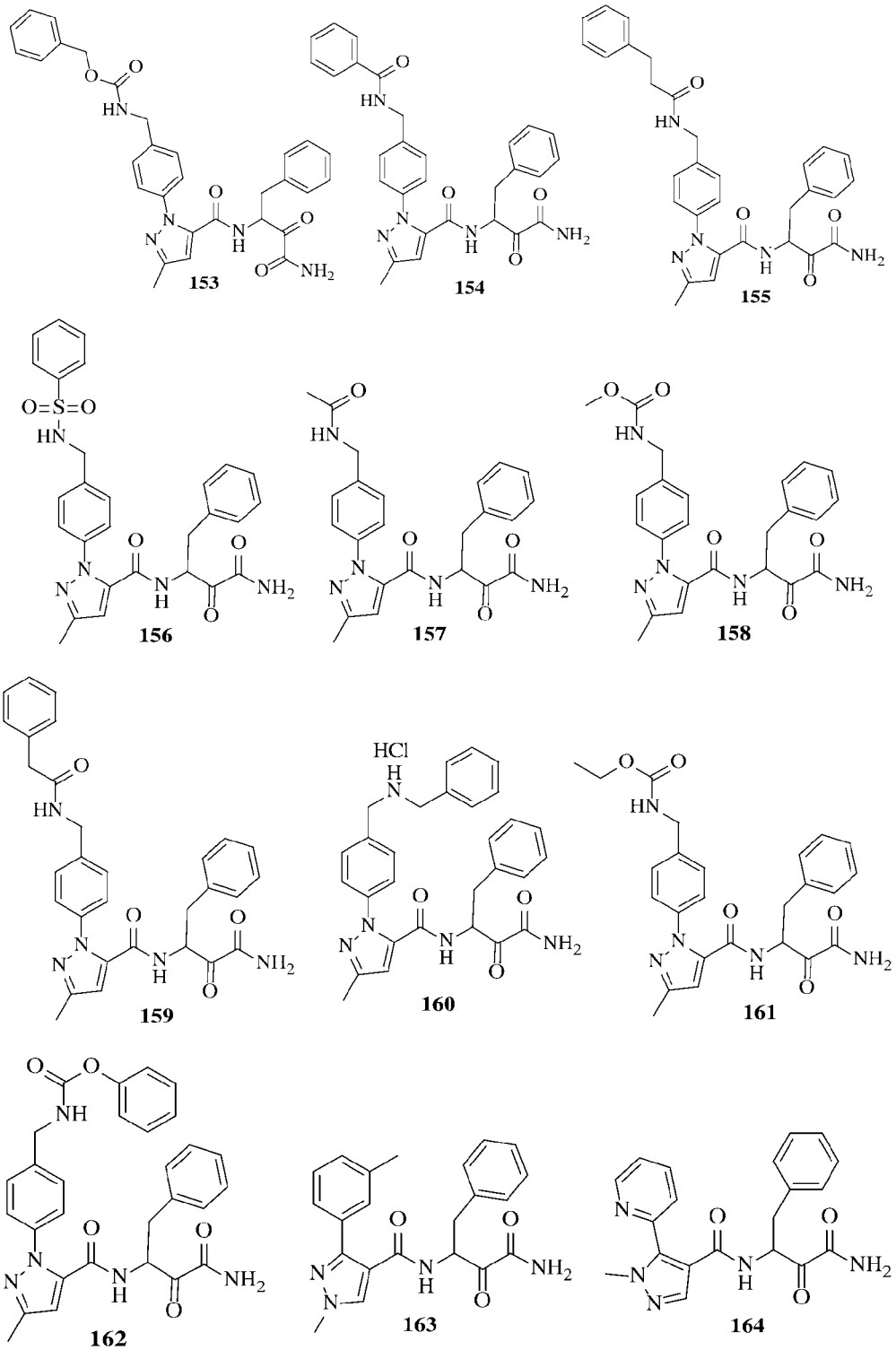

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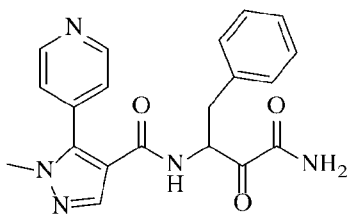

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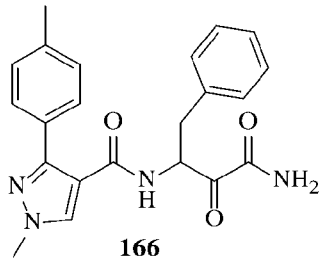

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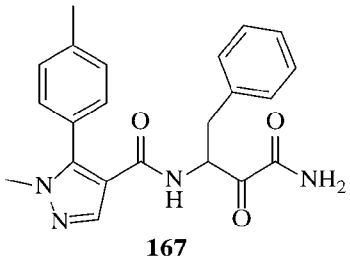

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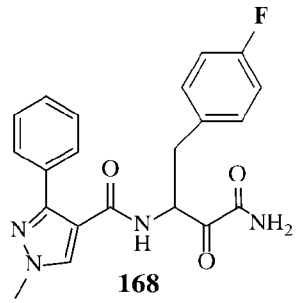

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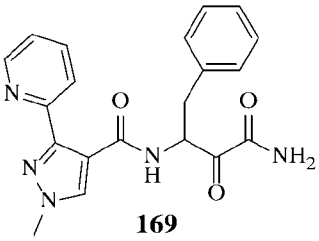

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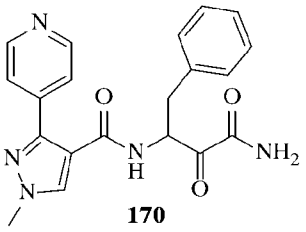

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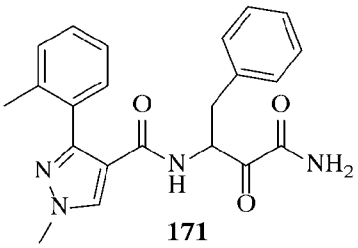

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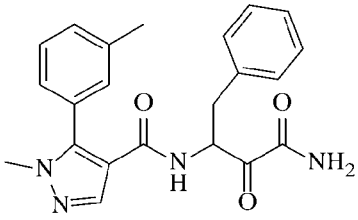

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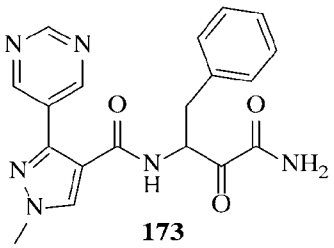

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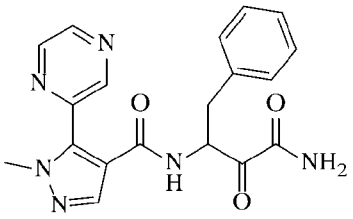

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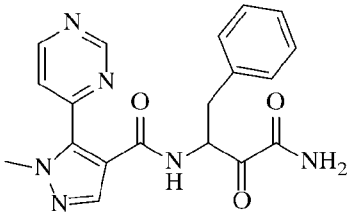

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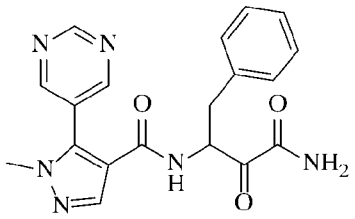

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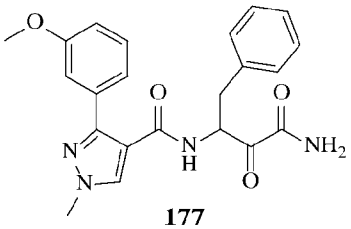

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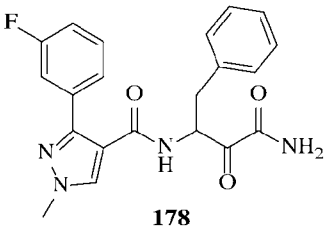

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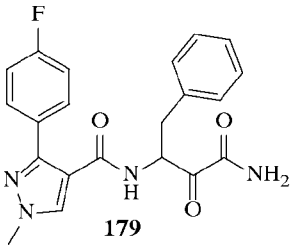

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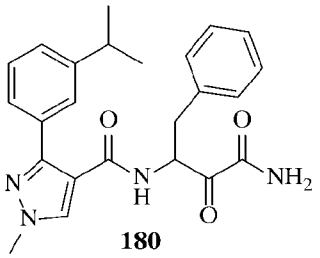

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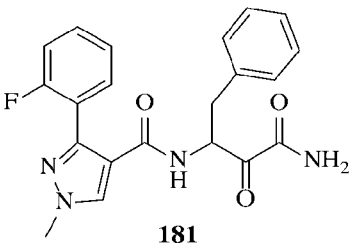

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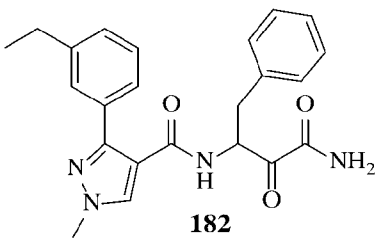

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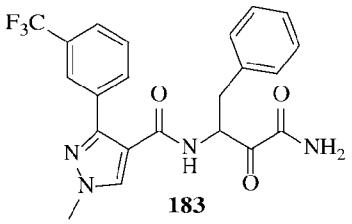

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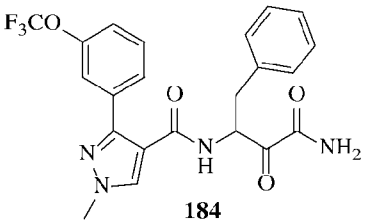

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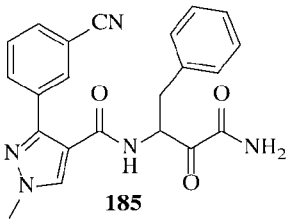

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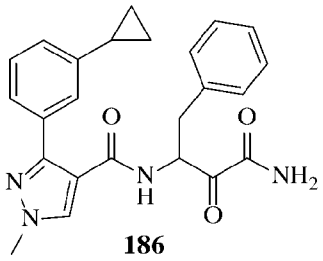

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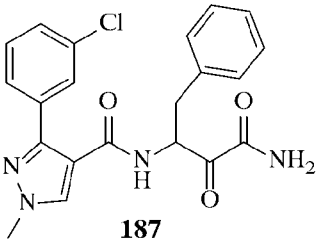

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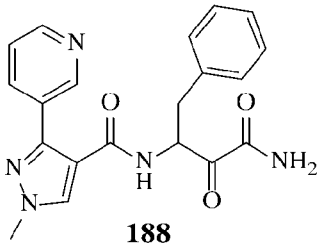

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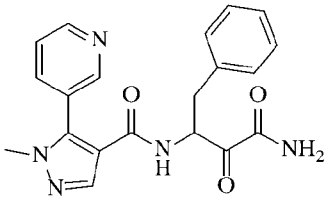

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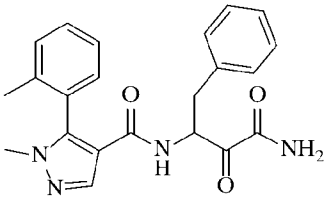

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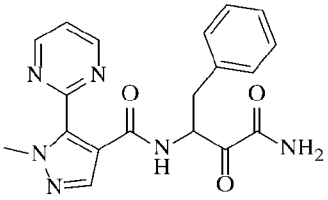

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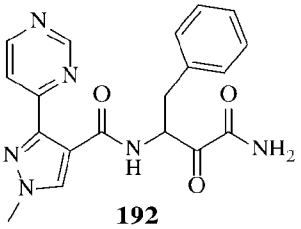

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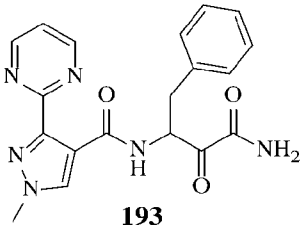

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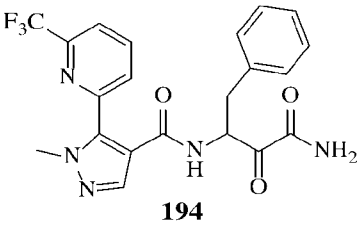

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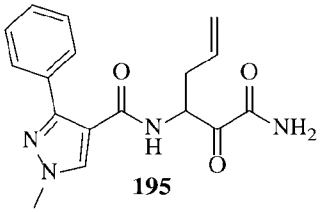

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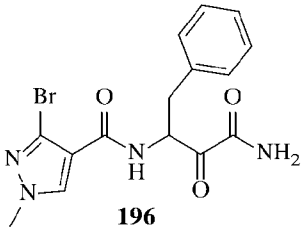

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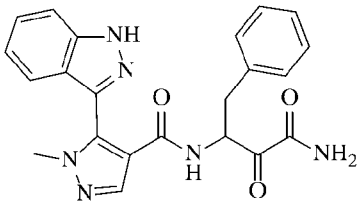

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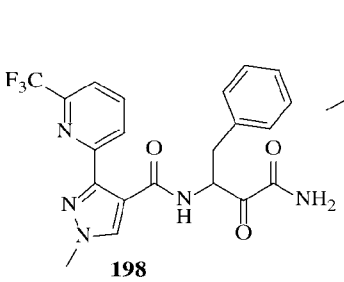

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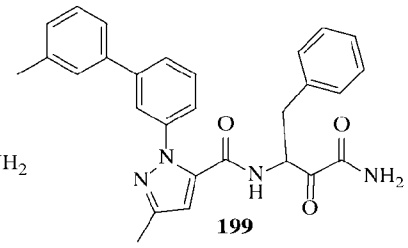

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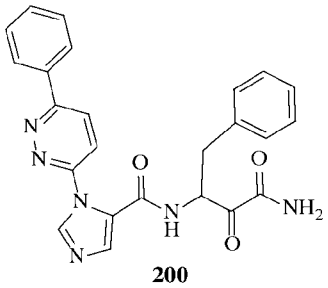

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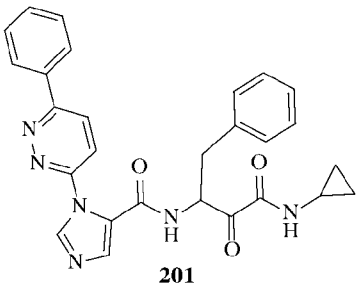

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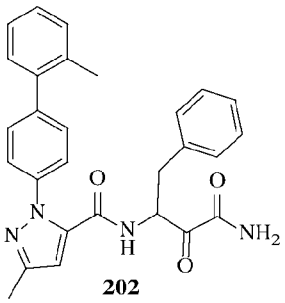

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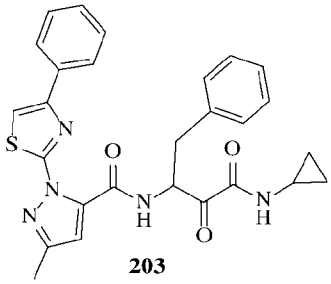

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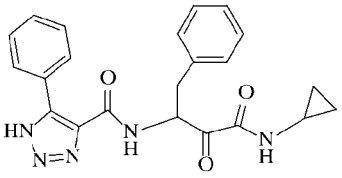

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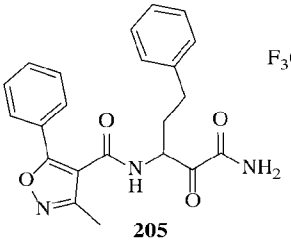

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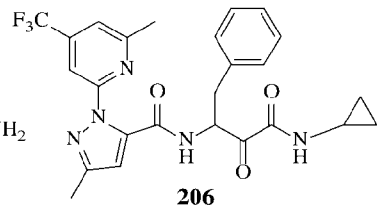

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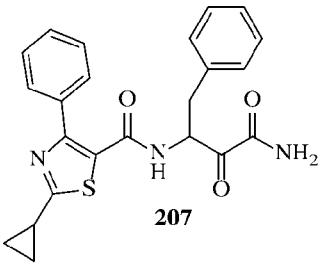

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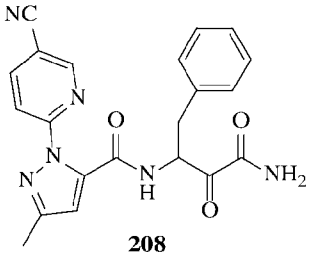

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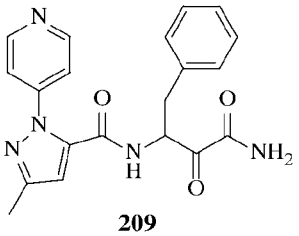

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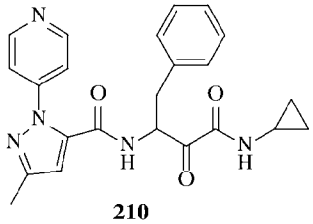

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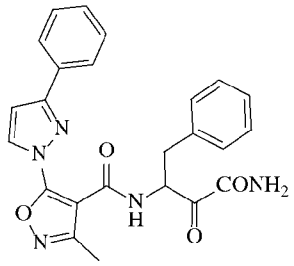

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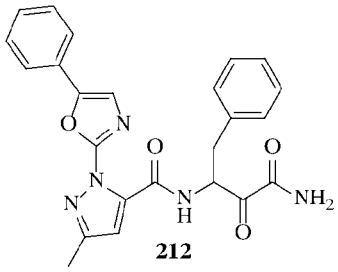

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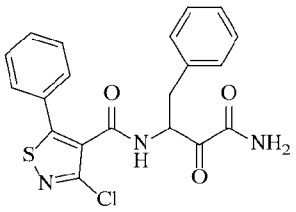

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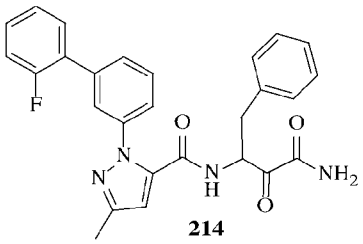

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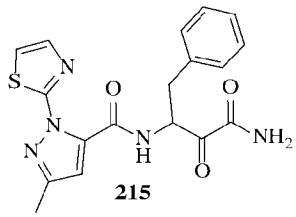

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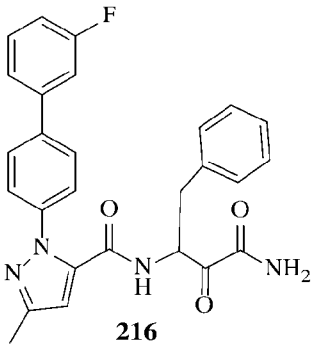

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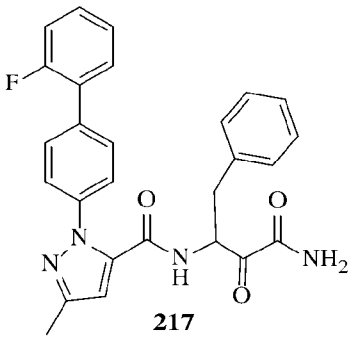

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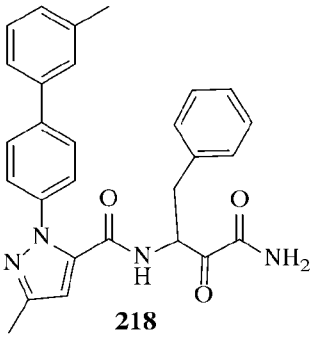

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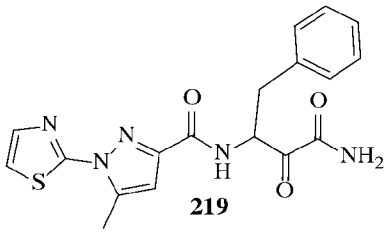

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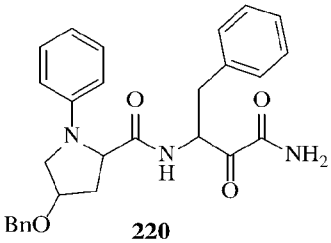

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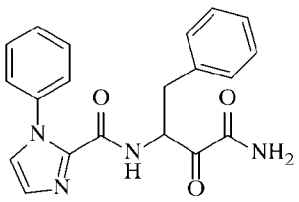

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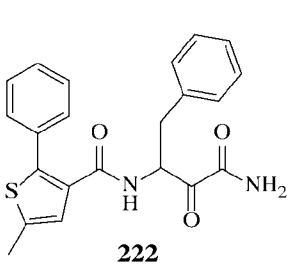

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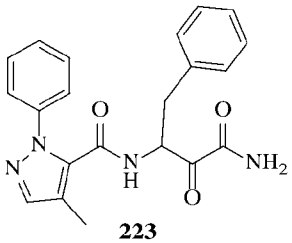

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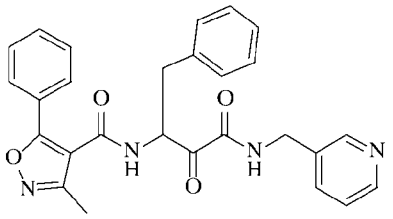

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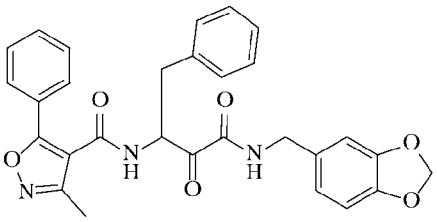

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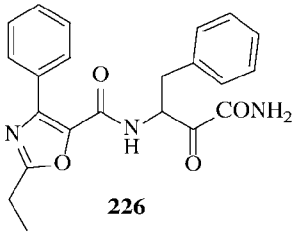

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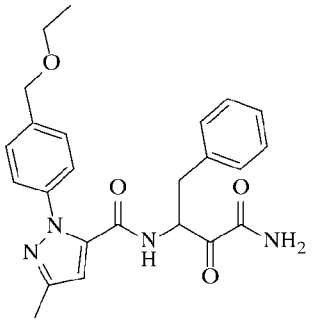

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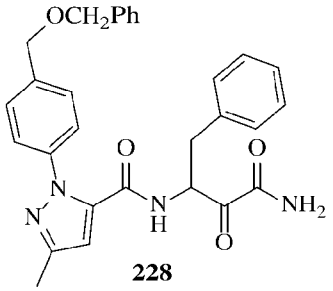

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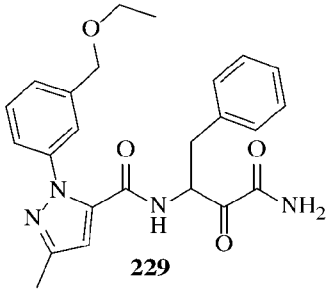

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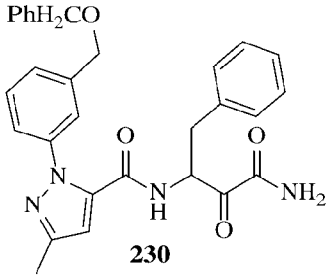

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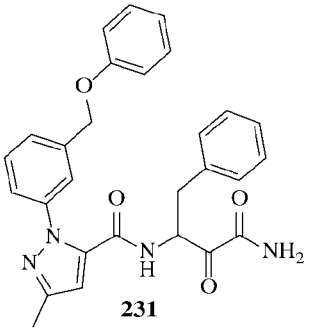

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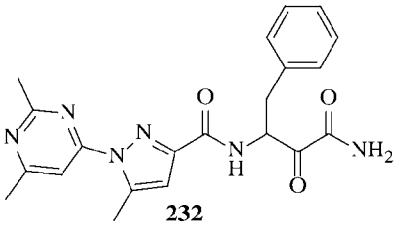

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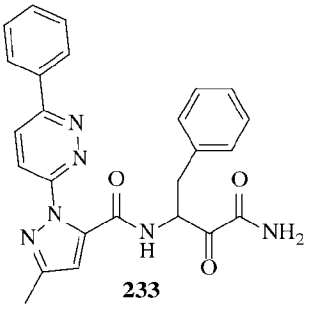

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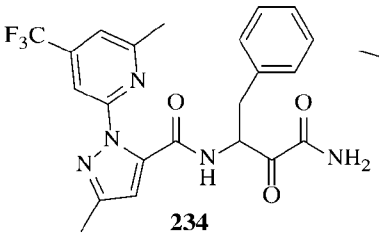

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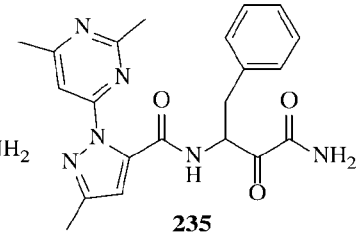

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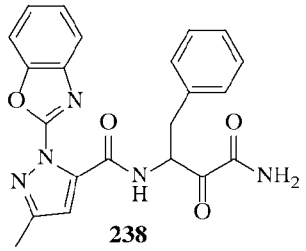

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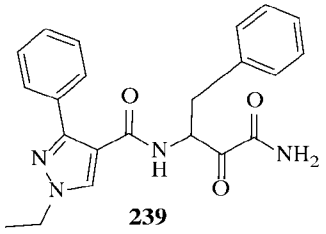

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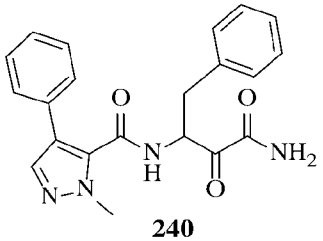

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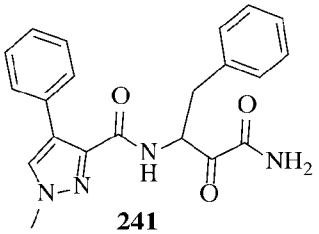

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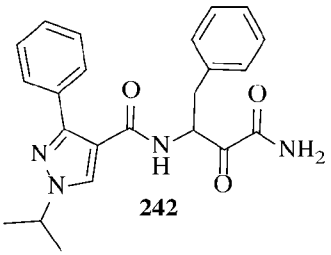

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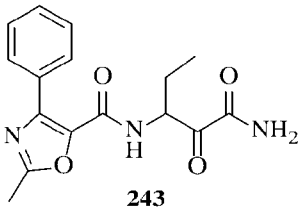

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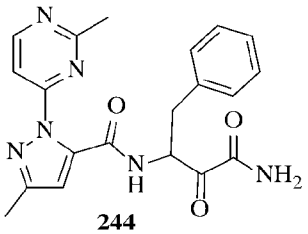

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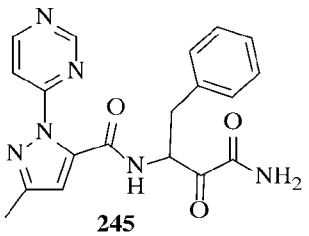

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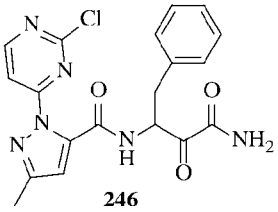

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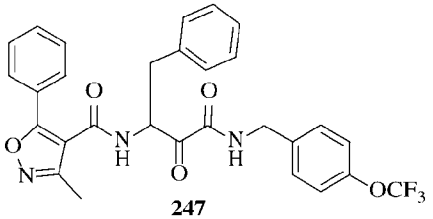

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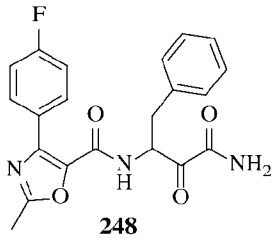

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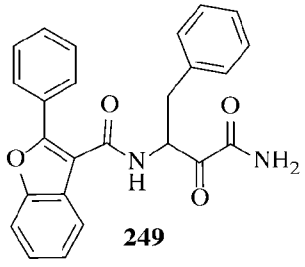

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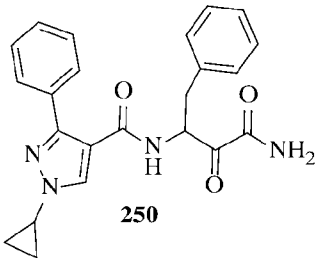

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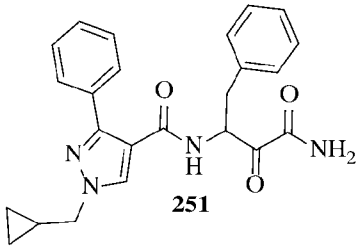

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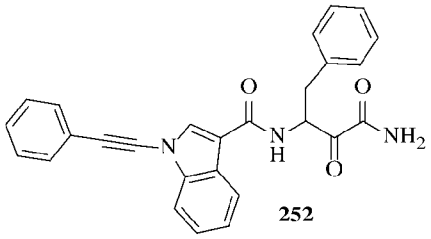

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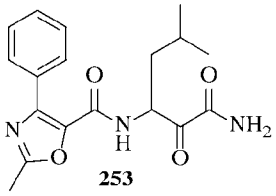

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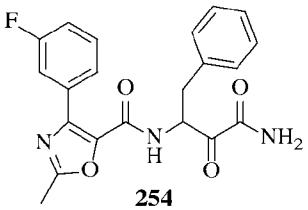

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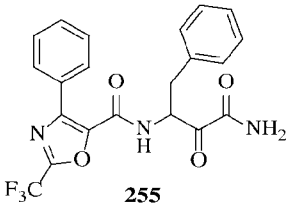

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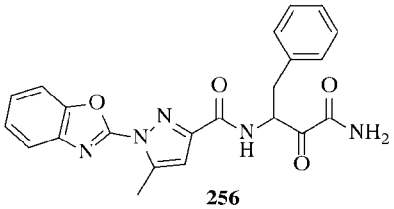

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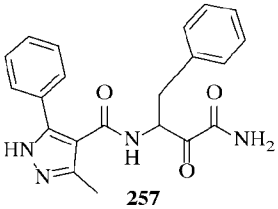

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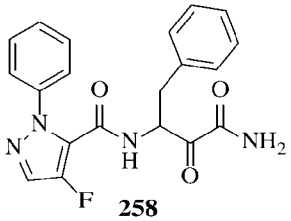

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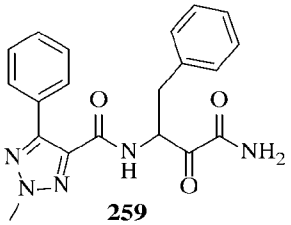

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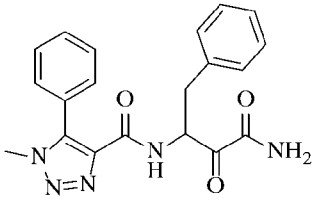

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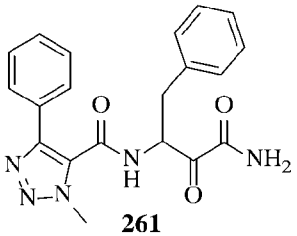

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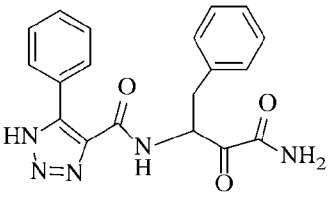

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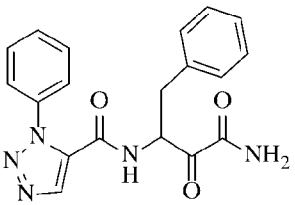

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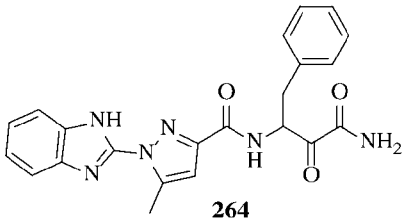

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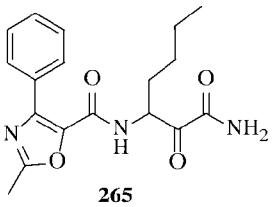

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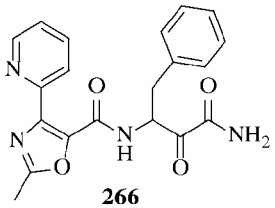

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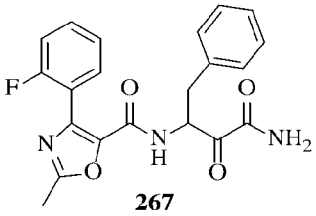

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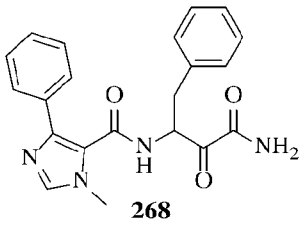

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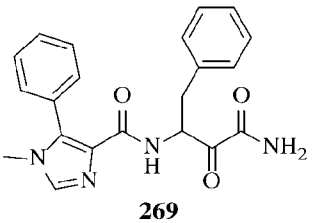

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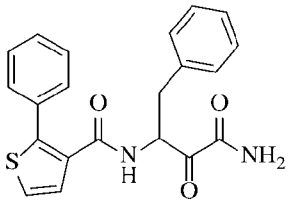

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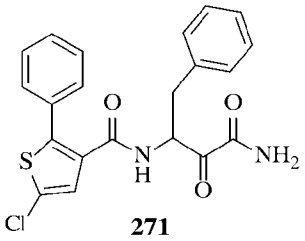

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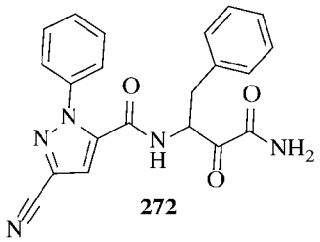

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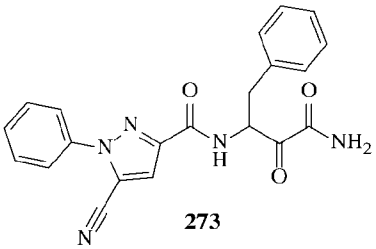

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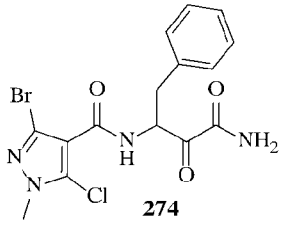

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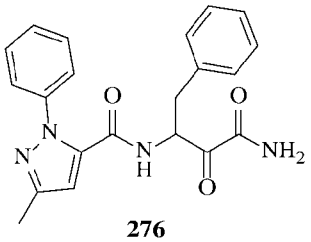

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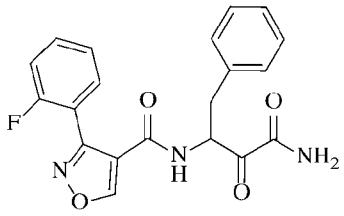

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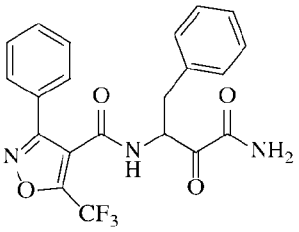

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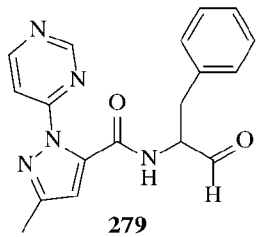

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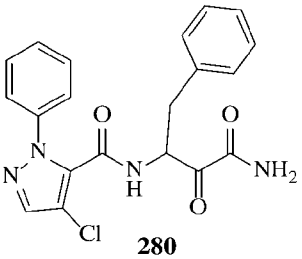

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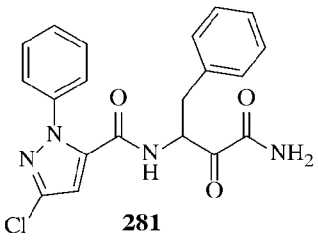

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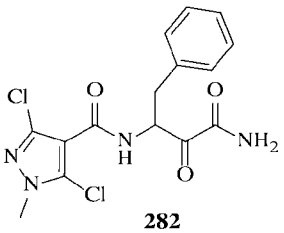

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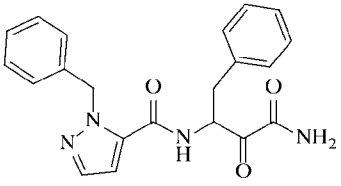

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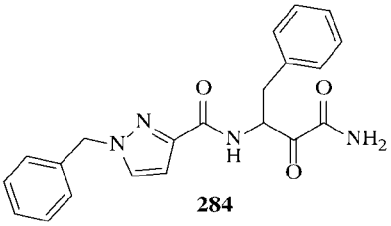

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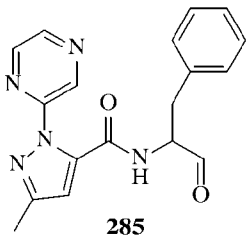

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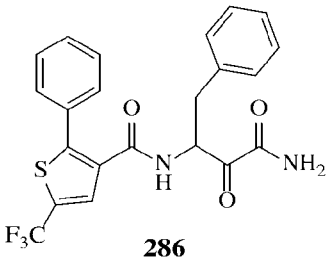

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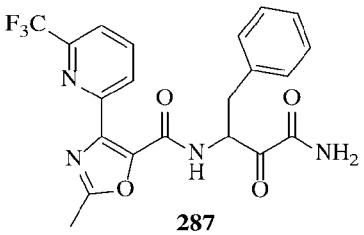

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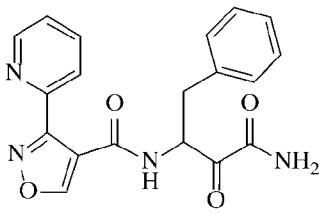

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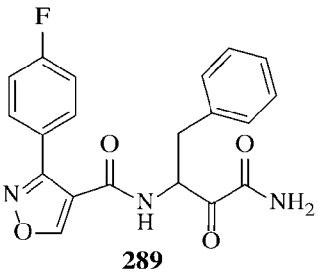

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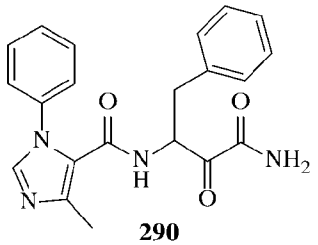

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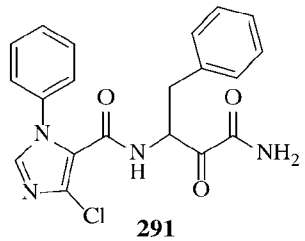

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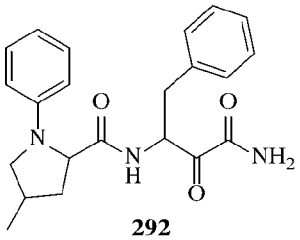

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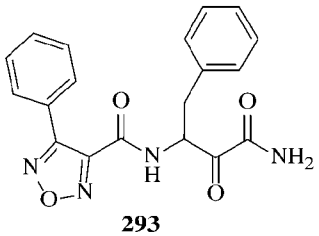

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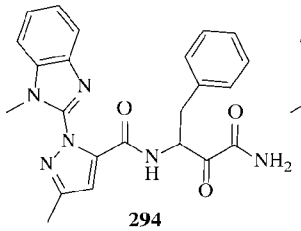

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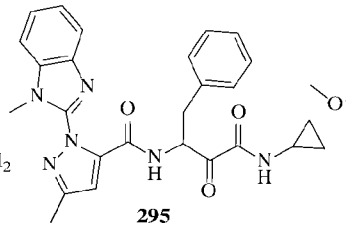

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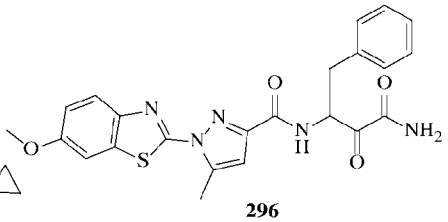

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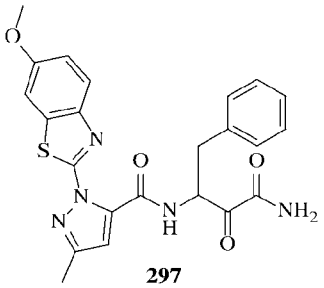

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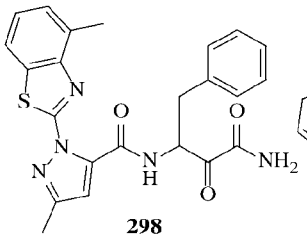

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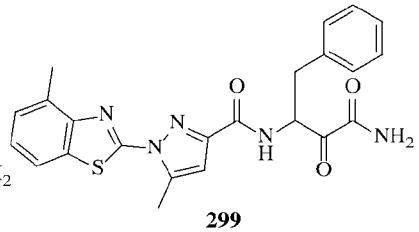

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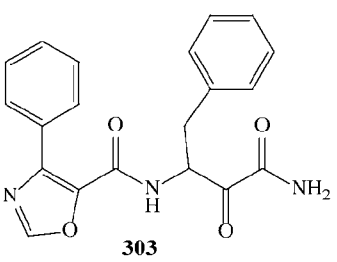
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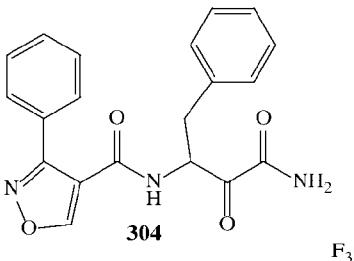
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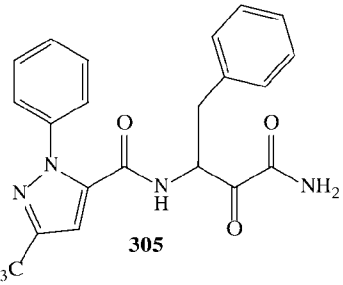
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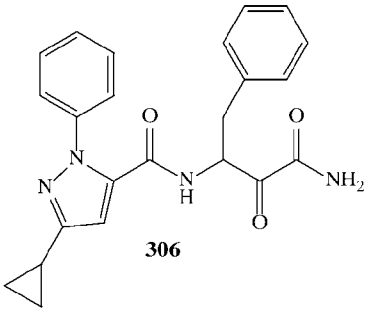
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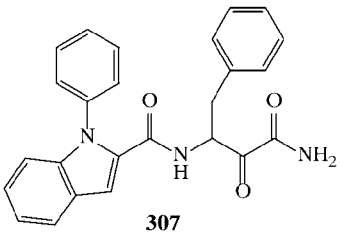
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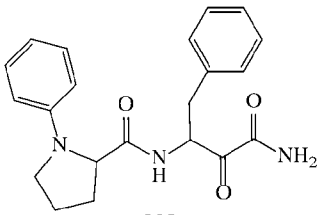
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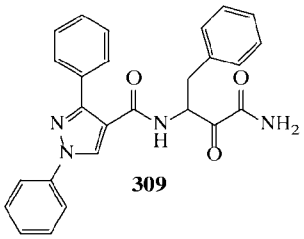
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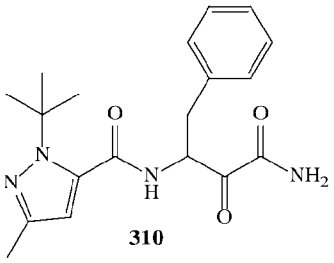
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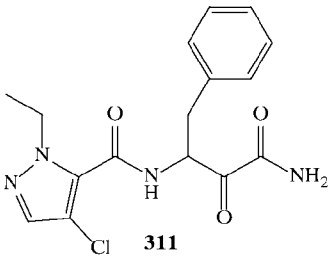
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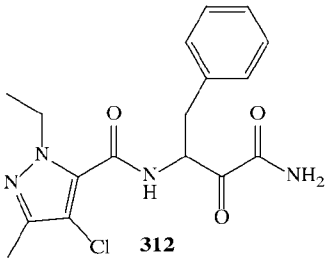
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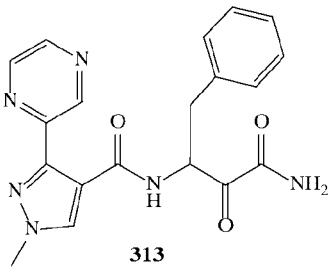
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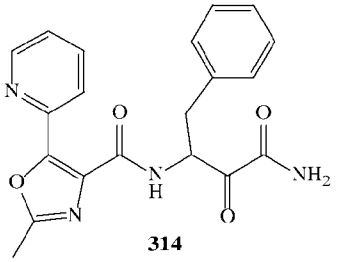
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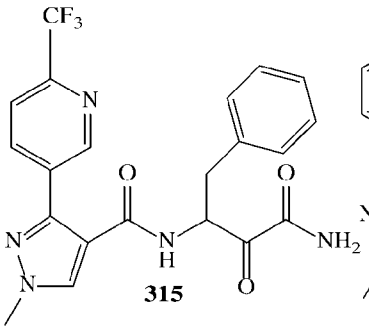
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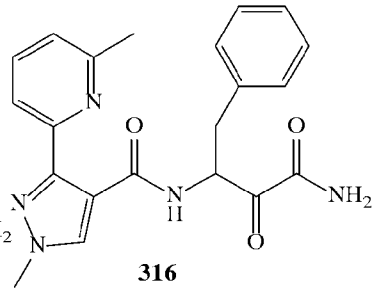
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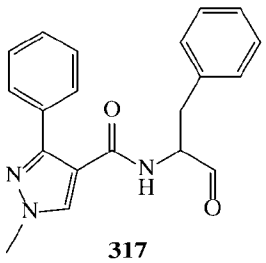
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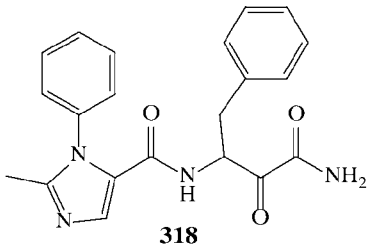

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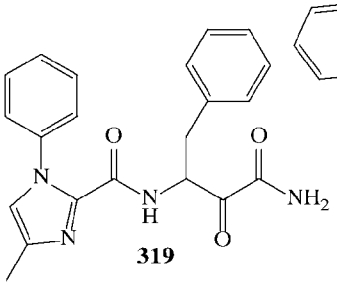

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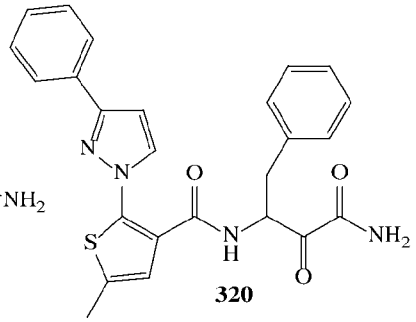

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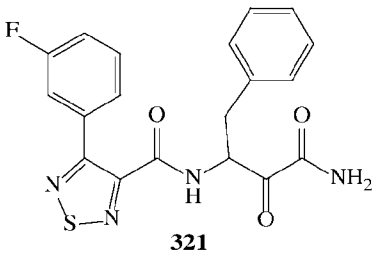

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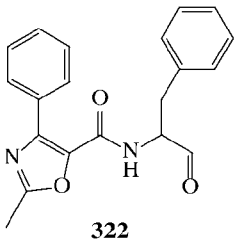

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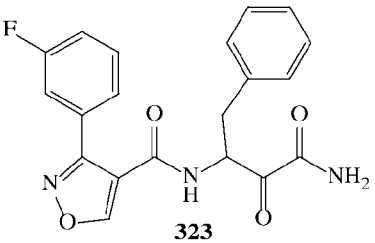

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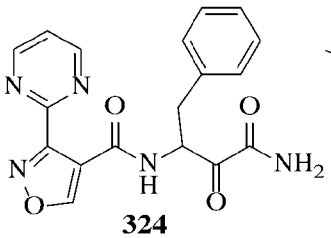

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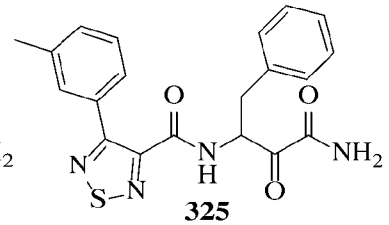

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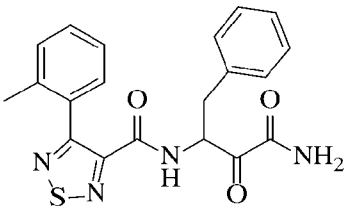

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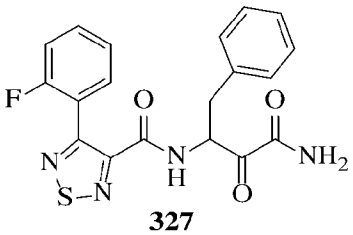

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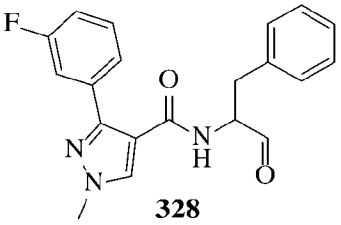

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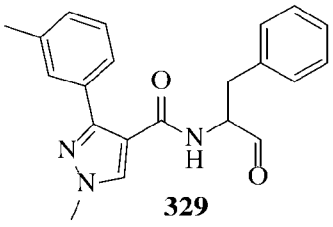

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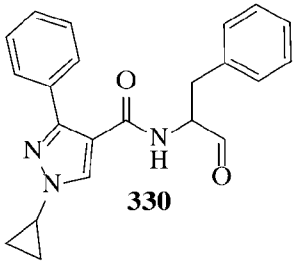

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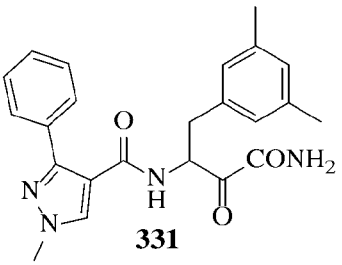

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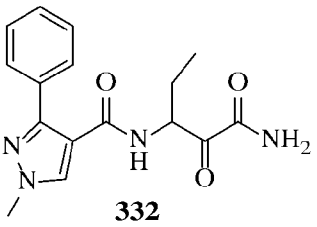

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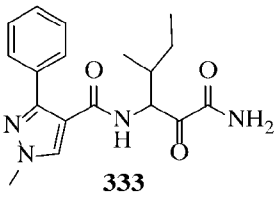

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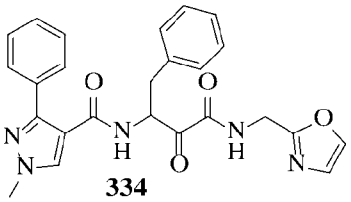

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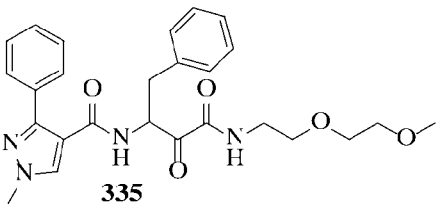

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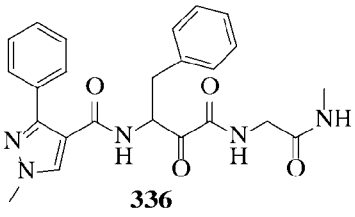

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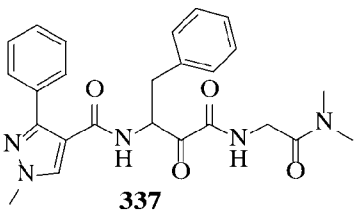

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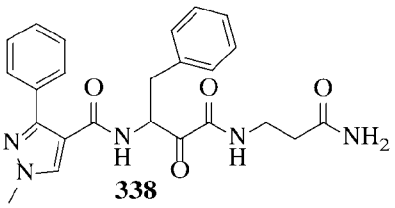

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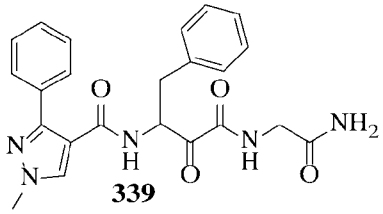

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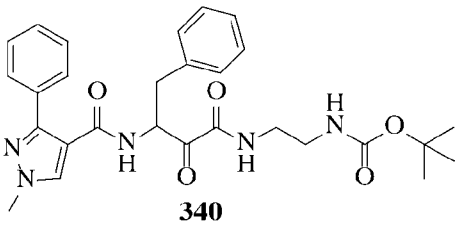

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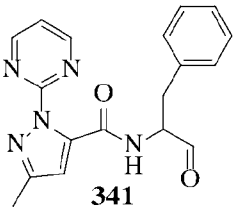

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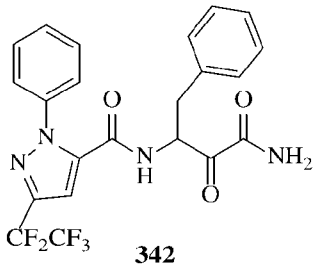

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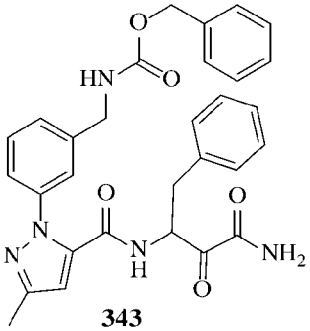

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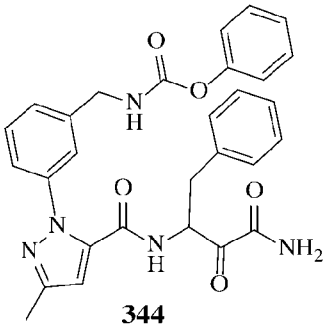

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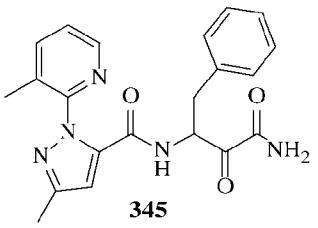

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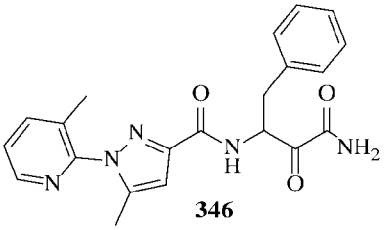

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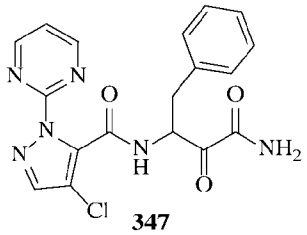

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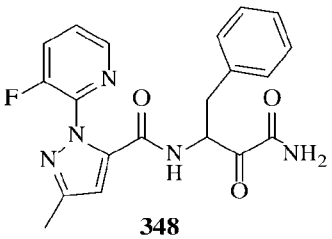

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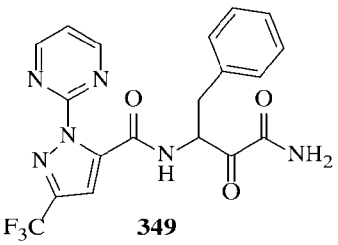

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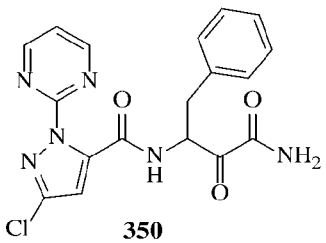

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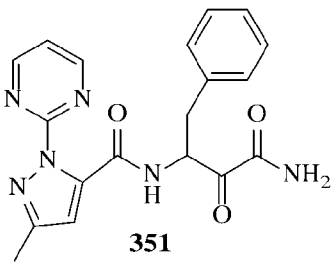

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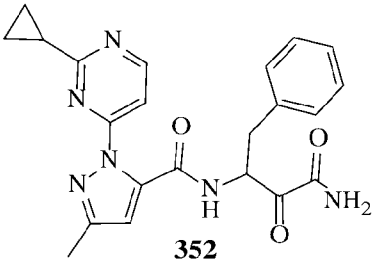

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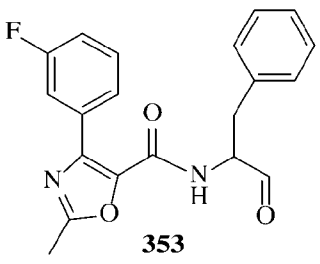

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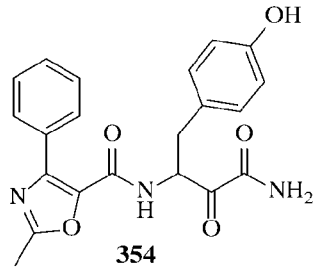

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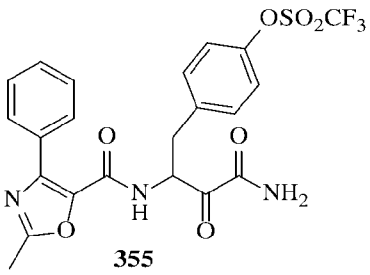

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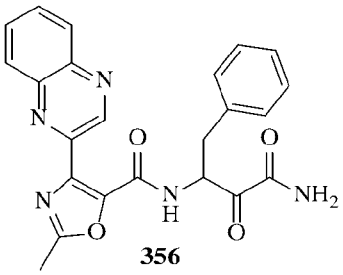

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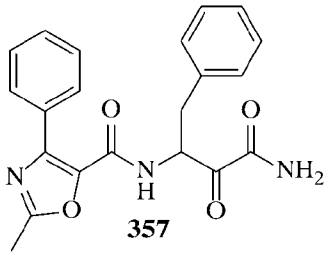

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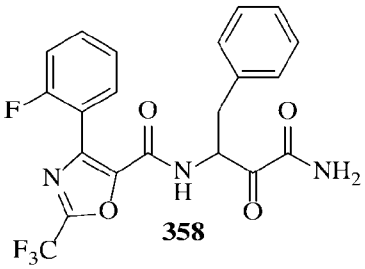

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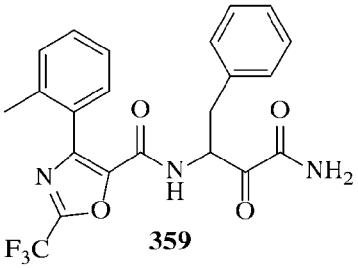

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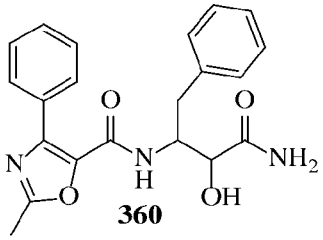

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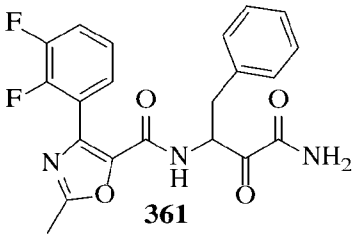

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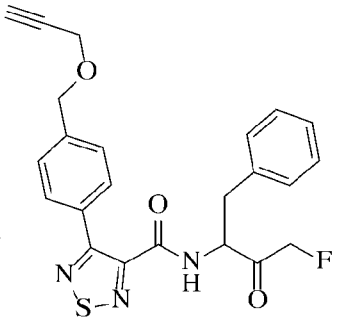

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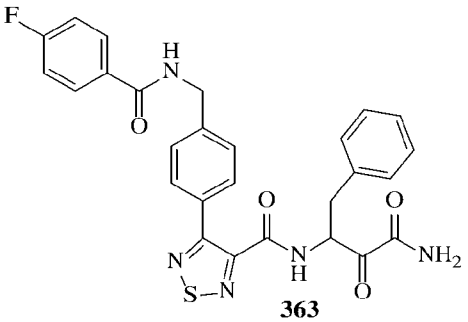

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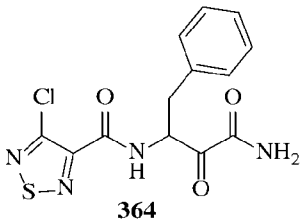

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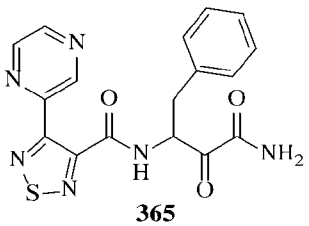

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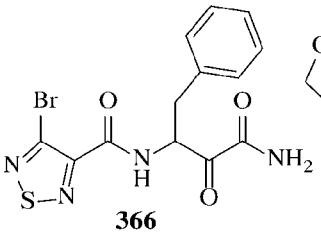

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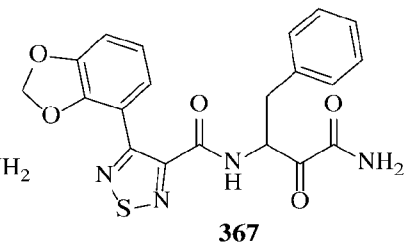

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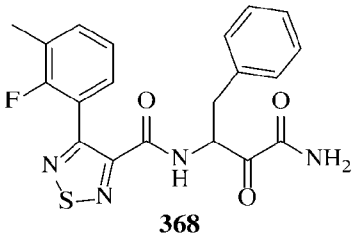

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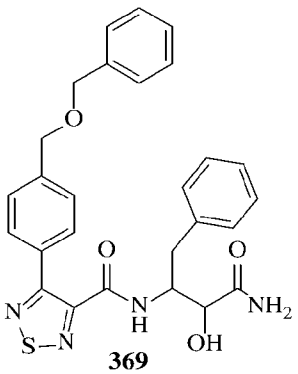

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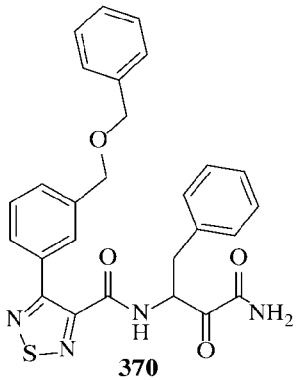

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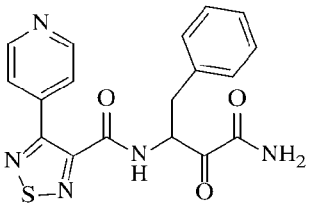

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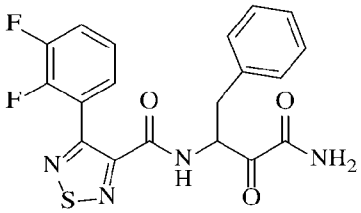

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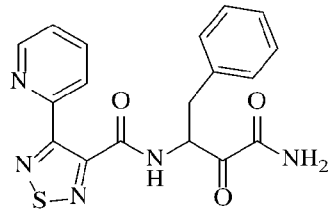

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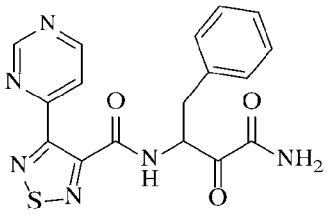

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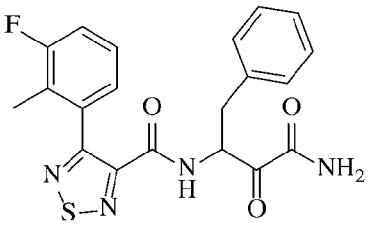

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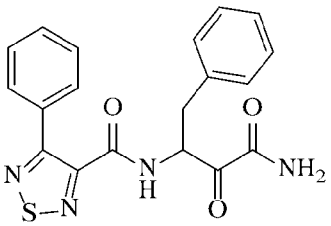

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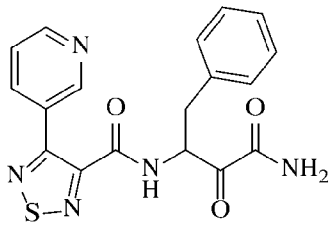

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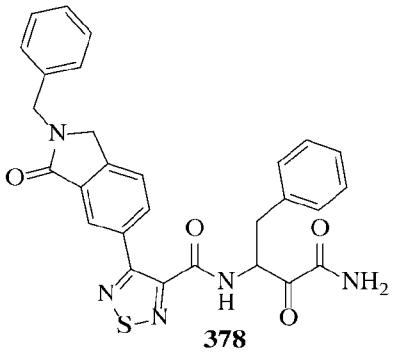

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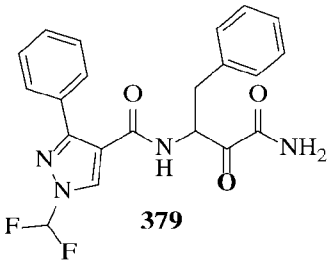

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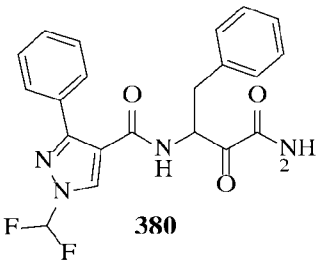

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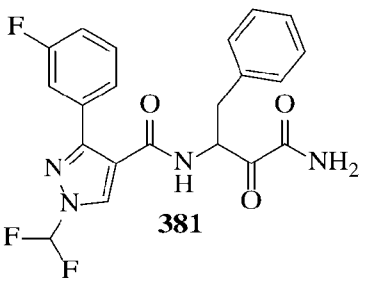

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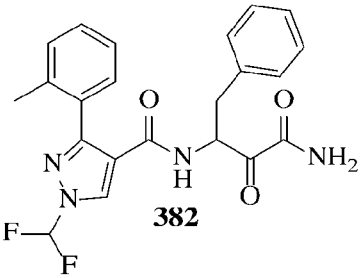

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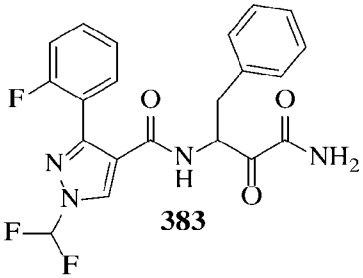

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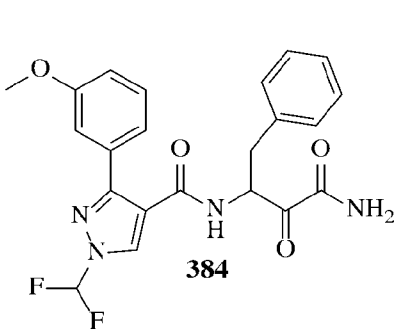

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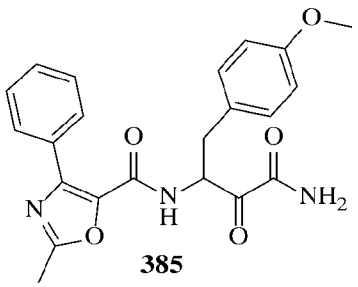

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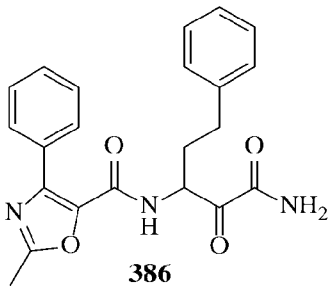

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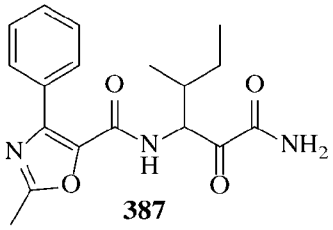

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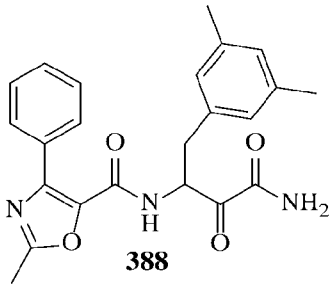

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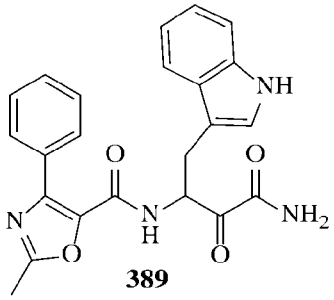

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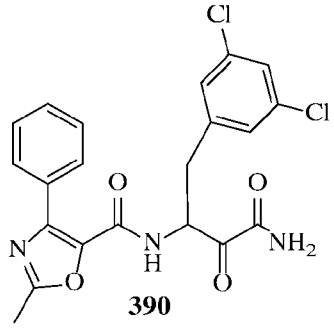

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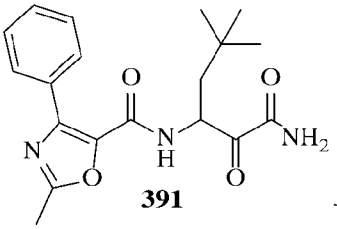

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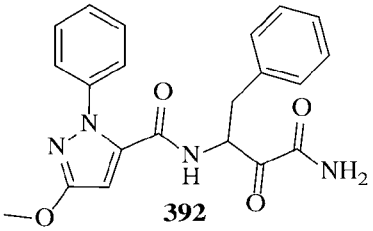

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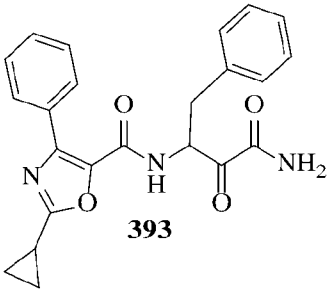

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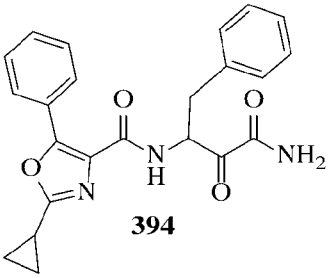

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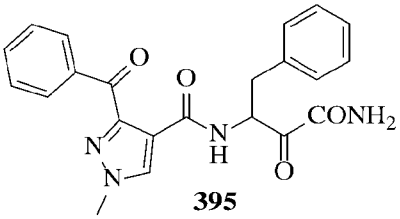

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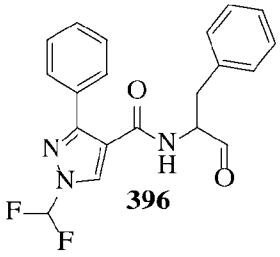

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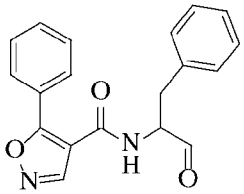

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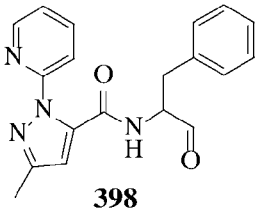

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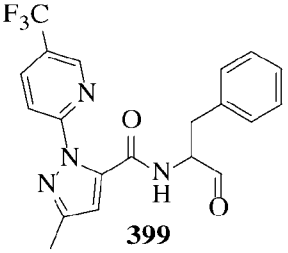

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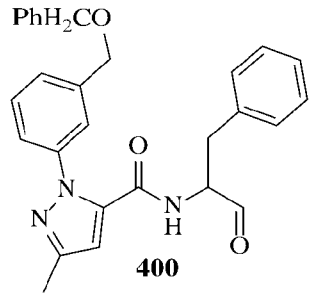

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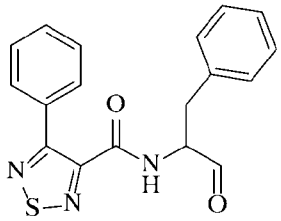

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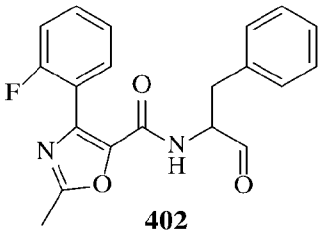

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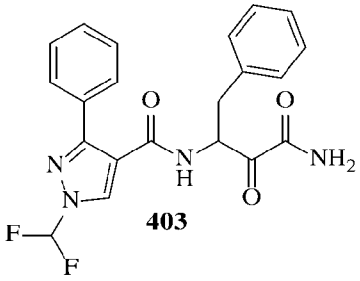

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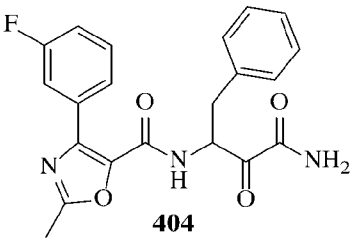

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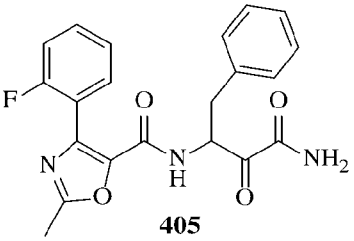

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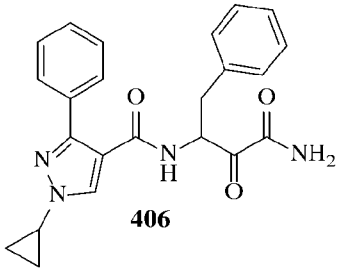

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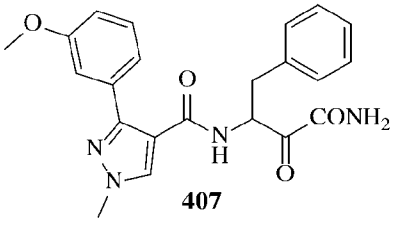

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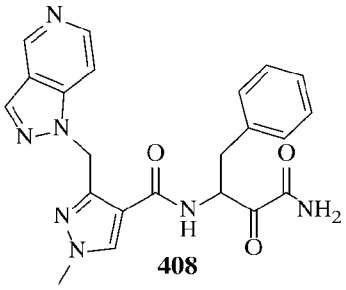

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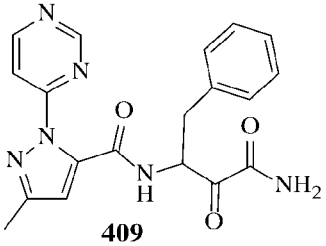

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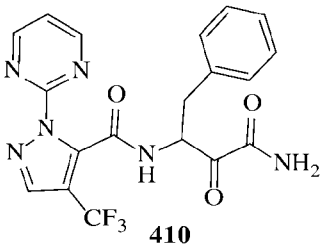

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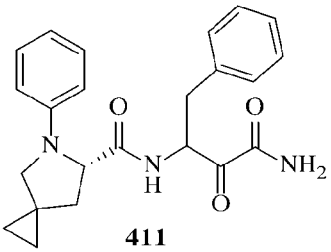

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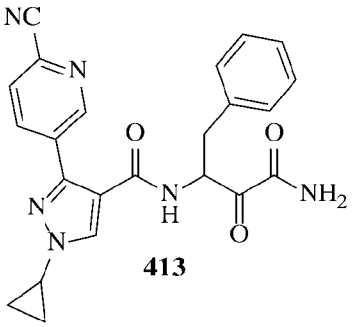

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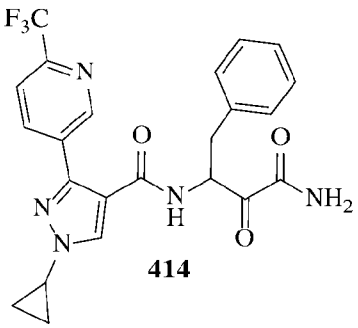

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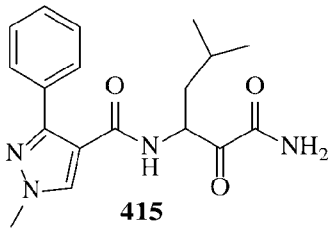

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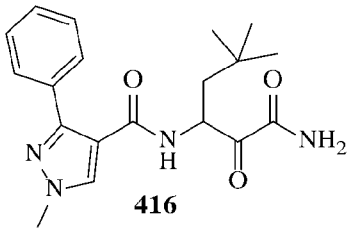

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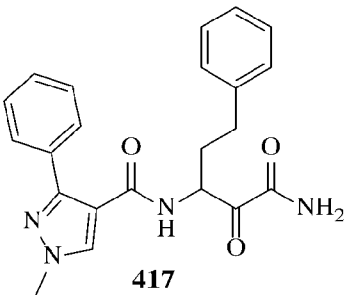

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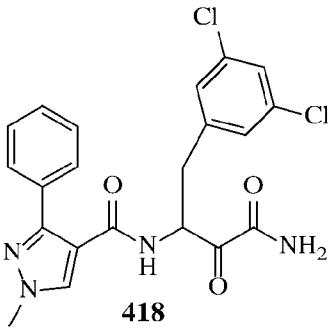

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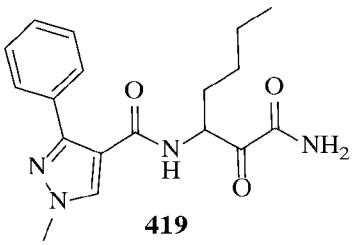

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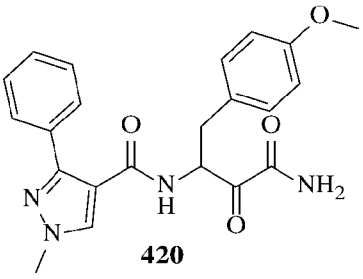

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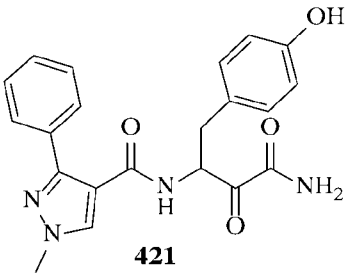

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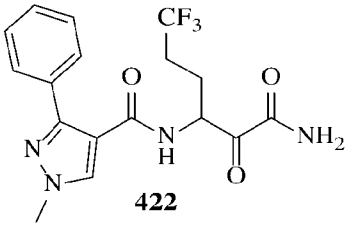

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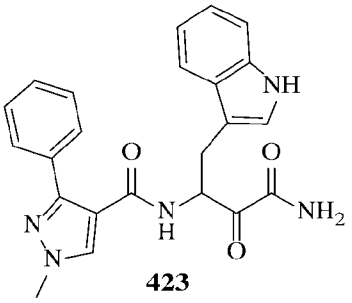

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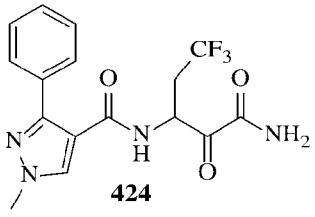

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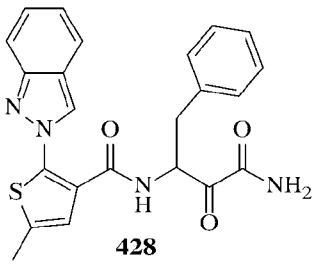

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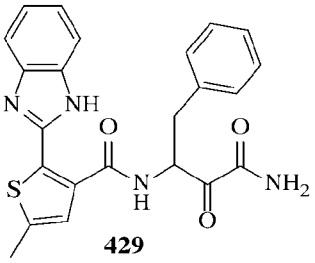

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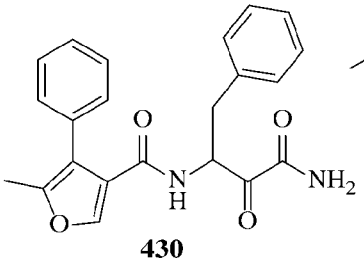

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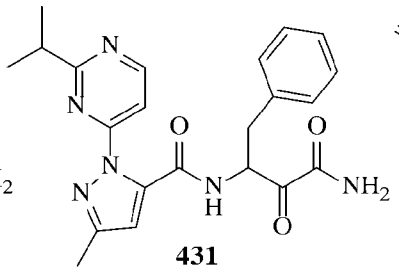

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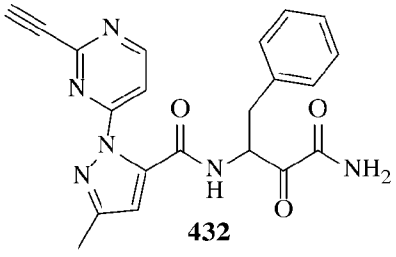

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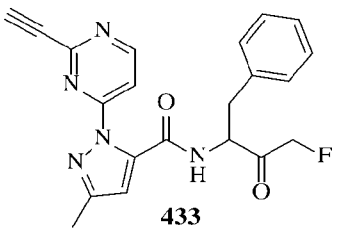

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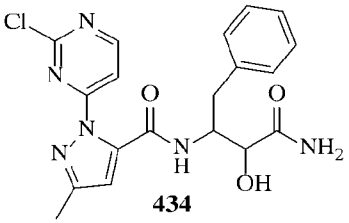

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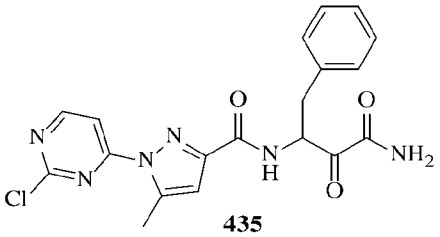

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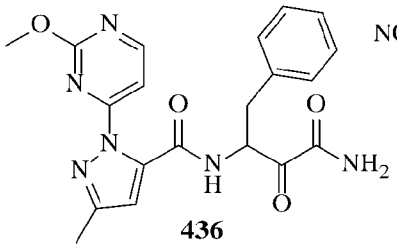

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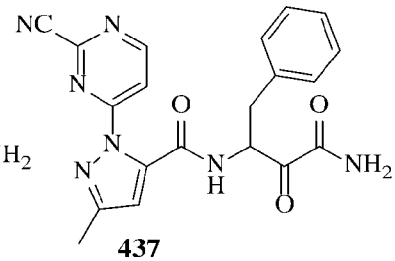

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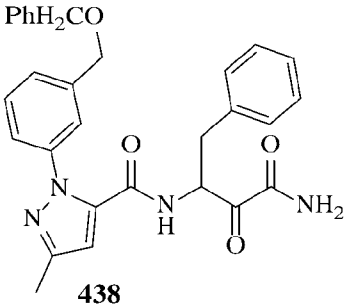

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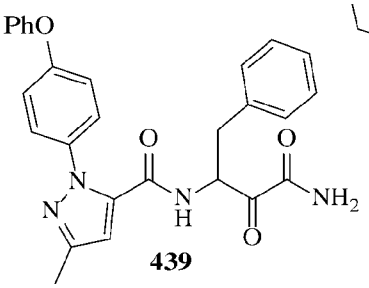

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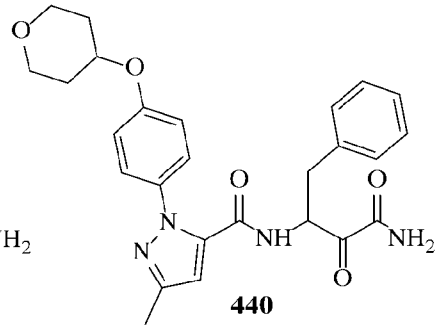

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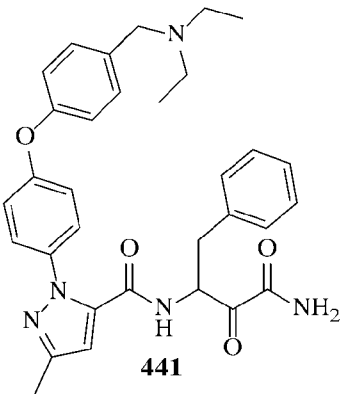

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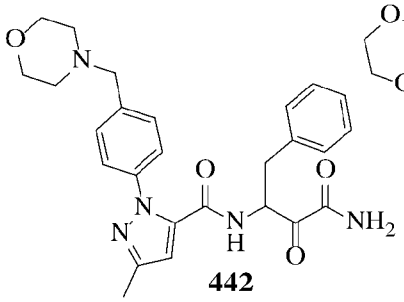

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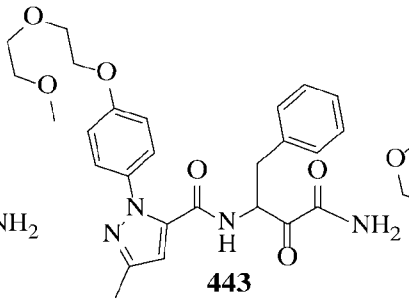

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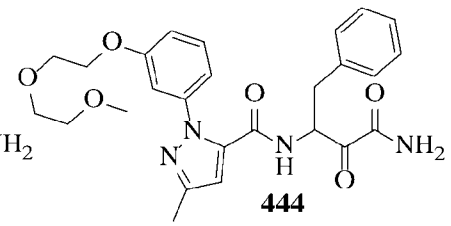

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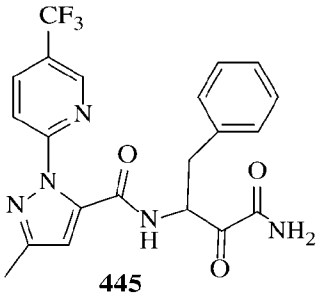

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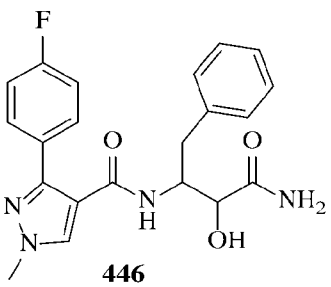

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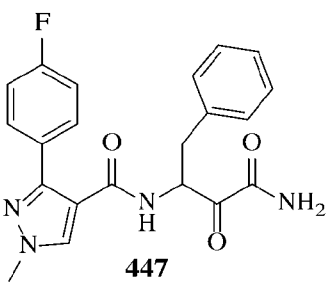

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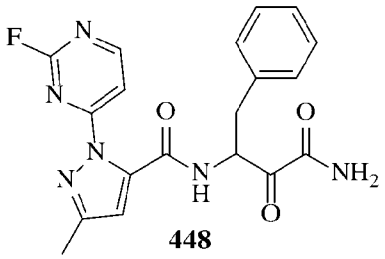

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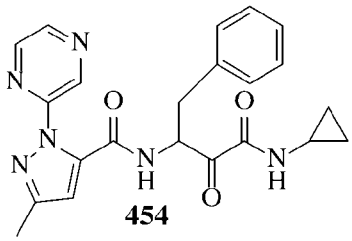

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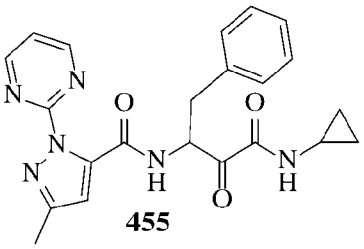

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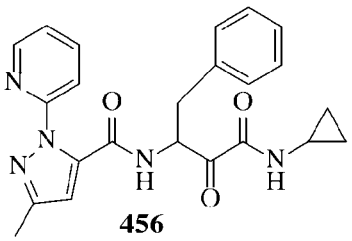

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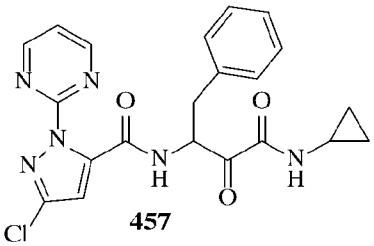

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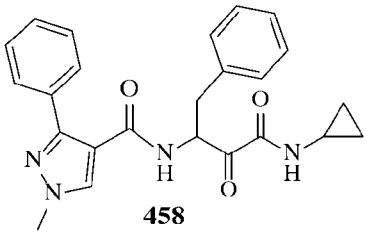

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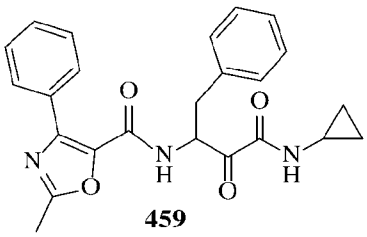

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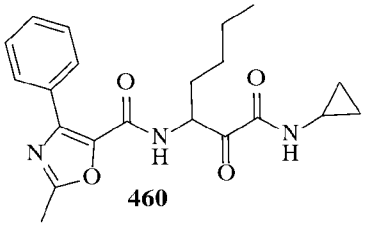

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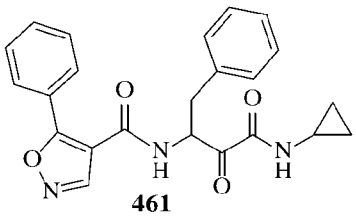

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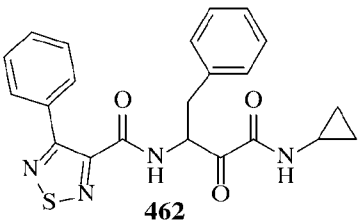

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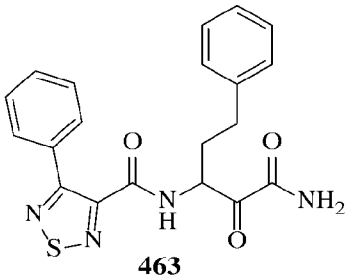

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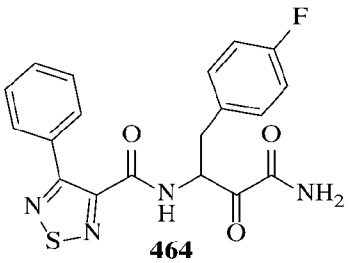

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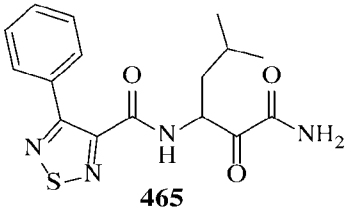

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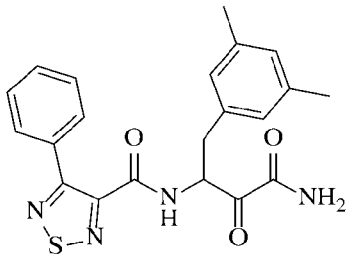

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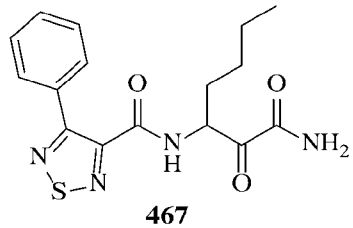

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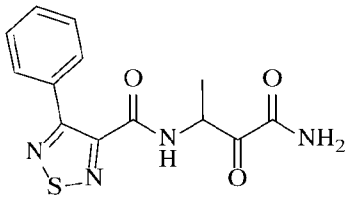

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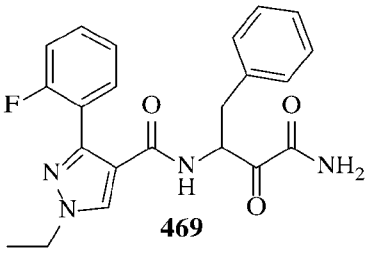

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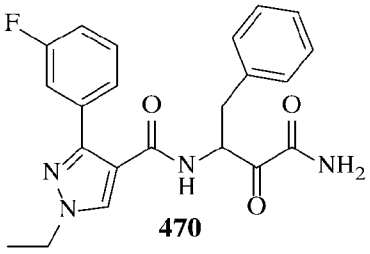

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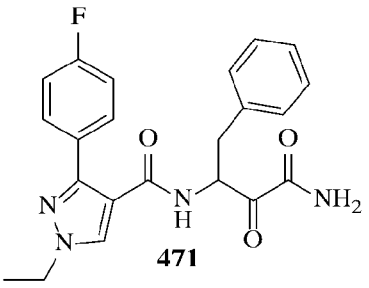

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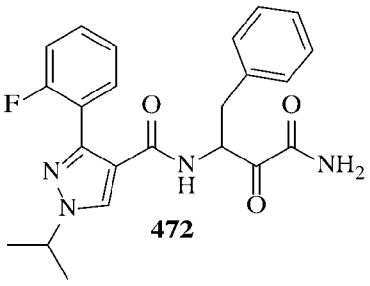

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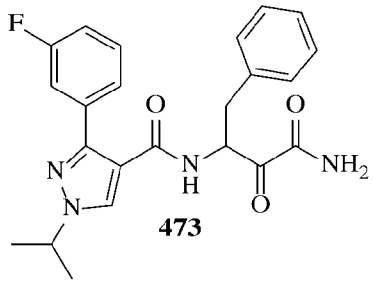

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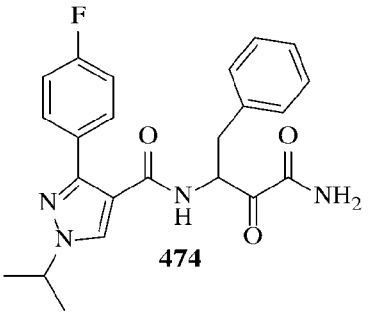

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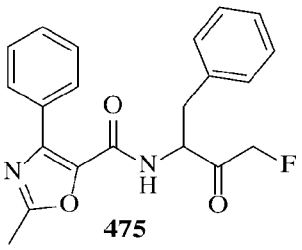

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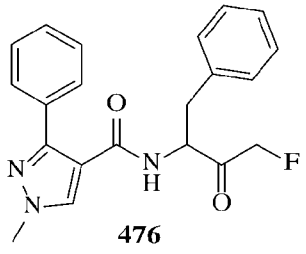

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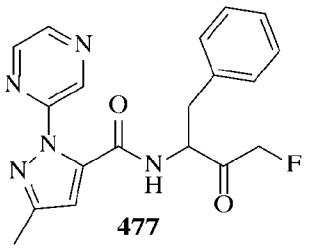

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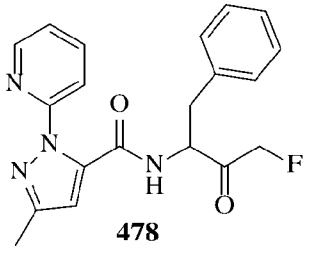

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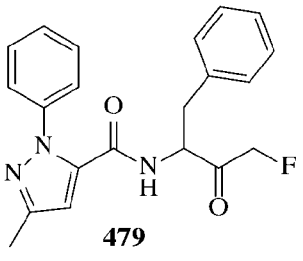

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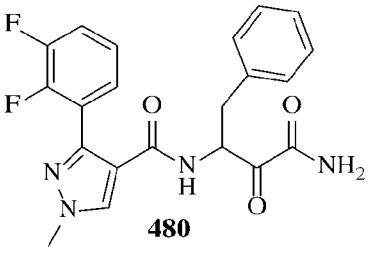

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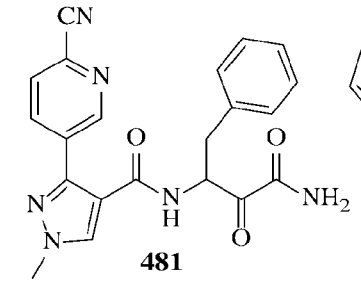

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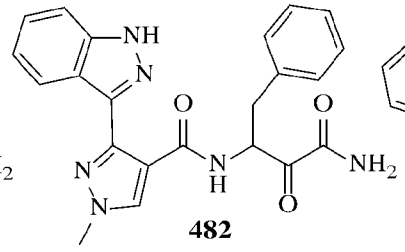

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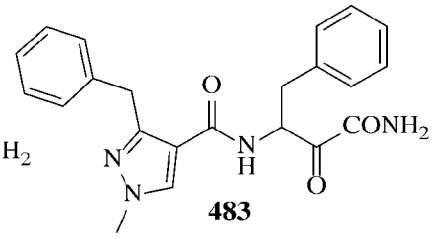

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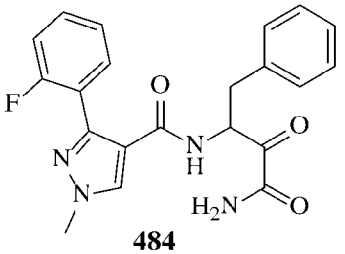

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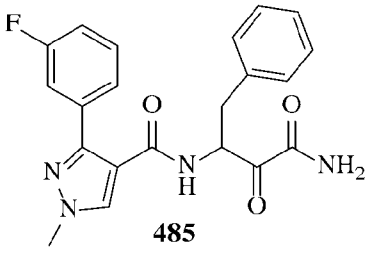

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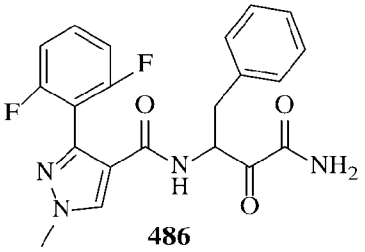

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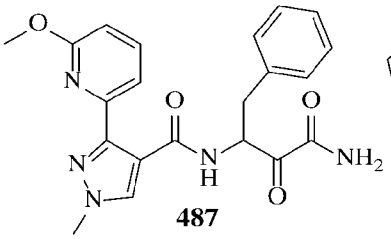

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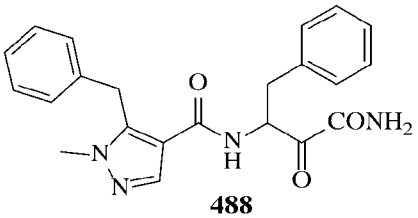

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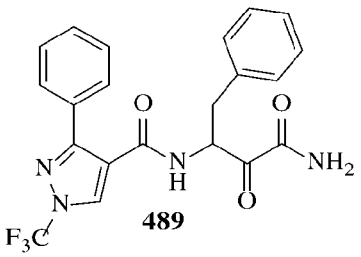

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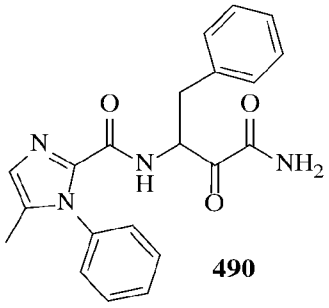

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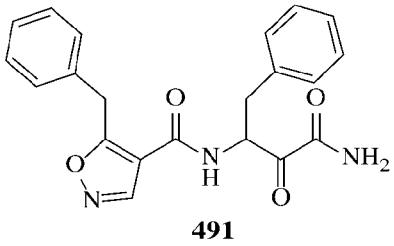

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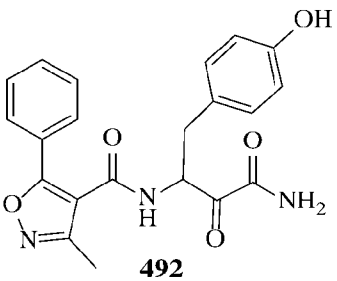

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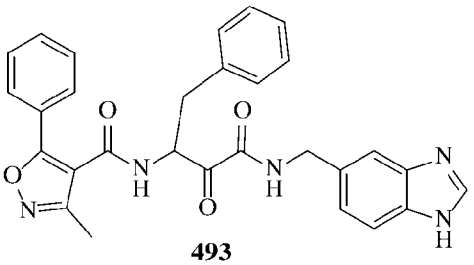

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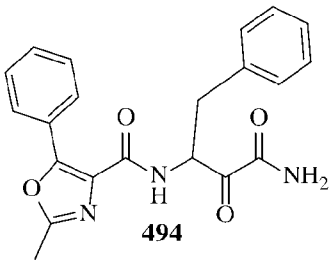

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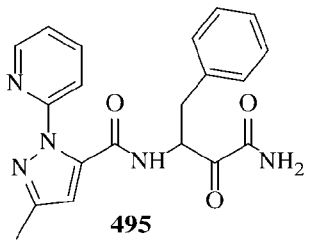

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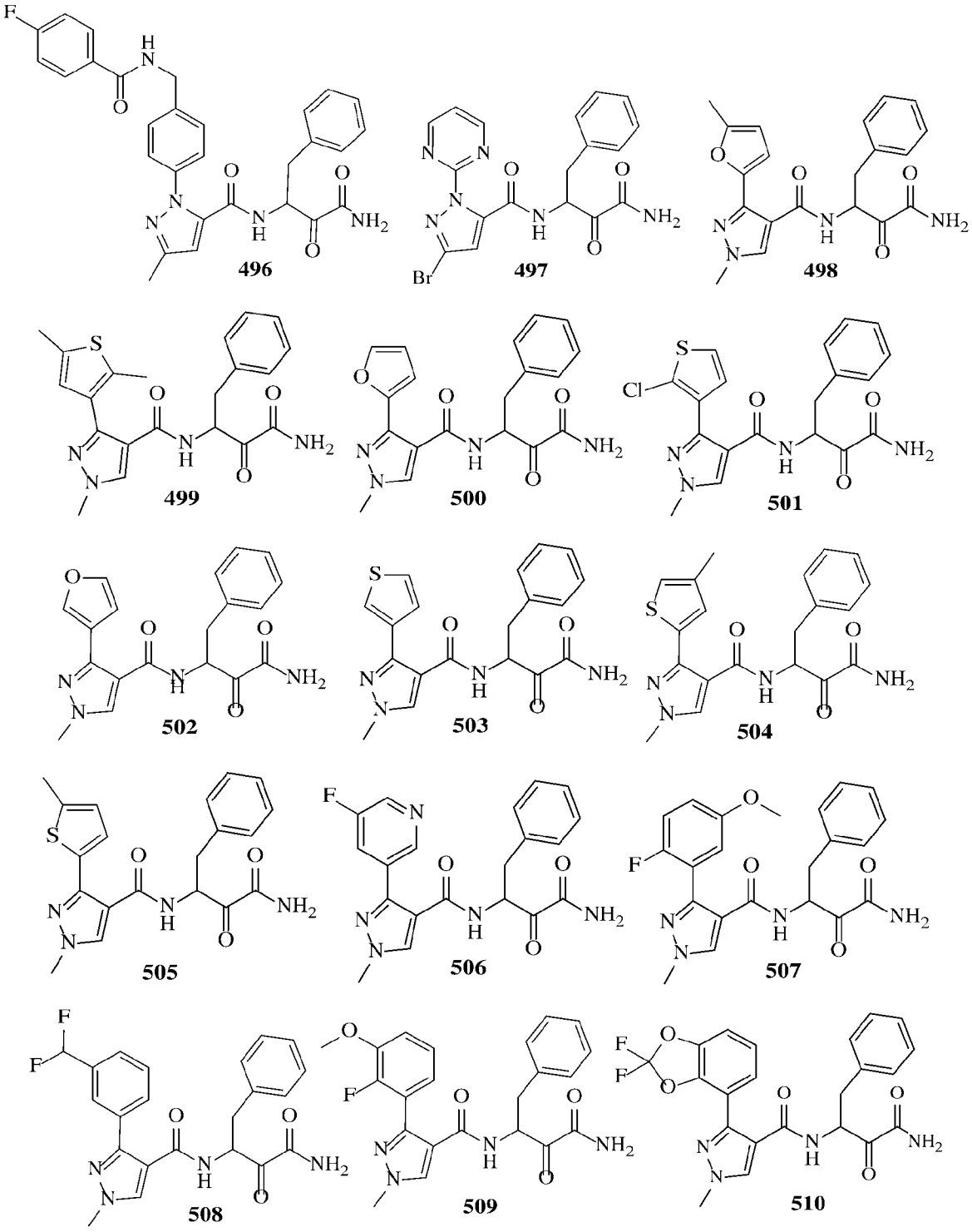

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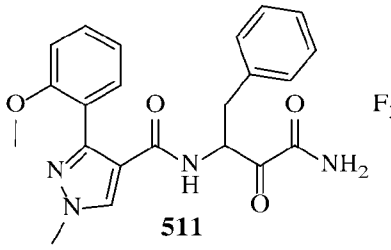

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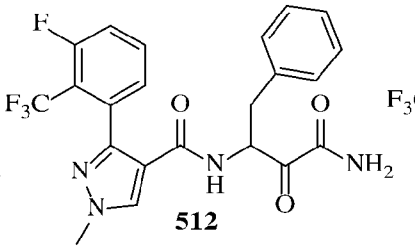

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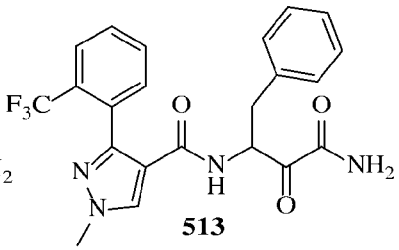

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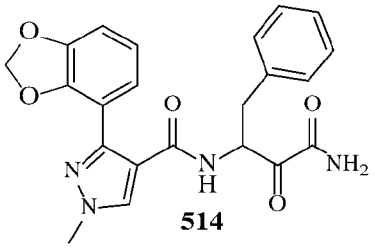

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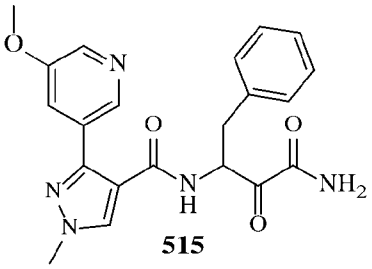

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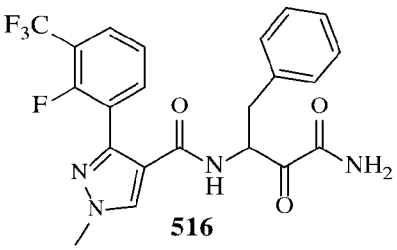

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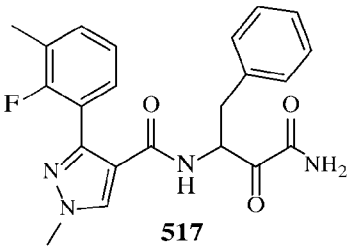

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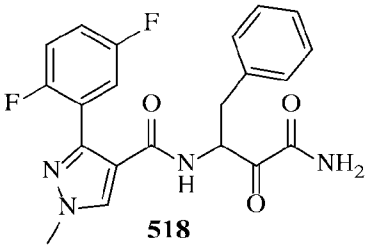

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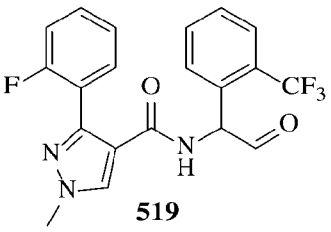

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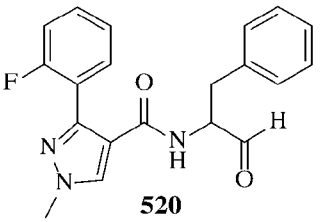

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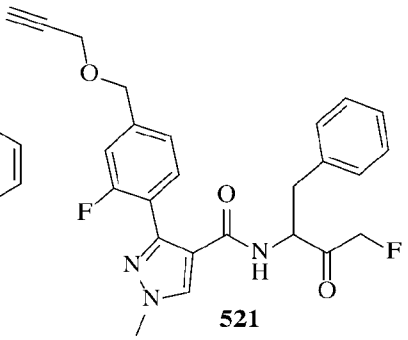

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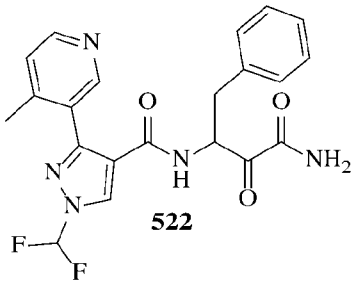

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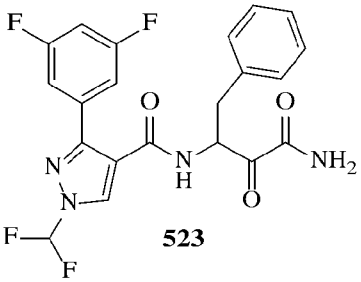

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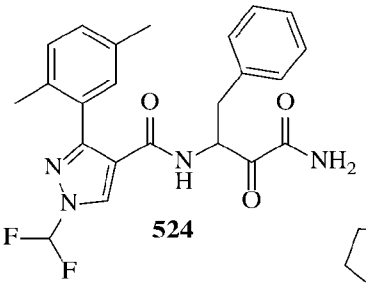

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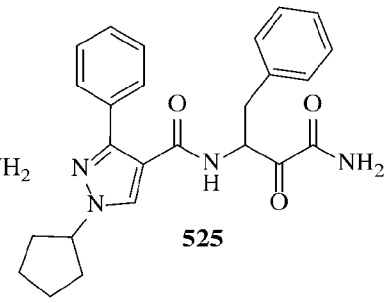

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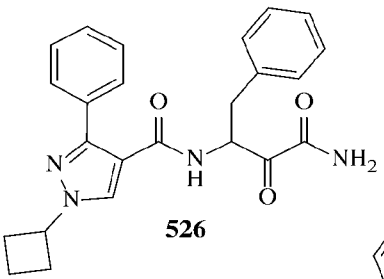

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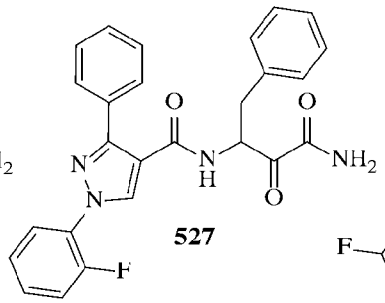

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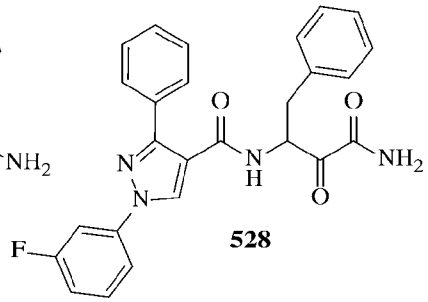

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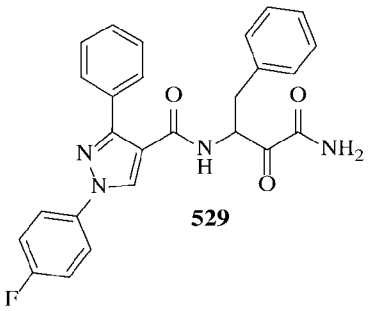

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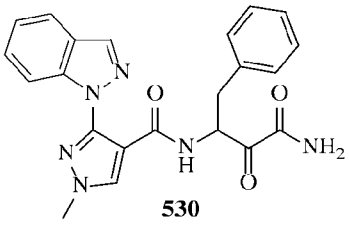

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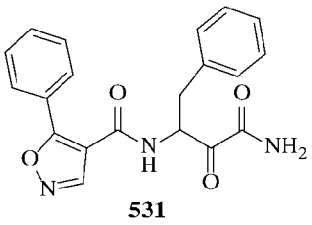

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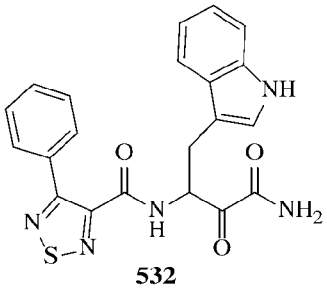

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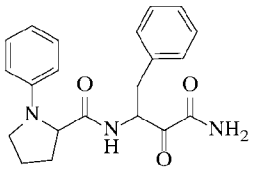

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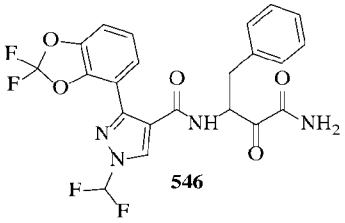

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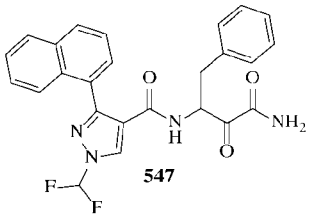

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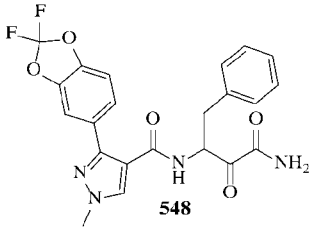

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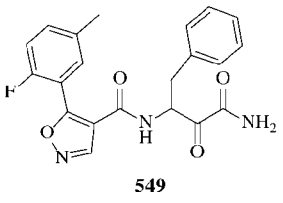

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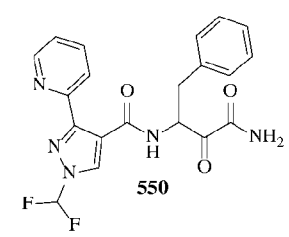
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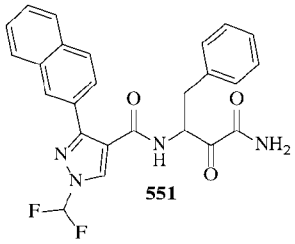
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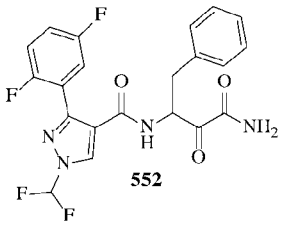
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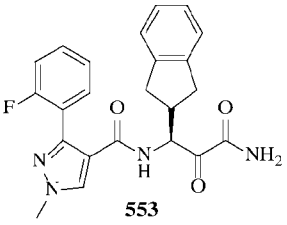
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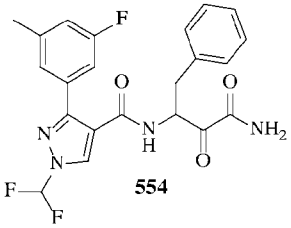
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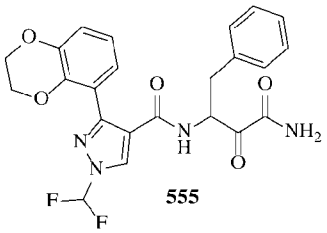
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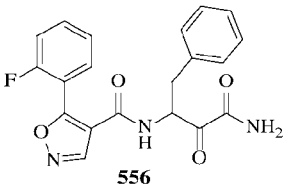
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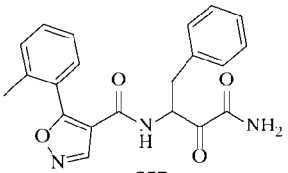
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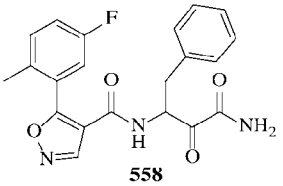
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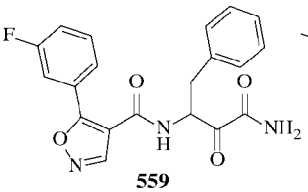
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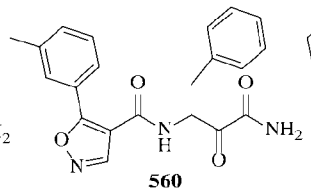
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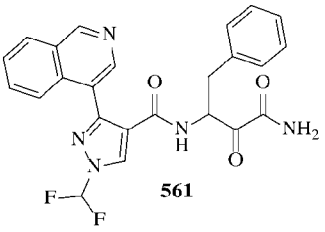
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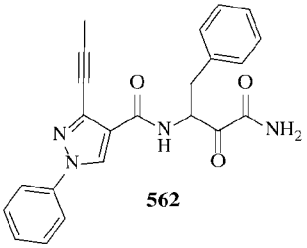
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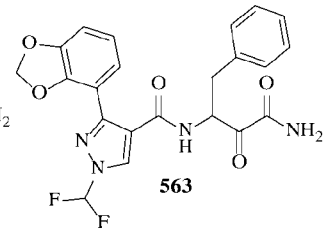
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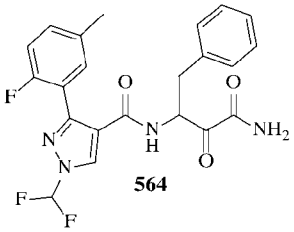
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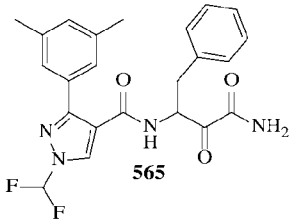
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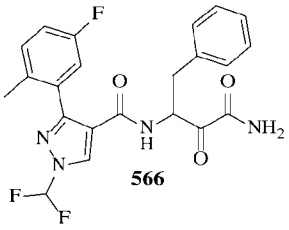
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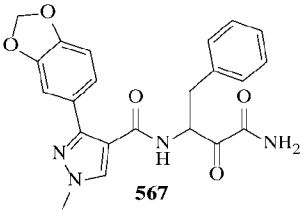
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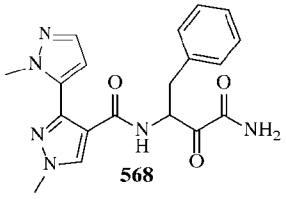
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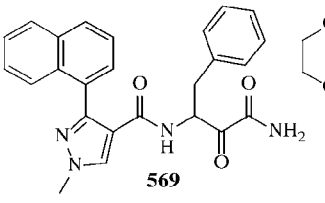
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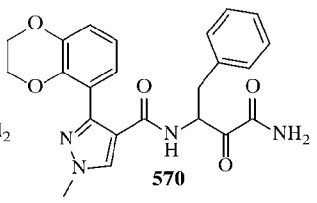
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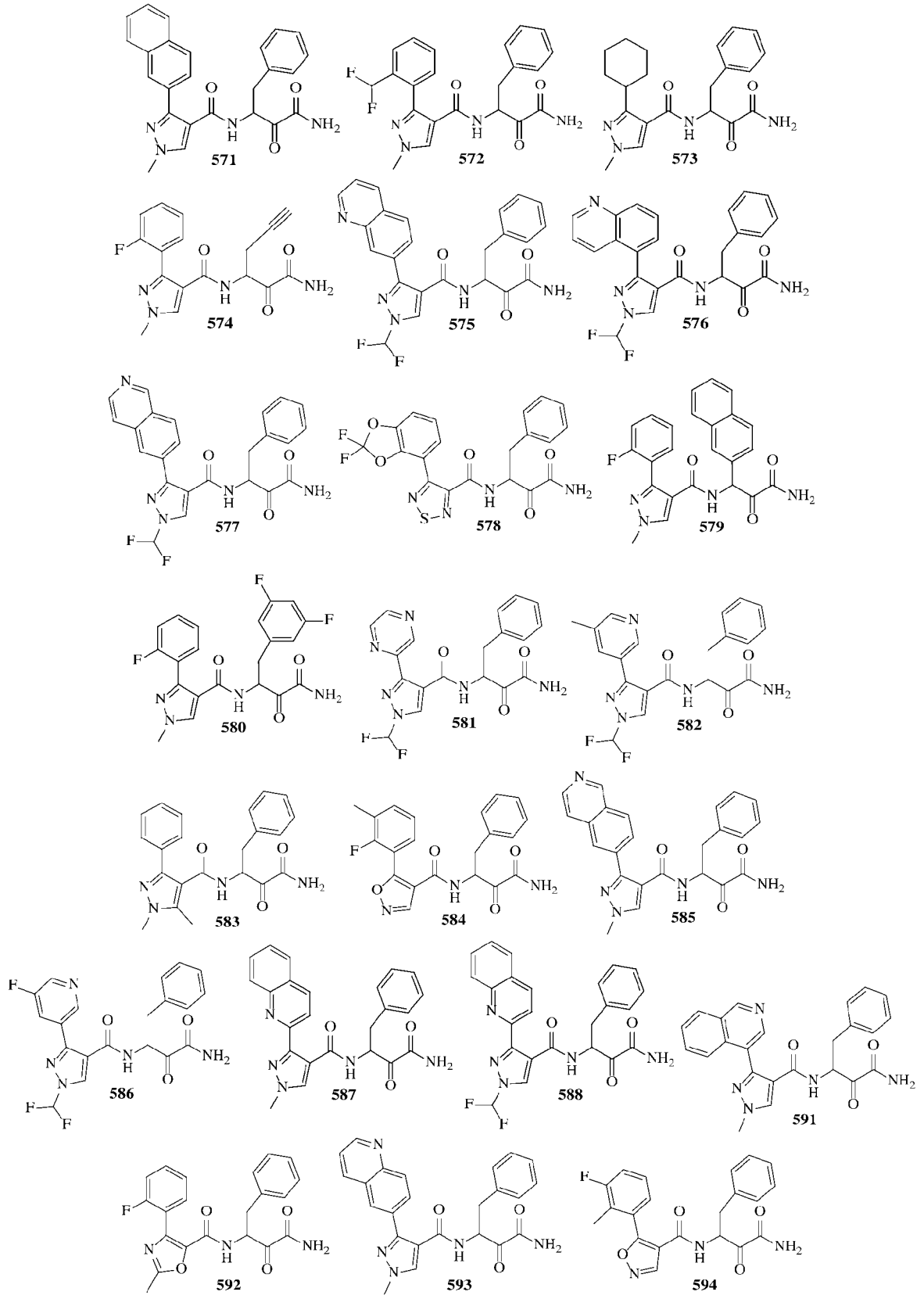

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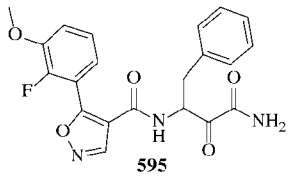
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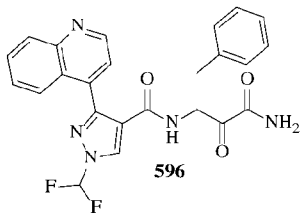
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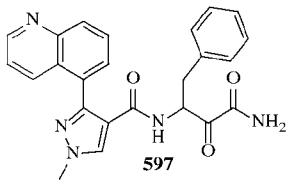
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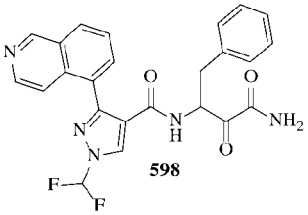
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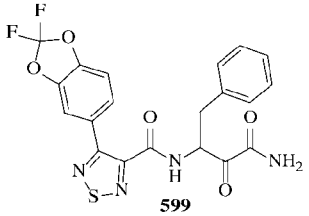
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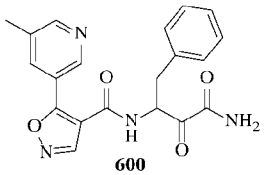
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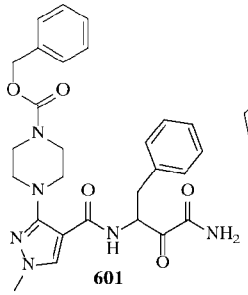
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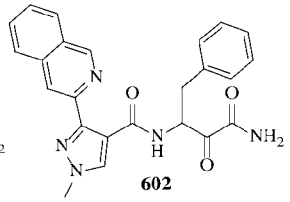
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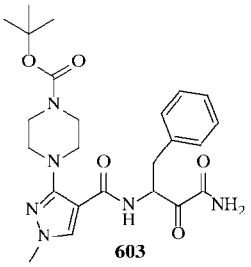
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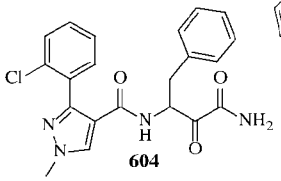
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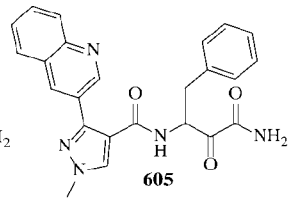
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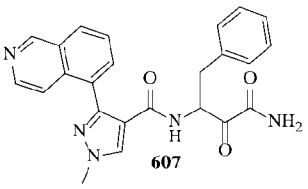
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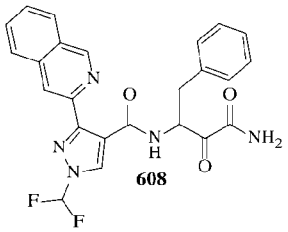
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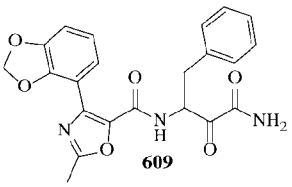
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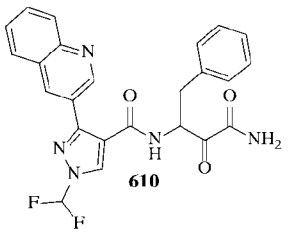
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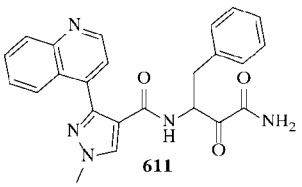
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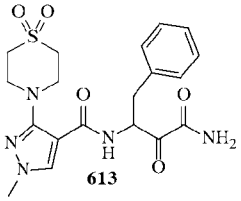
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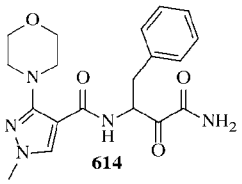
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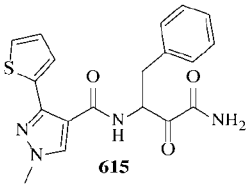
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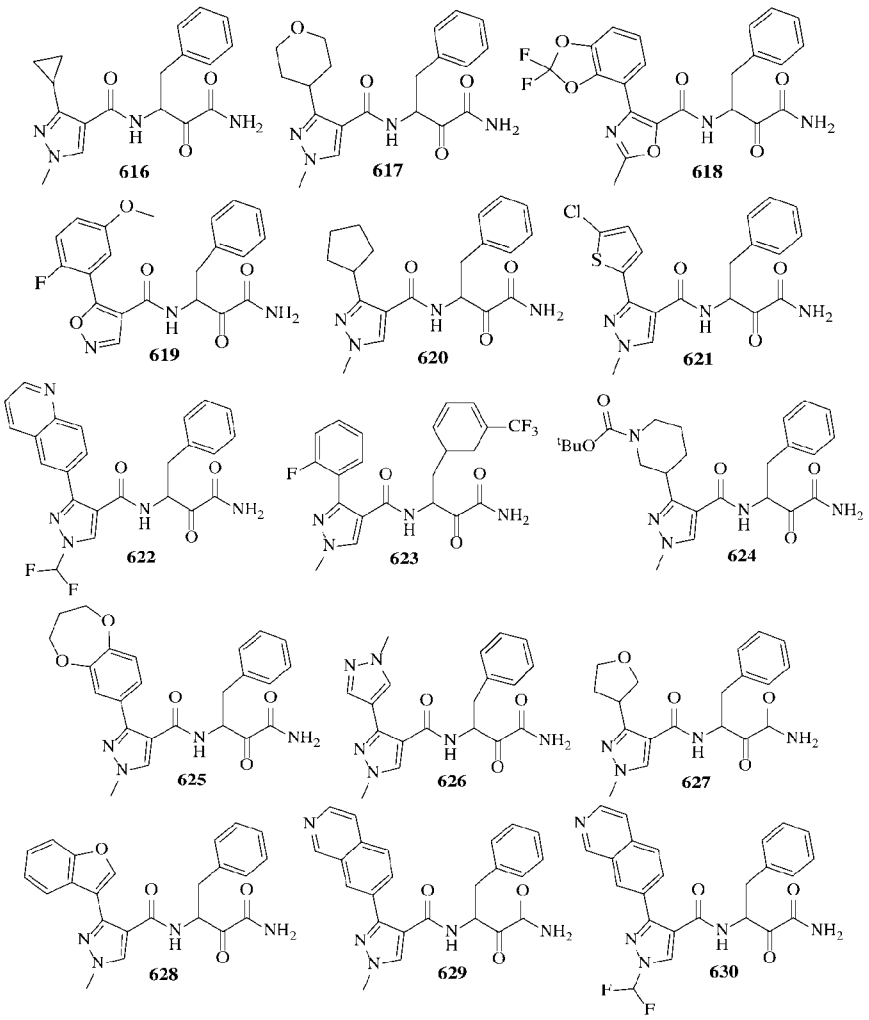

[0213] or a pharmaceutically acceptable salt thereof. Various embodiments include the S-enantiomer, the R-enantiomer, or the racemate of the above compounds.

[0214] Additional compounds suitable for use as described herein and that can be made by using the methods described herein are presented in **Table 1**.

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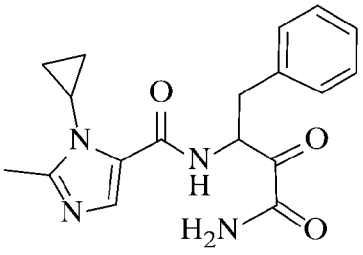
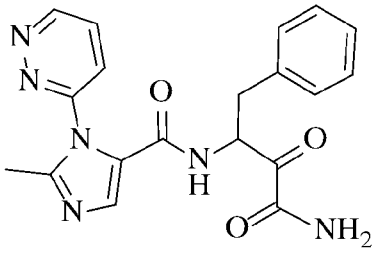
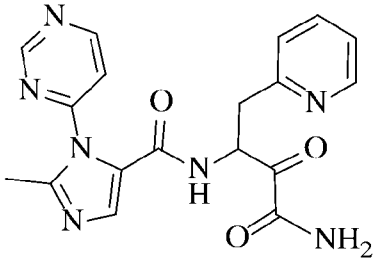
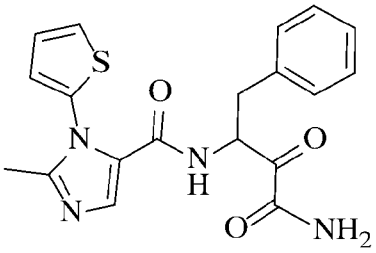
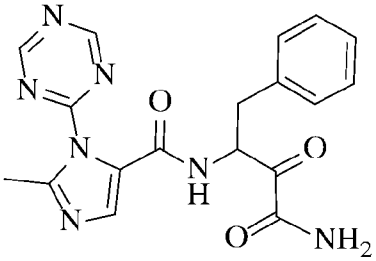
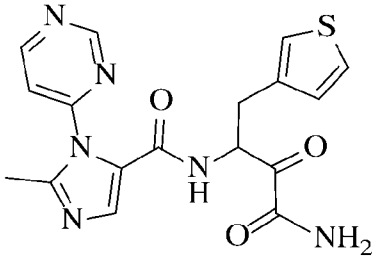
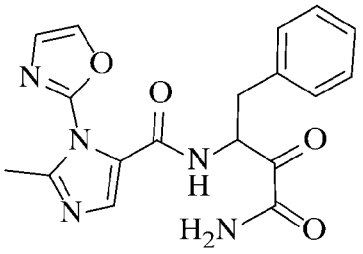
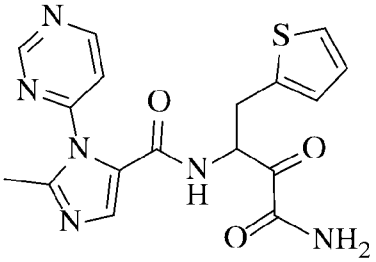
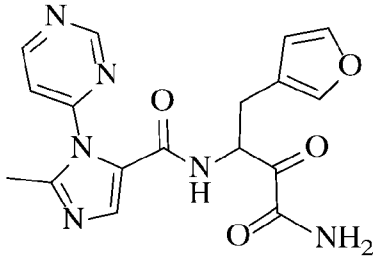
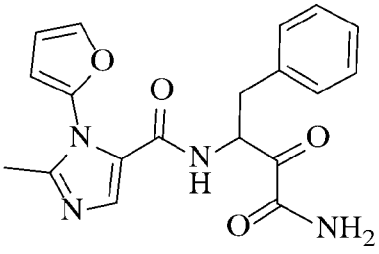
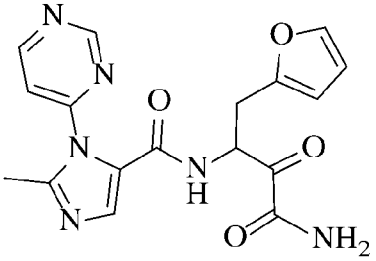
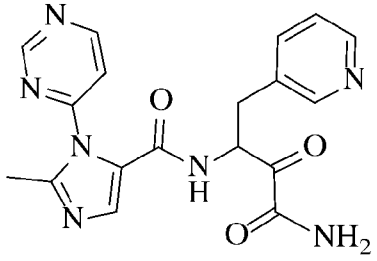
Table 1

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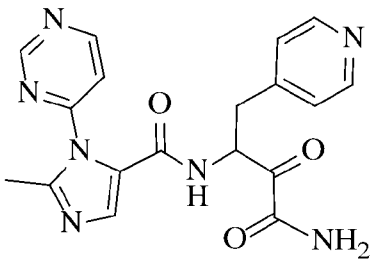	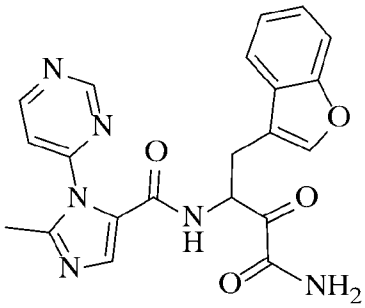	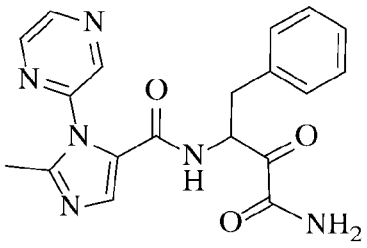
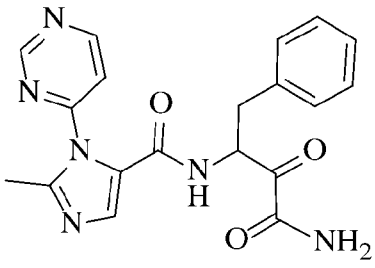	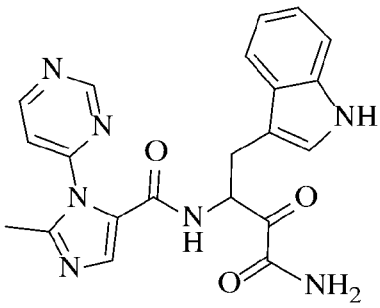	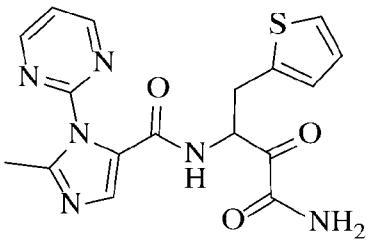
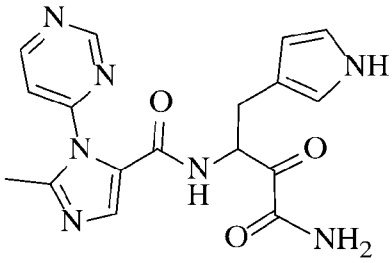	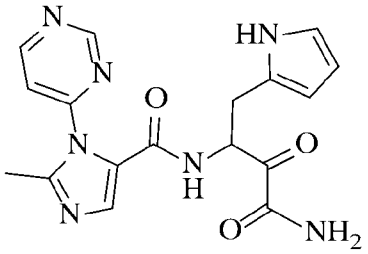	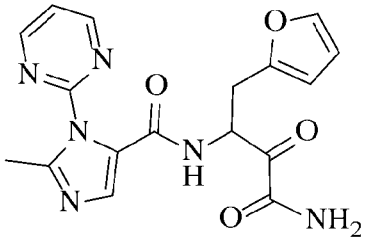
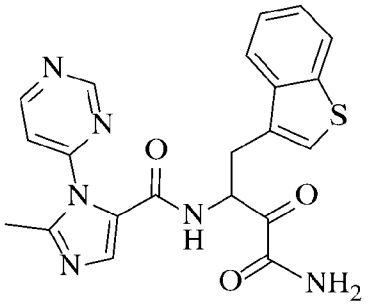	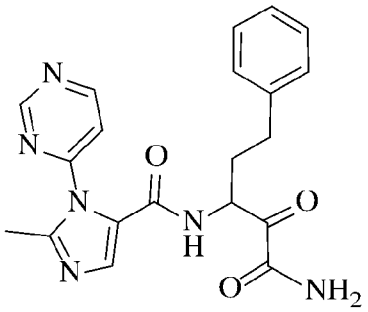	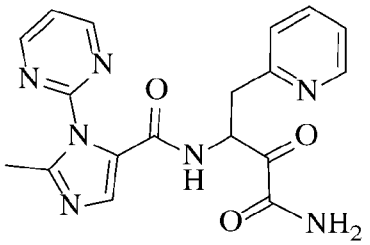

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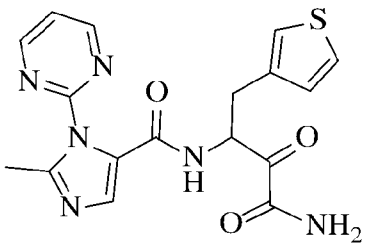	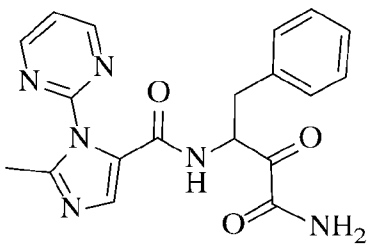	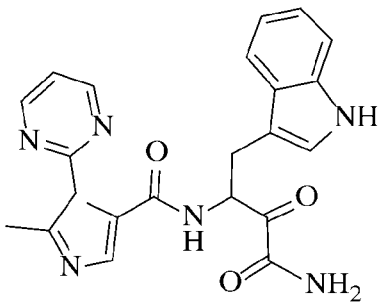
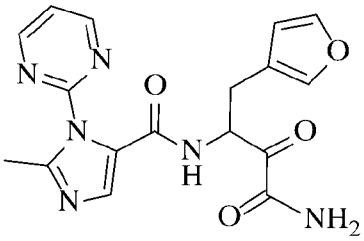	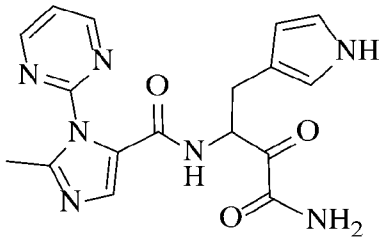	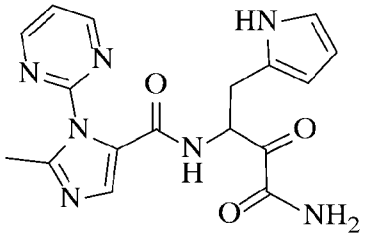
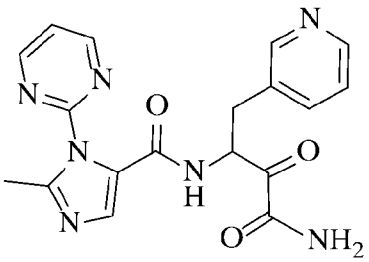	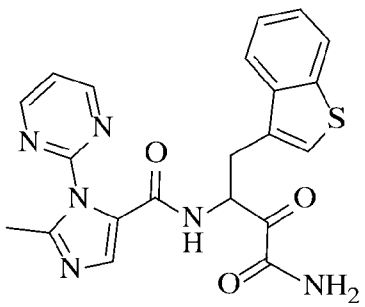	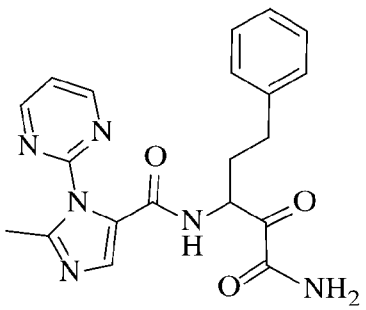
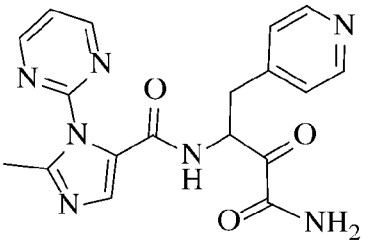	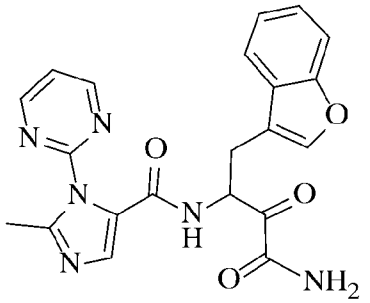	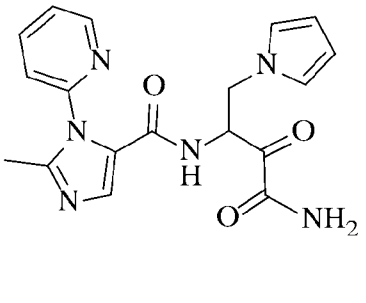

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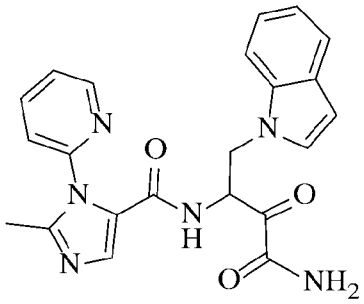	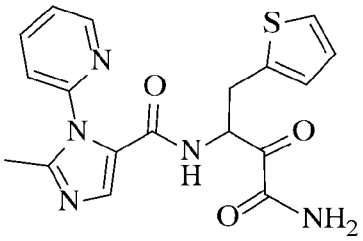	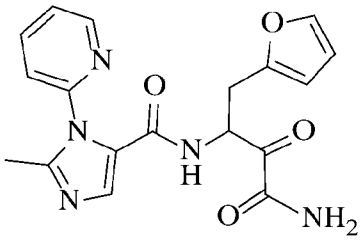
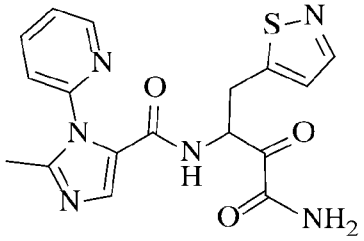	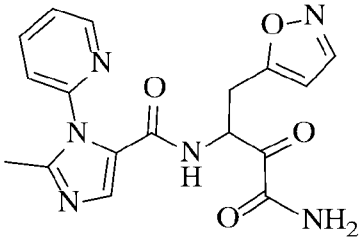	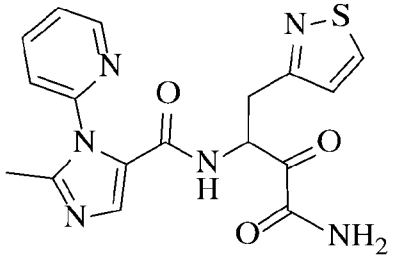
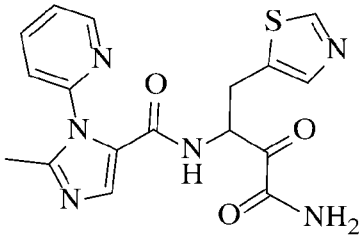	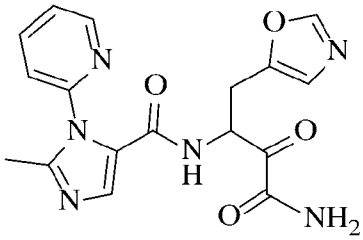	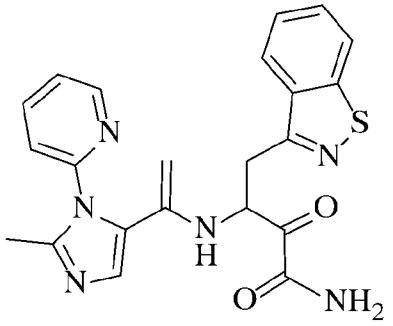
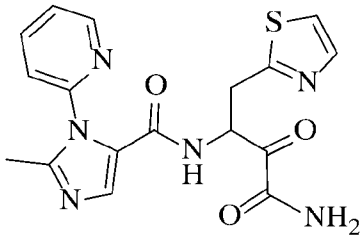	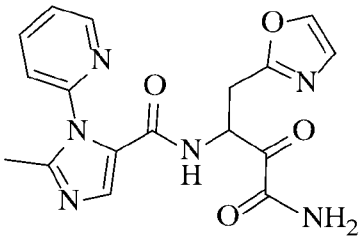	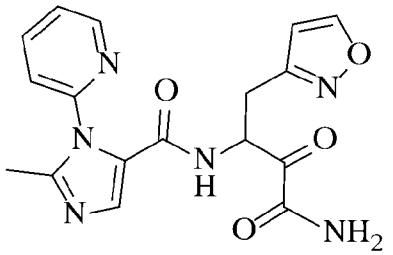

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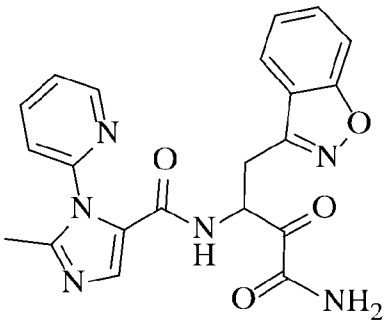	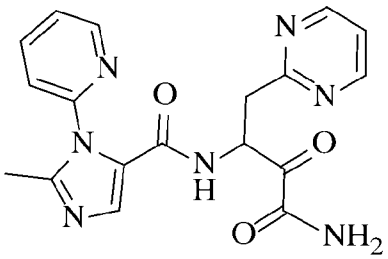	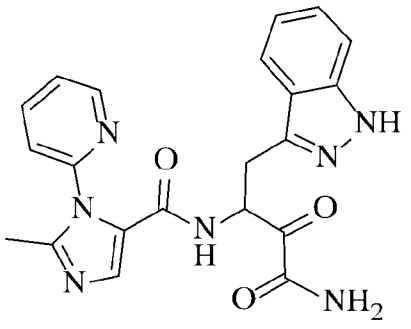
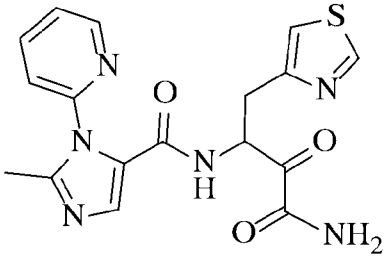	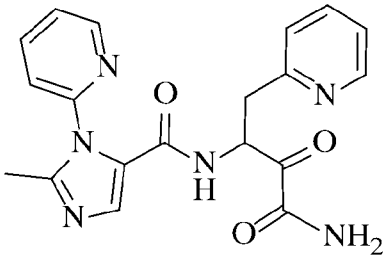	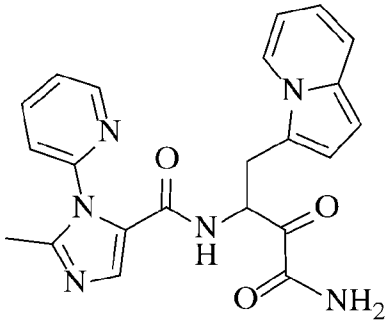
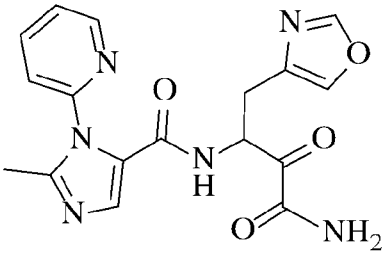	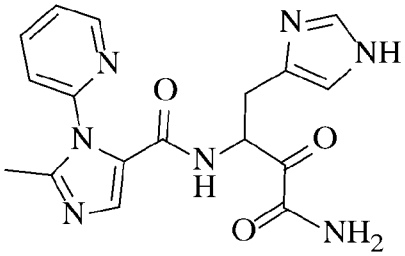	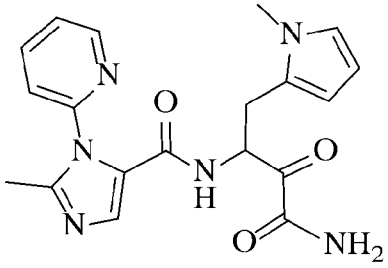
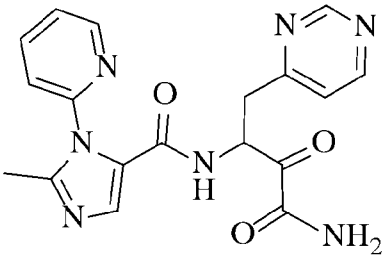	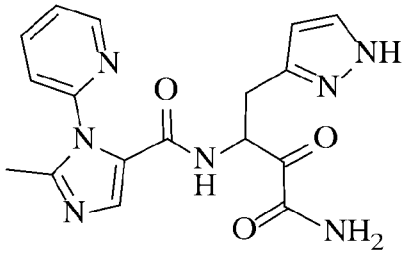	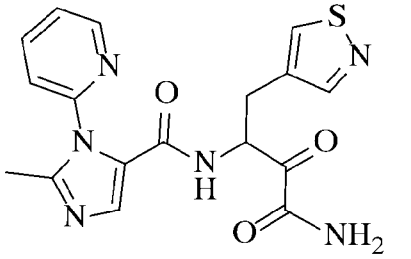

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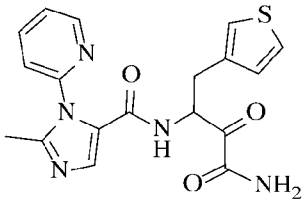	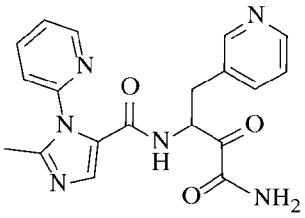	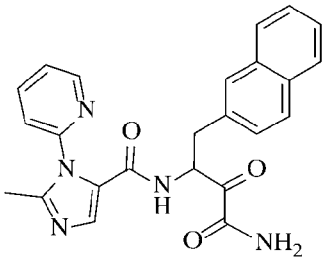
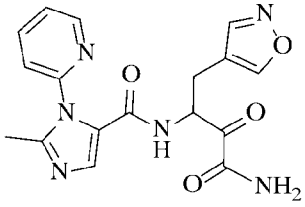	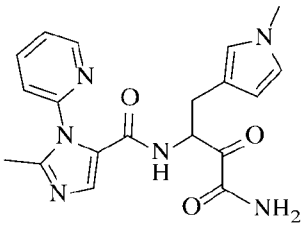	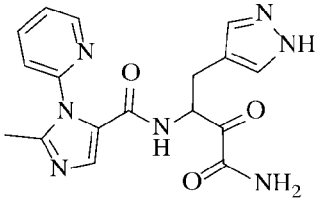
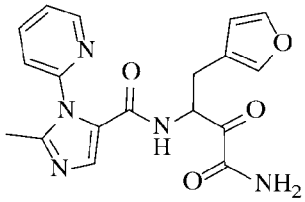	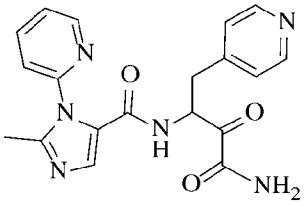	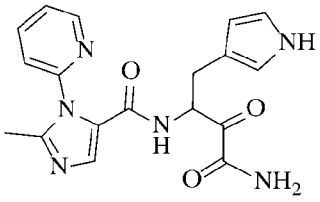
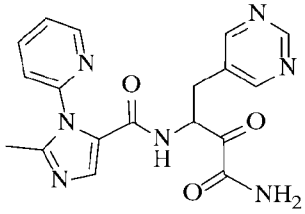	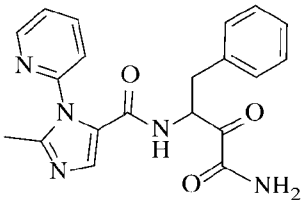	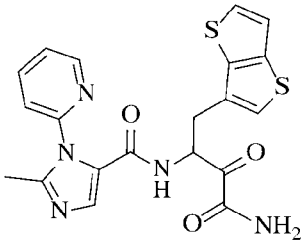

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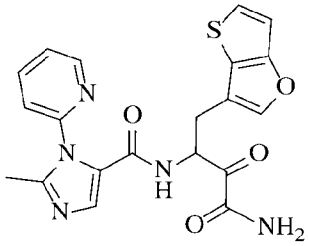	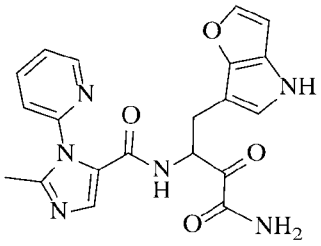	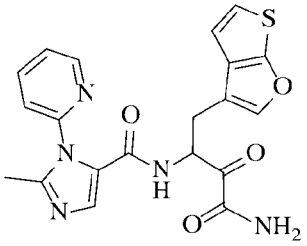
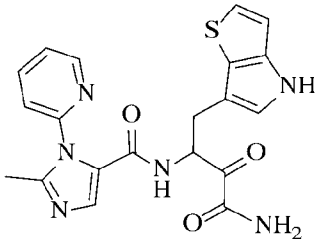	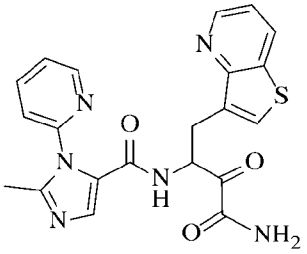	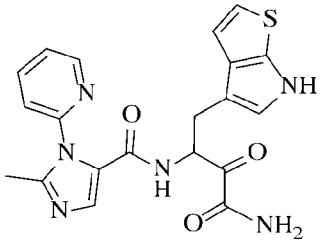
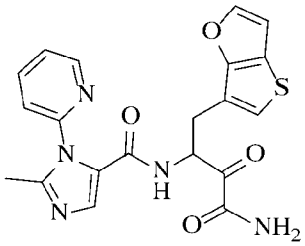	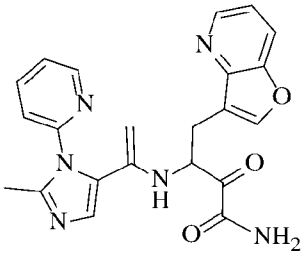	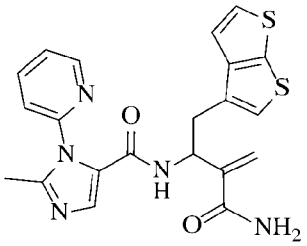
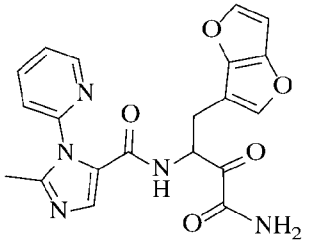	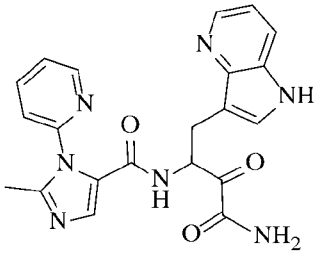	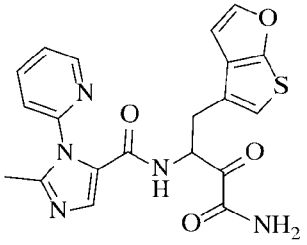

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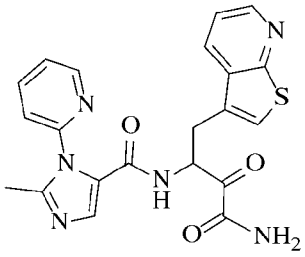	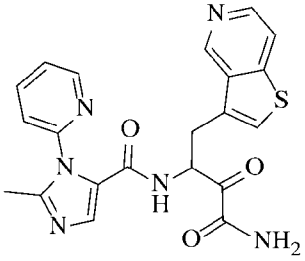	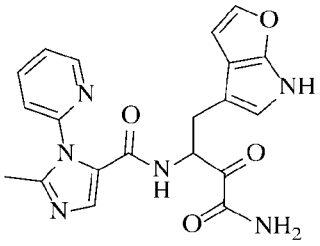
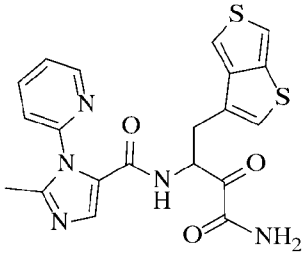	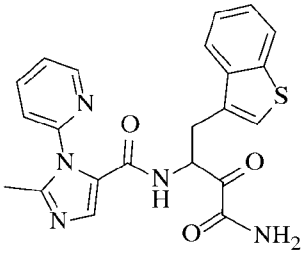	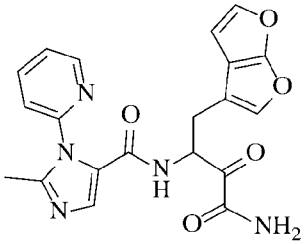
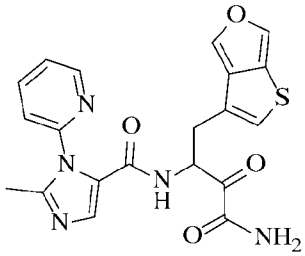	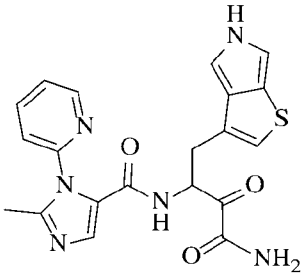	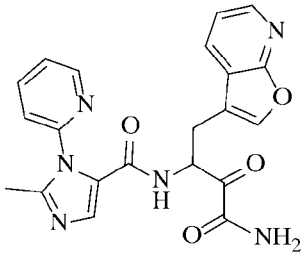
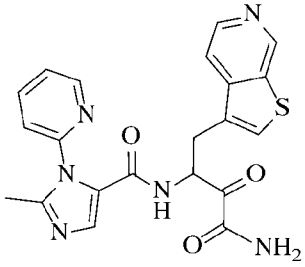	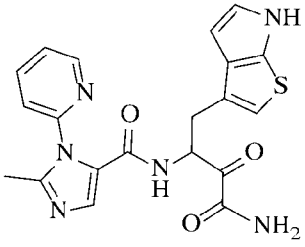	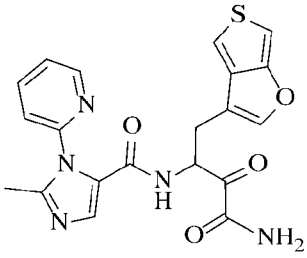

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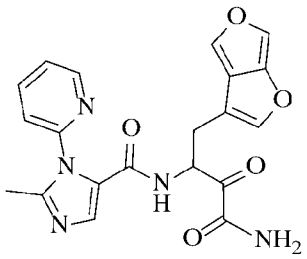	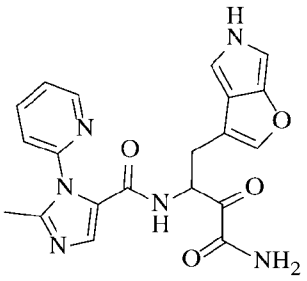	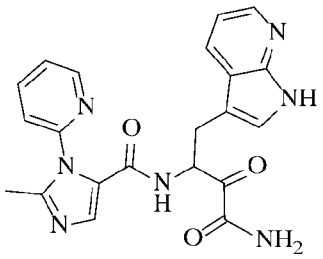
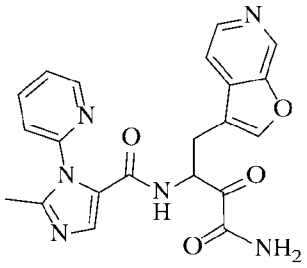	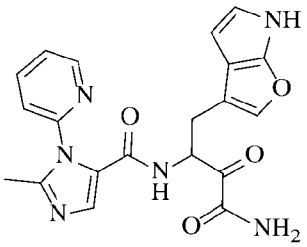	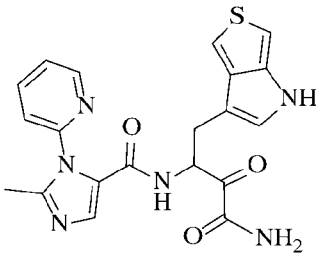
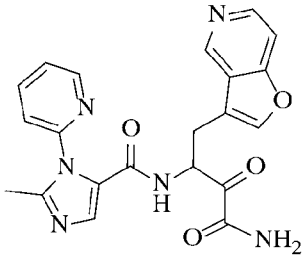	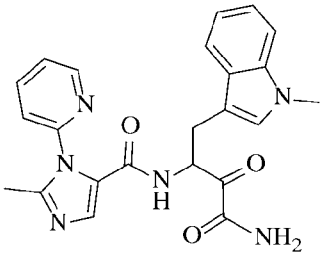	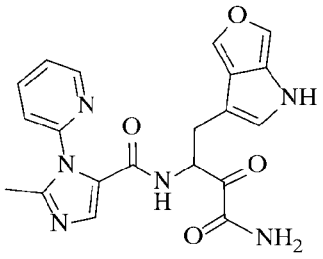
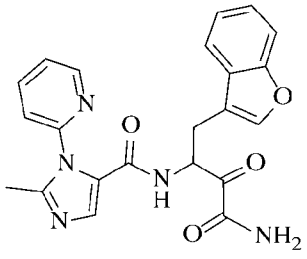	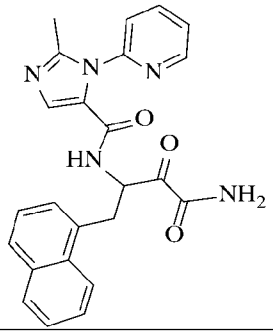	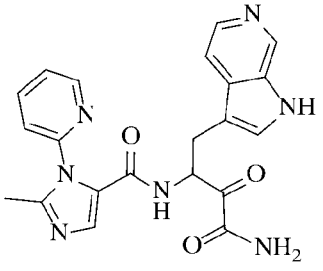

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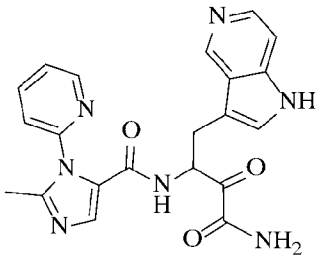	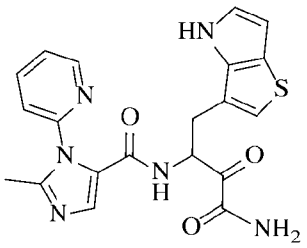	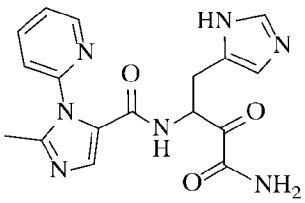
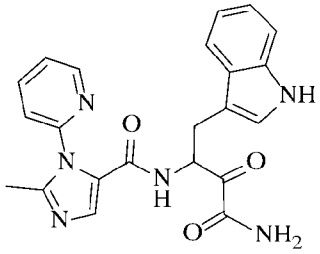	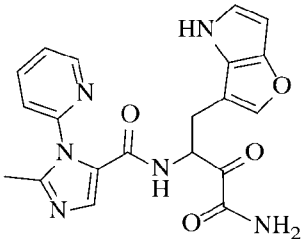	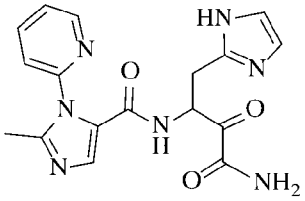
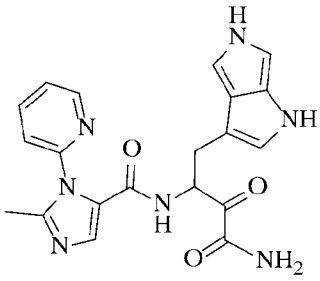	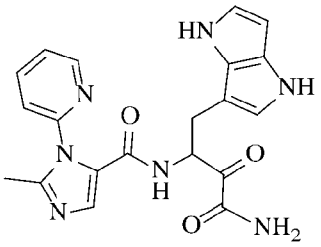	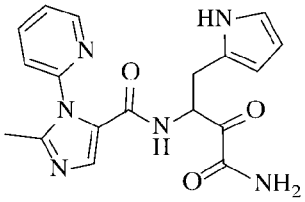
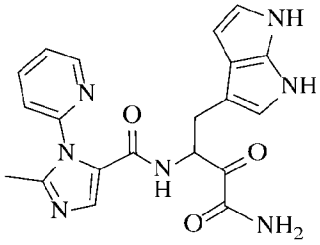	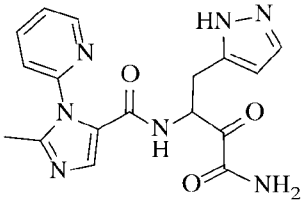	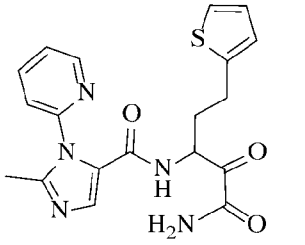

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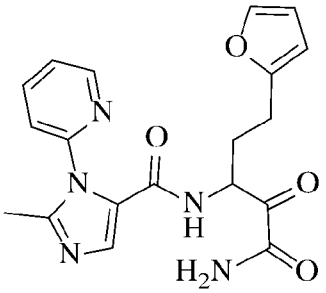	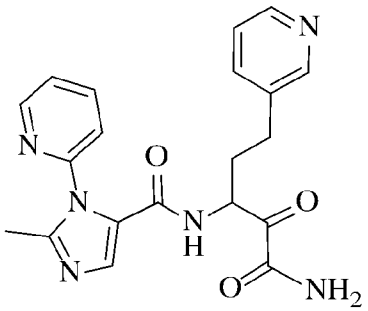	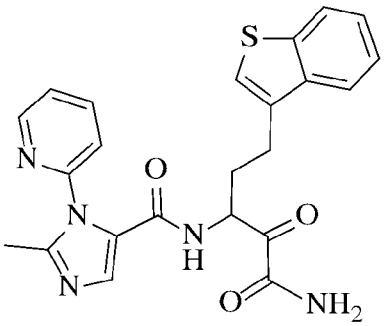
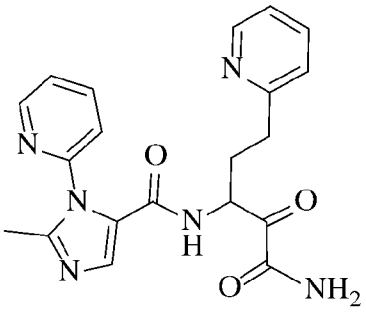	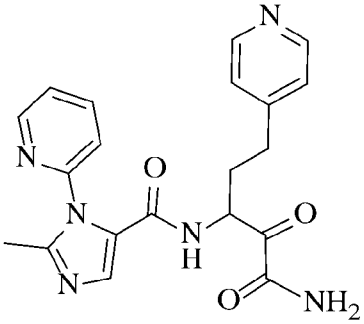	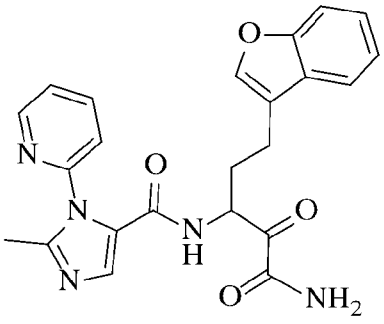
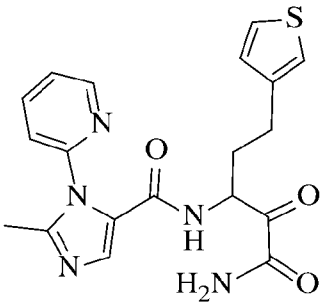	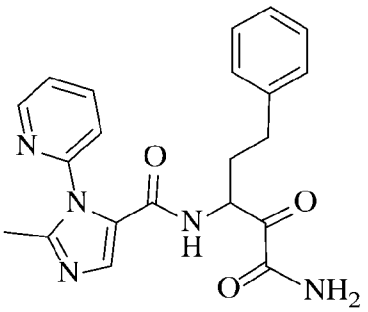	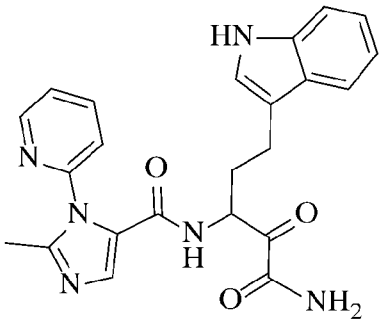
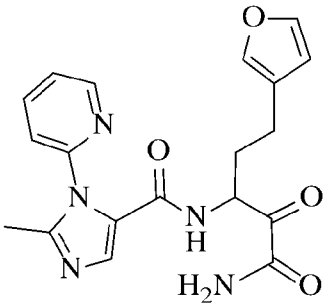	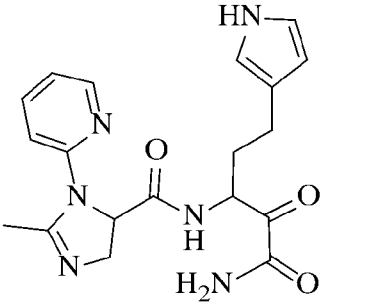	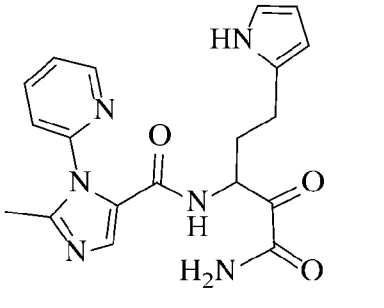

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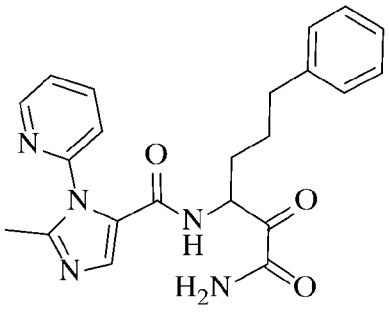	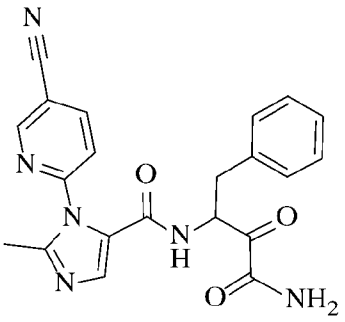	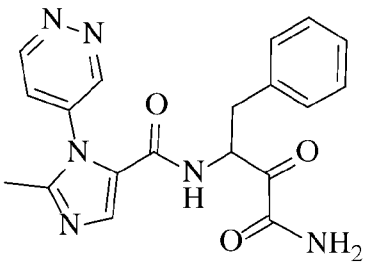
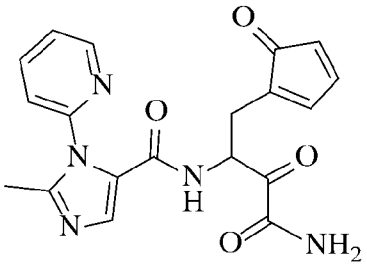	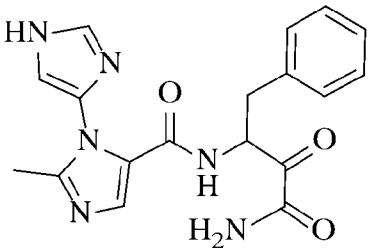	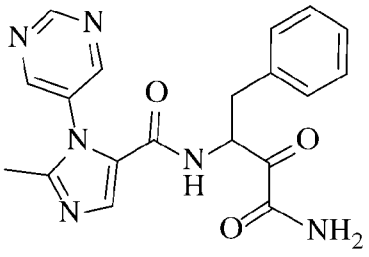
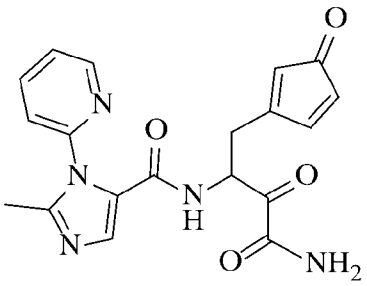	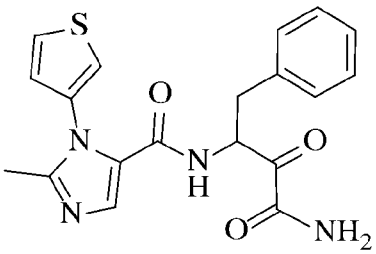	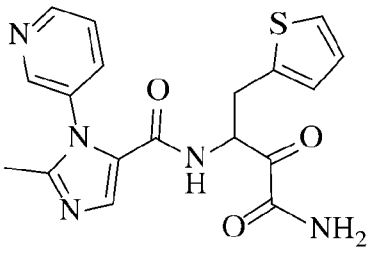
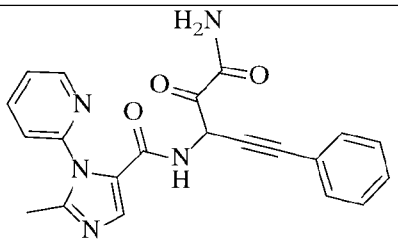	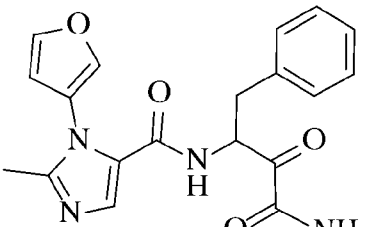	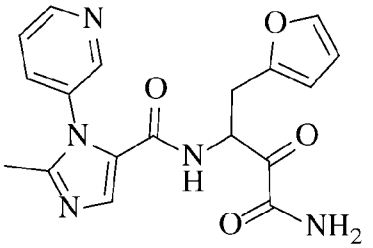

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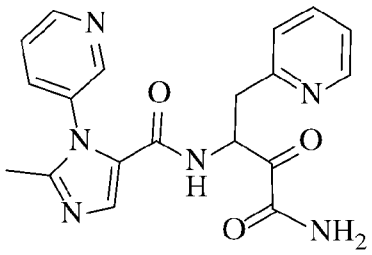	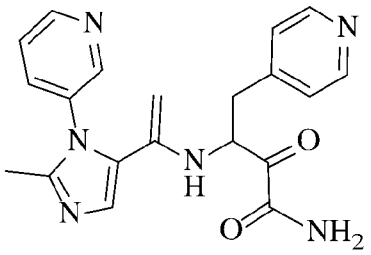	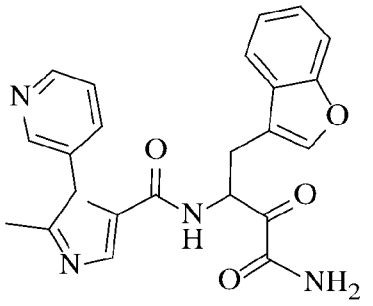
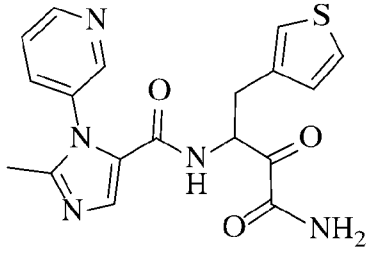	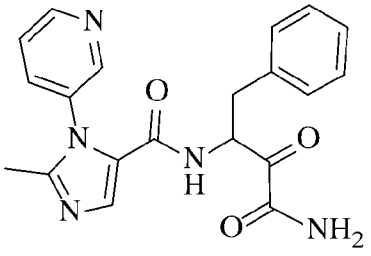	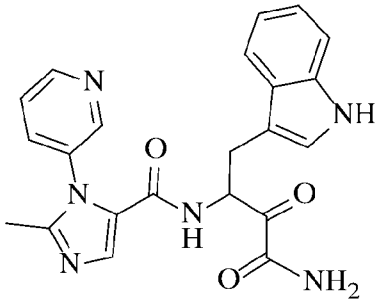
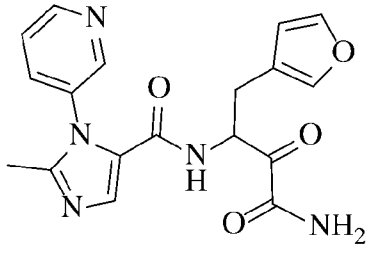	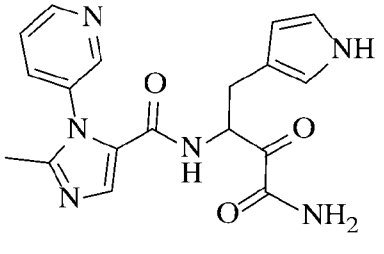	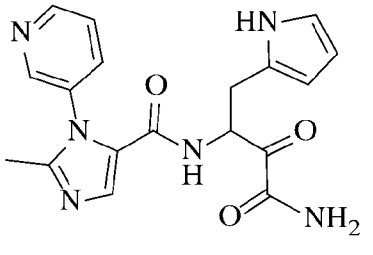
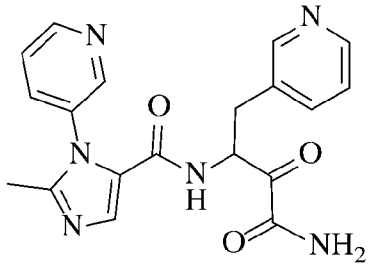	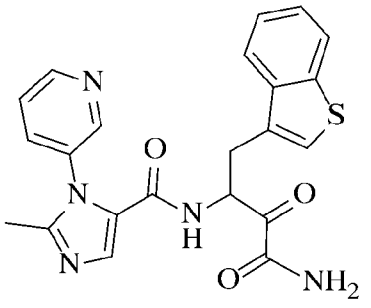	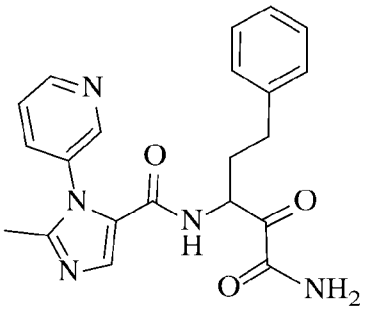

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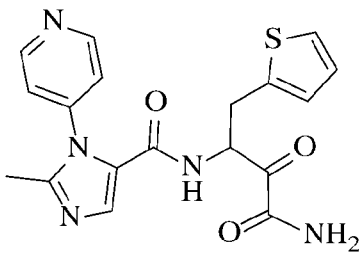	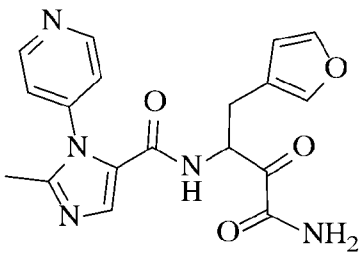	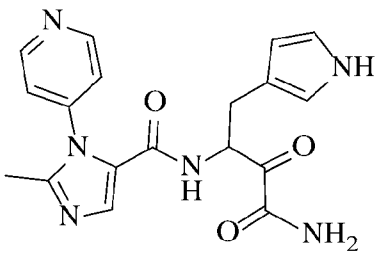
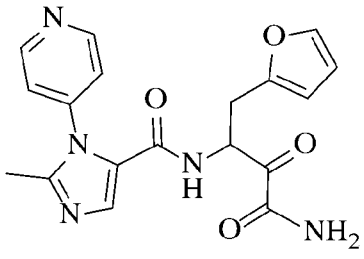	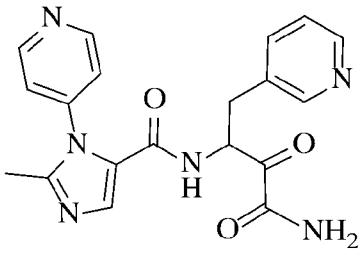	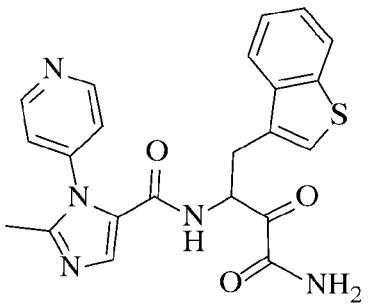
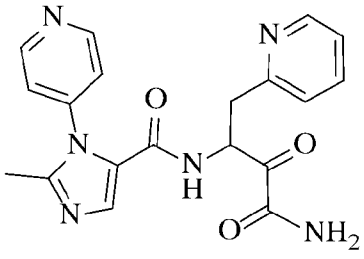	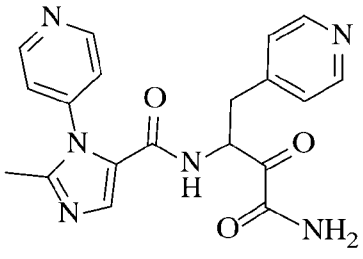	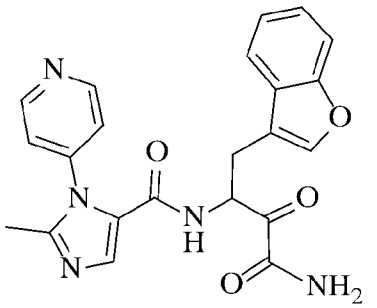
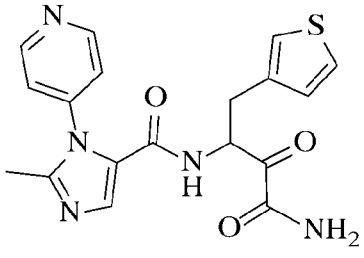	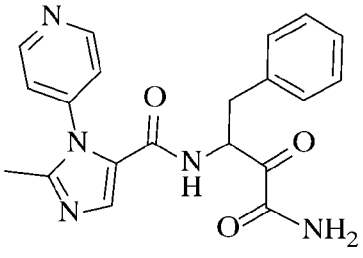	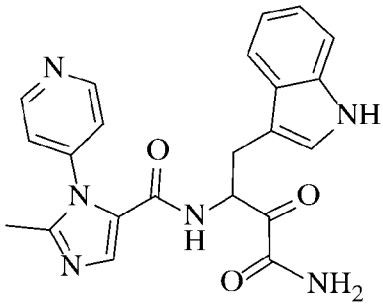

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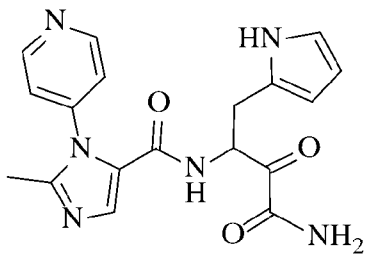	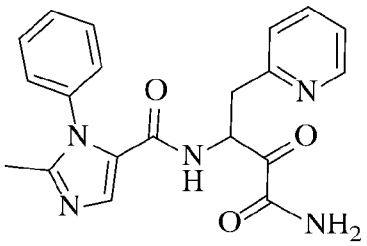	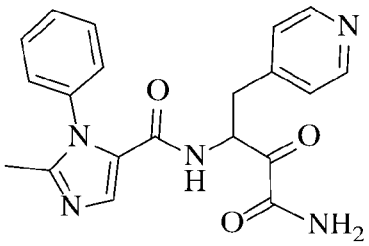
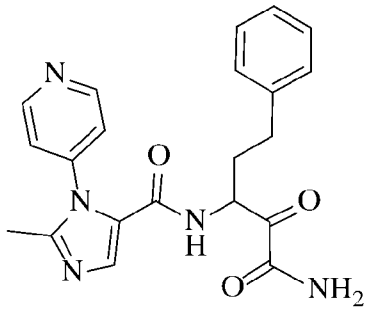	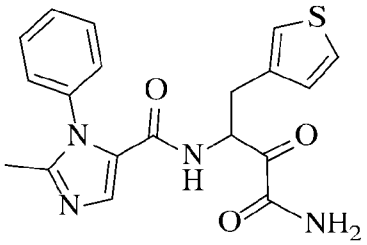	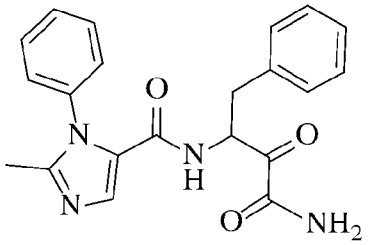
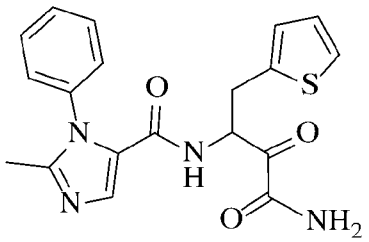	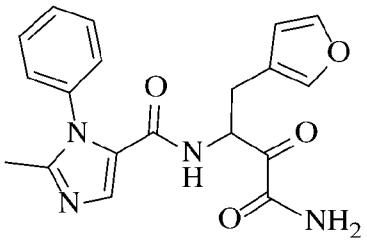	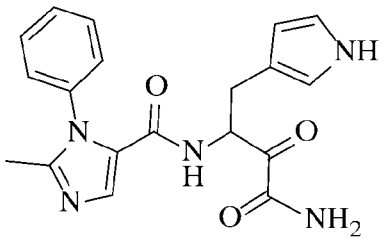
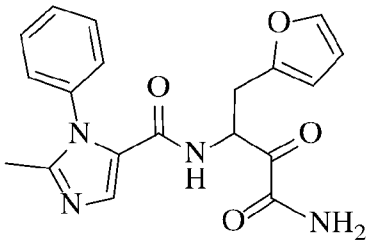	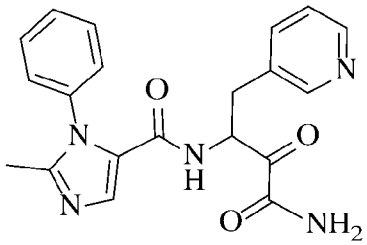	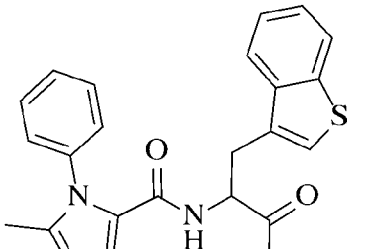

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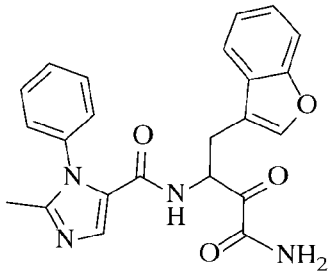	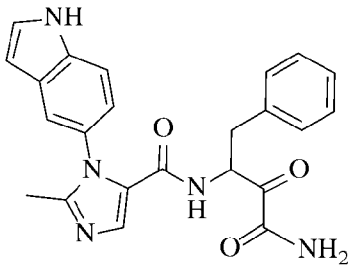	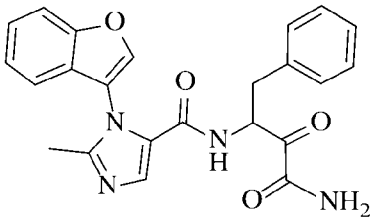
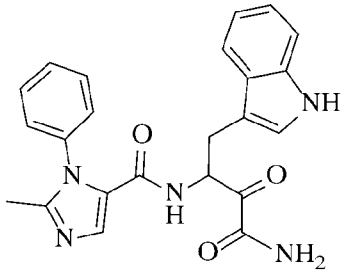	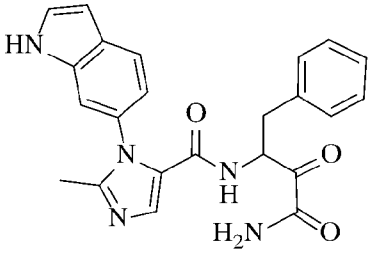	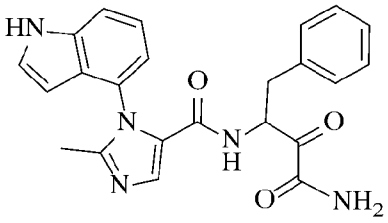
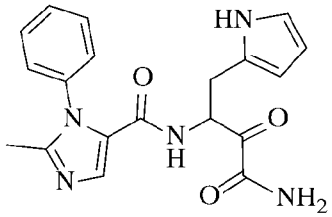	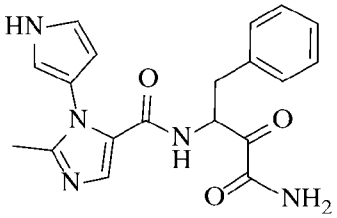	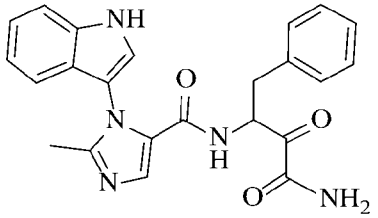
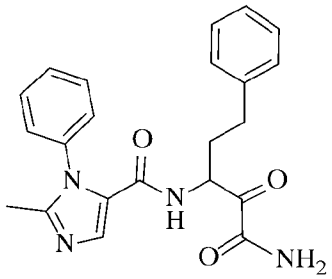	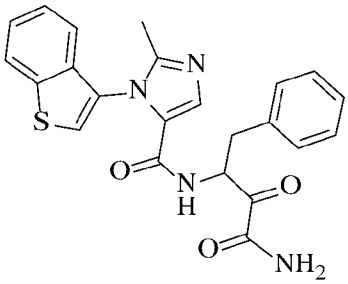	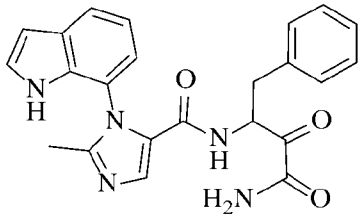

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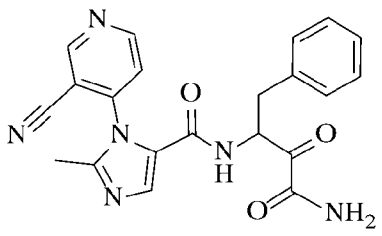	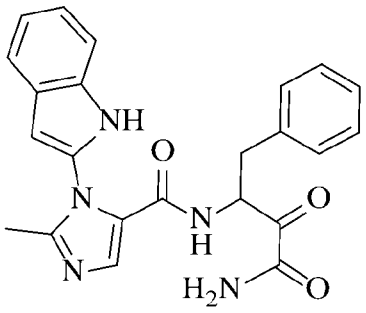	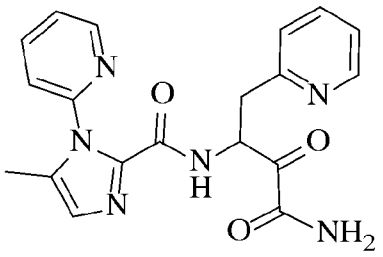
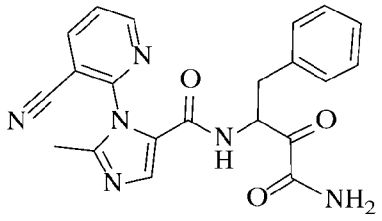	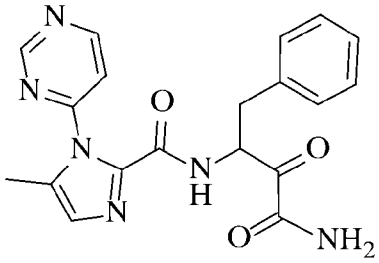	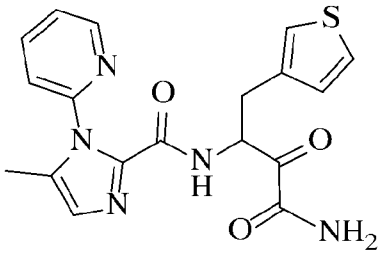
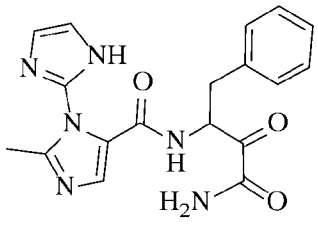	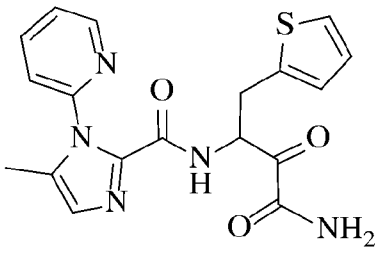	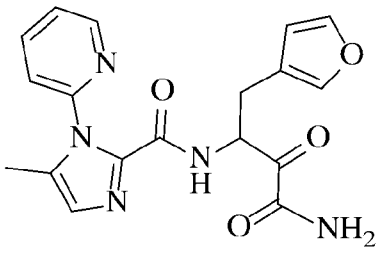
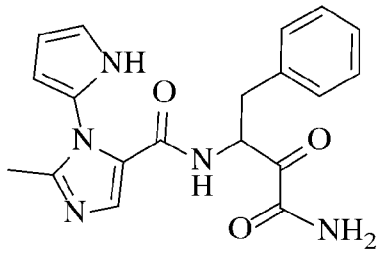	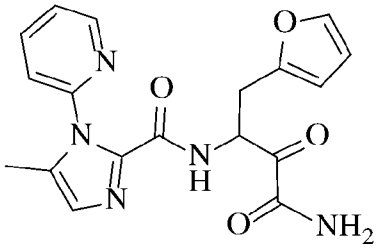	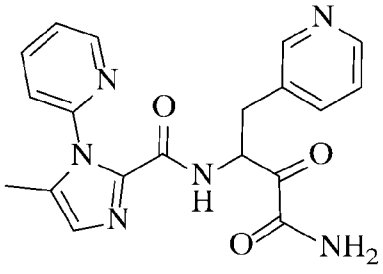

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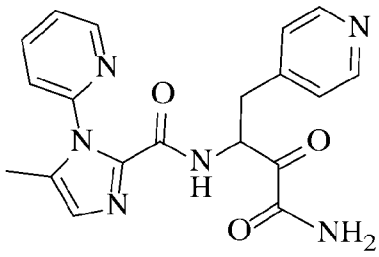	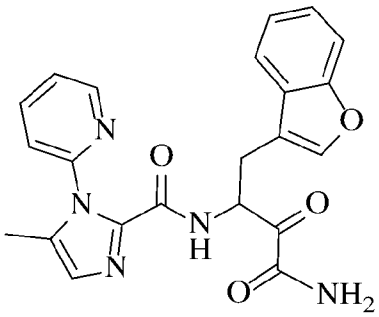	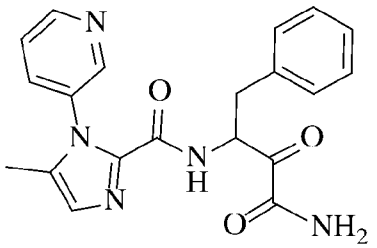
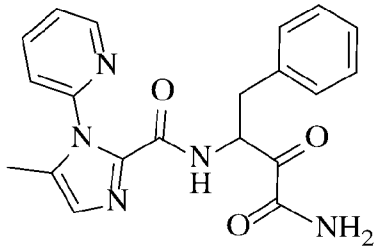	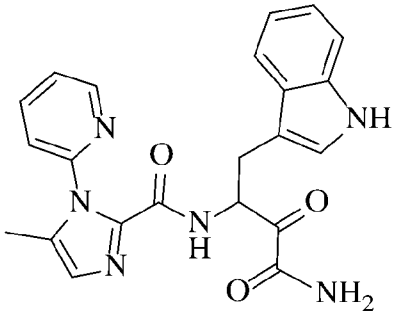	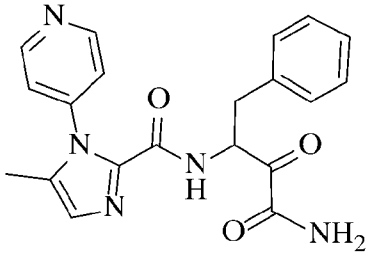
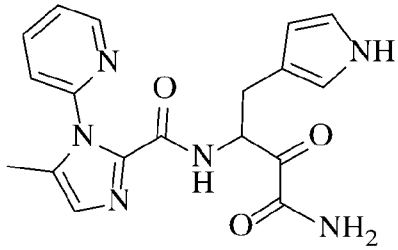	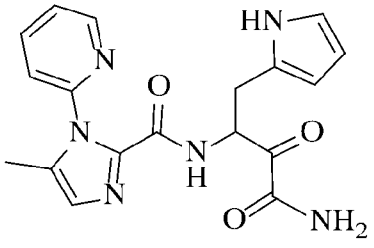	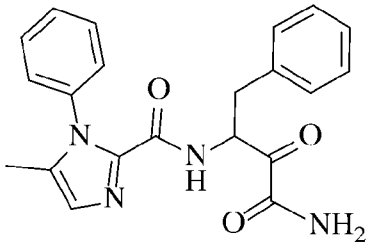
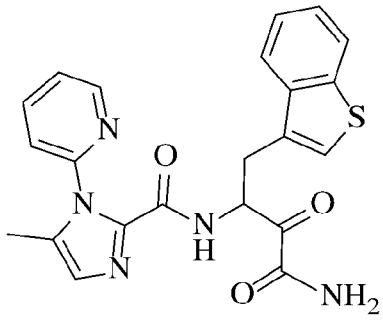	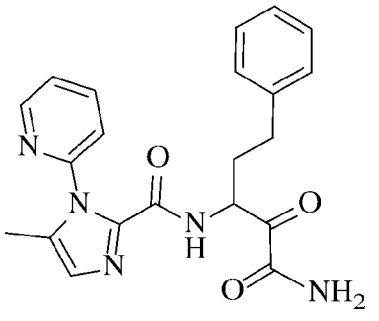	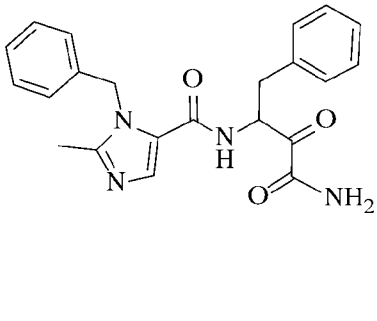

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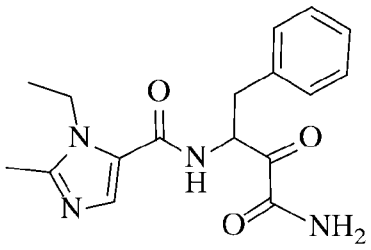	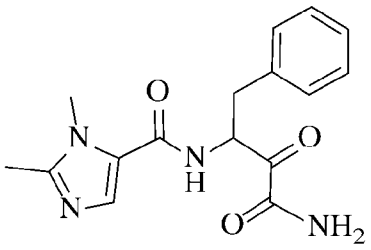	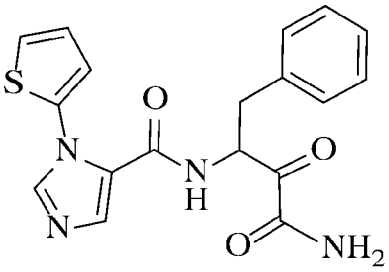
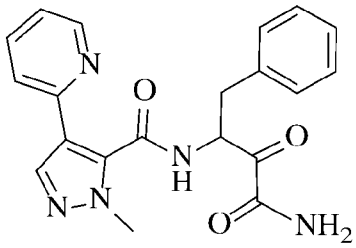	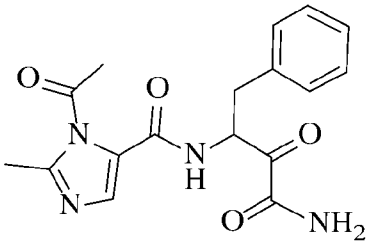	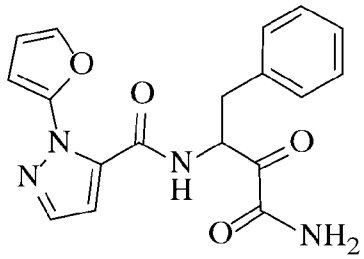
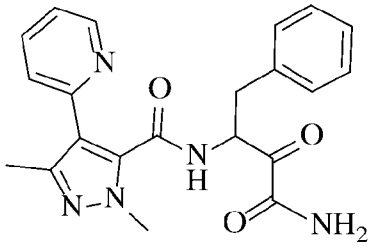	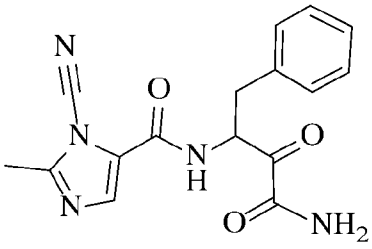	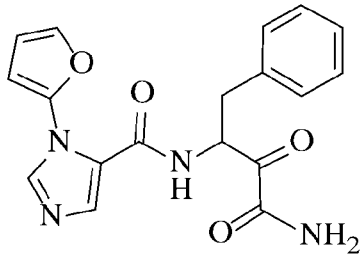
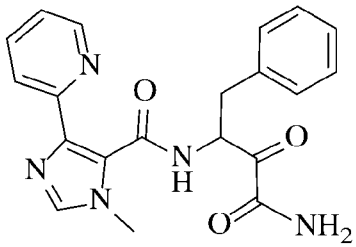	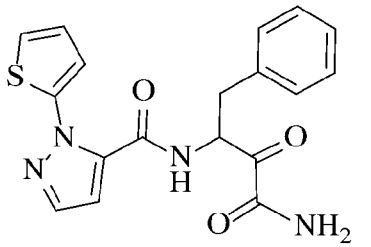	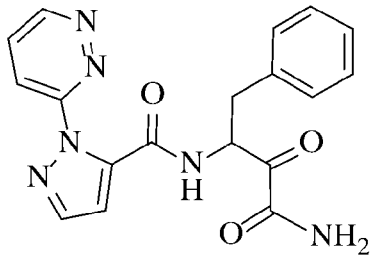

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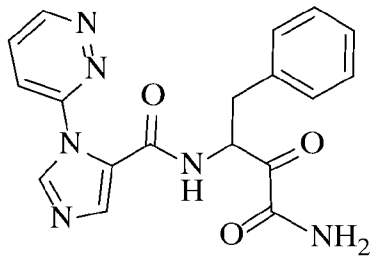	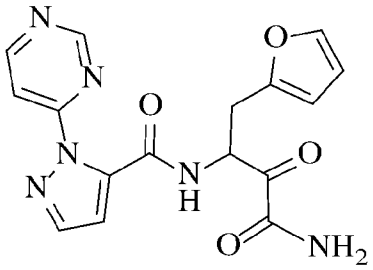	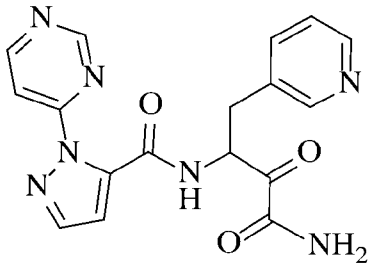
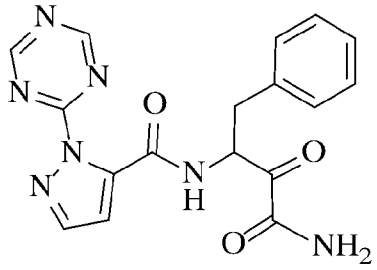	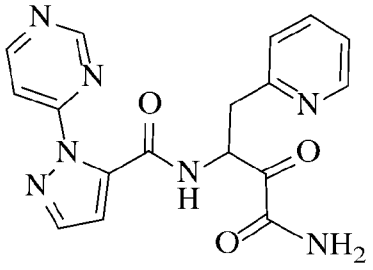	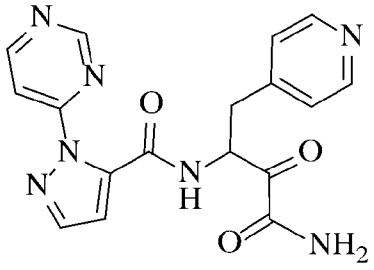
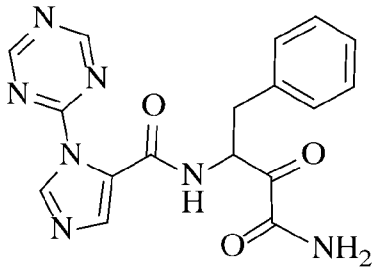	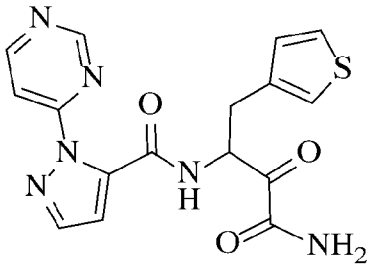	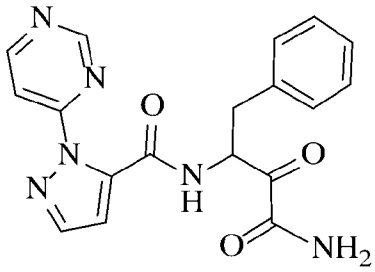
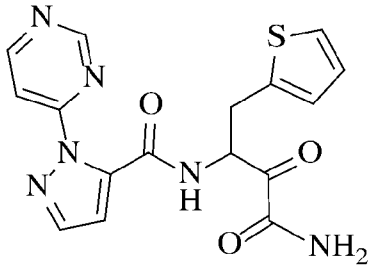	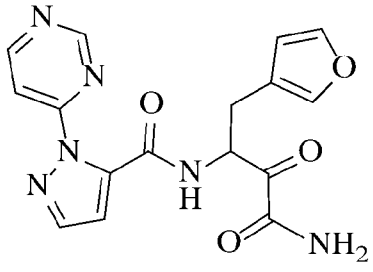	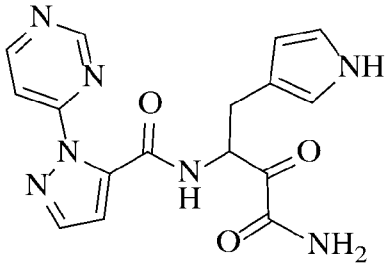

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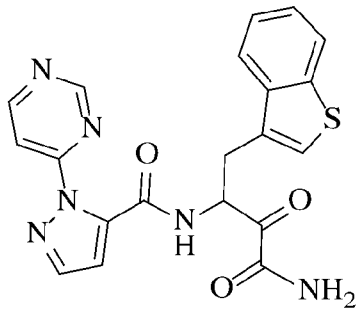	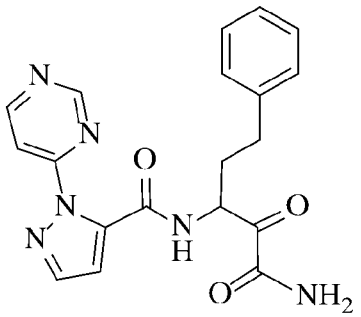	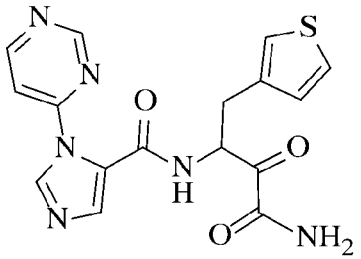
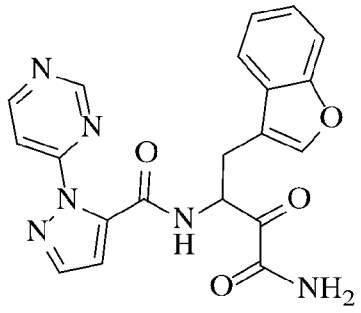	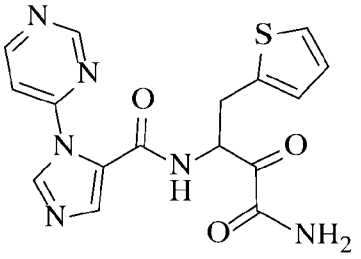	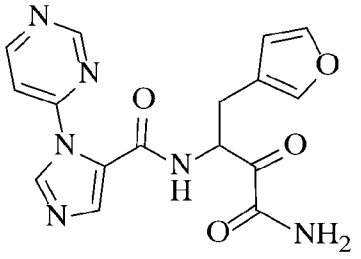
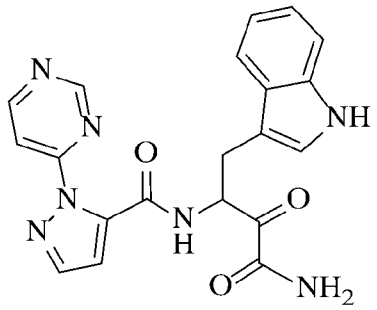	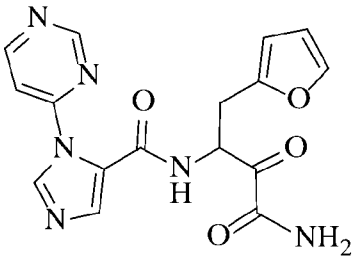	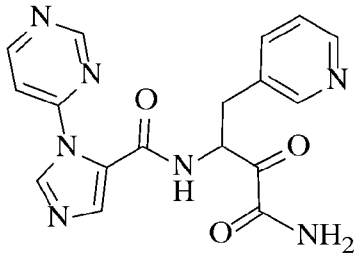
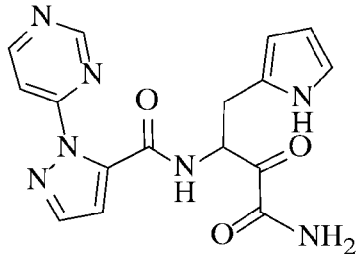	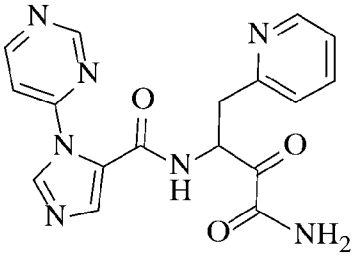	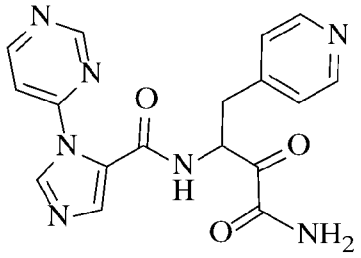

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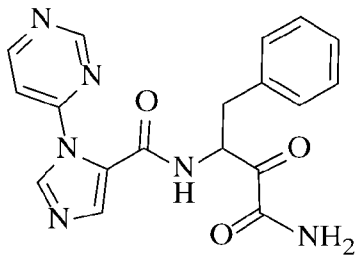	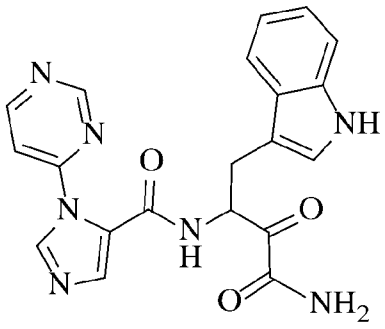	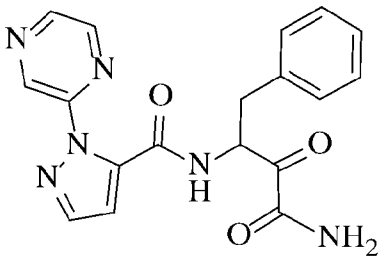
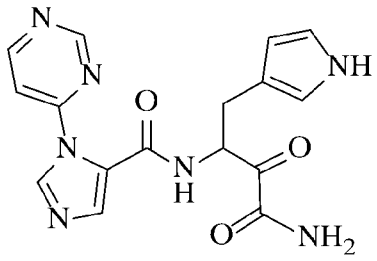	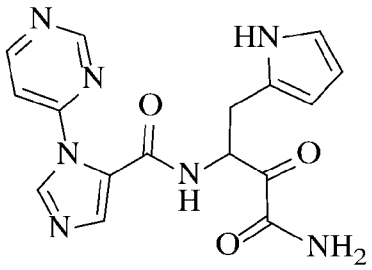	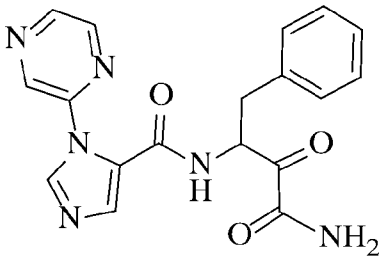
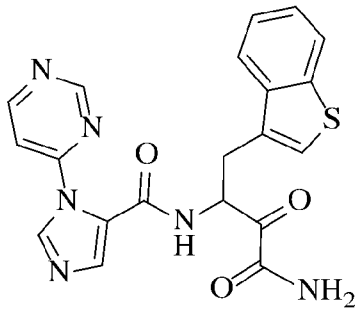	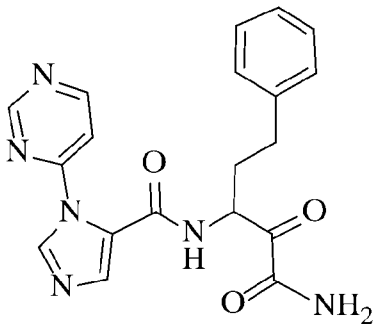	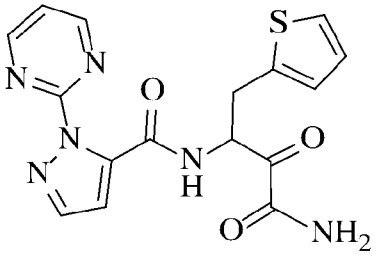
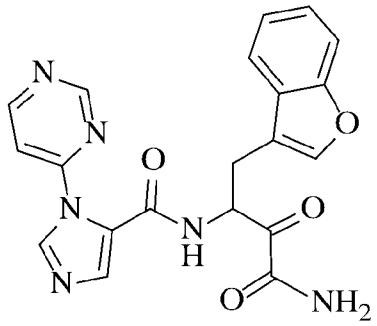	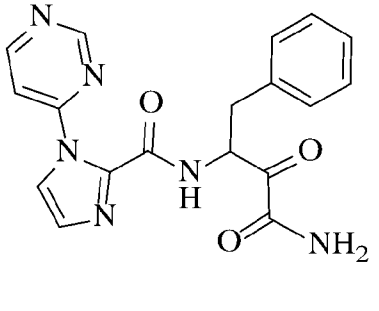	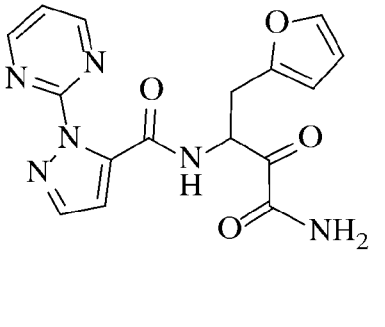

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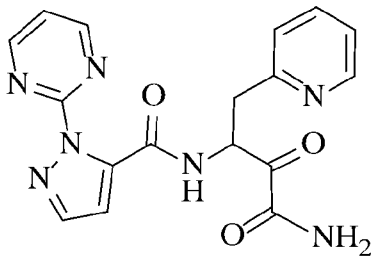	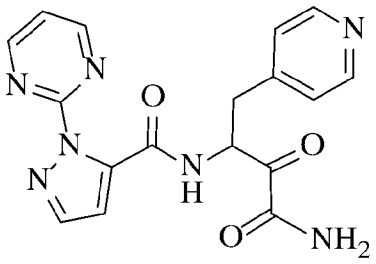	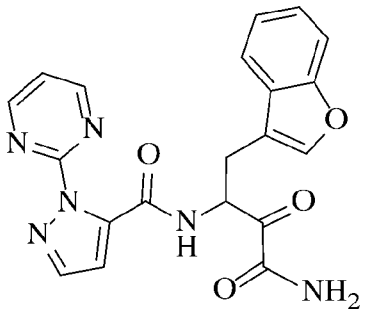
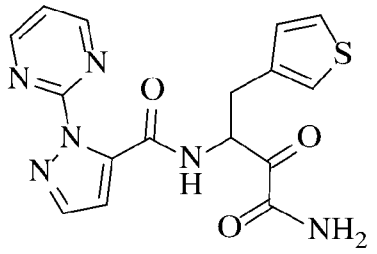	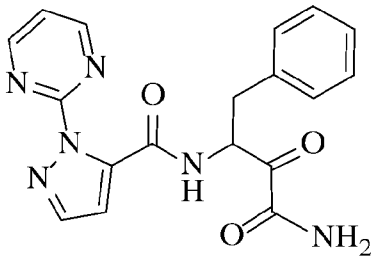	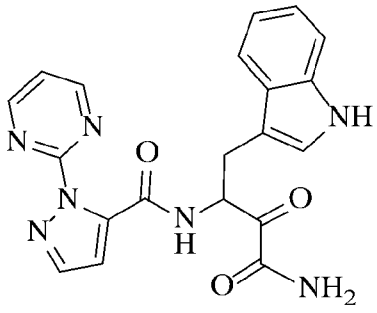
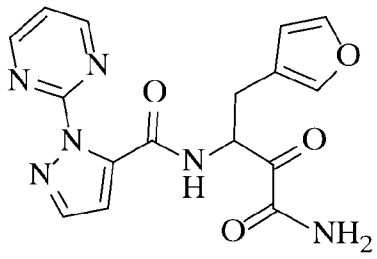	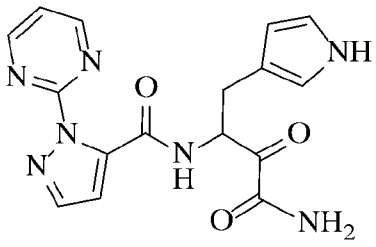	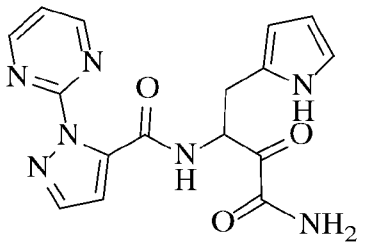
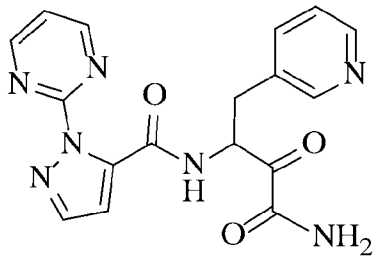	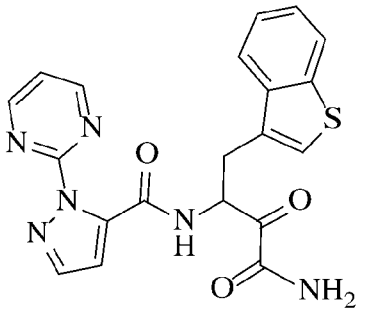	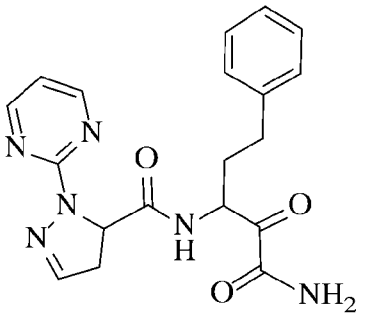

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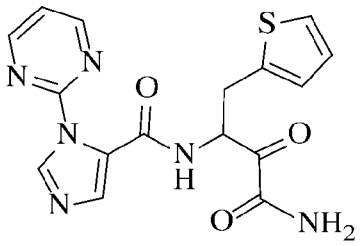	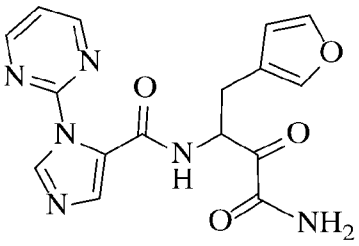	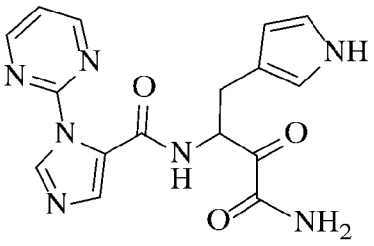
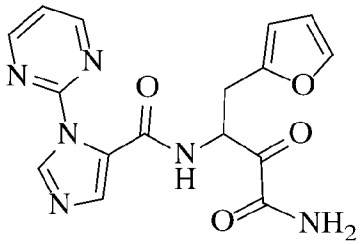	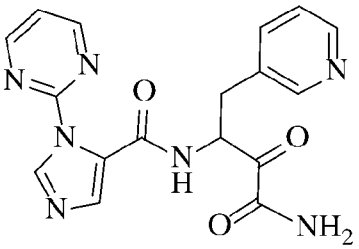	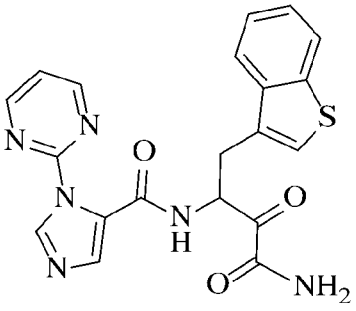
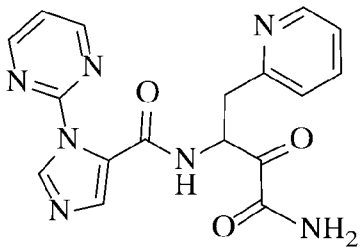	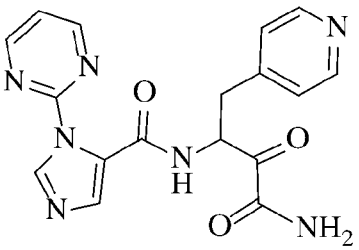	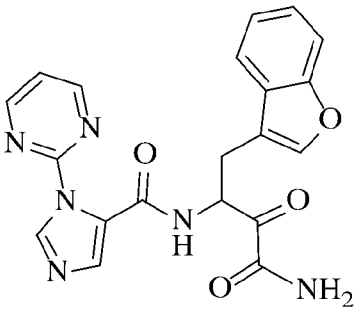
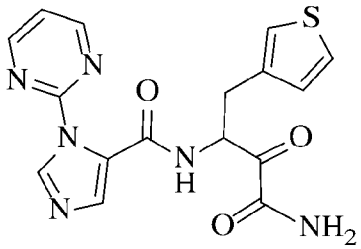	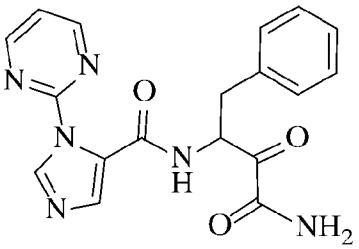	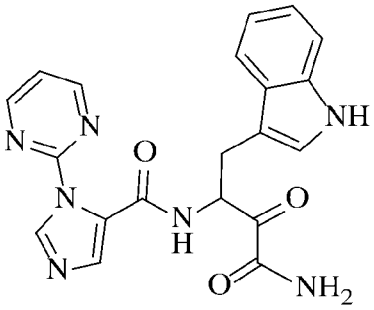

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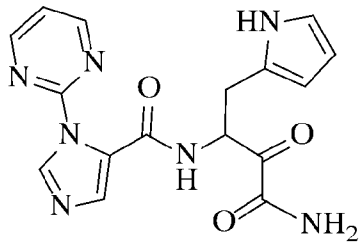	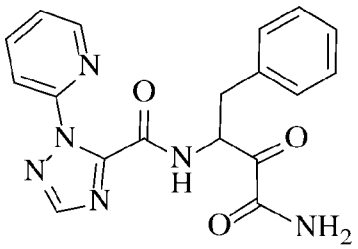	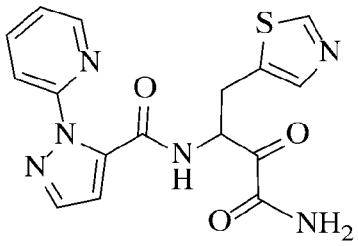
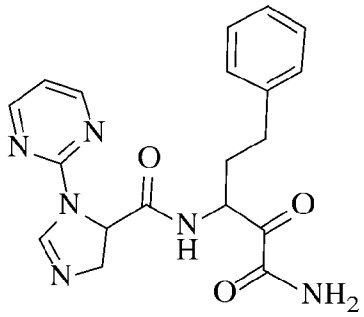	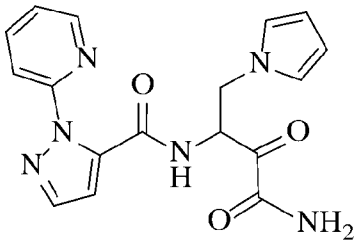	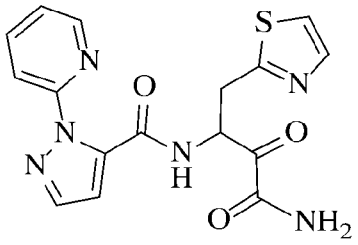
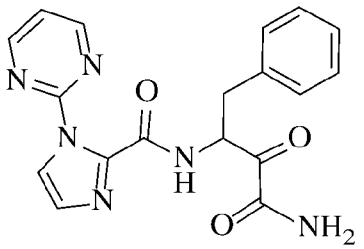	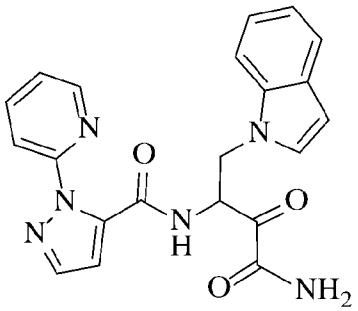	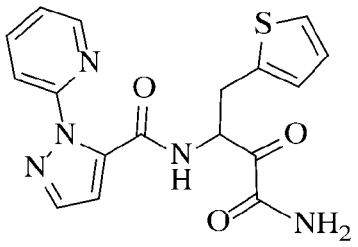
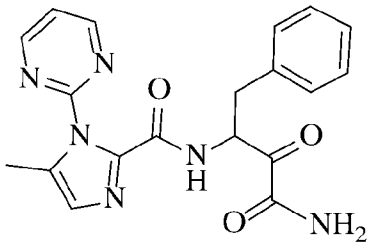	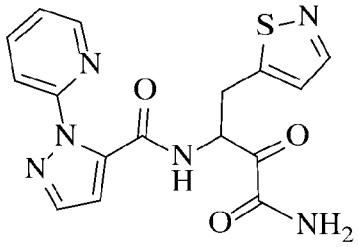	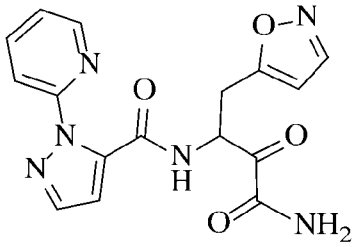

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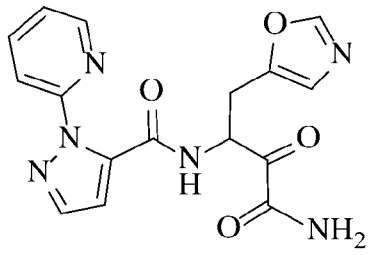	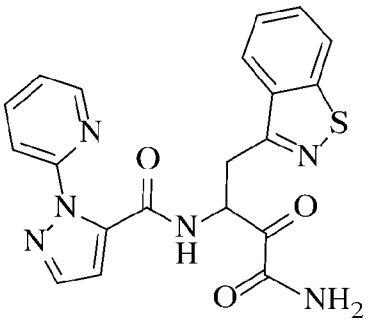	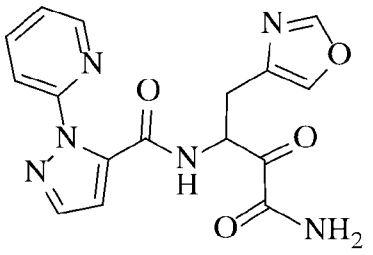
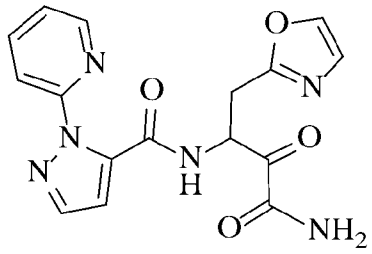	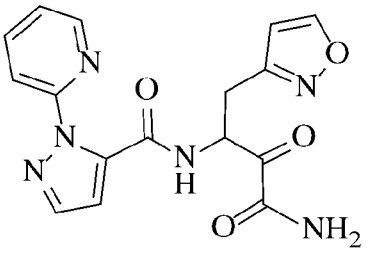	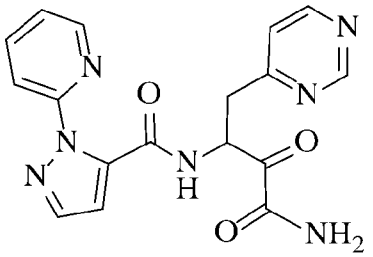
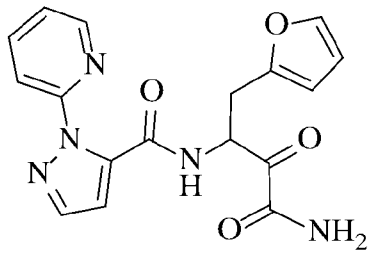	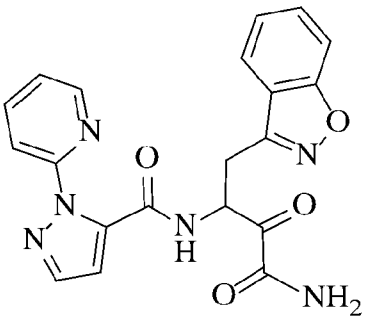	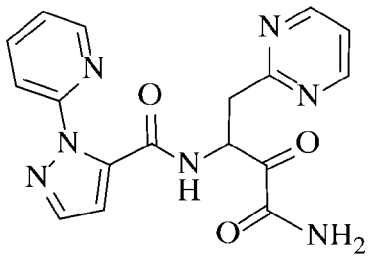
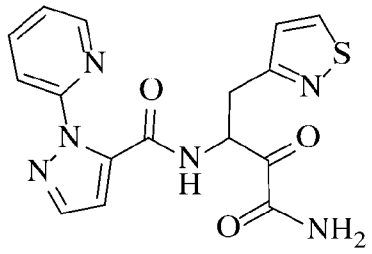	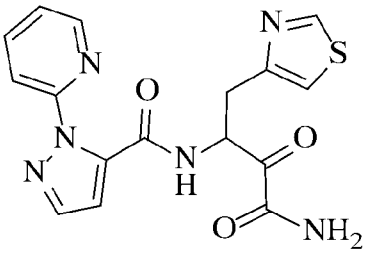	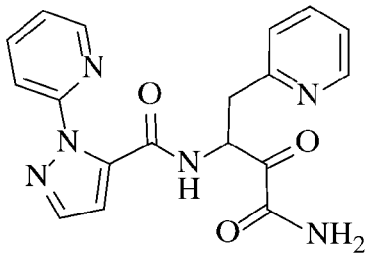

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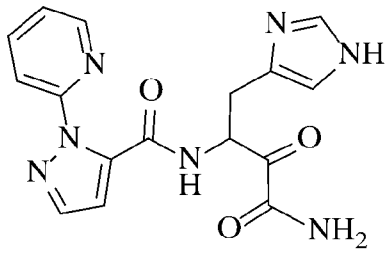	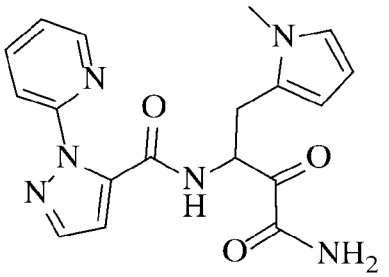	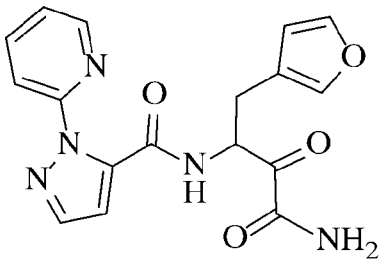
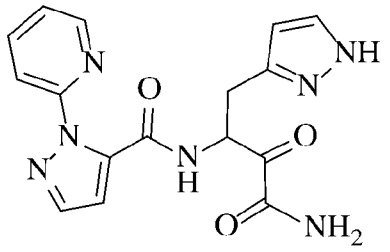	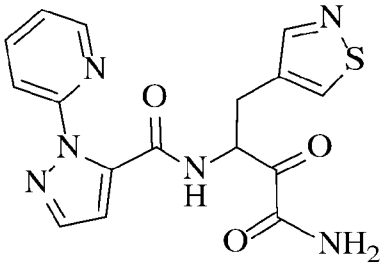	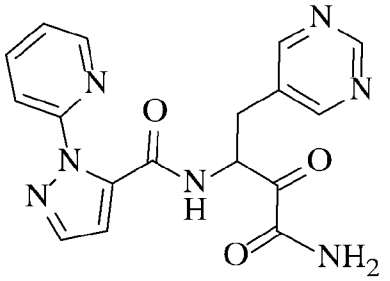
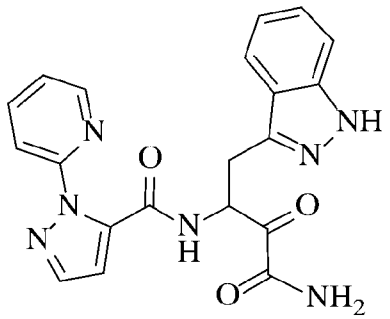	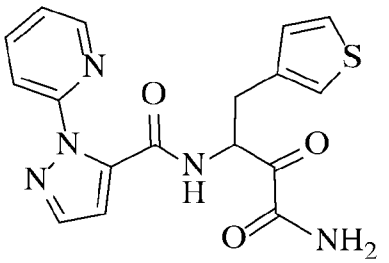	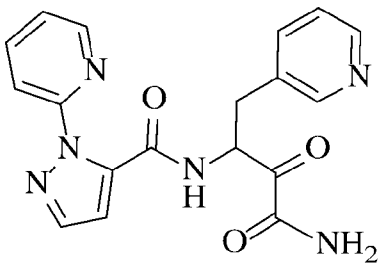
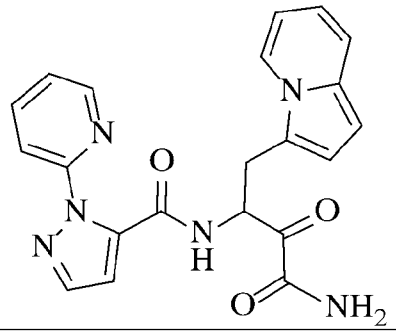	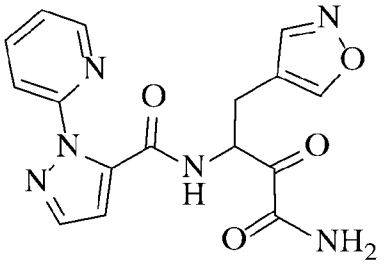	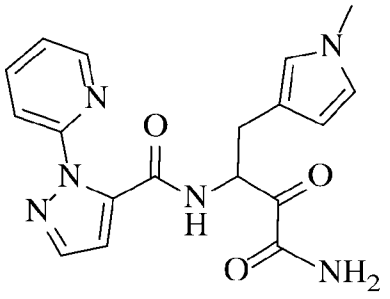

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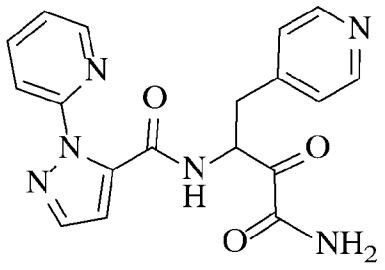	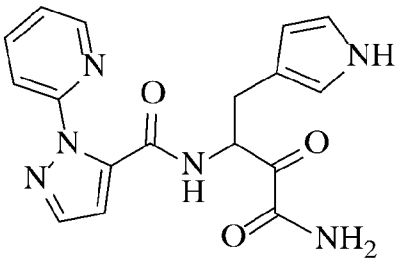	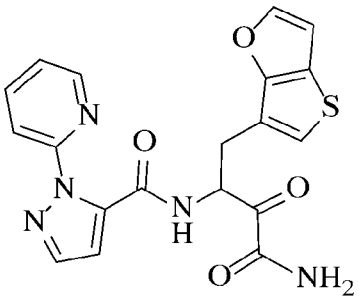
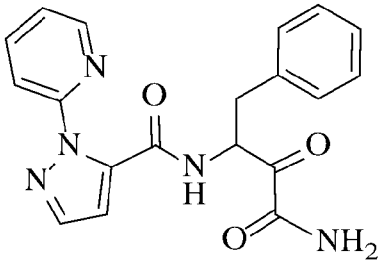	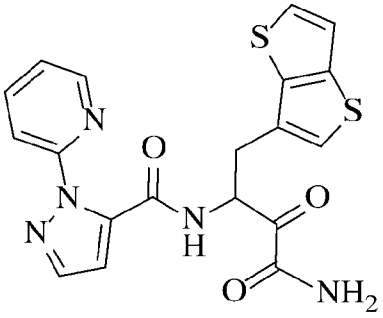	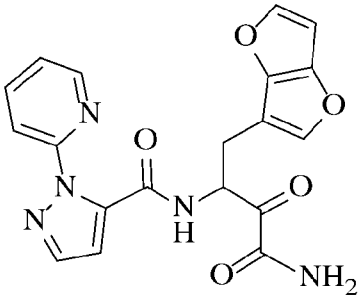
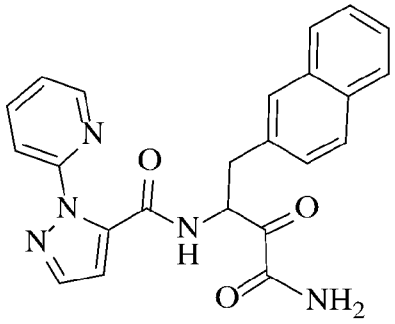	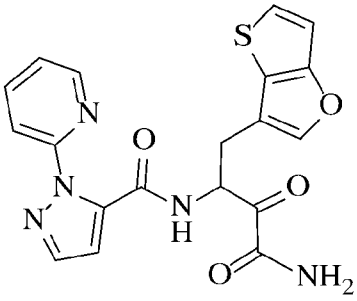	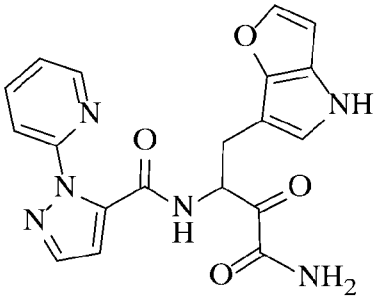
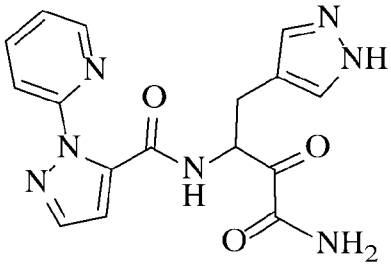	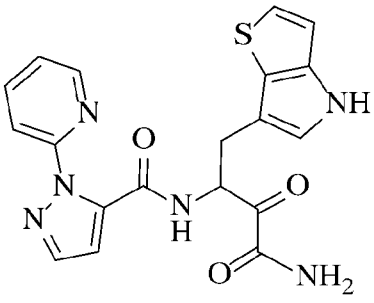	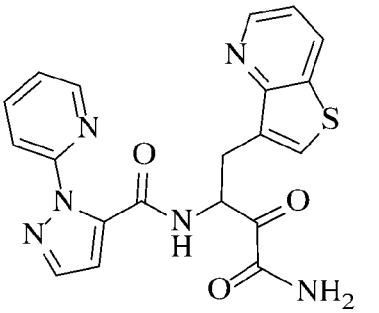

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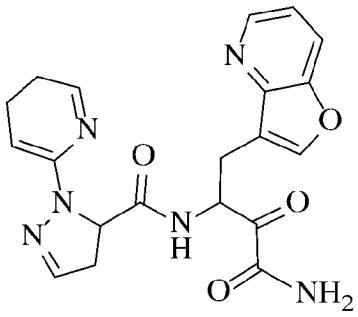	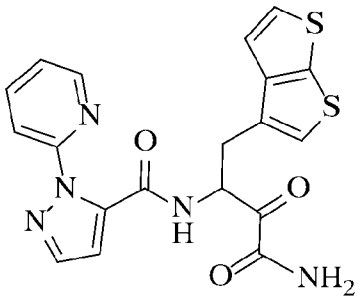	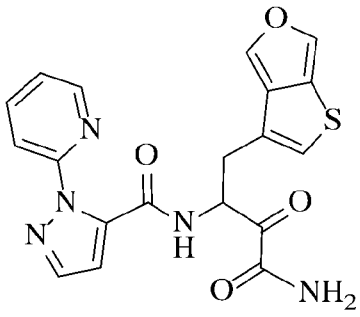
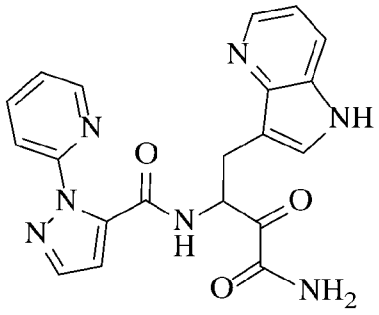	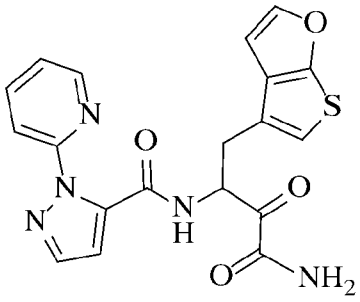	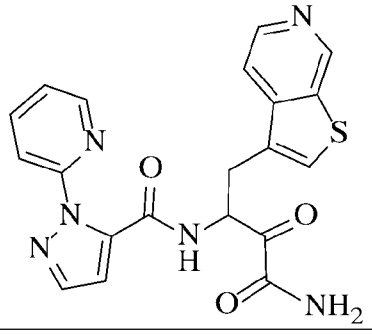
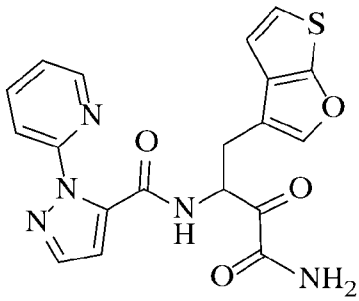	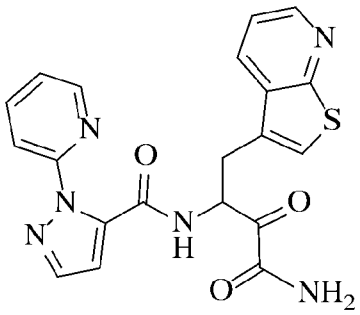	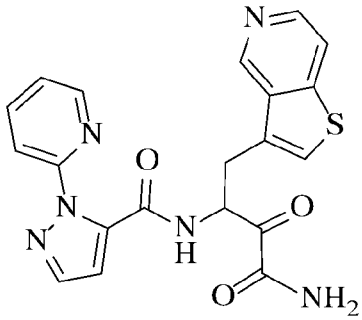
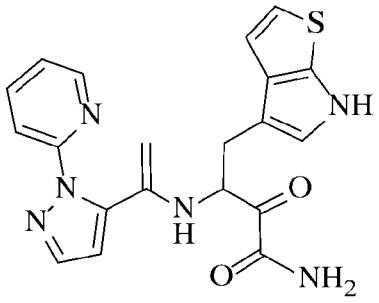	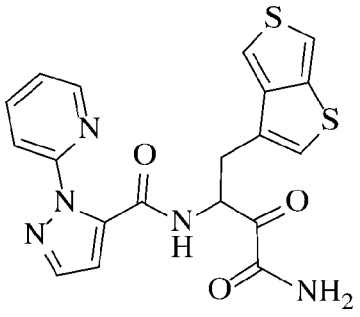	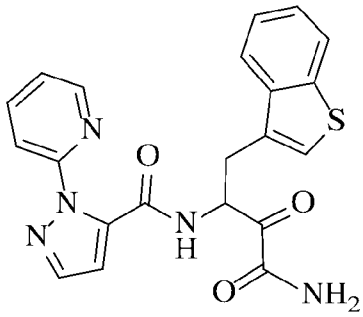

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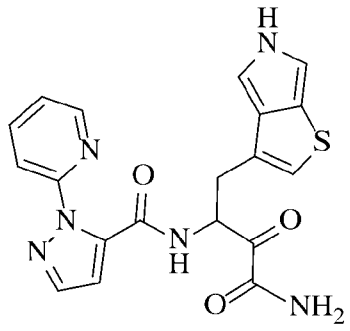	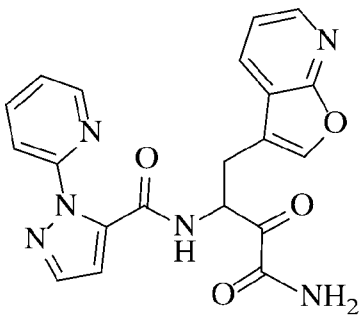	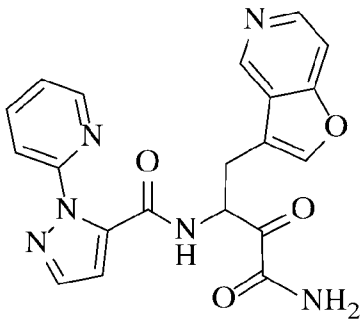
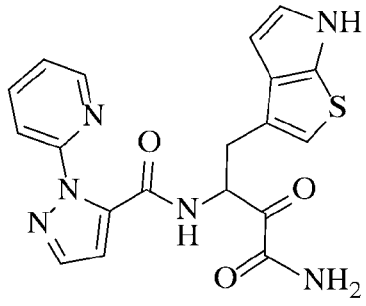	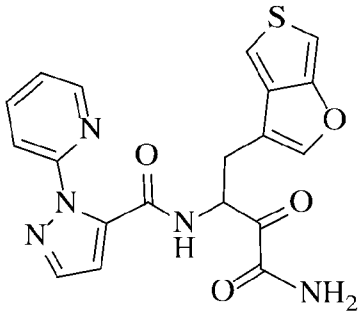	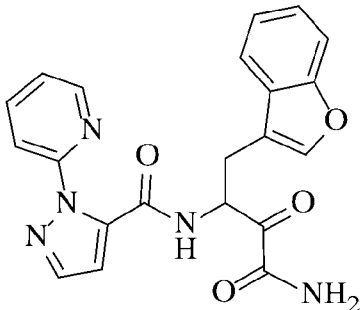
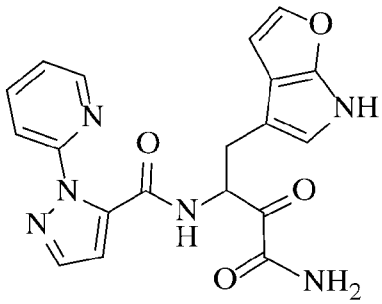	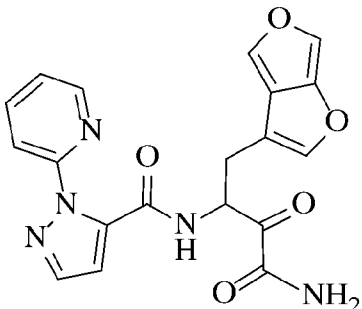	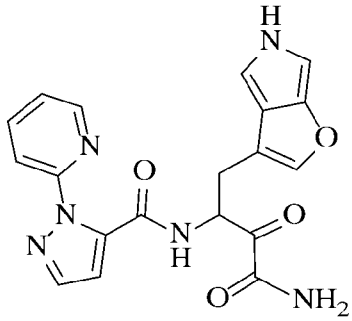
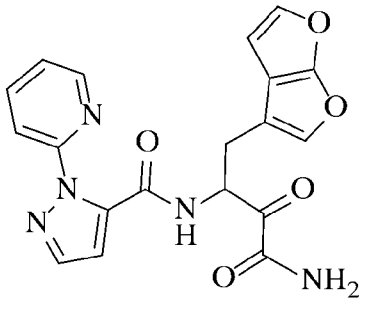	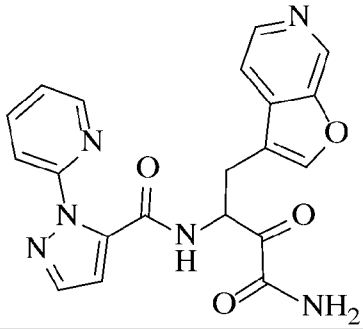	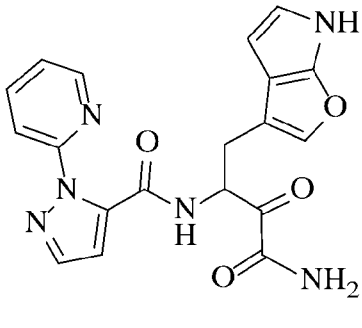

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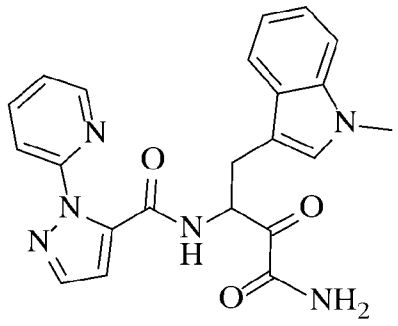	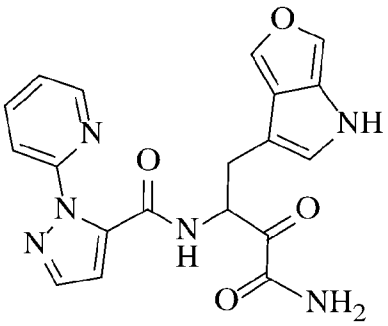	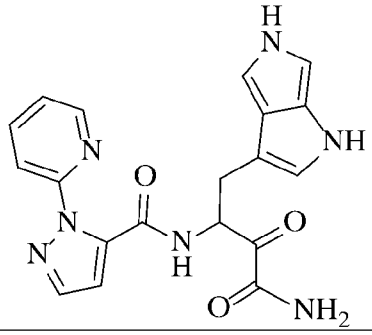
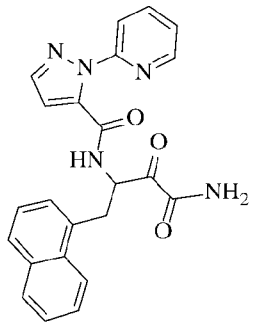	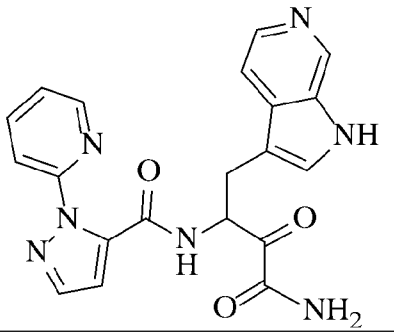	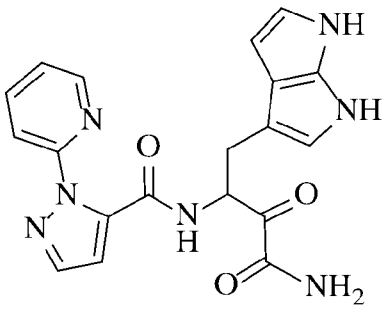
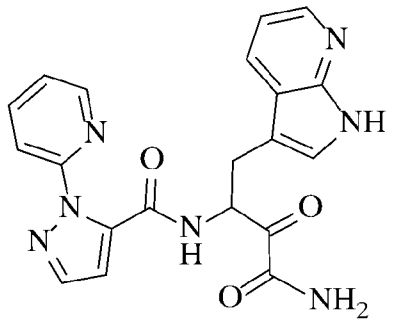	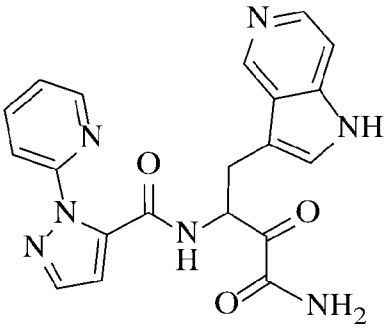	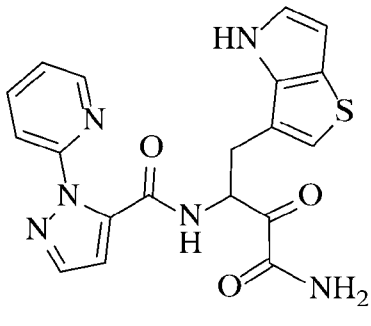
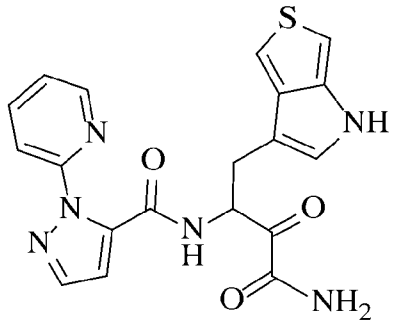	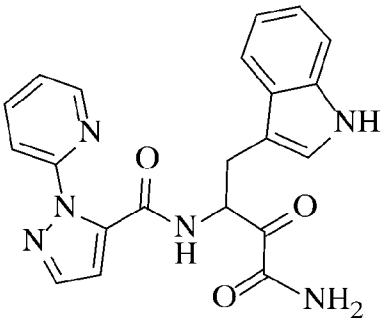	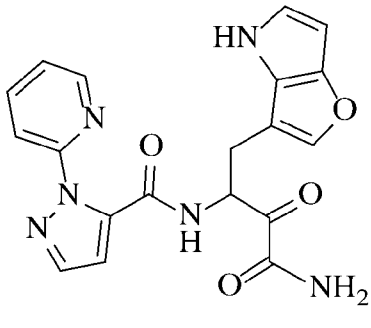

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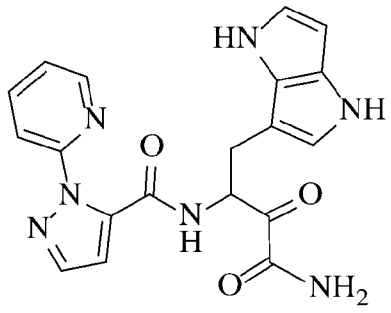	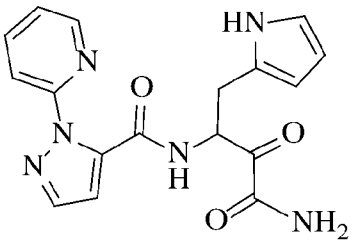	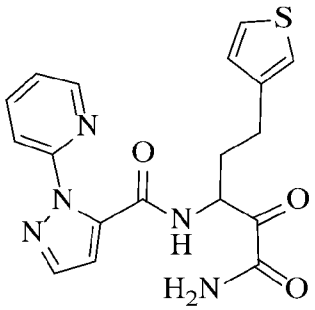
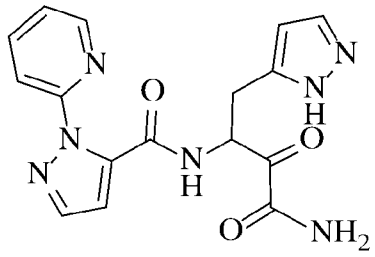	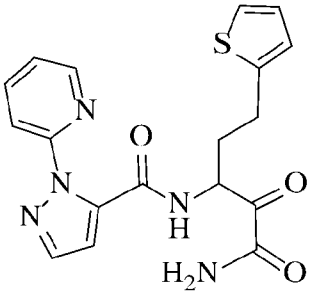	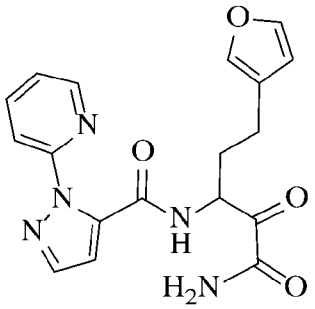
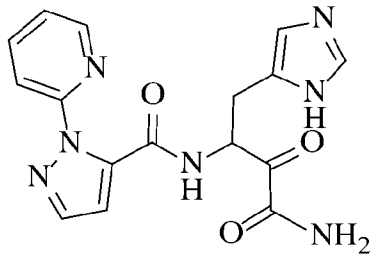	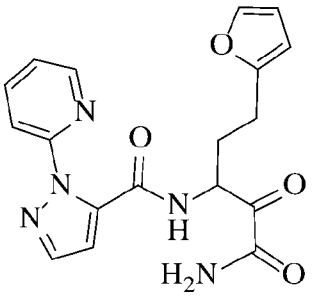	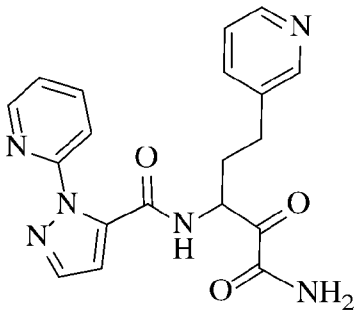
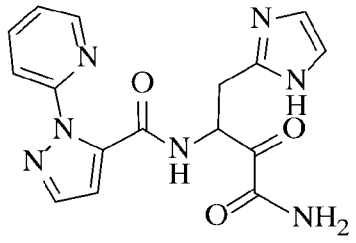	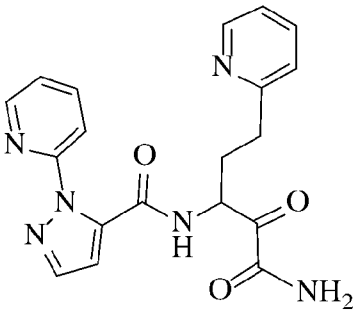	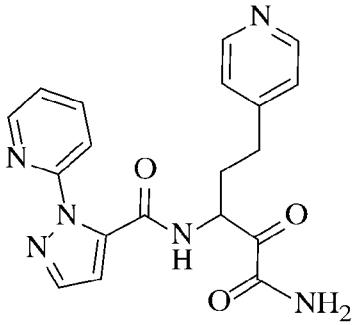

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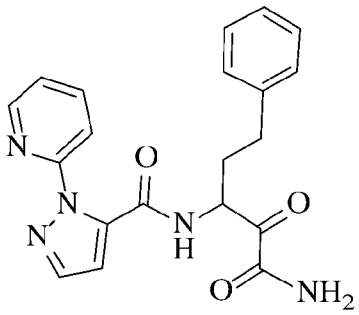	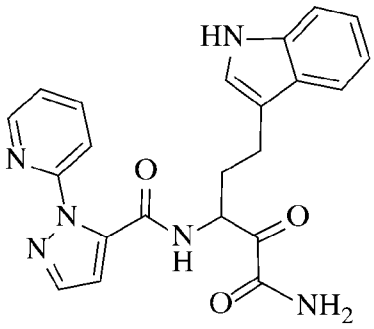	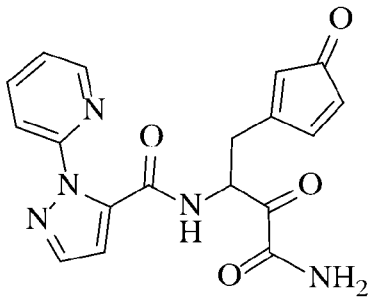
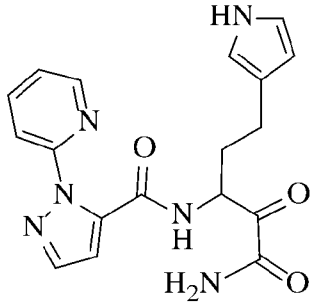	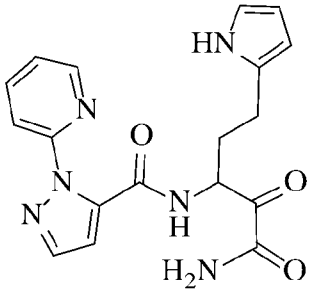	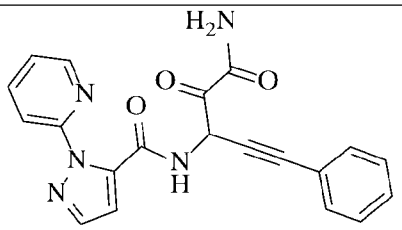
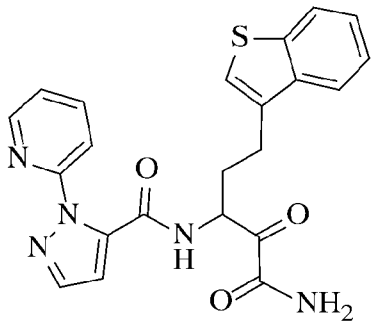	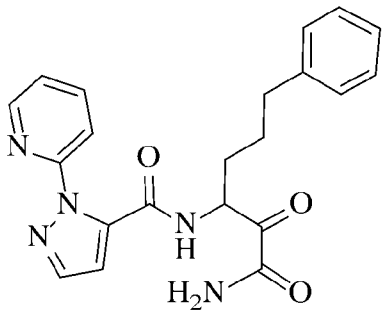	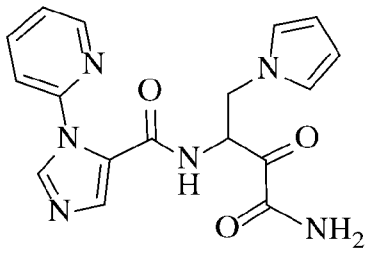
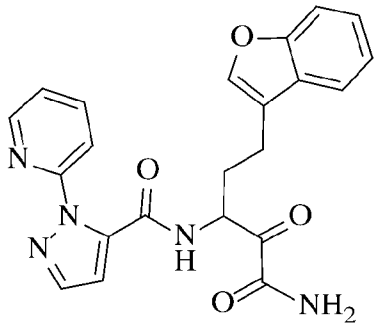	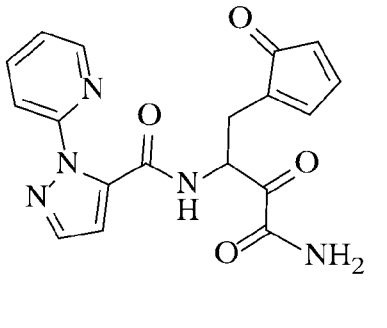	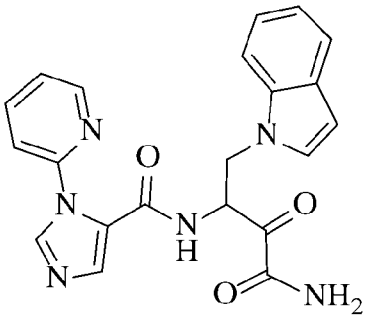

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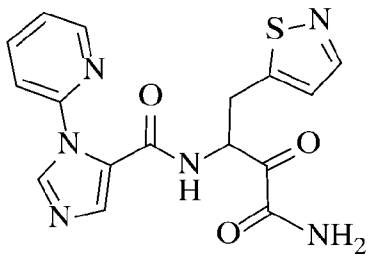	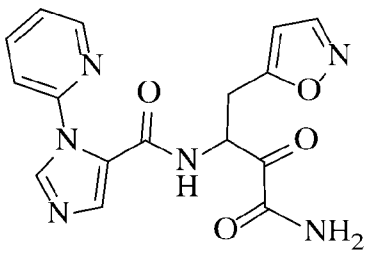	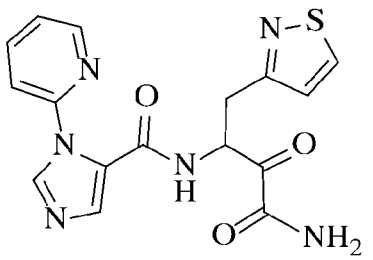
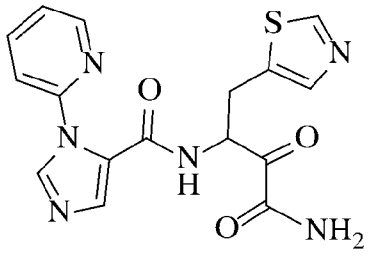	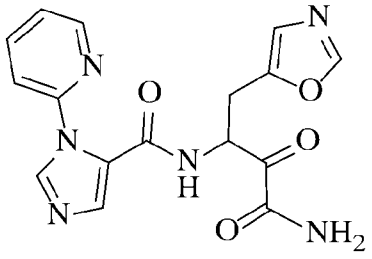	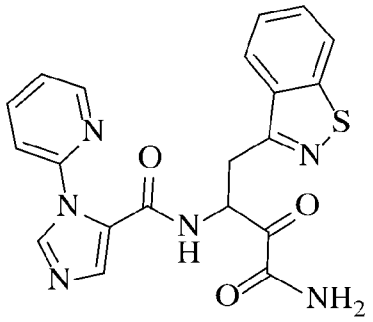
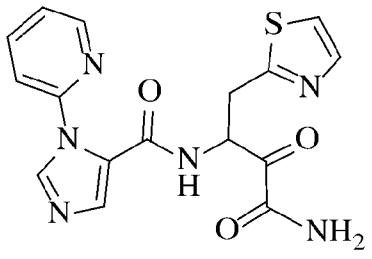	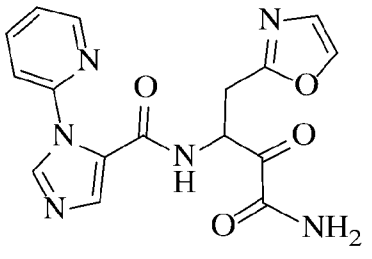	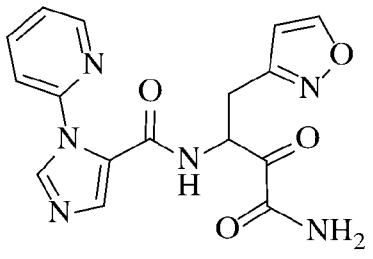
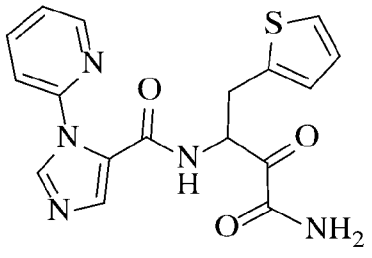	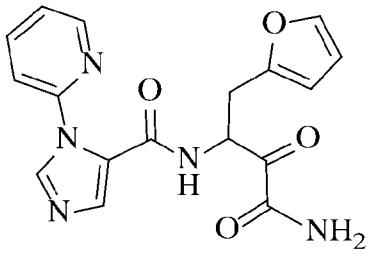	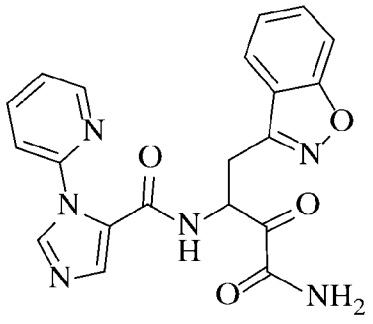

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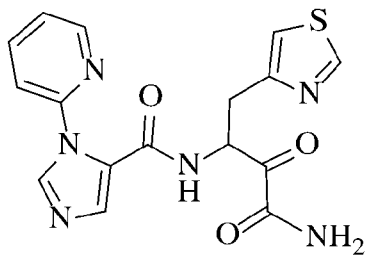	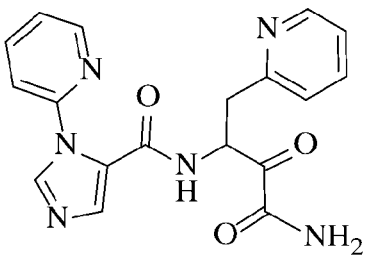	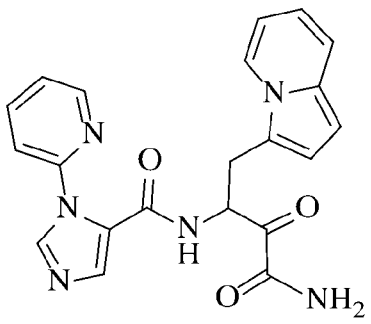
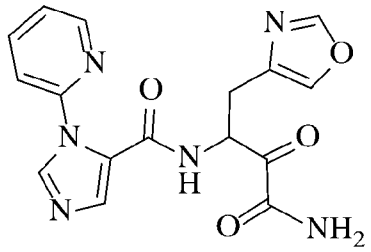	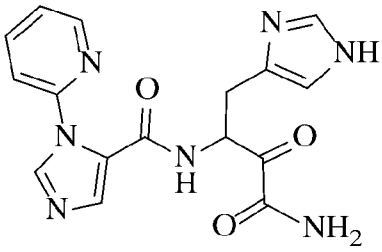	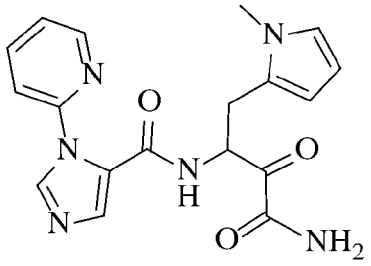
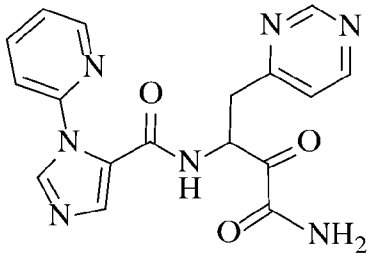	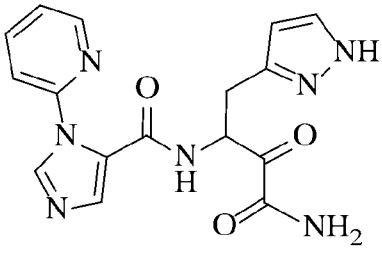	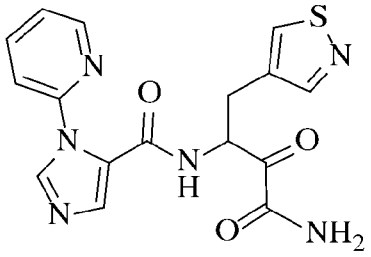
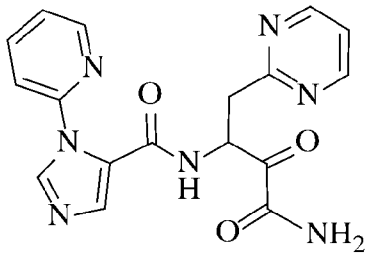	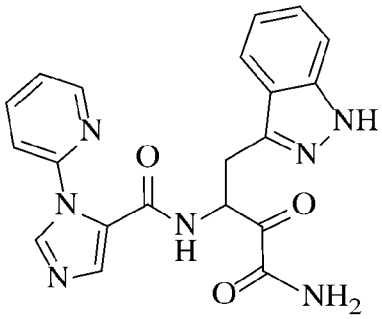	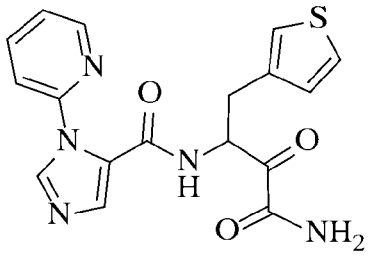

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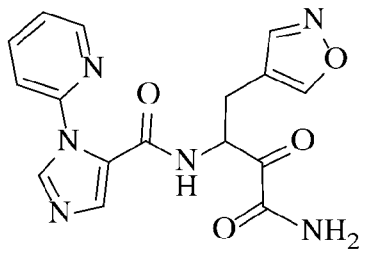	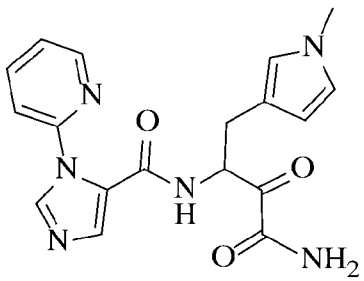	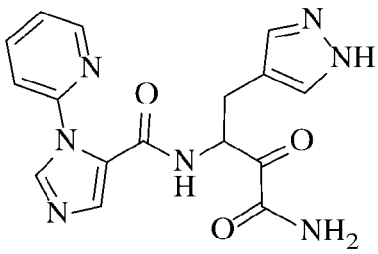
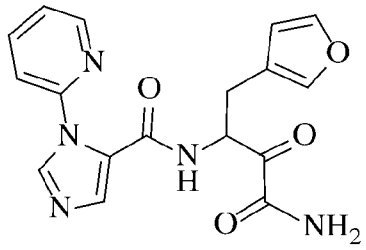	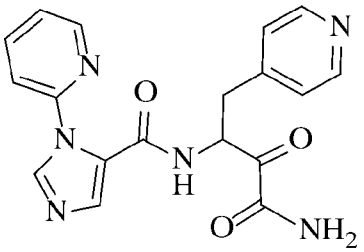	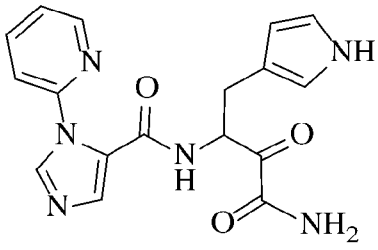
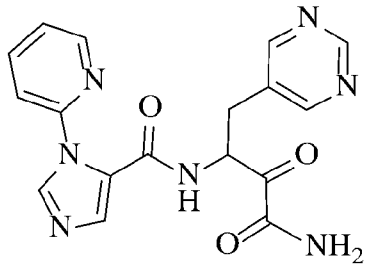	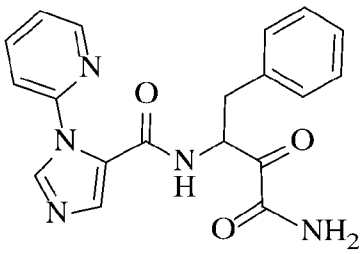	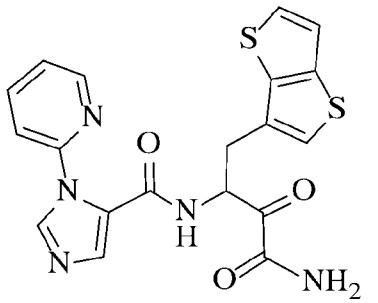
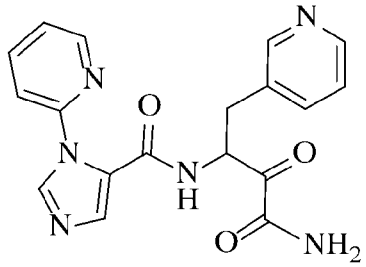	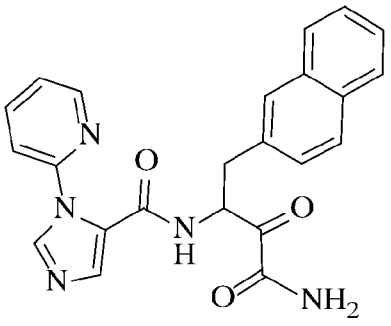	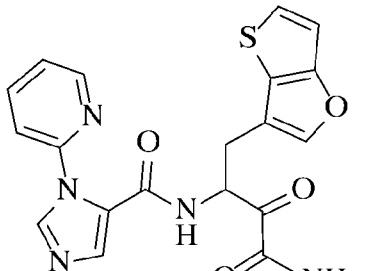

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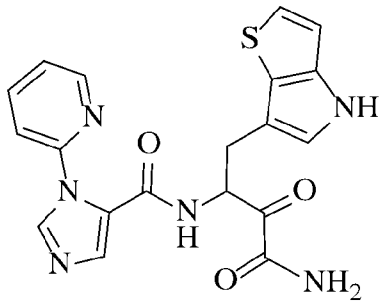	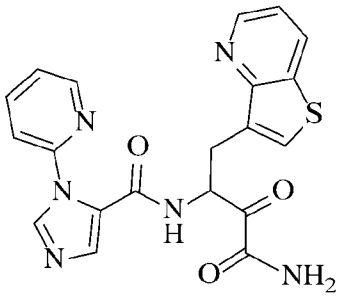	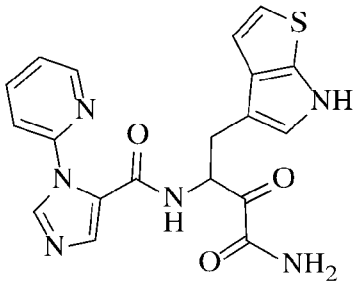
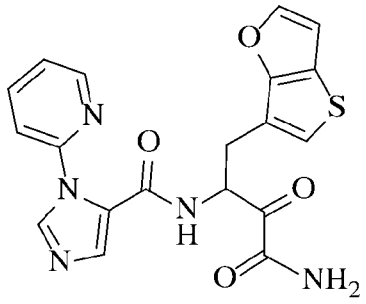	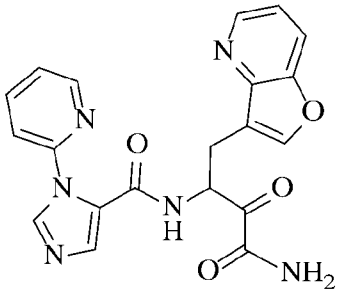	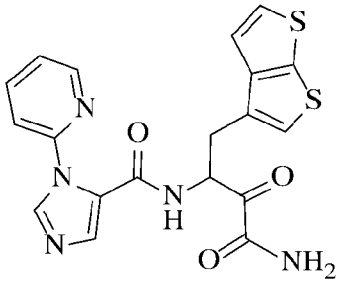
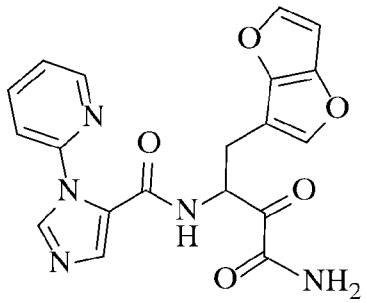	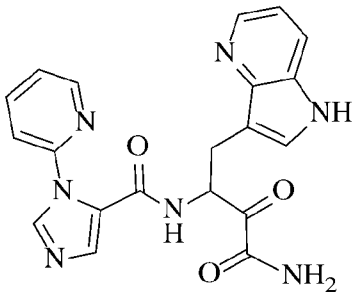	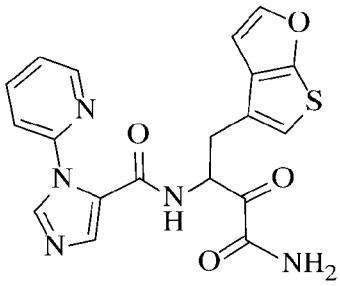
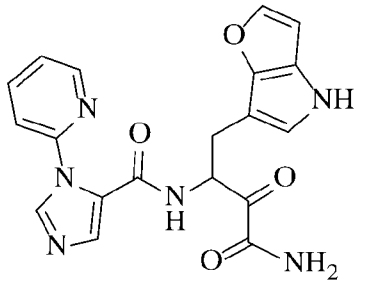	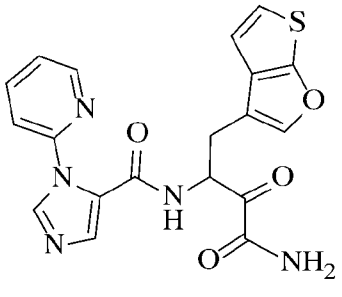	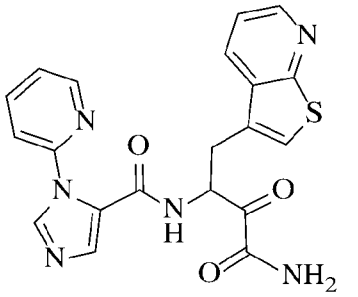

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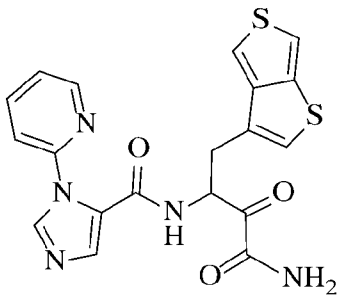	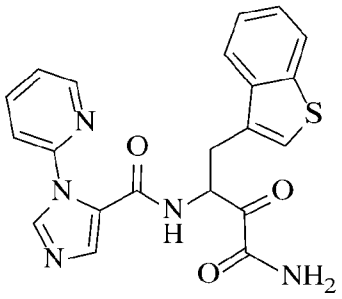	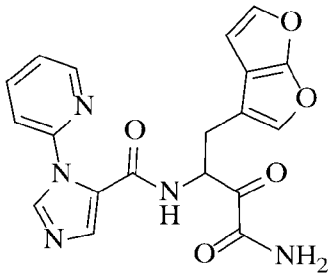
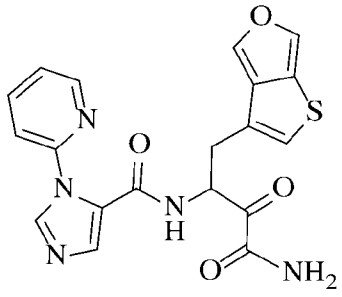	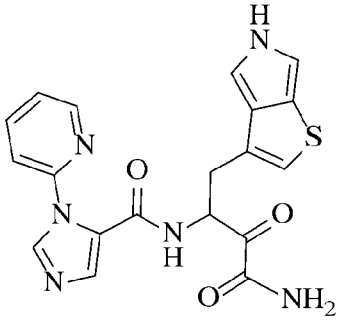	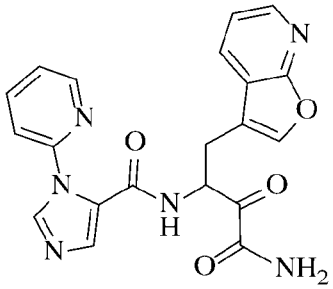
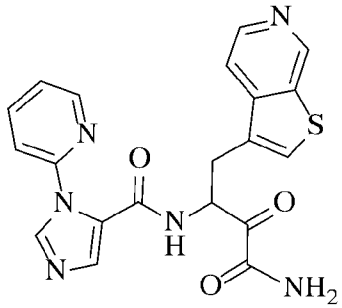	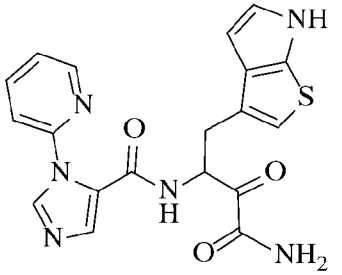	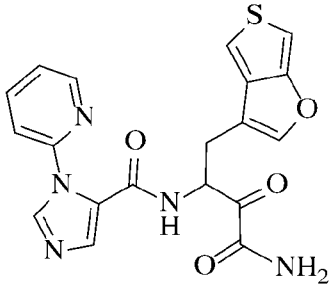
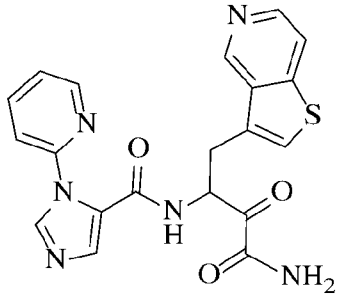	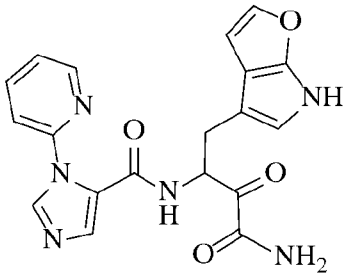	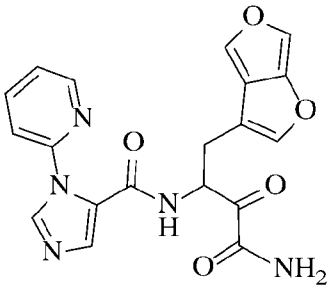

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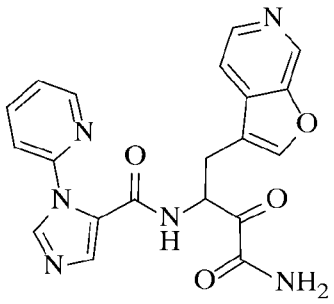	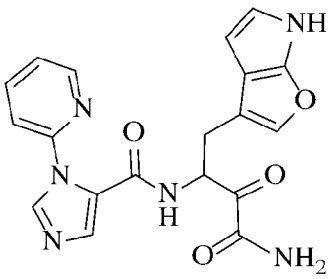	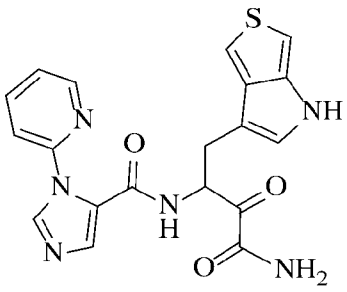
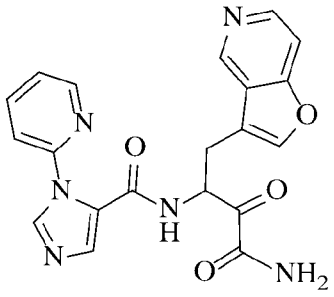	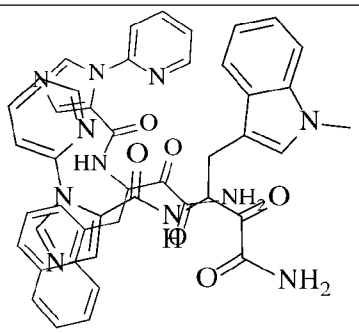	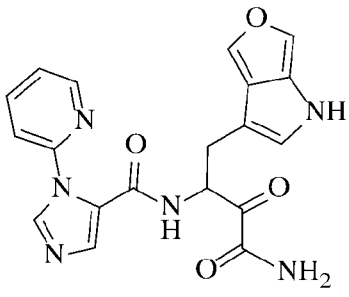
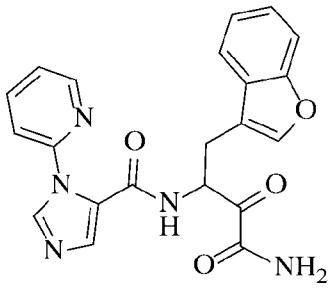		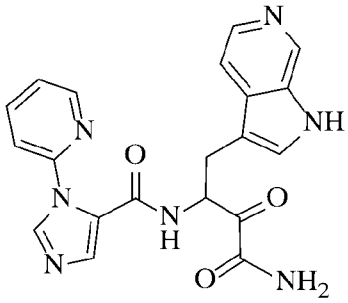
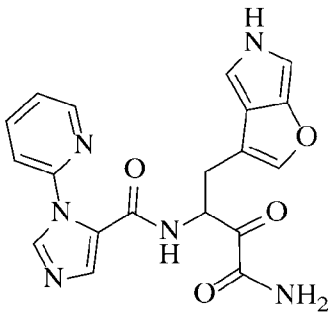	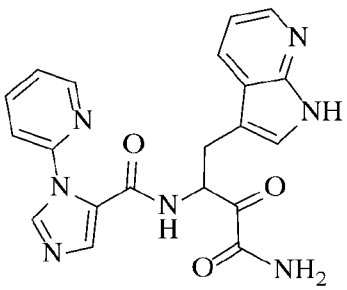	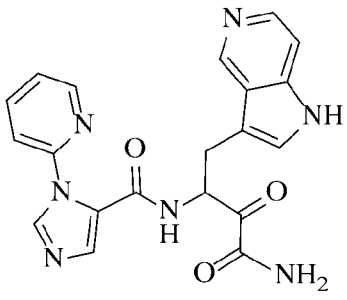

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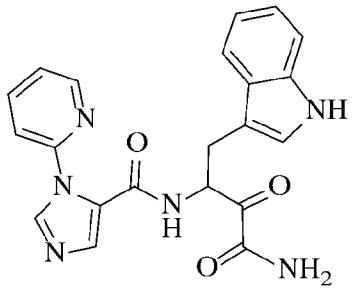	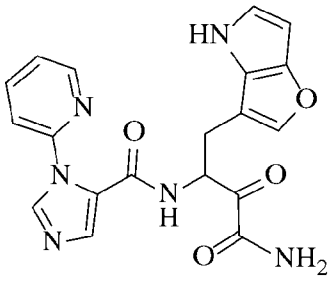	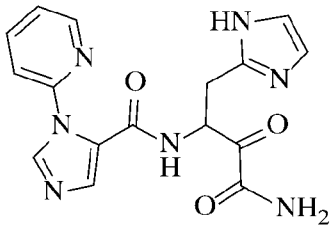
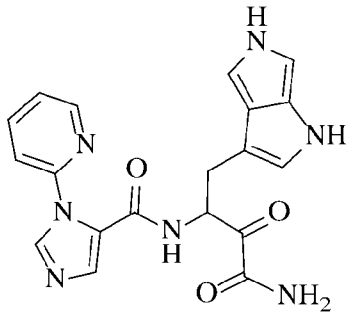	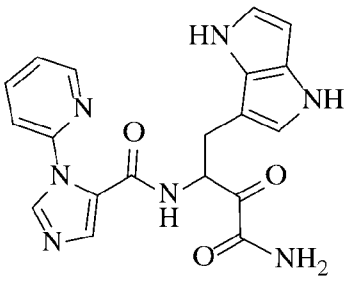	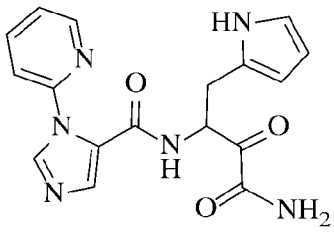
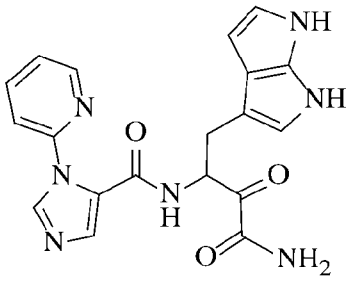	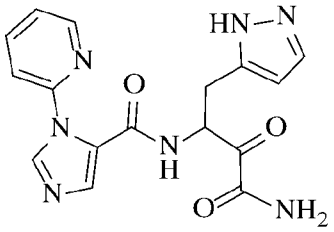	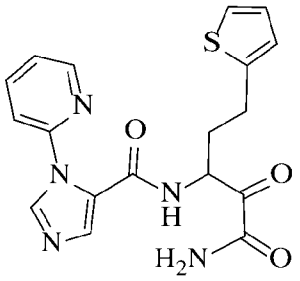
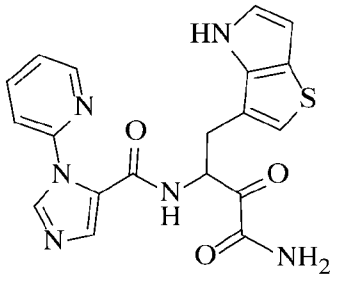	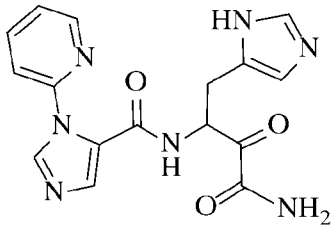	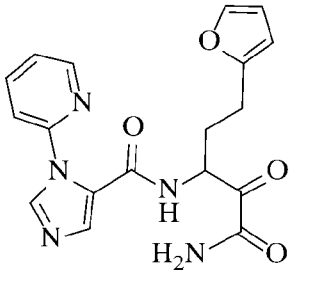

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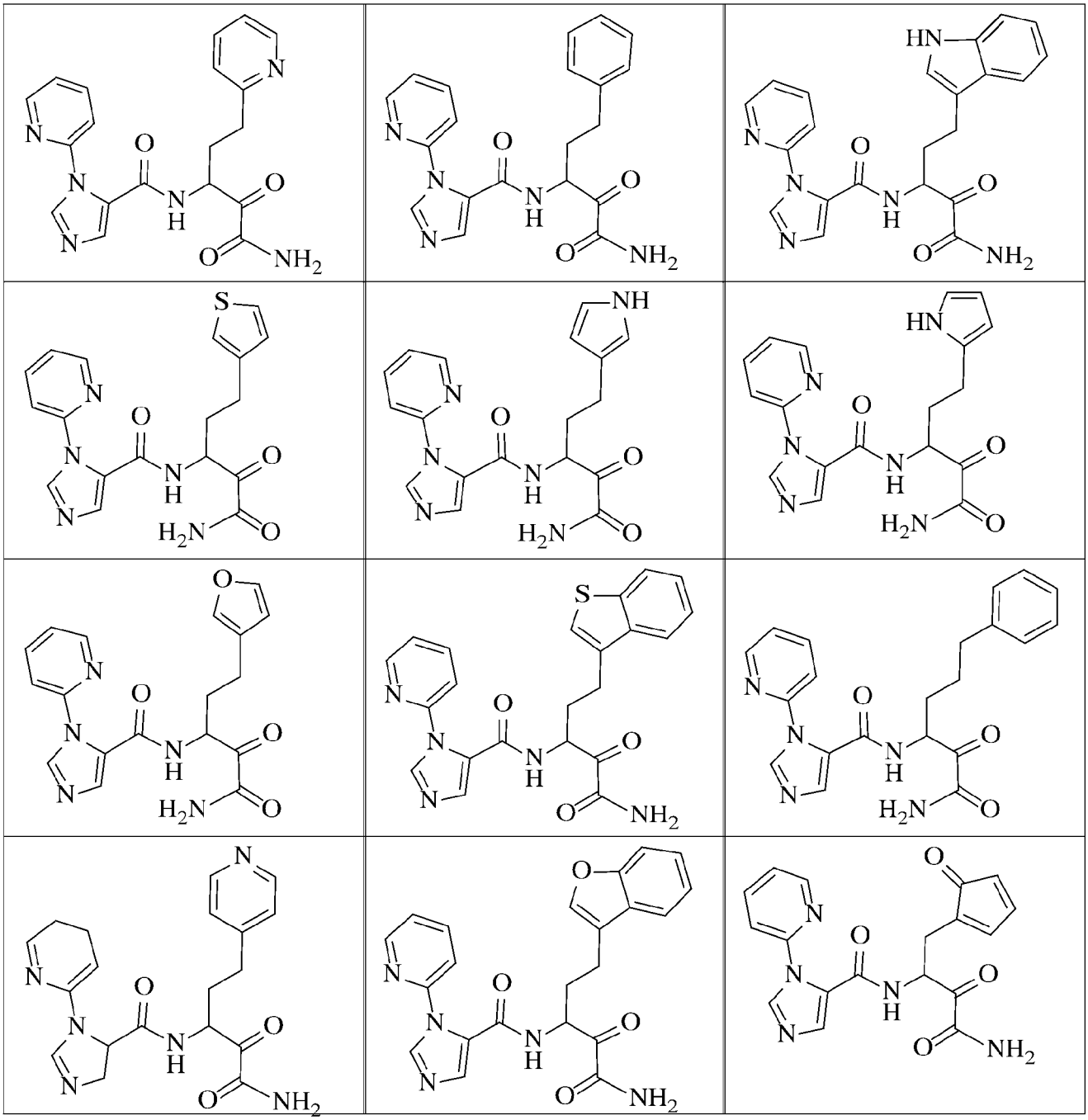

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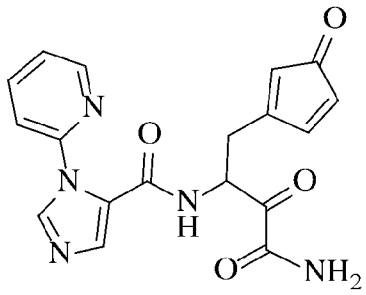	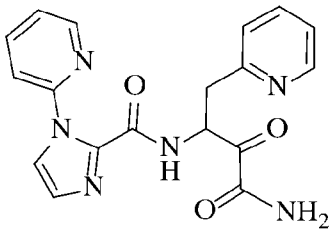	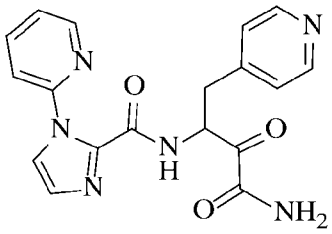
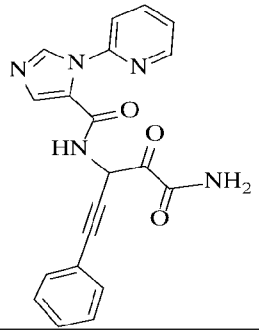	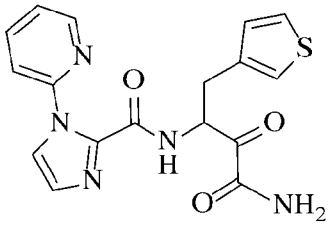	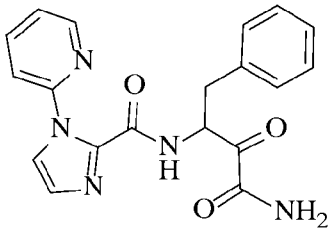
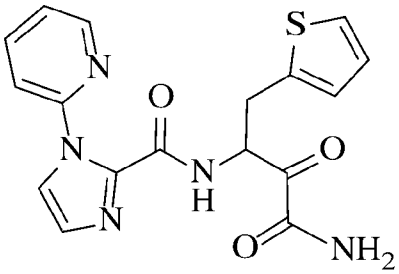	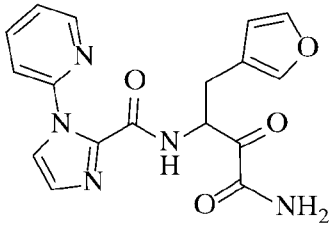	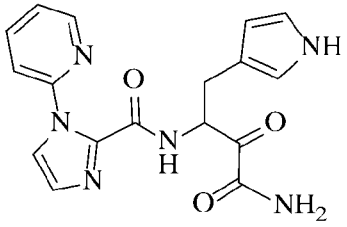
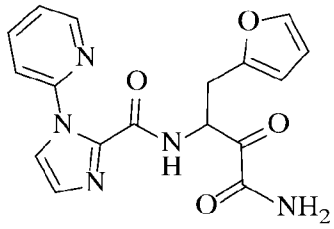	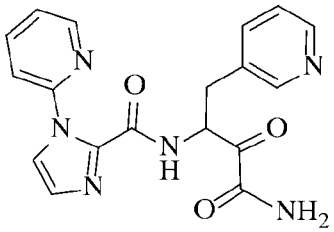	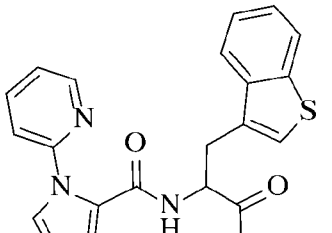

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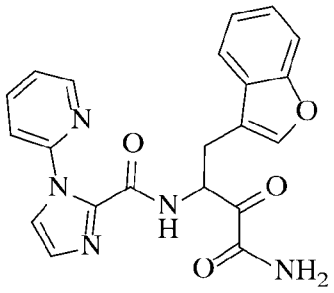	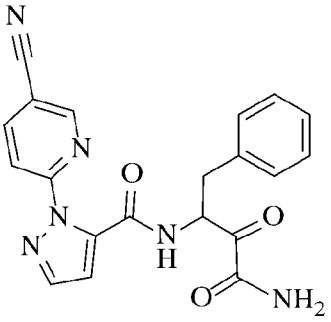	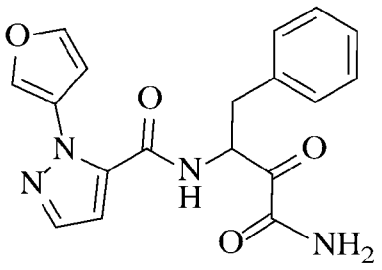
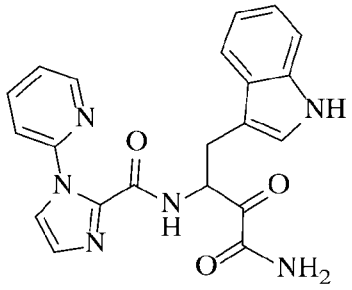	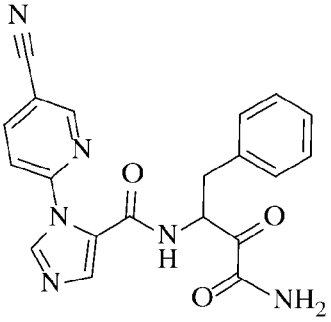	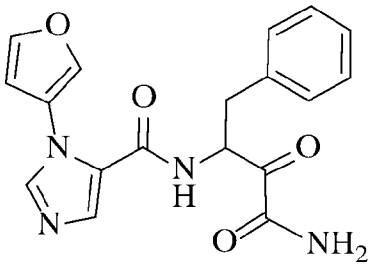
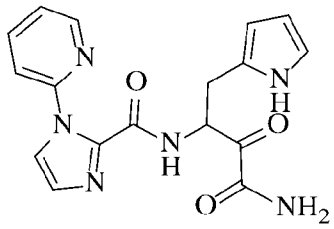	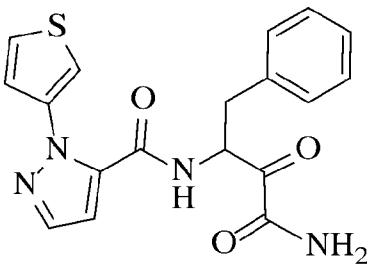	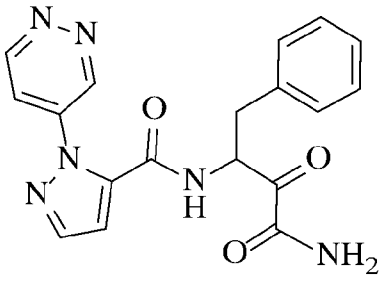
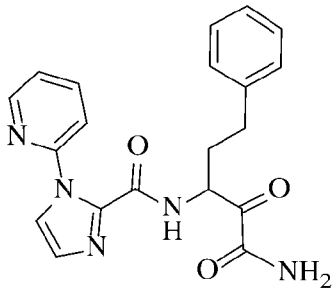	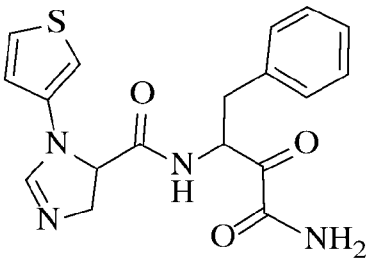	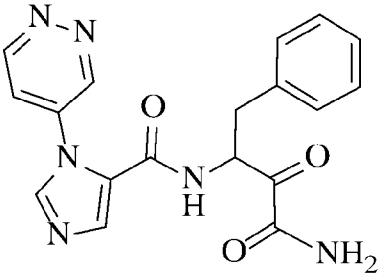

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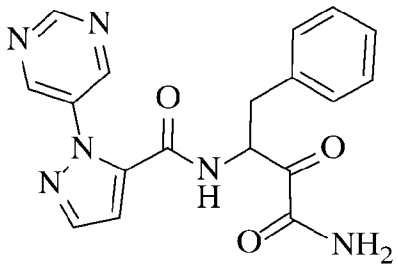	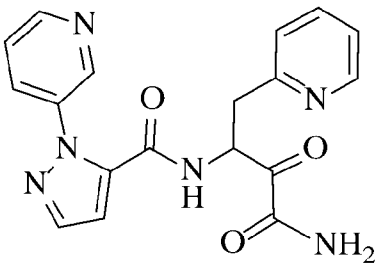	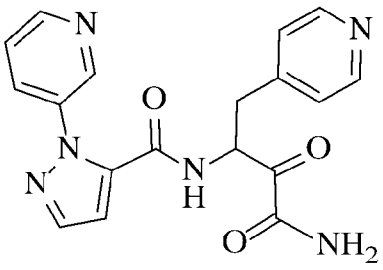
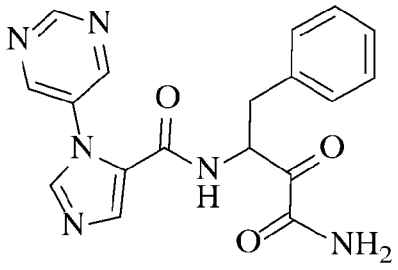	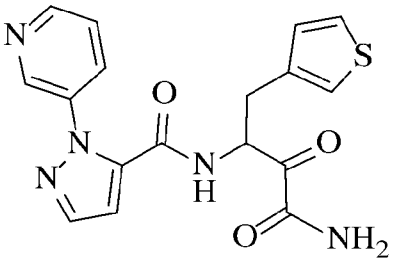	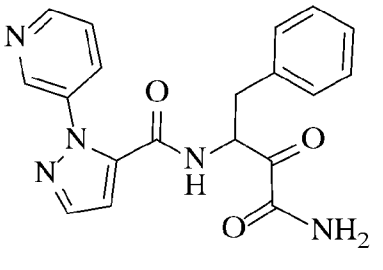
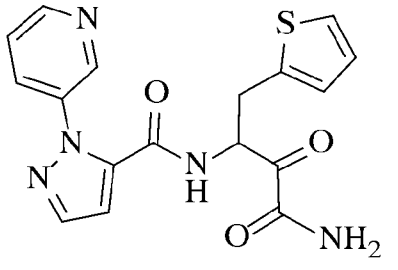	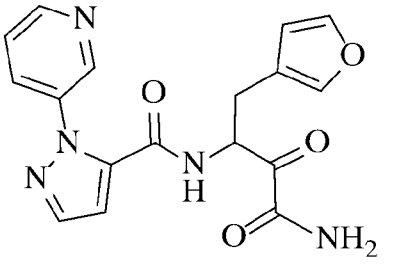	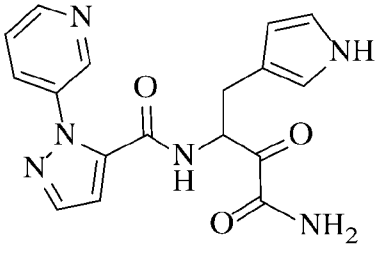
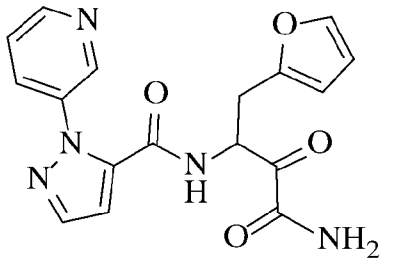	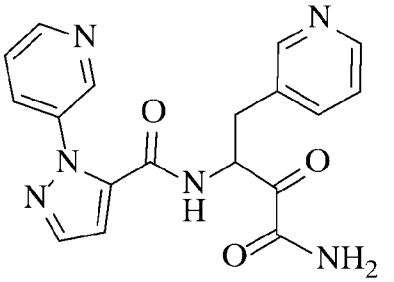	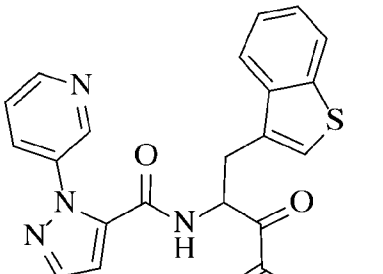

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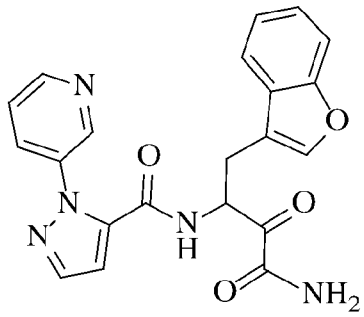	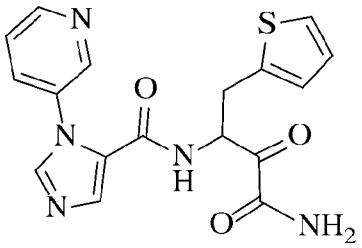	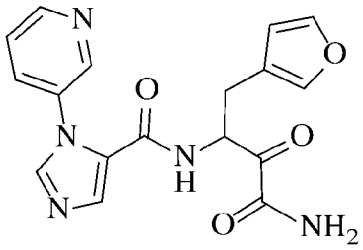
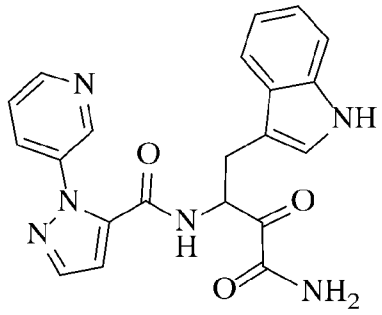	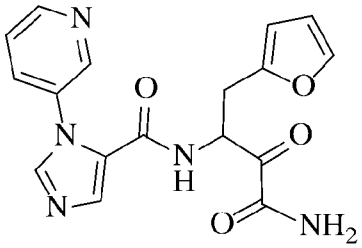	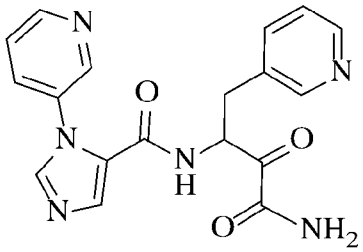
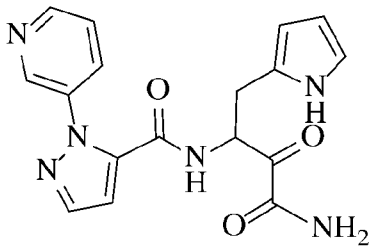	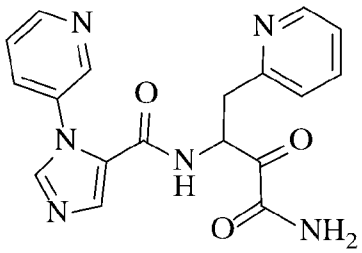	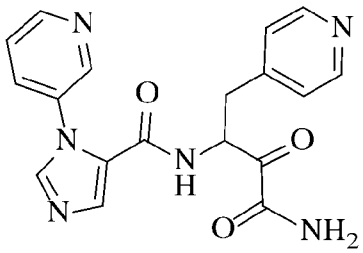
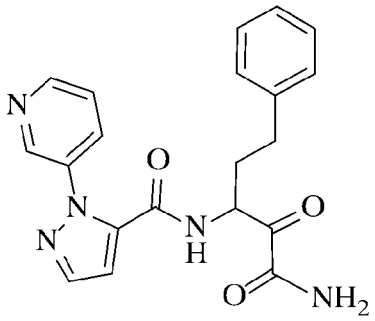	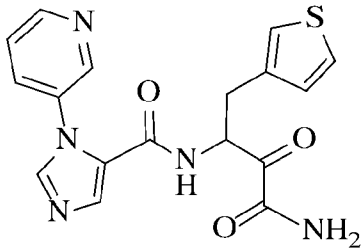	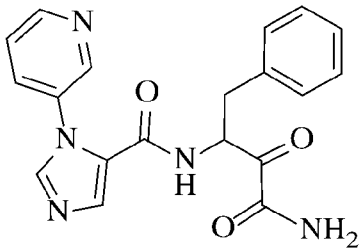

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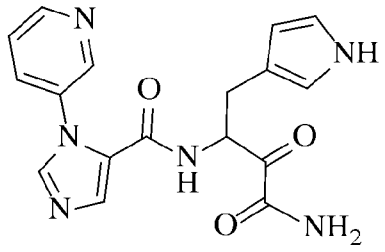	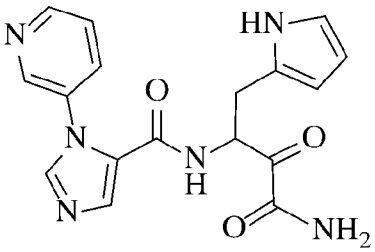	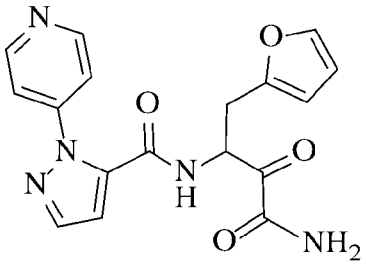
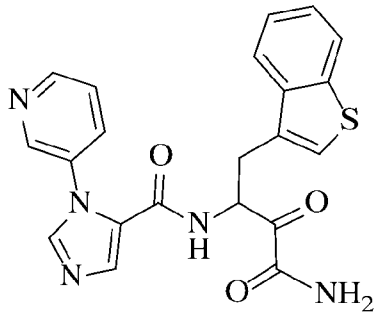	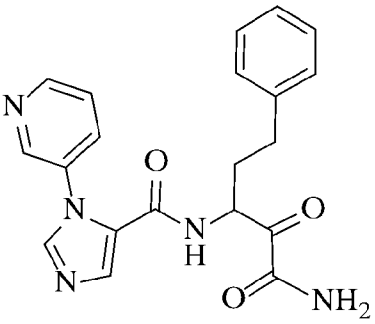	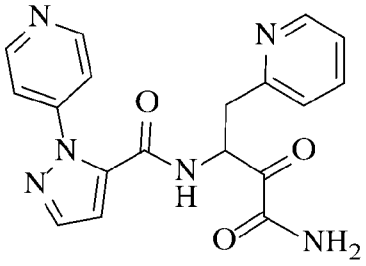
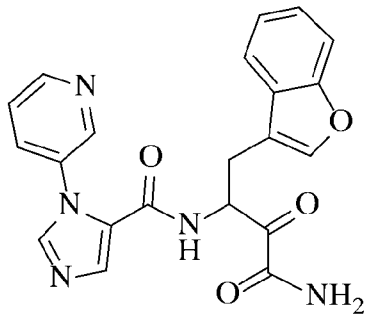	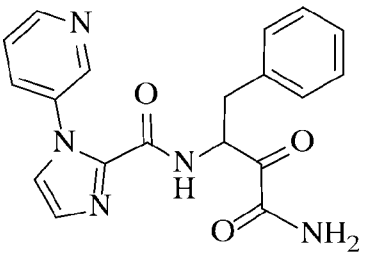	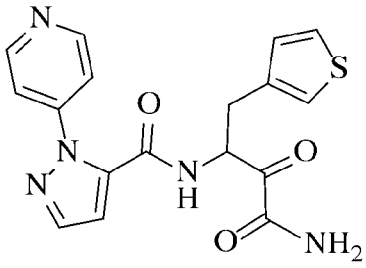
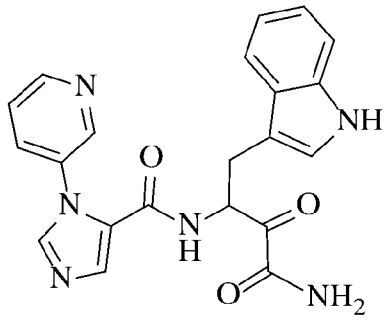	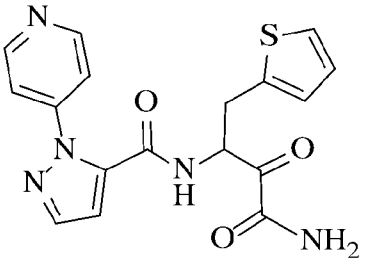	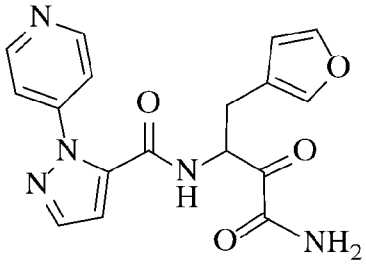

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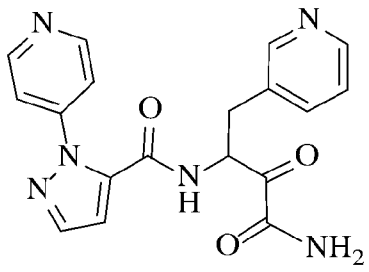	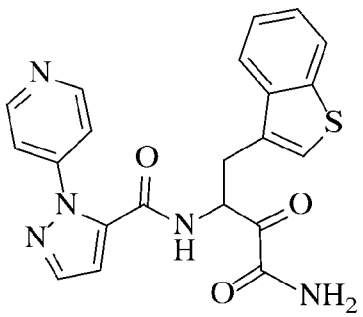	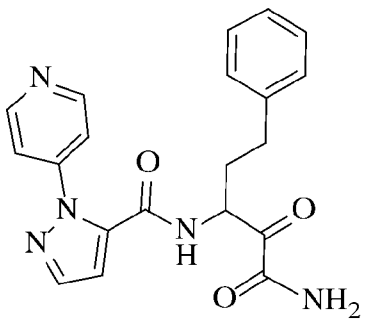
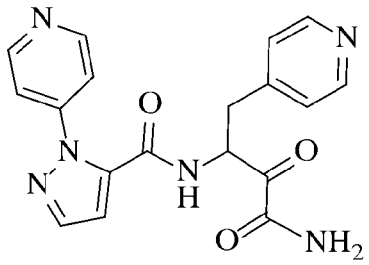	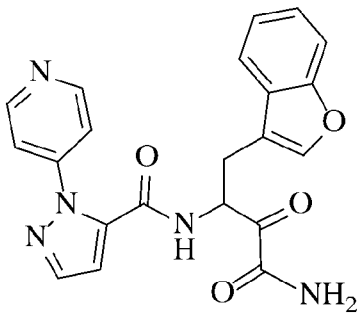	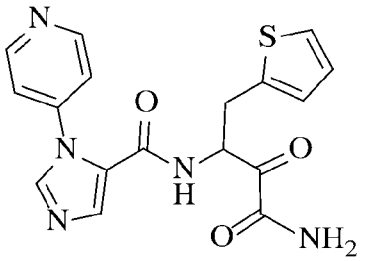
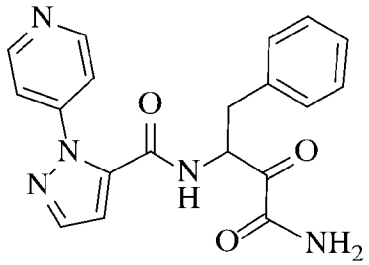	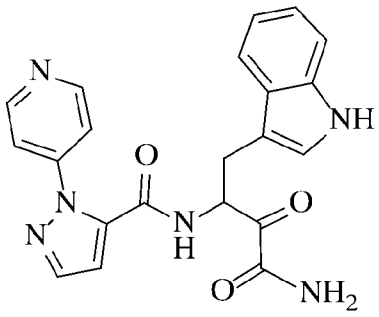	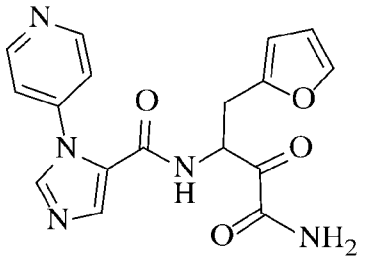
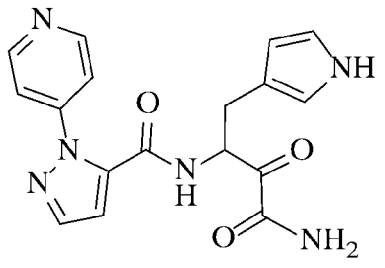	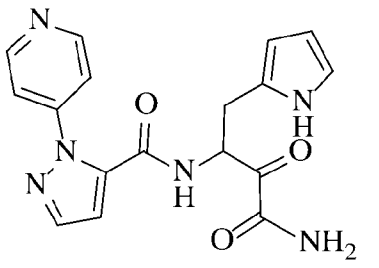	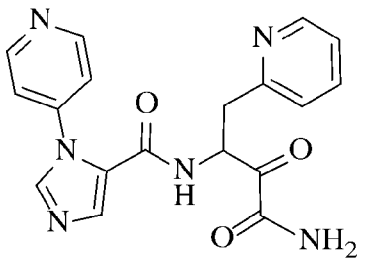

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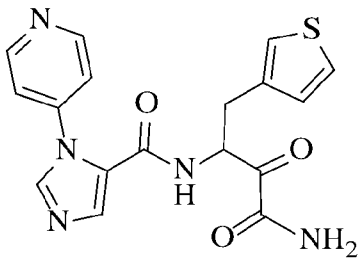	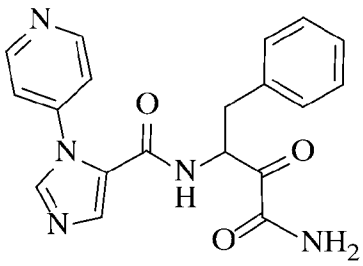	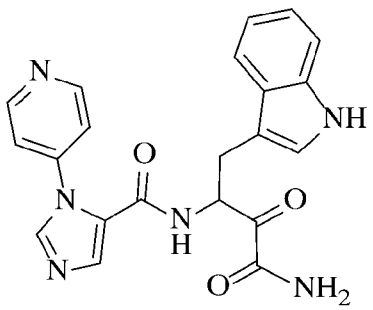
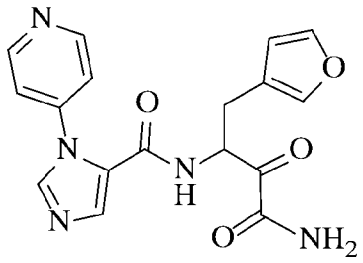	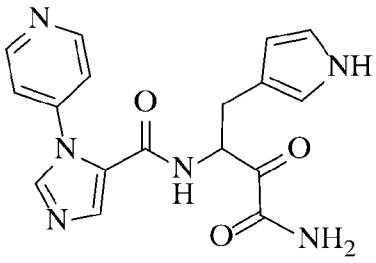	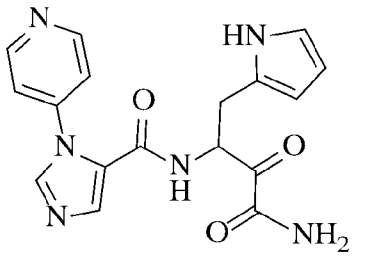
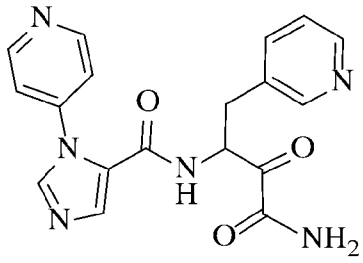	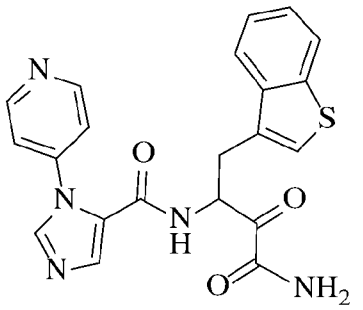	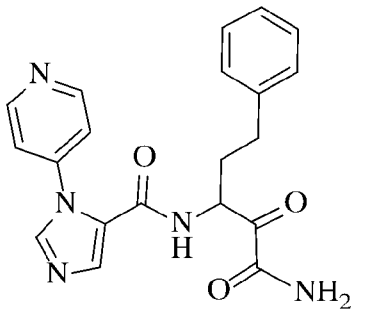
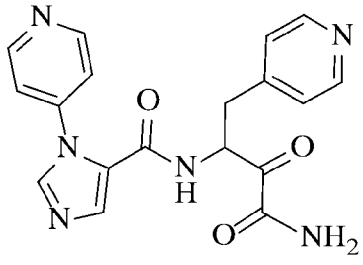	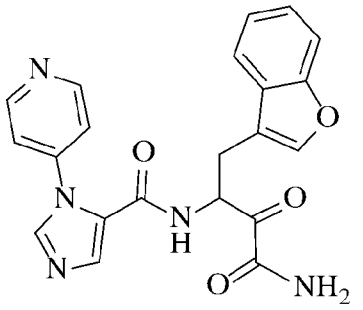	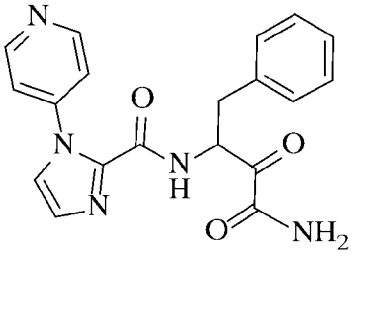

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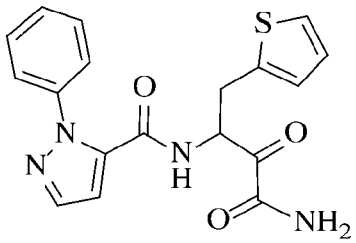	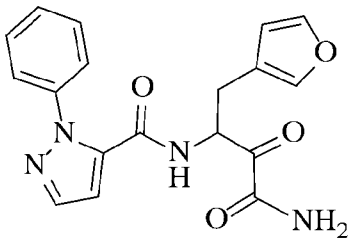	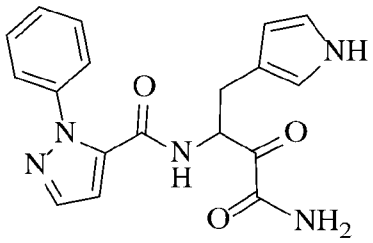
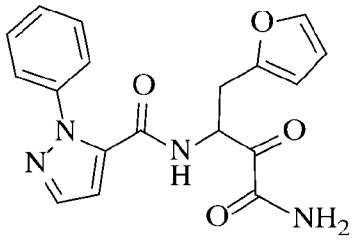	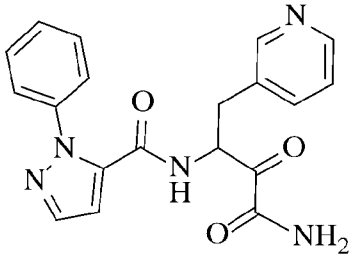	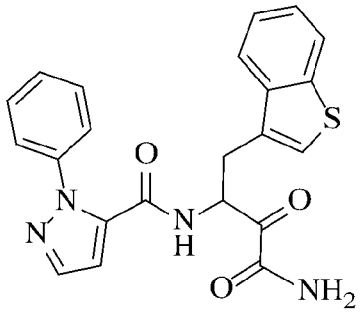
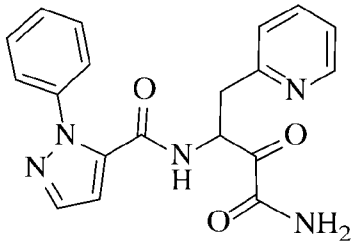	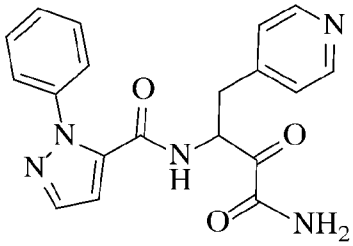	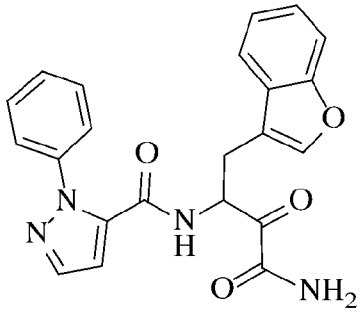
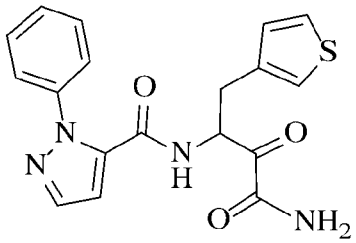	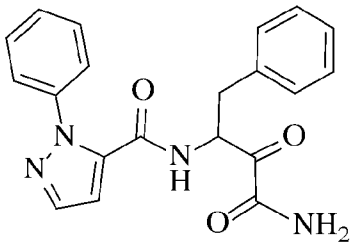	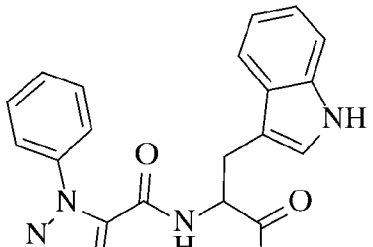

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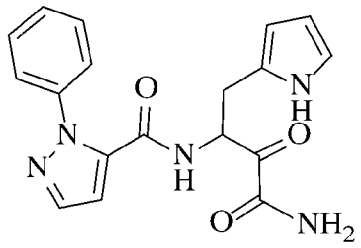	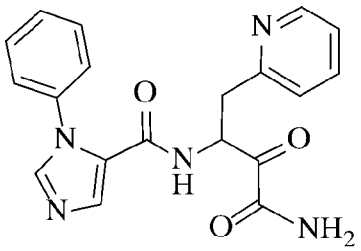	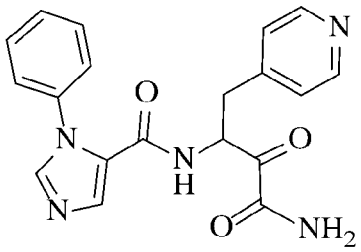
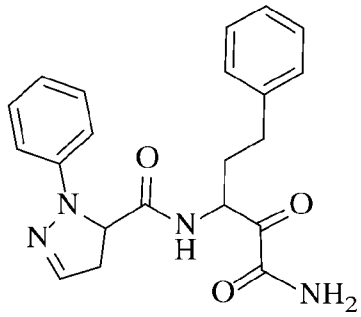	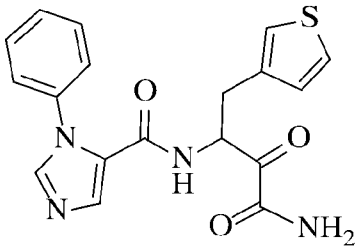	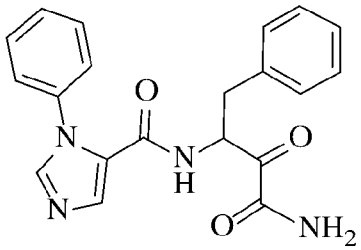
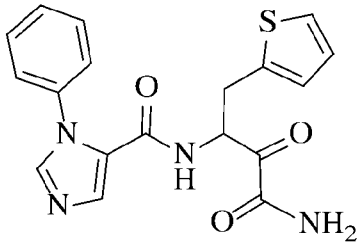	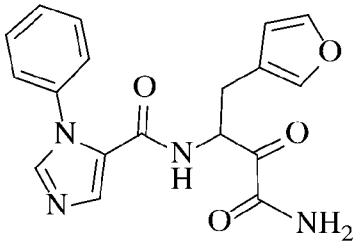	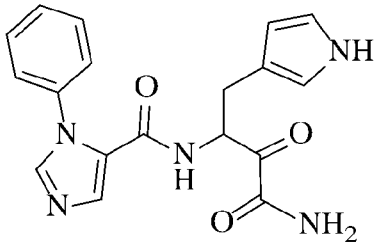
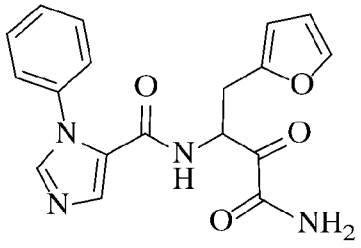	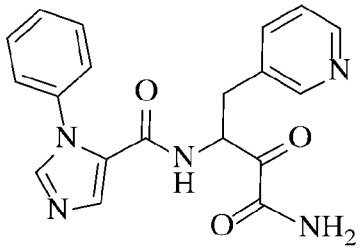	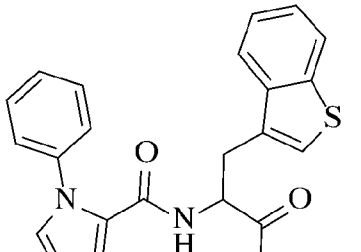

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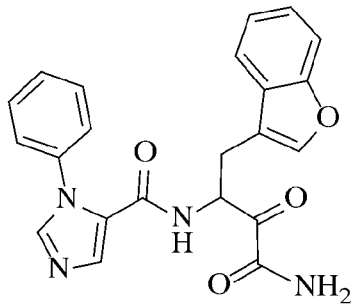	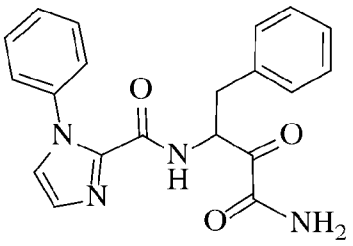	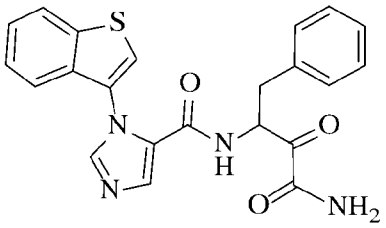
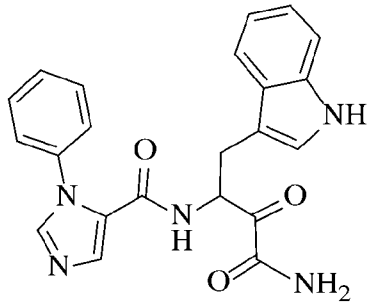	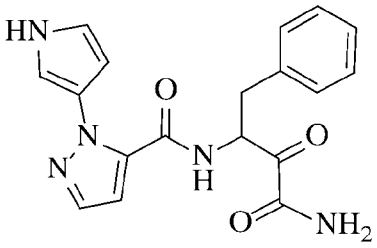	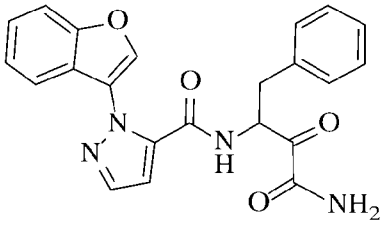
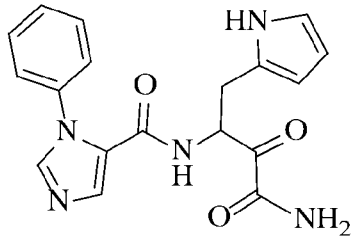	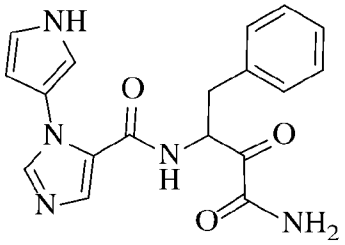	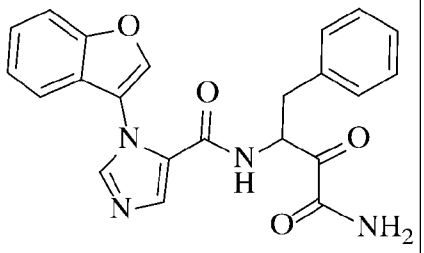
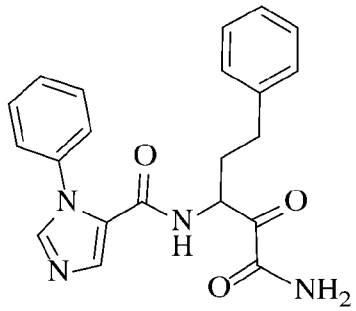	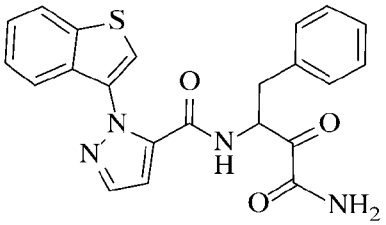	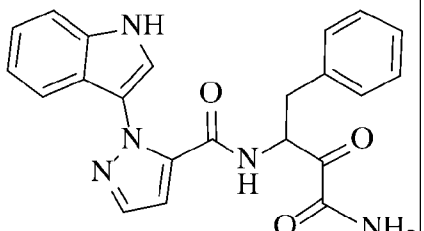

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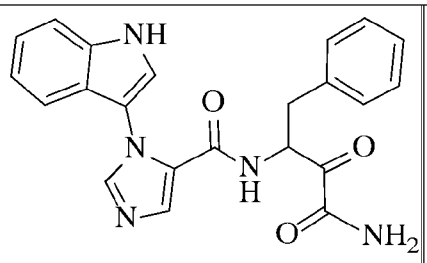	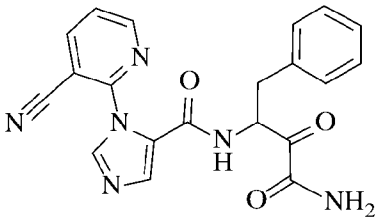	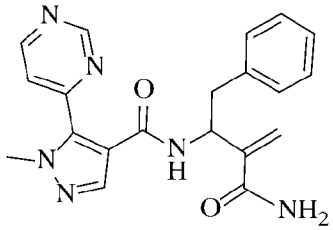
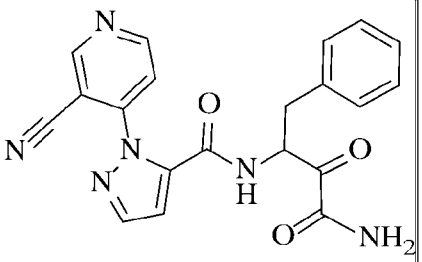	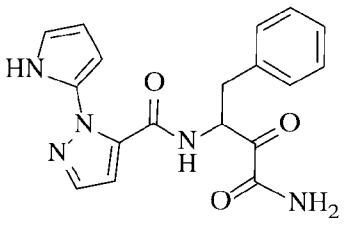	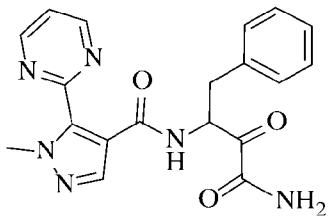
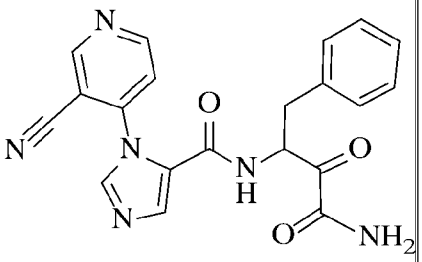	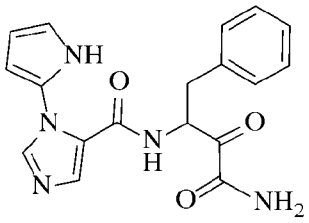	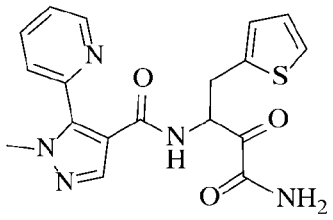
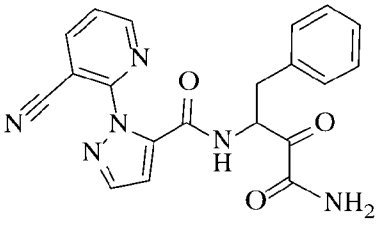	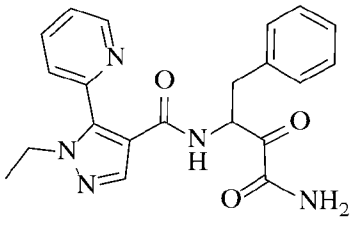	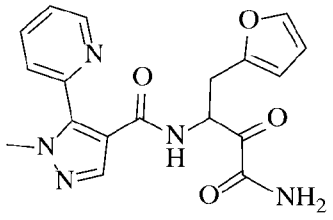

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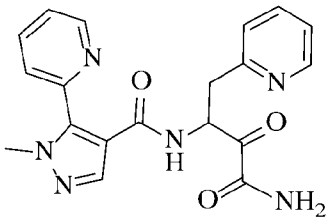	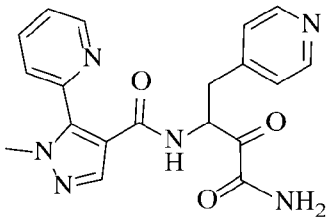	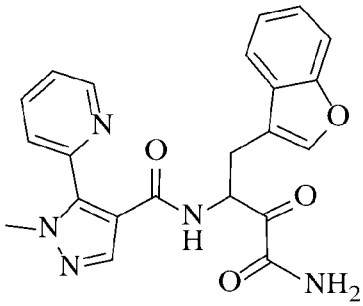
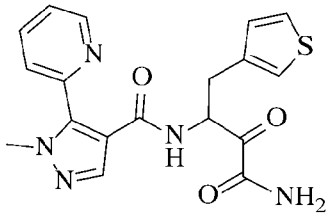	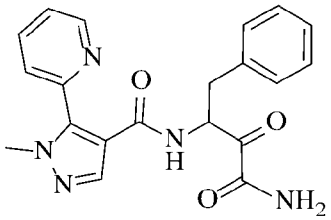	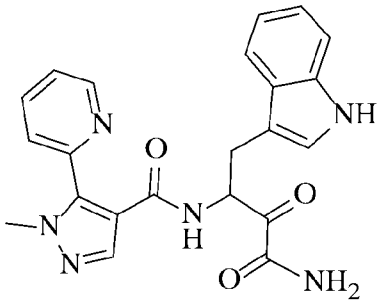
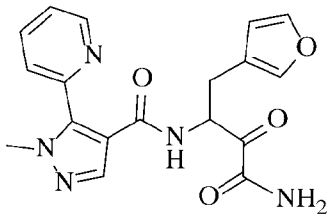	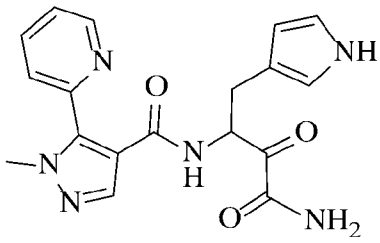	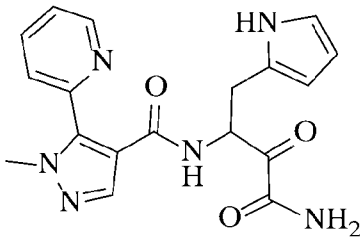
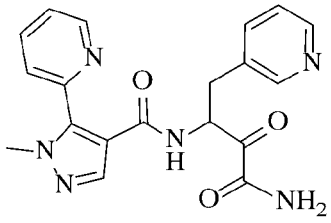	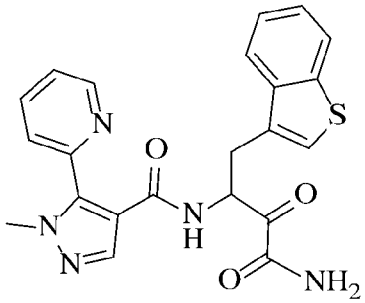	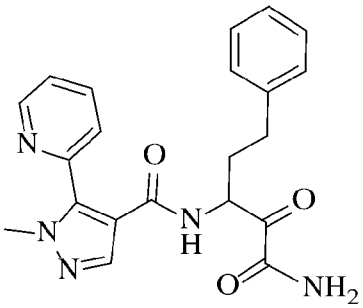

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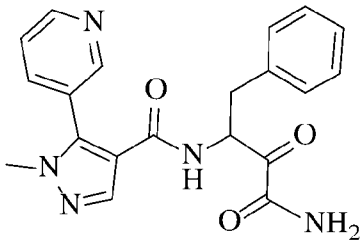	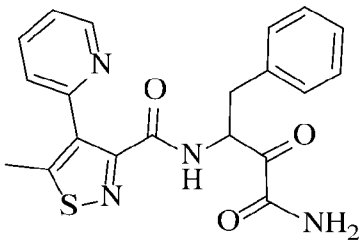	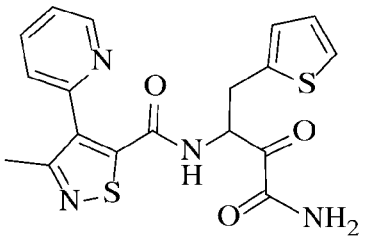
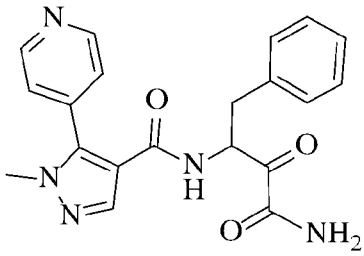	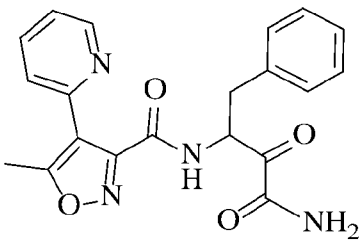	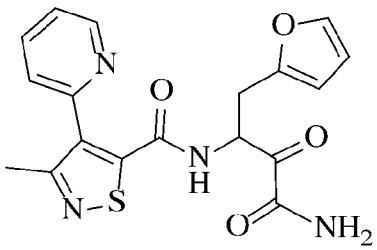
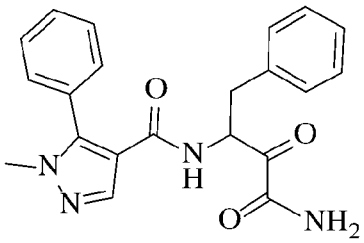	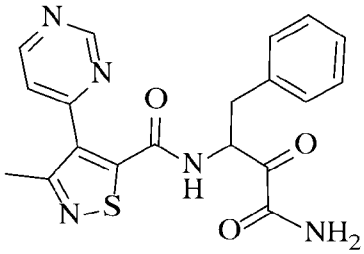	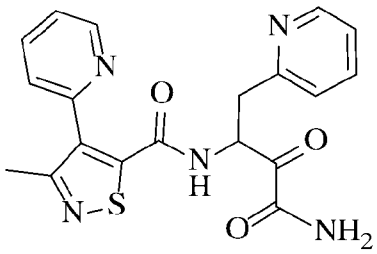
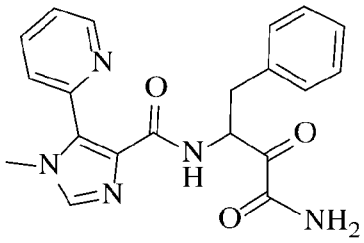	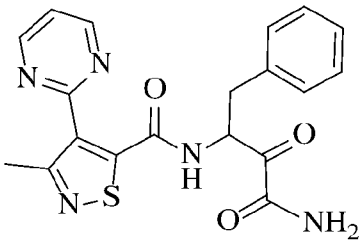	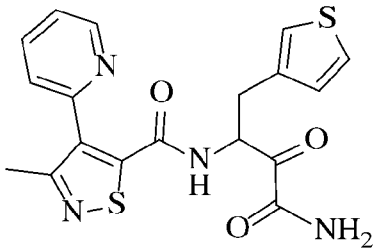

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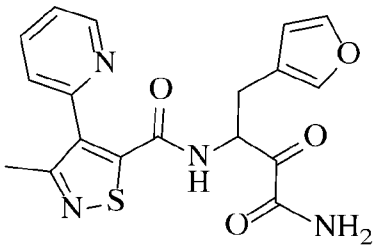	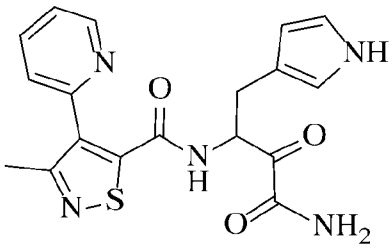	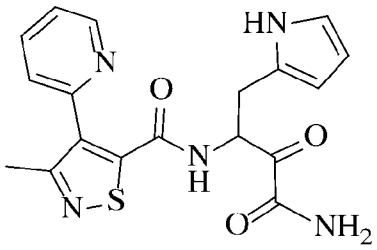
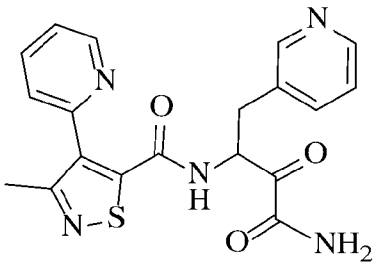	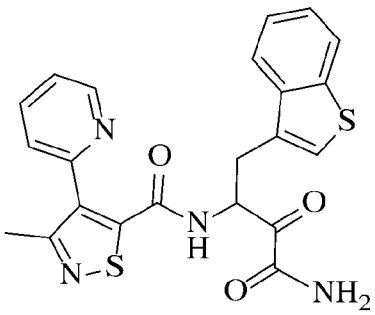	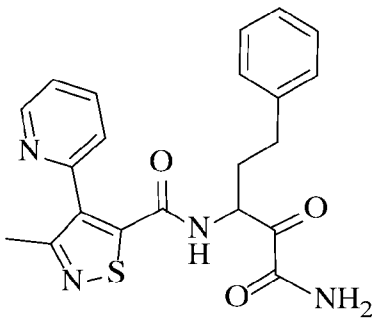
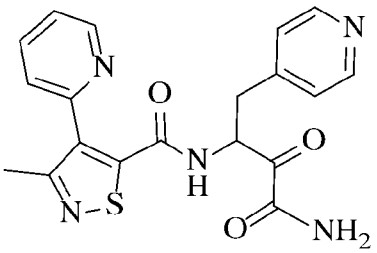	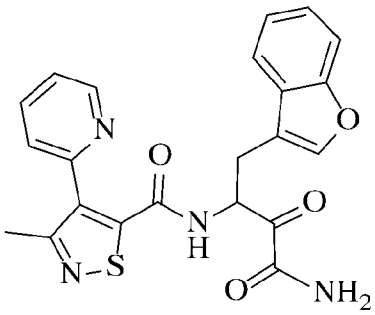	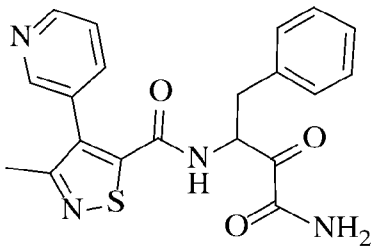
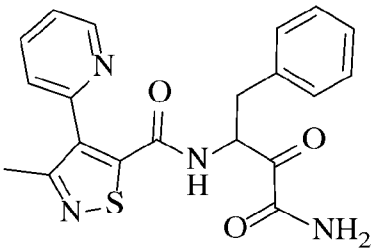	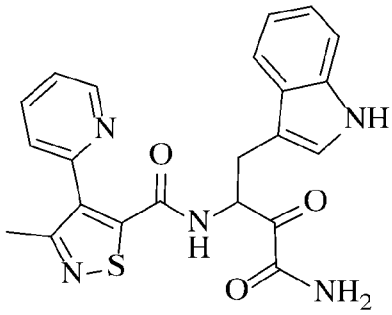	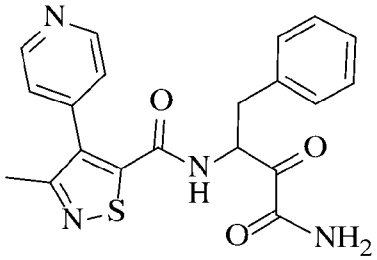

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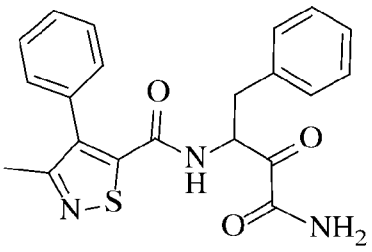	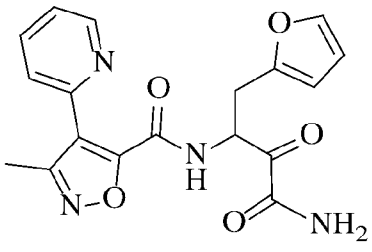	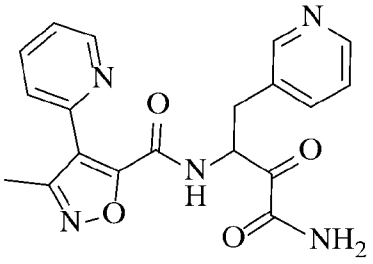
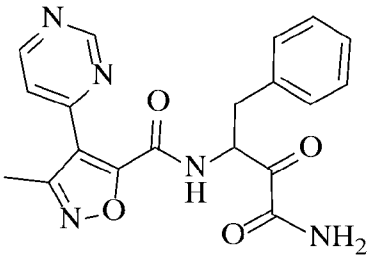	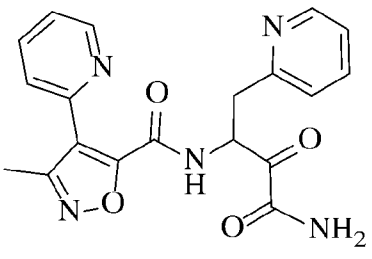	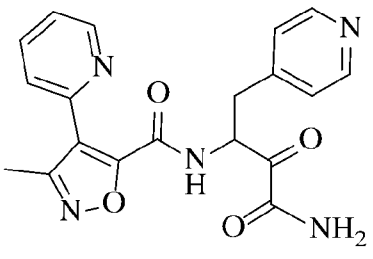
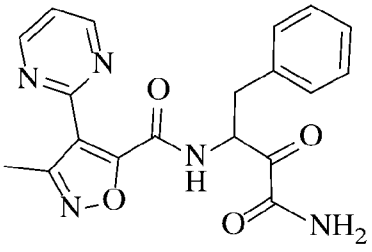	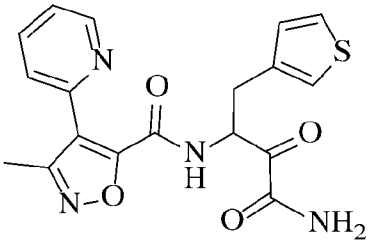	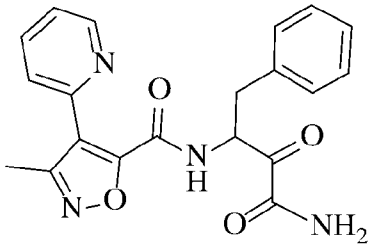
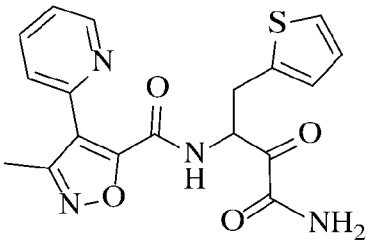	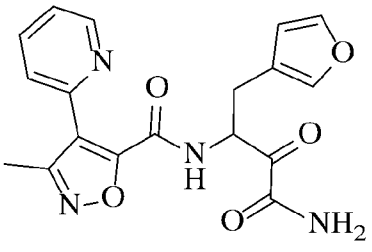	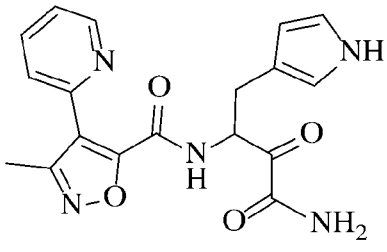

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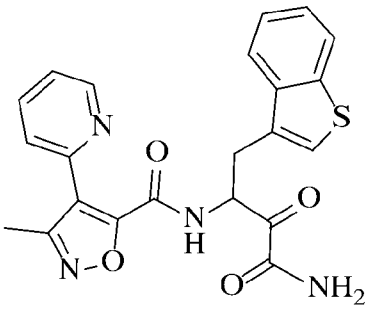	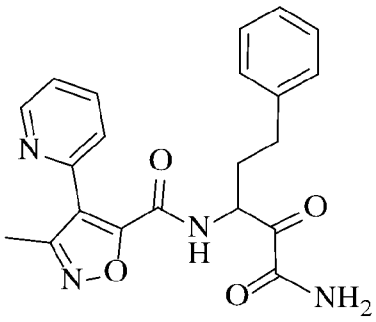	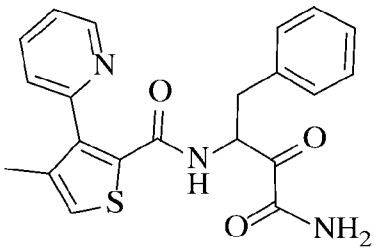
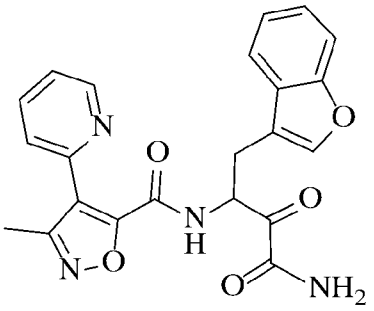	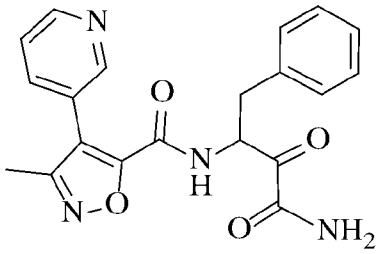	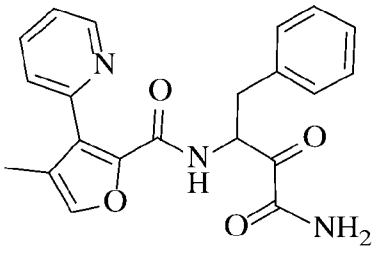
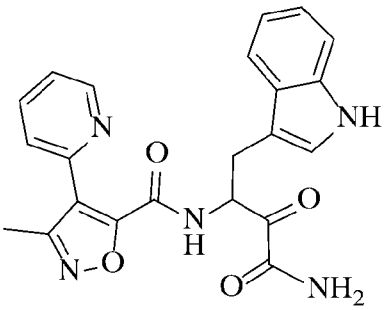	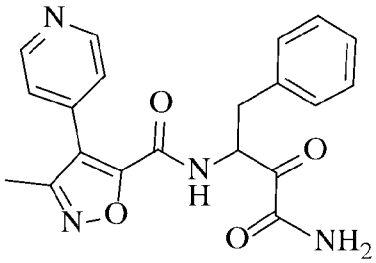	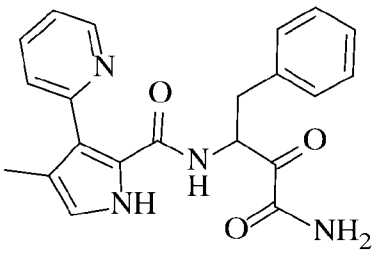
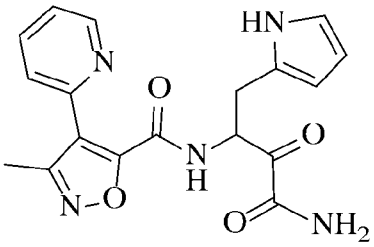	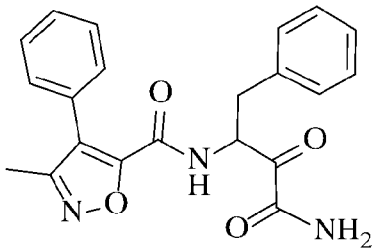	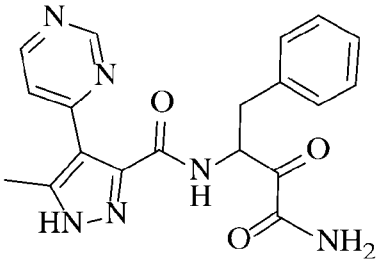

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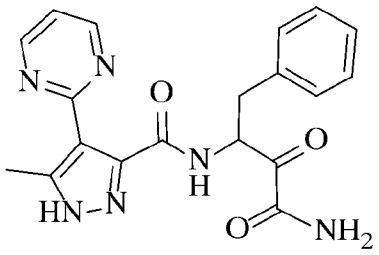	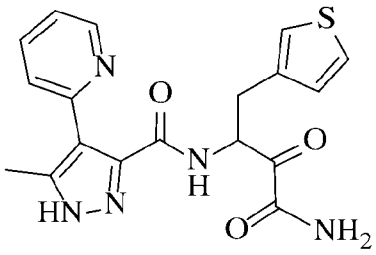	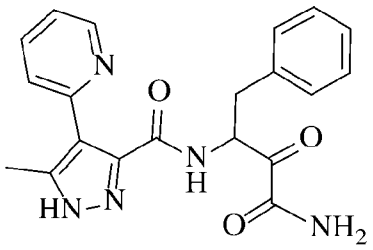
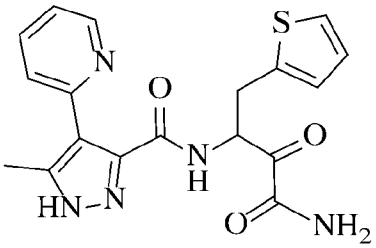	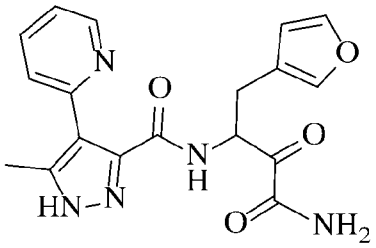	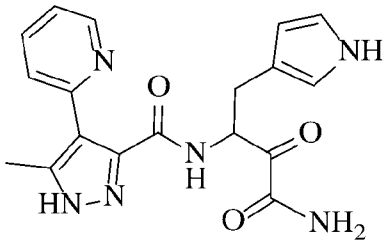
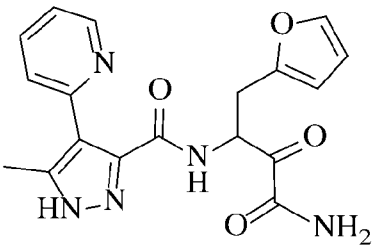	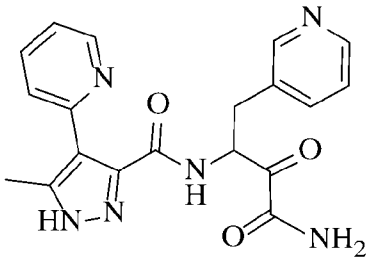	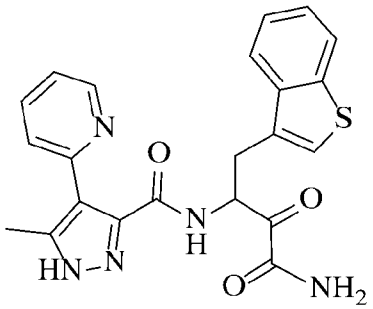
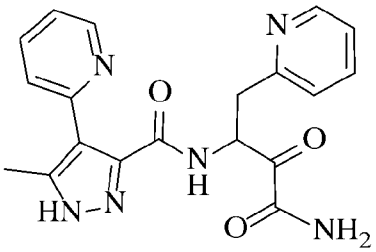	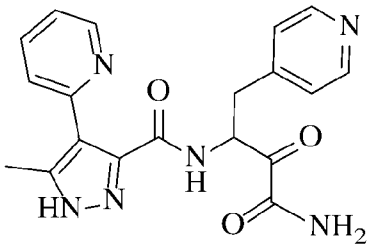	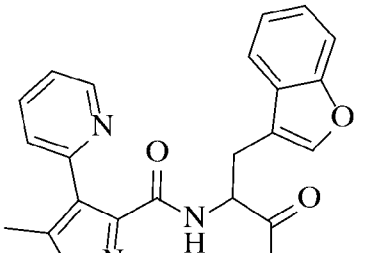

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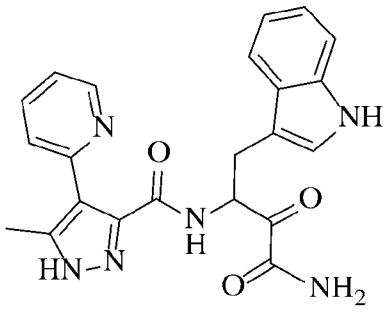	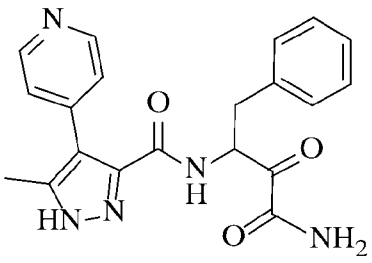	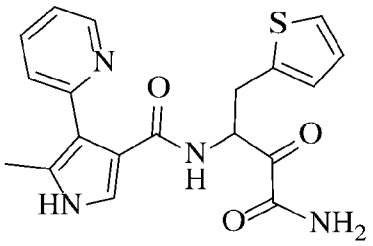
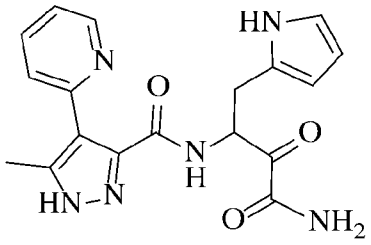	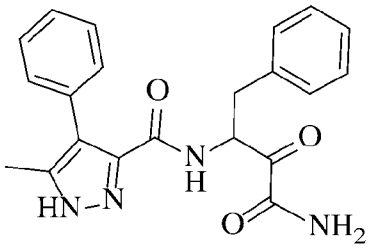	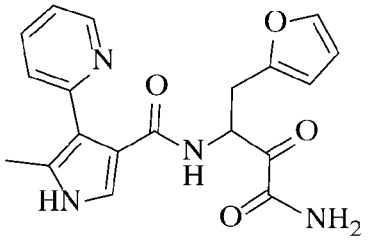
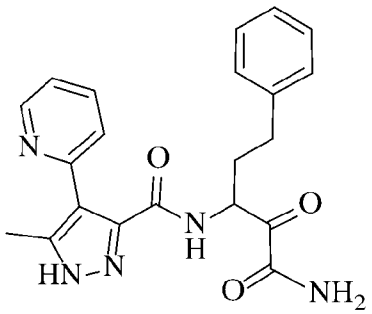	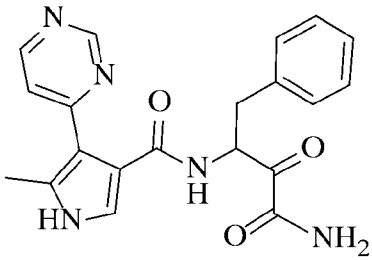	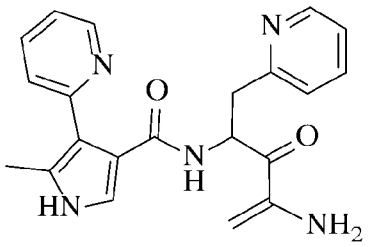
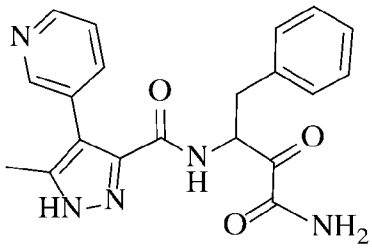	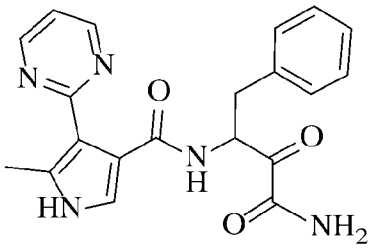	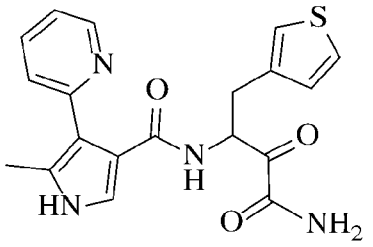

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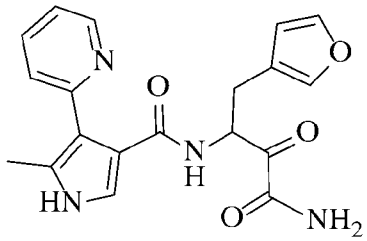	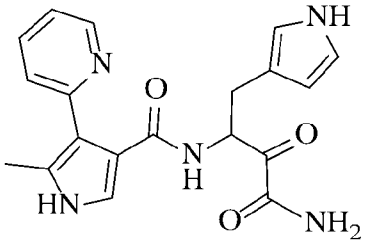	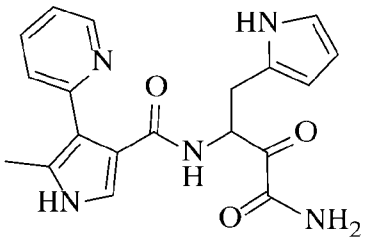
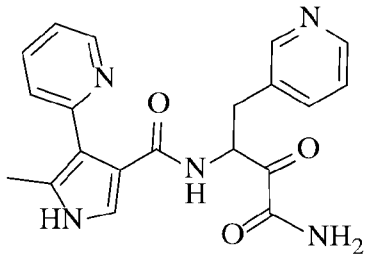	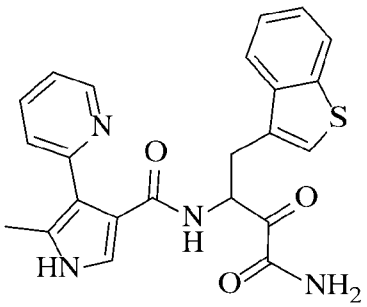	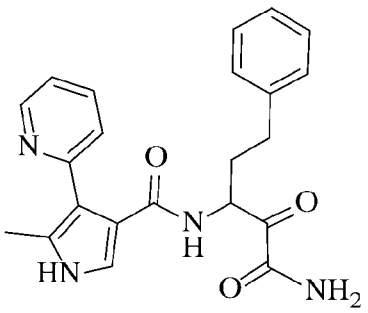
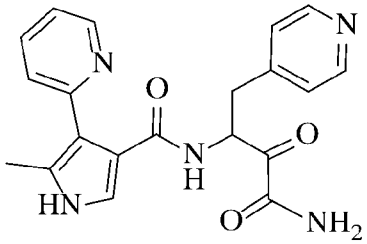	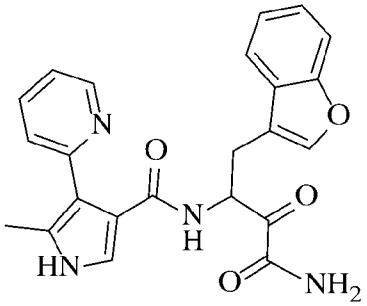	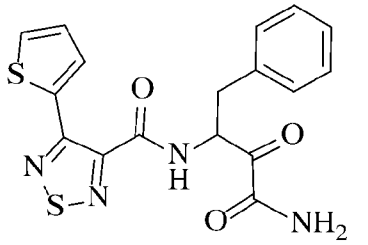
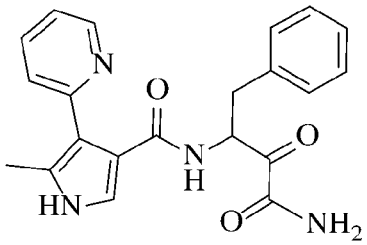	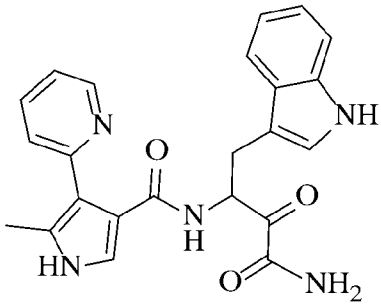	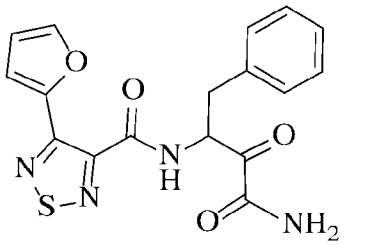

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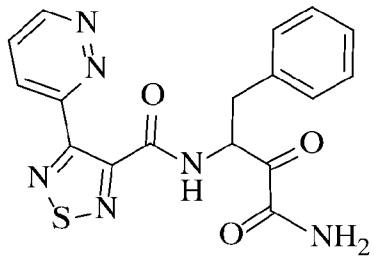	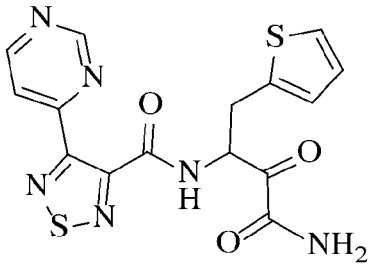	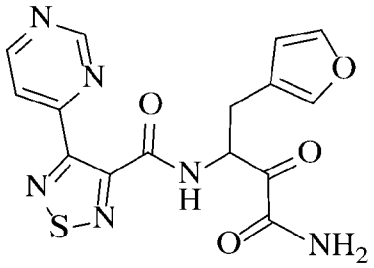
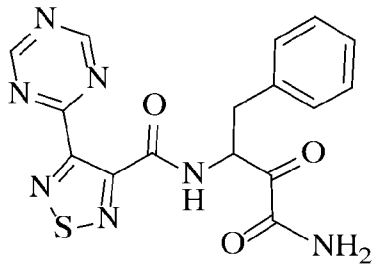	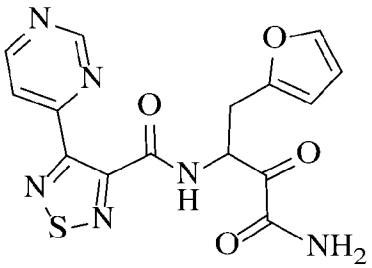	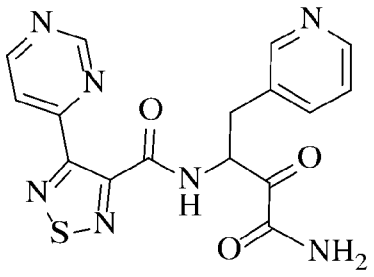
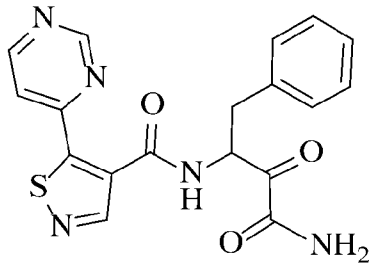	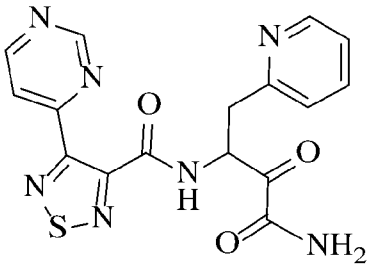	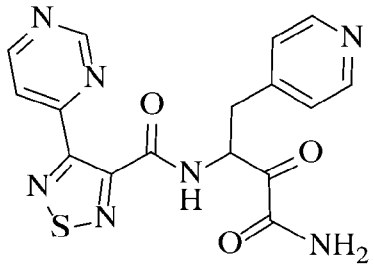
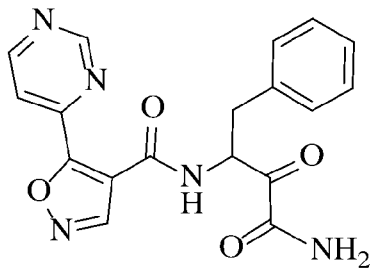	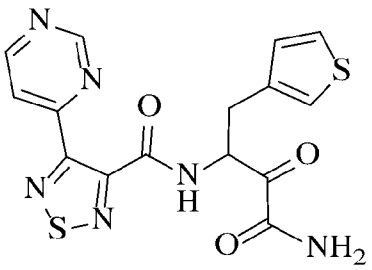	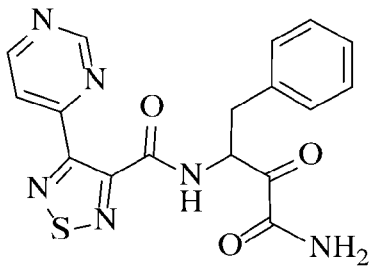

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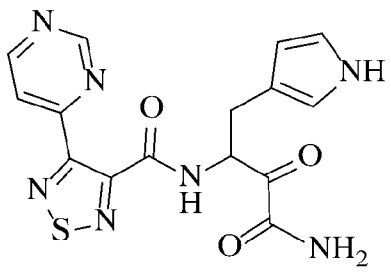	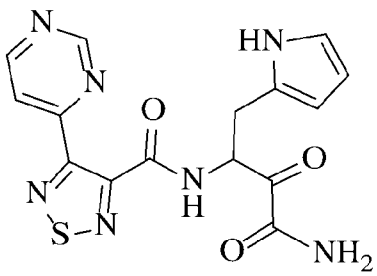	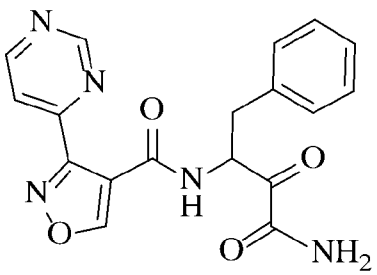
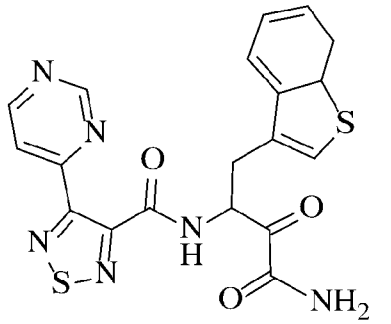	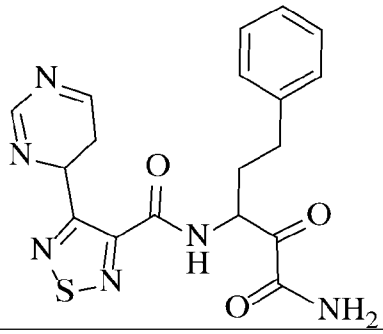	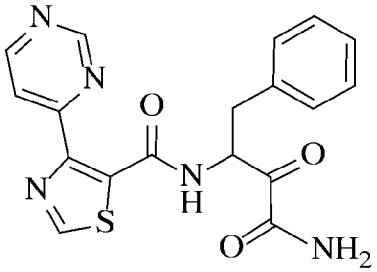
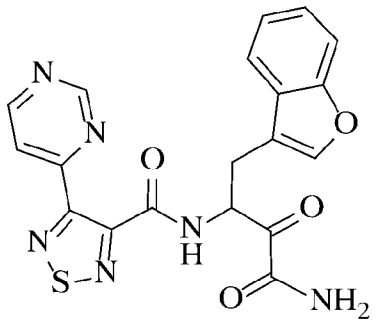	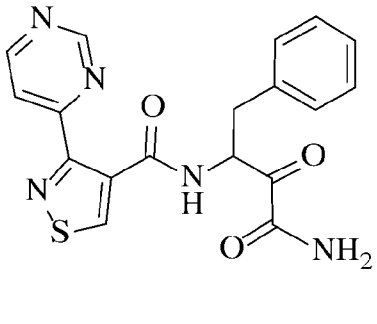	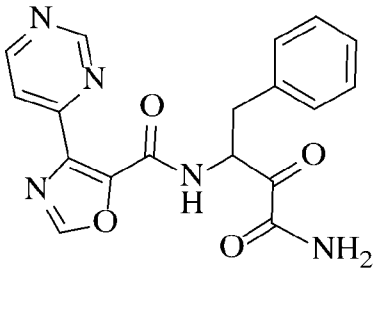
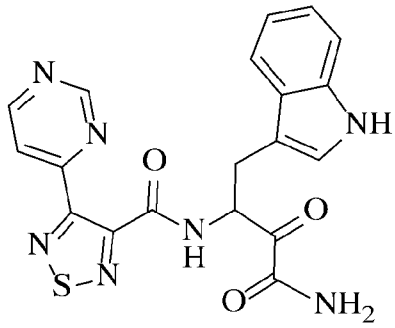	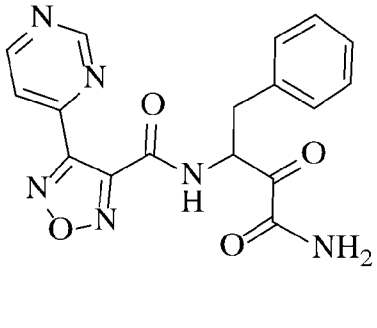	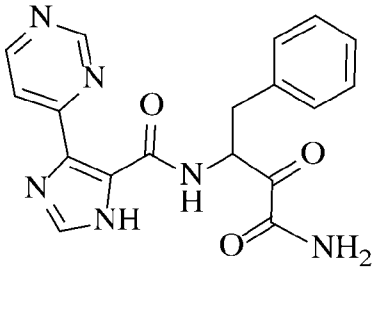

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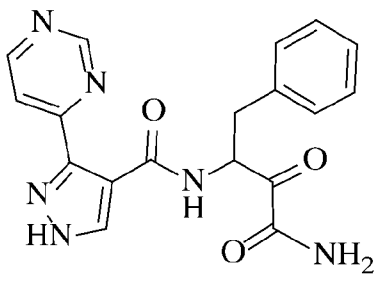	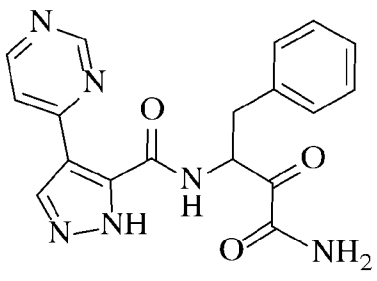	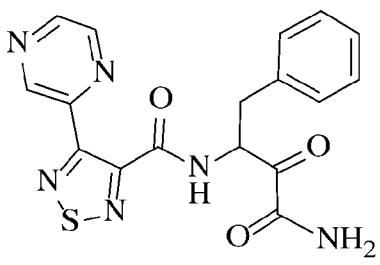
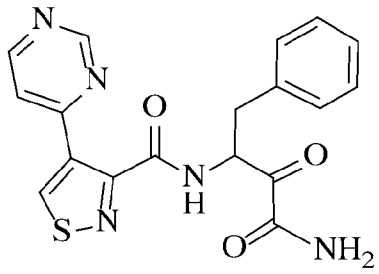	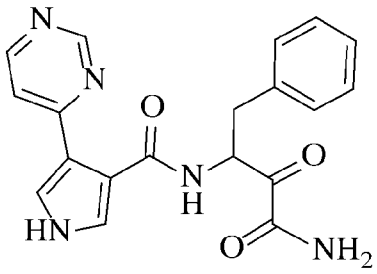	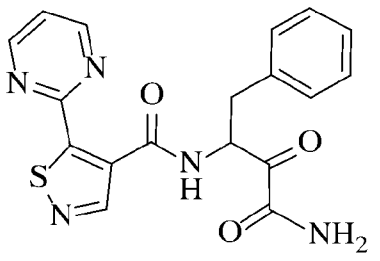
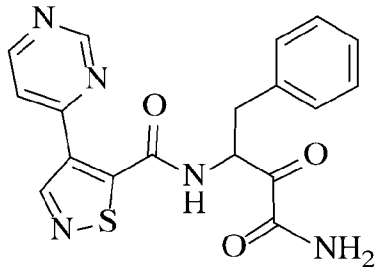	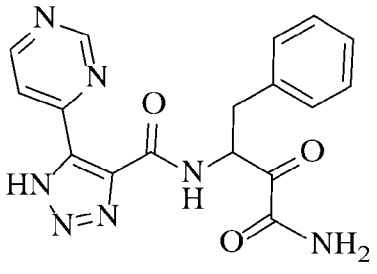	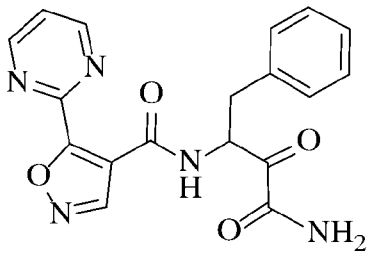
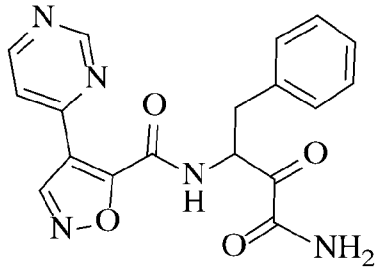	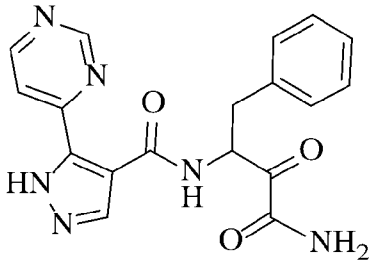	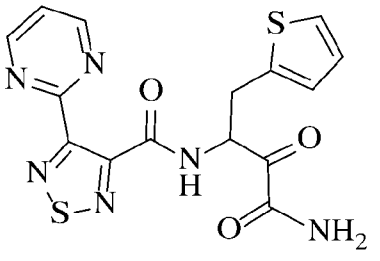

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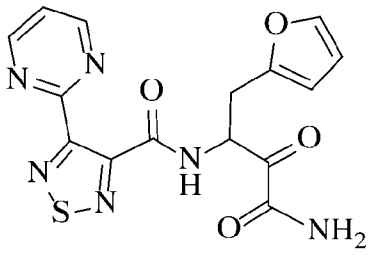	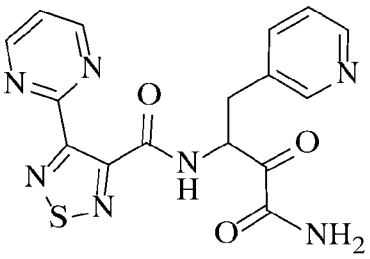	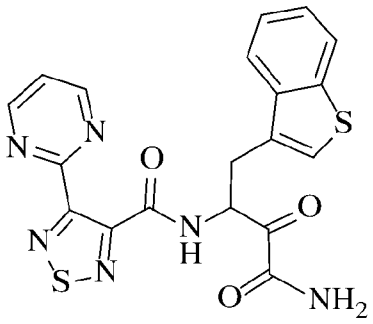
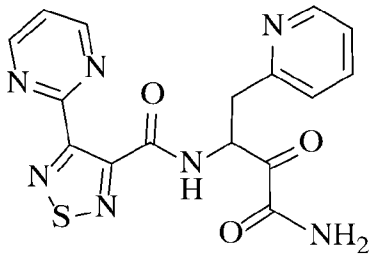	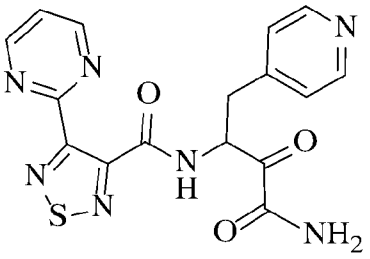	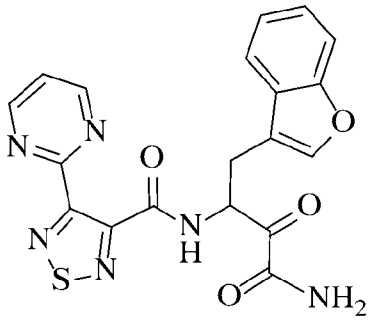
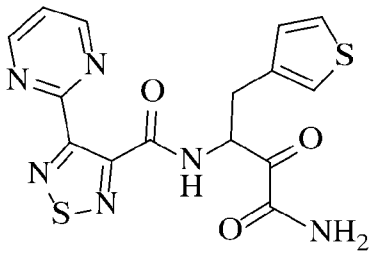	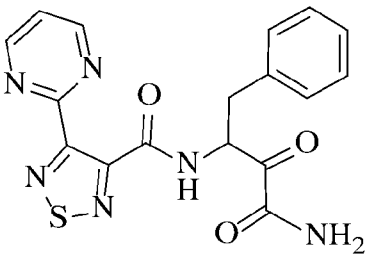	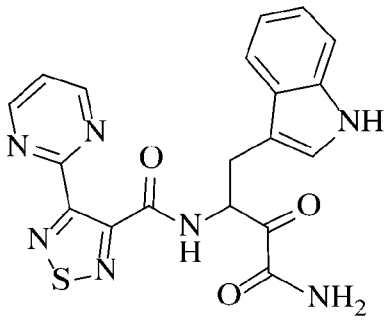
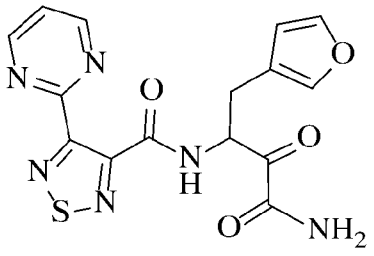	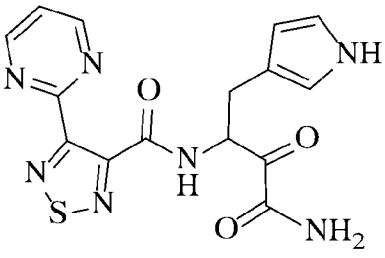	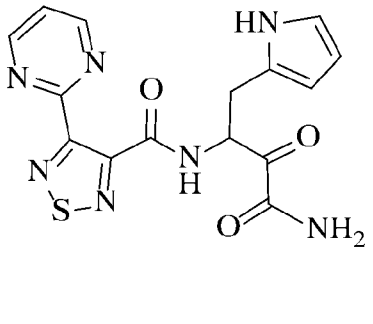

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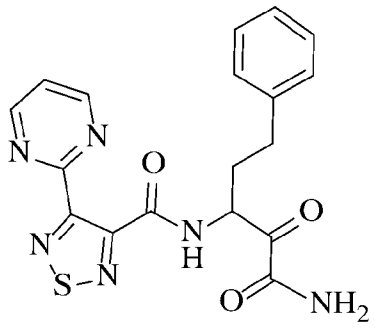	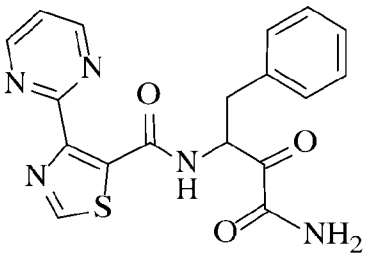	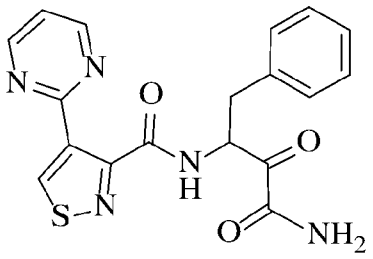
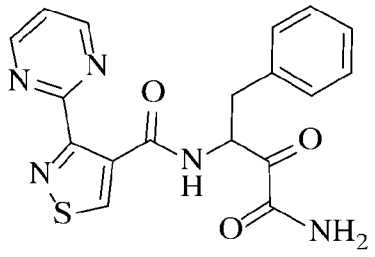	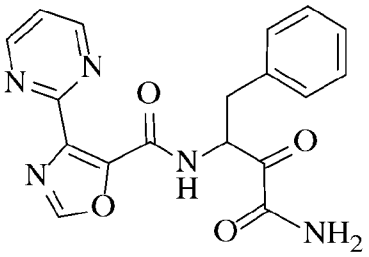	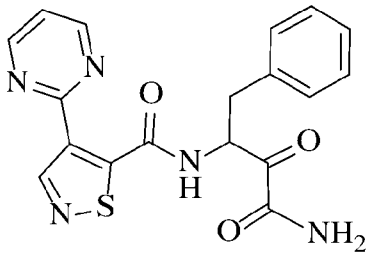
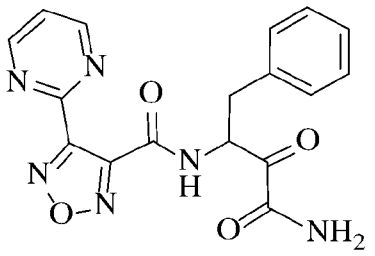	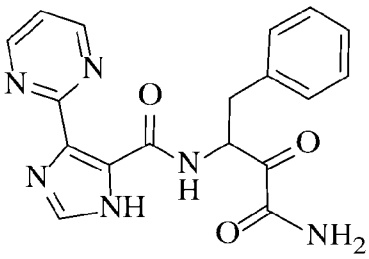	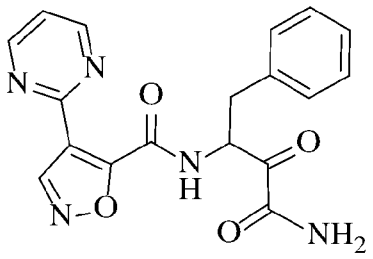
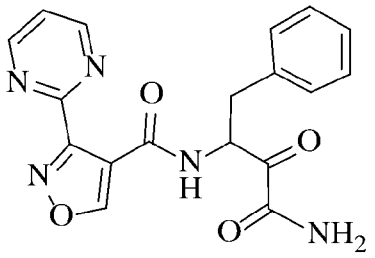	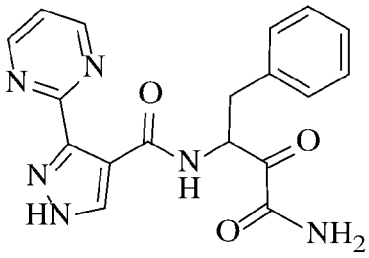	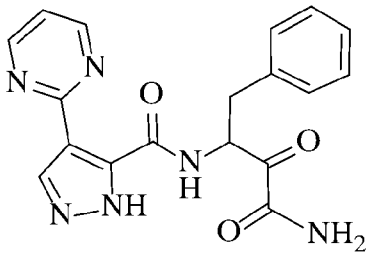

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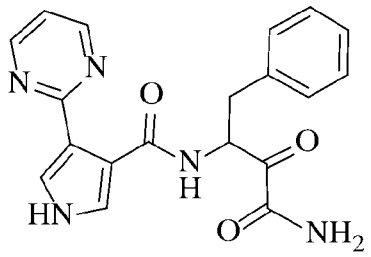	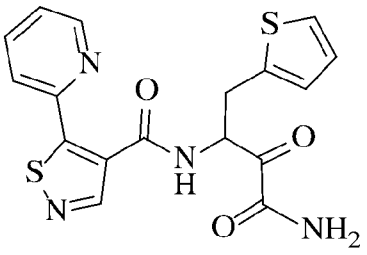	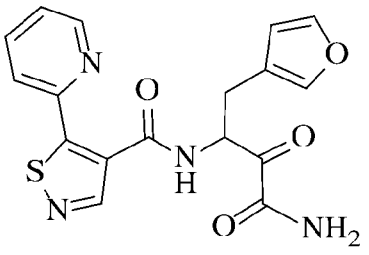
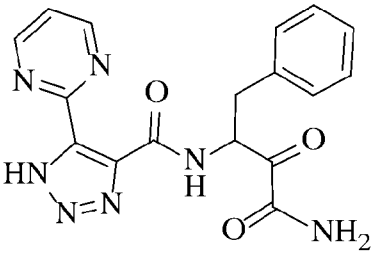	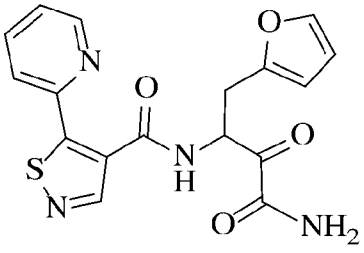	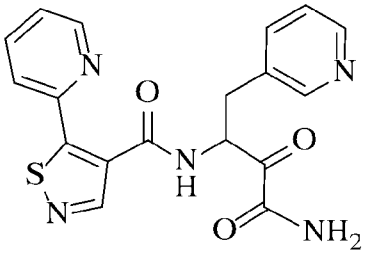
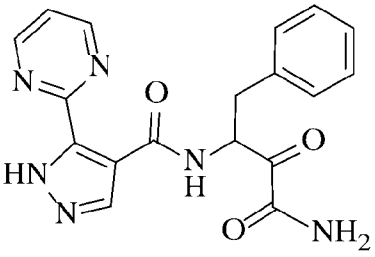	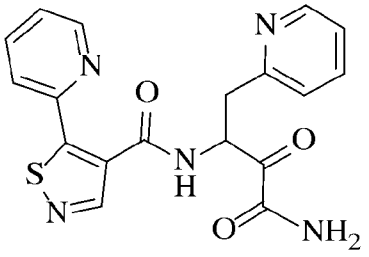	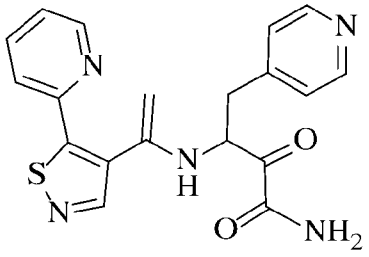
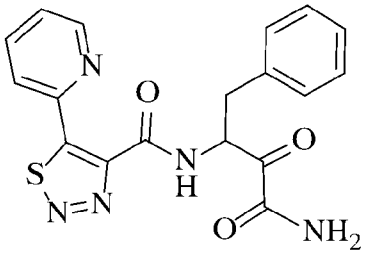	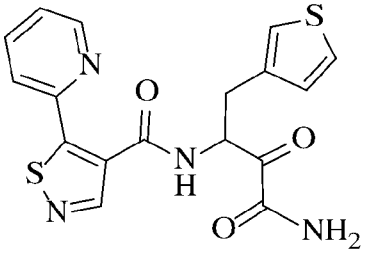	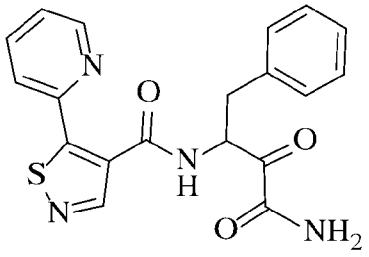

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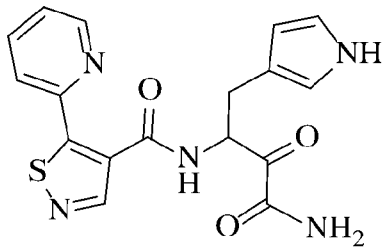	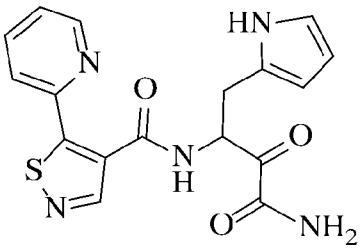	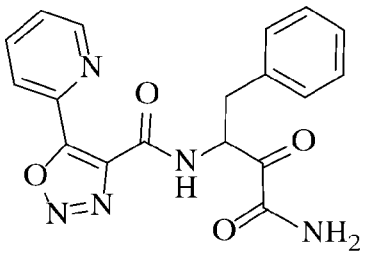
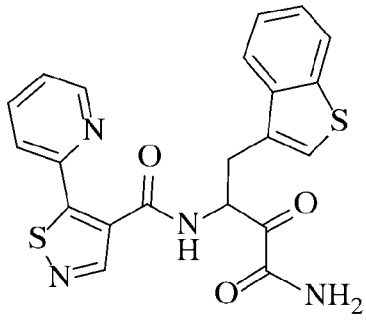	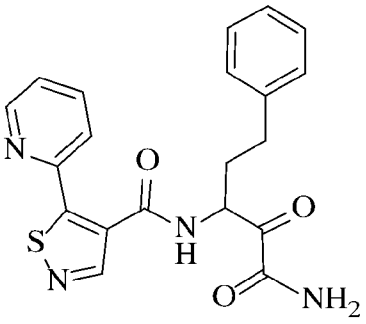	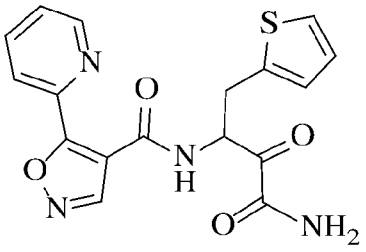
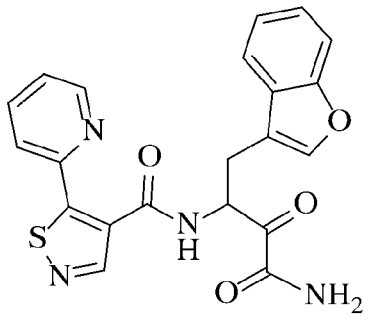	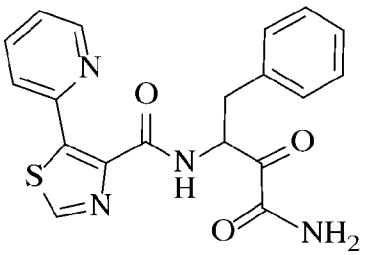	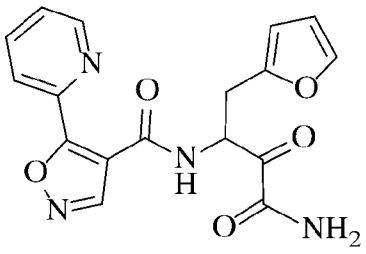
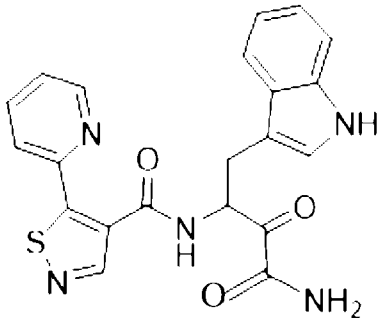	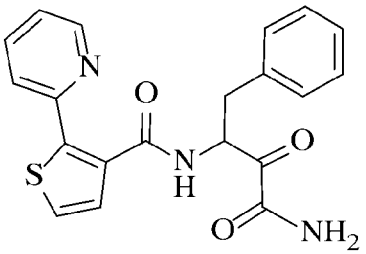	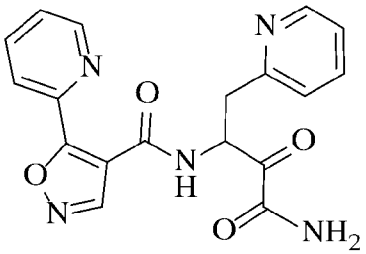

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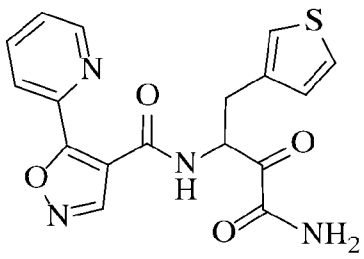	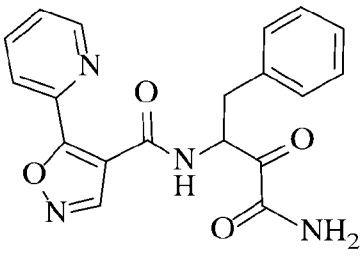	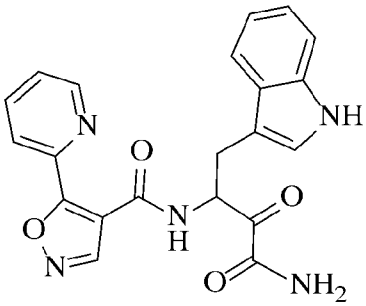
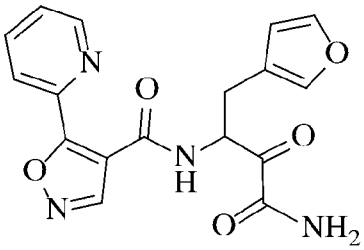	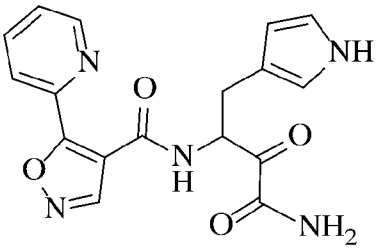	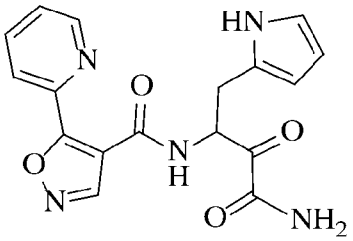
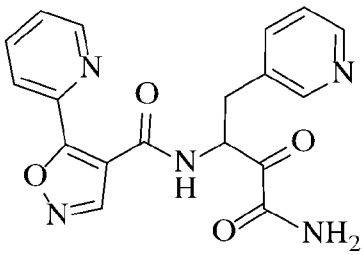	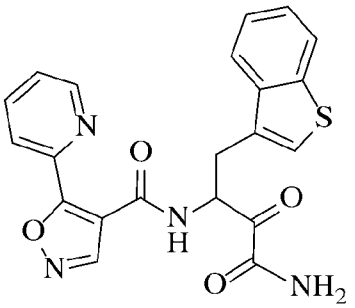	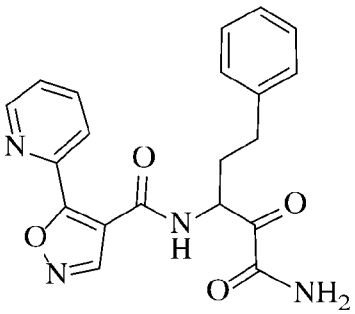
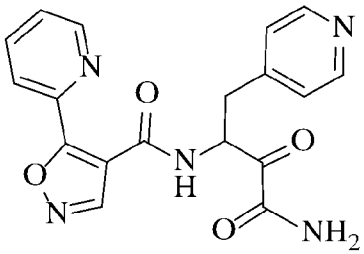	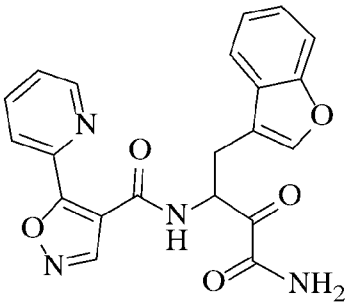	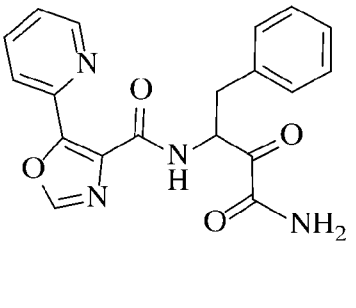

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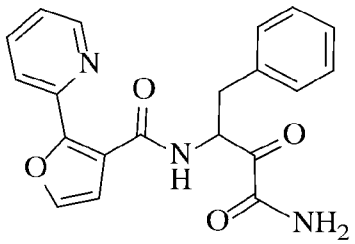	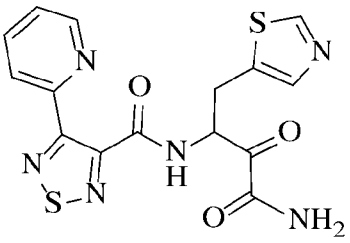	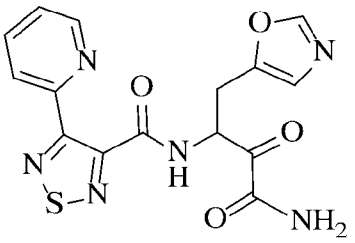
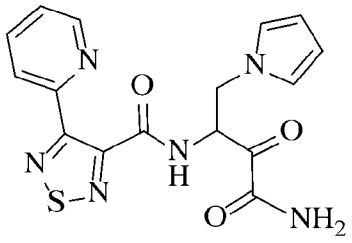	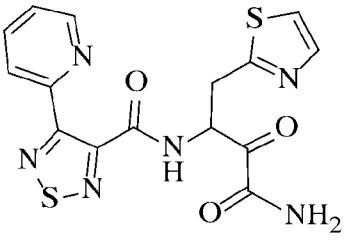	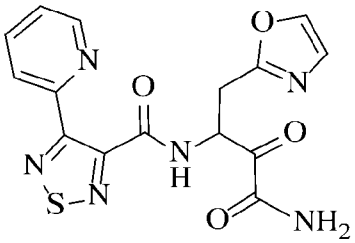
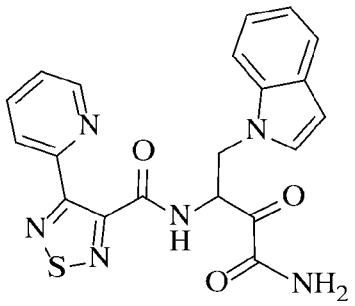	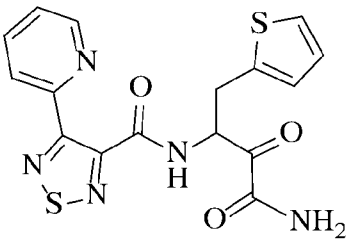	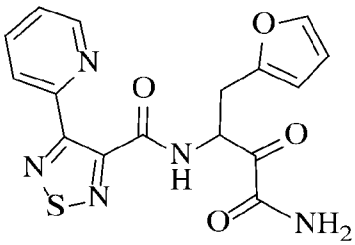
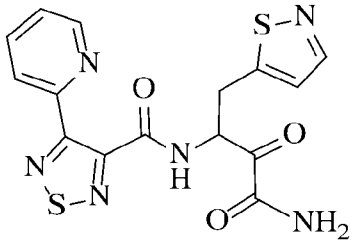	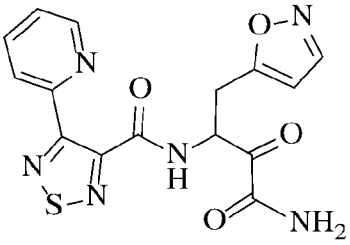	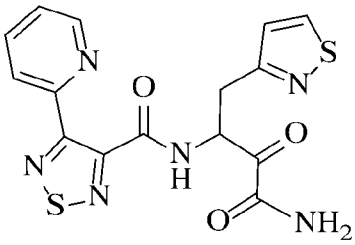

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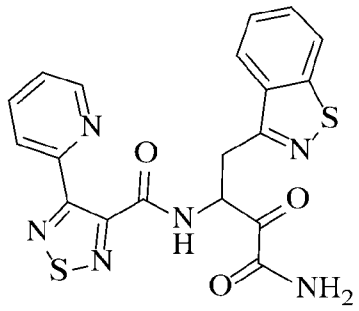	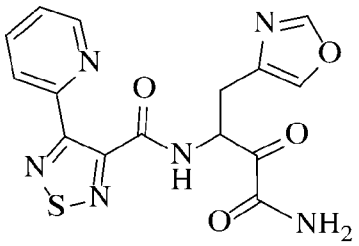	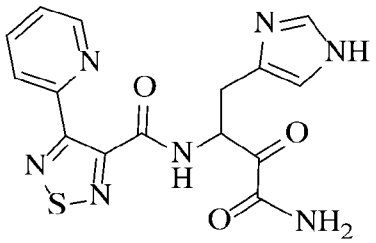
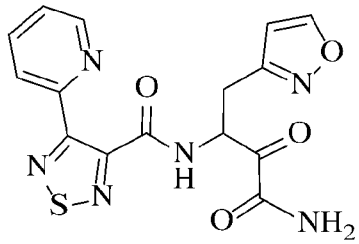	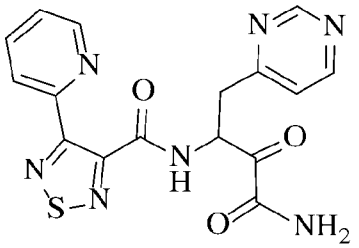	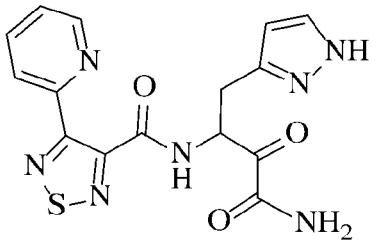
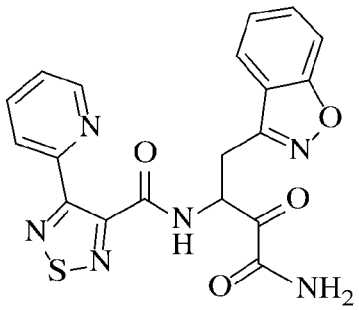	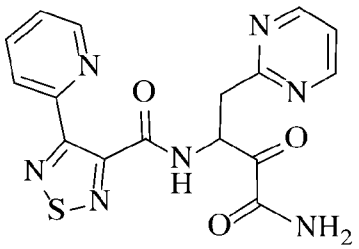	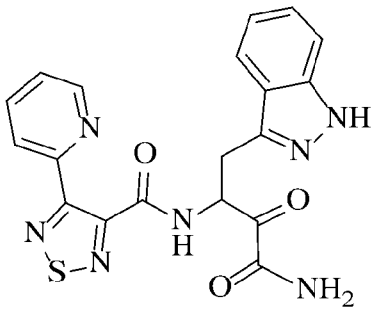
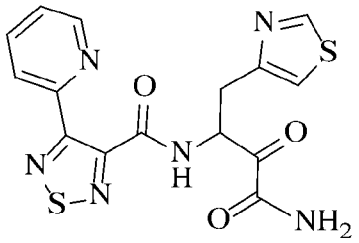	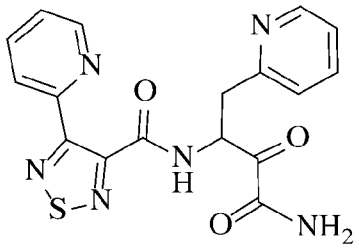	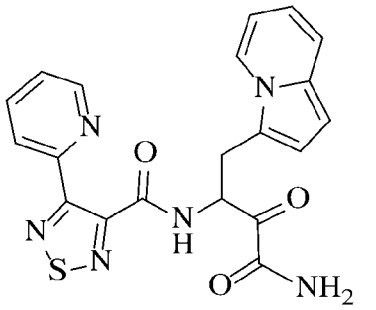

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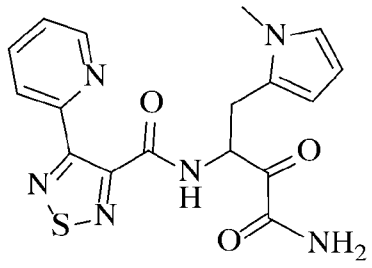	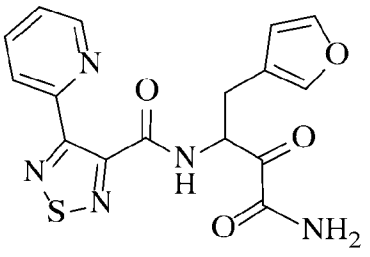	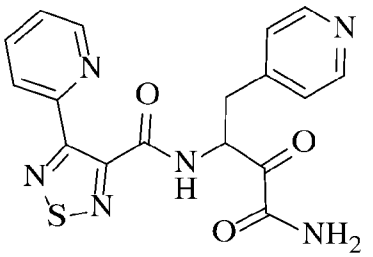
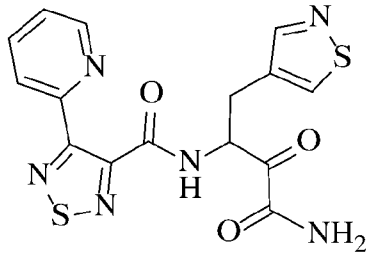	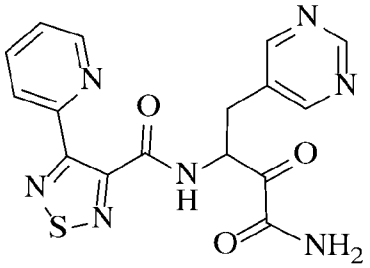	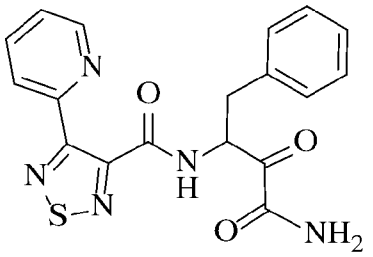
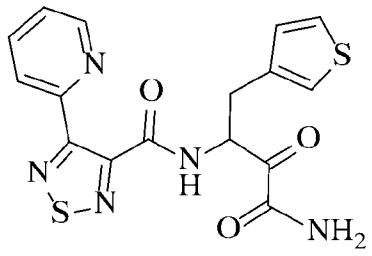	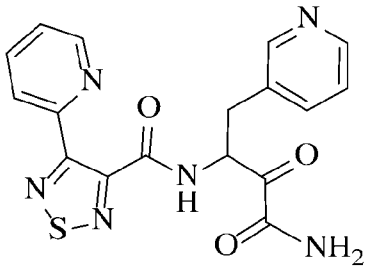	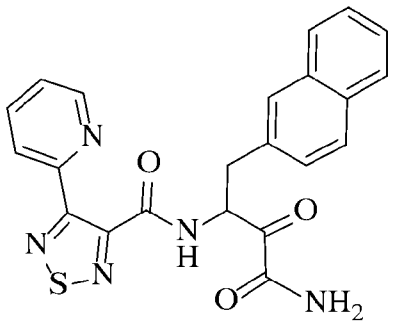
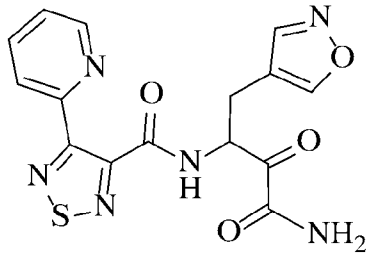	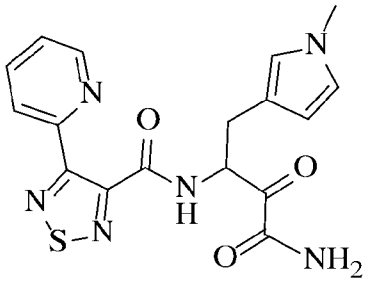	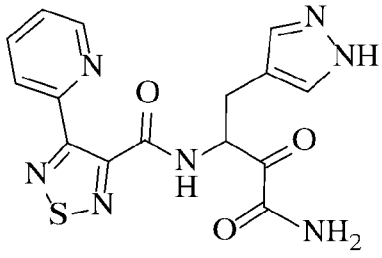

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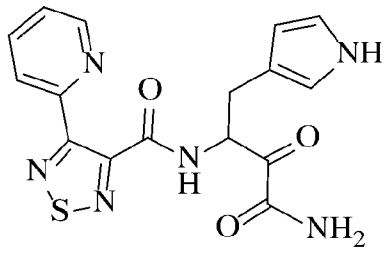	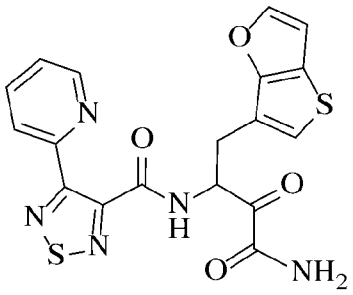	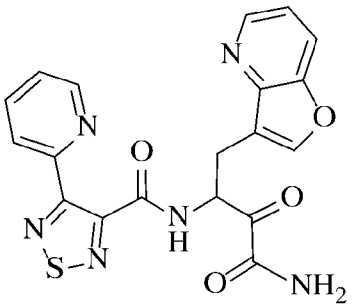
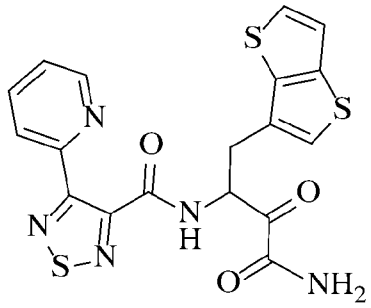	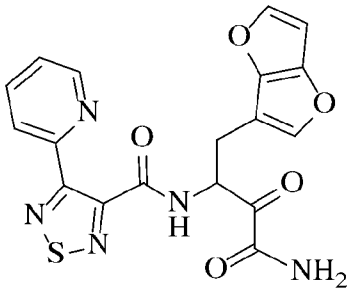	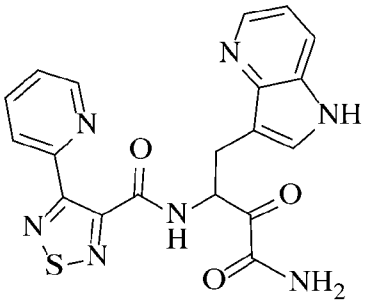
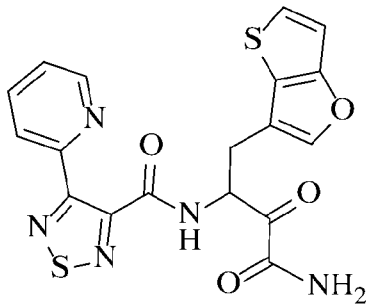	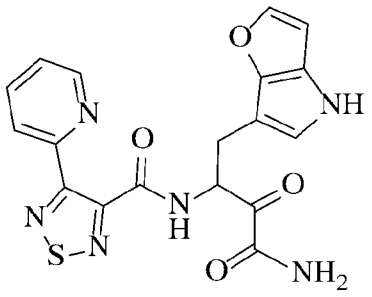	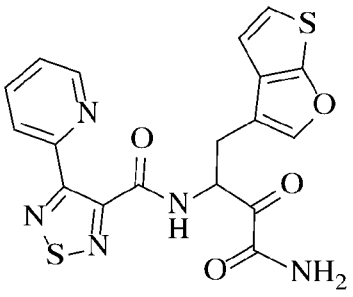
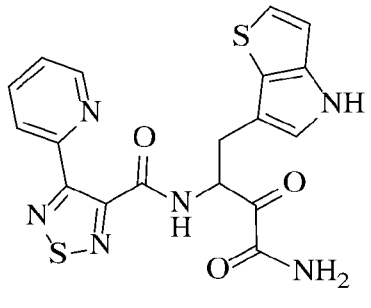	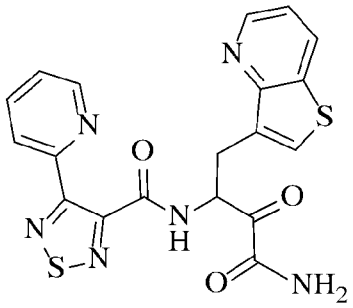	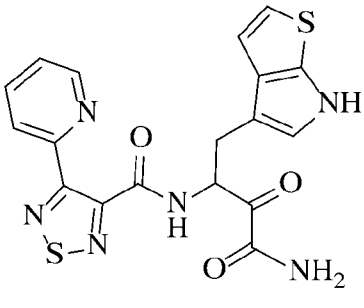

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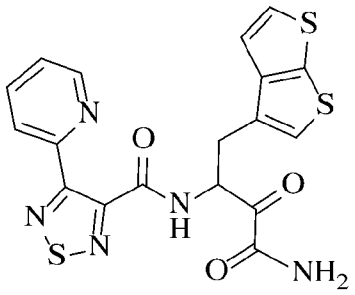	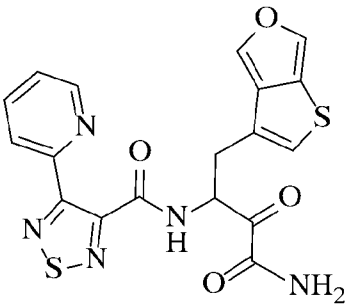	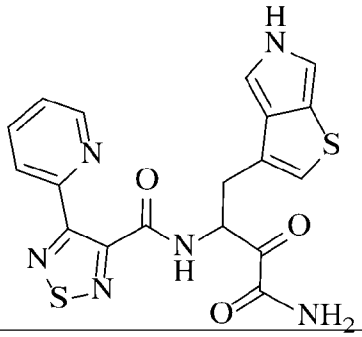
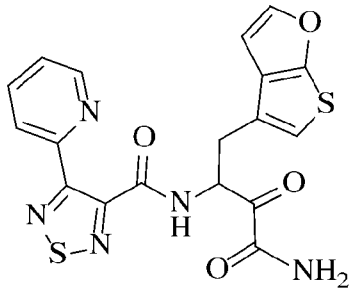	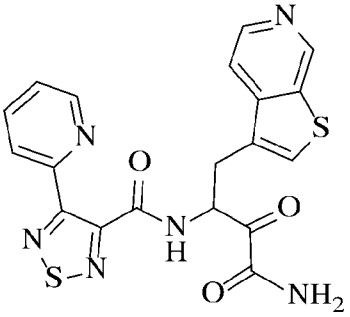	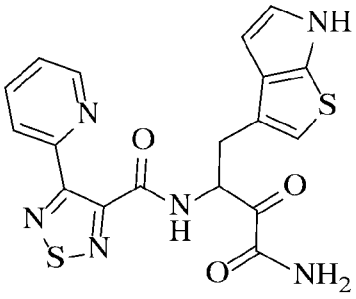
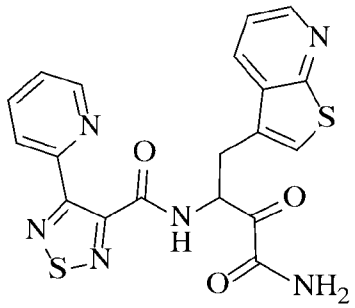	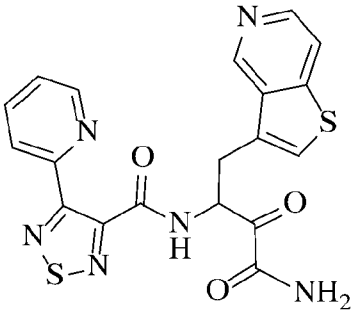	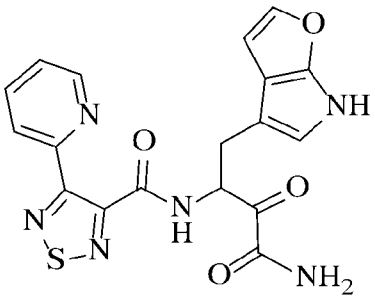
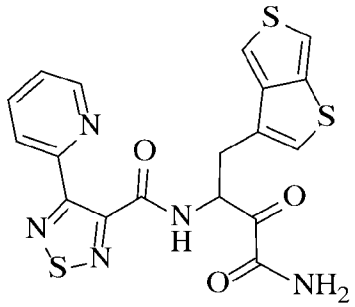	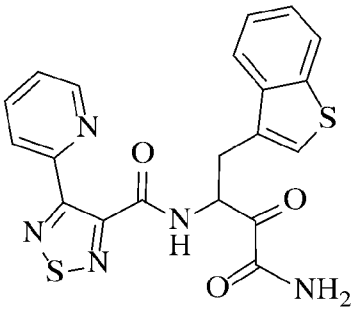	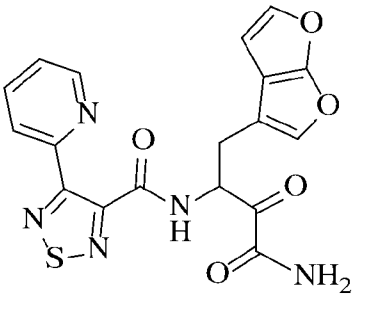

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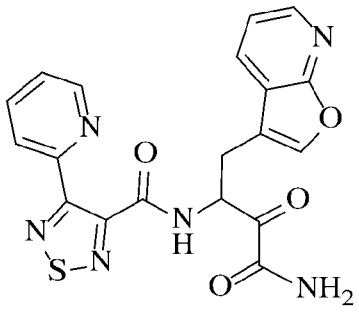	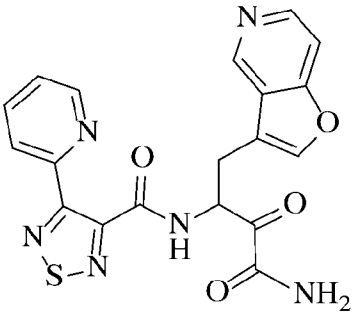	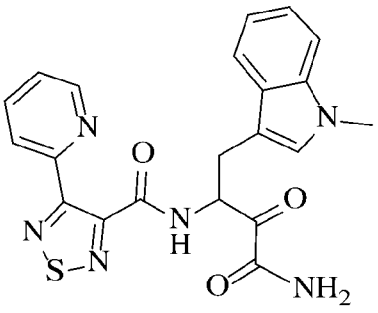
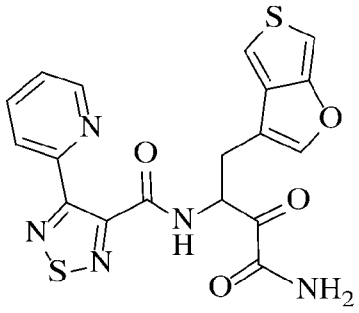	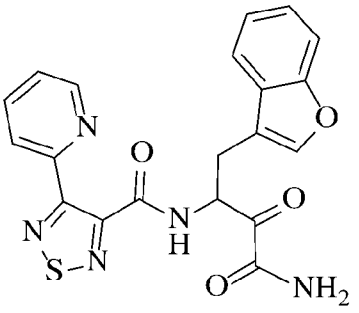	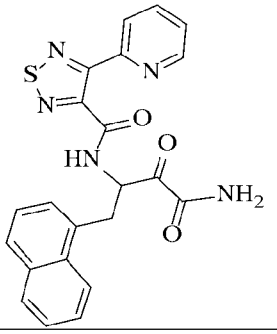
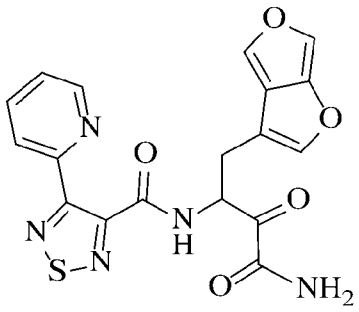	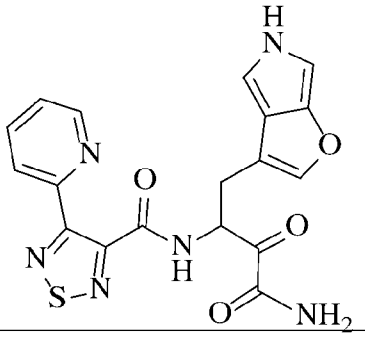	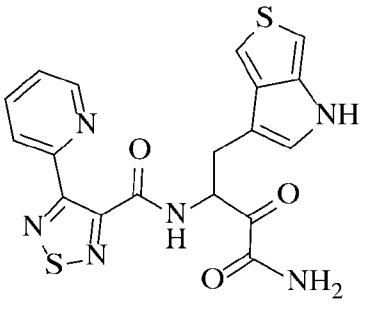
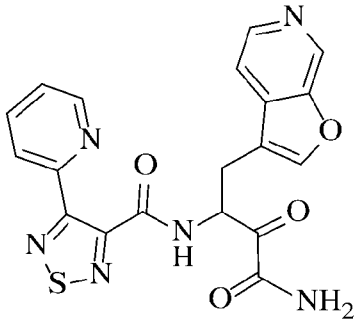	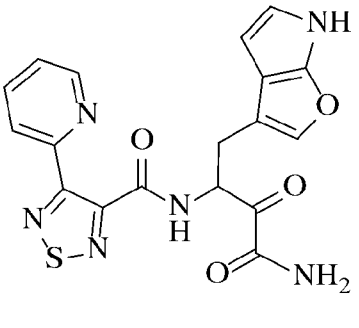	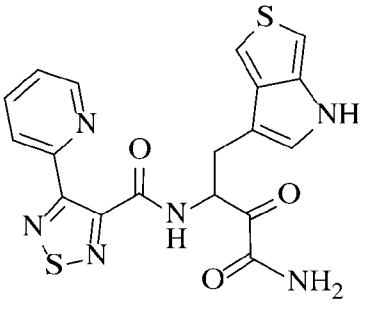

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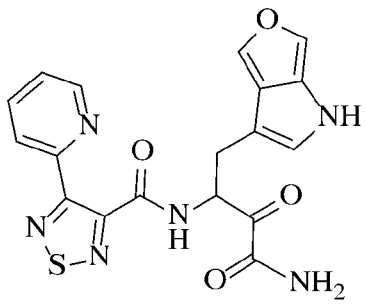	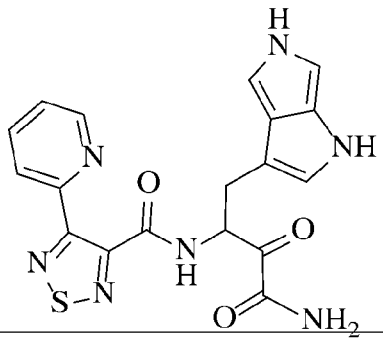	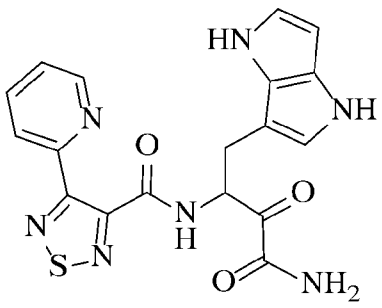
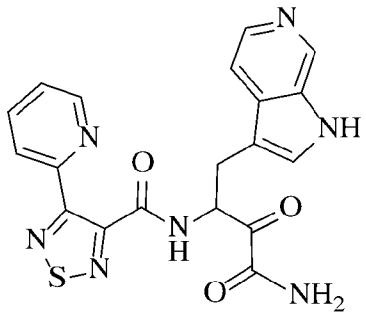	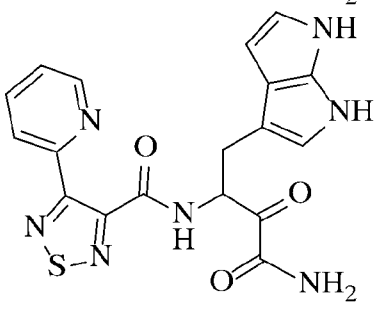	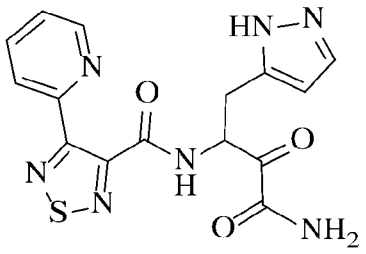
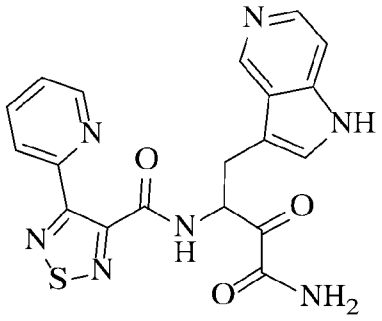	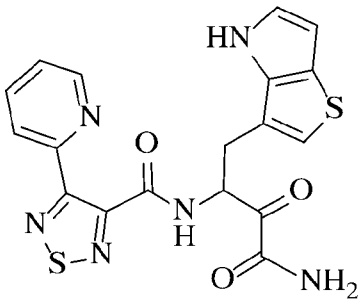	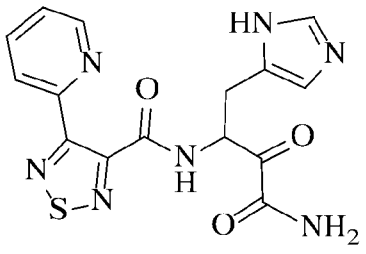
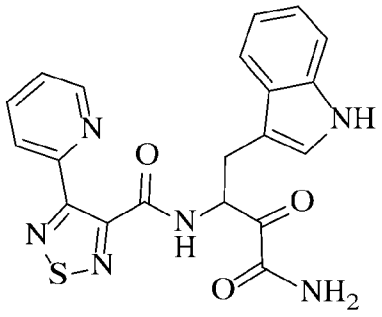	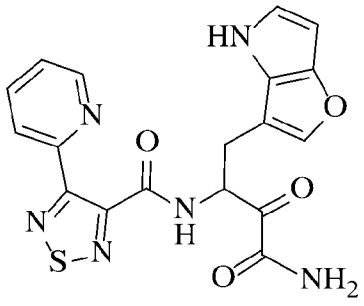	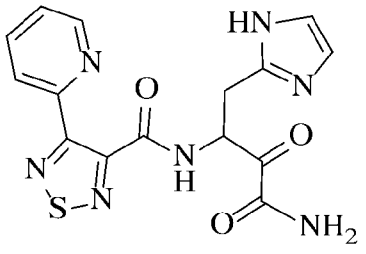

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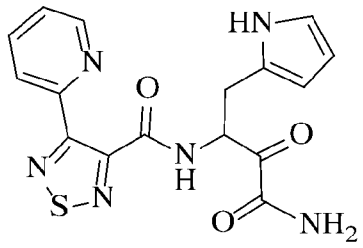	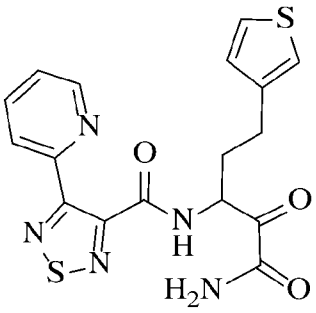	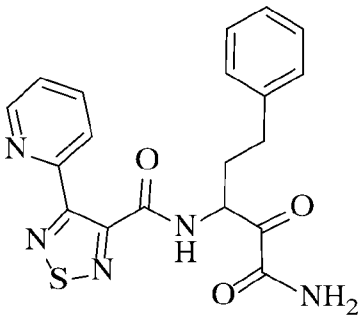
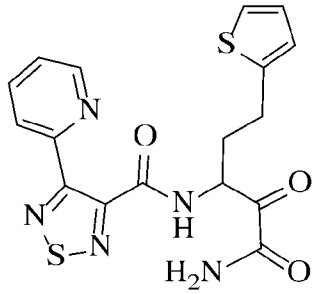	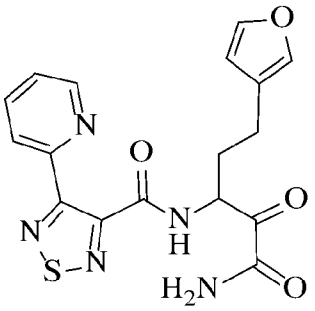	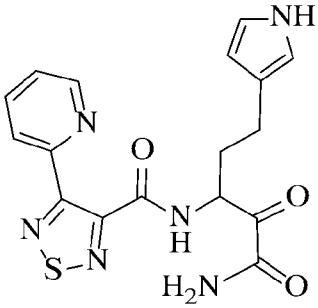
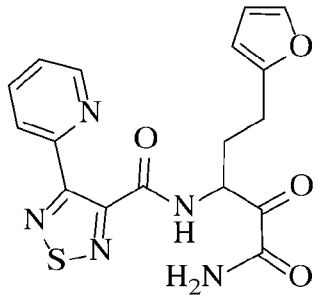	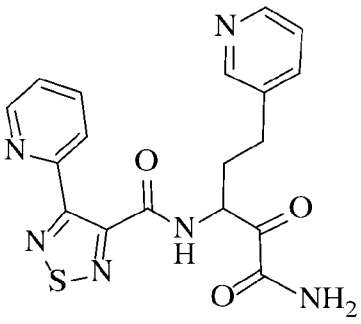	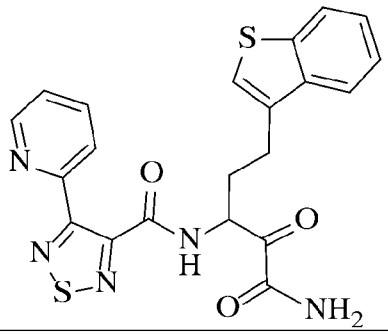
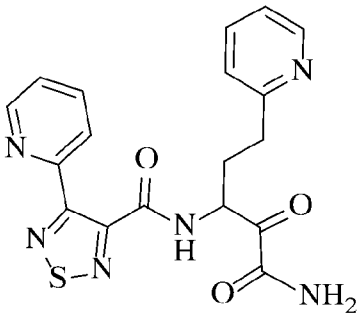	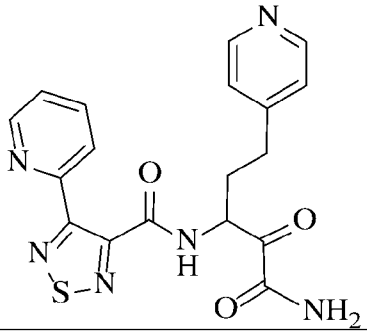	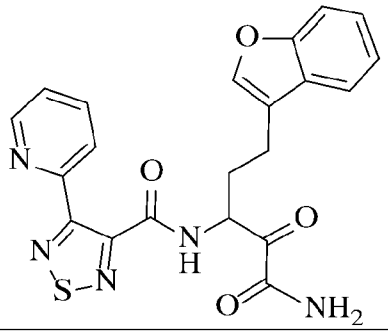

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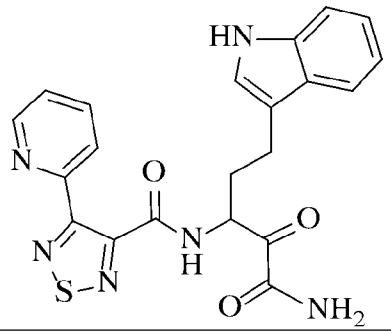	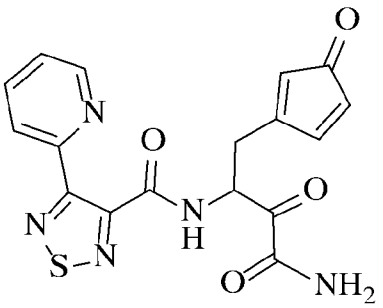	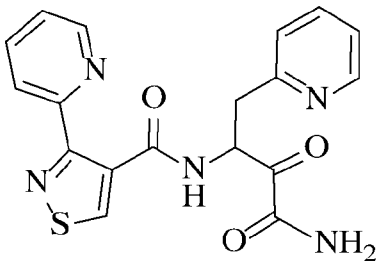
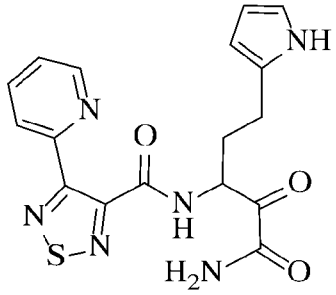	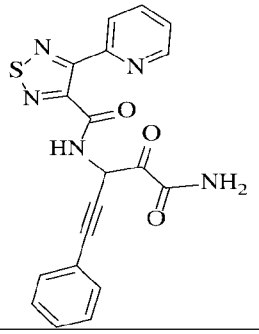	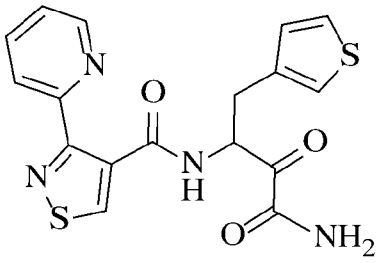
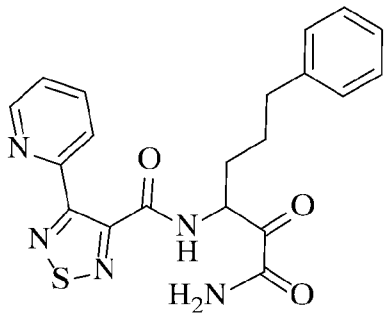	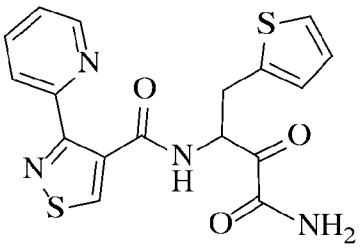	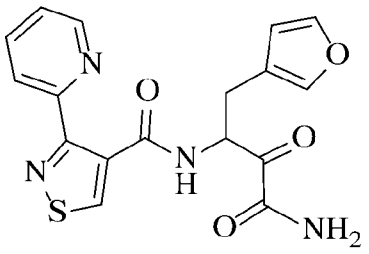
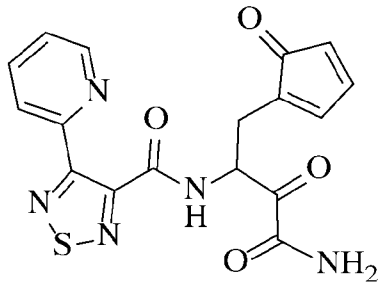	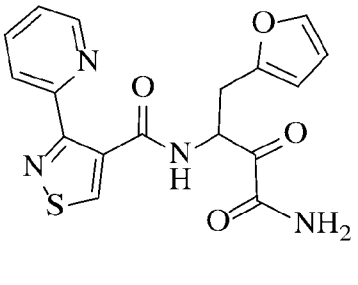	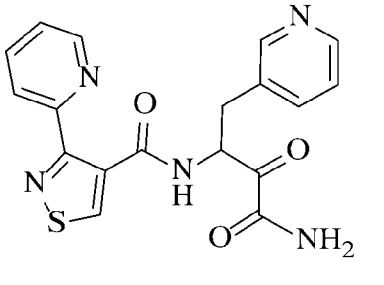

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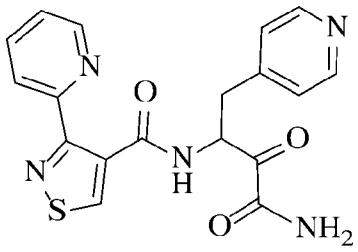	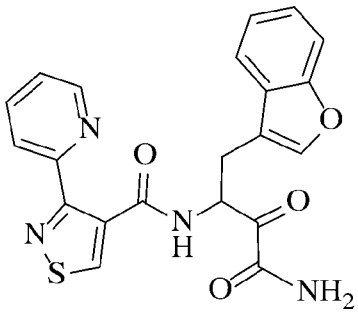	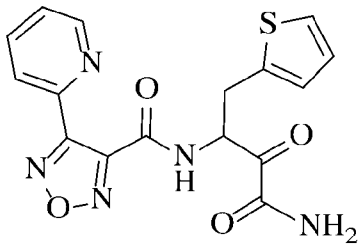
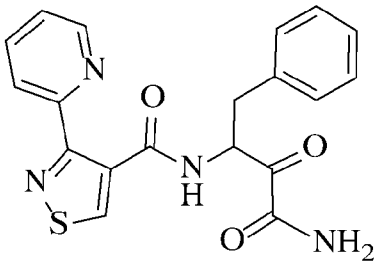	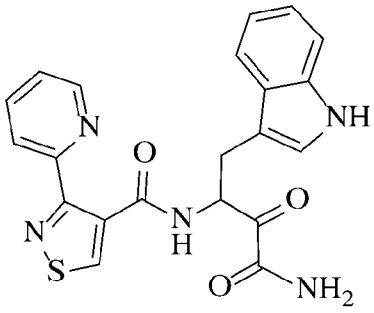	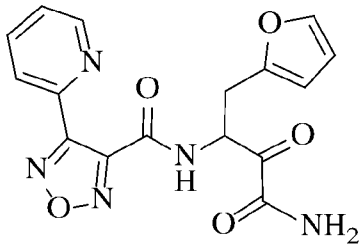
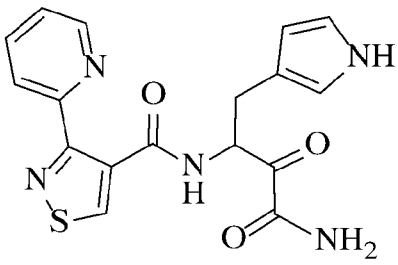	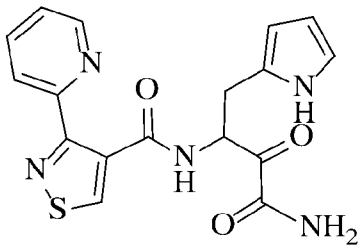	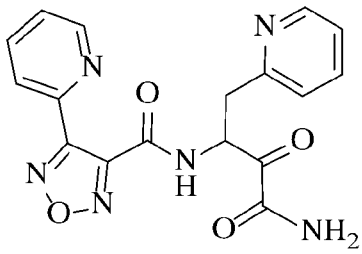
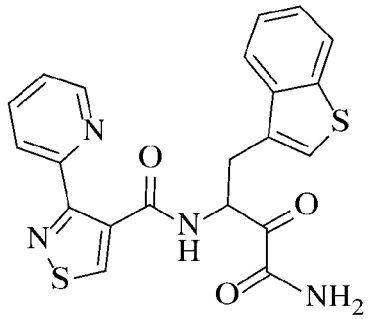	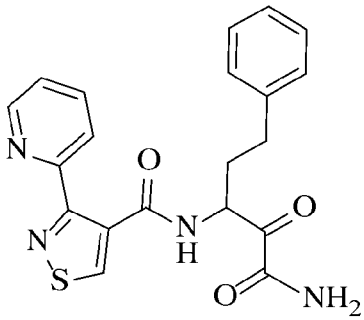	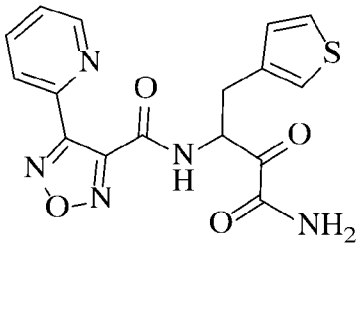

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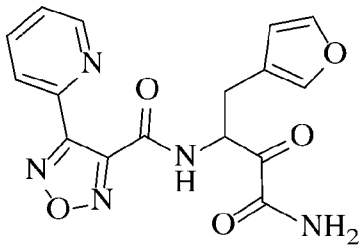	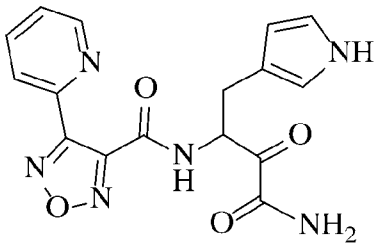	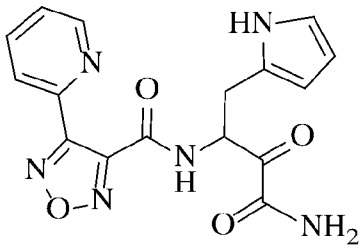
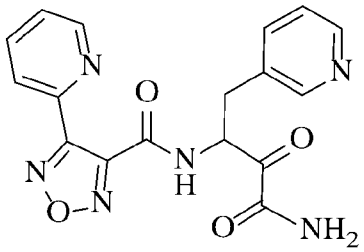	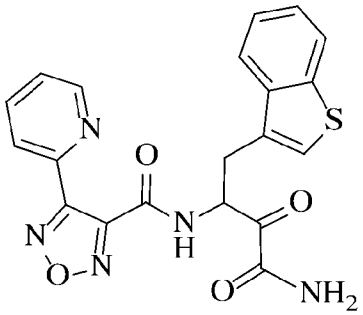	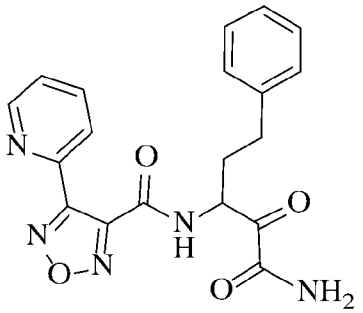
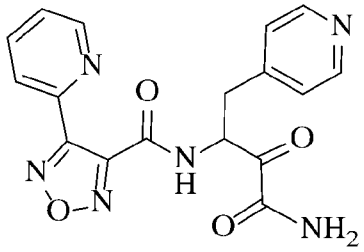	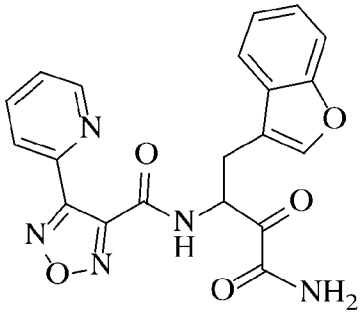	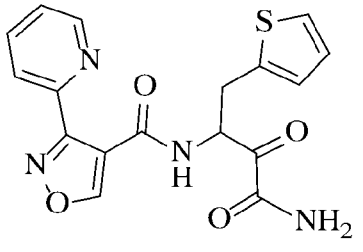
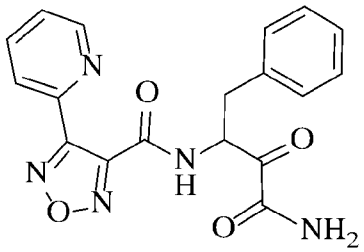	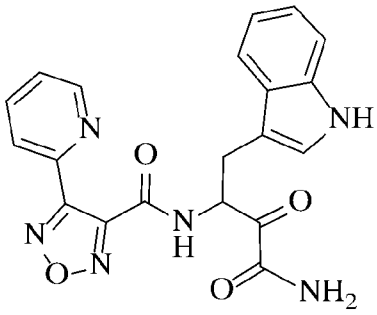	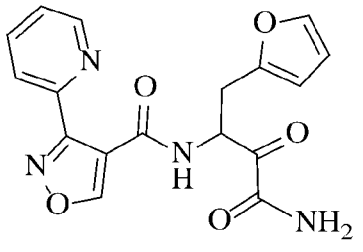

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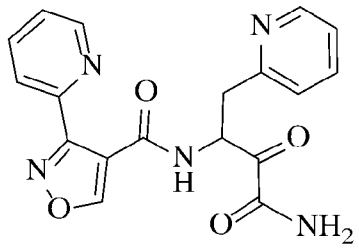	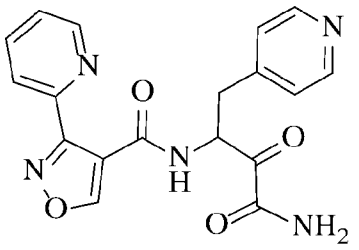	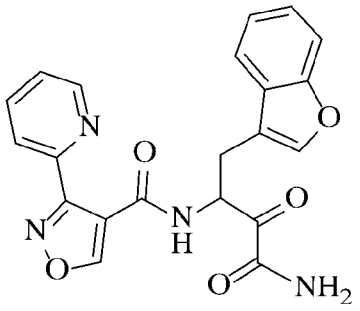
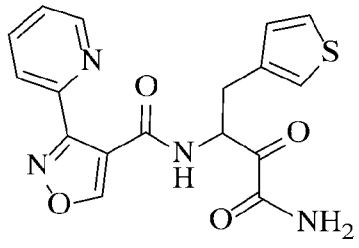	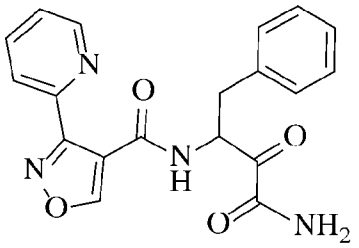	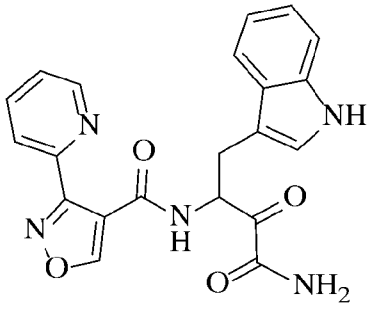
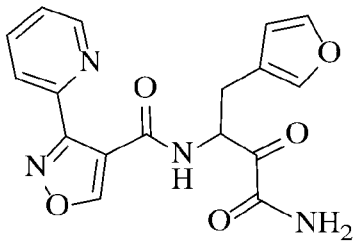	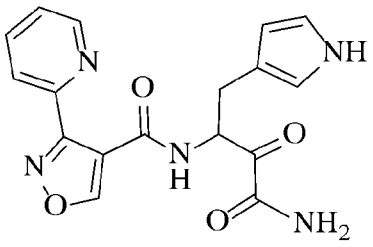	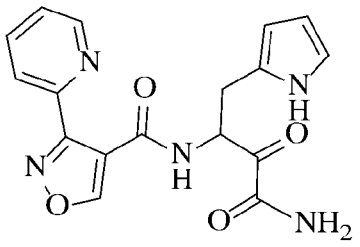
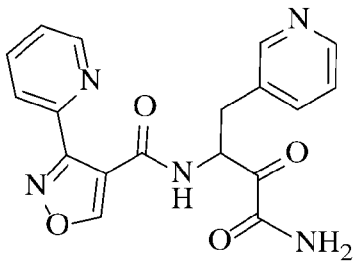	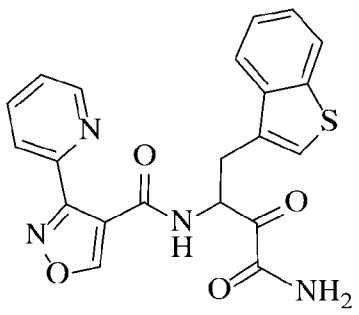	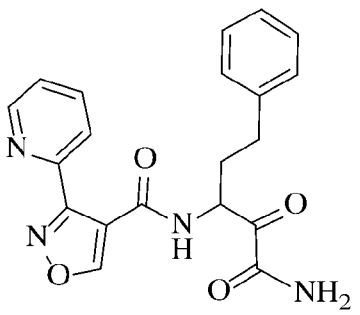

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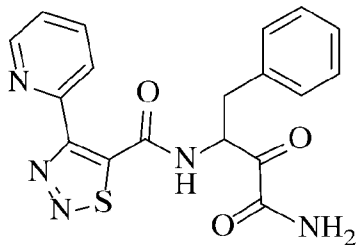	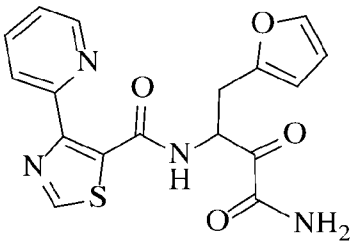	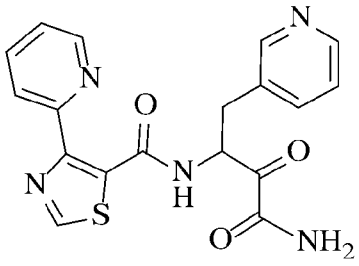
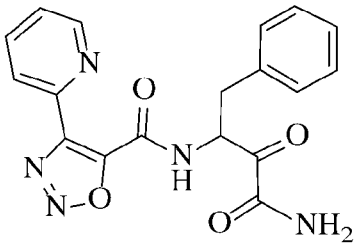	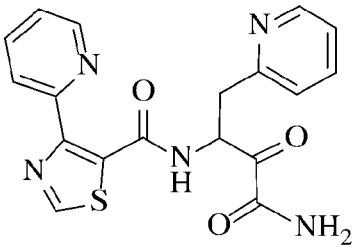	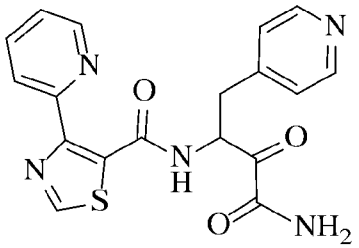
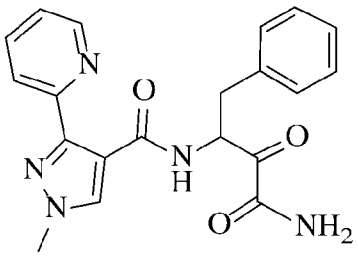	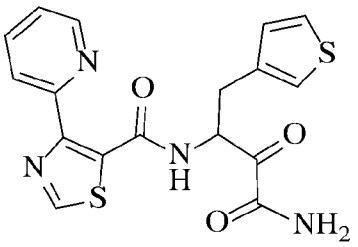	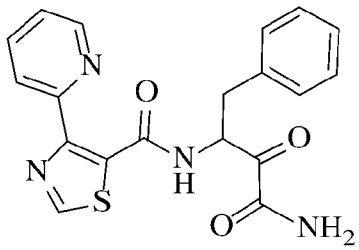
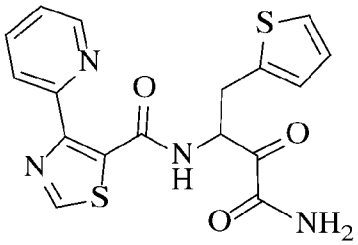	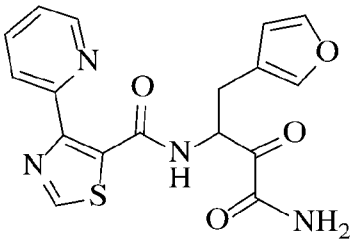	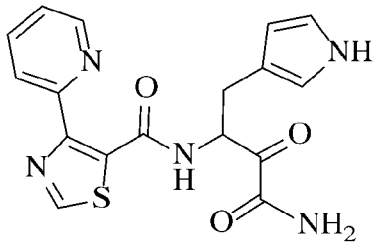

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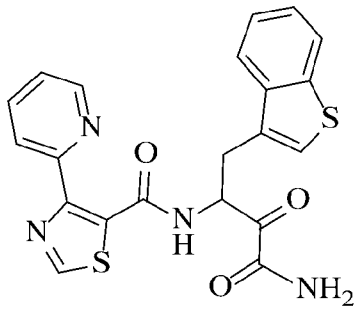	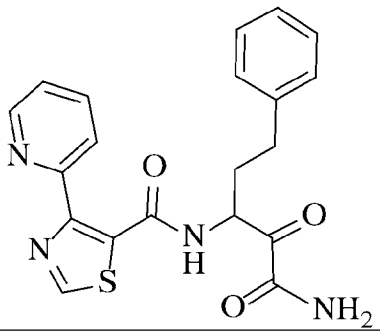	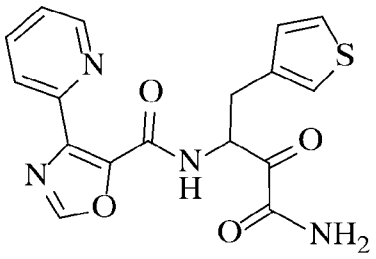
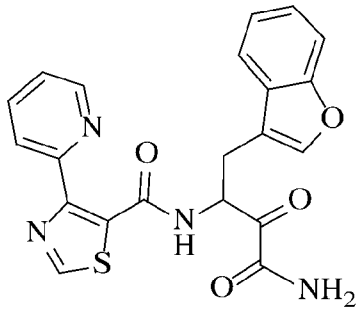	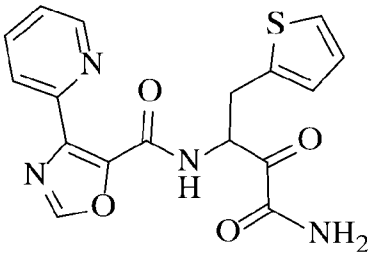	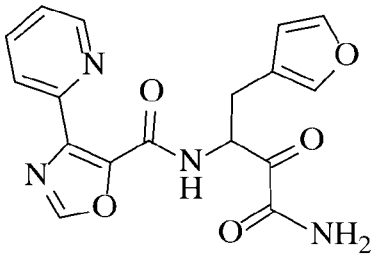
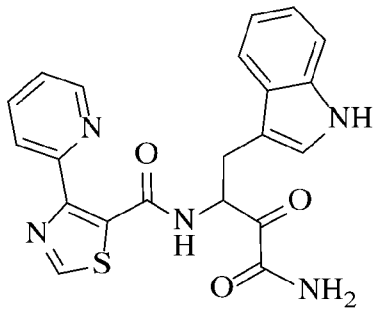	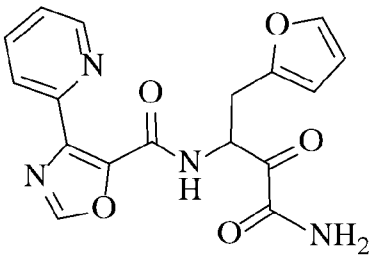	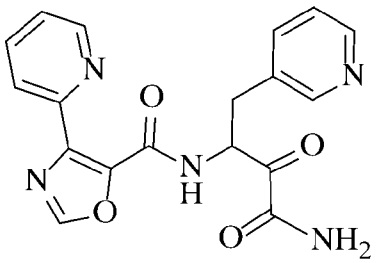
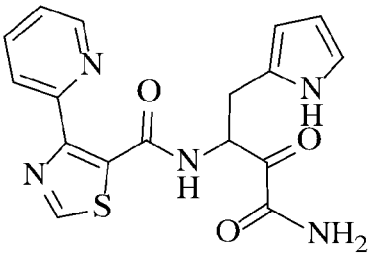	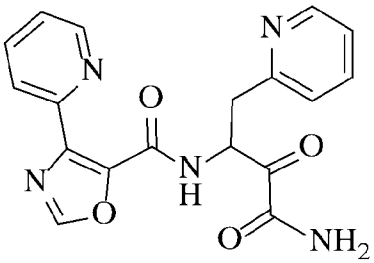	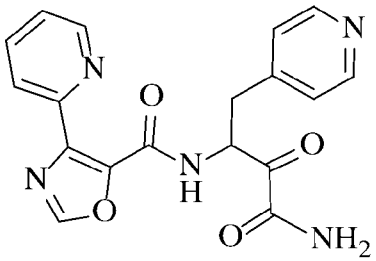

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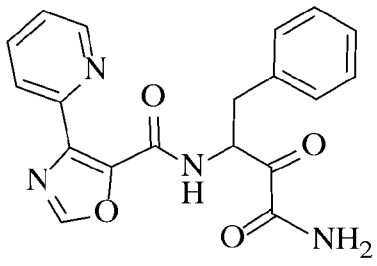	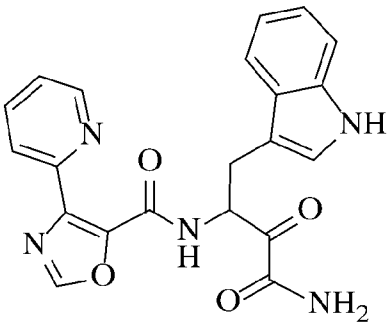	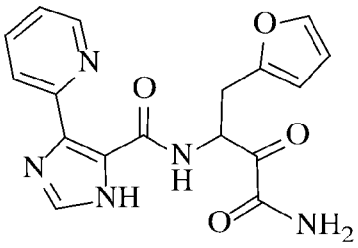
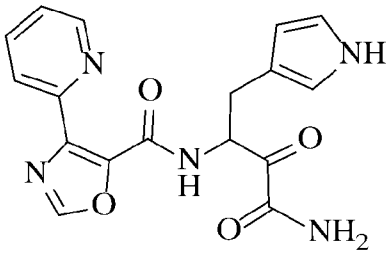	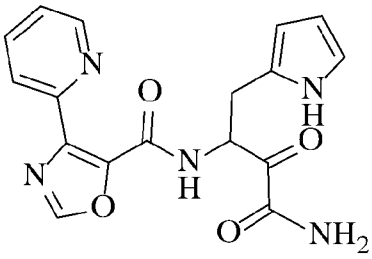	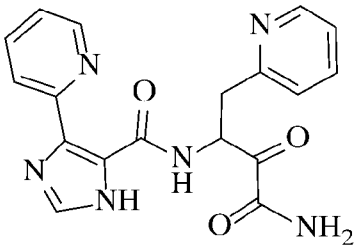
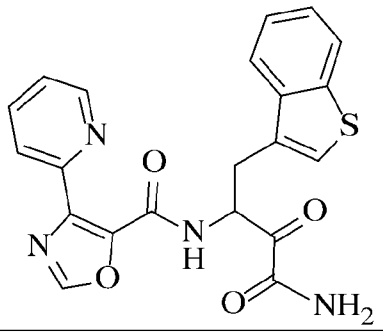	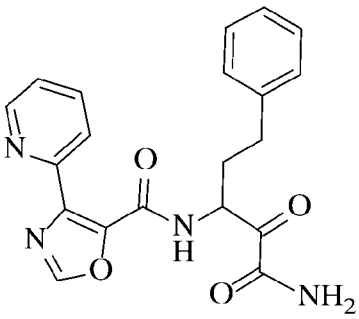	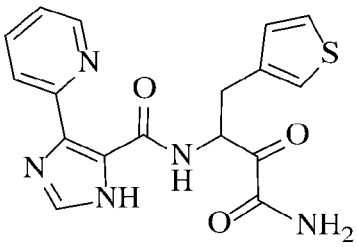
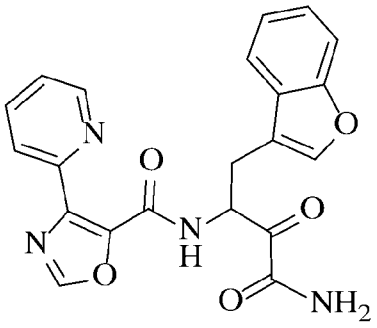	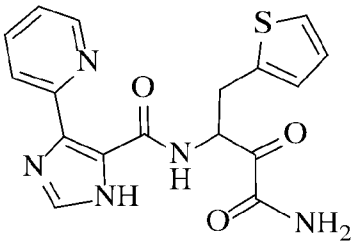	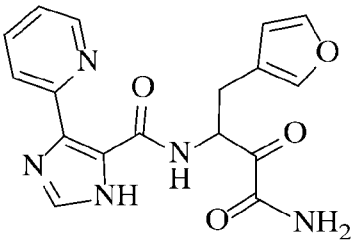

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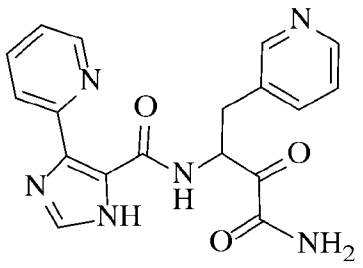	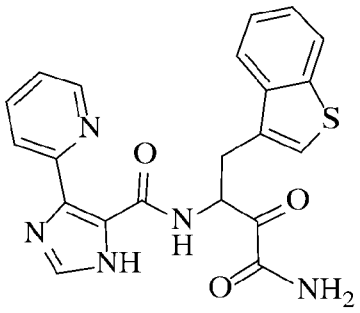	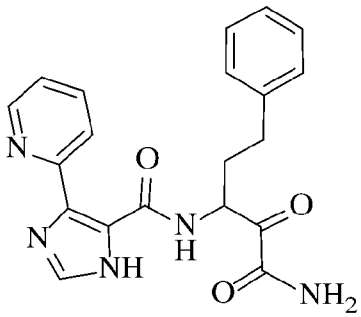
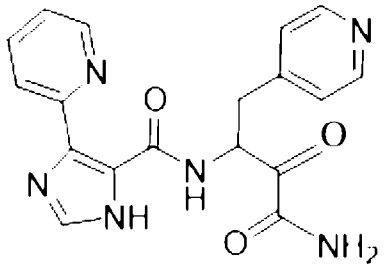	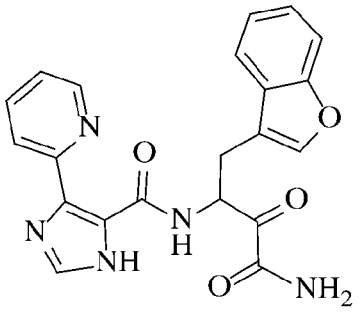	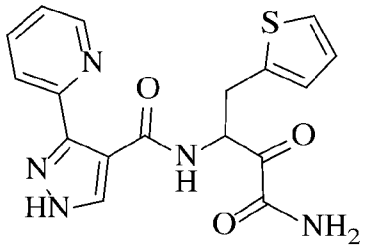
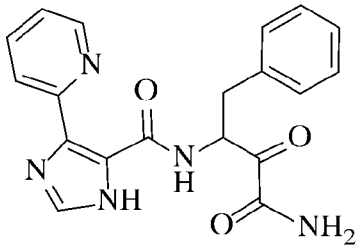	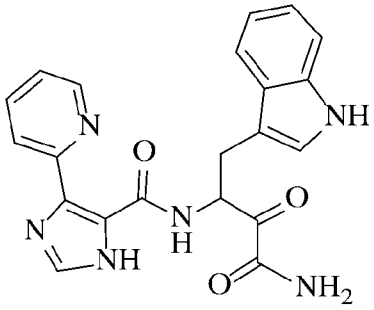	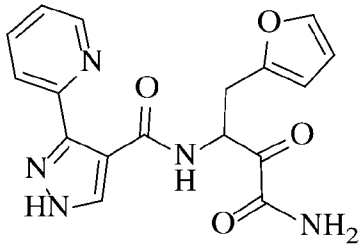
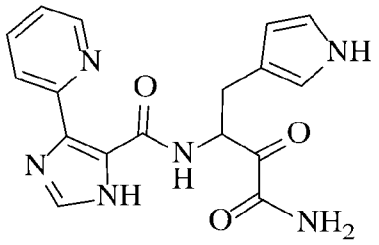	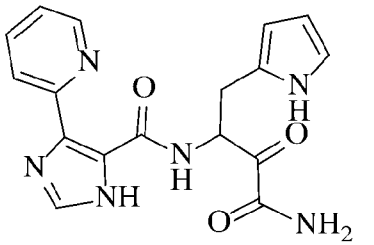	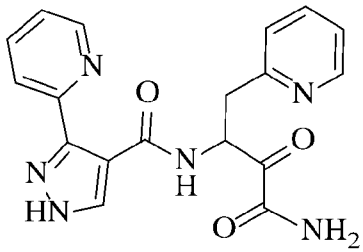

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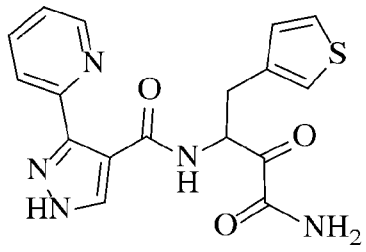	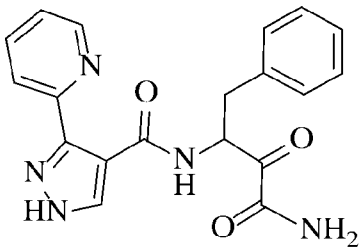	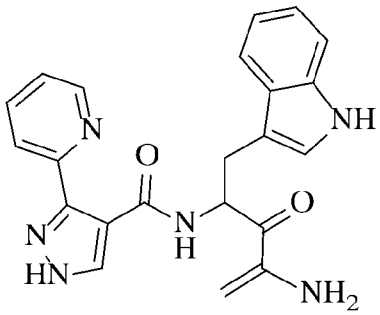
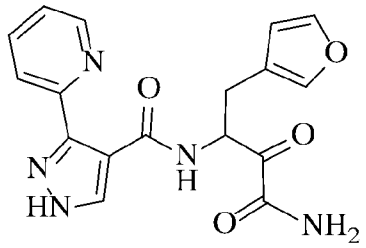	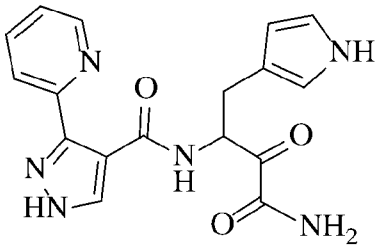	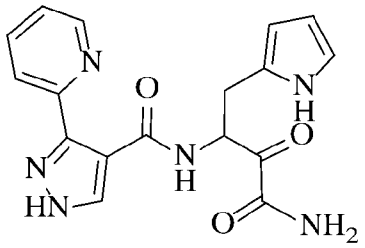
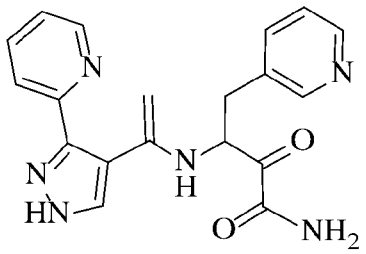	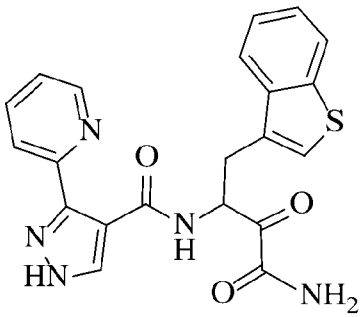	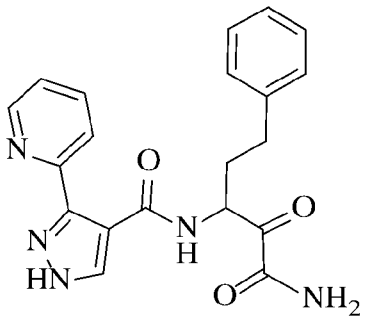
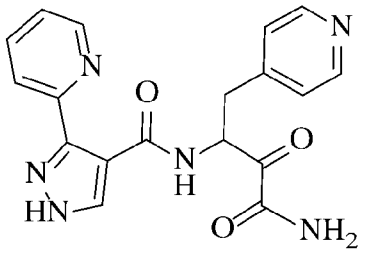	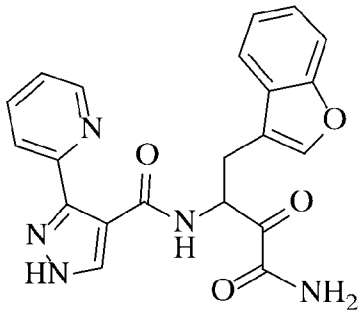	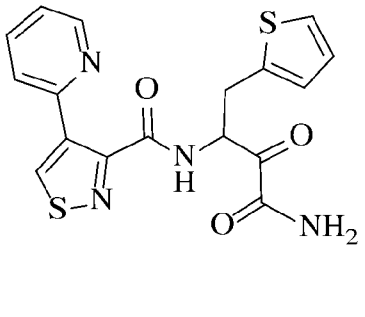

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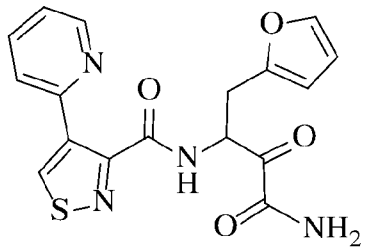	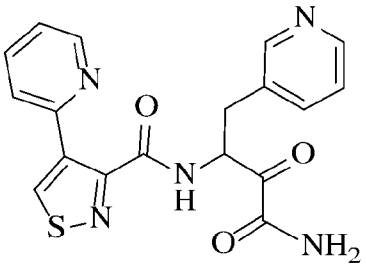	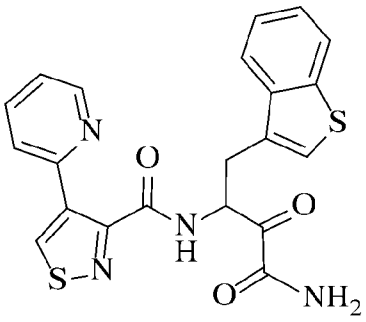
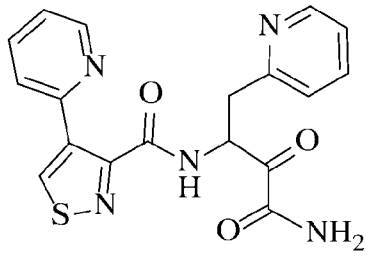	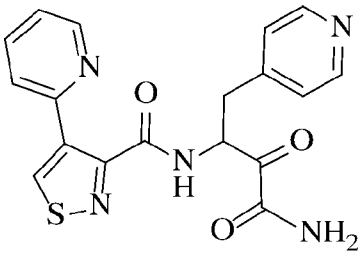	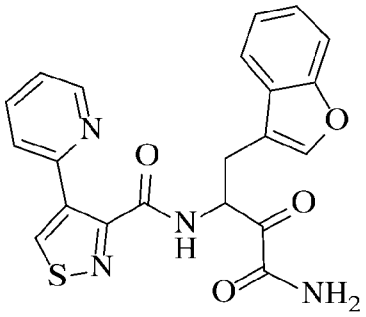
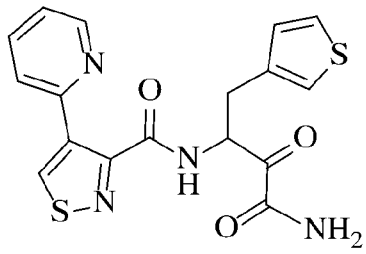	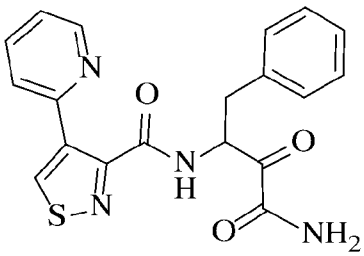	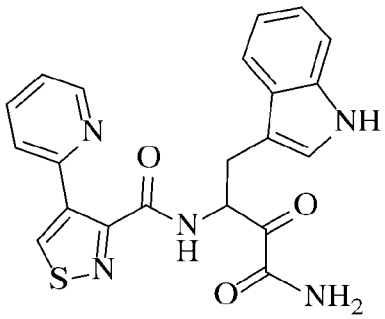
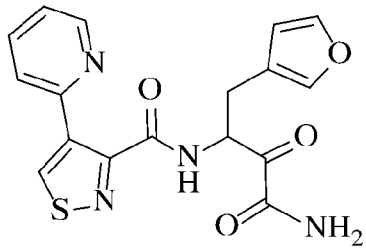	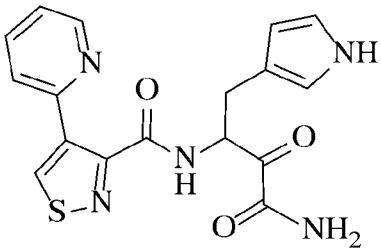	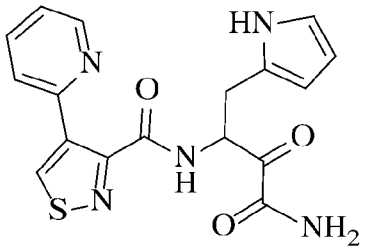

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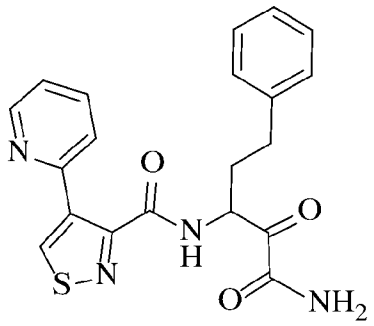	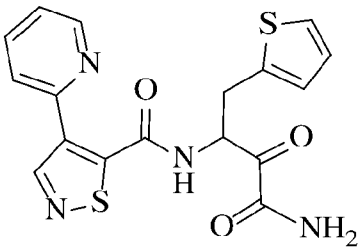	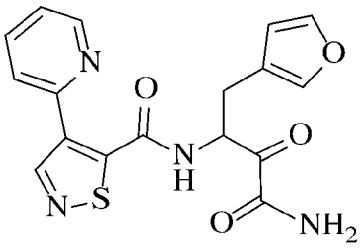
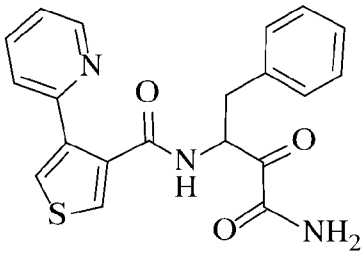	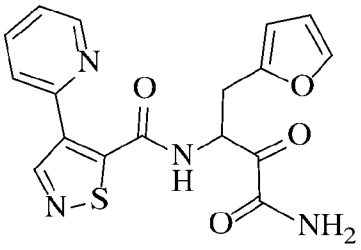	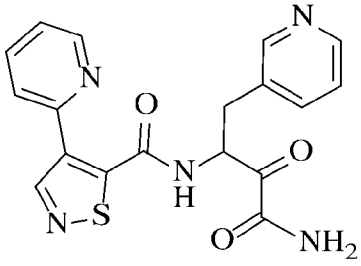
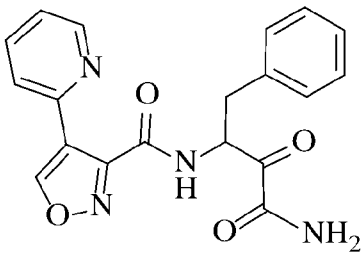	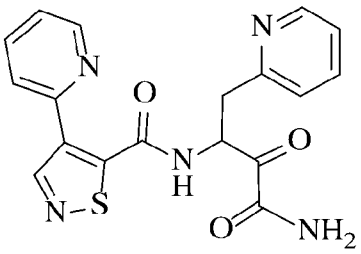	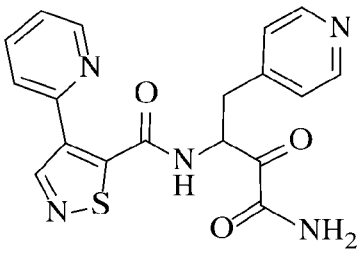
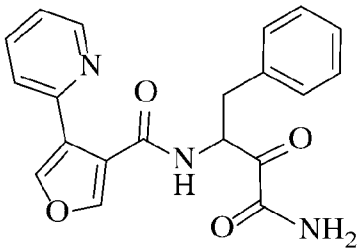	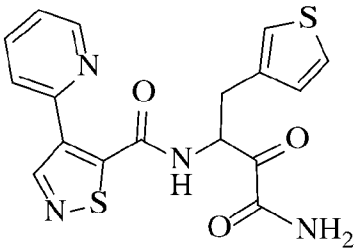	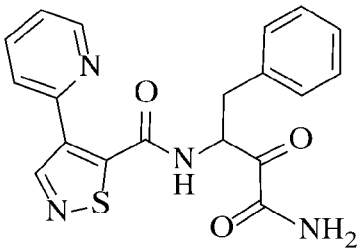

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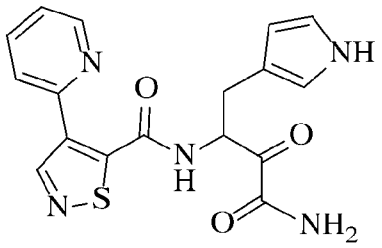	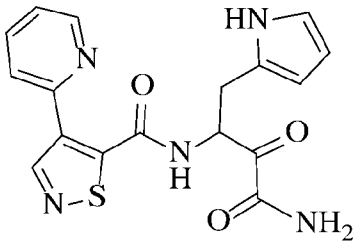	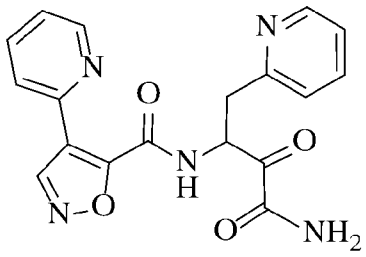
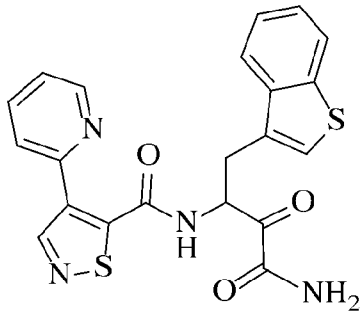	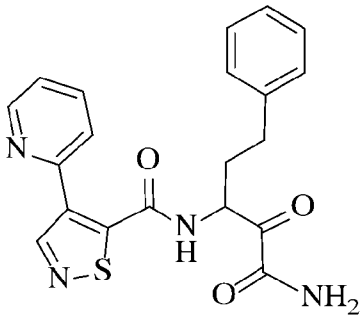	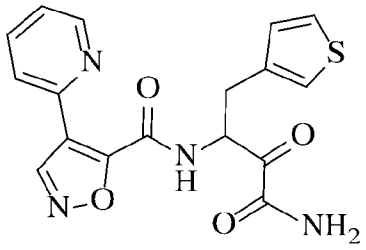
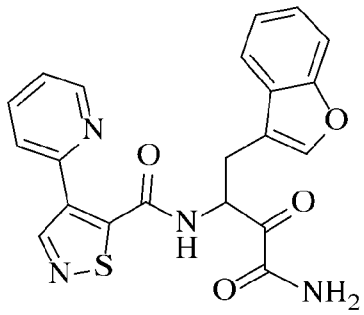	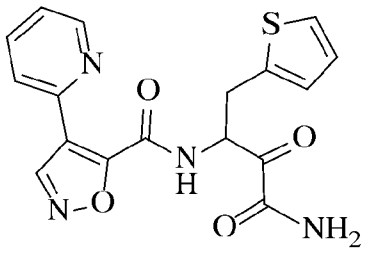	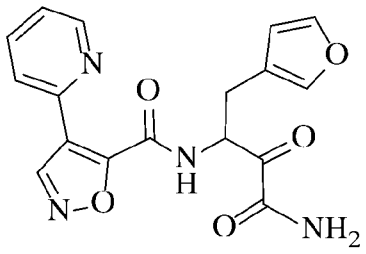
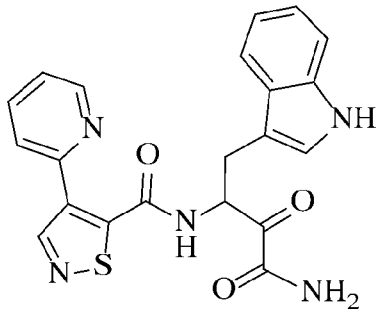	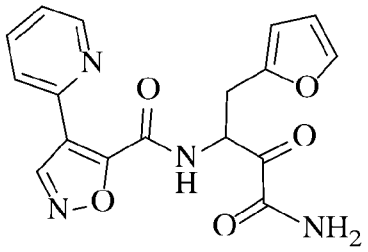	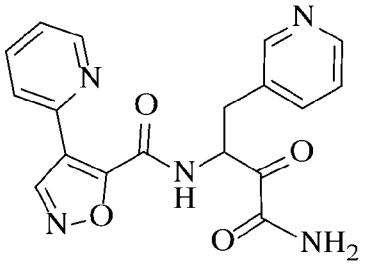

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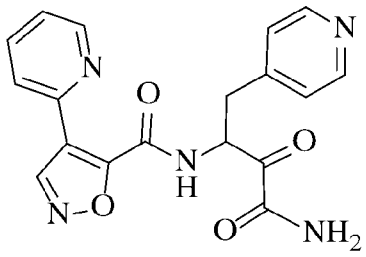	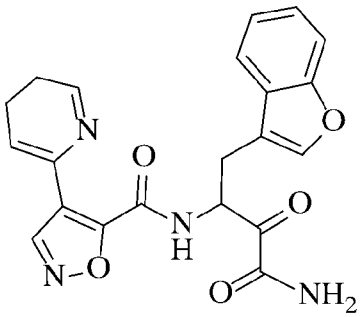	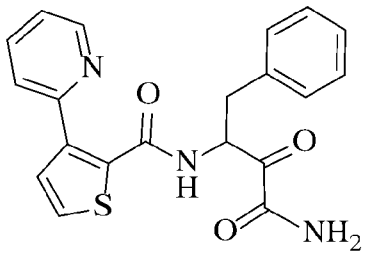
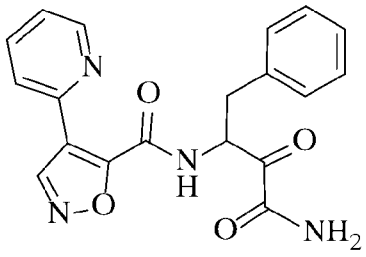	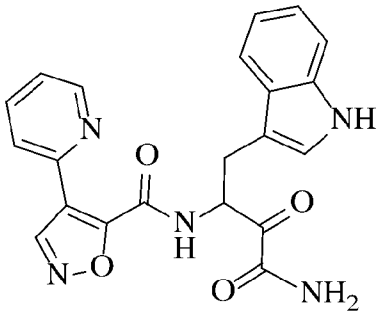	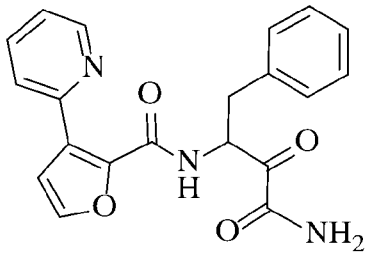
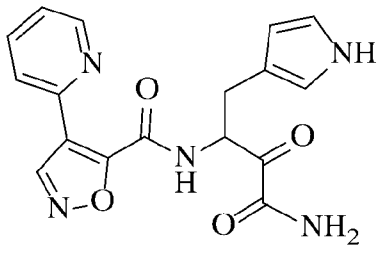	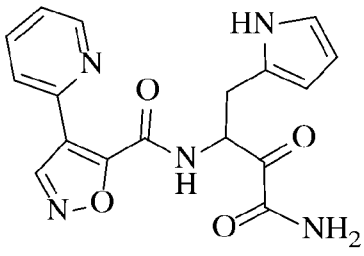	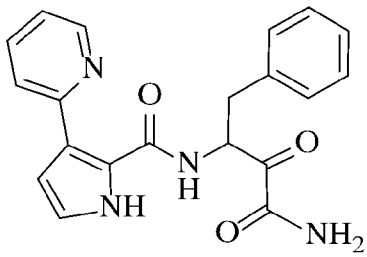
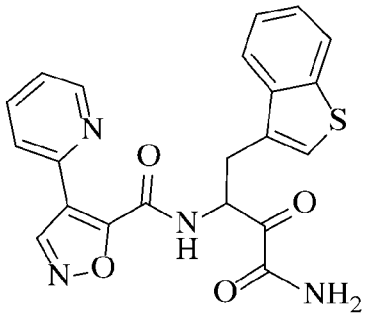	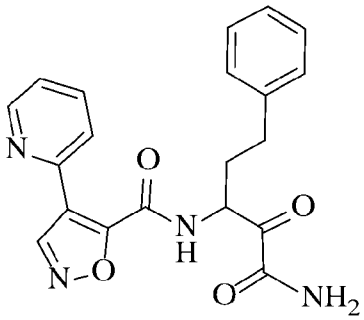	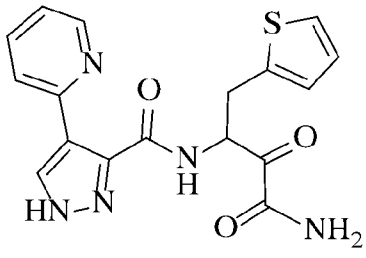

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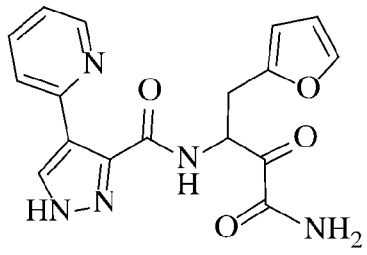	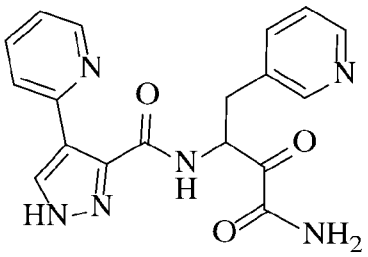	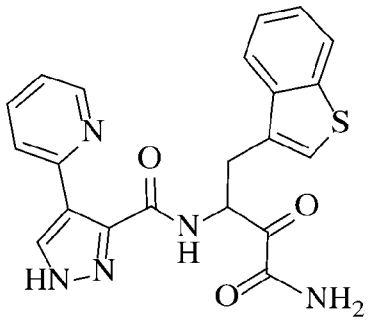
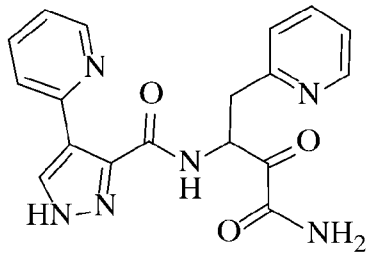	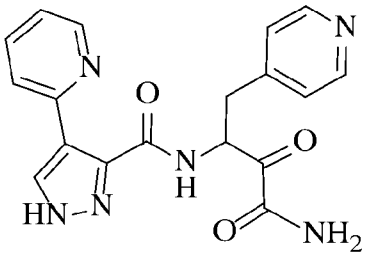	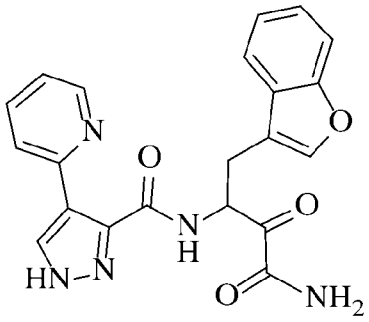
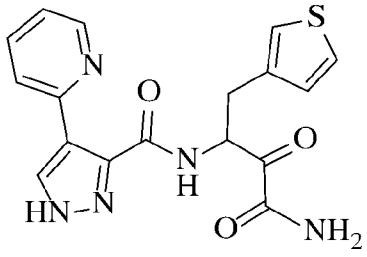	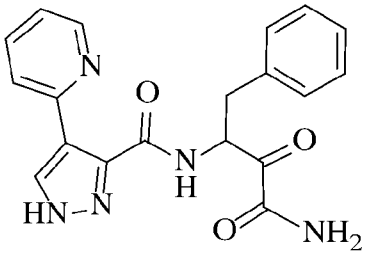	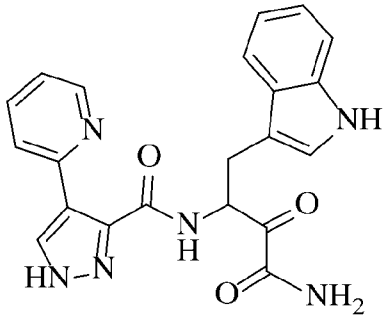
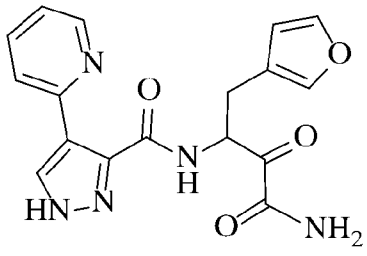	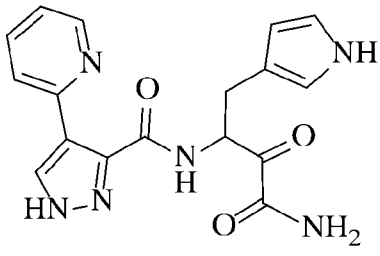	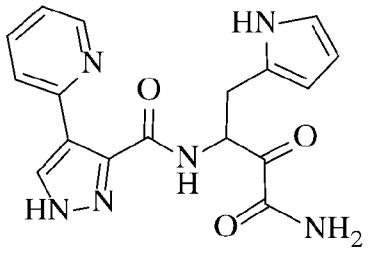

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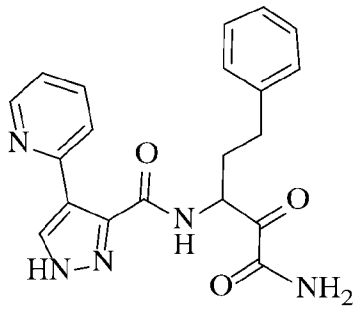	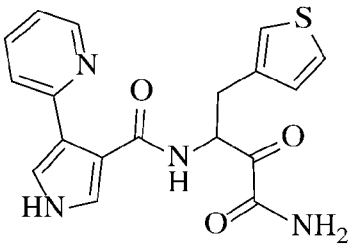	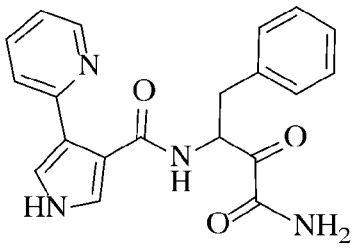
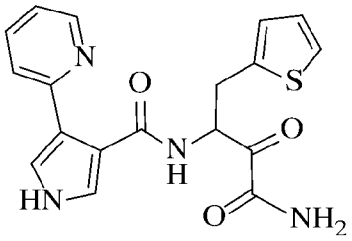	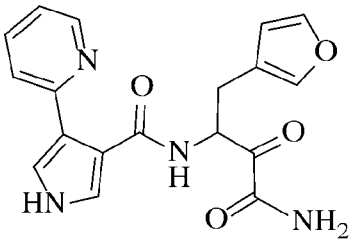	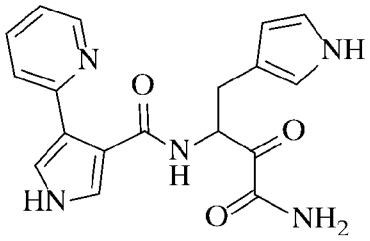
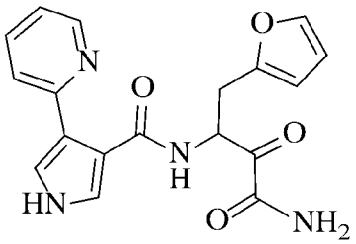	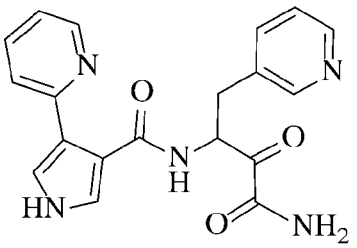	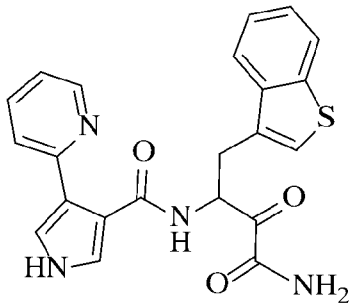
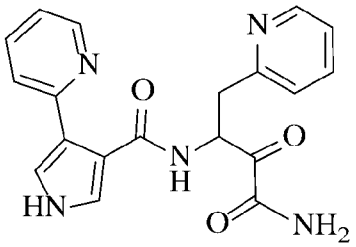	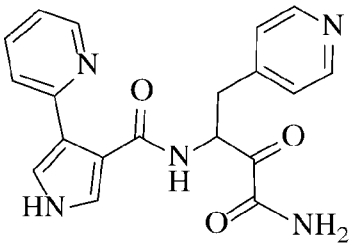	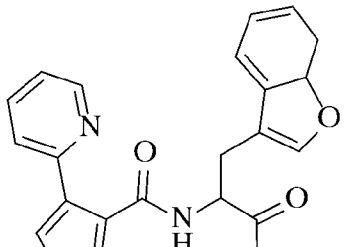

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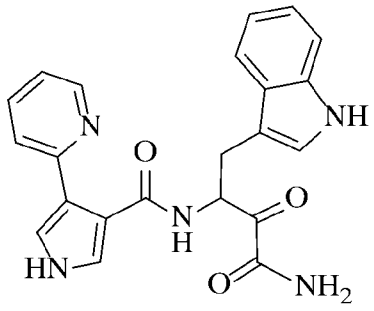	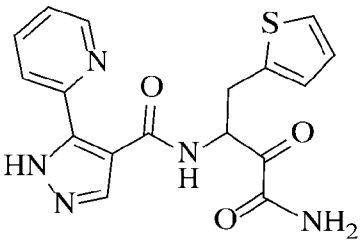	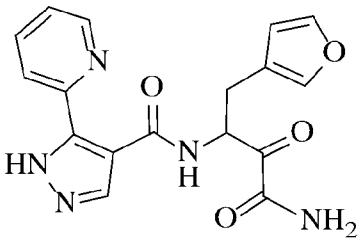
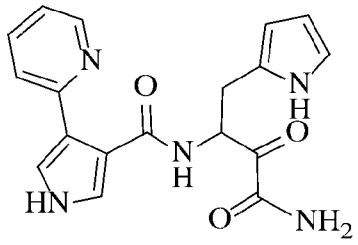	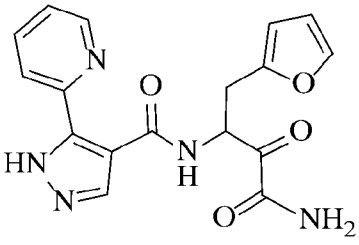	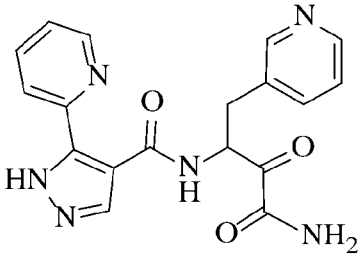
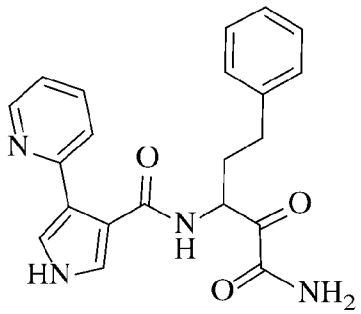	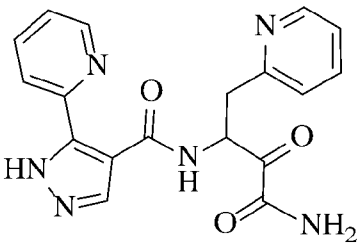	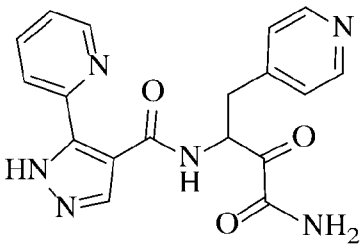
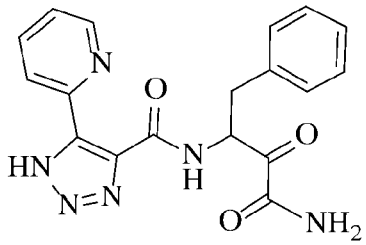	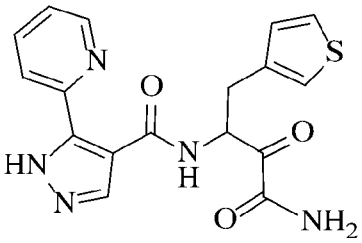	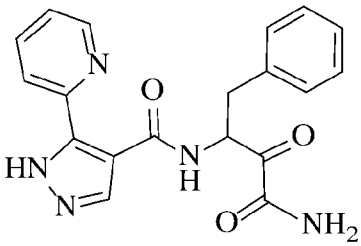

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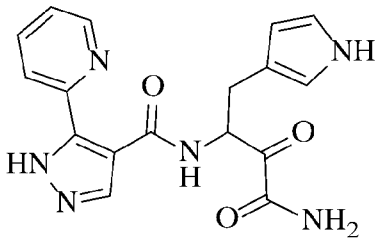	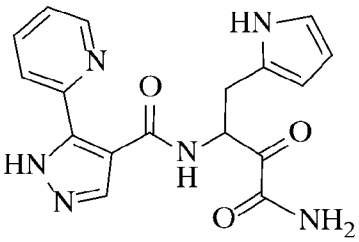	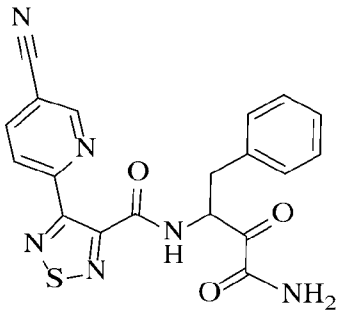
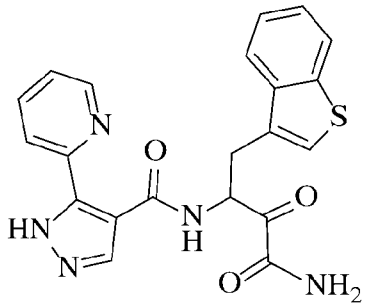	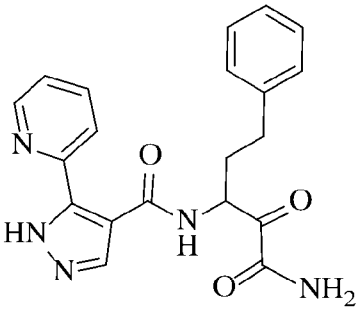	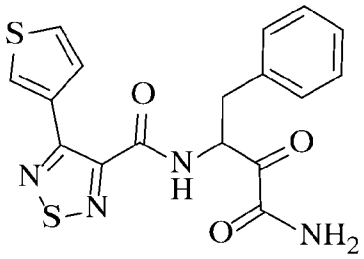
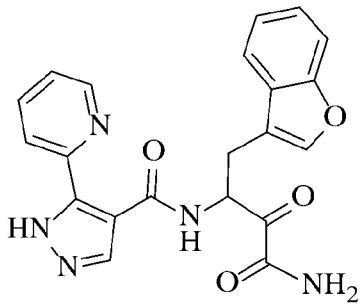	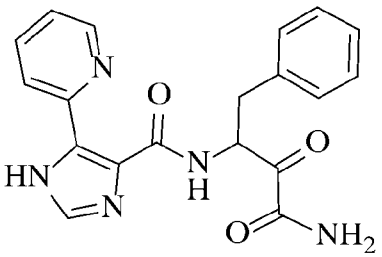	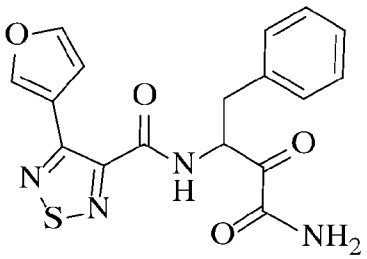
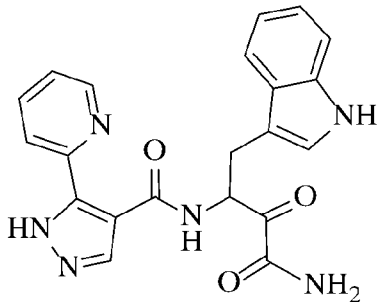	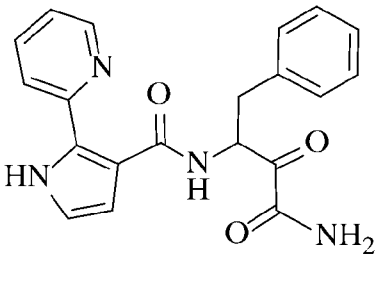	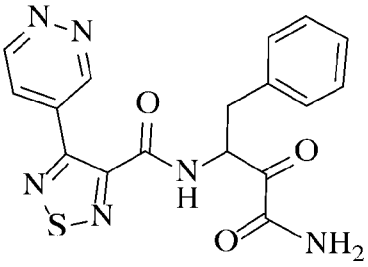

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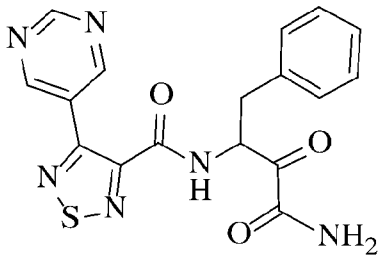	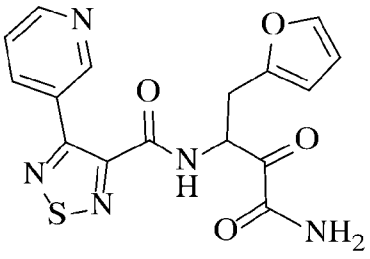	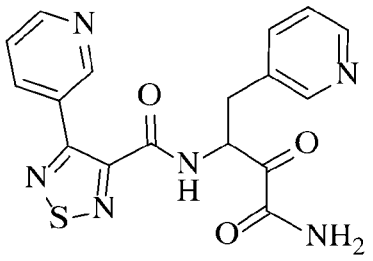
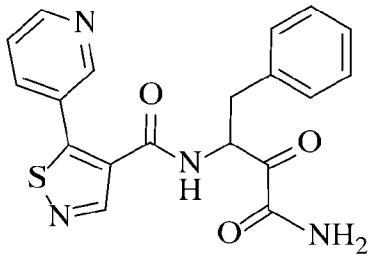	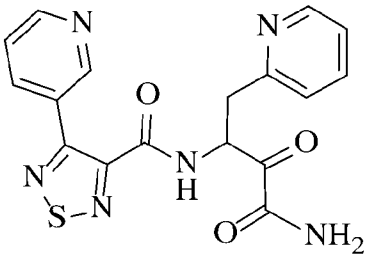	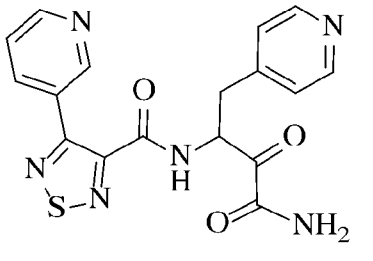
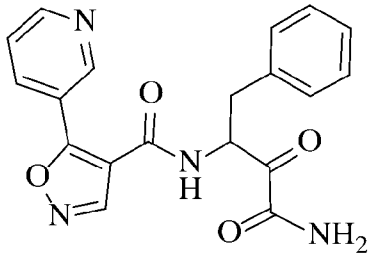	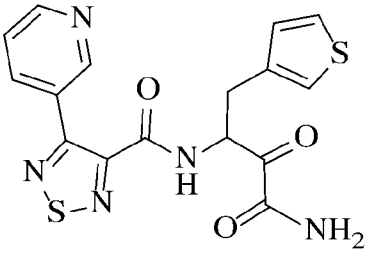	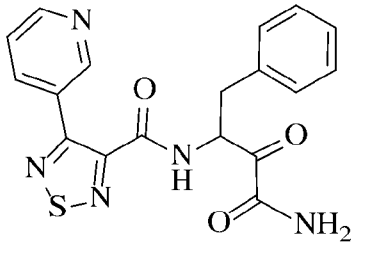
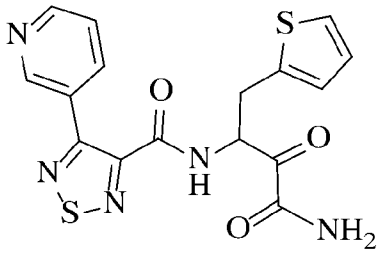	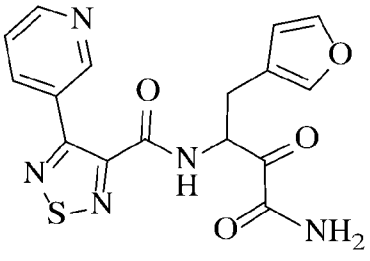	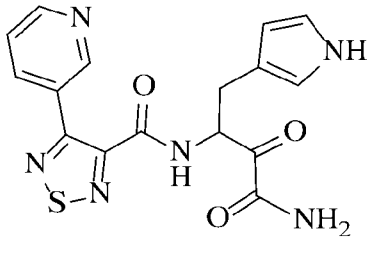

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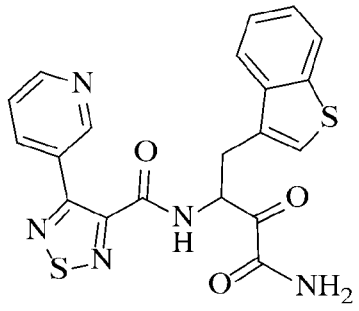	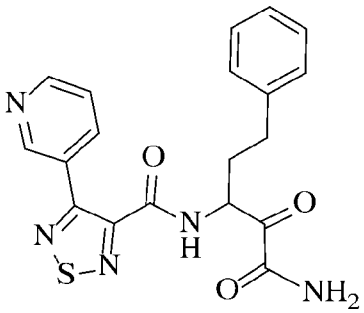	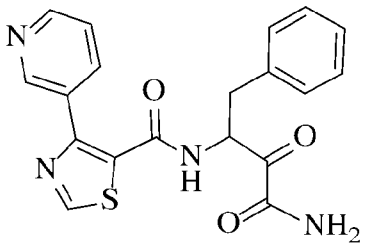
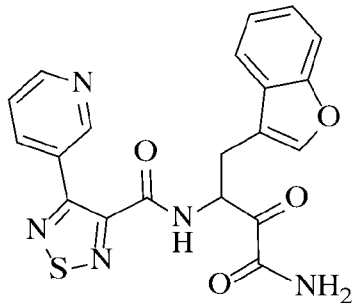	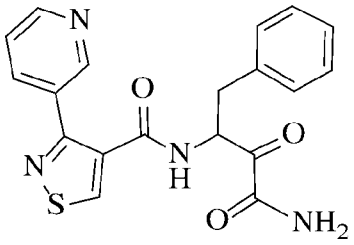	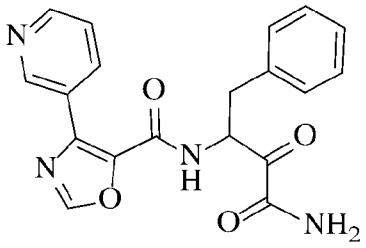
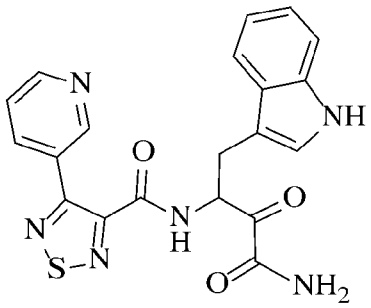	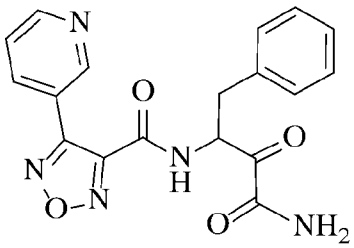	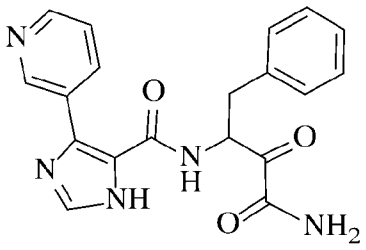
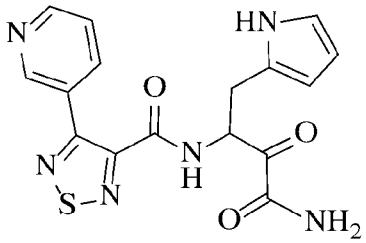	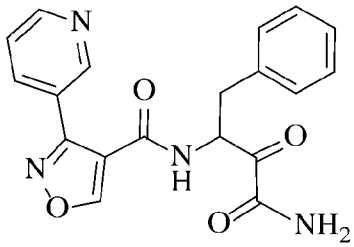	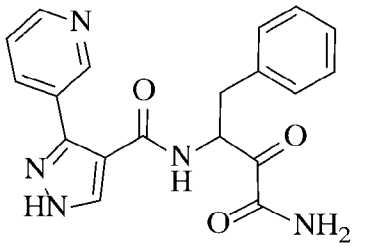

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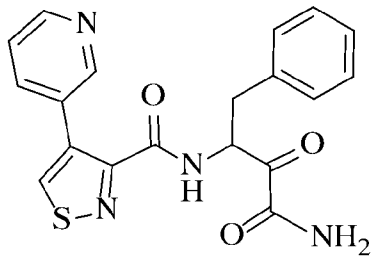	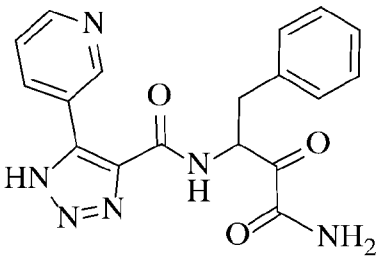	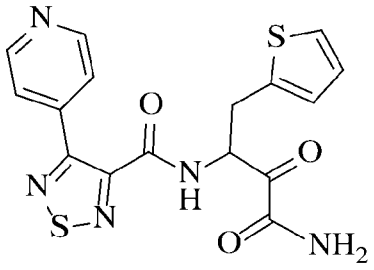
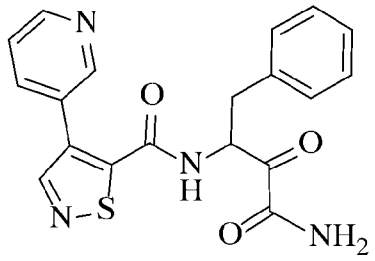	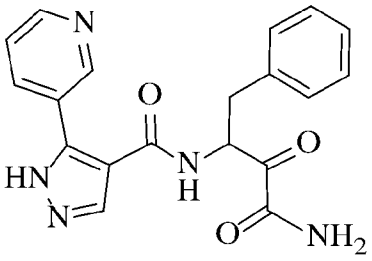	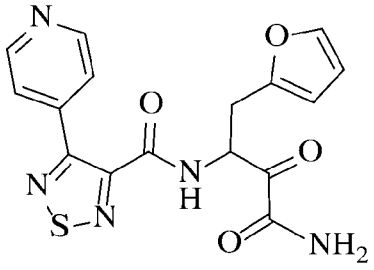
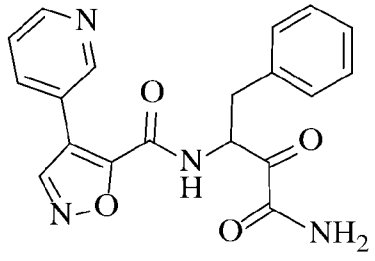	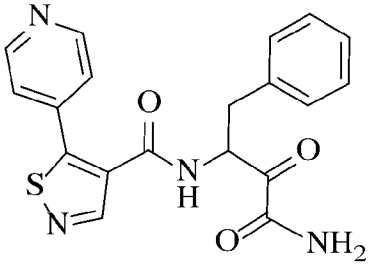	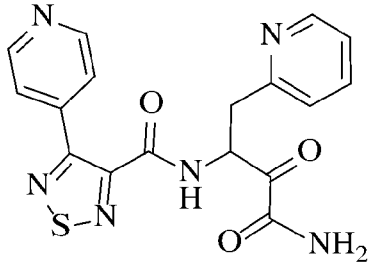
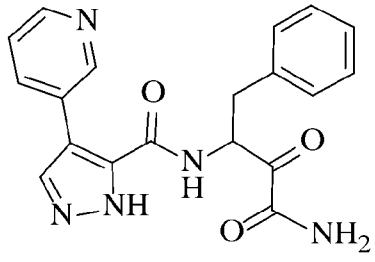	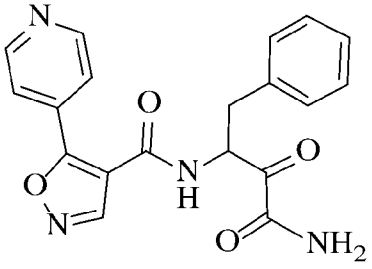	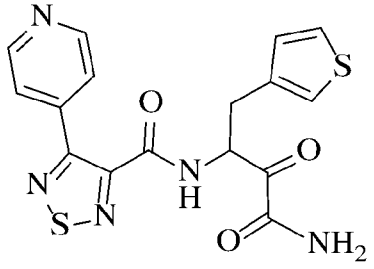

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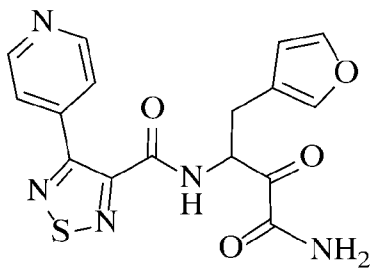	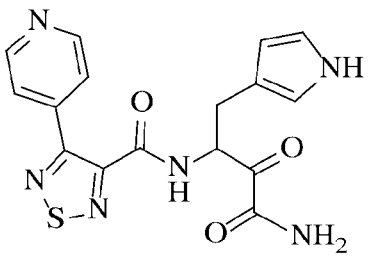	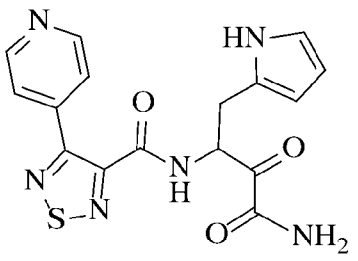
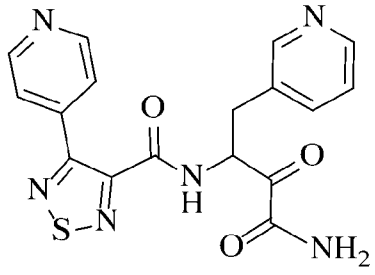	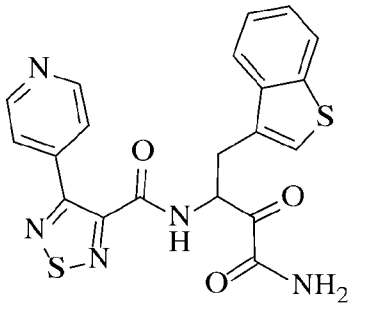	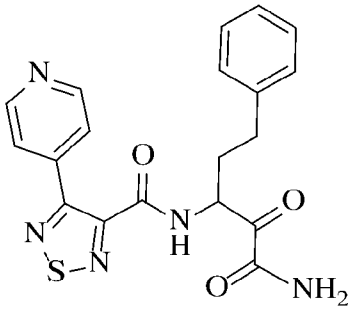
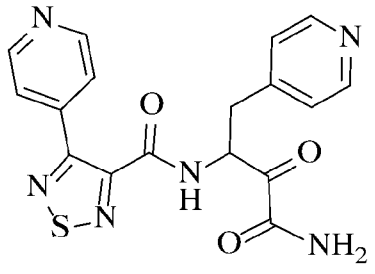	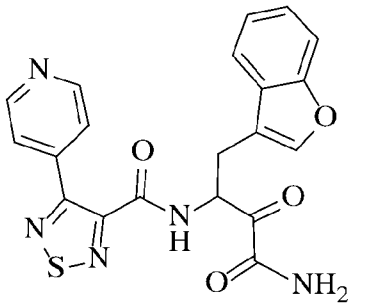	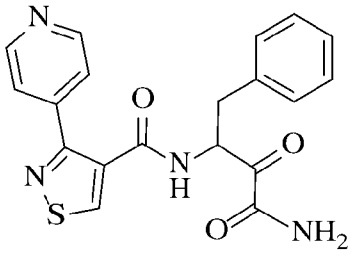
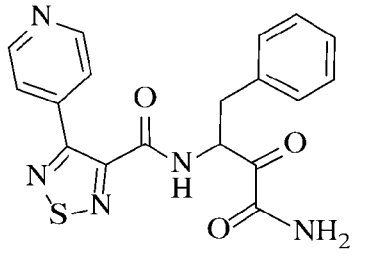	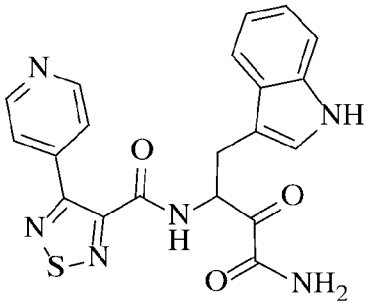	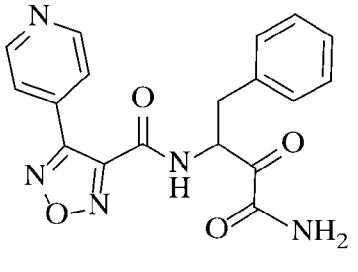

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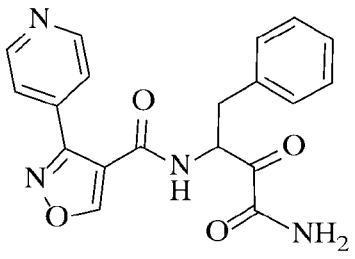	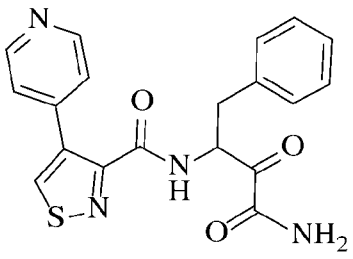	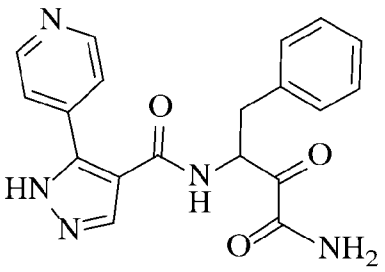
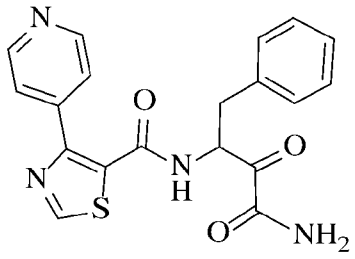	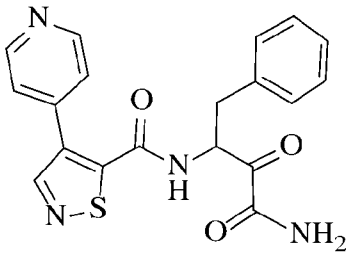	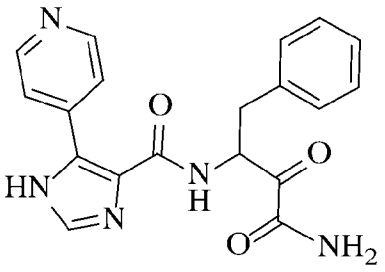
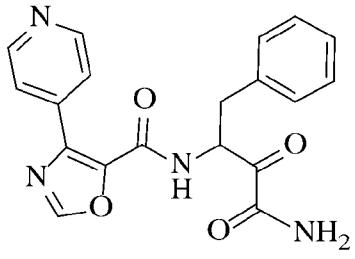	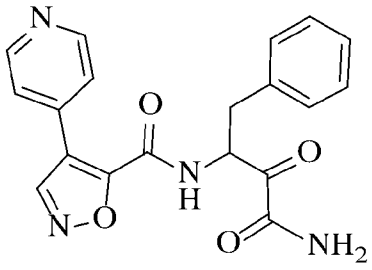	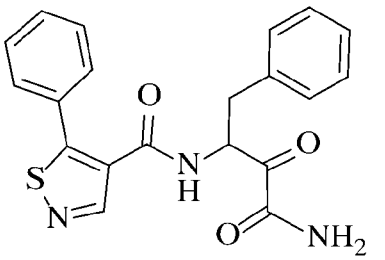
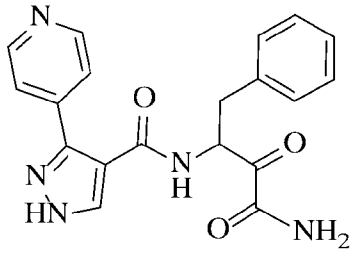	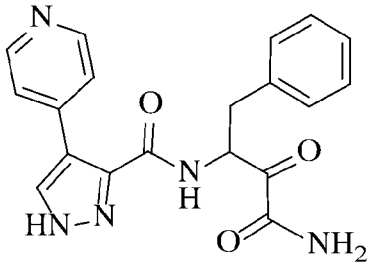	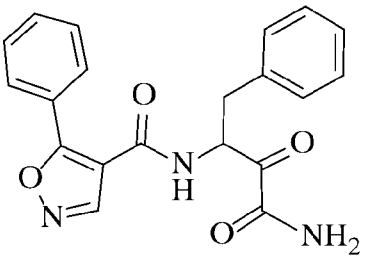

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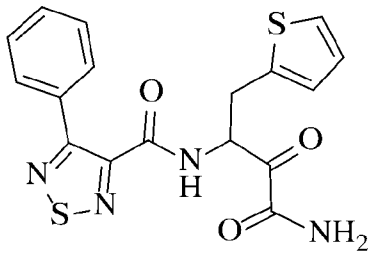	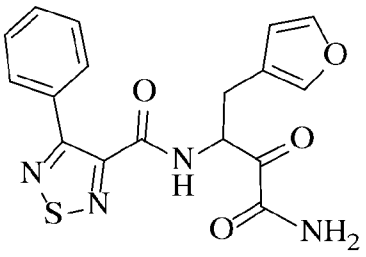	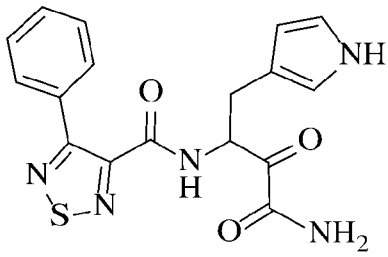
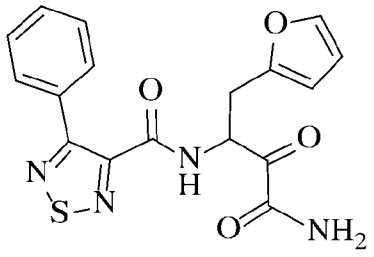	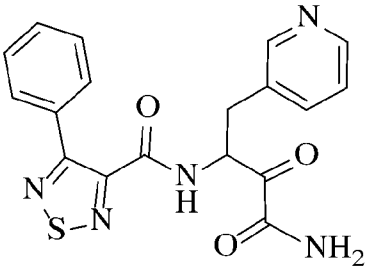	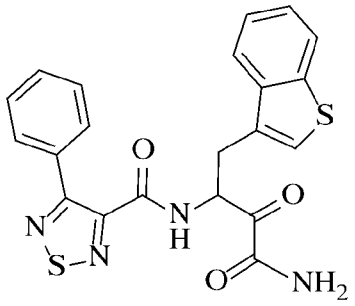
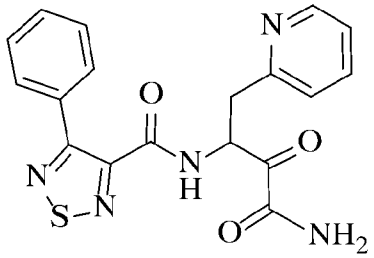	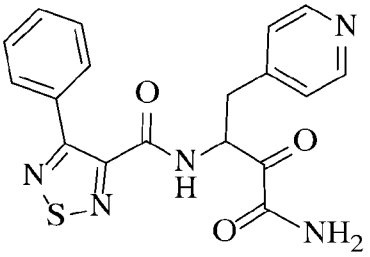	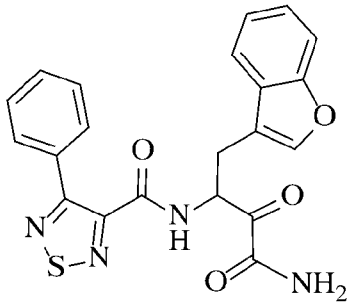
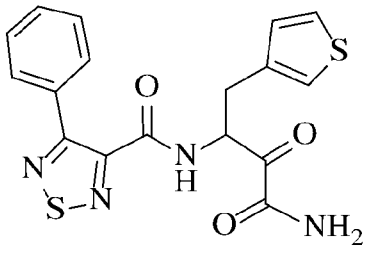	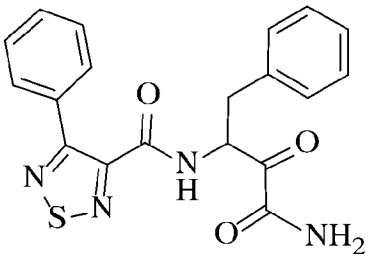	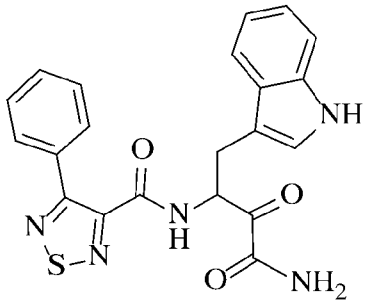

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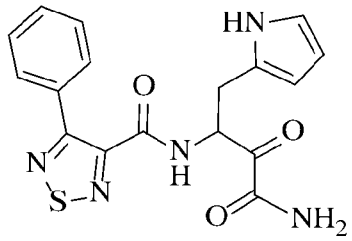	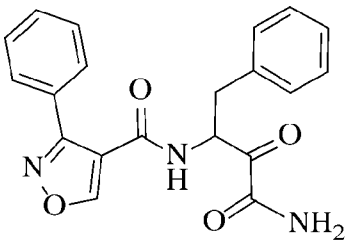	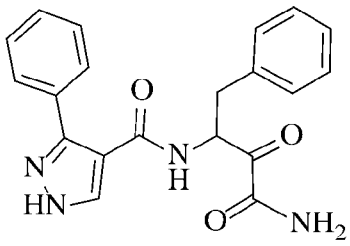
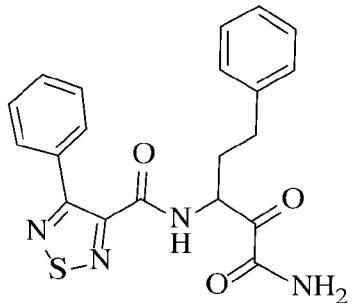	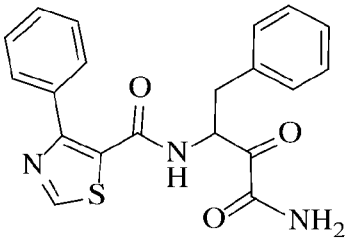	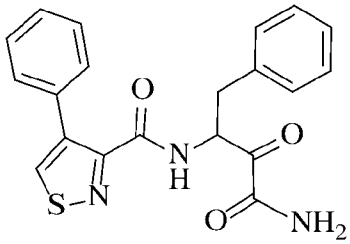
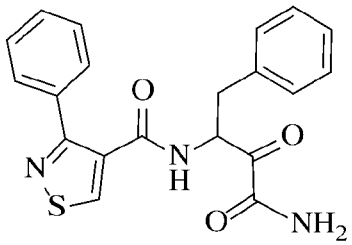	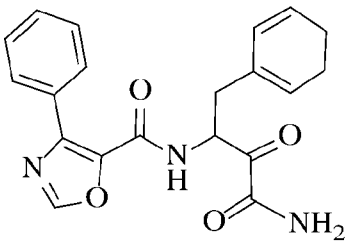	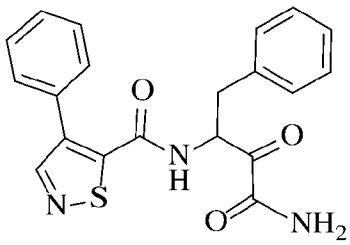
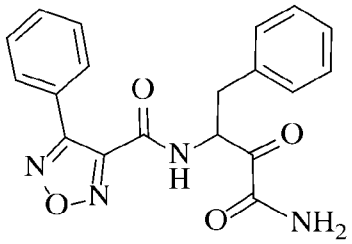	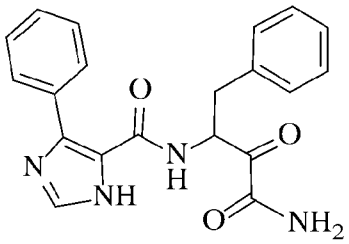	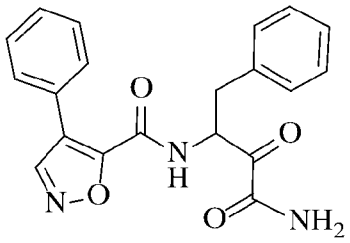

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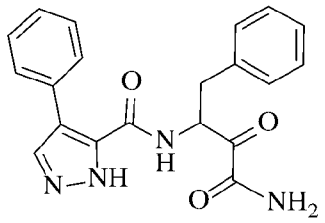	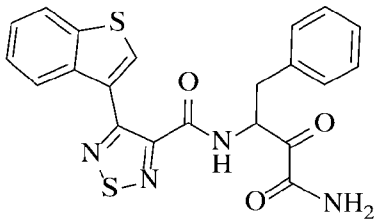	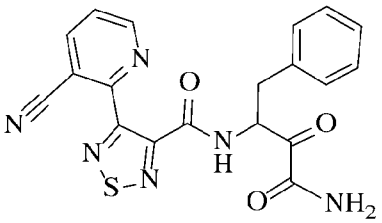
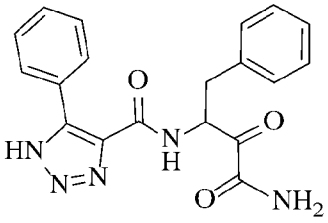	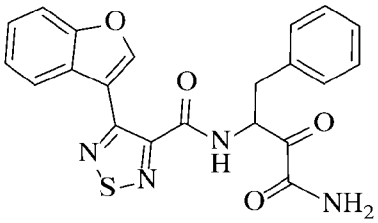	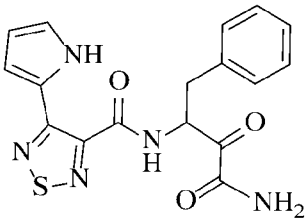
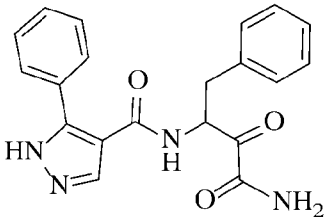	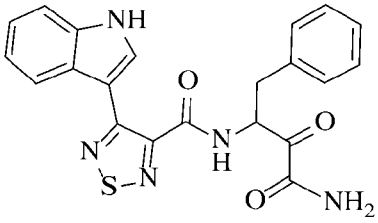	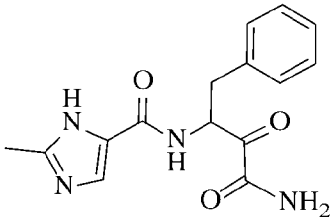
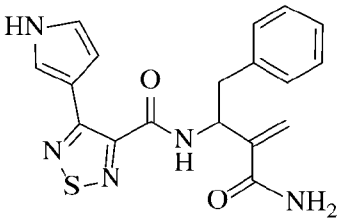	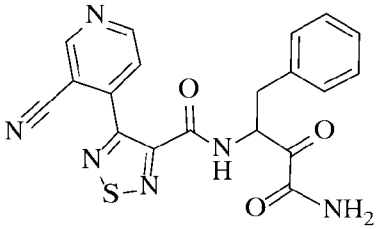	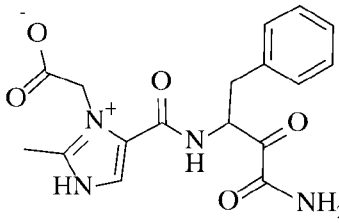

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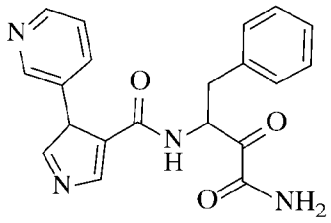	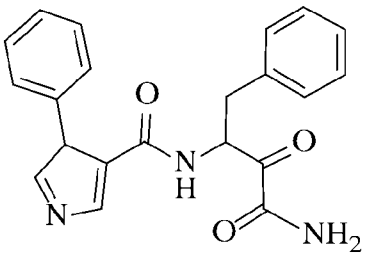	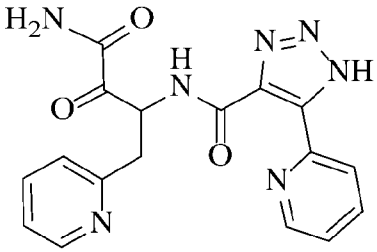
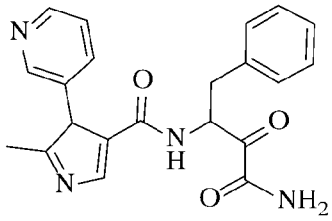	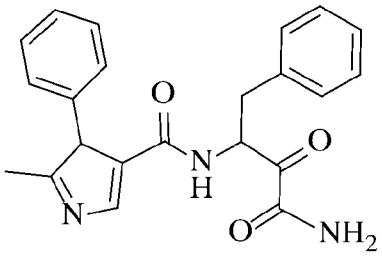	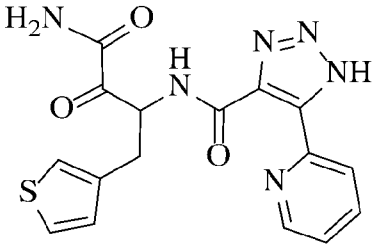
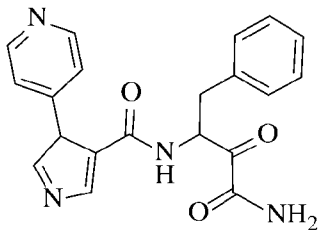	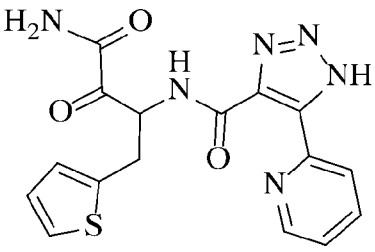	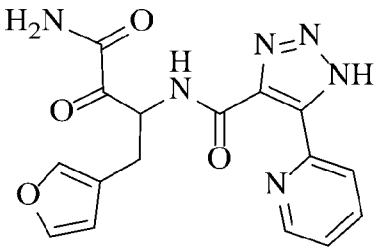
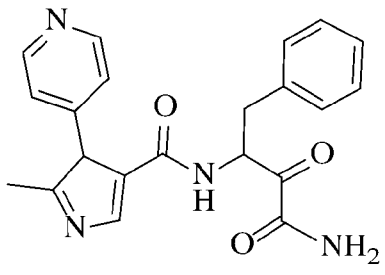	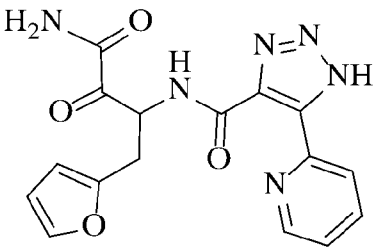	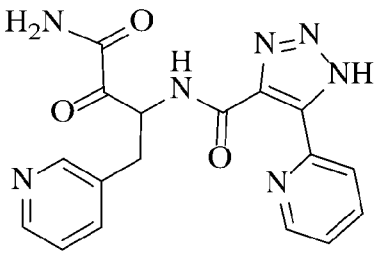

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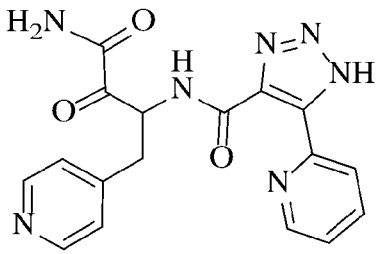	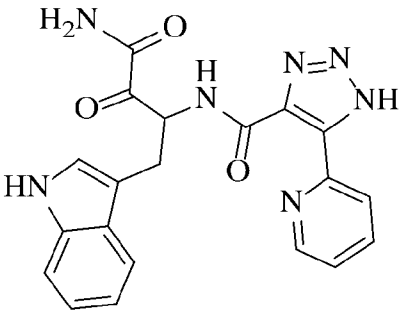	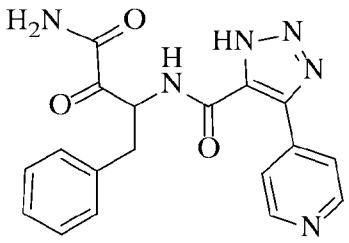
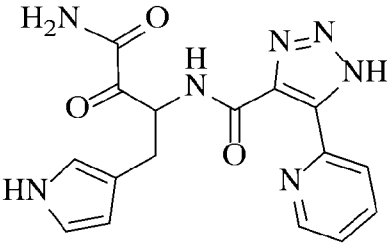	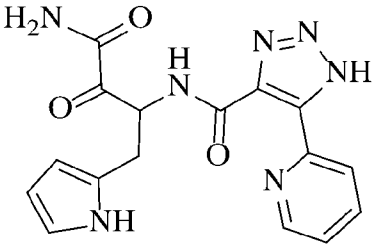	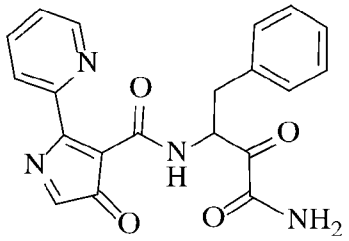
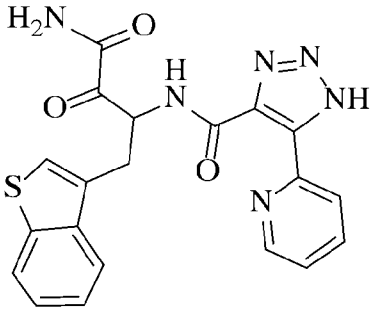	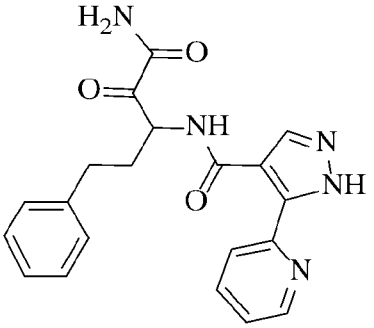	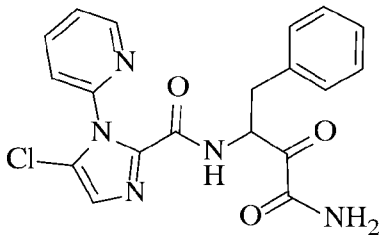
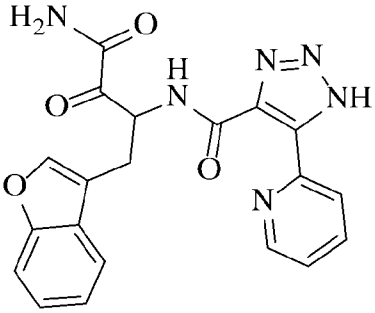	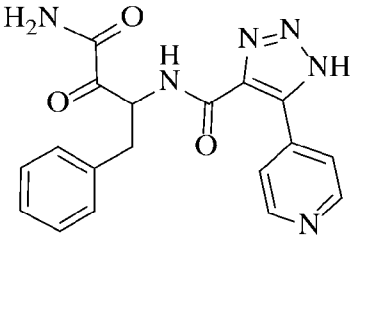	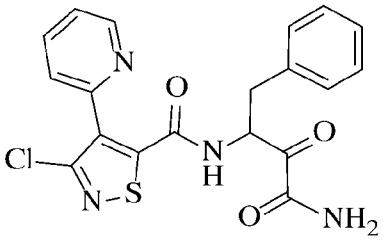

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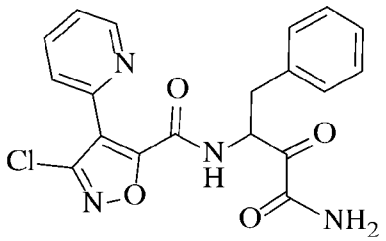	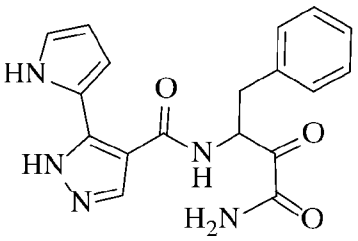	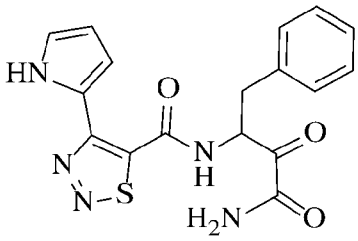
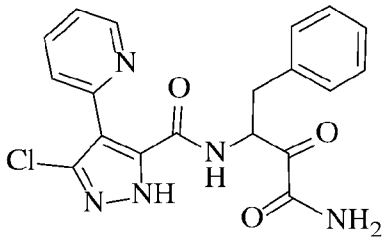	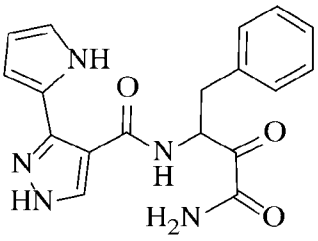	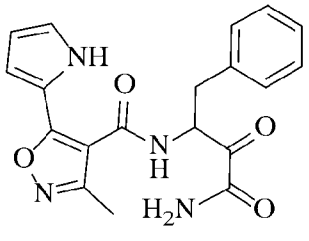
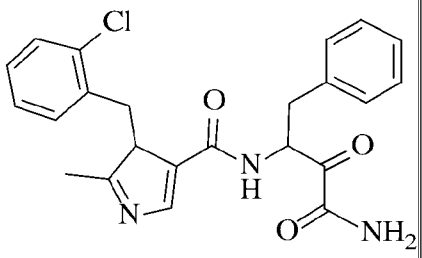	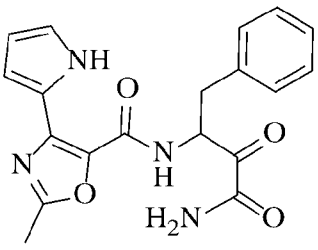	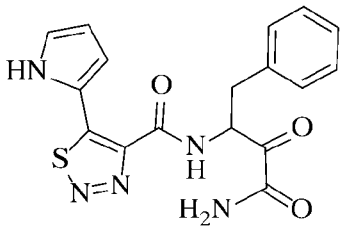
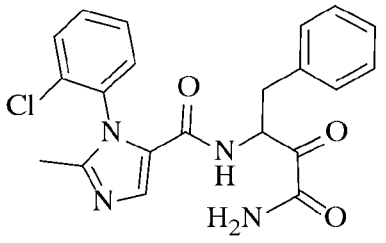	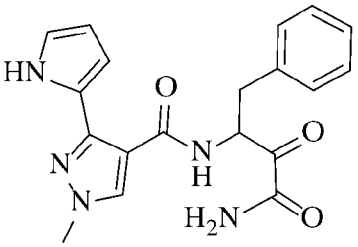	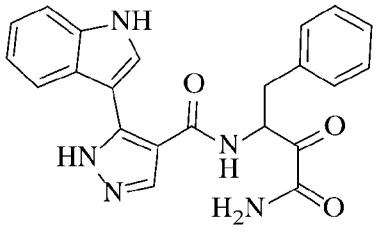

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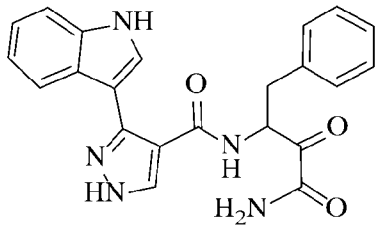	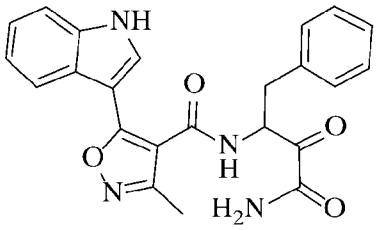	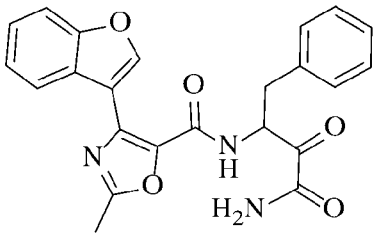
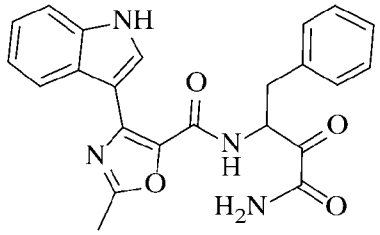	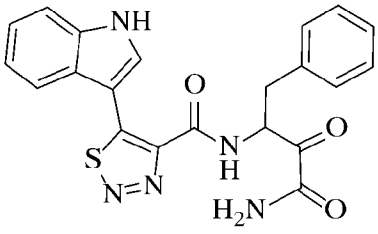	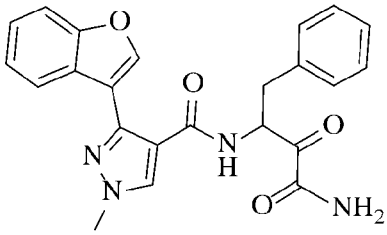
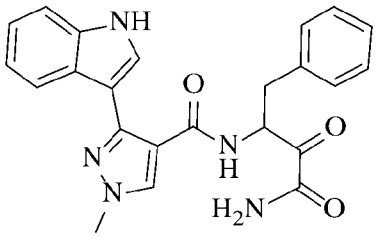	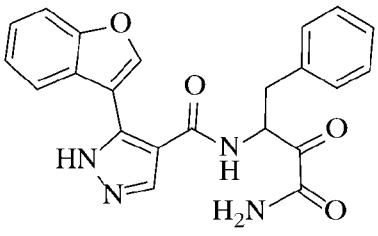	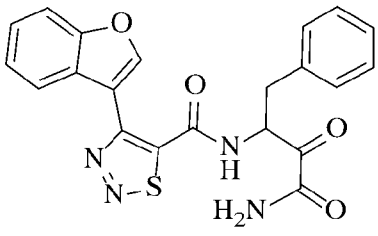
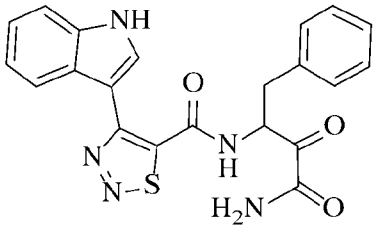	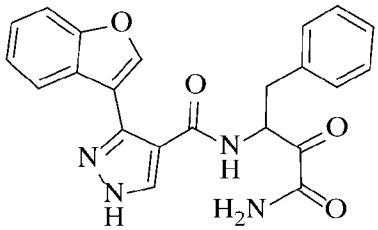	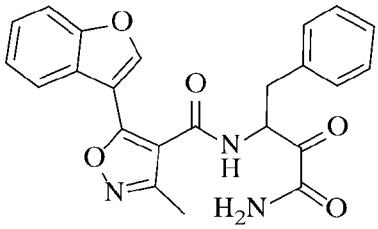

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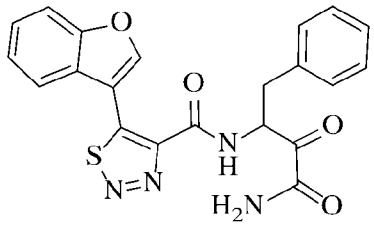	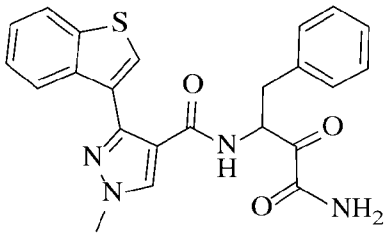	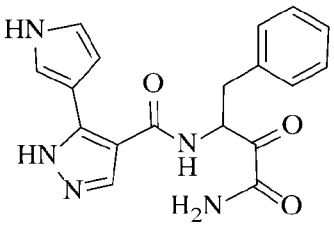
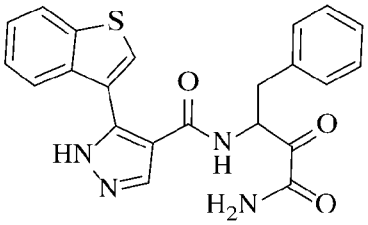	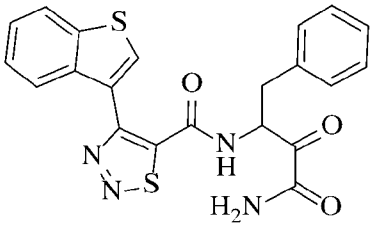	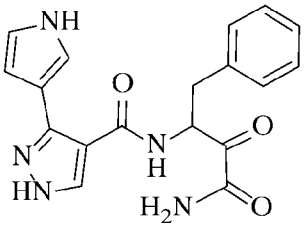
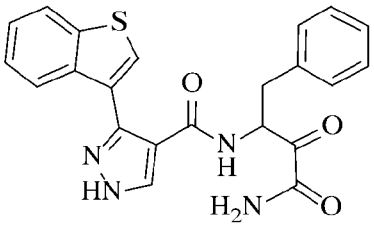	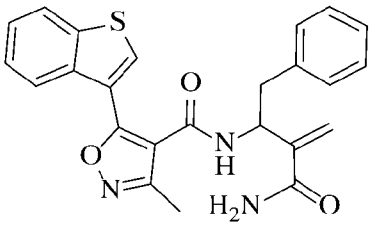	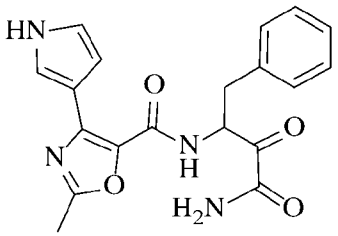
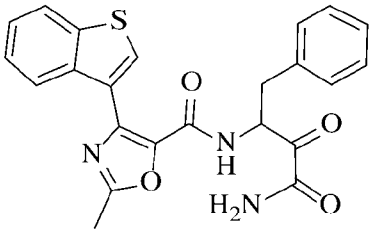	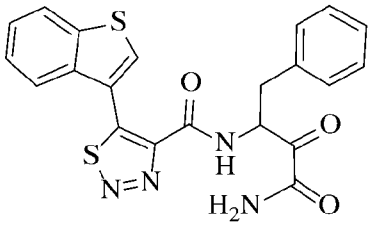	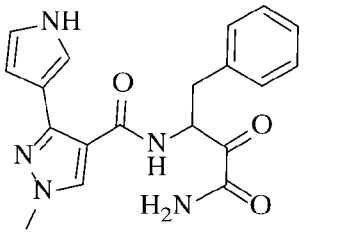

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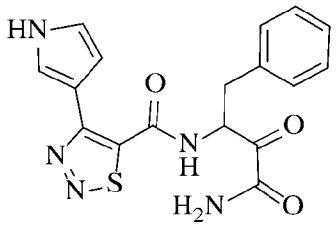	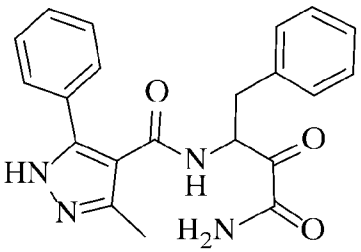	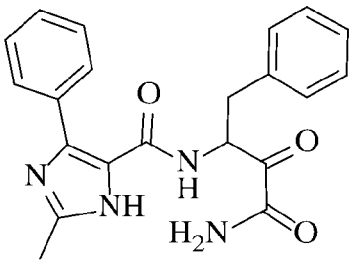
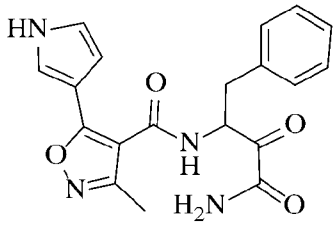	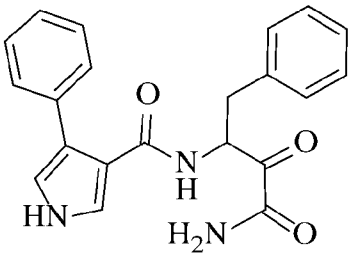	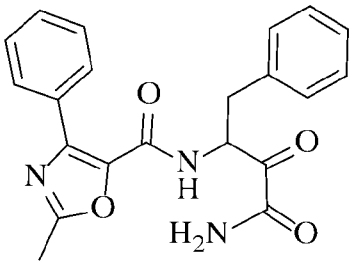
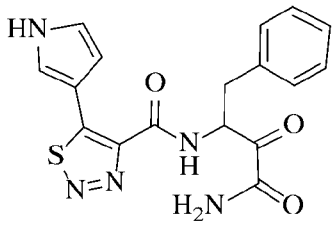	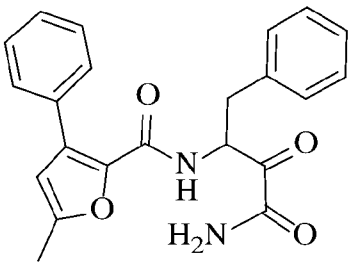	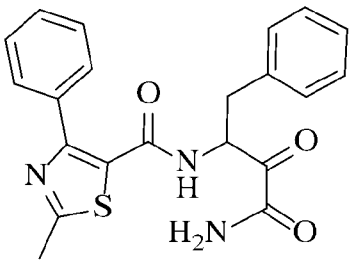
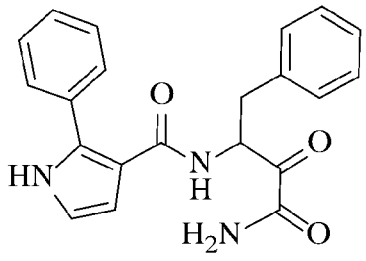	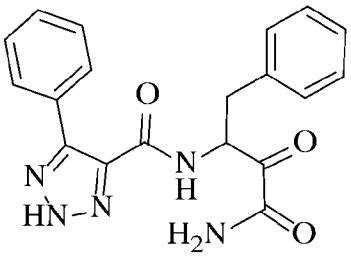	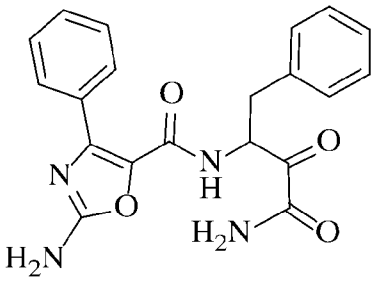

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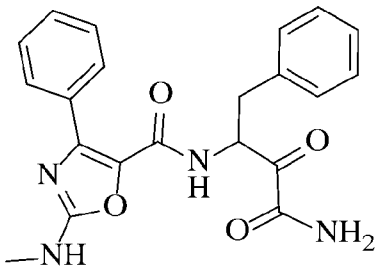	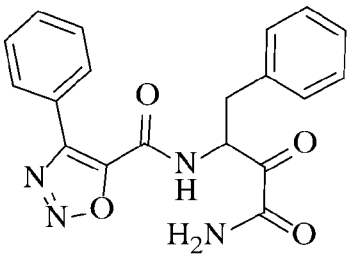	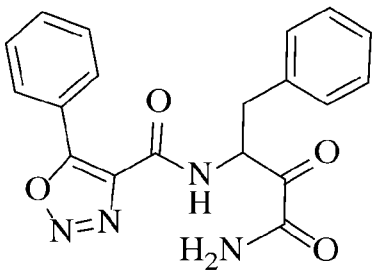
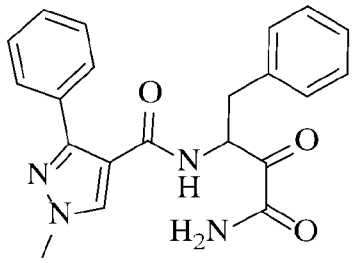	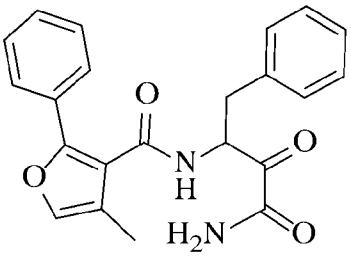	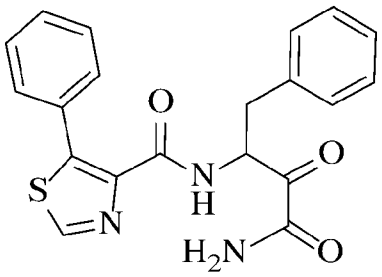
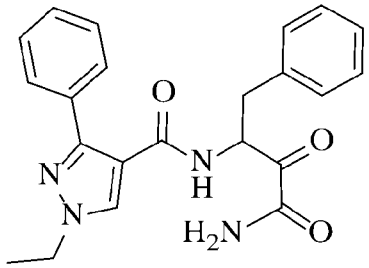	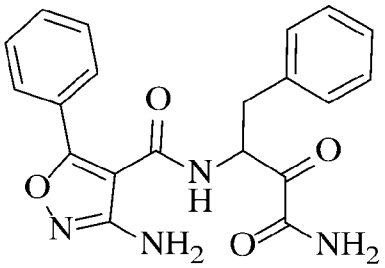	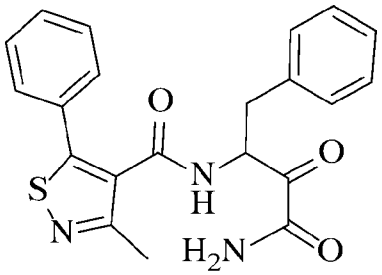
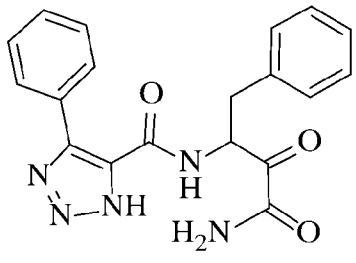	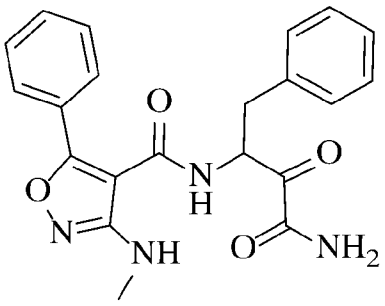	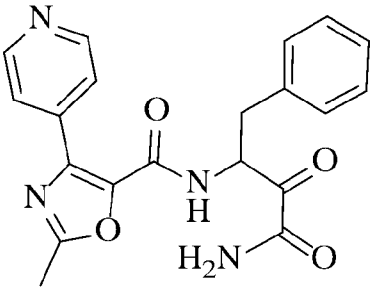

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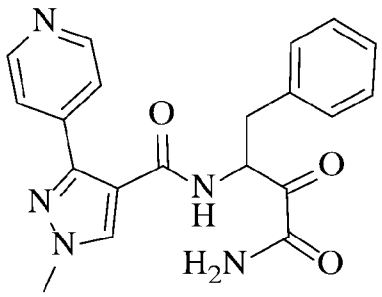	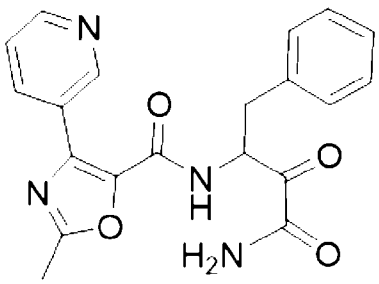	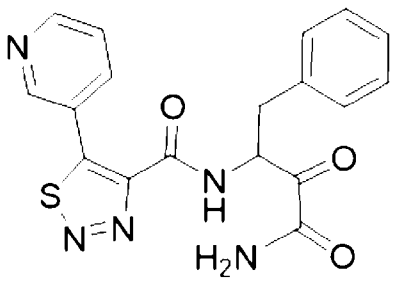
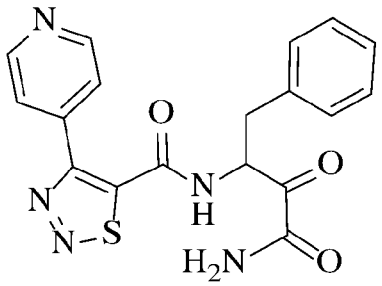	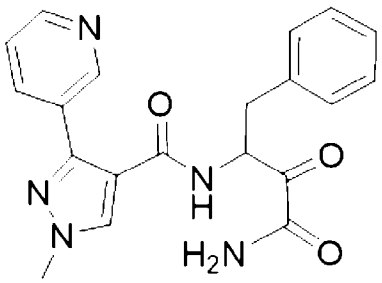	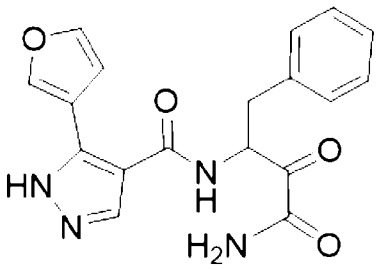
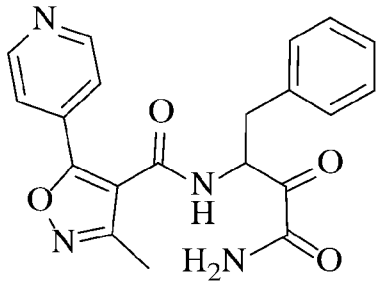	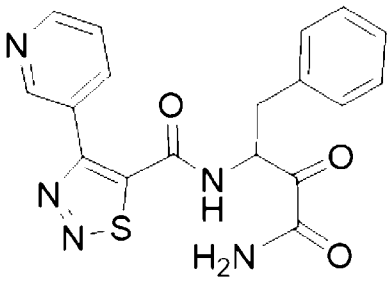	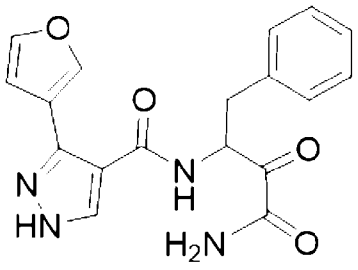
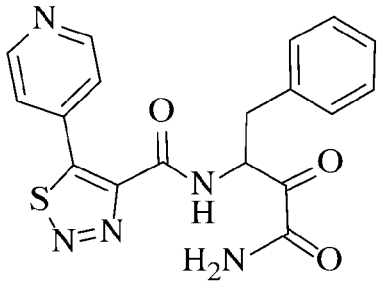	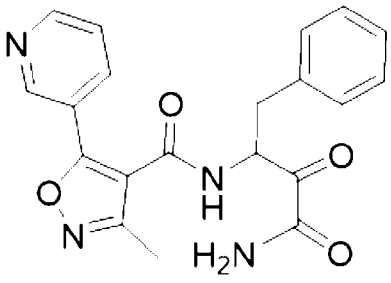	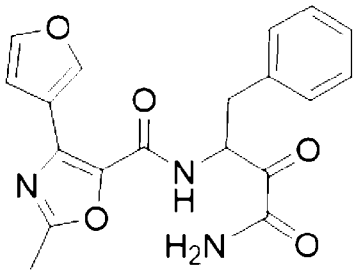

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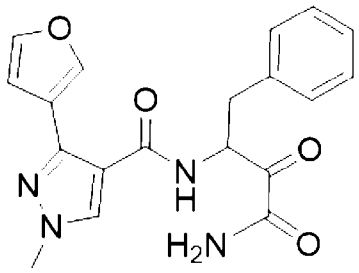	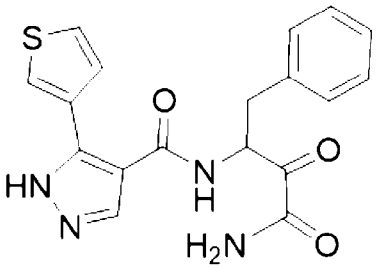	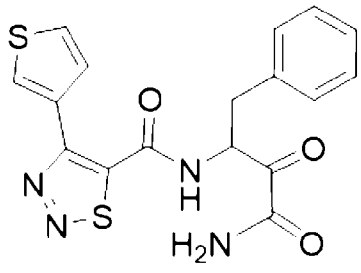
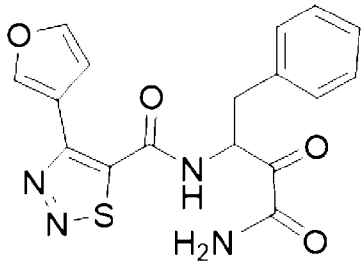	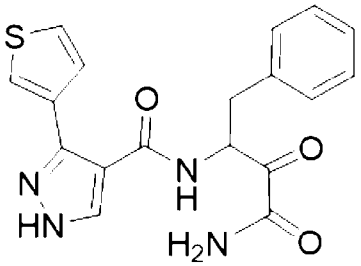	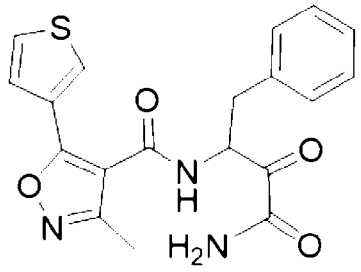
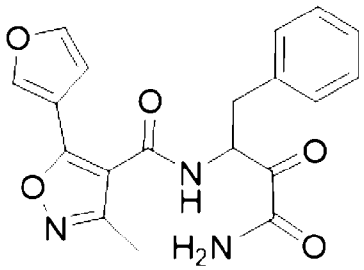	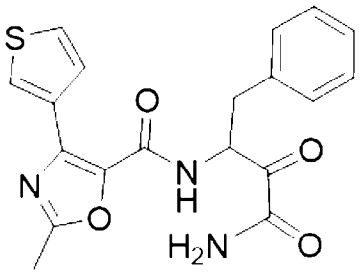	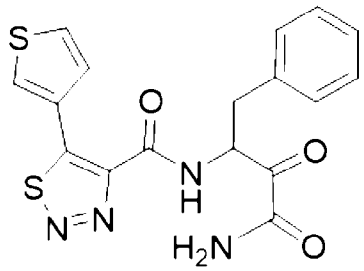
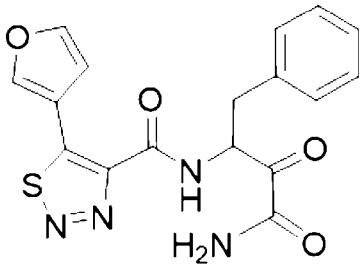	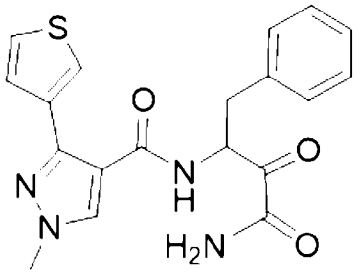	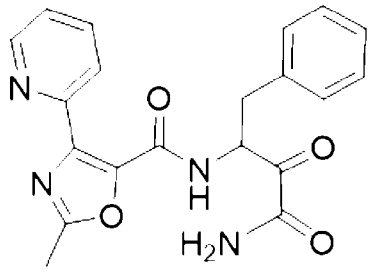

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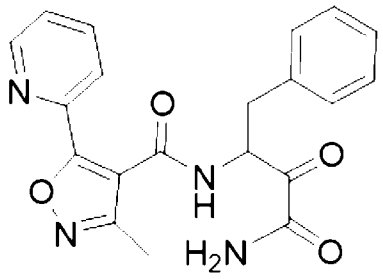	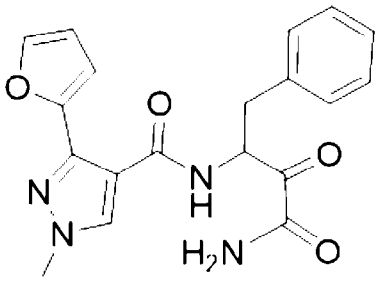	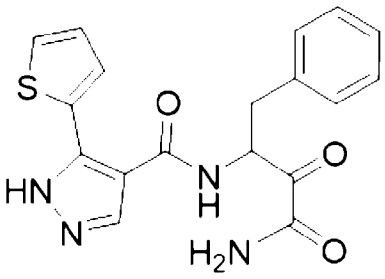
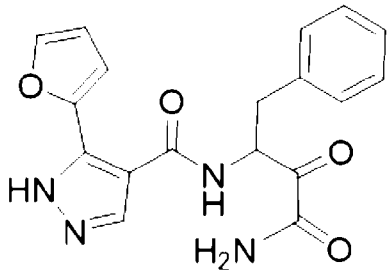	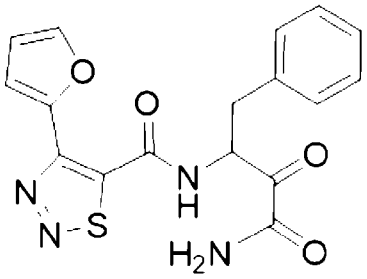	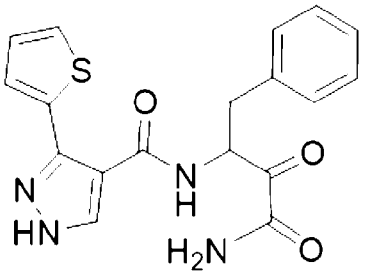
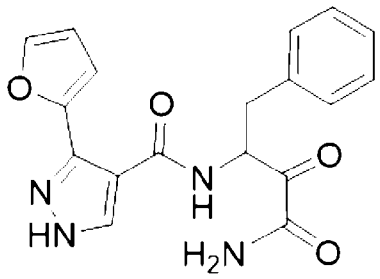	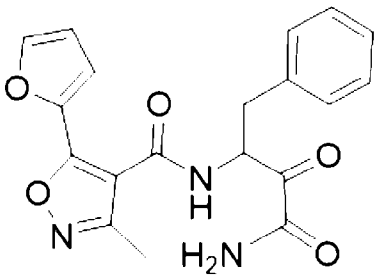	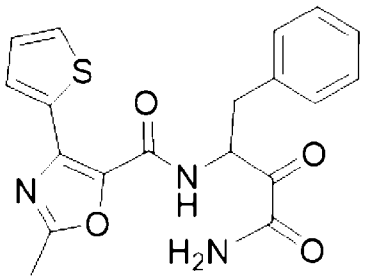
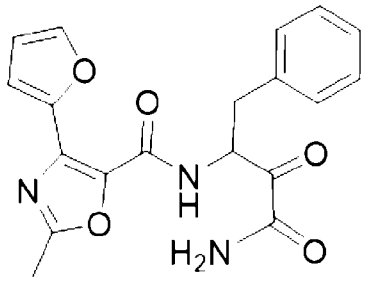	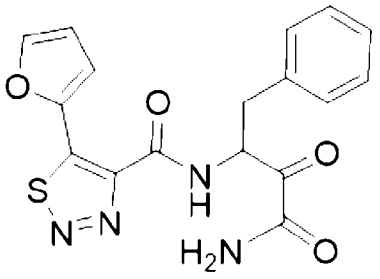	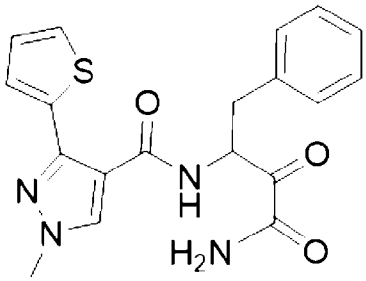

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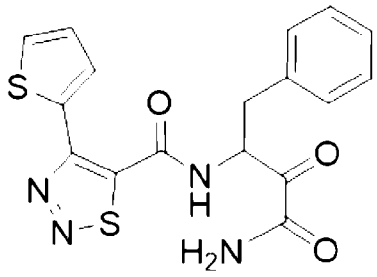	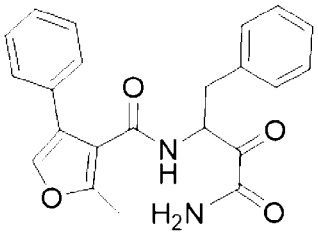	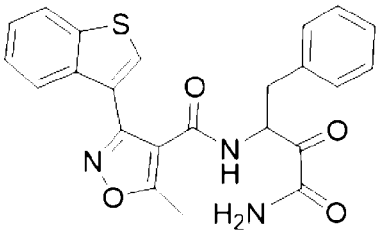
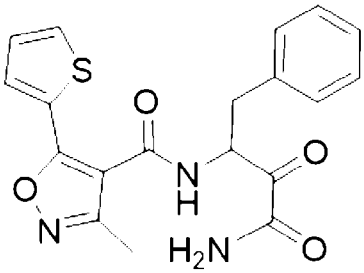	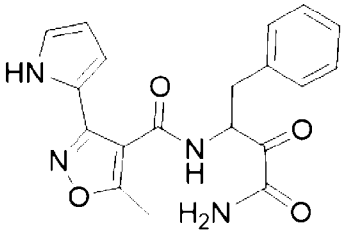	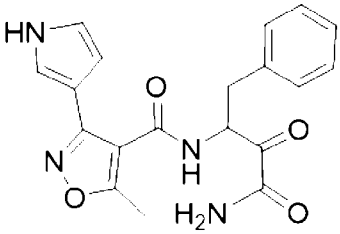
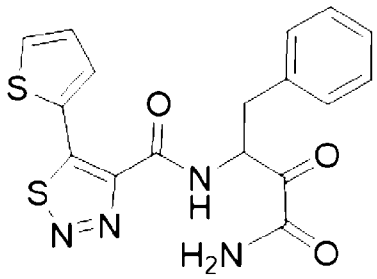	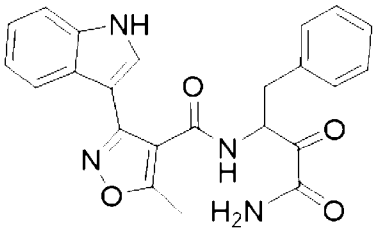	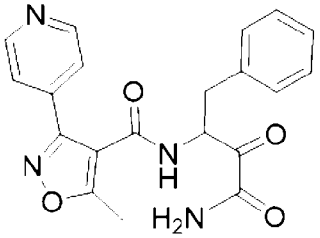
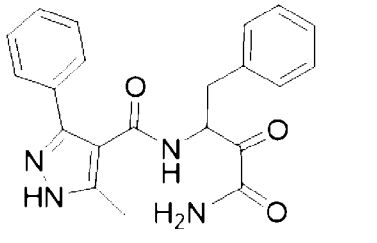	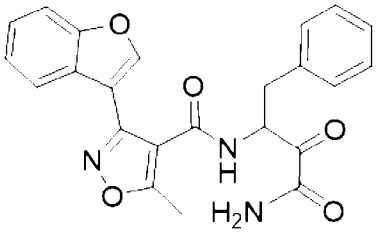	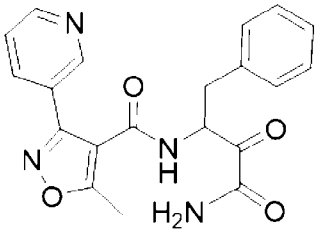

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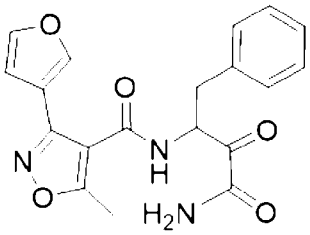	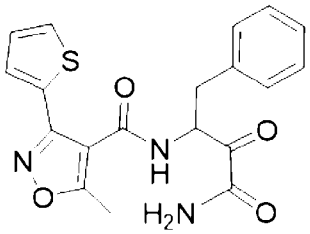	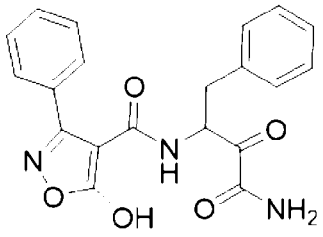
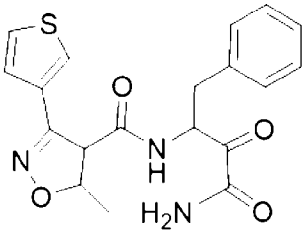	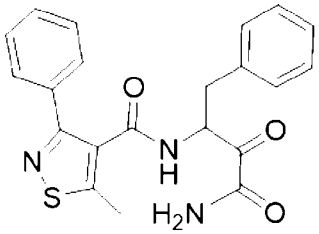	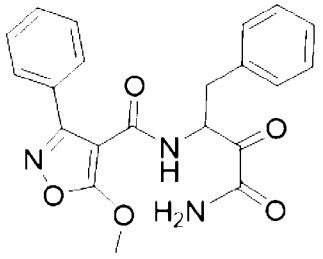
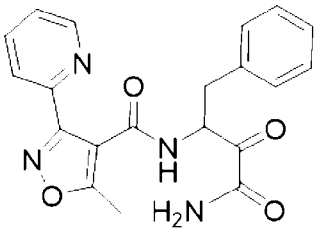	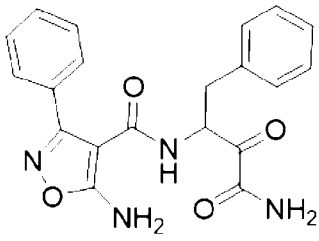	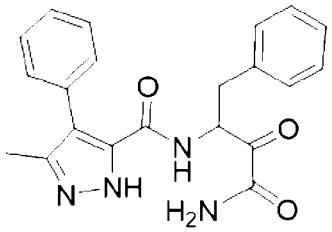
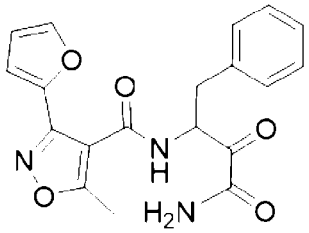	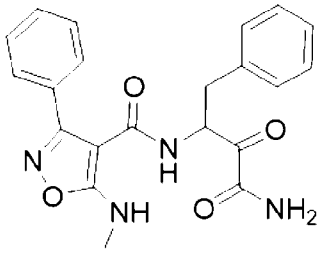	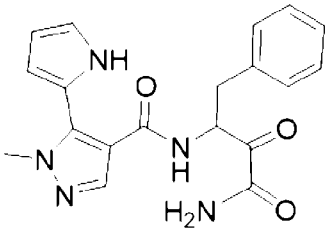

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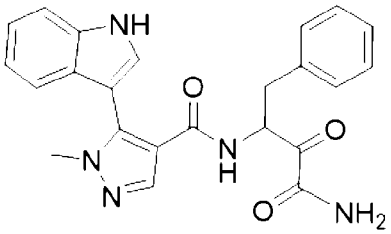	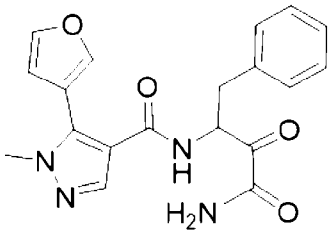	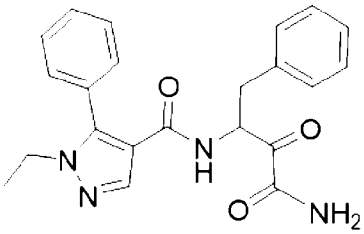
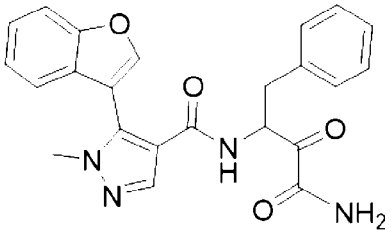	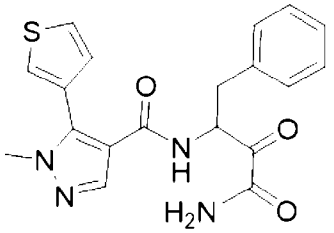	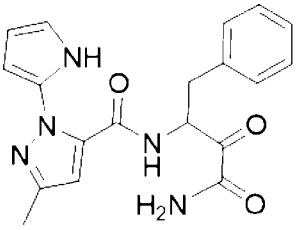
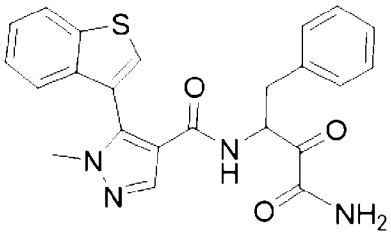	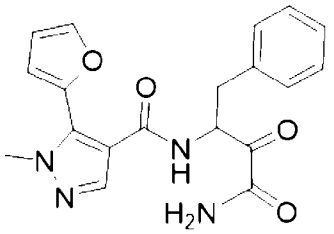	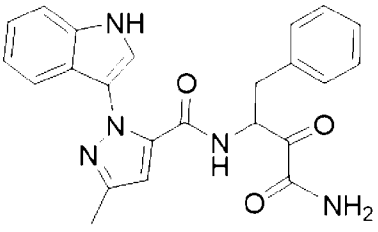
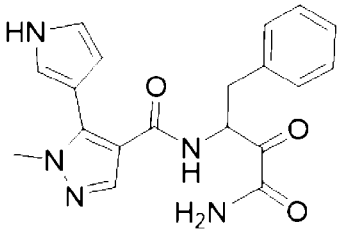	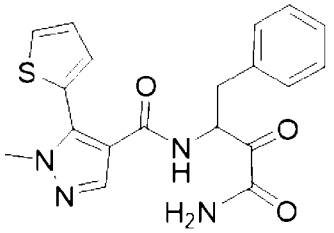	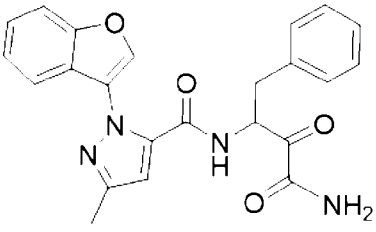

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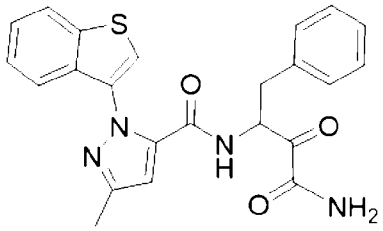	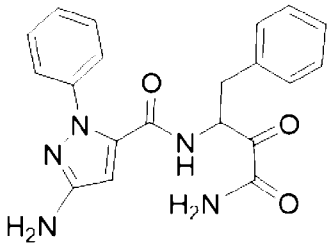	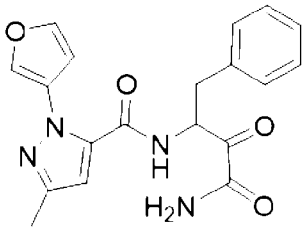
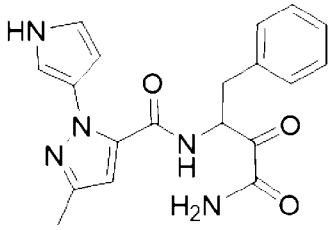	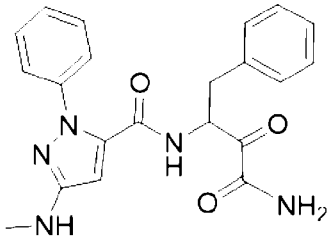	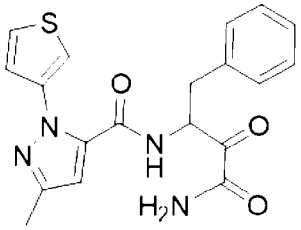
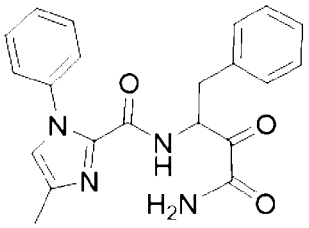	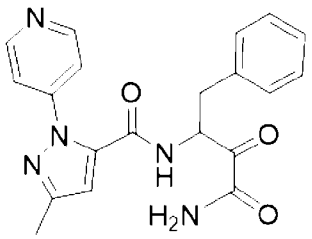	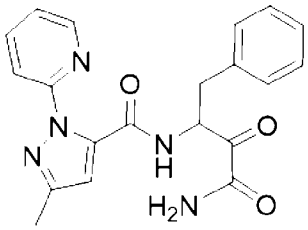
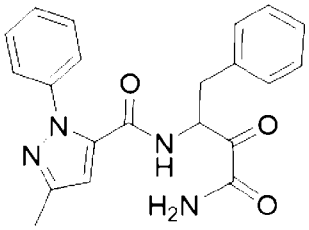	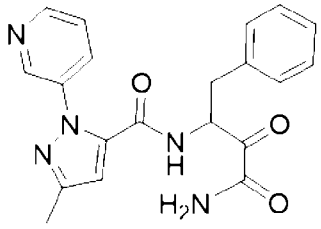	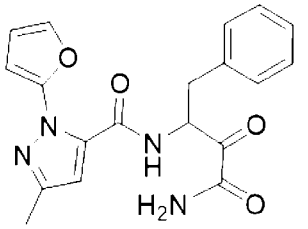

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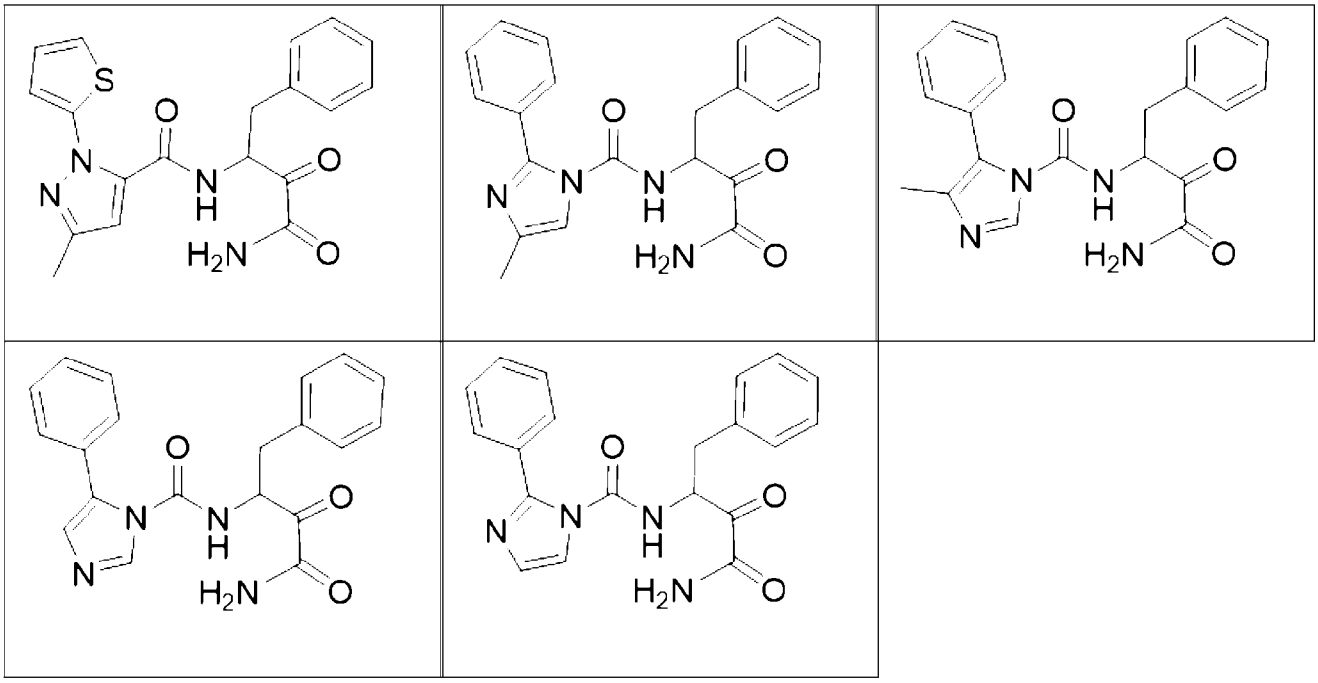


[0215] Where the compounds disclosed herein have at least one chiral center, they may exist as individual enantiomers and diastereomers or as mixtures of such isomers, including racemates. Separation of the individual isomers or selective synthesis of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art. Unless otherwise indicated, all such isomers and mixtures thereof are included in the scope of the compounds disclosed herein. Furthermore, compounds disclosed herein may exist in one or more crystalline or amorphous forms. Unless otherwise indicated, all such forms are included in the scope of the compounds disclosed herein including any polymorphic forms. In addition, some of the compounds disclosed herein may form solvates with water (i.e., hydrates) or common organic solvents. Unless otherwise indicated, such solvates are included in the scope of the compounds disclosed herein.

[0216] The skilled artisan will recognize that some structures described herein may be resonance forms or tautomers of compounds that may be fairly represented by other chemical structures, even when kinetically; the artisan recognizes that such structures may only represent a very small portion of a sample of such compound(s). Such compounds are considered within the scope of the structures depicted, though such resonance forms or tautomers are not represented herein.

Isotopically-Labeled Compounds

[0217] Isotopes may be present in the compounds described. Each chemical element as represented in a compound structure may include any isotope of said element. The isotopes may be isotopes of carbon, chlorine, fluorine, hydrogen, iodine, nitrogen, oxygen, phosphorous, sulfur, and technetium, including ^{11}C, ^{13}C, ^{14}C, ^{36}Cl, ^{18}F, ^{2}H, ^{3}H, ^{123}I, ^{125}I, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, and ^{99m}Tc. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise. Isotopically-labeled compounds of the present embodiments are useful in drug and substrate tissue distribution and target occupancy assays. For example, isotopically labeled compounds are

particularly useful in SPECT (single photon emission computed tomography) and in PET (positron emission tomography), as discussed further herein.

Definitions

[0218] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents, applications, published applications, and other publications are incorporated by reference in their entirety. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0219] A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, (ed. H. Bundgaard, Elsevier, 1985), which is hereby incorporated herein by reference in its entirety.

[0220] The term "pro-drug ester" refers to derivatives of the compounds disclosed herein formed by the addition of any of several ester-forming groups that are hydrolyzed under physiological conditions. Examples of pro-drug ester groups include pivoyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, as well as other such groups known in the art, including a (5-R-2-oxo-1,3-dioxolen-4-yl)methyl group. Other examples of pro-drug ester groups can be found in, for example, T. Higuchi and V. Stella, in "Pro-drugs as Novel Delivery Systems", Vol. 14, A.C.S. Symposium Series, American Chemical Society (1975); and "Bioreversible Carriers in Drug Design: Theory and Application", edited by E. B. Roche, Pergamon Press: New York, 14-21 (1987) (providing examples of esters useful as prodrugs for

compounds containing carboxyl groups). Each of the above-mentioned references is herein incorporated by reference in their entirety.

[0221] "Metabolites" of the compounds disclosed herein include active species that are produced upon introduction of the compounds into the biological milieu.

[0222] "Solvate" refers to the compound formed by the interaction of a solvent and a compound described herein, a metabolite, or salt thereof. Suitable solvates are pharmaceutically acceptable solvates including hydrates.

[0223] The term "pharmaceutically acceptable salt" refers to salts that retain the biological effectiveness and properties of a compound, which are not biologically or otherwise undesirable for use in a pharmaceutical. In many cases, the compounds herein are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like; particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. Many such salts are known in the art, as described in WO 87/05297, Johnston et al., published September 11, 1987 (incorporated by reference herein in its entirety).

[0224] As used herein, "C_a to C_b" or "C_{a-b}" in which "a" and "b" are integers refer to the number of carbon atoms in the specified group. That is, the group can contain from "a" to

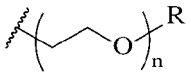
"b", inclusive, carbon atoms. Thus, for example, a "C_1 to C_4 alkyl" or "C_{1-4} alkyl" group refers to all alkyl groups having from 1 to 4 carbons, that is, CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$- and $(CH_3)_3C$-.

[0225] The term "halogen" or "halo," as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, *e.g.*, fluorine, chlorine, bromine, or iodine, with fluorine and chlorine being preferred.

[0226] As used herein, "alkyl" refers to a straight or branched hydrocarbon chain that is fully saturated (i.e., contains no double or triple bonds). The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; *e.g.*, "1 to 20 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 9 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 4 carbon atoms. The alkyl group of the compounds may be designated as "C_{1-4} alkyl" or similar designations. By way of example only, "C_{1-4} alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, and the like.

[0227] As used herein, "haloalkyl" refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms in the chain, substituting one or more hydrogens with halogens. Examples of haloalkyl groups include, but are not limited to, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CF_2CF_3$ and other groups that in light of the ordinary skill in the art and the teachings provided herein, would be considered equivalent to any one of the foregoing examples.

[0228] As used herein, "alkoxy" refers to the formula –OR wherein R is an alkyl as is defined above, such as "C_{1-9} alkoxy", including but not limited to methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, and tert-butoxy, and the like.

[0229] As used herein, "polyethylene glycol" refers to the formula  wherein n is an integer greater than one and R is a hydrogen or alkyl. The number of repeat units "n" may be indicated by referring to a number of members. Thus, for example, "2- to 5-membered polyethylene glycol" refers to n being an integer selected from two to five. In some embodiments, R is selected from methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, and tert-butoxy.

[0230] As used herein, "heteroalkyl" refers to a straight or branched hydrocarbon chain containing one or more heteroatoms, that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur, in the chain backbone. The heteroalkyl group may have 1 to 20 carbon atoms although the present definition also covers the occurrence of the term "heteroalkyl" where no numerical range is designated. The heteroalkyl group may also be a medium size heteroalkyl having 1 to 9 carbon atoms. The heteroalkyl group could also be a lower heteroalkyl having 1 to 4 carbon atoms. In various embodiments, the heteroalkyl may have from 1 to 4 heteroatoms, from 1 to 3 heteroatoms, 1 or 2 heteroatoms, or 1 heteroatom. The heteroalkyl group of the compounds may be designated as "C_{1-4} heteroalkyl" or similar designations. The heteroalkyl group may contain one or more heteroatoms. By way of example only, "C_{1-4} heteroalkyl" indicates that there are one to four carbon atoms in the heteroalkyl chain and additionally one or more heteroatoms in the backbone of the chain.

[0231] The term "aromatic" refers to a ring or ring system having a conjugated pi electron system and includes both carbocyclic aromatic (e.g., phenyl) and heterocyclic aromatic groups (e.g., pyridine). The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of atoms) groups provided that the entire ring system is aromatic.

[0232] As used herein, "aryl" refers to an aromatic ring or ring system (i.e., two or more fused rings that share two adjacent carbon atoms) containing only carbon in the ring backbone. When the aryl is a ring system, every ring in the system is aromatic. The aryl group may have 6 to 18 carbon atoms, although the present definition also covers the occurrence of the term "aryl" where no numerical range is designated. In some embodiments, the aryl group has 6 to 10 carbon atoms. The aryl group may be designated as "C_{6-10} aryl," "C_6 or C_{10} aryl," or similar

designations. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, azulenyl, and anthracenyl.

[0233] As used herein, "aryloxy" and "arylthio" refers to RO- and RS-, in which R is an aryl as is defined above, such as "C_{6-10} aryloxy" or "C_{6-10} arylthio" and the like, includingbut not limited to phenyloxy.

[0234] An "aralkyl" or "arylalkyl" is an aryl group connected, as a substituent, via an alkylene group, such "C_{7-14} aralkyl" and the like, including but not limited to benzyl, 2-phenylethyl, 3-phenylpropyl, and naphthylalkyl. In some cases, the alkylene group is a lower alkylene group (i.e., a C_{1-4} alkylene group).

[0235] As used herein, "heteroaryl" refers to an aromatic ring or ring system (i.e., two or more fused rings that share two adjacent atoms) that contain(s) one or more heteroatoms, that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur, in the ring backbone. When the heteroaryl is a ring system, every ring in the system is aromatic. The heteroaryl group may have 5-18 ring members (i.e., the number of atoms making up the ring backbone, including carbon atoms and heteroatoms), although the present definition also covers the occurrence of the term "heteroaryl" where no numerical range is designated. In some embodiments, the heteroaryl group has 5 to 10 ring members or 5 to 7 ring members. The heteroaryl group may be designated as "5-7 membered heteroaryl," "5-10 membered heteroaryl," or similar designations. In various embodiments, a heteroaryl contains from 1 to 4 heteroatoms, from 1 to 3 heteroatoms, from 1 to 2 heteroatoms, or 1 heteroatom. For example, in various embodiments, a heteroaryl contains 1 to 4 nitrogen atoms, 1 to 3 nitrogen atoms, 1 to 2 nitrogen atoms, 2 nitrogen atoms and 1 sulfur or oxygen atom, 1 nitrogen atom and 1 sulfur or oxygen atom, or 1 sulfur or oxygen atom. Examples of heteroaryl rings include, but are not limited to, furyl, thienyl, phthalazinyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, quinolinyl, isoquinlinyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indolyl, isoindolyl, and benzothienyl.

[0236] A "heteroaralkyl" or "heteroarylalkyl" is heteroaryl group connected, as a substituent, via an alkylene group. Examples include but are not limited to 2-thienylmethyl, 3-thienylmethyl, furylmethyl, thienylethyl, pyrrolylalkyl, pyridylalkyl, isoxazollylalkyl, and

imidazolylalkyl. In some cases, the alkylene group is a lower alkylene group (i.e., a C_{1-4} alkylene group).

[0237] As used herein, "carbocyclyl" means a non-aromatic cyclic ring or ring system containing only carbon atoms in the ring system backbone. When the carbocyclyl is a ring system, two or more rings may be joined together in a fused, bridged or spiro-connected fashion. Carbocyclyls may have any degree of saturation provided that at least one ring in a ring system is not aromatic. Thus, carbocyclyls include cycloalkyls, cycloalkenyls, and cycloalkynyls. The carbocyclyl group may have 3 to 20 carbon atoms, although the present definition also covers the occurrence of the term "carbocyclyl" where no numerical range is designated. The carbocyclyl group may also be a medium size carbocyclyl having 3 to 10 carbon atoms. The carbocyclyl group could also be a carbocyclyl having 3 to 6 carbon atoms. The carbocyclyl group may be designated as "C_{3-6} carbocyclyl" or similar designations. Examples of carbocyclyl rings include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,3-dihydro-indene, bicycle[2.2.2]octanyl, adamantyl, and spiro[4.4]nonanyl.

[0238] A "(carbocyclyl)alkyl" is a carbocyclyl group connected, as a substituent, via an alkylene group, such as "C_{4-10} (carbocyclyl)alkyl" and the like, including but not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopropylethyl, cyclopropylbutyl, cyclobutylethyl, cyclopropylisopropyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, cycloheptylmethyl, and the like. In some cases, the alkylene group is a lower alkylene group.

[0239] As used herein, "cycloalkyl" means a fully saturated carbocyclyl ring or ring system. Examples include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0240] As used herein, "cycloalkenyl" means a carbocyclyl ring or ring system having at least one double bond, wherein no ring in the ring system is aromatic. An example is cyclohexenyl.

[0241] As used herein, "heterocyclyl" means a non-aromatic cyclic ring or ring system containing at least one heteroatom in the ring backbone. Heterocyclyls may be joined together in a fused, bridged or spiro-connected fashion. Heterocyclyls may have any degree of saturation provided that at least one ring in the ring system is not aromatic. The heteroatom(s) may be present in either a non-aromatic or aromatic ring in the ring system. The heterocyclyl group may have 3 to 20 ring members (i.e., the number of atoms making up the ring backbone,

including carbon atoms and heteroatoms), although the present definition also covers the occurrence of the term "heterocyclyl" where no numerical range is designated. The heterocyclyl group may also be a medium size heterocyclyl having 3 to 10 ring members. The heterocyclyl group could also be a heterocyclyl having 3 to 6 ring members. The heterocyclyl group may be designated as "3-6 membered heterocyclyl" or similar designations.

[0242] In various embodiments, a heterocyclyl contains from 1 to 4 heteroatoms, from 1 to 3 heteroatoms, from 1 to 2 heteroatoms, or 1 heteroatom. For example, in various embodiments, a heterocyclyl contains 1 to 4 nitrogen atoms, 1 to 3 nitrogen atoms, 1 to 2 nitrogen atoms, 2 nitrogen atoms and 1 sulfur or oxygen atom, 1 nitrogen atom and 1 sulfur or oxygen atom, or 1 sulfur or oxygen atom. In preferred six membered monocyclic heterocyclyls, the heteroatom(s) are selected from one up to three of O, N or S, and in preferred five membered monocyclic heterocyclyls, the heteroatom(s) are selected from one or two heteroatoms selected from O, N, or S. Examples of heterocyclyl rings include, but are not limited to, azepinyl, acridinyl, carbazolyl, cinnolinyl, dioxolanyl, imidazolinyl, imidazolidinyl, morpholinyl, oxiranyl, oxepanyl, thiepanyl, piperidinyl, piperazinyl, dioxopiperazinyl, pyrrolidinyl, pyrrolidonyl, pyrrolidionyl, 4-piperidonyl, pyrazolinyl, pyrazolidinyl, 1,3-dioxinyl, 1,3-dioxanyl, 1,4-dioxinyl, 1,4-dioxanyl, 1,3-oxathianyl, 1,4-oxathiinyl, 1,4-oxathianyl, 2*H*-1,2-oxazinyl, trioxanyl, hexahydro-1,3,5-triazinyl, 1,3-dioxolyl, 1,3-dioxolanyl, 1,3-dithiolyl, 1,3-dithiolanyl, isoxazolinyl, isoxazolidinyl, oxazolinyl, oxazolidinyl, oxazolidinonyl, thiazolinyl, thiazolidinyl, 1,3-oxathiolanyl, indolinyl, isoindolinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydro-1,4-thiazinyl, thiamorpholinyl, dihydrobenzofuranyl, benzimidazolidinyl, and tetrahydroquinoline.

[0243] A "(heterocyclyl)alkyl" is a heterocyclyl group connected, as a substituent, via an alkylene group. Examples include, but are not limited to, imidazolinylmethyl and indolinylethyl.

[0244] As used herein, "acyl" refers to –C(=O)R, wherein R is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein. Non-limiting examples include formyl, acetyl, propanoyl, benzoyl, and acryl.

[0245] An "O-carboxy" group refers to a "-OC(=O)R" group in which R is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0246] A "C-carboxy" group refers to a "-C(=O)OR" group in which R is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein. A non-limiting example includes carboxyl (i.e., -C(=O)OH).

[0247] A "cyano" group refers to a "-CN" group.

[0248] A "cyanato" group refers to an "-OCN" group.

[0249] An "isocyanato" group refers to a "-NCO" group.

[0250] A "thiocyanato" group refers to a "-SCN" group.

[0251] An "isothiocyanato" group refers to an " -NCS" group.

[0252] A "sulfinyl" group refers to an "-S(=O)R" group in which R is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0253] A "sulfonyl" group refers to an "-SO_2R" group in which R is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0254] An "S-sulfonamido" group refers to a "-$SO_2NR_AR_B$" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0255] An "N-sulfonamido" group refers to a "-$N(R_A)SO_2R_B$" group in which R_A and R_b are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0256] An "O-carbamyl" group refers to a "-$OC(=O)NR_AR_B$" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0257] An "N-carbamyl" group refers to an "-$N(R_A)OC(=O)R_B$" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0258] An "O-thiocarbamyl" group refers to a "-$OC(=S)NR_AR_B$" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0259] An "N-thiocarbamyl" group refers to an "-$N(R_A)OC(=S)R_B$" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0260] A "C-amido" group refers to a "-$C(=O)NR_AR_B$" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0261] An "N-amido" group refers to a "-$N(R_A)C(=O)R_B$" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0262] An "amino" group refers to a "-NR_AR_B" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0263] An "aminoalkyl" group refers to an amino group connected via an alkylene group.

[0264] An "alkoxyalkyl" group refers to an alkoxy group connected via an alkylene group, such as a "C_{2-8} alkoxyalkyl" and the like.

[0265] As used herein, a "natural amino acid side chain" refers to the side-chain substituent of a naturally occuring amino acid. Naturally occurring amino acids have a substituent attached to the α–carbon. Naturally occurring amino acids include Arginine, Lysine, Aspartic acid, Glutamic

acid, Glutamine, Asparagine, Histidine, Serine, Threonine, Tyrosine, Cysteine, Methionine, Tryptophan, Alanine, Isoleucine, Leucine, Phenylalanine, Valine, Proline, and Glycine.

[0266] As used herein, a "non-natural amino acid side chain" refers to the side-chain substituent of a non-naturally occurring amino acid. Non-natural amino acids include β-amino acids (β^3 and β^2), Homo-amino acids, Proline and Pyruvic acid derivatives, 3-substituted Alanine derivatives, Glycine derivatives, Ring-substituted Phenylalanine and Tyrosine Derivatives, Linear core amino acids and N-methyl amino acids. Exemplary non-natural amino acids are available from Sigma-Aldridge, listed under "unnatural amino acids & derivatives." See also, Travis S. Young and Peter G. Schultz, "Beyond the Canonical 20 Amino Acids: Expanding the Genetic Lexicon," J. Biol. Chem. 2010 285: 11039-11044, which is incorporated by reference in its entirety.

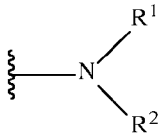
[0267] As used herein, a substituted group is derived from the unsubstituted parent group in which there has been an exchange of one or more hydrogen atoms for another atom or group. Unless otherwise indicated, when a group is deemed to be "substituted," it is meant that the group is substituted with one or more subsitutents independently selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_7 carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), C_3-C_7-carbocyclyl-C_1-C_6-alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heterocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heterocyclyl-C_1-C_6-alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), aryl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), aryl(C_1-C_6)alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heteroaryl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heteroaryl(C_1-C_6)alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, cyano, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkoxy(C_1-C_6)alkyl (i.e., ether), aryloxy, sulfhydryl (mercapto), halo(C_1-C_6)alkyl (e.g., $-CF_3$), halo(C_1-C_6)alkoxy (e.g., $-OCF_3$), C_1-C_6 alkylthio, arylthio, amino, amino(C_1-C_6)alkyl, nitro, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-

sulfonamido, C-carboxy, O-carboxy, acyl, cyanato, isocyanato, thiocyanato, isothiocyanato, sulfinyl, sulfonyl, and oxo (=O). Wherever a group is described as "optionally substituted" that group can be substituted with the above substituents.

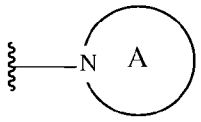
[0268] In some embodiments, substituted group(s) is (are) substituted with one or more substituent(s) individually and independently selected from C_1-C_4 alkyl, amino, hydroxy, and halogen.

[0269] It is to be understood that certain radical naming conventions can include either a mono-radical or a di-radical, depending on the context. For example, where a substituent requires two points of attachment to the rest of the molecule, it is understood that the substituent is a di-radical. For example, a substituent identified as alkyl that requires two points of attachment includes di-radicals such as $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, and the like. Other radical naming conventions clearly indicate that the radical is a di-radical such as "alkylene" or "alkenylene."

[0270] When two R groups are said to form a ring (e.g., a carbocyclyl, heterocyclyl, aryl, or heteroaryl ring) "together with the atom to which they are attached," it is meant that the collective unit of the atom and the two R groups are the recited ring. The ring is not otherwise limited by the definition of each R group when taken individually. For example, when the following substructure is present:



and R^1 and R^2 are defined as selected from the group consisting of hydrogen and alkyl, or R^1 and R^2 together with the nitrogen to which they are attached form a heterocyclyl, it is meant that R^1 and R^2 can be selected from hydrogen or alkyl, or alternatively, the substructure has structure:



where ring A is a heterocyclyl ring containing the depicted nitrogen.

[0271] Similarly, when two "adjacent" R groups are said to form a ring "together with the atoms to which they are attached," it is meant that the collective unit of the atoms,

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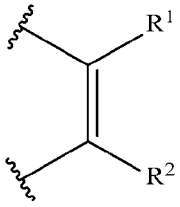
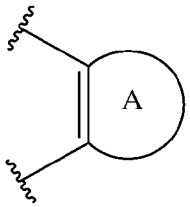
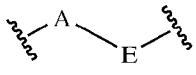
intervening bonds, and the two R groups are the recited ring. For example, when the following substructure is present:



and R^1 and R^2 are defined as selected from the group consisting of hydrogen and alkyl, or R^1 and R^2 together with the atoms to which they are attached form an aryl or carbocyclyl, it is meant that R^1 and R^2 can be selected from hydrogen or alkyl, or alternatively, the substructure has structure:

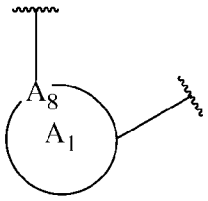


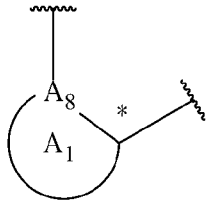
where A is an aryl ring or a carbocyclyl containing the depicted double bond.

[0272] Wherever a substituent is depicted as a di-radical (*i.e.*, has two points of attachment to the rest of the molecule), it is to be understood that the substituent can be attached in any directional configuration unless otherwise indicated. Thus, for example, a substituent depicted as –AE– or 

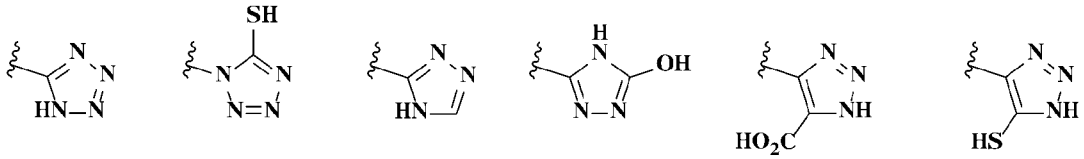
includes the substituent being oriented such that the **A** is attached at the leftmost attachment point of the molecule as well as the case in which **A** is attached at the rightmost attachment point of the molecule.

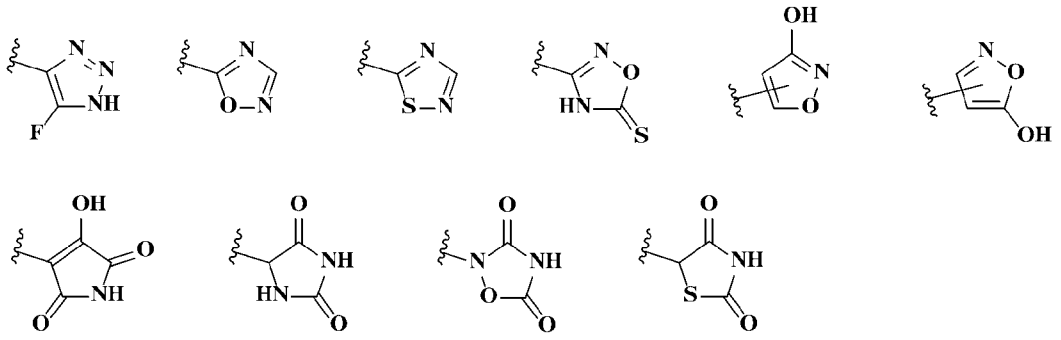
[0273] As used herein, the substructure:



means that the A_8 atom can be in any ring atom position within the ring or ring system A_1. The substructure:  means that the A_8 atom is in the ring atom position immediately adjacent (i.e., alpha) to the point of attachment indicated by *.

[0274] As used herein, "isosteres" of a chemical group are other chemical groups that exhibit the same or similar properties. For example, tetrazole is an isostere of carboxylic acid because it mimics the properties of carboxylic acid even though they both have very different molecular formulae. Tetrazole is one of many possible isosteric replacements for carboxylic acid. Other carboxylic acid isosteres contemplated include $-SO_3H$, $-SO_2HNR$, $-PO_2(R)_2$, $-PO_3(R)_2$, $-CONHNHSO_2R$, $-COHNSO_2R$, and $-CONRCN$, where R is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 3-10 membered heterocyclyl, as defined herein. In addition, carboxylic acid isosteres can include 5-7 membered carbocycles or heterocycles containing any combination of CH_2, O, S, or N in any chemically stable oxidation state, where any of the atoms of said ring structure are optionally substituted in one or more positions. The following structures are non-limiting examples of carbocyclic and heterocyclic isosteres contemplated. The atoms of said ring structure may be optionally substituted at one or more positions with R as defined above.





[0275] It is also contemplated that when chemical substituents are added to a carboxylic isostere, the compound retains the properties of a carboxylic isostere. It is contemplated that when a carboxylic isostere is optionally substituted with one or more moieties selected from R as defined above, then the substitution and substitution position is selected such that it does not eliminate the carboxylic acid isosteric properties of the compound. Similarly, it is also contemplated that the placement of one or more R substituents upon a carbocyclic or heterocyclic carboxylic acid isostere is not a substitution at one or more atom(s) that maintain(s) or is/are integral to the carboxylic acid isosteric properties of the compound, if such substituent(s) would destroy the carboxylic acid isosteric properties of the compound.

[0276] Other carboxylic acid isosteres not specifically exemplified in this specification are also contemplated.

[0277] The term "agent" or "test agent" includes any substance, molecule, element, compound, entity, or a combination thereof. It includes, but is not limited to, e.g., protein, polypeptide, peptide or mimetic, small organic molecule, polysaccharide, polynucleotide, and the like. It can be a natural product, a synthetic compound, or a chemical compound, or a combination of two or more substances. Unless otherwise specified, the terms "agent", "substance", and "compound" are used interchangeably herein.

[0278] The term "analog" is used herein to refer to a molecule that structurally resembles a reference molecule but which has been modified in a targeted and controlled manner, by replacing a specific substituent of the reference molecule with an alternate substituent. Compared to the reference molecule, an analog would be expected, by one skilled in the art, to exhibit the same, similar, or improved utility. Synthesis and screening of analogs, to identify variants of known compounds having improved characteristics (such as higher binding affinity for a target molecule) is an approach that is well known in pharmaceutical chemistry.

[0279] The term "mammal" is used in its usual biological sense. Thus, it specifically includes, but is not limited to, primates, including simians (chimpanzees, apes, monkeys) and humans, cattle, horses, sheep, goats, swine, rabbits, dogs, cats, rats and mice but also includes many other species.

[0280] The term "microbial infection" refers to the invasion of the host organism, whether the organism is a vertebrate, invertebrate, fish, plant, bird, or mammal, by pathogenic microbes. This includes the excessive growth of microbes that are normally present in or on the body of a mammal or other organism. More generally, a microbial infection can be any situation in which the presence of a microbial population(s) is damaging to a host mammal. Thus, a mammal is "suffering" from a microbial infection when excessive numbers of a microbial population are present in or on a mammal's body, or when the effects of the presence of a microbial population(s) is damaging the cells or other tissue of a mammal. Specifically, this description applies to a bacterial infection. Note that the compounds of preferred embodiments are also useful in treating microbial growth or contamination of cell cultures or other media, or inanimate surfaces or objects, and nothing herein should limit the preferred embodiments only to treatment of higher organisms, except when explicitly so specified in the claims.

[0281] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. In addition, various adjuvants such as are commonly used in the art may be included. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (1990); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press, which is incorporated herein by reference in its entirety.

[0282] "Subject" as used herein, means a human or a non-human mammal, e.g., a dog, a cat, a mouse, a rat, a cow, a sheep, a pig, a goat, a non-human primate or a bird, e.g., a chicken, as well as any other vertebrate or invertebrate.

[0283] An "effective amount" or a "therapeutically effective amount" as used herein refers to an amount of a therapeutic agent that is effective to relieve, to some extent, or to reduce the likelihood of onset of, one or more of the symptoms of a disease or condition, and includes curing a disease or condition. "Curing" means that the symptoms of a disease or condition are eliminated; however, certain long-term or permanent effects may exist even after a cure is obtained (such as extensive tissue damage).

[0284] "Treat," "treatment," or "treating," as used herein refers to administering a pharmaceutical composition for prophylactic and/or therapeutic purposes. The term "prophylactic treatment" refers to treating a subject who does not yet exhibit symptoms of a disease or condition, but who is susceptible to, or otherwise at risk of, a particular disease or condition, whereby the treatment reduces the likelihood that the patient will develop the disease or condition. The term "therapeutic treatment" refers to administering treatment to a

Methods of Preparation

[0285] The compounds disclosed herein may be synthesized by methods described below, or by modification of these methods. Ways of modifying the methodology include, among others, temperature, solvent, reagents etc., known to those skilled in the art. In general, during any of the processes for preparation of the compounds disclosed herein, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry* (ed. J.F.W. McOmie, Plenum Press, 1973); and P.G.M. Green, T.W. Wutts, *Protecting Groups in Organic Synthesis* (3rd ed.) Wiley, New York (1999), which are both hereby incorporated herein by reference in their entirety. The protecting groups may be removed at a convenient subsequent stage using methods known from the art. Synthetic chemistry transformations useful in synthesizing applicable compounds are known in the art and include e.g. those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers, **1989**, or L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, **1995**, which are both hereby incorporated herein by reference in their entirety. The routes shown and described herein are illustrative only and are not intended, nor are they to be construed, to limit the scope of the claims in any manner whatsoever. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to

devise alternate routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

[0286] In the following schemes, protecting groups for oxygen atoms are selected for their compatibility with the requisite synthetic steps as well as compatibility of the introduction and deprotection steps with the overall synthetic schemes (P.G.M. Green, T.W. Wutts, Protecting Groups in Organic Synthesis (3rd ed.) Wiley, New York (1999)).

[0287] If the compounds of the present technology contain one or more chiral centers, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or d(l) stereoisomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of the present technology, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

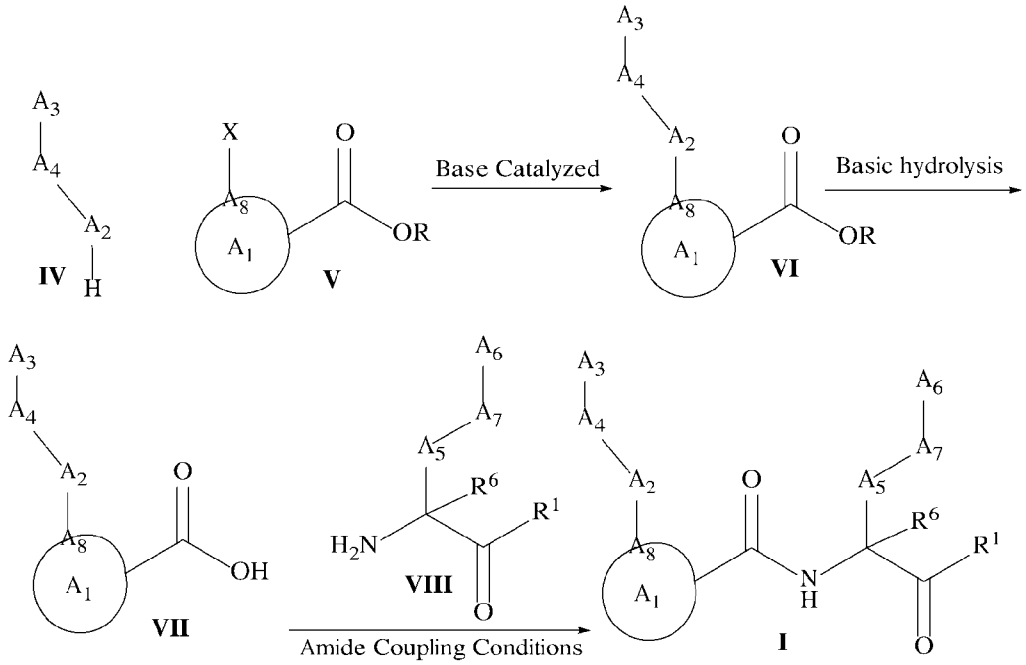
[0288] The starting materials for the following reactions are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the starting materials are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Bachem (Torrance, California , USA), Emka-Chemce or Sigma (St. Louis, Missouri, USA). Others may be prepared by procedures, or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley, and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5, and Supplementals (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley, and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley, and Sons, 5th Edition, 2001), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989)..

Synthesis of Compounds of Formula I

[0289] In one embodiment, the method involves reacting an appropriately substituted intermediate with an acidic hydrogen (**IV**) with an ester (**V**) under base catalyzed conditions to yield the ester derivative (**VI**). The resulting product was then subjected to hydrolysis under basic conditions to yield the carboxylic acid derivative (**VII**) which was then subjected to amide-

coupling conditions with an amino acid derivative (**VIII**) wherein the carboxylic acid group is functionalized with the R^1 group (**Scheme 1**). Alternatively, the carboxylic acid product (**VII**) is then subjected to amide coupling conditions with the amino alcohol derivative (**VIII-a**) to yield the corresponding adduct (**IX**). The resulting adduct (**IX**) is subjected to oxidation conditions with DMP oxidation (with hypervalent iodine) or by an oxidizing agent such as PCC (pyridinium chlorochromate) to yield the α-ketoamide product (**X**). Alternately, the adduct (**IX**) was subjected to oxidation conditions using EDC and dichloroacetic acid or using IBX as the oxidizing agent to yield the α-ketoamide product (**X**). The skilled artisan will once again appreciate that there are many other oxidizing conditions and agents which are within the scope of this disclosure to oxidize the hydroxyl group. This synthesis route is generally shown in **Scheme 2**.

Scheme 1:



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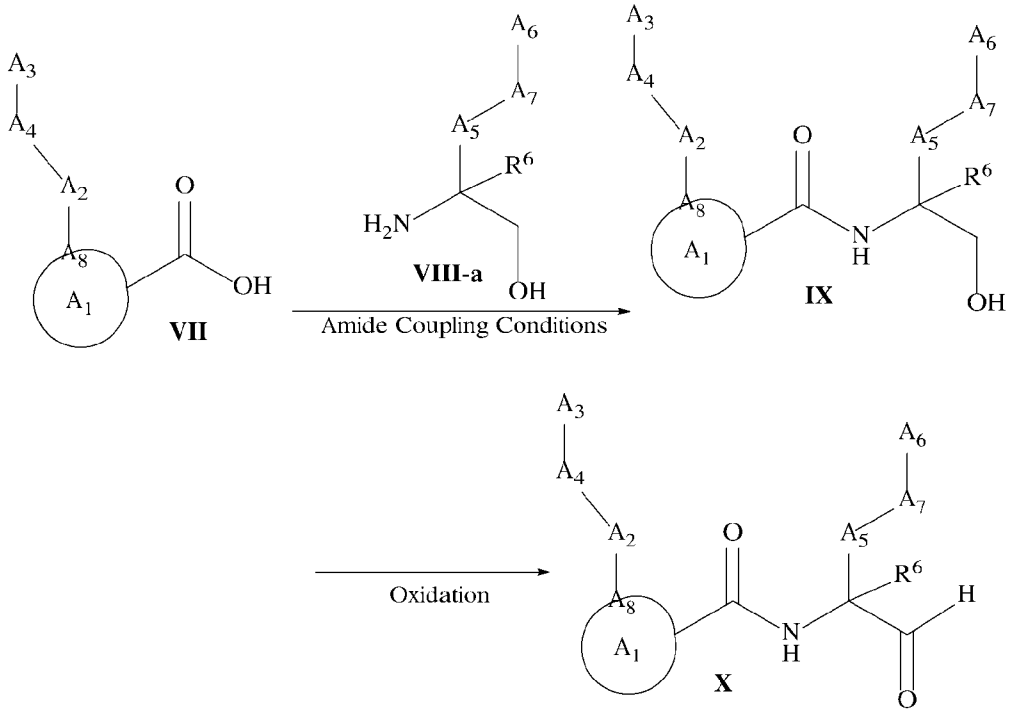
Scheme 2:



[0290] The following example schemes are provided for the guidance of the reader, and collectively represent an example method for making the compounds encompassed herein. Furthermore, other methods for preparing compounds described herein will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above.

Uses of Isotopically-Labeled Compounds

[0291] Some embodiments provide a method of using isotopically labeled compounds and prodrugs of the present disclosure in: (i) metabolic studies (preferably with ^{14}C), reaction kinetic studies (with, for example 2H or 3H); (ii) detection or imaging techniques [such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT)] including drug or substrate tissue distribution assays; or (**III**) in radioactive treatment of patients.

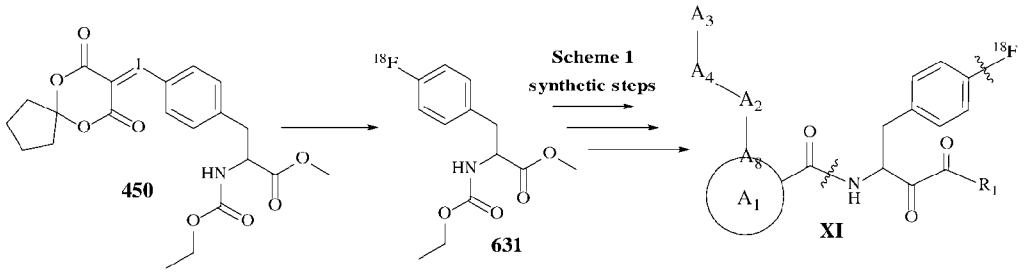
[0292] Isotopically labeled compounds and prodrugs of the embodiments thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. An ^{18}F or ^{11}C labeled compound may be particularly

preferred for PET, and an ^{123}I labeled compound may be particularly preferred for SPECT studies. Further substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements.

Synthesis of Isotopically Labeled Compounds

[0293] ^{18}F labeled compounds are synthesized as shown in the schemes below. In one embodiment, the method involves reacting the intermediate **450** with a ^{18}F-labeling agent using conditions as described in Rotstein, *et al.*, Spirocyclic hypervalent iodine(III)-mediated radiofluorination of non-activated and hindered aromatics, *Nature Communications,* **2014**, Vol. *5, 4365-4371* and Rotstein, *et al.*, Mechanistic Studies and Radiofluorination of Structurally Diverse Pharmaceuticals with Spirocyclic Iodonium(III) Ylides, *Chemical Science,* **2016**, Vol. *7, 4407-4417*, both of which are incorporated herein by reference in their entirety, to yield the ^{18}F-labeled intermediate methyl 2-((ethoxycarbonyl)amino)-3-(4-(fluoro-^{18}F)phenyl)propanoate (**631**) which is then transformed into the final α-ketoamide product represented by the general structure **XI** (**Scheme 3**).

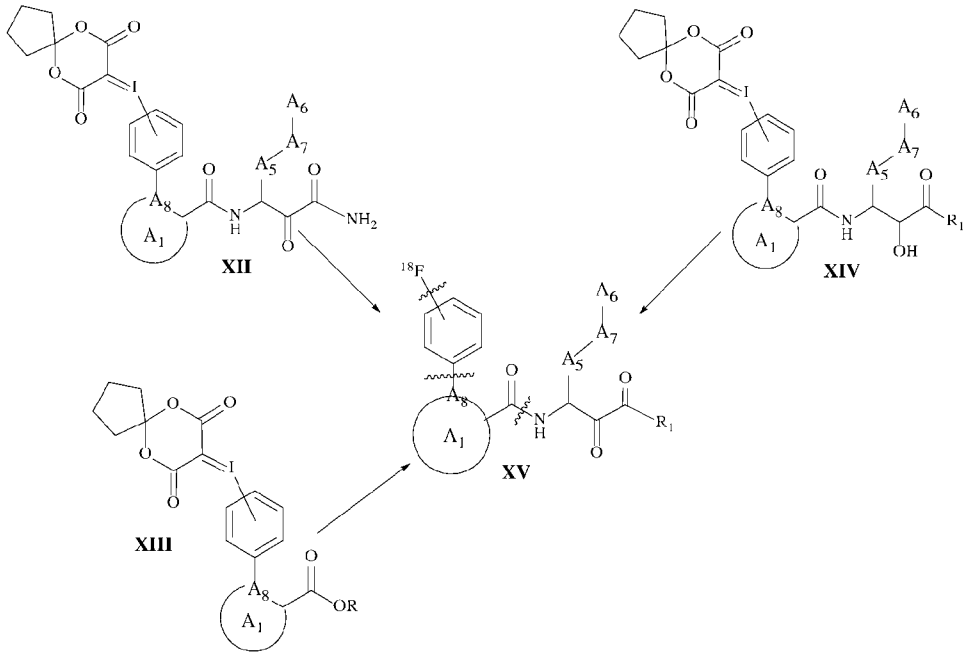
Scheme 3:



[0294] Alternately, ^{18}F-labeled compound **XV** is synthesized as shown in **Scheme 4**. In one embodiment, iodanylidene intermediate **XII** is used to introduce the ^{18}F label yielding using conditons as described in Rotstein, *et al.*, Spirocyclic hypervalent iodine(III)-mediated radiofluorination of non-activated and hindered aromatics, *Nature Communications,* **2014**, Vol. *5, 4365-4371* and Rotstein, *et al.*, Mechanistic Studies and Radiofluorination of Structurally Diverse Pharmaceuticals with Spirocyclic Iodonium(III) Ylides, *Chemical Science,* **2016**, Vol. *7, 4407-4417* to yield the labeled α-ketoamide product **XV**. In another embodiment, iodanylidene intermediate (**XIV**) is (**Scheme 4**) subjected to oxidation conditions with DMP oxidation (with

hypervalent iodine) or by an oxidizing agent such as PCC (pyridinium chlorochromate) to yield the α-ketoamide product (**XV**). In yet another embodiment, iodanylidene intermediate (**XIII**) (**Scheme 4**) is subjected to ^{18}F-labeling reaction conditions as described earlier followed by hydrolysis of the ester under basic conditions to yield the carboxylic acid derivative which is then subjected to amide-coupling conditions with an amino acid derivative wherein the carboxylic acid group is functionalized with the R^1 group to yield the labeled α-ketoamide product **XV**.

Scheme 4:



Administration and Pharmaceutical Compositions

[0295] The compounds are administered at a therapeutically effective dosage. While human dosage levels have yet to be optimized for the compounds described herein, generally, a daily dose may be from about 0.25 mg/kg to about 120 mg/kg or more of body weight, from about 0.5 mg/kg or less to about 70 mg/kg, from about 1.0 mg/kg to about 50 mg/kg of body weight, or from about 1.5 mg/kg to about 10 mg/kg of body weight. Thus, for administration to a 70 kg person, the dosage range would be from about 17 mg per day to about 8000 mg per day, from about 35 mg per day or less to about 7000 mg per day or more, from about 70 mg per day to about 6000 mg per day, from about 100 mg per day to about 5000 mg per day, or from about 200 mg to about 3000 mg per day. The amount of active compound administered will, of course, be

dependent on the subject and disease state being treated, the severity of the affliction, the manner and schedule of administration and the judgment of the prescribing physician.

[0296] Administration of the compounds disclosed herein or the pharmaceutically acceptable salts thereof can be via any of the accepted modes of administration for agents that serve similar utilities including, but not limited to, orally, subcutaneously, intravenously, intranasally, topically, transdermally, intraperitoneally, intramuscularly, intrapulmonarilly, vaginally, rectally, or intraocularly. Oral and parenteral administrations are customary in treating the indications that are the subject of the preferred embodiments.

[0297] The compounds useful as described above can be formulated into pharmaceutical compositions for use in treatment of these conditions. Standard pharmaceutical formulation techniques are used, such as those disclosed in Remington's The Science and Practice of Pharmacy, 21st Ed., Lippincott Williams & Wilkins (2005), incorporated by reference in its entirety. Accordingly, some embodiments include pharmaceutical compositions comprising: (a) a safe and therapeutically effective amount of a compound described herein (including enantiomers, diastereoisomers, tautomers, polymorphs, and solvates thereof), or pharmaceutically acceptable salts thereof; and (b) a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0298] In addition to the selected compound useful as described above, come embodiments include compositions containing a pharmaceutically-acceptable carrier. The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. In addition, various adjuvants such as are commonly used in the art may be included. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (1990); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press, which is incorporated herein by reference in its entirety.

[0299] Some examples of substances, which can serve as pharmaceutically-acceptable carriers or components thereof, are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TWEENS; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

[0300] The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is basically determined by the way the compound is to be administered.

[0301] The compositions described herein are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of a compound that is suitable for administration to an animal, preferably mammal subject, in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. Such dosage forms are contemplated to be administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during a course of therapy, though a single administration is not specifically excluded. The skilled artisan will recognize that the formulation does not specifically contemplate the entire course of therapy and such decisions are left for those skilled in the art of treatment rather than formulation.

[0302] The compositions useful as described above may be in any of a variety of suitable forms for a variety of routes for administration, for example, for oral, nasal, rectal, topical (including transdermal), ocular, intracerebral, intracranial, intrathecal, intra-arterial, intravenous, intramuscular, or other parental routes of administration. The skilled artisan will appreciate that oral and nasal compositions comprise compositions that are administered by

inhalation, and made using available methodologies. Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable carriers well-known in the art may be used. Pharmaceutically-acceptable carriers include, for example, solid or liquid fillers, diluents, hydrotropies, surface-active agents, and encapsulating substances. Optional pharmaceutically-active materials may be included, which do not substantially interfere with the inhibitory activity of the compound. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods described herein are described in the following references, all incorporated by reference herein: Modern Pharmaceutics, 4th Ed., Chapters 9 and 10 (Banker & Rhodes, editors, 2002); Lieberman *et al.*, Pharmaceutical Dosage Forms: Tablets (1989); and Ansel, Introduction to Pharmaceutical Dosage Forms 8th Edition (2004).

[0303] Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

[0304] The pharmaceutically-acceptable carrier suitable for the preparation of unit dosage forms for peroral administration is well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules typically

comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical, and can be readily made by a person skilled in the art.

[0305] Peroral compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

[0306] Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

[0307] Compositions described herein may optionally include other drug actives.

[0308] Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

[0309] A liquid composition, which is formulated for topical ophthalmic use, is formulated such that it can be administered topically to the eye. The comfort should be maximized as much as possible, although sometimes formulation considerations (e.g. drug stability) may necessitate less than optimal comfort. In the case that comfort cannot be maximized, the liquid should be formulated such that the liquid is tolerable to the patient for

topical ophthalmic use. Additionally, an ophthalmically acceptable liquid should either be packaged for single use, or contain a preservative to prevent contamination over multiple uses.

[0310] For ophthalmic application, solutions or medicaments are often prepared using a physiological saline solution as a major vehicle. Ophthalmic solutions should preferably be maintained at a comfortable pH with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

[0311] Preservatives that may be used in the pharmaceutical compositions disclosed herein include, but are not limited to, benzalkonium chloride, PHMB, chlorobutanol, thimerosal, phenylmercuric, acetate and phenylmercuric nitrate. A useful surfactant is, for example, Tween 80. Likewise, various useful vehicles may be used in the ophthalmic preparations disclosed herein. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

[0312] Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

[0313] Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. For many compositions, the pH will be between 4 and 9. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

[0314] In a similar vein, an ophthalmically acceptable antioxidant includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

[0315] Other excipient components, which may be included in the ophthalmic preparations, are chelating agents. A useful chelating agent is edetate disodium, although other chelating agents may also be used in place or in conjunction with it.

[0316] For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound disclosed herein are employed. Topical formulations may generally be comprised of a pharmaceutical carrier, co-solvent, emulsifier, penetration enhancer, preservative system, and emollient.

[0317] For intravenous administration, the compounds and compositions described herein may be dissolved or dispersed in a pharmaceutically acceptable diluent, such as a saline or dextrose solution. Suitable excipients may be included to achieve the desired pH, including but not limited to NaOH, sodium carbonate, sodium acetate, HCl, and citric acid. In various embodiments, the pH of the final composition ranges from 2 to 8, or preferably from 4 to 7. Antioxidant excipients may include sodium bisulfite, acetone sodium bisulfite, sodium formaldehyde, sulfoxylate, thiourea, and EDTA. Other non-limiting examples of suitable excipients found in the final intravenous composition may include sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran. Further acceptable excipients are described in Powell, et al., Compendium of Excipients for Parenteral Formulations, *PDA J Pharm Sci and Tech* **1998**, *52* 238-311 and Nema et al., Excipients and Their Role in Approved Injectable Products: Current Usage and Future Directions, *PDA J Pharm Sci and Tech* **2011**, *65* 287-332, both of which are incorporated herein by reference in their entirety. Antimicrobial agents may also be included to achieve a bacteriostatic or fungistatic solution, including but not limited to phenylmercuric nitrate, thimerosal, benzethonium chloride, benzalkonium chloride, phenol, cresol, and chlorobutanol.

[0318] The compositions for intravenous administration may be provided to caregivers in the form of one more solids that are reconstituted with a suitable diluent such as sterile water, saline or dextrose in water shortly prior to administration. In other embodiments, the compositions are provided in solution ready to administer parenterally. In still other embodiments, the compositions are provided in a solution that is further diluted prior to administration. In embodiments that include administering a combination of a compound described herein and another agent, the combination may be provided to caregivers as a mixture, or the caregivers may mix the two agents prior to administration, or the two agents may be administered separately.

[0319] The actual dose of the active compounds described herein depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

[0320] The compounds and compositions described herein, if desired, may be presented in a pack or dispenser device containing one or more unit dosage forms containing the

active ingredient. Such a pack or device may, for example, comprise metal or plastic foil, such as a blister pack, or glass, and rubber stoppers such as in vials. The pack or dispenser device may be accompanied by instructions for administration. Compounds and compositions described herein are formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

[0321] The amount of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt %) basis, from about 0.01 99.99 wt % of a compound of the present technology based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. Preferably, the compound is present at a level of about 1 80 wt %. Representative pharmaceutical formulations are described below.

Formulation Examples

[0322] The following are representative pharmaceutical formulations containing a compound of Formula I.

Formulation Example 1 -- Tablet formulation

[0323] The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet, mg
Compounds disclosed herein	400
cornstarch	50
croscarmellose sodium	25
lactose	120
magnesium stearate	5

Formulation Example 2 -- Capsule formulation

[0324] The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per capsule, mg
Compounds disclosed herein	200
lactose, spray-dried	148

magnesium stearate	2

Formulation Example 3 -- Suspension formulation

[0325] The following ingredients are mixed to form a suspension for oral administration.

Ingredient	Amount
Compounds disclosed herein	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
propyl paraben	0.05 g
granulated sugar	25.0 g
sorbitol (70% solution)	13.00 g
Veegum K (Vanderbilt Co.)	1.0 g
flavoring	0.035 mL
colorings	0.5 mg
distilled water	q.s. to 100 mL

Formulation Example 4 -- Injectable formulation

[0326] The following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
Compounds disclosed herein	0.2 mg-20 mg
sodium acetate buffer solution, 0.4 M	2.0 mL
HCl (1N) or NaOH (1N)	q.s. to suitable pH
water (distilled, sterile)	q.s. to 20 mL

Formulation Example 5 -- Suppository Formulation

[0327] A suppository of total weight 2.5 g is prepared by mixing the compound of the present technology with Witepsol® H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

Ingredient	Amount
Compounds disclosed herein	500 mg
Witepsol® H-15	balance

Methods of Treatment

[0328] The compounds disclosed herein or their tautomers and/or pharmaceutically acceptable salts thereof can effectively act as CAPN1, CAPN2, and/or CAPN9 inhibitors and

treat conditions affected at least in part by CAPN1, CAPN2, and/or CAPN9. Some embodiments provide pharmaceutical compositions comprising one or more compounds disclosed herein and a pharmaceutically acceptable excipient. Some embodiments provide a method for treating a fibrotic disease with an effective amount of one or more compounds as disclosed herein.

[0329] In some embodiments, the subject is a human.

[0330] Further embodiments include administering a combination of compounds to a subject in need thereof. A combination can include a compound, composition, pharmaceutical composition described herein with an additional medicament.

[0331] Some embodiments include co-administering a compound, composition, and/or pharmaceutical composition described herein, with an additional medicament. By "co-administration," it is meant that the two or more agents may be found in the patient's bloodstream at the same time, regardless of when or how they are actually administered. In one embodiment, the agents are administered simultaneously. In one such embodiment, administration in combination is accomplished by combining the agents in a single dosage form. In another embodiment, the agents are administered sequentially. In one embodiment the agents are administered through the same route, such as orally. In another embodiment, the agents are administered through different routes, such as one being administered orally and another being administered i.v.

[0332] Some embodiments include combinations of a compound, composition or pharmaceutical composition described herein with any other pharmaceutical compound approved for treating fibrotic or myofibroblast differentiation associated diseases or disorders..

[0333] Some embodiments provide a method for inhibiting CAPN1, CAPN2, and/or CAPN9 and/or a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9 with an effective amount of one or more compounds as disclosed herein.

[0334] The compounds disclosed herein are useful in inhibiting CAPN1, CAPN2, and/or CAPN9 enzymes and/or treating disorders relating to fibrosis or myofibroblast differentiation.

[0335] Some embodiments provide a method for inhibiting CAPN1, CAPN2, and/or CAPN9 which method comprises contacting cells (including neurons/microglia /invading macrophages) with an effective amount of one or more compounds as disclosed herein.

[0336] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds or a pharmaceutical composition disclosed herein comprising a pharmaceutically acceptable excipient.

[0337] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an effective amount of one or more compounds or a pharmaceutical composition disclosed herein comprising a pharmaceutically acceptable excipient.

[0338] Some embodiments provide a method for inhibiting CAPN1, CAPN2, and/or CAPN9 is provided wherein the method comprises contacting cells with an effective amount of one or more compounds disclosed herein. In some embodiments a method for inhibiting CAPN1, CAPN2, and/or CAPN9 is performed in-vitro or in-vivo.

[0339] Calpains are also expressed in cells other than neurons, microglia and invading macrophages. In particular, they are important in skeletal muscle and herein inhibition of calpains also refers to inhibition in these cells as well.

Selective inhibition

[0340] Some embodiments provide a method for competitive binding with calpastatin (CAST), the method comprising contacting a compound disclosed herein with CAPN1, CAPN2, and/or CAPN9 enzymes residing inside a subject. In such a method, the compound specifically inhibits one or more of the enzymes selected from the group consisting of: CAPN1, CAPN2, and CAPN9 by at least 2-fold, by at least 3-fold, by at least 4-fold, by at least 5-fold, by at least 10-fold, by at least 15-fold, by at least 20-fold, by at least 50-fold, by at least 100-fold, by at least 150-fold, by at least 200-fold, by at least 400-fold, or by at least 500-fold.

[0341] Some embodiments provide a method for selectively inhibiting CAPN1 in the presence of CAPN2 and CAPN9, which includes contacting cells (including neurons/microglia /invading macrophages) with an effective amount of one or more compounds disclosed herein.

[0342] Some embodiments provide a method for selectively inhibiting CAPN2 in the presence of CAPN1 and CAPN9, which includes contacting cells (including neurons/microglia /invading macrophages) with an effective amount of one or more compounds disclosed herein.

[0343] Some embodiments provide a method for selectively inhibiting CAPN9 in the presence of CAPN2 and CAPN1, which includes contacting cells (including neurons/microglia /invading macrophages) with an effective amount of one or more compounds disclosed herein.

[0344] Some embodiments provide a method for selectively inhibiting CAPN1 and CAPN2 in the presence of CAPN9, which includes contacting cells (including neurons/microglia /invading macrophages) with an effective amount of one or more compounds disclosed herein.

[0345] Some embodiments provide a method for selectively inhibiting CAPN1 and CAPN9 in the presence of CAPN2, which includes contacting cells (including neurons/microglia /invading macrophages) with an effective amount of one or more compounds disclosed herein.

[0346] Some embodiments provide a method for selectively inhibiting CAPN2 and CAPN9 in the presence of CAPN1, which includes contacting cells (including neurons/microglia /invading macrophages) with an effective amount of one or more compounds disclosed herein.

[0347] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds which specifically inhibits CAPN1, CAPN2, and/or CAPN9, said compounds or a pharmaceutical composition comprising one or more compounds disclosed herein and a pharmaceutically acceptable excipient.

[0348] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an effective amount of one or more compounds which specifically inhibits CAPN1, CAPN2, and/or CAPN9, said compounds being selected from compounds disclosed herein or a pharmaceutical composition comprising one or more compounds disclosed herein and a pharmaceutically acceptable excipient.

[0349] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds which selectively inhibits CAPN1, CAPN2, and/or CAPN9, said compounds being selected from compounds disclosed herein or a pharmaceutical composition comprising one or more compounds disclosed herein and a pharmaceutically acceptable excipient..

[0350] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an

effective amount of one or more compounds which selectively inhibits CAPN1, CAPN2, and/or CAPN9, said compounds being selected from compounds disclosed herein or a pharmaceutical composition comprising one or more compounds disclosed herein and a pharmaceutically acceptable excipient..

[0351] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds which specifically inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:5.

[0352] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds which specifically inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:10.

[0353] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds which specifically inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:20.

[0354] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds which specifically inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:50.

[0355] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds which specifically inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:100.

[0356] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds which specifically inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:200.

[0357] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds

which specifically inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:250.

[0358] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds which specifically inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:500.

[0359] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds which selectively inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:5.

[0360] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds which selectively inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:10.

[0361] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds which selectively inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:20.

[0362] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds which selectively inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:50.

[0363] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds which selectively inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:100.

[0364] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds which selectively inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:200.

[0365] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds which selectively inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:250.

[0366] Some embodiments provide a method for treating a fibrotic disease, which method comprises administering to a subject an effective amount of one or more compounds which selectively inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:500.

[0367] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an effective amount of one or more compounds which specifically inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:5.

[0368] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an effective amount of one or more compounds which specifically inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:10.

[0369] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an effective amount of one or more compounds which specifically inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:20.

[0370] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an effective amount of one or more compounds which specifically inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:50.

[0371] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an effective amount of one or more compounds which specifically inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:100.

[0372] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an

effective amount of one or more compounds which specifically inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:200.

[0373] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an effective amount of one or more compounds which specifically inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:250.

[0374] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an effective amount of one or more compounds which specifically inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:500.

[0375] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an effective amount of one or more compounds which selectively inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:5.

[0376] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an effective amount of one or more compounds which selectively inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:10.

[0377] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an effective amount of one or more compounds which selectively inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:20.

[0378] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an effective amount of one or more compounds which selectively inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:50.

[0379] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an effective amount of one or more compounds which selectively inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:100.

[0380] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an effective amount of one or more compounds which selectively inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:200.

[0381] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an effective amount of one or more compounds which selectively inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:250.

[0382] Some embodiments provide a method for treating a disease affected at least in part by CAPN1, CAPN2, and/or CAPN9, which method comprises administering to a subject an effective amount of one or more compounds which selectively inhibits two or more enzymes selected from the group consisting of CAPN1, CAPN2, and CAPN9 in a ratio of at least 1:1:500.

[0383] Some embodiments provide a method for prophylactic therapy or treatment of a subject having a fibrotic disorder wherein said method comprising administering an effective amount of one or more compounds disclosed herein to the subject in need thereof.

[0384] Some embodiments provide a method for prophylactic therapy or treatment of a subject having a disorder affected by CAPN1, CAPN2, and/or CAPN9 wherein said method comprising administering an effective amount of one or more compounds disclosed herein to the subject in need thereof.

[0385] Some embodiments provide a method for inhibiting myofibroblast differentiation (e.g., Epithelial/Endothelial-to-Mesenchymal Transition (EpMT/EnMT)) is provided wherein the method comprises contacting cells with an effective amount of one or more compounds disclosed herein. In one aspect, the method for inhibiting myofibroblast differentiation (e.g., Epithelial/Endothelial-to-Mesenchymal Transition (EpMT/EnMT)) is performed in-vitro or in-vivo.

[0386] Some embodiments provide a method for treating a disease or condition selected from the group consisting of or that produces a symptom selected from the group consisting of: liver fibrosis, renal fibrosis, lung fibrosis, hypersensitivity pneumonitis, interstitial fibrosis, systemic scleroderma, macular degeneration, pancreatic fibrosis, fibrosis of the spleen, cardiac fibrosis, mediastinal fibrosis, myelofibrosis, endomyocardial fibrosis, retroperitoneal

fibrosis, progressive massive fibrosis, nephrogenic systemic fibrosis, fibrotic complications of surgery, chronic allograft vasculopathy and/or chronic rejection in transplanted organs, ischemic-reperfusion injury associated fibrosis, injection fibrosis, cirrhosis, diffuse parenchymal lung disease, post-vasectomy pain syndrome, and rheumatoid arthritis diseases, wherein which method comprises administering to a subject an effective amount of one or more compounds disclosed herein to a subject in need thereof.

[0387] Some embodiments provide a method for treating liver fibrosis.

[0388] Some embodiments provide a method for treating cardiac fibrosis.

[0389] Some embodiments provide a method for treating fibrosis in rheumatoid arthritis diseases.

[0390] Some embodiments provide a method for treating a condition affected by CAPN1, CAPN2, and/or CAPN9, which is in both a therapeutic and prophylactic setting for subjects. Both methods comprise administering of one or more compounds disclosed herein to a subject in need thereof.

[0391] Some embodiments provide a method for treating stiff skin syndrome.

[0392] Preferred embodiments include combinations of a compound, composition or pharmaceutical composition described herein with other CAPN1, CAPN2, and/or CAPN9 inhibitor agents, such as anti-CAPN1, CAPN2, AND/OR CAPN9 antibodies or antibody fragments, CAPN1, CAPN2, and/or CAPN9 antisense, iRNA, or other small molecule CAPN1, CAPN2, and/or CAPN9 inhibitors.

[0393] Some embodiments include combinations of a compound, composition or pharmaceutical composition described herein to inhibit myofibroblast differentiation (e.g., Epithelial/Endothelial-to-Mesenchymal Transition (EpMT/EnMT)). Some embodiments include combinations of one or more of these compounds which are inhibitors of one or more (or all three) CAPN1, CAPN2, and/or CAPN9, alone or in combination with other TGFβ signaling inhibitors, could be used to treat or protect against or reduce a symptom of a fibrotic, sclerotic or post inflammatory disease or condition including: liver fibrosis, renal fibrosis, lung fibrosis, hypersensitivity pneumonitis, interstitial fibrosis, systemic scleroderma, macular degeneration, pancreatic fibrosis, fibrosis of the spleen, cardiac fibrosis, mediastinal fibrosis, myelofibrosis, endomyocardial fibrosis, retroperitoneal fibrosis, progressive massive fibrosis, nephrogenic

systemic fibrosis, fibrotic complications of surgery, chronic allograft vasculopathy and/or chronic rejection in transplanted organs, ischemic-reperfusion injury associated fibrosis, injection fibrosis, cirrhosis, diffuse parenchymal lung disease, postvasectomy pain syndrome, and rheumatoid arthritis.

[0394] Some embodiments include a combination of the compounds, compositions and/or pharmaceutical compositions described herein with an additional agent, such as anti-inflammatories including glucocorticoids, analgesics (e.g. ibuprofen), aspirin, and agents that modulate a Th2-immune response, immunosuppressants including methotrexate, mycophenolate, cyclophosphamide, cyclosporine, thalidomide, pomalidomide, leflunomide, hydroxychloroquine, azathioprine, soluble bovine cartilage, vasodilators including endothelin receptor antagonists, prostacyclin analogues, nifedipine, and sildenafil, IL-6 receptor antagonists, selective and non-selective tyrosine kinase inhibitors, Wnt-pathway modulators, PPAR activators, caspase-3 inhibitors, LPA receptor antagonists, B cell depleting agents, CCR2 antagonists, pirfenidone, cannabinoid receptor agonists, ROCK inhibitors, miRNA-targeting agents, toll-like receptor antagonists, CTGF-targeting agents, NADPH oxidase inhibitors, tryptase inhibitors, TGFD inhibitors, relaxin receptor agonists, and autologous adipose derived regenerative cells.

Indications

[0395] In some embodiments, the compounds and compositions comprising the compounds described herein can be used to treat a host of conditions arising from fibrosis or inflammation, and specifically including those associated with myofibroblast differentiation. Example conditions include liver fibrosis (alcoholic, viral, autoimmune, metabolic and hereditary chronic disease), renal fibrosis (e.g., resulting from chronic inflammation, infections or type II diabetes), lung fibrosis (idiopathic or resulting from environmental insults including toxic particles, sarcoidosis, asbestosis, hypersensitivity pneumonitis, bacterial infections including tuberculosis, medicines, etc.), interstitial fibrosis, systemic scleroderma (autoimmune disease in which many organs become fibrotic), macular degeneration (fibrotic disease of the eye), pancreatic fibrosis (resulting from, for example, alcohol abuse and chronic inflammatory disease of the pancreas), fibrosis of the spleen (from sickle cell anemia, other blood disorders), cardiac fibrosis (resulting from infection, inflammation and hypertrophy), mediastinal fibrosis, myelofibrosis, endomyocardial fibrosis, retroperitoneal fibrosis, progressive massive fibrosis,

nephrogenic systemic fibrosis, fibrotic complications of surgery, chronic allograft vasculopathy and/or chronic rejection in transplanted organs, ischemic reperfusion injury associated fibrosis, injection fibrosis, cirrhosis, diffuse parenchymal lung disease, post-vasectomy pain syndrome, and rheumatoid arthritis diseases or disorders.

[0396] To further illustrate this invention, the following examples are included. The examples should not, of course, be construed as specifically limiting the invention. Variations of these examples within the scope of the claims are within the purview of one skilled in the art and are considered to fall within the scope of the invention as described, and claimed herein. The reader will recognize that the skilled artisan, armed with the present disclosure, and skill in the art is able to prepare and use the invention without exhaustive examples. The following examples will further describe the present invention, and are used for the purposes of illustration only, and should not be considered as limiting.

EXAMPLES

General procedures

[0397] It will be apparent to the skilled artisan that methods for preparing precursors and functionality related to the compounds claimed herein are generally described in the literature. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. The skilled artisan given the literature and this disclosure is well equipped to prepare any of the compounds.

[0398] It is recognized that the skilled artisan in the art of organic chemistry can readily carry out manipulations without further direction, that is, it is well within the scope and practice of the skilled artisan to carry out these manipulations. These include reduction of carbonyl compounds to their corresponding alcohols, oxidations, acylations, aromatic substitutions, both electrophilic and nucleophilic, etherifications, esterification and saponification and the like. These manipulations are discussed in standard texts such as March Advanced Organic Chemistry (Wiley), Carey and Sundberg, Advanced Organic Chemistry (incorporated herein by reference in their entirety) and the like. All the intermediate compounds of the present invention were used without further purification unless otherwise specified.

[0399] The skilled artisan will readily appreciate that certain reactions are best carried out when other functionality is masked or protected in the molecule, thus avoiding any

undesirable side reactions and/or increasing the yield of the reaction. Often the skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within the scope of the skilled artisan. Examples of many of these manipulations can be found for example in T. Greene and P. Wuts Protecting Groups in Organic Synthesis, 4th Ed., John Wiley & Sons (2007), incorporated herein by reference in its entirety.

[0400] The following example schemes are provided for the guidance of the reader, and represent preferred methods for making the compounds exemplified herein. These methods are not limiting, and it will be apparent that other routes may be employed to prepare these compounds. Such methods specifically include solid phase based chemistries, including combinatorial chemistry. The skilled artisan is thoroughly equipped to prepare these compounds by those methods given the literature and this disclosure. The compound numberings used in the synthetic schemes depicted below are meant for those specific schemes only, and should not be construed as or confused with same numberings in other sections of the application.

[0401] Trademarks used herein are examples only and reflect illustrative materials used at the time of the invention. The skilled artisan will recognize that variations in lot, manufacturing processes, and the like, are expected. Hence the examples, and the trademarks used in them are non-limiting, and they are not intended to be limiting, but are merely an illustration of how a skilled artisan may choose to perform one or more of the embodiments of the invention.

[0402] The following abbreviations have the indicated meanings:

DCM	= dichloromethane
DIEA	= N,N-Diisopropylethylamine
DIPEA	= N,N-Diisopropylethylamine
DMF	= N,N-dimethylformamide
DMP	= Dess Martin Periodinane
DNs	= dinitrosulfonyl
ESBL	= extended-spectrum β-lactamase
EtOAc	= ethyl acetate

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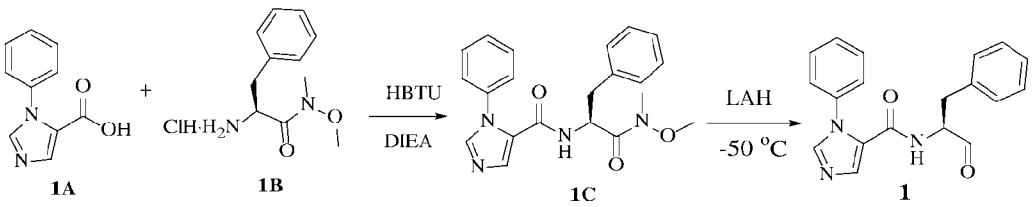
EA	= ethyl acetate
FCC	= Flash Column Chromatography
HATU	= 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
MeCN	= acetonitrile
NMR	= nuclear magnetic resonance
PE	= Petroleum Ether
Prep	= preparatory
Py	= pyridine
Sat.	= saturated aqueous
TBDMSCl	= *tert*-butyldimethylsilyl chloride
TBS	= *tert*-butyldimethylsilyl
TFA	= trifluoroacetic acid
THF	= tetrahydrofuran
TLC	= thin layer chromatography

[0403] The following example schemes are provided for the guidance of the reader, and collectively represent an example method for making the compounds provided herein. Furthermore, other methods for preparing compounds described herein will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above.

EXAMPLE 1

COMPOUNDS 1-2, 5-6, 8, 91-92

(*S*)-N-(1-OXO-3-PHENYLPROPAN-2-YL)-1-PHENYL-1H-IMIDAZOLE-5-CARBOXAMIDE (1)



1A 1B 1C 1

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[0404] A mixture of compound **1A** (102 mg, 1.0 eq), compound **1B** (160 mg, 1.2 eq) and HBTU (250 mg, 1.25 eq) in DMF (8 mL) was stirred at room temperature for 5mins, and then DIEA (0.3mL, 3.0eq) was added. After stirred at room temperature for 30mins, the reaction mixture was diluted with 50 mL ethyl acetate and 20 mL Hexane, washed with water, saturated $NaHCO_3$ and brine and concentrated in vacuo to afford intermediate compound **1C** (190 mg, yield 92%).

[0405] A solution of compound **1C** (190 mg, 1.0 eq) in dry THF (15 mL) was cooled to -50 °C under N_2, and then was added a solution of 1N LAH in THF (0.55 mL, 1.1 eq) dropwise at -50 °C. The reaction mixture was stirred at -30 °C to -10 °C for 2hrs, quenched with saturated $NaHCO_3$ at -20 °C, and then extracted with 3 x 30 mL ethyl acetate. The combined organic phase was dried over Na_2SO_4 to give the crude mixture, which was purified on silica gel column. Compound **1** (105 mg, 65%): MS (ESI) *m/z* $(M+H)^+$: 320.3; ^1H NMR (400 MHz, $CDCl_3$): δ 9.64 (s, 1H), 7.65 (s, 1H), 7.56 (s, 1H), 7.46 (m, 3H), 7.26-7.33 (m, 5H), 7.09 (m, 2H), 6.29 (d, 1H), 4.81(m, 1H), 3.19 (d, 2H) ppm

(*S*)-N-(1-OXO-3-PHENYLPROPAN-2-YL)-1-PHENYL-1H-PYRAZOLE-5-CARBOXAMIDE (2)

((*S*)-5-METHYL-N-(1-OXO-3-PHENYLPROPAN-2-YL)-1-PHENYL-1H-PYRAZOLE-3-CARBOXAMIDE (5)

(*S*)-N-(1-OXO-3-PHENYLPROPAN-2-YL)-4-PHENYLTHIAZOLE-5-CARBOXAMIDE (6)

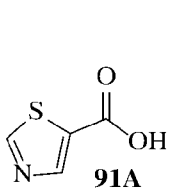
(*S*)-3-METHYL-N-(1-OXO-3-PHENYLPROPAN-2-YL)-1-PHENYL-1H-PYRAZOLE-5-CARBOXAMIDE (8)

[0406] Compounds **2**, **5**, **6** and **8** were prepared as in Example **1** using the corresponding carboxylic acid, respectively. Compound **2**: MS (ESI) *m/z* $(M+H)^+$: **320.2**; ^1H NMR (400 MHz, DMSO): δ 9.6 (s, 1H), 9.15 (d, 1H), 7.73 (s, 1H), 7.4 - 7.2 (m, 10H), 6.8 (s, 1H), 4.53 (m, 1H), 3.25 (dd, 1H), 2.8 (dd, 1H) ppm.

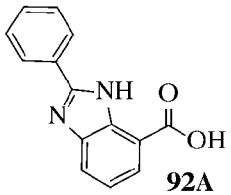
[0407] Compound **5**: MS (ESI) *m/z* $(M+H)^+$: **334.3**; ^1H NMR (400 MHz, $CDCl_3$): δ 9.67 (s, 1H), 7.54 - 7.4 (m, 6H), 7.3 - 7.2 (m, 5H), 6.73 (s, 1H), 4.82 (m, 1H), 3.21 (d, 2H), 2.33 (s, 3H) ppm.

[0408] Compound **6**: MS (ESI) *m/z* $(M+H)^+$: 337.5; ^1H NMR (400 MHz, $CDCl_3$): δ 9.56 (s, 1H), 8.88 (s, 1H), 7.5 - 7.34 (m, 5H), 7.27 - 7.2 (m, 3H), 6.94 (m, 2H), 6.35 (d, 1H), 4.73 (m, 1H), 3.1 (dd, 1H), 3.08 (dd, 1H) ppm.

[0409] Compound **8**: MS (ESI) *m/z* $(M+H)^+$: **334.3**; ^1H NMR (400 MHz, DMSO): δ 9.59 (s, 0.6H), 9.01 (d, 0.6 H), 8.35 (d, 0.4 H), 7.38 -7.06 (m, 10H), 6.58 (s, 0.6H), 6.48 (s, 0.4 H), 4.82 (m, 0.2 H), 4.54 (m, 0.6 H), 3.98 (m, 0.4 H), 3.25 (dd, 0.6 H), 2.98 (dd, 0.4 H), 2.78 (dd, 0.6 H), 2.7 (dd, 0.4 H), 2.48 (s, 1.8 H0, 2.21 (s, 1.2 H) ppm.



91A



92A

(*S*)-*N*-(1-OXO-3-PHENYLPROPAN-2-YL)THIAZOLE-5-CARBOXAMIDE (91)

[0410] Compound **91** was prepared as in Example **1** from the corresponding starting materials, compounds **91A** and **1B**. Compound **91**: ^1H NMR (400 MHz, $CDCl_3$): δ 9.69 (s, 1H), 8.85 (s, 1H), 8.21 (s, 1H), 7.06 (d, 1H), 7.32 -7.18 (m, 8H), 4.88 (m, 1H), 3.26 (m, 2H) ppm. MS (ESI) *m/z* $(M+H)^+$ 261.3.

(*S*)-*N*-(1-OXO-3-PHENYLPROPAN-2-YL)-2-PHENYL-1*H*-BENZO[*d*]IMIDAZOLE-7-CARBOXAMIDE (92)

[0411] Compound **92** was prepared as in Example **1** using the corresponding carboxylic acid. ^1H NMR (400 MHz, $CDCl_3$): δ 12.07 (s, 1H), 11.92 (d, 1H), 9.84 (s, 1H), 8.1 - 8.0 (m, 3H), 7.5 - 7.46 (m, 10H), 7.32 -7.18 (m, 8H), 5.04 (m, 1H), 3.34 (d, 2H) ppm. MS (ESI) *m/z* $(M+H)^+$ 370.4.

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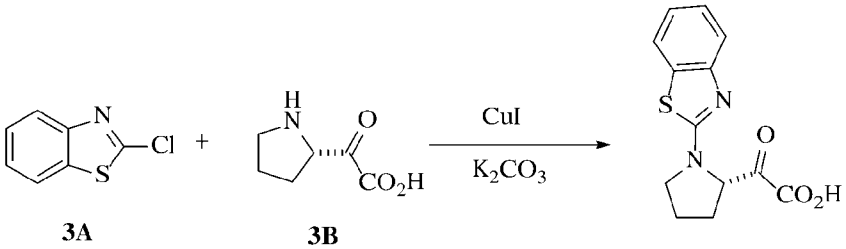
EXAMPLE 2

COMPOUNDS 3-4

(*S*)-1-(BENZO[*D*]THIAZOL-2-YL)-N-((*S*)-1-OXO-3-PHENYLPROPAN-2-YL)PYRROLIDINE-2-CARBOXAMIDE (3)



3A **3B** **3C**

[0412] A mixture of compound **3A** (500 mg, 1.0 eq), compound **3B** (738 mg, 1.0 eq), CuI (124 mg, 0.15 eq) and K_2CO_3 (1.8 g, 3.0 eq) in DMA (15 mL) was heated at 100 °C for 18 hrs, and then the inorganic was removed by filtration. The mixture was diluted with water (50 mL), adjusted pH ~ 6, and then extracted with 3 x 50 mL acetate to afford intermediate compound **3C**. Compound **3** was prepared as in Example **1** using the corresponding carboxylic acid, intermediate compound **3C**. Compound **3**: MS (ESI) *m/z* $(M+H)^+$: **380.2**; ^1H NMR (400 MHz, $CDCl_3$): δ 9.66 (s, 1H), 8.32 (d, 1H), 7.63 (d, 1H), 7.52 (d, 1H), 7.30 (t, 1H), 7.10 (t, 1H), 6.92-7.01 (m, 5H), 4.69 (m, 2H), 3.45 (m, 1H), 3.36 (m, 1H), 3.17 (dd, 1H), 2.90 (dd, 1H), 2.55 (m, 1H), 2.03 (m, 3H) ppm.

(*S*)-1-(BENZO[*D*]OXAZOL-2-YL)-N-((*S*)-1-OXO-3-PHENYLPROPAN-2-YL)PYRROLIDINE-2-CARBOXAMIDE (4)

[0413] Compound **4** was prepared as in Example **2** using the corresponding starting materials. MS (ESI) *m/z* $(M+H)^+$: **364.3**; ^1H NMR (400 MHz, $CDCl_3$): δ 9.65 (s, 1H), 7.69 (br d, 1H), 7.37 (d, 1H), 7.33 (t, 1H), 7.18 (t, 1H), 6.98-7.10 (m, 6H), 4.71 (m, 2H), 4.59 (m, 1H), 3.61 (m, 2H), 3.19 (dd, 1H), 2.97 (dd, 1H), 2.41 (m, 1H), 1.91-2.12 (m, 3H) ppm.

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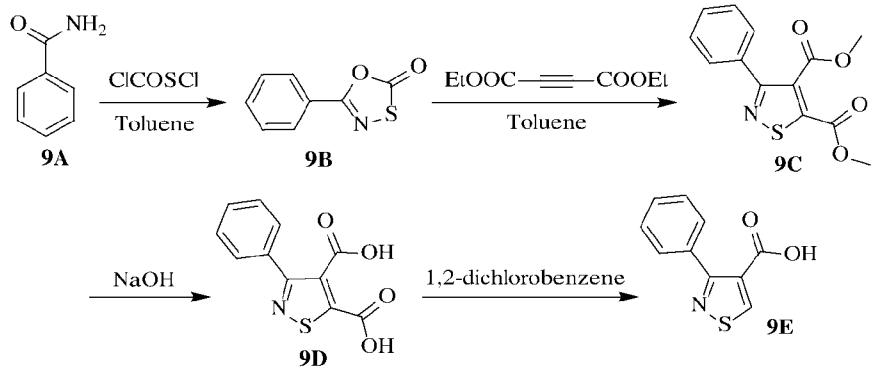
EXAMPLE 3

(*S*)-N-(1-OXO-3-PHENYLPROPAN-2-YL)-3-PHENYLISOTHIAZOLE-4-CARBOXAMIDE (9)



[0414] To a suspension of compound **9A** (1.2 g) in toluene (15 ml) was added chlorocarbonylsulfenyl chloride (1.3 ml). The mixture was heated at 100° C for 2 hrs to obtain a clear solution (gas evolution was observed). When TLC showed complete conversion, the reaction mixture was concentrated and the solid residue was triturated with hexane, filtered and dried to yield compound **9B**.

[0415] To a solution of compound **9B** (1.4 g) in α,α,α-trifluorotoluene (10 mL) was added diethyl acetylenedicarboxylate (2.0 ml). After heated in the microwave at 170° C for 1 hr, the reaction mixture was concentrated. and the oily residue was purified by flash column chromatography. The product-containing fractions were combined, concentrated, and the residue was triturated with hexane, filtered and dried to yield compound **9C**.

[0416] A solution of compound **9C** (2.1 g) and NaOH (1.4 g) in water (20 mL) was refluxed for 2.5 hrs. The reaction mixture was cooled, diluted with water (150 mL) and acidified with concentrated HCl (aqueous). A precipitate was formed. The water layer was extracted with EtOAc (2 × 200 mL; the precipitate slowly dissolved). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to yield compound **9D**.

[0417] A suspension of compound **9D** (1.8 g) in 1,2-dichlorobenzene (20 mL) was refluxed for 20 mins (gas formation is observed). The reaction mixture was cooled diluted with hexane (50 mL) and filtered to precipitate the product. To a suspension of the crude product in water (40 mL) was added 1N NaOH (10 ml). The water layer was extracted with ethyl acetate (2×100 mL) and acidified with concentrated HCl to pH ~ 3. The product was extracted with

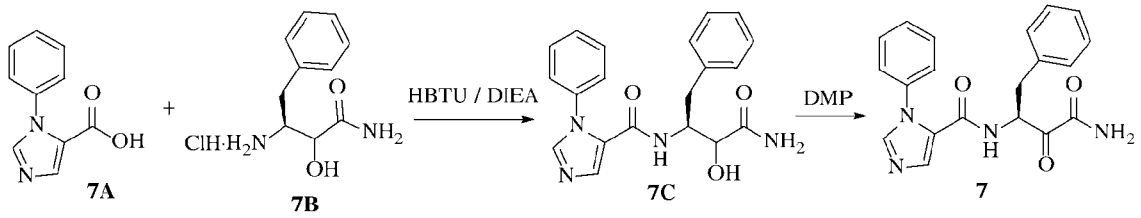
EtOAc (2 x 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to yield intermediate compound **9E**.

[0418] Compound **9** was prepared as in Example **1** using the corresponding carboxylic acid, intermediate compound **9E**. MS (ESI) *m/z* $(M+H)^+$: 359.1; ^1H NMR (400 MHz, $CDCl_3$): δ 9.59 (s, 1H), 9.16 (s, 1H), 7.56 - 7.5 (m, 2H), 7.48 - 7.4 (m, 3H), 7.27 - 7.22 (m, 3H), 6.94 (m, 2H), 6.15 (d, 1H), 4.79 (m, 1H), 3.1 (d, 2H) ppm.

EXAMPLE 4

COMPOUNDS 7, 10-11, 14, 18, 20

(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-PHENYL-1H-IMIDAZOLE-5-CARBOXAMIDE (7)



[0419] A mixture of compound **7A** (50 mg, 1.0 eq), compound **7B** (74 mg, 1.2 eq) and HBTU (126 mg, 1.25 eq) in DMF (3mL) was stirred at room temperature for 5 mins, and then DIEA (0.15 mL, 3.0 eq) was added. After stirred at room temperature for 30 mins, the reaction mixture was diluted with ethyl acetate (30 mL) and hexane (10 mL), washed with 1N HCl, water, saturated $NaHCO_3$ and brine and concentrated in vacuo to afford intermediate compound **7C** (65 mg, yield 67%) as white solid.

[0420] To a solution of compound **7C** (65 mg, 1.0 eq) in dry DCM (10ml) and DMSO (2 mL) was added DMP (305 mg, 4.0 eq). After stirred at room temperature for 1 hr, the mixture was diluted with DCM (30 mL), quenched by adding 10% aqueous $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (v/v = 1/1, ~ 10 mL). The organic layer was separated by extracting the aqueous layer with DCM (30 mL x 5). The combined organic layer was washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated to afford white solid, which was then triturated in CH_2Cl_2/Hexane to provide pure product compound **7** (29 mg, yield 45%). MS (ESI) *m/z* $(M+H)^-$: **363.4**; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.57 (s, 1H), 7.45 (m, 3H), 7.26-7.35 (m, 5H), 7.05 (m, 2H), 6.72 (s, 1H), 6.24 (d, 1H), 5.58 (m, 2H), 4.81(m, 1H), 3.38 (dd, 1H), 3.14 (dd, 1H) ppm.

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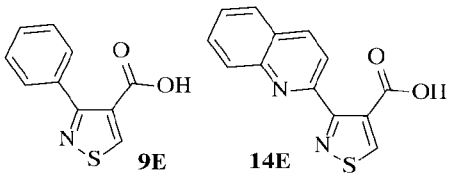
(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-PHENYL-1H-PYRAZOLE-5-CARBOXAMIDE (10)

[0421] Prepared as in Example **4** using the corresponding carboxylic acid. MS (ESI) *m/z* $(M+H)^+$: **363.3**; ^{1}H NMR (400 MHz, DMSO): δ 9.15 (d, 1H), 8.11 (s, 1H), 7.71 (s, 1H), 7.4 - 7.2 (m, 10H), 7.07 (d, 1H), 6.72 (s, 1H), 5.26 (m, 1H), 2.81 (dd, 1H), 2.64 (dd, 1H) ppm.



9E **14E**

(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-PHENYLISOTHIAZOLE-4-CARBOXAMIDE (11)

[0422] Prepared as in Example **4** using the corresponding carboxylic acid, intermediate compound **9E**. MS (ESI) *m/z* $(M+H)^+$ **380.2**; ^{1}H NMR (400 MHz, DMSO): δ 9.15 (d, 1H), 9.05 (s, 1H), 8.14 (s, 1H), 7.89 (s, 1H), 7.5 -7.4 (m, 2H), 7.3 -7.2 (m, 8H), 5.34 (m, 1H), 3.2 (d, 2H) ppm.

(*S*)-1-(BENZO[*D*]OXAZOL-2-YL)-N-((*S*)-1-OXO-3-PHENYLPROPAN-2-YL)PYRROLIDINE-2-CARBOXAMIDE (14)

[0423] Intermediate compound **14E** was prepared as in Example **3**. Compound **14** was then prepared as in Example **4** using the corresponding intermediate carboxylic acid, compound **14E**. Compound **14**: MS (ESI) *m/z* $(M+H)^+$: **431.5**; ^{1}H NMR (400 MHz, DMSO): δ 9.14 (s, 1H), 9.05 (d, 1H), 8.16 (d, 1H), 7.9 (s, 1H), 7.62 -7.56 (m, 2H), 7.3 -7.2 (m, 8H), 5.36 (m, 1H), 3.17 (dd, 1H), 2.78 (dd, 1H) ppm.

(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-PHENYLTHIAZOLE-5-CARBOXAMIDE (18)

[0424] Prepared as in Example **4** using the corresponding carboxylic acid. MS (ESI) *m/z* $(M+H)^+$: **380.1**; ^{1}H NMR (400 MHz, DMSO): δ 10.11(d, 1H), 9.33 (s, 1H), 8.49 (d, 1H), 8.13 (s, 1H), 8.07 (d, 1H), 8.03 (d, 1H), 7.85 (s, 1H), 7.74 (m, 2H), 7.65 (m, 1H), 7.12 - 7 (m, 5H), 5.51 (m, 1H), 3.18 (dd, 1H) 2.89 (dd, 1H) ppm.

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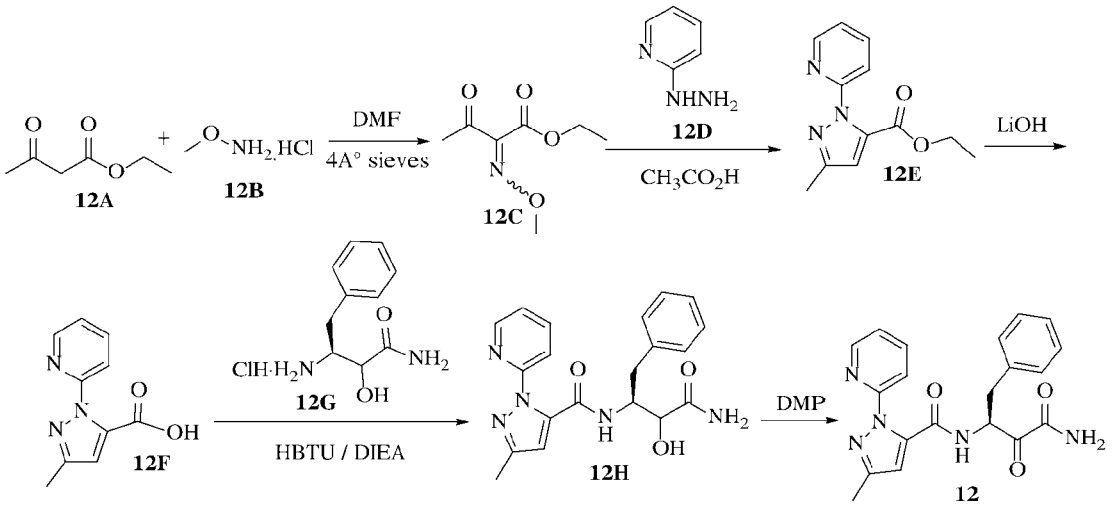
(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-(BENZO[*D*][1,3]DIOXOL-5-YL)-3-METHYLISOXAZOLE-4-CARBOXAMIDE (20)

[0425] Prepared as in Example **4** using the corresponding carboxylic acid. MS (ESI) *m/z* $(M+H)^+$: **422.1**; ^1H NMR (400 MHz, DMSO-d6): δ 8.88 (d, 1H), 8.19 (s, 1H), 7.91 (s, 1H), 7.17-7.30 (m, 7H), 6.94 (d, 1H), 6.11 (s, 2H), 5.45 (m, 1H), 3.22 (dd, 1H), 2.72 (dd, 1H), 2.03 (s, 3H) ppm.

EXAMPLE 5

COMPOUNDS 12-13, 15-17, 19, 27, 44, 47, 54, 60, 94, 117-118, 128, 148, 207, 235, 303-305, 309-312, 23, 39, 456, 461, 492

(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(PYRIDIN-2-YL)-1H-PYRAZOLE-5-CARBOXAMIDE (12)



[0426] To a solution of compound **12A** (5.0 g, 1.0eq) and compound **12B** (2.64 g, 1.0eq) in dry DMF (20 mL) was added 4A° molecular sieve (5.0 g, powder). The resulting mixture was stirred room temperature under N_2 for 20 hrs, filtrated to remove the molecular sieves, diluted with hexane (80 mL) and ethyl acetate (80 mL), and then washed with 3 x 50 mL water, 50 mL saturated $NaHCO_3$ and brine. The crude mixture was purified on silica gel column to provide compound **12C** (3.2 g, yield 48%) as clear oil.

[0427] A mixture of compound **12C** (350 mg, 1.0eq) and compound **12D** (190 mg, 1.0 eq) in acetic acid (8 mL) was heated at 100 °C for 1hr. The residue, upon in-vauo removal of solvent, was suspended in ethyl acetate (80 mL), washed with saturated $NaHCO_3$ and brine. The crude mixture was purified on silica gel column to provide compound **12E** (100 mg,

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yield 25%). Compound **12E** (100 mg) was treated with LiOH in MeOH/water to afford compound **12F** (87 mg, yield 100%).

[0428] A mixture of compound **12F** (85 mg, 1.0 eq), compound **12G** (116 mg, 1.2 eq) and HBTU (190 mg, 1.2 eq) in DMF (5 mL) was stirred at room temperature for 5 mins, and then DIEA (0.3 mL, 4.0 eq) was added. After stirred at room temperature for 30 mins, the mixture was diluted with 50 mL ethyl acetate and 20 mL hexane, washed with 1N HCl, water, saturated $NaHCO_3$ and brine and concentrated in vacuo to afford intermediate compound **12H** (150 mg, yield 94%) as white solid.

[0429] To a solution of compound **12H** (150 mg, 1.0 eq) in dry DCM (20ml) and DMSO (2.5 mL) was added DMP (673 mg, 4.0 eq). After stirred at room temperature for 1 hr, the mixture was diluted with DCM (80 mL), quenched by adding 10% $Na_2S_2O_3$/saturated $NaHCO_3$ (v/v = 1/1, ~ 20 mL). The organic layer was separated. The aqueous layer was extracted with DCM (30 mL x 2). The combined organic layer was washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated to afford white solid. The solid was triturated in CH_2Cl_2/Hexane to provide pure compound **12** (95 mg, yield 64%). MS (ESI) *m/z* $(M+H)^+$: **378.3**; ^1H NMR (400 MHz, DMSO-d6): δ 9.15 (d, 1H), 8.21 (d, 1H), 7.91 (t, 1H), 7.82 (s, 1H), 7.54 (d, 1H), 7.17-7.32 (m, 6H), 6.49 (s, 1H), 5.29 (m, 1H), 3.15 (dd, 1H), 2.84 (dd, 1H), 2.23 (s, 3H) ppm.

(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(BENZO[D]THIAZOL-2-YL)-3-METHYL-1H-PYRAZOLE-5-CARBOXAMIDE (13)

(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(QUINOLIN-2-YL)-1H-PYRAZOLE-5-CARBOXAMIDE (15)

(*S*)-1-([1,1'-BIPHENYL]-3-YL)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1H-PYRAZOLE-5-CARBOXAMIDE (16)

(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(4-(METHYLSULFONYL)PHENYL)-1H-PYRAZOLE-5-CARBOXAMIDE (17)

(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(4-(TRIFLUOROMETHOXY)PHENYL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (19)

[0430] Compounds **13**, **15-17** and **19** were prepared, respectively, as in Example **5** by utilizing the corresponding hydrazine derivative.

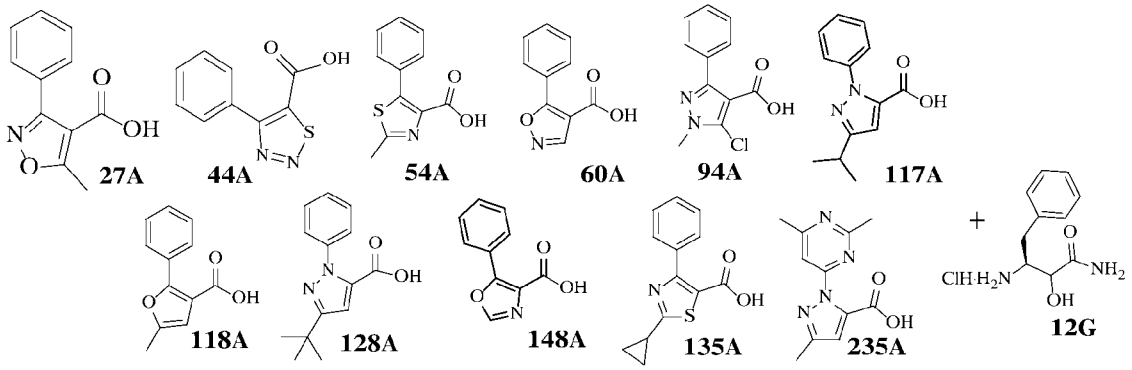
[0431] Compound **13**: MS (ESI) *m/z* $(M+H)^+$: **434.3**; ^1H NMR (400 MHz, DMSO-d6): δ 10.09 (d, 1H), 8.10 (d, 1H), 7.99 (d, 1H), 7.83 (s, 1H), 7.62 (d, 1H), 7.40 (m, 2H), 7.04-7.24 (m, 5H), 6.68 (s, 1H), 5.51 (m, 1H), 3.16 (dd, 1H), 2.95 (dd, 1H), 2.24 (s, 3H) ppm.

[0432] Compound: **15**: MS (ESI) *m/z* $(M+H)^+$: **428.4**; ŧH NMR (400 MHz, DMSO): δ 9.28 (d, 0.5 H), 8.77 (d, 0.5 H), 8.45 (d, 1H), 8 (d, 1H), 7.9 - 7.5 (6 H), 7.2 - 7.1 (6 H), 5.4 (m, 0.5 H4.44 (m, 0.5 H), 3.2 - 2.7 (m, 2H) ppm.

[0433] Compound **16**: MS (ESI) *m/z* $(M+H)^+$: **453.3**; ^1H NMR (400 MHz, DMSO-d6): δ 9.10 (d, 1H), 8.09 (s, 1H), 7.87 (s, 1H), 7.35-7.62 (m, 8H), 7.19-7.29 (m, 5H), 7.09 (d, 1H), 6.61 (s, 1H), 5.30 (m, 1H), 3.17 (dd, 1H), 2.81 (dd, 1H), 2.25 (s, 3H) ppm.

[0434] Compound **17**: MS (ESI) *m/z* $(M+H)^+$: **455.3**; ^1H NMR (400 MHz, DMSO-d6): δ 9.27 (d, 1H), 8.14 (s, 1H), 7.88 (m, 2H), 7.82 (d, 1H), 7.35-7.62 (m, 8H), 7.19-7.45 (m, 7H), 6.62 (s, 1H), 5.25 (m, 1H), 3.19 (m, 4H), 2.82 (dd, 1H), 2.25 (s, 3H) ppm.

[0435] Compound **19**: MS (ESI) *m/z* $(M+H)^+$: **461.3**; ^1H NMR (400 MHz, DMSO-d6): δ 9.15 (d, 1H), 8.11 (s, 1H), 7.87 (s, 1H), 7.82 (d, 1H), 7.21-7.35 (m, 9H), 6.61 (s, 1H), 5.23 (m, 1H), 3.20 (dd, 1H), 2.82 (dd, 1H), 2.24 (s, 3H) ppm.



(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-METHYL-3-PHENYLISOXAZOLE-4-CARBOXAMIDE (27)

[0436] Compound **27** (30.0 mg, 43.0% yield, white solid) was prepared as in Example **12** from the corresponding carboxylic acid, compound **27A**. Compound **27**: ^1H NMR (400MHz, DMSO-d_6) δ 8.94 (d, J = 7.6 Hz, 1H), 8.17 (s, 1H), 7.90 (s, 1H), 7.49 - 7.41 (m, 3H), 7.41 - 7.34 (m, 2H), 7.33 - 7.21 (m, 5H), 5.42 - 5.35 (m, 1H), 3.29 - 3.21 (m, 1H), 2.80 - 2.70 (m, 1H), 2.35 - 2.27 (m, 3H). MS (ESI) *m/z* $(M+H)^+$ 378.1.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-PHENYL-1,2,3-THIADIAZOLE-5-CARBOXAMIDE (44)

[0437] Compound **44** (42.4 mg, yield: 47.7%, white solid) was prepared as in Example **12** from the corresponding intermediate carboxylic acid, compound **44A**. Compound **44**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (br d, J = 7.5 Hz, 1 H), 8.19 (s, 1 H), 7.93 (s, 1 H), 7.79 - 7.67 (m, 2 H), 7.52 - 7.39 (m, 3 H), 7.34 - 7.21 (m, 5 H), 5.52 - 5.39 (m, 1 H), 3.23 (dd, J = 14.0, 3.5 Hz, 1 H), 2.78 (dd, J = 13.6, 10.5 Hz, 1 H). MS (ESI) *m/z* $(M+H)^+$ 381.0.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-2-METHYL-5-PHENYLTHIAZOLE-4-CARBOXAMIDE (54)

[0438] Compound **54** (75 mg, yield: 75.4%, white solid) was prepared as in Example **12** from the corresponding intermediate carboxylic acid, compound **54A**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (br d, J = 7.7 Hz, 1 H) 8.05 (br s, 1 H) 7.81 (br s, 1 H) 7.43 - 7.29 (m, 1 H) 7.41 - 7.29 (m, 1 H) 7.29 - 7.29 (m, 1 H) 7.41 - 7.29 (m, 1 H) 7.30 - 7.28 (m, 1 H) 7.28 - 7.08 (m, 5 H) 5.37 (td, J = 8.1, 4.5 Hz, 1 H) 3.22 - 3.09 (m, 1 H) 3.17 (br dd, J = 14.0, 4.1 Hz, 1 H) 3.06 – 2.92 (m, 1 H) 2.72 - 2.60 (m, 3 H). MS (ESI) *m/z* $(M+H)^-$ 394.0.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (60)

[0439] Compound **60** (40 mg, yield 36.20%, white solid) was prepared as in Example **5** from the corresponding carboxylic acid, compound **60A**. Compound **60**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.02 (d, J=7.5 Hz, 1H), 8.83 (s, 1H), 8.16 (s, 1H),7.92 - 7.78 (m, 3H), 7.59 - 7.42 (m, 3H), 7.35 - 7.17 (m, 4H), 5.43 - 5.34 (m, 1H),3.27 - 3.17 (m, 1H), 2.90 - 2.79 (m, 1H). MS (ESI) *m/z* $(M+H)^+$ 364.1.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-CHLORO-1-METHYL-3-PHENYL-1*H*-PYRAZOLE-4-CARBOXAMIDE (94)

[0440] Compound **94** was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **94A**. Compound **94**: ^{1}H NMR (400 MHz, DMSO): δ 8.8 (d, 1H), 8.16 (s, 1H), 7.89 (s, 1H), 7.5 - 7.46 (m, 2H), 7.32 -7.18 (m, 8H), 5.41 (m, 1H), 3.82 (s, 3H), 3.17 (dd, 1H), 2.76 (dd, 1H) ppm. MS (ESI) *m/z* $(M+H)^+$ 410.9.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-ISOPROPYL-1-PHENYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (117)

[0441] Compound **117** (10 mg, yield 18.29%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **117A**. Compound **117**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.36 (d, J=7.8 Hz, 1H), 8.09 (s, 1H), 7.84 (s, 1H), 7.63 - 7.47 (m, 5H), 7.32 - 7.14 (m, 5H), 6.66 (s, 1H), 5.50 - 5.39 (m, 1H), 3.23 - 3.13 (m, 1H), 3.09 - 2.89 (m, 2H), 1.12 (d, J=6.8 Hz, 6H). MS (ESI) m/z $(M + H)^+$ 405.2.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-METHYL-2-PHENYLFURAN-3-CARBOXAMIDE (118)

[0442] Compound **118** (58 mg, yield: 55.4%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **118A**. Compound **118**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.54 (d, J = 7.5 Hz, 1H), 8.08 (s, 1H), 7.81 (s, 1H), 7.68 (d, J = 7.0 Hz, 2H), 7.35 - 7.26 (m, 7H), 7.23 - 7.17 (m, 1H), 6.39 (d, J = 0.9 Hz, 1H), 5.30 (br d, J = 0.7 Hz, 1H), 3.19 - 3.12 (m, 1H), 2.88 - 2.79 (m, 1H), 2.33 - 2.29 (m, 3H). MS (ESI) m/z $(M+H)^+$ 377.1.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-(TERT-BUTYL)-1-PHENYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (128)

[0443] Compound **128** (101.7 mg, 68.04% yield, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **128A**. Compound **128**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 - 7.44 (m, 3H), 7.42 - 7.35 (m, 2H), 7.34 - 7.28 (m, 1H), 7.25 - 7.14 (m, 5H), 6.74 (br s, 1H), 6.70 (s, 1H), 5.73 - 5.64 (m, 1H), 5.53 (br s, 1H), 3.44 - 3.35 (m, 1H), 3.18 - 3.09 (m, 1H), 1.16 (s, 9H). MS (ESI) m/z $(M+1)^+$ 419.3.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-PHENYLOXAZOLE-4-CARBOXAMIDE (148)

[0444] Compound **148** (10 mg, yield: 30.8%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **148A**. Compound **148**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.44 (d, J=7.7 Hz, 1H), 8.14 - 8.03 (m, 3H), 7.85 (s, 1H), 7.49 - 7.42 (m, 3H), 7.30 - 7.15 (m, 5H), 5.49 - 5.40 (m, 1H), 3.26 - 3.17 (m, 1H), 3.12 - 3.02 (m, 1H). MS (ESI) m/z $(M +H)^+$ 364.1.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-2-CYCLOPROPYL-4-PHENYLTHIAZOLE-5-CARBOXAMIDE (207)

[0445] Compound **207** (54.0 mg, 44.09% yield, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **135A**. Compound **207**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.45 (m, 2H), 7.43 - 7.38 (m, 3H), 7.21 - 7.17 (m, 3H), 6.79-6.77 (m, 2H), 6.70 (s, 1H), 6.19 – 6.17 (d, J = 6.0Hz, 1H), 5.53 (s, 1H), 5.50 – 5.45 (m, 1H), 3.25 - 3.21 (m, 1H), 2.90- 2.85 (m, 1H), 2.33-2.27 (m, 1H), 1.19 – 1.16 (m, 2H), 1.13 – 1.10 (m, 2H). MS (ESI) *m/z* $(M+1)^+$ 420.1.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(2,6-DIMETHYLPYRIMIDIN-4-YL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (235)

[0446] Compound **235** (61.6 mg, 51.11% yield, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **235A**. Compound **235**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (d, J = 7.2 Hz, 1H), 7.57 (s, 1H), 7.21 - 7.16 (m, 3H), 7.11 - 7.06 (m, 2H), 6.87 (s, 1H), 6.75 (br s, 1H), 5.84 - 5.76 (m, 1H), 5.56 (br s, 1H), 3.49 - 3.31 (m, 2H), 2.55 (s, 3H), 2.34 - 2.32 (m, 6H). MS (ESI) *m/z* $(M+1)^+$ 407.1.

((*S*)-*N*-(1-AMINO-1,2-DIOXOPENTAN-3-YL)-3-METHYL-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (47)

[0447] Compound **47** (90.00 mg, yield 60.4%, white solid) was prepared as in Example **5** from the corresponding starting materials, **23A** and **47A**. Compound **47**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.98 (d, J = 6.6 Hz, 1H), 8.12 (br s, 1H), 7.88 - 7.79 (m, 3H),7.57 - 7.50 (m, 3H), 5.12 - 5.02 (m, 1H), 2.32 (s, 3H), 1.95 - 1.77 (m,1H), 1.65 - 1.48 (m, 1H), 0.93 (t, J=7.4 Hz, 3H). MS (ESI) *m/z* $(M+H)^+$ 316.1.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-PHENYLOXAZOLE-5-CARBOXAMIDE (303)

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-PHENYLISOXAZOLE-4-CARBOXAMIDE (304)

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-PHENYL-3-(TRIFLUOROMETHYL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (305)

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1,3-DIPHENYL-1*H*-PYRAZOLE-4-CARBOXAMIDE (309)

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(TERT-BUTYL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (310)

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-CHLORO-1-ETHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (311)

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-CHLORO-1-ETHYL-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (312)

[0448] Compounds **303-305** and **309-312** were prepared as in Example **5** from the corresponding carboxylic acid with compound **12G**, respectively.

[0449] Compound **303**: ^{1}H NMR (400MHz, DMSO-d_6) δ ^{1}H NMR (400 MHz, DMSO): δ 8.51 (s, 1H), 7.9 - 7.85 (m, 2H), 7.81 (d, 1H), 7.4 - 7.0 (m, 10H), 4.53 (m, 1H), 2.98 (dd, 1H), 2.57 (dd, 1H) ppm. MS (ESI) *m/z* $(M+H)^+$ 364.3.

[0450] Compound **304**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.2 - 8.9 (m, 1H), 8.11 (m, 1H), 7.7 - 7.1 (m, 12H), 5.3 (m, 0.5 H), 4.4 (m, 0.5H), 2.85 - 2.55 (m, 2H) ppm. MS (ESI) *m/z* $(M+H)^+$ 364.3.

[0451] Compound **305**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.3 (d, 1H), 8.07 (s, 1H), 7.83 (s, 1H), 7.4 - 7.1 (m, 10H), 5.24 (m, 1H), 3.14 (dd, 1H), 2.74 (dd, 1H) ppm. MS (ESI) *m/z* $(M+H)^+$ 431.3.

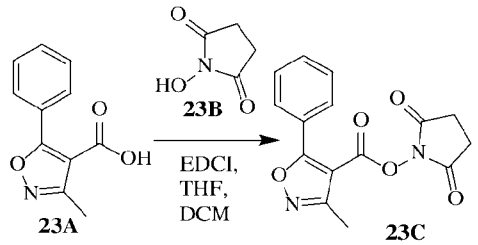
[0452] Compound **309**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.7 (m, 1H), 8.49 (d, 1H), 8.1 - 7.1 (m, 17H), 5.31 (m, 0.5 H), 4.6 - 4.4 (m, 0.5H), 3.1 - 2.7 (m, 2H) ppm. MS (ESI) *m/z* $(M+H)^+$ 439.3.

[0453] Compound **310**: ^{1}H NMR (400MHz, DMSO-d_6) δ 7.75 (d, 1H), 7.4 - 7.1 (m, 5H), 6.38 (s, 1H), 6.1 (d, 2H), 4.48 (m, 1H), 3.02 (dd, 1H), 2.52 (dd, 1H) 2.08 (s, 3H), 1.31 (s, 9H) ppm. MS (ESI) *m/z* $(M+H)^+$ 379.3.

[0454] Compound **311**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.89 (d, 1H), 8.13 (d, 1H), 7.86 (s, 1H), 7.33 (s, 1H), 7.3 - 7.1 (m, 5H), 6.8 (s, 1H), 5.38 (m, 1H), 3.99 (q, 2H), 3.21 (dd, 1H), 2.78 (dd, 1H) 1.11 (t, 3H) ppm. MS (ESI) *m/z* $(M+H)^-$ 349.2.

[0455] Compound **312**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.74 (d, 1H), 8.1 (s, 1H), 7.83 (s, 1H), 7.4 - 7.2 (m, 5H), 6.58 (s, 1H), 5.29 (m, 1H), 4.25 (q, 2H), 3.18 (dd, 1H), 2.87 (dd, 1H), 2.13 (s, 3H), 1.15 (t, 3H) ppm. MS (ESI) *m/z* $(M+H)^+$ 329.1.

(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (23)



[0456] To a solution of compound **23A** (500 mg, 2.46 mmol) in THF (10 mL) was added **23B** (311 mg, 2.71 mmol) and EDCI (566 mg, 2.95 mmol) with DCM (10 mL). The mixture was stirred at 25 °C for 3 hrs. The reaction mixture was concentrated and diluted with EA (20 mL). Then the mixture was washed with HCl (1M, 20 mL), saturated aqueous $NaHCO_3$ (20 mL), dried over Na_2SO_4 and concentrated. Compound **23C** (800 mg, crude, yellow oil): ^{1}H NMR (400MHz, DMSO-d_6) δ 7.93 - 7.88 (m, 2H), 7.69 - 7.63 (m, 1H), 7.62 - 7.56 (m, 2H), 2.87 (s, 4H), 2.54 - 2.51 (m, 3H).

[0457] Compound **23** (30.0 mg, yield 35.0%, white solid) was prepared as in Example **5** from the corresponding intermediate compounds **23C** and **12G**. Compound **23**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.08 (br d, J = 8.0 Hz, 1H), 8.22 (s, 1H), 7.94 (s, 1H), 7.64 (br d, J = 7.2 Hz, 2H), 7.55 - 7.41 (m, 3H), 7.35 - 7.21 (m, 5H), 5.54 - 5.45 (m, 1H), 3.29 - 3.23 (m, 1H), 2.81 - 2.71 (m, 1H), 2.09 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 378.0.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-(4-PHENYL-1*H*-PYRAZOL-1-YL)THIAZOLE-5-CARBOXAMIDE (39)

[0458] Compound **39** (5.20 mg, 26.12% yield, white solid) was prepared as in Example **5** from the corresponding starting materials, compounds **21F** and **12G**. Compound **39**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.75 (d, J = 4.8 Hz, 1H), 8.73 - 8.71 (m, 1H), 8.73 (s, 1H), 8.66 (s, 1H), 7.69 (s, 1H), 7.54 (d, J = 7.6 Hz, 2H), 7.45 - 7.41 (m, 2H), 7.35 - 7.31 (m, 1H), 7.29 - 7.27 (m, 1H), 7.25 - 7.21 (m, 4H), 6.78 (br s, 1H), 5.82 - 5.74 (m, 1H), 5.48 (br s, 1H), 3.46 - 3.41 (m, 1H), 3.27 - 3.20 (m, 1H). MS (ESI) *m/z* $(M+H)^+$ 446.1.

***N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(PYRIDIN-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (456)**

[0459] Compound **456** (240 mg, 86.0% yield, white solid) was prepared as in compound **12** from the corresponding starting materials, compounds **12F** and 3-amino-*N*-cyclopropyl-2-hydroxy-4-phenylbutanamide hydrochloride. Compound **456**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.15 (d, J = 7.2 Hz, 1H), 8.80 (d, J = 5.2 Hz, 1H), 8.21 - 8.17 (m, 1H), 7.92 - 7.86 (m, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.33 - 7.16 (m, 6H), 6.50 (s, 1H), 5.36 - 5.27 (m, 1H), 3.17 - 3.09 (m, 1H), 2.88 - 2.79 (m, 1H), 2.79 - 2.70 (m, 1H), 2.24 (s, 3H), 0.69 - 0.53 (m, 4H). MS (ESI) *m/z* $(M+H)^+$ 418.2.

***N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (461)**

[0460] Compound **461** (270 mg, 68.77% yield, white solid) was prepared as in compound **12** from the corresponding starting materials, compounds **60A** and 3-amino-*N*-cyclopropyl-2-hydroxy-4-phenylbutanamide hydrochloride. Compound **461**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.04 (d, J = 7.5 Hz, 1H), 8.87 (d, J = 4.8 Hz, 1H), 8.82 (s, 1H), 7.85 (d, J = 7.3 Hz, 2H), 7.59 - 7.44 (m, 3H), 7.36 - 7.19 (m, 5H), 5.37 (br.s., 1H), 3.27 - 3.17 (m, 1H), 2.90 - 2.73 (m, 2H), 0.72 - 0.51 (m, 4H). MS (ESI) *m/z* $(M+H)^+$ 404.1.

(*S*)-*N*-(4-AMINO-1-(4-HYDROXYPHENYL)-3,4-DIOXOBUTAN-2-YL)-3-METHYL-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (492)

[0461] Compound **492** (35 mg, 60.9% yield, white solid) was prepared as in compound **12** from the corresponding starting materials, compounds **23A** and (3*S*)-3-amino-4-(4-(*tert*-butoxy)phenyl)-2-hydroxybutanamide followed by removal of the *tert*-butyl group to obtain

the final compound **492**. Compound **492**: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.29 (s, 1H), 9.01 (d, J = 7.5 Hz, 1H), 8.19 (s, 1H), 7.92 (s, 1H), 7.66 - 7.41 (m, 5H), 7.07 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.6 Hz, 2H), 5.46 - 5.29 (m, 1H), 3.13 (br d, J = 10.8 Hz, 1H), 2.63 (br d, J = 2.9 Hz, 1H), 2.13 (s, 3H). MS (ESI) m/z $(M+H)^+$ 394.1.

***N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(PYRIDIN-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (495)**

[0462] Compound **495** (4.0 g, 44.68% yield, white solid) was prepared as in compound **12** from the corresponding starting materials, compounds **12F** and 3-amino-2-hydroxy-4-phenylbutanamide hydrochloride to obtain the final compound **495**. Compound **495**: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.74 (br d, J = 9.0 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.20 - 7.08 (m, 5H), 7.04 (d, J = 9.0 Hz, 1H), 6.97 (d, J = 8.5 Hz, 2H), 5.40 (d, J = 6.3 Hz, 1H), 4.96 (s, 2H), 4.79 (d, J = 2.3 Hz, 2H), 4.48 - 4.15 (m, 2H), 3.97 - 3.86 (m, 1H), 3.68 (t, J = 8.2 Hz, 1H), 3.63 - 3.49 (m, 2H), 2.98 (dd, J = 3.4, 13.9 Hz, 1H), 2.70 - 2.59 (m, 1H), 1.78 (qd, J = 6.8, 13.6 Hz, 1H), 0.72 (d, J = 6.8 Hz, 3H), 0.69 - 0.62 (m, 1H), 0.67 (d, J = 6.8 Hz, 2H). MS (ESI) m/z $(M+Na)^+$ 493.1.

***N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (531)**

[0463] Compound **531** (4.0 g, 44.68% yield, white solid) was prepared as in compound **12** from the corresponding starting materials, compounds **60A** and 3-amino-2-hydroxy-4-phenylbutanamide hydrochloride to obtain the final compound **531**. Compound **531**: ^{1}H NMR (CD_3CN, 400 MHz): δ 8.52 (s, 1H), 7.84 - 7.75 (m, 2H), 7.57 - 7.51 (m, 1H), 7.51 - 7.43 (m, 2H), 7.32 - 7.23 (m, 3H), 7.23 - 7.17 (m, 2H), 7.17 - 7.07 (m, 1H), 7.06 - 6.93 (m, 1H), 6.23 (s, 1H), 5.55 - 5.47 (m, 1H), 3.29 (dd, J = 4.9, 14.1 Hz, 1H), 2.92 (dd, J = 8.9, 14.0 Hz, 1H). MS (ESI) m/z $(M+H)^-$ 364.1.

EXAMPLE 6

Compounds 21-22, 322, 29, 31, 75, 90, 279

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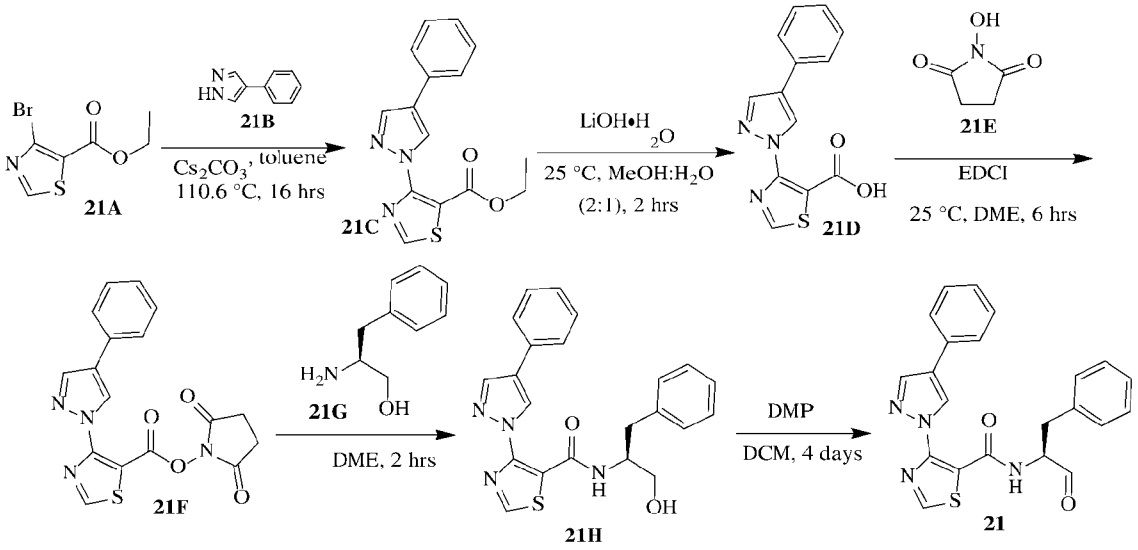
(*S*)-N-(1-OXO-3-PHENYLPROPAN-2-YL)-4-(4-PHENYL-1H-PYRAZOL-1-YL)THIAZOLE-5-CARBOXAMIDE (21)



[0464] A mixture consisting of compound **21A** (500 mg, 2.12 mmol), compound **21B** (306 mg, 2.12 mmol) and Cs_2CO_3 (2.07 g, 6.36 mmol) was stirred at 110.6 °C for 16 hrs. The reaction mixture was cooled to room-temperature, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Petroleum ether: Ethyl acetate = 3:2 and then Acetic acid: Ethyl acetate = 1:100) to afford compound **21C** (80 mg, 12.61% yield) as a light yellow solid, and compound **21D** (125 mg, 21.73% yield) as a yellow solid.

[0465] Compound **21C**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.85 (s, 1H), 8.49 (s, 1H), 8.07 (s, 1H), 7.57 (d, J = 7.6 Hz, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.30 - 7.26 (m, 1H), 4.41 - 4.32 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H).

[0466] Compound **21D**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ14.70 (br. s., 1H), 9.33 (s, 1H), 8.87 (d, J = 0.8 Hz, 1H), 8.41 (d, J = 0.8 Hz, 1H), 7.75 - 7.71 (m, 2H), 7.43 - 7.38 (m, 2H), 7.30 - 7.24 (m, 1H). MS (ESI) *m/z* $(M+H)^+$ 271.8.

[0467] To a solution of compound **21C** (80 mg, 267.25 umol) in MeOH (5 mL) and H_2O (2.5 mL) was added LiOH (19.20 mg, 801.75 umol) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 2 hrs. The mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (10 mL) and adjusted with 1N HCl to pH ~ 3, extracted with ethyl acetate 90 mL (30 mL x 3). The combined organic layers were washed with

brine 30 mL, dried over anhyrous Na_2SO_4, filtered and concentrated under reduced pressure to afford intermediate compound **21D** (71.1 mg, 98.07% yield) as white solid. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.84 (s, 1H), 8.78 (d, J = 0.8 Hz, 1H), 8.13 (d, J = 0.8 Hz, 1H), 7.60 - 7.56 (m, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.39 - 7.34 (m, 1H). MS (ESI) m/z $(M+H)^+$ 271.8.

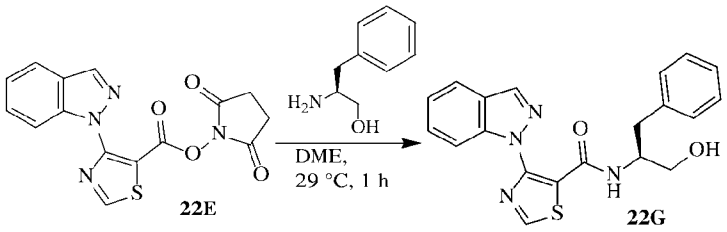
[0468] To a solution of compound **21D** (80 mg, 294.89 umol) and 1-hydroxypyrrolidine-2,5-dione (**21E**) (35.6 mg, 309.63 umol) in DME (3.50 mL) was added EDCI (84.8 mg, 442.34 umol) in one portion at 25 °C under N_2. The resultant mixture was stirred at 25 °C for 6 hrs. The mixture was concentrated under reduced pressure, diluted with EtOAc (100 mL), washed with 1N HCl (10 mL) and saturated aqueous $NaHCO_3$ (10 mL x 3), and then washed with brine (20 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford intermediate compound **21F** (100 mg, crude) as yellow oil. MS (ESI) m/z $(M+H)^+$ 368.9.

[0469] A mixture consisting of compound **21F** (100 mg, 271.47 umol) and compound **21G** (41.1 mg, 271.47 umol) in DME (3 mL) was stirred at 25 °C for 2 hrs. The mixture was concentrated in vacuum, diluted with ethyl acetate (100 mL), washed with 1N HCl (10 mL) and saturated aqueous $NaHCO_3$ (10 mL x 3), and then washed with brine (20 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by flash silica gel chromatography (Petroleum ether: Ethyl acetate = 3:2) to afford compound **21H** (65 mg, 59.20% yield). ^1H NMR ($CDCl_3$, 400 MHz): δ 10.54 (d, J = 7.6 Hz, 1H), 9.21 (d, J=0.4 Hz, 1H), 8.93 (s, 1H), 8.40 (s, 1H), 7.78 (d, J=7.6 Hz, 2H), 7.45 – 7.38 (m, 2H), 7.31 - 7.26 (m, 1H), 7.24 - 7.18 (m, 4H), 7.15 – 7.10 (m, 1H), 4.96 – 4.89 (m, 1H), 4.13 – 4.02 (m, 1H), 3.52 - 3.43 (m, 2H), 2.97 – 2.91 (m, 1H), 2.82 – 2.74 (m, 1H). MS (ESI) m/z $(M+H)^-$ 405.0.

[0470] DMP (63 mg, 148.34 umol) was added to a solution of compound **21H** (30 mg, 74.17 umol) in dichloromethane (6 mL). The mixture was stirred at 25 °C for 12 hrs. Additional DMP (63 mg, 148.34 umol) was added and the mixture was stirred for additional 6 hrs at 25 °C. Additional DMP (157 mg, 0.37 mmol) was added. After stirred for additional 39 hrs, the mixture was diluted with dichloromethane (35 mL), quenched by the addition of 10 % $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (v/v = 1/1, ~35 mL). The organic layer was separated and the aqueous layer was extracted with DCM (20 mL x 2). The combined organic layer was washed

with H_2O (10 mL), brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was triturated with *i*-Pr_2O (3 mL). The insoluble substance was collected and dried in vacuum. Compound **21** (20 mg, 67% yield, pale yellow solid): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.71 (br. d, J = 6.0 Hz, 1H), 9.67 (s, 1H), 8.68 (s, 1H), 8.60 (s, 1H), 7.66 (s, 1H), 7.48 - 7.46 (m, 2H), 7.36 - 7.34 (m, 3H), 7.24 - 7.22 (m, 2H), 7.20 - 7.16 (m, 3H), 4.86 - 4.81(m, 1H), 3.21 - 3.18 (m, 2H). MS (ESI) *m/z* $(M+H)^+$ 403.1.

(*S*)-4-(1H-INDAZOL-1-YL)-N-(1-OXO-3-PHENYLPROPAN-2-YL)THIAZOLE-5-CARBOXAMIDE (22)



[0471] Compound **22** (4.70 mg, 16.87% yield, yellow solid) was prepared as in Example **6** from the corresponding starting materials through intermediate compound **22E** and then compound **22G**. Compound **22**: ^{1}H NMR (CD_3CN, 400 MHz): δ 10.41 (br. s, 1H), 9.67 (s, 1H), 9.04 (s, 1H), 8.21 – 8.19 (m, 1H), 8.15 (s, 1H), 7.91 - 7.89 (m, 1H), 7.61 - 7.58 (m, 1H), 7.40 - 7.37 (m, 1H) 7.12 - 7.10 (m, 5H) 4.77 - 4.72 (m, 1H), 3.29 - 3.24 (m, 1H), 3.11 - 3.05 (m, 1H). MS (ESI) *m/z* $(M+H)^+$ 377.0.

(*S*)-2-METHYL-*N*-(1-OXO-3-PHENYLPROPAN-2-YL)-4-PHENYLOXAZOLE-5-CARBOXAMIDE (322)

[0472] Compound **322** (102.9 mg, 36.1% yield, off-white solid) was prepared as in Example **6** from the corresponding intermediate compounds **107B** and **21G** ((*S*)-2-amino-3-phenylpropan-1-ol). Compound **322**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.17 - 8.09 (m, 2H), 7.47 - 7.36 (m, 3H), 7.35 - 7.26 (m, 3H), 7.19 (d, J = 6.84 Hz, 2H), 6.82 (d, J = 6.00 Hz, 1H), 4.96 - 4.86 (m, 1H), 3.40 - 3.28 (m, 1H), 3.26 - 3.19 (m, 1H), 2.55 (s, 3H). MS (ESI) *m/z* $(M+1)^+$ 335.1.

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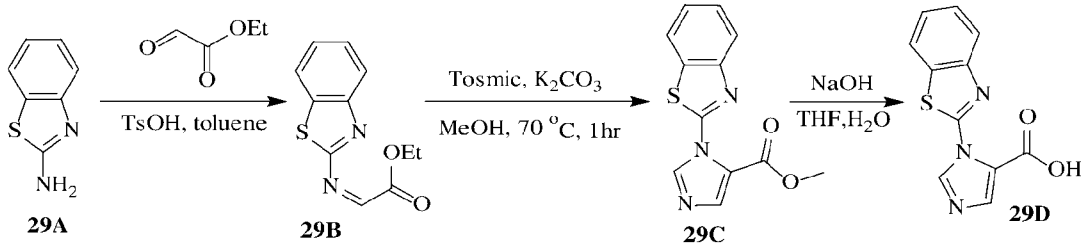
(*S*)-1-(BENZO[*D*]THIAZOL-2-YL)-N-(1-OXO-3-PHENYLPROPAN-2-YL)-1H-IMIDAZOLE-5-CARBOXAMIDE (29)



[0473] A mixture of compound **29A** (20 g, 133 mmol), ethyl 2-oxoacetate (136 g, 665 mmol), $TsOH.H_2O$ (2.5 g, 13.3 mmol) in toluene (200 mL) was stirred at 120 °C for 1 hour. TLC (Petroleum ether: Ethyl acetate = 3: 1, R_f = 0.5) indicated reactant **29A** was almost consumed and one new spot formed. LCMS showed one peak with desired MS was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Petroleum ether: Ethyl acetate = 20: 1 to 5: 1) to give compound **29B** (30.0 g, crude) as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.98 - 7.78 (m, 1H), 7.77 - 7.57 (m, 1H), 7.55 - 7.31 (m, 1H), 7.30 - 7.07 (m, 1H), 5.38 - 5.26 (m, 1H), 4.33 - 4.21 (m, 3H). **MS (ESI)** *m/z* $(M+H)^+$ 234.9.

[0474] A mixture of methyl **29B** (10 g, 45.4 mmol), Tosmic (17.7 g, 90.8 mmol), K_2CO_3 (9.4 g, 68.1 mmol) in MeOH (200 mL) was stirred at 70 °C for 0.5 hour. TLC (Petroleum ether: Ethyl acetate = 3: 1, R_f = 0.4) indicated **29B** was consumed completely and some new spots formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Petroleum ether: Ethyl acetate = 20: 1 to 3: 1) to give compound **29C** (1.2 g, yield: 10.2%) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.22 (d, *J* = 0.9 Hz, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.93 - 7.88 (m, 3H), 7.58 (dt, *J* = 1.3, 7.7 Hz, 1H), 7.52 - 7.49 (m, 1H), 7.49 - 7.43 (m, 1H), 4.58 (s, 1H), 3.87 (s, 3H), 2.51 (s, 1H). MS (ESI) *m/z* $(M+H)^+$ 259.9.

[0475] To a solution of **29C** (1.1 g, 4.24 mmol in THF (30 mL), H_2O (5 mL) was added NaOH (339 mg, 8.48 mmol). The reaction mixture was stirred at 25 °C for 3hrs. LCMS showed **29C** was consumed completely and one main peak with desired MS was detected. The reaction mixture was concentrated to give a residue. The residue was dissolved in water (10 mL), adjusted by aqueous HCl (2M) to pH ~ 5, filtered and the filtered cake was concentrated to

give the product **29D** (600 mg, yield: 57.7%) as a gray solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.48 (d, J = 1.1 Hz, 1H), 8.22 - 8.18 (m, 1H), 8.06 (dd, J = 0.8, 8.0 Hz, 1H), 7.81 (d, J = 0.9 Hz, 1H), 7.64 - 7.53 (m, 2H). MS (ESI) *m/z* $(M+H)^+$ 245.9.

[0476] Compound **29** (55.00 mg, yield: 76.12%, offwhite solid) was prepared as in Example **21** from the corresponding intermediate compounds **29D** and **21G**. Compound **29**: ^{1}H NMR (400MHz ,$CDCl_3$) δ 9.75 (s, 1 H), 9.01 (d, J = 6.2 Hz, 1 H), 8.14 (s, 1 H), 7.90 - 7.75 (m, 3 H), 7.57 - 7.42 (m, 2 H), 7.19 - 7.00 (m, 5 H), 5.04 - 4.94 (m, 1 H), 3.37 - 3.21 (m, 2 H). MS (ESI) *m/z* $(M+H)^+$ 377.2.

(*S*)-N-(1-OXO-3-PHENYLPROPAN-2-YL)-1-(PYRIDIN-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (31)

[0477] Compound **31** (25 mg, yield: 57.86%, light yellow solid) was prepared as in Example **6** from the corresponding intermediate compounds **24E** and **21G**. Compound **31**: ^{1}H NMR (400MHz ,$CDCl_3$) δ 9.70 (s, 1 H), 8.45 - 8.39 (m, 1 H), 7.94 (d, J = 1.1 Hz, 1 H), 7.89 - 7.82 (m, 1 H), 7.67 - 7.59 (m, 2 H), 7.39 - 7.32 (m, 2 H), 7.30 - 7.27 (m, 1 H), 7.26 - 7.21 (m, 2 H), 7.17 - 7.11 (m, 2 H), 4.87 (q, J = 6.6 Hz, 1 H), 3.25 (dd, J = 2.5, 6.5 Hz, 2 H). MS (ESI) *m/z* $(M+H)^+$ 321.1.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(5-PHENYLPYRIMIDIN-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (75)

[0478] Compound **75** (43.1 mg, yield: 66.6%, white solid) was prepared as in Example **6** from the corresponding intermediate compounds **74E** and **21G**. Compound **75**:. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.79 (s, 1H), 9.61 (br d, J = 6.0 Hz, 1H), 8.75 (s, 2H), 8.65 (s, 1H), 7.84 (s, 1H), 7.58 - 7.53 (m, 5H), 7.25 - 7.14 (m, 5H), 5.06 - 5.01 (m, 1H), 3.43 - 3.38 (m, 1H), 3.33 - 3.28 (m, 1H). MS (ESI) *m/z* $(M+H)^+$ 398.1.

(*S*)-1-(1*H*-BENZO[*d*]IMIDAZOL-2-YL)-*N*-(1-OXO-3-PHENYLPROPAN-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (90)

[0479] Compound **90** (20 mg, yield: 44.4%, white solid) was prepared as in Example **6** from the corresponding intermediate compounds **70D** and **21G** ((*S*)-2-amino-3-phenylpropan-1-ol). Compound **90**: ^{1}H NMR (400MHz,$CDCl_3$) δ 12.77 (br s, 1H), 12.87 - 12.63 (m, 1H), 9.75 (s, 1H), 8.85 (s, 1H), 7.71 (br s, 1H), 7.57 (s, 1H), 7.50 (br s, 1H), 7.36 - 7.27 (m, 4H), 7.19 (br d,

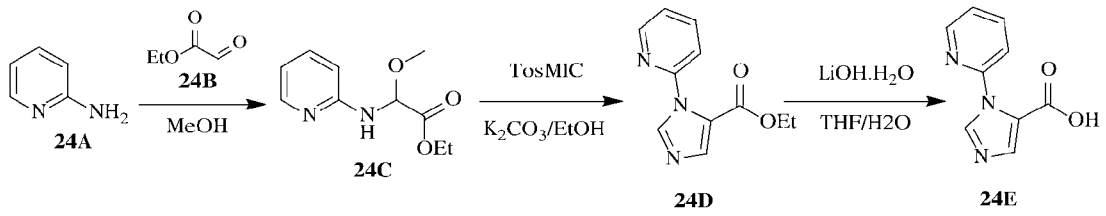
J = 6.8 Hz, 2H), 6.99 (br d, J = 5.3 Hz, 1H), 4.93 (q, J = 6.7 Hz, 1H), 3.32 (d, J = 6.4 Hz, 2H). MS (ESI) m/z $(M+H)^-$ 360.1.

(*S*)-3-METHYL-*N*-(1-OXO-3-PHENYLPROPAN-2-YL)-1-(PYRIMIDIN-4-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (279)

[0480] Compound **279** (102.0 mg, 304.15 umol, 55.26% yield, white solid) was prepared as in Example **6** from the corresponding intermediate compounds **245D** and **21G** ((*S*)-2-amino-3-phenylpropan-1-ol). Compound **279**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88(d, J = 5.6 Hz, 1H), 9.76 (s, 1H), 8.74 (d, J = 5.6 Hz, 1H), 8.61 (s, 1H), 7.91 – 7.87 (m, 1H), 7.27 – 7.23 (m, 3H), 7.19 – 7.17 (m, 2H), 8.89 (s, 1H), 5.02 – 4.97 (m, 1H), 3.40 – 3.35 (m, 1H), 3.30 – 3.25 (m, 1H), 2.34 (s, 1H). MS (ESI) m/z $(M+1)^+$ 336.1.

EXAMPLE 7

(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(PYRIDIN-2-YL)-1H-IMIDAZOLE-5-CARBOXAMIDE (24)



[0481] To a solution of compound **24B** (16.2 g, 79.7 mmol) in MeOH (25 mL) was added compound **24A** (5 g, 53.1 mmol). The mixture was stirred at 80 °C for 6 hrs. TLC (Petroleum ether: Ethyl acetate = 2:1, R_f = 0.24) indicated compound **24A** was remained and one major new spot with lower polarity was detected. Then the reaction mixture was concentrated under reduced pressure to give a residue. Then the residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 30:1 to 15:1) to give compound **24C** (6 g, yield: 53.7%) as a yellow oil.

[0482] To a mixture of compound **24C** (6 g, 28.5 mmol) in EtOH (15 mL) was added TosMIC (8.3 g, 42.8 mmol), K_2CO_3 (11.8 g, 85.6 mmol). The mixture was stirred at 80 °C for 12 hrs. TLC (Petroleum ether: Ethyl acetate = 1: 1, R_f = 0.70) indicated compound **24C** remained and one major new spot with higher polarity was detected. Then the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 30: 1 to 3: 1) to give compound

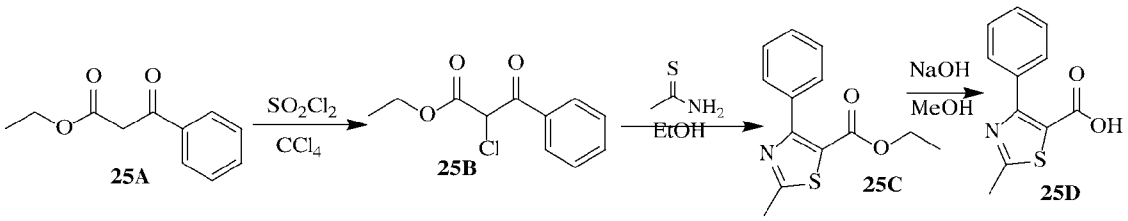
24D (1.60 g, yield: 25.8%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 - 8.54 (m, 1H), 7.98 (s, 1H), 7.92 - 7.83 (m, 2H), 7.45 - 7.38 (m, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 4H).

[0483] To a solution of compound **24D** (1.6 g, 7.37 mmol) in THF (15 mL) and H_2O (5 mL) was added $LiOH.H_2O$ (618 mg, 14.7 mmol). The reaction mixture was stirred at 25 °C for 12 hrs. LCMS showed compound **24D** was consumed completely and one main peak with desired MS was detected. Then the mixture was adjusted to pH ~ 5 by adding HCl (1M), and then white solid was precipitate out. The white solid was filtered and dried over to give compound **24E** (1 g, yield: 71.7%) as a white solid. MS (ESI) *m/z* $(M+H)^+$ 189.1.

[0484] Compound **24** (20 mg, yield: 33.5%, yellow solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **24E**, and compound **12G**. Compound **24**: ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.95 (d, *J* = 7.6 Hz, 1H), 8.50 - 8.38 (m, 1H), 8.12 (s, 1H), 8.03 (br.s., 1H), 7.89 - 7.85 (m, 1H), 7.80 (br.s., 1H), 7.53 (s, 1H), 7.43 - 7.40 (m, 1H), 7.33 - 7.25 (m, 4H), 7.24 - 7.19 (m, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 5.25 - 5.20 (m, 1H), 3.17 (dd, *J* = 4.0, 14.4 Hz, 1H), 2.83 (dd, *J* = 10.0, 13.6 Hz, 1H). MS (ESI) *m/z* $(M+H)^+$ 364.1.

EXAMPLE 8

(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-2-METHYL-4-PHENYLTHIAZOLE-5-CARBOXAMIDE (25)



[0485] To a solution of compound **25A** (20 g, 104 mmol) in CCl_4 (200 ml) was added SO_2Cl_2 (14 g, 104 mmol) at 45-50 °C during a period of 0.3 h. Then the mixture was stirred at 45 – 50 °C for 1 h. The reaction mixture was diluted with ice-water (200 mL). The organic layer was separated, washed with H_2O (200 mL x 2), brine (200 mL) dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford compound **25B** (25.g, crude) as pale yellow oil, which was used for next step directly. ^{1}H NMR ($CDCl_3$,400MHz,): δ 8.03 - 7.98 (m, 2H), 7.67 - 7.62 (m, 1H), 7.54 - 7.50 (m, 2H), 5.62 (s, 1H), 4.32 - 4.26 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H).

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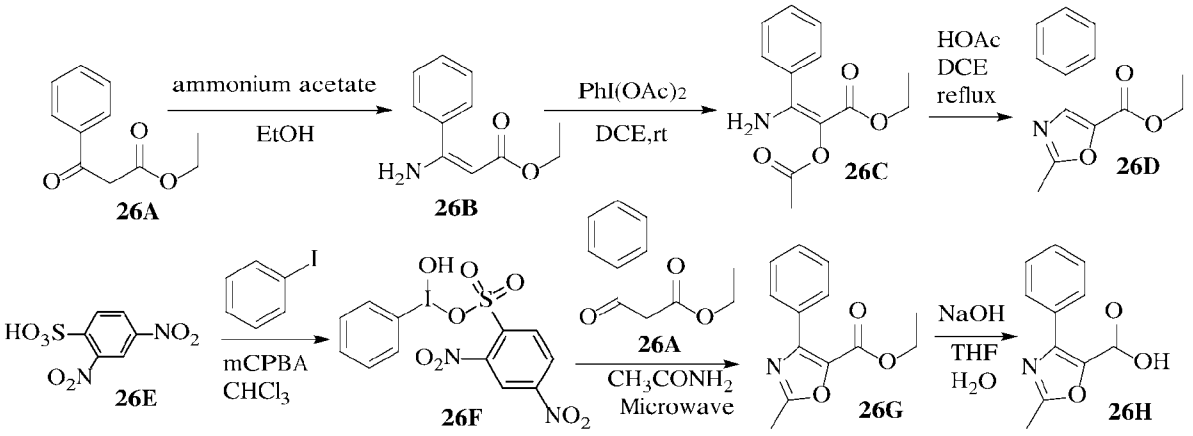
[0486] A mixture of compound **25B** (6.8 g, 30 mmol) and thioacetamide (2.25 g, 30.0 mmol) in EtOH (75 mL) was heated to 80 °C and stirred for 6 hrs. The solvent was distilled off under reduced pressure. The residue was purified by a silica gel column chromatography (eluent: Petroleum Ether/Ethyl Acetate = 50/1) to afford compound **25C** (3.0 g, yield 40.4%) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.77 - 7.71 (m, 2H), 7.47 - 7.40 (m, 3H), 4.28 (q, J = 7.2 Hz, 2H), 2.77 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H).

[0487] A solution of NaOH (2N, 12 mL, 24 mmol) was added to a solution of compound **25C** (1.24 g, 5.01 mmol) in MeOH/H_2O mixture (39 mL/13 mL). The mixture was stirred at 25 °C for 3 hrs. The mixture was diluted with H_2O (5 mL). The volatile solvent was removed by evaporation. The residue was treated with HCl (1N) until pH ~ 3. The precipitate was collected by filtration, dried under reduced pressure to afford compound **25D** (650 mg, yield 59.2%) as white solid, which was used directly in next step. ^{1}H NMR (DMSO-d_6, 400 MHz):δ 7.72 - 7.65 (m, 2H), 7.43 - 7.36 (m, 3H), 2.68 (s, 3H).

[0488] Compound **25** (25 mg, yield 42%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **25D**. Compound **25**: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.81 (d, J = 7.6 Hz, 1H), 8.12 (s, 1H), 7.86 (s, 1H), 7.55 - 7.53 (m, 2H), 7.31 - 7.19 (m, 8H), 5.35 - 5.31 (m, 1H), 3.15 (dd, J = 3.6, 13.8 Hz, 1H), 2.77 (dd, J = 9.9, 13.8 Hz, 1H), 2.67 (s, 3H). MS (ESI) m/z $(M+H)^+$ 394.1.

EXAMPLE 9

(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-2-METHYL-4-PHENYLOXAZOLE-5-CARBOXAMIDE (26)



[0489] To a mixture of compound **26A** (7.2 g, 37.46 mmol, 6.5 mL) and ammonium acetate (5.8 g, 74.92 mmol) were mixed in EtOH (70 mL) and refluxed at 80 °C for 16 hrs. After removal of the solvent, the residue was dissolved in water (50 mL), extracted with EtOAc (100 mL x 2). This combined organic phase was washed with *sat.* $NaHCO_3$ (50 mL x 2) and brine (50 mL), dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 20: 1 to 10: 1) to give compound **26B** (3.5 g, yield: 48.9%) as yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.57 - 7.53 (m, 2H), 7.48 - 7.37 (m, 3H), 5.07 - 4.89 (m, 1H), 4.22 - 4.11 (m, 2H), 1.33 - 1.25 (m, 3H).

[0490] To a mixture of compound **26B** (2 g, 10.46 mmol) in DCE (4 mL) was added $PhI(OAc)_2$ (4.4 g, 13.60 mmol) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 16 hrs. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL) and extracted with DCM (50 mL x 3). The organic layers were combined and dried over anhydrous Na_2SO_4. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 20: 1 to 5: 1) to give compound **26C** (400 mg, yield: 15.3%) as yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.58 (dd, J = 1.1, 7.7 Hz, 1H), 7.44 - 7.39 (m, 4H), 4.28 - 4.21 (m, 2H), 1.94 (s, 3H), 1.66 - 1.60 (m, 1H), 1.62 (br s, 1H), 1.30 - 1.26 (m, 3H).

[0491] To a mixture of compound **26C** (400 mg, 1.60 mmol) in DCE (5 mL) and AcOH (10 mL) was stirred at 90 °C for 16 hrs. The solvent was removed. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 10: 1 to 5: 1) to give compound **26D** (220 mg, yield: 53.0%) as yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.11 - 7.89 (m, 2H), 7.56 - 7.32 (m, 3H), 4.40 (t, J = 7.3 Hz, 2H), 2.59 (s, 3H), 1.39 (q, J = 7.1 Hz, 3H). MS (ESI) m/z $(M+H)^+$ 231.8.

[0492] To a mixture of iodobenzene (2.5 g, 12.25 mmol, 1.4 mL) and compound **26E** (3.59 g, 13.48 mmol) in $CHCl_3$ (25 mL), was added *m*-CPBA (2.33 g, 13.48 mmol). The mixture was stirred for 2 hrs at 25 °C under an N_2 atmosphere. After the reaction, MTBE (20 mL) was added to the reaction mixture, and the resulting mixture was filtered and the solid was washed with MTBE (30 mL) Compound **26F** was obtained as a white solid

[0493] Ethyl 3-oxo-3-phenyl-propanoate **26A** (500 mg, 2.60 mmol) and compound **26F** (1.58 g, 3.38 mmol,) in CH_3CN (30 mL) were heated to reflux for 1 h at 80 °C, and acetamide (461 mg, 7.80 mmol) was added to the mixture. The reaction mixture was heated at

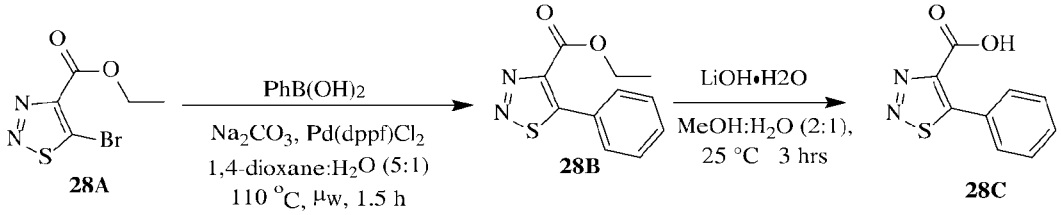
120 °C for 0.1 h under microwave irradiation. After being cooled to room temperature, the suspension was diluted with saturated $NaHCO_3$ solution (30 mL), extracted with EtOAc (10 mL x 2), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 10/1) and by preparatory-TLC (SiO_2, Petroleum ether/Ethyl acetate = 5/1). Compound **26G** (50 mg, yield: 8.32%) was obtained as a white solid. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.06 - 7.93 (m, 2H), 7.48 - 7.39 (m, 3H), 4.38 (q, J = 7.1 Hz, 2H), 2.58 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H). **MS (ESI)** m/z $(M+H)^+$ 231.8.

[0494] To a mixture of compound **26G** (60 mg, 259.46 umol) in THF (2 mL) and H_2O (2 mL) was added NaOH (1 M, 778 uL) in one portion at 0 °C. The mixture was stirred at 25 °C for 16 hrs. The mixture was extracted with MTBE (2 x 30 mL) and washed with water (3 x 30 mL). The water layers were acidified to pH ~ 4 with 1N HCl, then, the solution extracted with EtOAc (3 x 30 mL). The organic layers were dried over Na_2SO_4 and concentrated to give compound **5** (50 mg, yield: 86.6%) as yellow oil, which was used directly for next step without further purification. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.05 - 8.01 (m, 2H), 7.48 - 7.43 (m, 3H), 2.62 (s, 3H). MS (ESI) m/z $(M+H)^+$ 203.8.

[0495] Compound **26** (15 mg, yield: 23.0%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **26H**. Compound **26**: ^1H NMR ($CDCl_3$, 400 MHz): δ 8.08 (br d, J = 6.6 Hz, 2H), 7.41 (br d, J = 6.8 Hz, 2H), 7.32 - 7.24 (m, 4H), 7.13 (br d, J = 6.6 Hz, 2H), 6.77 (br s, 2H), 5.76 - 5.68 (m, 1H), 5.55 (br s, 1H), 3.45 (br dd, J = 5.3, 14.3 Hz, 1H), 3.24 (br dd, J = 7.3, 14.1 Hz, 1H), 2.56 (s, 3H). MS (ESI) m/z $(M+H)^+$ 378.1.

EXAMPLE 10

(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-PHENYL-1,2,3-THIADIAZOLE-4-CARBOXAMIDE (28)



[0496] A mixture consisting of compound **28A** (200 mg, 843.63umol), phenyl boronic acid (23 mg, 110.98 umol) and Na_2CO_3 (22.4 mg, 2.11 mmol) was stirred at 110 °C for

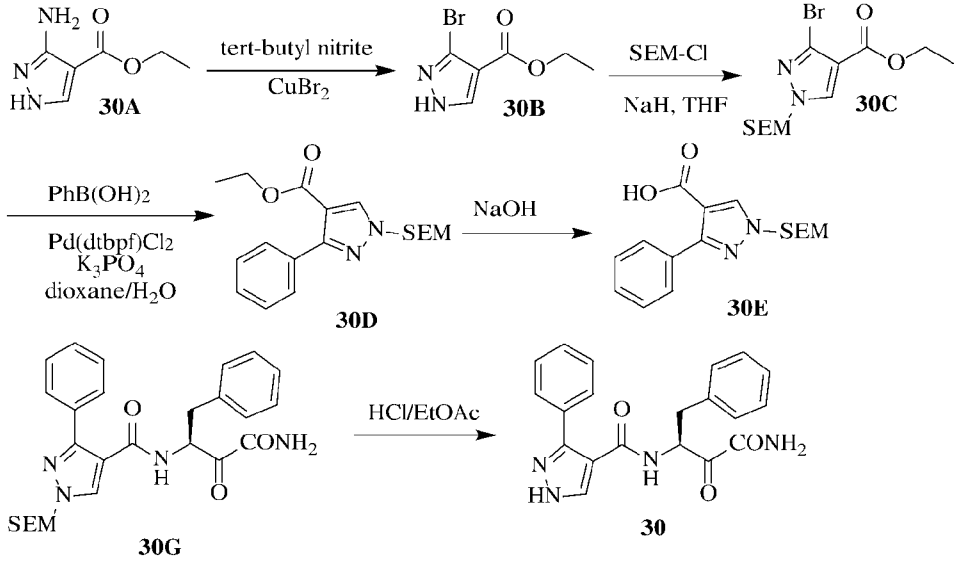
1.5 hrs under microwave. The reaction mixture was cooled to room-temperature, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Pre-HPLC (base condition) to afford compound **28B** (23 mg, yield 11.64%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ7.44 - 7.58 (m, 5 H), 4.44 (q, J = 7.20 Hz, 2 H), 1.32 (t, J = 7.17 Hz, 3 H).

[0497] To a mixture of compound **28B** (50 mg, 213.43 umol) in MeOH (3 mL) and H_2O (1.50 mL) was added $LiOH•H_2O$ (26.9 mg, 640.29 umol) in one portion and the mixture was stirred at 25 °C for 3 hrs. The reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was diluted with H_2O (8 mL), adjusted to pH ~ 3 with 1N HCl, and then extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give intermediate compound **28C** (38 mg, crude) as brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 - 7.57 (m, 2H), 7.54 - 7.45 (m, 3H). MS (ESI) m/z $(M+1)^+$ 206.7.

[0498] Compound **28** (18.9 mg, 38.00% yield, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **28C.** Compound **28**: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.07 (d, J = 7.2 Hz, 1H), 7.59 - 7.53 (m, 2H), 7.49 - 7.41 (m, 3H), 7.33 - 7.27 (m, 3H), 7.23 - 7.19 (m, 2H), 6.77 (br s, 1H), 5.84 - 5.76 (m, 1H), 5.52 (br s, 1H), 3.51 - 3.45 (m, 1H), 3.25 - 3.18 (m, 1H). MS (ESI) m/z $(M+1)^+$ 381.1.

EXAMPLE 11

(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-PHENYL-1*H*-PYRAZOLE-4-CARBOXAMIDE (30)



[0499] To a solution of *t*-BuONO (3.8 mL, 30.94 mmol) in CH_3CN (60 mL) was added $CuBr_2$ (6.91 g, 30.94 mmol). The mixture was stirred at 25 °C for 1 h under N_2. Then compound **30A** (4 g, 25.78 mmol) was added protionwise. The mixture was then heated to 70 °C and stirred for 12 hrs. The reaction was washed with H_2O (100 mL), extracted with EtOAc (100 mL x 2). The organics were collected, dried with Na_2SO_4, filtered and concentrated to afford intermediate compound **30B** (6 g, crude) as black brown oil. MS (ESI) *m/z* $(M+H)^+$ 218.9, 220.9.

[0500] To a solution of NaH (1.64 g, 41.09 mmol, 60% purity) in THF (80 mL) at 0 °C was added a solution of compound **30B** (6 g, 27.39 mmol) in THF (20 mL). After addition, the mixture was warmed up to 25°C and stirred for 2 hrs. Then the solution was cooled to 0 °C and a solution of SEM-Cl (5.34 mL, 30.13 mmol) in THF (100 mL) was added at 0 °C. The mixture was then warmed up to 25 °C and stirred for 12 hrs. The reaction was quenched with H_2O (100 mL) dropwise. The mixture was extracted with EtOAc (100 mL x 2). The organics were collected and concentrated. The residue was purified by column (Petroleum Ether: Ethyl Acetate = 10:1) to afford compound **30C** (3 g, yield: 31.14%) as yellow oil.

[0501] To a solution of compound **30C** (2.60 g, 7.44 mmol) and $PhB(OH)_2$ (1.09 g, 8.93 mmol) in dioxane (36 mL) and H_2O (12 mL) was added $Pd(dtbpf)Cl_2$ (485 mg, 0.74 mmol) and K_3PO_4 (4.74 g, 22.32 mmol). The mixture was stirred at 70 °C under N_2 for 2 hrs. The reaction was diluted with H_2O (20 mL), extracted with EtOAc (20 mL x 2). The organics were collected and concentrated. The residue was purified by column (Petroleum Ether: Ethyl Acetate = 10:1) to afford compound **30D** (2.40 g, yield: 93.1%) as colorless oil. MS (ESI) *m/z* $(M+H)^+$ 347.1. ^1H NMR (400MHz, DMSO-d_6) δ 8.60 (s, 1H), 7.78 - 7.72 (m, 2H), 7.56 - 7.34 (m, 3H), 5.52 (s, 2H), 4.25 - 4.16 (m, 2H), 3.70 - 3.62 (m, 2H), 1.26 (t, *J*=7.1 Hz, 3H), 0.94 - 0.85 (m, 2H), 0.03 - 0.02 (m, 9H).

[0502] A solution of compound **30D** (200 mg, 577.20 umol) in MeOH (4 mL), and then NaOH (230 mg, 5.77 mmol) in H_2O (4 mL) was added dropwise. The mixture was stirred at 25 °C for 19 hrs. The reaction mixture was diluted by addition H_2O (10 mL), and then extracted with MTBE (10 mL x 2). The water layers were neutralized by 1N HCl to pH ~ 3, and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the compound

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30E (140 mg, yield: 76.17%) as a yellow oil. ^{1}H-NMR (400MHz, DMSO-d_6) δ 12.41 (br s, 1H), 8.54 (s, 1H), 7.81 - 7.74 (m, 2H), 7.53 - 7.36 (m, 3H), 5.50 (s, 2H), 3.66 (t, J = 8.0 Hz, 2H), 0.90 (t, J = 7.9 Hz, 2H), 0.01 - 0.04 (m, 9H).

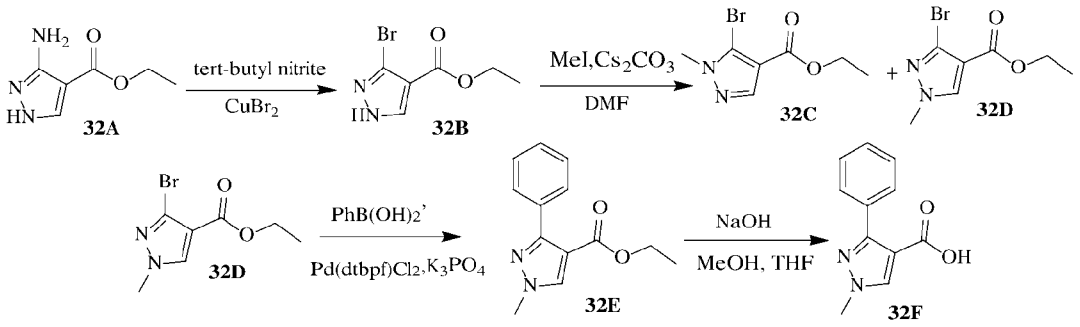
[0503] Compound **30G** (140 mg, yield: 93.72%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **30E**. Compound **30G**: ^{1}H-NMR (400MHz, DMSO-d_6) δ 8.54 (d, J = 7.3 Hz, 1H), 8.25 (s, 1H), 8.15 - 8.00 (m, 1H), 7.87 (s, 1H), 7.66 - 7.52 (m, 2H), 7.43 - 7.23 (m, 9H), 5.46 (br d, J = 6.8 Hz, 1H), 5.38 - 5.30 (m, 1H), 3.76 - 3.57 (m, 2H), 3.27 - 3.12 (m, 1H), 2.96 - 2.76 (m, 1H), 0.94 - 0.89 (m, 2H), 0.03 - 0.00 (m, 9H).

[0504] To a solution of compound **30G** (18.00 mg, 36.54 umol) in ethyl acetate (1.00 mL) was added 4M HCl/EtOAc (5.00 mL). Then the reaction was stirred at 30 °C for 4hrs. The reaction mixture was added petroleum ether (50 mL), the mixture was stirred for 3 mins, filtered and the desired solid was dried in vacuo to give compound **30** (6.00 mg, yield: 45.31%) as white solid. ^{1}H NMR (400MHz, DMSO-d6) δ 8.34 (d, J=7.5 Hz, 1H), 8.02 (s, 1H), 7.99 - 7.95 (m, 1H), 7.77 (s, 1H), 7.59 - 7.53 (m, 2H), 7.35 - 7.28 (m, 4H), 7.28 - 7.23 (m, 5H), 7.23 - 7.16 (m, 2H), 5.30 - 5.21(m, 1H), 3.19 - 3.10 (m, 1H), 2.83 (dd, J=9.8, 13.8 Hz, 1H). MS (ESI) m/z $(M+H)^+$ 363.1.

EXAMPLE 12

COMPOUNDS 32, 458, 476-479, 521

(*S*)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-METHYL-3-PHENYL-1*H*-PYRAZOLE-4-CARBOXAMIDE (32)



[0505] To a solution of t-BuONO (3.19 g, 30.94 mmol, 3.67 mL) in CH_3CN (60 mL) was added $CuBr_2$ (6.91 g, 30.94 mmol). The mixture was stirred at 25 °C for 1 hour under N_2. Then compound **32A** (4.00 g, 25.78 mmol) was added portionwise. After heated to 70 °C and

stirred for 12 hrs, the mixture was concentrated and diluted with ethyl acetate (100 mL). The mixture was then washed with HCl (1M, 100 mL), saturated $NaHCO_3$ (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated to obtain intermediate compound **32B** (5.6 g, crude) as yellow oil. MS (ESI) *m/z* $(M+H)^+$ 220.9.

[0506] To a solution of compound **32B** (5.6 g, 25.57 mmol) in DMF (200 mL) was added MeI (14.52 g, 102.28 mmol, 6.37 mL) and Cs_2CO_3 (33.32 g, 102.28 mmol). The mixture was stirred at 25 °C for 12 hrs. The mixture was diluted with H_2O (1000 mL) and extracted with ethyl acetate (500 mL), then the organic layer was washed with brine (500 mL x 3), dried over Na_2SO_4 and concentrated. The residue (4 g) was purified by preparatory-HPLC (basic condition). The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=10/1 to 5:1). Compound **32C** (1g, yield: 16.8%) was obtained as a white solid. Compound **32D** (2 g, yield: 33.6%) was obtained as a white solid.

[0507] Compound **32C** : ^{1}H NMR (400MHz, DMSO-d_6) δ 7.93 (s, 1H), 4.24 - 4.18 (m, 2H), 3.85 (s, 3H), 1.28 - 1.23 (m, 3H).

[0508] Compound **32D** : ^{1}H NMR (400MHz, DMSO-d_6) δ 8.33 (s, 1H), 4.22 - 4.16 (m, 2H), 3.83 (s, 3H), 1.26 - 1.22 (m, 3H).

[0509] A mixture of ethyl compound **32D** (500.0 mg, 2.15 mmol), phenylboronic acid (314.6 mg, 2.58 mmol), $Pd(dtbpf)Cl_2$ (140.1 mg, 215.00 umol), K_3PO_4 (1.37 g, 6.45 mmol) in dioxane (30 mL) and H_2O (10 mL) was degassed and purged with N_2 for 3 times. After stirred at 70 °C for 1 hour under N_2 atmosphere, the mixture was concentrated and diluted with ethyl acetate (30 mL). The mixture was then washed with HCl (1M, 50 mL), saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated to obtain intermediate compound **32E** (480 mg, crude) as a brown oil. MS (ESI) *m/z* $(M+H)^+$ 230.9.

[0510] To a solution of compound **32E** (380.0 mg, 1.65 mmol) in MeOH (5 mL) and THF (5 mL) was added NaOH (2 M, 16.5 mL). The mixture was stirred at 60 °C for 1 hour. The mixture was concentrated and diluted with H_2O (10 mL), the mixture was extracted with ethyl acetate (10 mL), the water phase was added HCl (1M) until pH ~ 3, then the mixture was extracted with ethyl acetate (20 mL), the organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated. Compound **32F** (320 mg, yield: 95.9%) was obtained as a brown

solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 12.03 - 11.85 (m, 1H), 8.27 (s, 1H), 7.74 - 7.68 (m, 2H), 7.40 - 7.30 (m, 3H), 3.87 (s, 3H).

[0511] Compound **32** (40.0 mg, yield: 64.7%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **32F**. Compound **32**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.33 (d, J = 7.2 Hz, 1H), 8.05 (s, 2H), 7.81 (br s, 1H), 7.63 - 7.53 (m, 2H), 7.39 - 7.20 (m, 8H), 5.33 - 5.26 (m, 1H), 3.93 - 3.86 (m, 3H), 3.21 - 3.13 (m, 1H), 2.88 - 2.79 (m, 1H). MS (ESI) *m/z* $(M+H)^+$ 377.1.

_N_-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-METHYL-3-PHENYL-1_H_-PYRAZOLE-4-CARBOXAMIDE (458)

[0512] Compound **458** (270 mg, yield: 67.4%, white solid) was prepared as in compound **12** from the corresponding intermediate carboxylic acid, compound **32F** and 3-amino-N-cyclopropyl-2-hydroxy-4-phenylbutanamide hydrochloride. Compound **458**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.80 (d, J = 4.4 Hz, 1H), 8.38 (d, J = 7.3 Hz, 1H), 8.05 (s, 1H), 7.56 (s, 2H), 7.36 - 7.17 (m, 8H), 5.28 (s, 1H), 3.89 (s, 3H), 3.16 (d, J = 11.2 Hz, 1H), 2.89 - 2.73 (m, 2H), 0.71 - 0.52 (m, 4H). MS (ESI) *m/z* $(M+H)^+$ 417.1.

(_S_)-_N_-(4-FLUORO-3-OXO-1-PHENYLBUTAN-2-YL)-1-METHYL-3-PHENYL-1_H_-PYRAZOLE-4-CARBOXAMIDE (476)

[0513] Compound **476** (36.8 mg, yield: 34.22%, white solid) was prepared as in compound **12** from the corresponding intermediate carboxylic acid, compound **32F** and (2*S*,3*S*)-3-amino-1-fluoro-4-phenylbutan-2-ol hydrochloride. Compound **476**: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.52 - 7.47 (m, 2H), 7.46 - 7.37 (m, 3H), 7.25 - 7.19 (m, 3H), 6.94 - 6.84 (m, 2H), 6.06 (d, J = 6.4 Hz, 1H), 5.03 - 4.71 (m, 3H), 3.93 (s, 3H), 3.09 - 3.01 (m, 1H), 2.85 - 2.76 (m, 1H). **MS (ESI)** *m/z* $(M+H)^+$ 366.1.

(_S_)-N-(4-FLUORO-3-OXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(PYRAZIN-2-YL)-1_H_-PYRAZOLE-5-CARBOXAMIDE (477)

[0514] Compound **477** (110 mg, yield: 90.33%, white solid) was prepared as in compound **12** from the corresponding intermediate carboxylic acid, compound **85B** and (2*S*,3*S*)-3-amino-1-fluoro-4-phenylbutan-2-ol hydrochloride. Compound **477**: ^{1}H NMR (400MHz, $CDCl_3$) δ 9.20 (s, 1H), 9.08 - 9.00 (m, 1H), 8.50 - 8.48 (m, 1H), 8.11 (s, 1H), 7.27 - 7.24 (m, 3H),

7.17 - 7.12 (m, 2H), 6.79 (s, 1H), 5.33 - 5.24 (m, 1H), 5.11 - 4.79 (m, 2H), 3.45 - 3.33 (m, 1H), 3.15 - 3.11 (m, 1H), 2.38 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 368.1.

(*S*)-*N*-(4-FLUORO-3-OXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(PYRIDIN-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (478)

[0515] Compound **478** (82 mg, yield: 54.97%, white solid) was prepared as in compound **12** from the corresponding intermediate carboxylic acid, compound **12F** and (2*S*,3*S*)-3-amino-1-fluoro-4-phenylbutan-2-ol hydrochloride. Compound **478**: ^{1}H NMR (400MHz, $CDCl_3$) δ 10.70 (d, *J* = 6.40 Hz, 1H), 8.14 (d, *J* = 4.40 Hz, 1H), 7.92 - 7.83 (m, 2H), 7.26 - 7.14 (m, 6H), 6.88 (s, 1H), 5.24 - 5.20 (m, 1H), 5.05 – 4.74 (m, 2H), 3.29 - 3.18 (m, 2H), 2.35 (s, 3H). MS (ESI) *m/z* $(M+1)^+$ 367.2.

(*S*)-*N*-(4-FLUORO-3-OXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-PHENYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (479)

[0516] Compound **479** (100 mg, yield: 82.06%, white solid) was prepared as in compound **12** from the corresponding intermediate carboxylic acid, 3-methyl-1-phenyl-1*H*-pyrazole-5-carboxylic acid and (2*S*,3*S*)-3-amino-1-fluoro-4-phenylbutan-2-ol hydrochloride. Compound **479**: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.46 - 7.28 (m, 8H), 7.08 - 7.03 (m, 2H), 6.51 (s, 1H), 6.28 (br d, *J* = 7.0 Hz, 1H), 5.20 - 5.13 (m, 1H), 5.03 - 4.73 (m, 2H), 3.22 - 3.15 (m, 1H), 3.02 - 2.95 (m, 1H), 2.35 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 366.1.

(*S*)-*N*-(4-FLUORO-3-OXO-1-PHENYLBUTAN-2-YL)-3-(2-FLUORO-4-((PROP-2-YN-1-YLOXY)METHYL)PHENYL)-1-METHYL-1*H*-PYRAZOLE-4-CARBOXAMIDE (521)

[0517] Compound **521** (250 mg, yield: 78.40%, white solid) was prepared using coupling conditions as in compound **476** from the corresponding intermediate ethyl 3-iodo-1-methyl-1*H*-pyrazole-4-carboxylate and (2-fluoro-4-(hydroxymethyl)phenyl)boronic acid followed by alkylation with 3-bromoprop-1-yne and then the intermediate obtained was subjected to hydrolysis and coupling with (2*S*,3*S*)-3-amino-1-fluoro-4-phenylbutan-2-ol hydrochloride as in compound **12** to yield compound **521**. Compound **521**: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.40 (t, *J*=7.6 Hz, 1H), 7.24 - 7.13 (m, 5H), 6.94-6.92 (m, 2H), 5.97 (d, *J*=6.4 Hz, 1H), 5.09 - 5.01 (m, 1H), 4.96 - 4.83 (m, 1H), 4.83 - 4.70 (m, 1H), 4.66 (s, 2H), 4.19 (d, *J*=2.4 Hz, 2H), 3.95 (s, 3H), 3.03 (d, *J*=6.4 Hz, 1H), 2.95 - 2.88 (m, 1H), 2.49 (t, *J*=2.3 Hz, 1H). MS (ESI) *m/z* $(M+H)^+$ 452.2.

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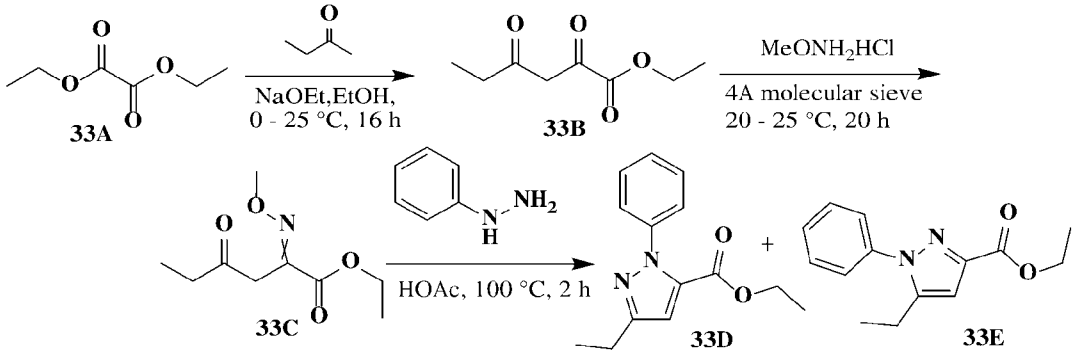
EXAMPLE 13

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-ETHYL-1-PHENYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (33)



33A 33B 33C 33D 33E

[0518] A mixture of compound **33A** (46.73 mL, 342.14 mmol) and butan-2-one (30.46 mL, 342.14 mmol) was added dropwise to the solution of NaOEt (prepared by Na (9.5 g) in EtOH (200 mL)) at 0 °C. Then the reaction was stirred at 20-25 °C for 16 hrs. The reaction was adjusted to pH ~ 6-7 with HCl (2M) and then removed the solvent to give a residue, which was diluted with ethyl acetate (500 mL), washed with brine (150 mL), dried over Na_2SO_4 and concentrated to give the crude product which was purified by flash column chromatography (Petroleum Ether : Ethyl Acetate = 1:0 to 10:1) to give compound **33B** (23.0 g, yield: 39.0 %) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 14.34 (br s, 1H), 6.31 (s, 1H), 4.28 (q, J = 7.2 Hz, 2H), 2.47 (q, J = 7.3 Hz, 2H), 1.34 - 1.27 (m, 3H), 1.11 (t, J = 7.5 Hz, 3H).

[0519] The mixture of compound **33B** (10 g, 58.08 mmol), O-methylhydroxylamine (4.85 g, 58.08 mmol, HCl) and 4A° molecular sieve (10 g) in DMF (100 mL) was stirred at 20-25 °C for 20 hrs. Filtered to remove the 4A° molecular sieve and the filtrate was diluted with H_2O (800 mL), extracted with ethyl acetate (300 mL x 3). The organic phase was combined and washed with brine (300 mL x 3) and concentrated to give the crude product, which was purified by flash column chromatography (Petroleum Ether : Ethyl Acetate = 1:0 to 5:1) to give compound **33C** (3.5 g, yield: 29.95%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.41 - 4.29 (m, 2H), 4.06 (s, 3H), 3.71 (s, 2H), 2.60 - 2.46 (m, 2H), 1.42 - 1.32 (m, 3H), 1.08 (t, J = 7.3 Hz, 3H).

[0520] The mixture of compound **33C** (3.5 g, 17.39 mmol) and phenylhydrazine (1.88 g, 17.39 mmol) in AcOH (20 mL) was stirred at 100 °C for 2 hrs. The solvent was

removed and the residue was adjusted to pH ~ 7-8 with saturated $NaHCO_3$ aqueous and extracted with ethyl acetate (60 mL x 2). The organic phase were combined and washed with brine (50 mL), concentrated to give a residue, which was purified by flash column chromatography (Petroleum Ether : Ethyl Acetate = 1:0 to 5:1) to give compound **33D** (0.3 g, 1.23 mmol, 7.05% yield) as a yellow solid and compound **33E** (3.0 g, 12.21 mmol, yield 70.19%) as a yellow oil.

[0521] Compound **33D** : ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 - 7.37 (m, 5H), 6.87 (s, 1H), 4.24 (q, J = 7.0 Hz, 2H), 2.76 (q, J = 7.5 Hz, 2H), 1.32 (t, J = 7.5 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H). MS (ESI) *m/z* $(M+H)^+$ 245.0. Compound **33E** : ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 - 7.31 (m, 1H), 6.70 (s, 1H), 4.35 (q, J = 7.1 Hz, 1H), 2.58 (q, J = 7.4 Hz, 1H), 1.33 (t, J = 7.2 Hz, 1H), 1.16 (t, J = 7.5 Hz, 1H). MS (ESI) *m/z* $(M+H)^+$ 245.0.

[0522] The mixture of compound **33D** (3.0 g, 12.28 mmol) and $LiOH.H_2O$ (3.09 g, 73.68 mmol) in MeOH (10 mL) and H_2O (3 mL) was stirred at 25 °C for 16 hrs. The reaction was adjusted with HCl (2M) to pH ~ 3-4 and removed the solvent. The residue was extracted with ethyl acetate (100 mL x 3) and combined, washed with brine (100 mL), dried over Na_2SO_4. Filter and the filtrate were concentrated to give compound **33F** (2.7 g, crude) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.58 (br s, 1H), 7.46 - 7.34 (m, 5H), 6.89 (s, 1H), 2.73 (q, J = 7.6 Hz, 2H), 1.28 (t, J = 7.6 Hz, 3H). MS (ESI) *m/z* $(M+H)^+$ 216.9.

[0523] The mixture of compound **33F** (2.7 g, 12.49 mmol) and 1-hydroxypyrrolidine-2,5-dione (1.44 g, 12.49 mmol) in THF (20 mL) was stirred at 0 °C for 15 min, then solution of DCC (2.6 g, 12.61 mmol, 2.55 mL) in THF (10 mL) was added dropwise at 0 °C and stirred at 25-30 °C for 16 hrs. After filtered and the filtrate was concentrated to give compound **33G** (4.0 g, crude) as a yellow solid. The product was used directly in next step.

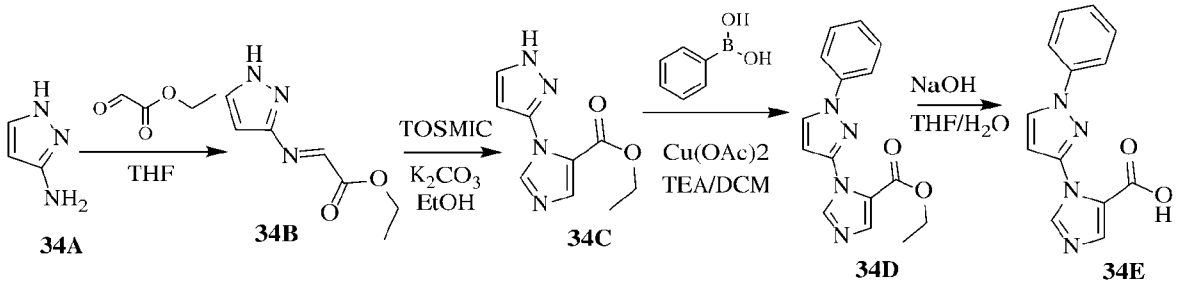
[0524] The mixture of compound **33G** (0.2 g, 638.35 umol), compound **12G** (147.3 mg, 638.35 umol, HCl) and DIEA (0.25 mL, 1.28 mmol) in DMF (10 mL) was stirred at 20-25 °C for 16 hrs. The reaction was diluted with H_2O (60 mL) and ethyl acetate (30 mL) and stirred at 20-25 °C for 0.5 h. White solid precipitated out and was filtered, the filter cake was washed with H_2O (10 mL x 2) and dried over under reduced pressure to give compound **33H** (100.0 mg, yield: 39.24%) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.53 - 8.11 (m, 1H), 7.40 - 7.20 (m, 10H), 7.16 - 7.01 (m, 2H), 6.59 (s, 1H), 5.96 - 5.69 (m, 1H), 4.49 - 4.36 (m, 1H), 4.03 -

3.90 (m, 1H), 2.96 - 2.70 (m, 2H), 2.62 (q, J = 7.7 Hz, 2H), 1.22 (t, J = 7.5 Hz, 3H). MS (ESI) m/z $(M+H)^+$ 393.0.

[0525] The mixture of compound **33H** (100 mg, 254.81 umol) and DMP (540.4 mg, 1.27 mmol, 394.44 uL) in DMSO (5.0 mL) was stirred at 25-30 °C for 16 hrs. The reaction was diluted with DCM (20 mL) and quenched with a mixture of saturated $NaHCO_3$ aqueous and $Na_2S_2O_3$ aqueous (10%) (80 mL, 1:1) and stirred at 20-25 °C for 0.5 hours. White solid precipitated out and was filtered, the filter cake was washed with H_2O (3 mL x 2) and dried under reduced pressure to give compopund **33** (20.0 mg, yield: 20%) as a white solid. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.10 (d, J = 7.9 Hz, 1H), 8.10 (s, 1H), 7.85 (s, 1H), 7.36 - 7.20 (m, 8H), 7.18 - 7.10 (m, 2H), 6.58 (s, 1H), 5.30 - 5.21 (m, 1H), 3.18 (dd, J = 3.5, 13.9 Hz, 1H), 2.80 (dd, J = 10.6, 13.7 Hz, 1H), 2.60 (q, J =7.7 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H). MS (ESI) m/z $(M+H)^+$ 391.1.

EXAMPLE 14

(*S*)-*N*-(1-OXO-3-PHENYLPROPAN-2-YL)-1-(1-PHENYL-1*H*-PYRAZOL-3-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (34)



[0526] To a solution of **34A** (15 g, 180.53 mmol) in THF (200 mL) was added ethyl 2-oxoacetate (47.9 g, 234.69 mmol). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was filtered and concentrated under reduced pressure to give intermediate compound **34B** (55.3 g, crude) as brown solid. MS (ESI) m/z $(M+H)^+$ 167.8.

[0527] To a solution of **34B** (40 g, 239 mmol) in EtOH (400 mL) was added K_2CO_3 (50 g, 362 mol) and 1-(isocyanomethylsulfonyl)-4-methyl-benzene (40 g, 204.88 mmol). The mixture was stirred at 90 °C for 0.5 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 5: 2) to afford compound **34C** (12 g, yield: 24.3%) as brown solid. ^1H NMR (400 MHz, $CDCl_3$) δ 11.80 - 11.35 (m, 1H), 7.87 (d, J = 1.10 Hz, 1H),

7.84 (d, J = 1.10 Hz, 1 H), 7.58 (d, J = 2.43 Hz, 1H), 6.45 (d, J = 2.43 Hz, 1H), 4.25 (q, J = 7.06 Hz, 2H), 1.29 (t, J = 7.17 Hz, 3H). MS (ESI) *m/z* $(M+H)^+$ 207.0.

[0528] A mixture of **34C** (5 g, 24.3mmol), phenylboronic acid (4.4 g, 36.4mmol), $Cu(OAc)_2$ (4.4 g, 24.3mmol), triethylamine (7.4 g, 72.8mmol) in DCM (200 mL) was degassed and purged with O_2 for 3 times, and then the mixture was stirred at 25 °C for 10 hrs under O_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate= 1: 0 to 2: 1). Compound **34D** (2.3 g, yield: 33.6%) was obtained as a white solid. ^1H NMR (400MHz, $CDCl_3$) δ 8.04 - 7.94 (m, 2H), 7.87 (s, 1H), 7.71 (br d, J = 7.7 Hz, 2H), 7.49 (br t, J = 7.1 Hz, 2H), 7.36 (br d, J = 7.1 Hz, 1H), 7.27 (d, J = 2.0 Hz, 2H), 6.70 - 6.61 (m, 1H), 4.29 (dd, J = 2.1, 7.2 Hz, 2H), 1.38 - 1.22 (m, 3H). MS (ESI) *m/z* $(M+H)^+$ 282.9.

[0529] To a solution of **34D** (2.5 g, 8.86 mmol) in THF (30 mL) and H_2O (6 mL) was added NaOH (708 mg, 17.7 mmol). The mixture was stirred at 80 °C for 1.5 hrs. The reaction mixture was concentrated under reduced pressure to remove THF, and then washed with EtOAc (20 mL). The aqueous layer was acidized with 1M HCl (to pH ~ 5) and then extracted with EtOAc (30 mL x 3). The combined organic layer was washed with H_2O (40 mL), brine (40 mL), dried over Na_2SO_4, filtered and concentrated to afford intermediate compound **34E** (1.90 g, yield: 84.31%) as yellow solid. ^1H NMR (400MHz, DMSO-d_6) δ 8.62 (d, J = 2.6 Hz, 1H), 8.19 (s, 1H), 7.86 (d, J = 7.9 Hz, 2H), 7.76 (s, 1H), 7.53 (t, J = 7.9 Hz, 2H), 7.39 - 7.31 (m, 1H), 6.77 (d, J = 2.6 Hz, 1H). MS (ESI) *m/z* $(M+H)^+$ 254.9.

[0530] Compound **34** (50 mg, yield: 62.8%, white solid) was prepared as in Example **6** from the corresponding intermediate compounds **34E** and **21G**. Compound **34**: ^1H NMR (400MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.95 (d, J = 2.4 Hz, 1H), 7.89 (s, 1H), 7.67 (s, 1H), 7.58 (d, J = 8.2 Hz, 2H), 7.45 (t, J = 7.8 Hz, 2H), 7.36 - 7.31 (m, 1H), 7.26 - 7.19 (m, 4H), 7.08 (d, J = 6.4 Hz, 2H), 6.55 (d, J = 2.4 Hz, 1H), 4.84 (q, J = 6.4 Hz, 1H), 3.21 (d, J = 6.4 Hz, 2H). MS (ESI) *m/z* $(M + H_2O + H)^+$ 404.1.

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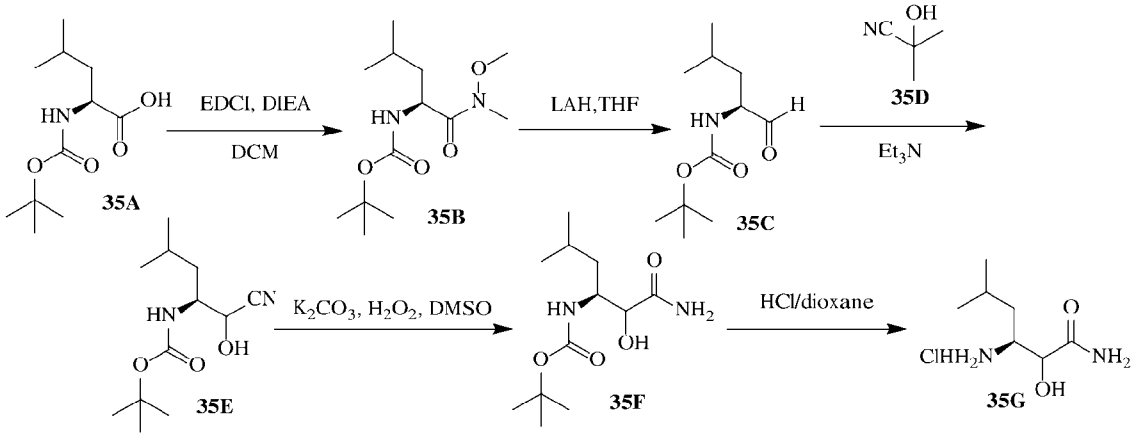
EXAMPLE 15

COMPOUNDS 35, 205

(*S*)-*N*-(1-AMINO-5-METHYL-1,2-DIOXOHEXAN-3-YL)-3-METHYL-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (35)



[0531] To a solution of compound **35A** (20 g, 86.47 mmol), N-methoxymethanamine (12.65 g, 129.71 mmol, HCl), HOBt (11.68 g, 86.47 mmol) in DCM (400 mL) was added DIEA (33.53 g, 259.41 mmol, 45.31 mL) at 0 °C. After that, the reaction mixture was stirred at 0 °C for 0.1 h, and then EDCI (19.89 g, 103.76 mmol) was added, after addition, the reaction mixture was stirred at 25 °C for 16 hrs. The reaction mixture was concentrated to give a residue and the residue was dissloved in EtOAc (400 mL), washed with 1N HCl (400 mL x 2), sat.$NaHCO_3$ (400 mL x 2) and brine (400 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, Petroleum Ether~Petroleum Ether: EtOAc = 10: 1). Compound **35B** (40.32 g, yield: 84.98%) was obtained as a colorless oil. ^1H NMR (400MHz, $CDCl_3$) δ 5.04 (br d, J = 9.0 Hz, 1H), 4.71 (br s, 1H), 3.77 (s, 3H), 3.18 (s, 3H), 1.80 - 1.63 (m, 2H), 1.42 (s, 10H), 0.93 (dd, J = 6.5, 14.2 Hz, 6H).

[0532] To a mixture of LAH (1.53 g, 40.41 mmol) in THF (200 mL) was added dropwise a solution of compound **35B** (10.08 g, 36.74 mmol) in THF (100 mL) at 0 °C under N_2 atmosphere. After addition, the reaction mixture was stirred at 0 °C for 2 hrs. EtOAc (150 mL) was added dropwise into the reaction mixture at 0 °C and acidified to pH ~ 1~2 with 1N HCl, then added saturated aqueous $NaHCO_3$ (150 mL x 3) and brine (150 mL). The organic layer was dried over Na_2SO_4 and concentrated. The compound **35C** (27.89 g, yield: 88.15%) was obtained as a yellow oil, which was used for next step directly without purification. ^1H NMR (400MHz,

$CDCl_3$): δ 9.71 - 9.32 (m, 1H), 4.99 (br s, 1H), 4.20 (br d, J = 2.9 Hz, 1H), 1.79 - 1.69 (m, 1H), 1.67 - 1.57 (m, 1H), 1.43 - 1.40 (m, 10H), 0.93 (dd, J = 1.4, 6.5 Hz, 6H).

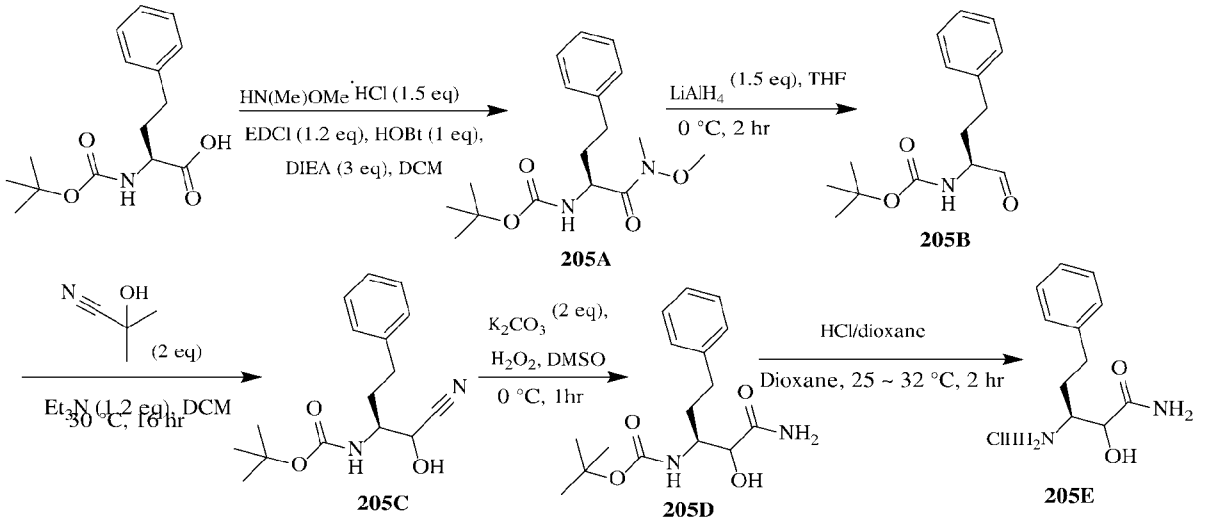
[0533] To a solution of compound **35C** (4 g, 18.58 mmol), compound **35D** (3.16 g, 37.16 mmol, 3.40 mL) and Et_3N (2.26 g, 22.30 mmol, 3.09 mL) in dry DCM (40 mL) was stirred at 25 °C for 16 hrs. The reaction mixture was diluted with 50 mL DCM, washed with 0.5 N HCl (100 mL), water (100 mL) and brine (100 mL). The organic phase was dried over Na_2SO4, concentrated. Then the residue was purified by column chromatography (SiO_2, Petroleum Ether: EtOAc = 10: 1). Compound **35E** (3.9 g, yield: 86.63%) was obtained as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$): δ 4.80 (br s, 1H), 4.58 - 4.36 (m, 1H), 4.02 - 3.91 (m, 0.5H), 3.77 (br s, 0.5H), 1.75 - 1.60 (m, 2H), 1.51 - 1.33 (m, 10H), 1.03 - 0.89 (m, 6H)

[0534] To a solution of compound **35E** (15 g, 61.90 mmol) and K_2CO_3 (17.11 g, 123.80 mmol) in DMSO (300 mL) was added H_2O_2 (70.17 g, 2.15 mol, 60 mL) under N_2 at 0 °C. After addition, the reaction mixture was stirred at 0 °C for 1 h. Then the reaction mixture was diluted with water (150 mL) and quenched with saturated aqueous $Na_2S_2O_3$ (300 mL) slowly at ice water. The mixture was extracted with EtOAc (300 mL x 3) and the combined extracts were washed with saturated aqueous $Na_2S_2O_3$ (300 mL x 3). The organic layer was dried over Na_2SO_4 and concentrated. The residue was diluted with EtOAc (20 mL) and MTBE (200 mL), the solid was collected and dried in vacuo. Compound **35F** (15.15 g, yield: 47.01%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.31 - 6.96 (m, 2H), 6.33 (br d, J = 9.0 Hz, 0.6H), 5.95 (d, J = 9.5 Hz, 0.4H), 5.44 (br d, J = 5.1 Hz, 1H), 3.93 - 3.65 (m, 2H), 1.57 - 1.47 (m, 1H), 1.41 - 1.23 (m, 10H), 0.95 - 0.70 (m, 7H).

[0535] To a solution of compound **35F** (5.42 g, 20.82 mmol) in dioxane (10 mL) was added HCl/dioxane (4M, 55 mL) at 25 °C. After addition, the reaction mixture was stirred at 25 °C for 2 hrs. The reaction was concentrated, and 40 mL of MTBE was added into the reaction mixture and the mixture was stirred for 5 min. Then the mixture was filtered to afford desired compound. Compound **35G** (3.8 g, yield: 92.80%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.12 (br s, 1.5H), 7.87 (br s, 0.5H), 7.57 - 7.35 (m, 2H), 4.22 (d, J = 2.5 Hz, 0.7H), 4.02 (d, J = 3.8 Hz, 0.3H), 3.57 (s, 1H), 3.45 (br d, J = 3.5 Hz, 1H), 1.81 - 1.58 (m, 1H), 1.54 - 1.33 (m, 1.3H), 1.21 (ddd, J = 4.3, 9.5, 14.1 Hz, 0.7H), 0.93 - 0.67 (m, 6H).

[0536] Compound **35** (48 mg, yield: 44.55%, white solid) was prepared as in Example **5** from the corresponding intermediate compounds **23A** and **35G**. Compound **35**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.99 (br d, J = 7.1 Hz, 1H), 8.13 (s, 1H), 7.89 - 7.77 (m, 3H), 7.54 - 7.48 (m, 3H), 5.20 (ddd, J = 3.3, 7.0, 10.6 Hz, 1H), 2.29 (s, 3H), 1.74 - 1.62 (m, 1H), 1.56 - 1.36 (m, 2H), 0.92 (d, J = 6.4 Hz, 3H), 0.89 - 0.84 (m, 3H).

(*S*)-*N*-(1-AMINO-1,2-DIOXO-5-PHENYLPENTAN-3-YL)-3-METHYL-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (205)



[0537] To a mixture of (S)-2-((tert-butoxycarbonyl)amino)-4-phenylbutanoic acid (5 g, 17.90 mmol) and N-methoxymethanamine (2.76 g, 28.26 mmol, HCl), HOBt (2.55 g, 18.84 mmol) in DCM (100.00 mL) was added dropwise DIEA (9.88 mL, 56.53 mmol) and EDCI (4.33 g, 22.61 mmol) in portion at 0°C under N_2. The mixture was stirred at 0 °C for 30 min, then the mixture was stirred at 25°C for 16 hours. The reaction mixture was diluted with H_2O (200 mL). The two layers were separated and the aqueous phase was extracted with Ethyl Acetate (2 x 150 mL). The combined organic layers were washed with 0.5 N HCl (2 x 150 mL) and $NaHCO_3$ (2 x 150 mL), dried over Na_2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10:1 to 3:1) to afford compound **205A** (4.15 g, 68.32% yield) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.35 - 7.23 (m, 2H), 7.22 - 7.04 (m, 4H), 4.45 - 4.21 (m, 1H), 3.59 (s, 3H), 3.06 (s, 3H), 2.81 - 2.68 (m, 1H), 2.61 - 2.54 (m , 1H), 1.86 - 1.65 (m, 2H), 1.45 - 1.29 (s, 9H).

[0538] To a solution of $LiAlH_4$ (88.3 mg, 2.32 mmol) in THF (15 mL) was added drop wise a solution of compound **205A** (500 mg, 1.55 mmol) in THF (15 mL) at 0 °C under N_2 atmosphere. After addition, the reaction mixture was stirred at 0 °C for 2 hours. The mixture was diluted with ethyl acetate (100 mL) and washed with 1N HCl (20 mL), saturated $NaHCO_3$ (2 x 20 mL), brine (15 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford compound **205B** (400 mg, 1.52 mmol) a s a yellow oil. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.4 (s, 1H), 7.33 - 7.05 (m, 5H), 3.82 - 3.72 (m, 1H), 2.71 - 2.51 (m, 2H), 1.97 - 1.9 (m, 1H), 1.81 - 1.66 (m, 1H), 1.51 - 1.25 (m, 10H).

[0539] A solution of compound **205B** (1.86 g, 7.06 mmol), 2-hydroxy-2-methylpropanenitrile (1.29 mL, 14.12 mmol) and Et_3N (1.17 mL, 8.47 mmol) in dry DCM (60 mL) was stirred at 30 °C for 16 hours. The reaction mixture was diluted with DCM (50 mL), washed with 0.5N HCl (20 mL), water (20 mL) and brine (20 mL). The organic phase was dried over Na2SO4, concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 3:1) to afford compound **205C** (900mg, 43.90% yield) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.44 - 7.21 (m, 5H), 6.75 - 6.58 (m, 1H), 4.70 - 4.29 (m, 1H), 3.80 - 3.51 (m, 1H), 2.86 - 2.68 (m, 1H), 2.62 - 2.59 (m, 1H), 2.04 - 1.64 (m, 2H), 1.53 - 1.43 (m, 9H).

[0540] To a solution of compound **205C** (900 mg, 3.1 mmol) and K_2CO_3 (856.9 mg, 6.2 mmol) in DMSO (18 mL) was added H_2O_2 (3.06 mL, 106.14 mmol) at 0 °C. After addition, the reaction mixture was stirred at 0 °C for 1h. The reaction mixture was diulted with water (200 mL) and quenched with saturated aqueous $Na_2S_2O_3$ (500 mL) slowly at ice water.The mixture was extracted with EtOAc (3 x 500 mL) and the combined extracts were washed with saturated aqueous $Na_2S_2O_3$ (2 x 300 mL).The organic layer was dried over Na_2SO_4 and concentrated. The mixture was treated with MTBE and then it was filtered to afford Compound **205D** (500 mg, 52.30% yield) as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 - 7.11 (m, 1H), 6.81 - 6.67 (m, 1H), 5.54 - 5.35 (m, 1H), 5.19 - 5.05 (m, 2H), 4.28 - 4.12 (m, 1H), 3.85 - 3.72 (s, 1H), 2.81 - 2.54 (m, 2H), 2.24 - 1.99 (m, 2H), 2.98 - 2.78 (m, 1H), 1.65 - 1.41 (m, 9H).

[0541] To a solution of compound **205D** (250 mg, 810.71 umol) in dioxane (2 mL) was added HCl/dioxane (4M, 1.06 mL) at 25 °C. After addition, the reation was stirred at 32°C for 2 hours and concentrated. The residue was purified by column chromatography (SiO_2,

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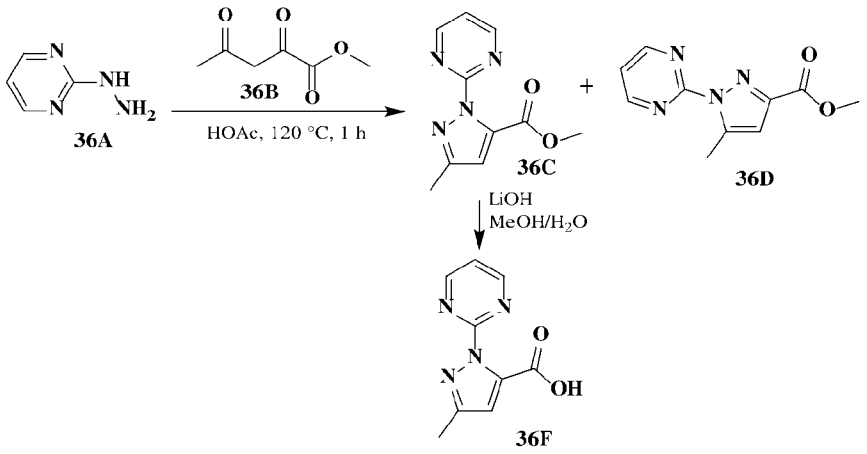
Petroleum ether/Ethyl acetate = 10: 1 to 1: 2) to afford compound **205E** (180 mg, 90.64% yield) as white solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.15 - 8.02 (m, 1H), 8.01 - 7.75 (m, 1H), 7.65 - 7.48 (m, 2H), 7.37 - 7.26 (m, 2H), 7.25 - 7.05 (m, 5H), 6.52 - 6.24 (s, 1H), 4.16 - 4.05 (m, 1H), 3.45 - 3.39 (m, 1H), 1.95 - 1.61 (m, 2H), 1.41 - 1.28 (m, 2H).

[0542] Compound **205** (23.5 mg, 31.69% yield, yellow solid) was prepared as in Example **5** from the corresponding intermediate compounds **23A** and **205E**. Compound **205**: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.84 - 7.72 (m, 2H), 7.60 - 7.50 (m, 3H), 7.26 - 7.12 (m, 4H), 7.07 - 7.00 (m, 2H), 6.66 (br s, 1H), 6.19 (br s, 1H), 5.51 - 5.34 (m, 2H), 2.66 - 2.54 (m, 2H), 2.47 (s, 3H), 2.38 - 2.25 (m, 1H), 1.99 - 1.85 (m, 1H). MS (ESI) *m/z* $(M+H)^+$ 392.1.

EXAMPLE 16

COMPOUNDS 36, 49, 409, 455

(S)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(PYRIMIDIN-2-YL)-1H-PYRAZOLE-5-CARBOXAMIDE (36)



[0543] To a solution of compound **36B** (1.31 g, 9.08 mmol) in AcOH (50 mL) was added compound **36A** (1 g, 9.08 mmol). The mixture was stirred at 120 °C for 1 h. The mixture was in DCM (50 mL). The organic layer was washed with water (10 mL), $NaHCO_3$ to pH ~ 8~9 and dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 10:1 to 5:1) to afford compounds **36C** and **36D**. Compound **36C** (500 mg, 2.29 mmol, 25.24% yield, white solid): ^{1}H NMR (400MHz, DMSO-d_6) δ 9.03 - 8.79 (m, 2H), 7.67 - 7.45 (m, 1H), 6.87 (s, 1H), 3.73 (s, 3H), 2.29 (s, 3H). Compound **36D** (1 g, 50.47% yield, white solid): ^{1}H NMR (400MHz, DMSO-d_6) δ 9.03 - 8.89 (m, *J*=4.9 Hz, 2H), 7.67 - 7.55 (m, 1H), 6.81 (s, 1H), 3.84 (s, 3H), 2.60 (s, 3H).

[0544] Intermediate compound **36F** (39.6 mg, 90% yield, white solid) was prepared as in Example **85** from compound **36C**. MS (ESI) *m/z* $(M+1)^+$ 205. Compound **36** (15.5 mg, 43.77% yield, brown solid) was prepared as in Example 5 from the corresponding intermediate compound **36F**. Compound **36**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.99 - 8.95 (m, 2H), 8.50 - 8.39 (m, 1H), 8.11 (s, 1H), 7.85 (s, 1H), 7.65 - 7.57 (m, 1H), 7.31 - 7.17 (m, 5H), 6.68 (s, 1H), 5.51 - 5.45 (m, 1H), 3.26 - 3.18 (m, 1H), 3.13 - 3.03 (m, 1H), 2.58 (s, 3H).

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(PYRIMIDIN-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (49)

[0545] Following the procedure as used for compound **36**, compound **49** (21 mg, 38.4% yield, white solid) was prepared from the corresponding intermediate compound **36D**. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.08 - 8.98 (m, 1H), 8.76 - 8.70 (m, 2H), 8.05 (s, 1H), 7.82 (s, 1H), 7.49 - 7.44 (m, 1H), 7.35 - 7.26 (m, 4H), 7.26 - 7.19 (m, 1H), 6.58 (s, 1H), 5.31 - 5.25 (m, 1H), 3.19 - 3.09 (m, 1H), 2.90 - 2.78 (m, 1H), 2.27 (s, 3H). MS (ESI) *m/z* $(M+Na)^+$ 379.

***N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(PYRIMIDIN-4-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (409)**

[0546] Following the procedure as used for compound **36**, compound **409** (4225.7 mg, 80.2% yield, white solid) was prepared from the corresponding starting materials, namely 4-hydrazinylpyrimidine and intermediate compound **274D**. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.22 (d, J = 7.2 Hz, 1H), 8.84 (d, J = 5.6 Hz, 1H), 8.75 (s, 1H), 8.14 (s, 1H), 7.89 (s, 1H), 7.78 - 7.74 (m, 1H), 7.31 - 7.21 (m, 5H), 6.52 (s, 1H), 5.41 - 5.33 (m, 1H), 3.22 - 3.12 (m, 1H), 2.90 - 2.78 (m, 1H), 2.28 (s, 3H). MS (ESI) *m/z* $(M+1)^+$ 379.0.

***N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(PYRIMIDIN-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (455)**

[0547] Following the procedure as used for compound **36**, compound **455** (180 mg, 71.6% yield, white solid) was prepared from the corresponding starting materials, namely 36F and 3-amino-*N*-cyclopropyl-2-hydroxy-4-phenylbutanamide. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.05 - 9.00 (m, 1H), 9.03 (d, J = 7.3 Hz, 1H), 8.78 (d, J = 5.1 Hz, 1H), 8.69 (d, J = 4.9 Hz, 2H), 7.44 (t, J = 4.9 Hz, 1H), 7.29 - 7.18 (m, 5H), 6.56 (s, 1H), 5.31 - 5.24 (m, 1H), 3.12 (dd, J = 3.7, 13.9 Hz, 1H), 2.84 - 2.71 (m, 2H), 2.24 (s, 2H), 2.27 - 2.19 (m, 1H), 0.67 - 0.54 (m, 4H). MS (ESI) *m/z* $(M+H)^+$ 419.2.

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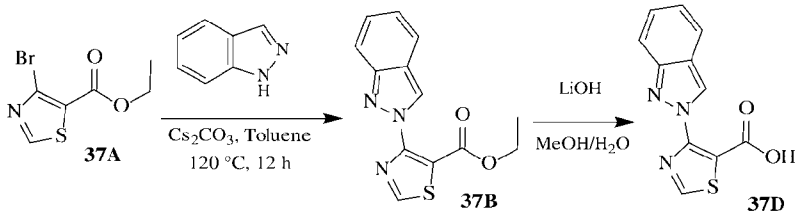
EXAMPLE 17

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-(2*H*-INDAZOL-2-YL)THIAZOLE-5-CARBOXAMIDE (37)



[0548] A mixture of compound **37A** (250 mg, 2.12 mmol), Cs_2CO_3 (2.07 g, 6.36 mmol) in toluene (40 mL) was stirred at 110 °C for 13 hrs. The mixture was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 10/1 to 5:1) to afford compound **37B** (43.75 mg, 7.55% yield) as white solid. MS (ESI) *m/z* $(M+1)^+$ 274. ^1H NMR (400MHz, CDCl3) δ 8.93 (s, 1H), 8.68 (s, 1H), 7.85 - 7.65 (m, 2H), 7.39 - 7.30 (m, 1H), 7.17 - 7.05 (m, 1H), 4.44 - 4.24 (m, 2H), 1.28 (m, 3H).

[0549] A mixture of compound **37B** (35 mg, 128.06 umol), LiOH (9.2 mg, 384.18 umol) in water (1 mL) and MeOH (5 mL) was stirred at 27 °C for 2 hrs. MeOH was evaporated. To the residue was added water (10 mL). The mixture was extracted with MTBE (5 mL) and separated. The aqueous layer was acidified to pH ~ 3 with 1N HCl and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried and concentrated to afford compound **37D** (25.3 mg, 80.55% yield) as brown solid.

[0550] Compound **37** (4 mg, 8.47 umol, yield 5.95%, yellow solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **37D**. Compound **37**: ^1H NMR (400MHz, $CDCl_3$) δ 12.72 - 12.49 (m, 1H), 8.97 (s, 1H), 8.80 (s, 1H), 7.80 - 7.64 (m, 1H), 7.46 - 7.29 (m, 2H), 7.20 - 6.98 (m, 6H), 6.83 - 6.72 (m, 1H), 5.97 - 5.84 (m, 1H), 5.52 - 5.40 (m, 1H), 3.56 - 3.33 (m, 2H).

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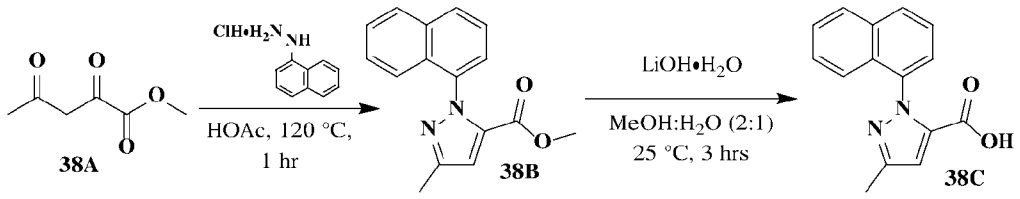
EXAMPLE 18

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(NAPHTHALEN-1-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (38)



[0551] A mixture consisting of compound naphthalen-1-yl hydrazine hydrochloride (4.05 g, 20.81 mmol) and compound **38A** (3.0 g, 20.81 mmol) in AcOH (30 mL) was stirred at 120 °C for 1 hour. The reaction mixture was cooled to 25 °C, concentrated under reduced pressure and diluted with CH_2Cl_2 (100 mL). The organic phase was washed with sat. $NaHCO_3$ (20 mL x 2), dried over anhydrous Na_2SO_4, filtered, and the filtration was concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (Petroleum ether: Ethyl acetate = 4:1) to afford compound **38B** (154.3 mg, 2.79% yield) as a brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.57 - 7.52 (m, 1H), 7.51 - 7.47 (m, 2H), 7.46 - 7.41 (m, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.90 (s, 1H), 3.62 (s, 3H), 2.43 (s, 3H). MS (ESI) *m/z* $(M+1)^+$ 267.1.

[0552] To a mixture of compound **38B** (160 mg, 570.78 umol) in MeOH (10 mL) and H_2O (5 mL) was added $LiOH.H_2O$ (71.9 mg, 1.71 mmol) in one portion and the mixture was stirred at 25 °C for 3 hrs. The reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was diluted with H_2O (10 mL), adjusted to pH ~ 3 with 1N HCl, and then extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give intermediate compound **38C** (140 mg, yield 97.23%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 - 7.83 (m, 2H), 7.52 - 7.44 (m, 2H), 7.44 - 7.36 (m, 2H), 7.15 (d, J = 8.4 Hz, 1H), 6.87 (s, 1H), 2.37 (s, 3H). MS (ESI) *m/z* $(M+1)^+$ 252.9.

[0553] Compound **38** (10.6 mg, yield 13.31%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **38C**. Compound **38**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 - 7.89 (m, 2H), 7.57 - 7.43 (m, 4H), 7.28 (d, J = 8.4 Hz, 1H), 7.22 - 7.10 (m, 3H), 6.82 - 6.72 (m, 2H), 6.69 (s, 1H), 6.54 (br s, 1H), 6.16 (d, J = 6.8 Hz, 1H),

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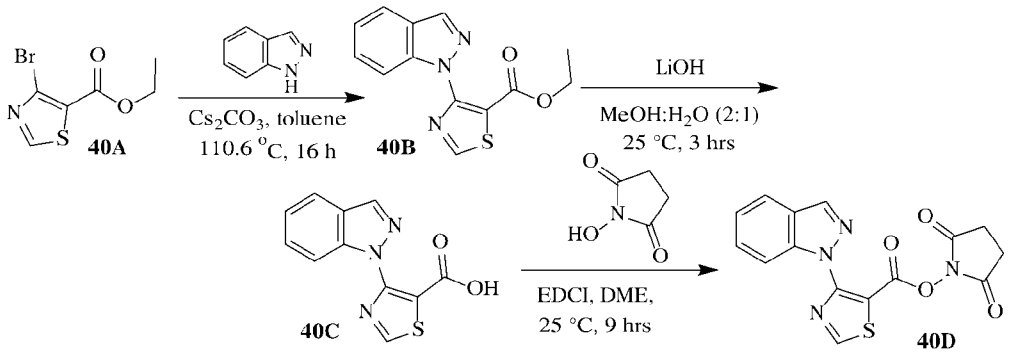
5.48 - 5.33 (m, 2H), 3.19 - 3.09 (m, 1H), 2.94 - 2.84 (m, 1H), 2.40 (s, 3H). MS (ESI) *m/z* $(M+1)^+$ 427.2.

EXAMPLE 19

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-(1*H*-INDAZOL-1-YL)THIAZOLE-5-CARBOXAMIDE (40)



[0554] A mixture consisting of compound **40A** (500 mg, 2.12 mmol), indazole (250.5 mg, 2.12 mmol), Cs_2CO_3 (2.07 g, 6.36 mmol) in toluene (40 mL) was stirred at 110.6 °C for 16 hrs. The reaction mixture was cooled to 25 °C, filtered, concentrated under reduced pressure. The obtained residue was purified by preparatory-HPLC (HCl condition) to afford compound **40B** (56 mg, 9.67% yield) as a light yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.94 (s, 1H), 8.26 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.48 - 7.43 (m, 1H), 7.28 - 7.24 (m, 1H), 4.24 (q, J = 7.2 Hz, 2H), 1.17 - 1.12 (m, 1H), 1.14 (t, J = 7.2 Hz, 2H).

[0555] To a mixture of compound **40B** (50 mg, 182.94 umol) in MeOH (2 mL) was added LiOH (13.1 mg, 548.83 umol) in one portion and the mixture was stirred at 25 °C for 3 hrs. The reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was diluted with H_2O (8 mL), adjusted to pH ~ 3 with 1 N HCl, and then extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give intermediate compound **40C** (42 mg, 93.61% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.95 (s, 1H), 8.73 (d, J = 8.4 Hz, 1H), 8.38 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H).

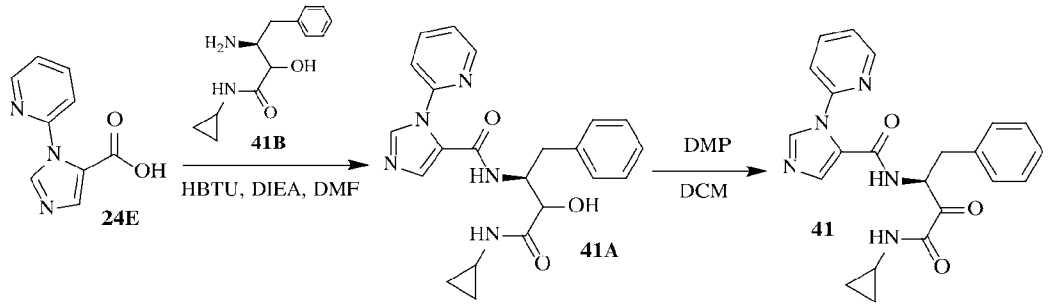
[0556] To a solution consisting of compound **40C** (42 mg, 171.25 umol) and 1-hydroxypyrrolidine-2,5-dione (20.7 mg, 179.81 umol) in DME (5 mL) was added EDCI (49.24

mg, 256.87 umol) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 9 hrs. The reaction mixture was concentrated under reduced pressure to remove DME. The residue was diluted with EtOAc (60 mL), washed with 1N HCl (10 mL) and saturated aqueous $NaHCO_3$ (10 mL x 3). The organic layers was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford intermediate compound **40D** (60 mg, crude) as a light yellow oil. MS (ESI) *m/z* $(M+1)^+$ 342.8.

[0557] Compound **40** (15.10 mg, 50.57% yield, white solid) was prepared as in Example **6** from the corresponding starting materials, compounds **40D** and **12G**. Compound **40**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.07 (d, J = 6.0 Hz, 1H), 8.85 (s, 1H), 8.33 - 8.28 (m, 1H), 7.86 (d, J = 0.8 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.57 - 7.52 (m, 1H), 7.35 - 7.31 (m, 1H), 7.16 - 7.08 (m, 5H), 6.77 (br s, 1H), 5.81 - 5.75 (m, 1H), 5.55 (br s, 1H), 3.43 - 3.37 (m, 1H), 3.26 - 3.19 (m, 1H). MS (ESI) *m/z* $(M+1)^+$ 420.1.

EXAMPLE 20

COMPOUNDS 41-43, 64-65, 67, 71, 76, 87, 100, 116, 132, 134-135, 137, 203-204 (*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(PYRIDIN-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (41)



[0558] To a mixture of compound **24E** (100 mg, 528 umol) and compound **41B** (148 mg, 634 umol) in DMF (1.5 mL) was added HBTU (240 mg, 634 umol) in one portion at 25 °C and stirred for 5 mins, and then DIEA (273 mg, 2.1 mmol) was added. The mixture was stirred at 25 °C for 30 mins. LCMS showed compound **24E** remained and desired MS was detected. Then the residue was purified by preparatory-HPLC (TFA condition) to give compound **41A** (130 mg, yield: 60.6%) as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.12 (br s, 1H), 8.49 (br d, J = 3.8 Hz, 1H), 7.95 - 7.74 (m, 2H), 7.50 (br s, 1H), 7.37 - 7.16 (m, 5H), 7.13 -

7.01 (m, 1H), 4.69 - 4.52 (m, 1H), 4.22 - 4.03 (m, 1H), 3.29 (br s, 1H), 3.11 - 2.74 (m, 2H), 2.69 - 2.51 (m, 1H), 0.77 - 0.59 (m, 2H), 0.56 - 0.38 (m, 2H). MS (ESI) *m/z* $(M+H)^+$ 405.2.

[0559] To a solution of compound **41A** (130 mg, 320 umol) in DCM (10 mL) was added DMP (543 mg, 1.3 mmol, 397 uL) in one portion at 0 °C. The mixture was stirred at 25 °C for 10 mins. LCMS showed compound **41A** was consumed completely and one main peak with desired MS was detected. Then the mixture was diluted with DCM (80 mL), quenched by adding 10% $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (v/v = 1/1, 20 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (30 mL x 2). The combined organic layer was washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated to afford white solid. Then the residue was purified by re-crystallization from isopropyl ether (20 mL) to give compound **41** (20.6 mg, yield: 30.9%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.96 (d, J = 7.8 Hz, 1H), 8.79 (br d, J = 5.0 Hz, 1H), 8.45 (br d, J = 4.6 Hz, 1H), 8.14 (s, 1H), 7.88 (t, J = 7.8 Hz, 1H), 7.57 (s, 1H), 7.44 (dd, J = 7.0, 5.2 Hz, 1H), 7.34 - 7.28 (m, 4H), 7.24 (br d, J = 4.2 Hz, 1H), 7.18 (d, J = 8.2 Hz, 1H), 5.32 - 5.22 (m, 1H), 3.31 (s, 1H), 3.19 (dd, J = 13.8, 3.6 Hz, 1H), 2.89 - 2.71 (m, 2H), 0.70 - 0.64 (m, 2H), 0.60 - 0.55 (m, 2H). MS (ESI) *m/z* $(M+H)^+$ 403.2.

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(1-PHENYL-1*H*-PYRAZOL-3-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (42)

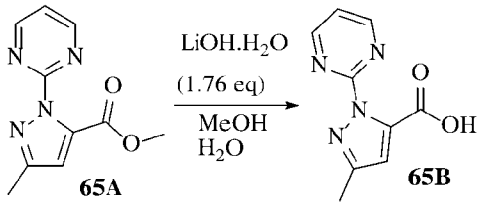
[0560] Compound **42** (19.3 mg, yield: 55.2%, yellow solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **34E**. ^1H NMR (400 MHz, DMSO-d_6) δ 8.91 (d, J = 7.7 Hz, 1 H), 8.82 (d, J = 5.1 Hz, 1 H), 8.57 (d, J = 2.6 Hz, 1 H), 8.14 (s, 1 H), 7.83 (d, J = 7.9 Hz, 2 H), 7.63 (s, 1 H), 7.53 (t, J = 8.0 Hz, 2 H), 7.36 (t, J = 7.4 Hz, 1 H), 7.32 (d, J = 4.4 Hz, 4 H), 7.27 - 7.20 (m, 1 H), 6.48 (d, J = 2.6 Hz, 1 H), 5.34 - 5.26 (m, 1 H), 3.21 (dd, J = 13.8, 3.6 Hz, 1 H), 2.86 (dd, J = 13.8, 10.3 Hz, 1 H), 2.81 - 2.72 (m, 1 H), 0.71 - 0.63 (m, 2 H), 0.62 - 0.53 (m, 2 H). MS (ESI) *m/z* $(M+H)^+$ 469.1.

(*S*)-1-(BENZO[*D*]THIAZOL-2-YL)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (43)

[0561] Compound **43** (24.4 mg, yield: 43%, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **29D**. Compound **43**: ^1H NMR (400 MHz, DMSO-d_6) δ 9.13 (d, J = 7.7 Hz, 1 H), 8.77 (br d, J = 4.9 Hz, 1 H), 8.39 (s, 1

H), 8.08 (d, J = 7.9 Hz, 1 H), 7.96 (d, J = 8.2 Hz, 1 H), 7.67 (s, 1 H), 7.59 - 7.43 (m, 2 H), 7.27 (d, J = 4.0 Hz, 4 H), 7.22 - 7.12 (m, 1 H), 5.34 - 5.16 (m, 1 H), 3.18 (dd, J = 13.9, 3.3 Hz, 1 H), 2.83 (dd, J = 13.7, 10.1 Hz, 1 H), 2.72 (br d, J = 4.2 Hz, 1 H), 0.69 - 0.58 (m, 2 H), 0.54 (br d, J = 2.9 Hz, 2 H). MS (ESI) m/z $(M+H)^+$ 460.1

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(PYRIMIDIN-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (65)



[0562] A mixture of compound **65A** (80 mg, 366.62 umol) in MeOH (5 mL) and H_2O (1 mL) was added $LiOH.H_2O$ (27.1 mg, 645.87 umol).The mixture was stirred at 31°C for 1h. The mixture was evaporated to remove MeOH, then it was washed with water (3 x 50 mL) and extracted with MTBE (2 x 50 mL). The water layers were acidized to pH ~ 4 with 1N HCl, then, the solution extracted with ethyl acetate (3 x 100 mL). The organic layers were dried over Na_2SO_4 and concentrated to give compound **65B** (50 mg, 66.79% yield) was obtained as white solid.

[0563] Compound **65** (11.8 mg, 87.93% yield, white solid) was prepared as in Example **20** from the corresponding intermediate compounds **65B** and **41B**. Compound **65**: ^1H NMR (400MHz, DMSO-d_6) δ 8.94 (s, 2H), 8.87 - 8.79(m, 1 H), 8.51 - 8.44 (m,1H), 7.62 - 7.55 (m,1H), 7.34 - 7.09 (m, 5H), 6.65 (s, 1H), 5.53 - 5.39 (m, 1H), 3.26 - 3.12 (m, 4H), 3.10 - 3.00 (m, 1H),2.81 - 2.71 (m,1H), 2.56 (s, 3H), 0.71 - 0.54 (m, 4H). MS (ESI) m/z $(M+H)^+$ 419.2.

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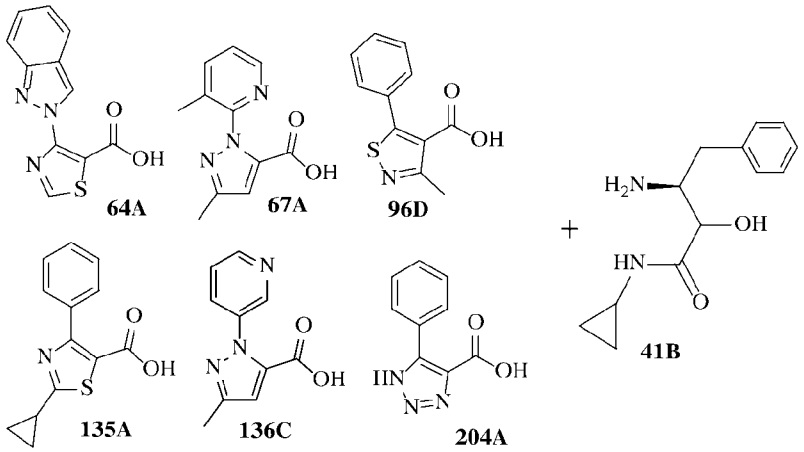

(S)-N-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-(2H-INDAZOL-2-YL)THIAZOLE-5-CARBOXAMIDE (64)

[0564] Compound **64** (48.2 mg 87.93% yield, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **64A**. Compound **64**: ^{1}H NMR (400MHz, DMSO-d_6) δ 11.99 - 11.83 (m, 1H), 9.33 (s, 1H), 9.16 (s, 1H), 8.95 - 8.84 (m, 1H), 7.93 - 7.80 (m, 1H), 7.56 - 7.50 (m, 1H), 7.44 - 7.33 (m, 1H), 7.27 - 7.15 (m, 1H), 7.12 - 6.99 (m, 5H), 5.71 - 5.60 (m, 1H), 3.34 - 3.24 (m, 3H), 3.19 - 3.10 (m, 1H), 2.84 - 2.74 (m, 1H), 0.73 - 0.54 (m, 4H). MS (ESI) *m/z* $(M+H)^+$ 460.1.

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(3-METHYLPYRIDIN-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (67)

[0565] Compound **67** (30.8 mg, 38.6% yield, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **67A**. Compound **67**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, J = 4.4 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.2 (d, J = 7.2 Hz, 1H), 7.34 - 7.26 (m, 2H), 7.25 - 7.20 (m, 3H), 6.99 (d, J = 4.4 Hz, 2H), 6.86 (s, 1H), 6.56 (s, 1H), 5.66 - 5.58 (m, 1H), 3.38 - 3.29 (m, 1H), 3.21 - 3.13 (m, 1H), 2.82 - 2.74 (m, 1H), 2.34 (s, 3H), 2.16 (s, 3H), 0.91 - 0.84 (m, 2H), 0.64 - 0.57 (m, 2H). MS (ESI) *m/z* $(M+H)^+$ 432.1.

(*S*)-1-(1*H*-BENZO[*d*]IMIDAZOL-2-YL)-N-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (71)

[0566] Compound **71** (75 mg, yield: 78.1%, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **70D**. Compound **71**: ^{1}H NMR (400MHz, DMSO-d_6) δ 12.93 (br s, 1H), 9.25 (br s, 1H), 8.74 (d, J = 4.9 Hz, 1H), 8.29 (s, 1H), 7.83 (s, 1H), 7.52 (br s, 2H), 7.30 - 7.18 (m, 6H), 7.18 - 7.13 (m, 1H), 5.42 - 5.25 (m, 1H),

3.17 (dd, J = 3.5, 13.7 Hz, 1H), 2.83 (dd, J = 10.0, 13.8 Hz, 1H), 2.74 - 2.64 (m, 1H), 0.70 - 0.42 (m, 4H). MS (ESI) m/z $(M+H)^+$ 443.0.

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(5-PHENYLPYRIMIDIN-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (76)

[0567] Compound **76** (24.7 mg, yield: 44.7%, white solid) was prepared as in Example **20** from the corresponding intermediate compound **74E**. Compound **76**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.46 (br d, J = 6.4 Hz, 1H), 8.66 (s, 2H), 8.62 (s, 1H), 7.80 (s, 1H), 7.57 - 7.49 (m, 5H), 7.22 - 7.16 (m, 2H), 7.16 - 7.07 (m, 3H), 6.93 (br s, 1H), 5.86 - 5.82 (m, 1H), 3.53 - 3.46 (m, 1H), 3.41 - 3.32 (m, 1H), 2.86 -2.82 (m, 1H), 0.92 - 0.86 (m, 2H), 0.64 -0.62 (m, 2H). MS (ESI) m/z $(M+H)^-$ 481.0.

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-(4-PHENYL-1*H*-PYRAZOL-1-YL)THIAZOLE-5-CARBOXAMIDE (87)

[0568] Compound **87** (60.0 mg, 75.3% yield, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **21D**. ^{1}H NMR (400MHz, $CDCl_3$) δ 11.72 (br. d, J = 6.0 Hz, 1H), 8.73 (s, 1H), 8.68 - 8.64 (m, 1H), 7.76 - 7.72 (m, 1H), 7.58 - 7.52 (m, 2H), 7.48 - 7.40 (m, 2H), 7.37 - 7.30 (m, 1H), 7.29 - 7.21 (m, 5H), 6.97 - 6.91 (m, 1H), 5.86 - 5.74 (m, 1H), 3.53 - 3.41 (m, 1H), 3.29 - 3.17 (m, 1H), 2.88 - 2.75 (m, 1H), 0.93 - 0.82 (m, 2H), 0.68 - 0.58 (m, 2H). MS (ESI) m/z $(M+1)^+$ 486.1.

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (100)

[0569] Compound **100** (85 mg, yield: 83.27%, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **23A**. Compound **100**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.09 (d, J = 7.5 Hz, 1H), 8.94 (br d, J = 5.1 Hz, 1H), 7.62 (d, J = 7.1 Hz, 2H), 7.53 - 7.46 (m, 1H), 7.44 - 7.39 (m, 2H), 7.32 - 7.20 (m, 5H), 5.48 (ddd, J = 3.3, 7.6, 10.7 Hz, 1H), 3.25 (br dd, J = 3.2, 14.0 Hz, 1H), 2.85 - 2.67 (m, 2H), 2.07 (s, 3H), 0.73 - 0.56 (m, 4H). MS (ESI) m/z $(M+H)^+$ 418.1.

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-5-PHENYLISOTHIAZOLE-4-CARBOXAMIDE (116)

[0570] Compound **116** (88.00 mg, 87.41% yield, off-white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **96D**. Compound

116: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.44 (s, 5H), 7.20 - 7.09 (m, 3H), 6.86 (br s, 1H), 6.77 - 6.68 (m, 2H), 5.93 (br d, J=6.6 Hz, 1H), 5.68 - 5.57 (m, 1H), 3.24 - 3.14 (m, 1H), 2.99 - 2.89 (m, 1H), 2.83 - 2.73 (m, 1H), 2.46 (s, 3H), 0.93 - 0.81 (m, 2H), 0.69 - 0.53 (m, 2H). MS (ESI) *m/z* $(M+H)^+$ 434.1.

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(PYRIDIN-3-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (132)

[0571] Compound **132** (72.8 mg, 60.40% yield, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **136C**. Compound **132**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, J = 2.4 Hz, 1H), 8.57 - 8.54 (m, 1H), 7.72 - 7.66 (m, 1H), 7.34 - 7.26 (m, 4H), 7.10 - 7.05 (m, 2H), 7.03 - 6.94 (m, 1H), 6.64 - 6.56 (m, 1H), 6.44 (s, 1H), 5.62 - 5.54 (m, 1H), 3.44 - 3.36 (m, 1H), 3.18 - 3.10 (m, 1H), 2.85 - 2.76 (m, 1H), 2.33 (s, 3H), 0.92 - 0.85 (m, 2H), 0.66 - 0.59 (m, 2H). MS (ESI) *m/z* $(M+1)^+$ 418.1.

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(ISOQUINOLIN-4-YL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (134)

[0572] Compound **134** (57.4 mg, 62.9% yield, yellow solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **133D**. Compound **134**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (br s, 1H), 8.47 (br s, 1H), 8.06 (d, J = 7.6 Hz, 1H), 7.74 - 7.61 (m, 2H), 7.43 (d, J = 8.0 Hz, 1H), 7.25 - 7.20 (m, 3H), 6.92 (br s, 2H), 6.84 (br s, 1H), 6.60 (s, 1H), 6.46 (d, J = 7.2 Hz, 1H), 5.50 - 5.41 (m, 1H), 3.30 - 3.22 (m, 1H), 3.14 - 3.04 (m, 1H), 2.79 - 2.70 (m, 1H), 2.40 (s, 3H), 0.87 - 0.82 (m, 2H), 0.63 - 0.53 (m, 2H). MS (ESI) *m/z* $(M+H)^+$ 468.1.

(*S*)-2-CYCLOPROPYL-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-PHENYLTHIAZOLE-5-CARBOXAMIDE (135)

[0573] Compound **135** (52.8 mg, 53.03% yield, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **135A**. Compound **135**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1H NMR (400 MHz, CDCl3) δ 7.53 - 7.45 (m, 2H), 7.45 - 7.35 (m, 3H), 7.22 - 7.11 (m, 3H), 6.85 (br s, 1H), 6.80 - 6.70 (m, 2H), 6.17 (d, J = 6.4 Hz, 1H), 5.54 - 5.45 (m, 1H), 3.27 - 3.22 (m, 1H), 2.89 - 2.84 (m, 1H),2.80 - 2.75 (m, 1H), 2.33 - 2.26 (m, 1H), 1.20 - 1.14 (m, 2H), 1.13 - 1.08 (m, 2H), 0.91 - 0.79 (m, 2H), 0.64 - 0.54 (m, 2H). MS (ESI) *m/z* $(M+H)^+$ 460.1.

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(*S*)-3-(*tert*-BUTYL)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-PHENYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (137)

[0574] Compound **137** (96.70 mg, 64.74% yield, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **128A**. Compound **137**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 - 7.45 (m, 3H), 7.41 - 7.36 (m, 2H), 7.31 - 7.27(m, 1H), 7.25 - 7.13 (m, 5H), 6.87 (br s, 1H), 6.69 (s, 1H), 5.77 - 5.68 (m, 1H), 3.44 - 3.36 (m, 1H), 3.17 - 3.09 (m, 1H), 2.82 - 2.74 (m, 1H), 1.16 (s, 9H), 0.89 - 0.81 (m, 2H), 0.64 - 0.54 (m, 2H). MS (ESI) *m/z* $(M+H)^+$ 459.2.

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(4-PHENYLTHIAZOL-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (203)

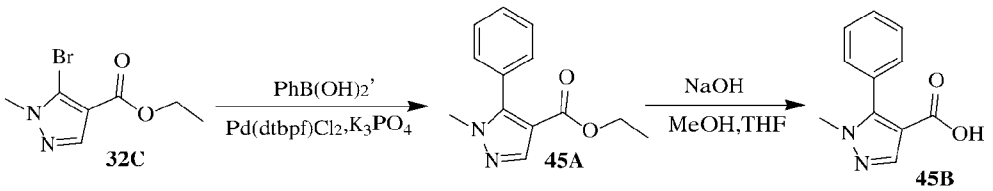
[0575] Compound **203** (30 mg, yield 60.18%, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **82D**. Compound **203**: ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.69 - 7.64 (m, 2H), 7.41 - 7.33 (m, 3H), 7.22 (s, 1H), 7.12 - 7.06 (m, 3H), 7.01 - 6.94 (m, 3H), 6.84 (br s, 1H), 5.65 - 5.58 (m, 1H), 3.41 - 3.34 (m, 1H), 2.97 - 2.89 (m, 1H), 2.79 - 2.71 (m, 1H), 2.32 (s, 3H), 0.86 - 0.80 (m, 2H), 0.61 - 0.53 (m, 2H). MS (ESI) m/z $(M+H)^+$ 500.1.

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-PHENYL-1*H*-1,2,3-TRIAZOLE-4-CARBOXAMIDE (204)

[0576] Compound **204** (4 mg, 8.9% yield, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **204A**. Compound **204**: ^{1}H NMR ($CDCl_3$, 400 MHz) T = 80 : δ 8.55 (br s, 1H), 8.41 (d, *J* = 7.2 Hz, 1H), 7.82 - 7.78 (m, 2H), 7.50 - 7.35 (m, 4H), 7.32 - 7.20 (m, 5H), 5.51 - 5.45 (m, 1H), 3.30 - 3.22 (m, 1H), 3.05 (br s, 1H), 2.81 - 2.74 (m, 1H), 0.71 - 0.66 (m, 2H), 0.64 - 0.59 (m, 2H). MS (ESI) *m/z* $(M+H)^+$ 404.1.

EXAMPLE 21

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-METHYL-5-PHENYL-1*H*-PYRAZOLE-4-CARBOXAMIDE (45)



[0577] A mixture of ethyl compound **32C** (500.0 mg, 2.15 mmol), phenylboronic acid (262.1 mg, 2.15 mmol), Pd(dtbpf)Cl_2 (140.1 mg, 215.00 umol), K_3PO_4 (1.37 g, 6.45 mmol) in dioxane (30 mL) and H_2O (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 70 °C for 1 hour under N_2 atmosphere. The mixture was concentrated and diluted with ethyl acetate (30 mL), washed with HCl (1M, 50 mL), sarurated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated to afford intermediate compound **45A** (490 mg, crude) as a brown oil. MS (ESI) *m/z* $(M+H)^+$ 230.9.

[0578] To a solution of compound **45A** (490.0 mg, 2.13 mmol) in MeOH (5 mL) and THF (5 mL) was added NaOH (2M, 21.28 mL). The mixture was stirred at 60 °C for 1 hour. The mixture was concentrated and diluted with H_2O (10 mL), the mixture was extracted with ethyl acetate (10 mL), the water phase was added HCl (1M) until pH ~ 3, then the mixture was extracted with ethyl acetate (20 mL), the organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated. Compound **45B** (400 mg, yield: 93.0%) was obtained as a brown solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 12.09 (br s, 1H), 7.87 (s, 1H), 7.50 - 7.40 (m, 5H), 3.63 (s, 3H).

[0579] Compound **45** (50.0 mg, yield: 71.4%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **45B**. Compound **45**: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.55 - 7.43 (m, 3H), 7.32 - 7.27 (m, 2H), 7.23 - 7.15 (m, 3H), 6.85 - 6.65 (m, 3H), 5.80 - 5.71 (m, 1H), 5.55 - 5.40 (m, 2H), 3.71 - 3.60 (m, 3H), 3.29 - 3.19 (m, 1H), 2.94 - 2.84 (m, 1H), 2.94 - 2.84 (m, 1H). MS (ESI) *m/z* $(M+H)^+$ 377.1.

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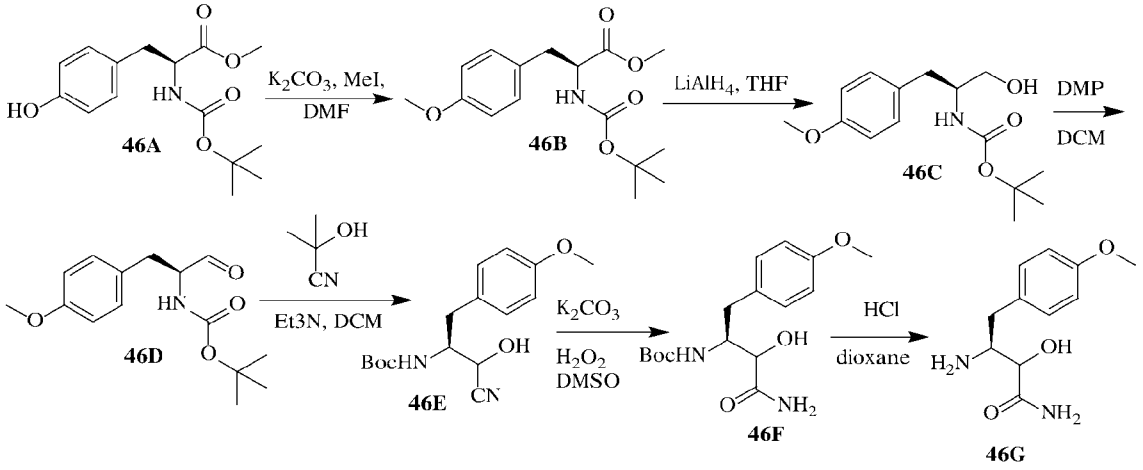
EXAMPLE 22

(*S*)-*N*-(4-AMINO-1-(4-METHOXYPHENYL)-3,4-DIOXOBUTAN-2-YL)-3-METHYL-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (46)



[0580] To a solution of compound **46A** (13 g, 44.02 mmol, 1 eq) in DMF (150 mL) was added K_2CO_3 (12.17 g, 88.04 mmol, 2 eq) at 0 °C. After addition, the mixture was stirred at this temperature for 0.2 h, and then CH_3I (8.97 g, 63.20 mmol, 3.93 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 18.8 hours. The reaction mixture was diluted with EtOAc (50 mL). The combined organic layers were washed with brine (100 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the compound **46B** (13.4 g, yield: 98.4%) as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.04 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 7.7 Hz, 2H), 4.96 (br d, J = 7.3 Hz, 1H), 4.55 (br d, J = 7.1 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.09 - 2.94 (m, 2H), 1.43 (s, 9H).

[0581] To a solution of LAH (490 mg, 12.92 mmol, 2 eq.) in THF (10 mL) was degassed and purged with N_2 for 3 times at 0 °C and the mixture of compound **46B** (2 g, 6.46 mmol, 1 eq) in THF (30 mL) was added dropwise, and then the mixture was stirred at 0 °C for 2 hrs under N_2 atmosphere. The reaction mixture was quenched by addition H_2O (0.5 mL), then add NaOH (15% in H_2O, 0.5 mL), H_2O (1.5 mL), and then diluted with EtOAc (20 mL), dried over Na_2SO_4, and stirred for 30 min, then filtered to give the organic layers. The combined organic layers were washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the compound **46C** (1.48 g, yield: 81.4%) was obtained as a colorles oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.12 (d, J = 8.4 Hz, 2H), 6.89 - 6.78 (m, 2H), 4.69 (br

s, 1H), 3.88 - 3.80 (m, 1H), 3.79 (s, 3H), 3.69 - 3.48 (m, 2H), 2.77 (d, J = 7.1 Hz, 2H), 1.41 (s, 9H).

[0582] A solution of DMP (1.51 g, 3.56 mmol) in DCM (10 mL) was degassed and purged with N_2 for 3 times, and then compound **46C** (500 mg, 1.78 mmol) in DCM (10 mL) was added dropwise, and then the mixture was stirred at 25 °C for 20 hrs under N_2 atmosphere. The reaction mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ (15 mL) and saturated aqueous $NaHCO_3$ (15 mL), and then diluted with DCM (10 mL) and extracted with H_2O (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the compound **46D** (430 mg, yield: 86.48%) was obtained as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.13 - 7.02 (m, 2H), 6.84 (br d, J=8.6 Hz, 2H), 5.05 (br d, J=5.5 Hz, 1H), 4.46 - 4.32 (m, 1H), 3.78 (s, 3H), 3.06 (br d, J = 6.4 Hz, 2H), 1.43 (s, 9H).

[0583] To a solution of compound **46D** (1.53 g, 5.48 mmol) in DCM (20 mL) was added compound 2-hydroxy-2-methylpropanenitrile (3.30 g, 38.78 mmol, 3.55 mL) and Et_3N (832 mg, 8.22 mmol, 1.14 mL). The mixture was stirred at 25 °C for 2 hrs. The reaction mixture was quenched by addition 1N HCl (20 mL), and then diluted with H_2O (20 mL) and extracted with DCM (20 mL x 2). The combined organic layers were washed with brine (20 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 10/1 to 4:1) to give the compound **46E** (980 mg, yield: 58.37%) was obtained as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.16 - 6.97 (m, 2H), 6.90 - 6.71 (m, 2H), 4.96 - 4.72 (m, 1H), 4.52 - 4.37 (m, 1H), 3.74 - 3.72 (m, 3H), 3.07 - 2.66 (m, 2H), 1.37 (s, 9H).

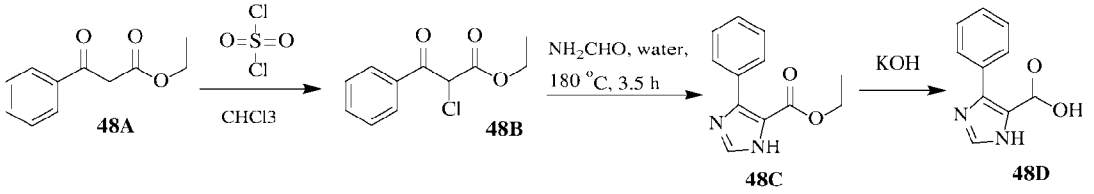
[0584] To a solution of compound **46E** (980 mg, 3.20 mmol) and K_2CO_3 (885 mg, 6.40 mmol) in DMSO (15 mL) was added H_2O_2 (9.3 mL, purity: 30%). The mixture was stirred at 0 °C for 2 hrs. The reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the compound **46F** (560 mg, yield: 53.95%) was obtained as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.16 - 6.97 (m, 2H), 6.90 - 6.71 (m, 2H), 4.96 - 4.72 (m, 1H), 4.52 - 4.37 (m, 1H), 3.74 - 3.72 (m, 3H), 3.07 - 2.66 (m, 2H), 1.37 (s, 9H).

[0585] To a solution of compound **46F** (500 mg, 1.54 mmol) in EtOAc (5 mL) was added HCl/EtOAc (4 M, 5 mL). The mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with MTBE (20 mL), and filtered to give the compound **46G** (300 mg, yield: 73.97%, HCl) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.06 - 7.81 (m, 3H), 7.51 (br s, 2H), 7.26 - 7.07 (m, 2H), 6.95 - 6.79 (m, 2H), 6.65 - 6.35 (m, 1H), 4.21 - 3.78 (m, 1H), 3.71 (d, J = 1.5 Hz, 3H), 3.53 (br s, 1H), 2.87 - 2.62 (m, 2H).

[0586] Compound **46** (65 mg, yield: 65.3%, white solid) was prepared as in Example **15** from the corresponding intermediate compounds, **23A** and **46G**. Compouond **46**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.05 - 8.64 (m, 1H), 8.18 (s, 1H), 7.90 (s, 1H), 7.67 - 7.55 (m, 2H), 7.53 - 7.32 (m, 3H), 7.24 - 7.10 (m, 2H), 6.89 - 6.76 (m, 2H), 5.48 - 5.36 (m, 1H), 3.74 - 3.65 (m, 3H), 3.23 - 2.95 (m, 1H), 2.76 - 2.58 (m, 1H), 2.17 - 2.00 (m, 3H). MS (ESI) m/z $(M+H)^+$ 408.1.

EXAMPLE 23

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-PHENYL-1*H*-IMIDAZOLE-5-CARBOXAMIDE (48)



[0587] To a solution of compound **48A** (40 g) in $CHCl_3$ (200 mL) cooled to 0 °C was added dropwise sulfuryl dichloride (34 g). The mixture was warmed to 30 °C for 0.5 h and heated at 70 °C for 5 hrs. After cooling to room temperature, the reaction mixture was diluted with chloroform (40 mL), washed with aqueous $NaHCO_3$ (40 mL x 2), water (20 mL) and then brine (30 mL) successively. The organic phase was dried over Na_2SO_4 and evaporated to afford compound **48B** (47 g, crude) was obtained as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.06 - 7.87 (m, 2H), 7.67 - 7.56 (m, 1H), 7.52 - 7.42 (m, 1H), 7.48 - 7.39 (m, 1H), 7.48 - 7.39 (m, 1H), 7.67 - 7.38 (m, 1H), 7.26 (s, 1H), 5.61 (s, 1H), 5.29 - 5.26 (m, 1H), 4.39 - 4.21 (m, 2H), 1.70 (s, 1H), 1.40 - 1.14 (m, 3H).

[0588] A solution of compound **48B** (20 g) in NH_2CHO (40 g, 882.40 mmol, 35 mL) and Water (3.2 g, 176.48 mmol) was heated at 180 °C for 3.5 hrs. The mixture was allowed to cool to room temperature, then water (50 ml) was added and the mixture was extracted with

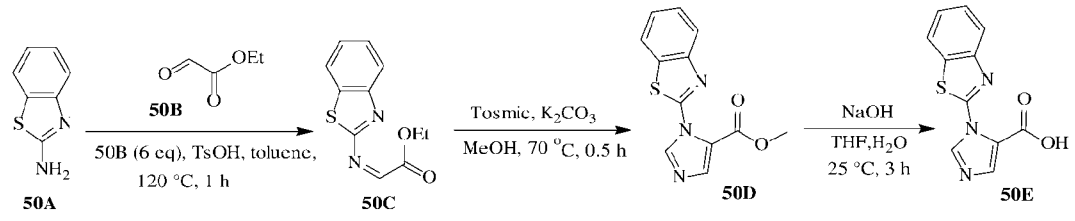
DCM (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of 0 ~ 100% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to afford compound **48C** (1.3 g) as yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.09 (d, J=7.3 Hz, 7H), 4.28 - 4.08 (m, 2H), 1.24 (br t, J=6.8 Hz, 1H), 1.29 - 1.10 (m, 1H).

[0589] To a solution of ethyl compound **48C** (800 mg, 3.70 mmol) in EtOH (20 mL) was added a solution of KOH (2.1 g, 37.00 mmol) in H_2O (20 mL) at 0 °C. After addition, the reaction mixture was stirred at 70 °C for 16 hrs 20 mL of water was added into the reaction mixture and the mixture was extracted with MTBE (20 mL). The aqueous layer was acidified with 1N HCl to pH ~ 4 and filtered to afford desired compound. The filtrate was extracted with EtOAc (50 mL x 3). The combined extracts were washed with brine (50 mL) and dried over Na_2SO_4, the mixture was concentrated in vacuum to afford desired compound **48D** (500 mg, yield 71.81%) as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 13.42 - 12.33 (m, 1H), 7.97 - 7.67 (m, 3H), 7.48 - 7.21 (m, 3H).

[0590] Compound **48** (10 mg, yield 25.1%, light yellow solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **48D**. Compound **48**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.30 - 8.17(m, 1H), 8.00-7.53 (m, 5H), 7.46 - 7.13 (m, 8H), 5.50 - 5.30 (m, 1H), 4.31 - 4.05 (m, 1H), 3.32 - 3.21(m, 1H), 2.71-2.61 (m, 1H). MS (ESI) *m/z* $(M+H)^+$ 363.2.

EXAMPLE 24

(S)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(BENZO[*d*]THIAZOL-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (50)



[0591] A mixture of compound **50A** (20 g, 133 mmol), compound **50B** (136 g, 665 mmol), $TsOH.H_2O$ (2.5 g, 13.3 mmol) in toluene (200 mL) was stirred at 120 °C for 1 hour. TLC (Petroleum ether: Ethyl acetate = 3:1, R_f ~ 0.5) indicated **50A** was almost consumed and

one new spot formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Petroleum ether: Ethyl acetate = 20:1 to 5:1) to give compound **50C** (30 g, crude) as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.98 - 7.78 (m, 1H), 7.77 - 7.57 (m, 1H), 7.55 - 7.31 (m, 1H), 7.30 - 7.07 (m, 1H), 5.38 - 5.26 (m, 1H), 4.33 - 4.21 (m, 3H). MS (ESI) *m/z* $(M+H)^+$ 234.9.

[0592] A mixture of methyl **50C** (10 g, 45.4 mmol), TosMIC (17.7 g, 90.8 mmol), K_2CO_3 (9.4 g, 68.1 mmol) in MeOH (200 mL) was stirred at 70 °C for 0.5 hour. TLC (Petroleum ether: Ethyl acetate = 3:1, R_f = 0.4) indicated **50C** was consumed completely and some new spots formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Petroleum ether: Ethyl acetate = 20:1 to 3:1) to give compound **50D** (1.2 g, yield: 10.2%) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.22 (d, J = 0.9 Hz, 1H), 8.06 (d, J = 7.9 Hz, 1H), 7.93 - 7.88 (m, 3H), 7.58 (dt, J = 1.3, 7.7 Hz, 1H), 7.52 - 7.49 (m, 1H), 7.49 - 7.43 (m, 1H), 4.58 (s, 1H), 3.87 (s, 3H), 2.51 (s, 1H). MS (ESI) *m/z* $(M+H)^+$ 259.9.

[0593] To a solution of **50D** (1.1 g, 4.24 mmol in THF (30 mL), H_2O (5 mL) was added NaOH (339 mg, 8.48 mmol). The reaction mixture was stirred at 25 °C for 3 hrs. LCMS showed **50D** was consumed completely and one main peak with desired MS was detected. The reaction mixture was concentrated to give a residue. The residue was dissolved in water (10 mL), adjusted pH ~ 5 by aqueous HCl, filtered and the filtered cake was concentrated to give the product **50E** (0.6 g, yield: 57.7%) as a gray solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.48 (d, J = 1.1 Hz, 1H), 8.22 - 8.18 (m, 1H), 8.06 (dd, J = 0.8, 8.0 Hz, 1H), 7.81 (d, J = 0.9 Hz, 1H), 7.64 - 7.53 (m, 2H). MS (ESI) *m/z* $(M+H)^+$ 245.9.

[0594] Compound **50** (12.9 mg, yield: 18.8%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **50E**. Compound **50**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (br d, J = 7.7 Hz, 1 H) 8.39 (s, 1 H) 8.12 - 8.03 (m, 2 H) 7.96 (d, J = 8.2 Hz, 1 H) 7.81 (s, 1 H) 7.66 (s, 1 H) 7.57 - 7.45 (m, 2 H) 7.26 (d, J = 4.2 Hz, 4 H) 7.20 - 7.16 (m, 1 H) 5.33 - 5.20 (m, 1 H) 3.18 (br dd, J = 13.9, 3.5 Hz, 1 H) 2.90 - 2.76 (m, 1 H). MS (ESI) *m/z* $(M+H)^-$ 420.0.

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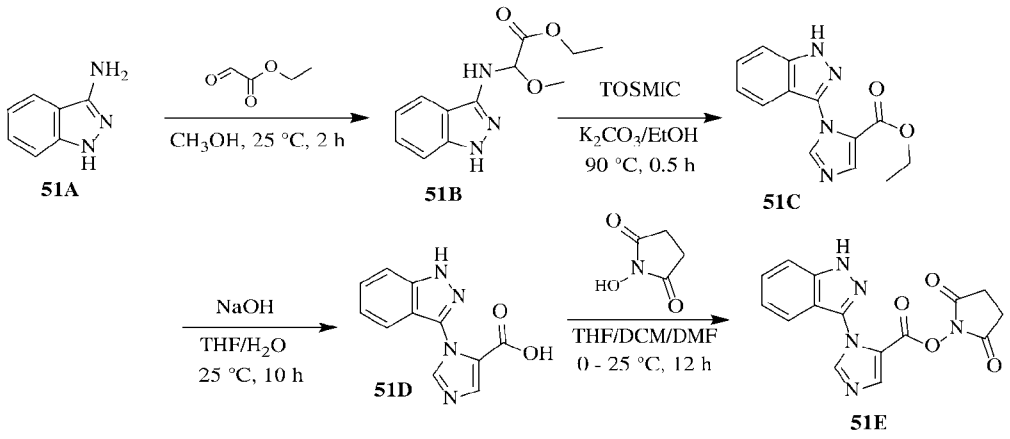
EXAMPLE 25

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(1*H*-INDAZOL-3-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (51)



[0595] To a solution of **51A** (8.7 g, 65.3 mmol) in MeOH (90 mL) was added ethyl 2-oxoacetate (20 g, 98.01 mmol). After stirred at 25 °C for 2 hours, the mixture was filtered and concentrated to give crude product **51B** (15 g, crude) as brown solid, which was used for the next step without purification.

[0596] To a solution of **51B** (15 g, 69.1 mmol) in EtOH (400 mL) was added K_2CO_3 (14.5 g, 104 mmol) and TosMIC (11.6 g 59.4 mmol). After stirred at 90 °C for 0.5 hour, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1:0 to 1:1) to give compound **51C** (2.9 g, yield: 16.4%) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 11.04 (br s, 1H), 7.98 (d, J = 0.7 Hz, 1H), 7.91 (s, 1H), 7.48 - 7.41 (m, 3H), 7.25 - 7.19 (m, 1H), 4.24 - 4.14 (m, 2H), 1.14 (t, J = 7.1 Hz, 3H).

[0597] To a solution of **51C** (2.9 g, 11.3 mmol) in THF (40 mL) and H_2O (8 mL) was added NaOH (905 mg, 22.6 mmol). The mixture was stirred at 25 °C for 10 hours. The mixture was concentrated under reduced pressure to remove the organic solvent, and extracted with EtOAc (20 mL). The aqueous layer was acidized with 1M HCl to pH ~ 5 and then extracted with EtOAc (30 mL x 3). The combined organic layer was washed with H_2O (40 mL), brine (40 mL), dried over Na_2SO_4, filtered and concentrated to give **51D** (1.5 g, yield: 58.1%) as yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 13.35 (s, 1H), 8.16 (s, 1H), 7.83 (s, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.47 - 7.41 (m, 2H), 7.20 - 7.15 (m, 1H). MS (ESI) m/z $(M+H)^+$ 228.9.

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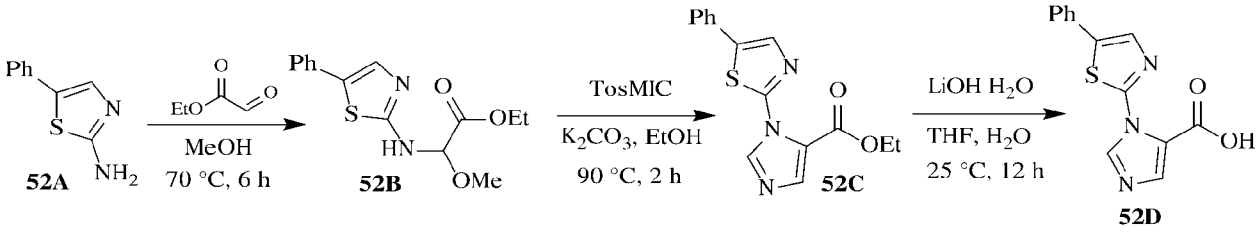
[0598] To a solution of **51D** (500 mg, 2.19 mmol,) and 1-hydroxypyrrolidine-2,5-dione (252 mg, 2.19 mmol) in THF (10 mL), DCM (5 mL) and DMF (10 mL) was added EDCI (420 mg, 2.19 mmol) at 0 °C. After addition, the mixture was stirred at 25°C for 12 h. The solvent was removed under vacuum. The residue was diluted with EtOAc (50 mL), washed with 1N HCl (20 mL), saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organics were combined, dried over Na_2SO_4, filtered, and concentrated to give crude **51E** (476 mg, yield: 66.8%) as yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 13.52 (s, 1H), 8.57 (s, 1H), 8.32 (s, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.49 - 7.43 (m, 2H), 7.24 - 7.17 (m, 1H), 2.77 (s, 5H).

[0599] Compound **51** (28.5 mg, yield: 29.1%, yellow solid) was prepared as in Example **20** from the corresponding intermediate compounds **51E** and **41B**. Compound **51**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.66 (br s, 1 H), 7.86 (s, 1 H), 7.73 (s, 1 H), 7.49 - 7.34 (m, 3 H), 7.34 - 7.28 (m, 1 H), 7.23 - 7.10 (m, 4 H), 7.09 - 6.90 (m, 3 H), 5.65 - 5.53 (m, 1 H), 3.33 (dd, J = 14.1, 5.1 Hz, 1 H), 3.15 (dd, J = 14.1, 7.3 Hz, 1 H), 2.75 (td, J = 7.2, 3.6 Hz, 1 H), 0.76 - 0.86 (m, 2 H), 0.55 (br d, J = 2.6 Hz, 2 H). MS (ESI) m/z $(M+H)^+$ 443.1.

EXAMPLE 26

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(5-PHENYLTHIAZOL-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (52)



[0600] A mixture of compound **52A** (4.2 g, 23.8 mmol) and ethyl 2-oxoacetate (14.6 g, 71.4 mmol) in MeOH (40 mL) was stirred at 70 °C for 6 hours. TLC (Petroleum ether: Ethyl acetate = 2:1, R_f ~ 0.7) indicated compound **52A** was consumed completely, and one major new spot with lower polarity was detected. The reaction mixture was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 20:1 to 10:1) to give compound **52B** (7 g, crude) as a yellow oil.

[0601] To a mixture of compound **52B** (7 g, 23.9 mmol) and K_2CO_3 (6.6 g, 47.8 mmol) in EtOH (15 mL) was added TosMIC (6.9 g, 35.9 mmol). The mixture was stirred at 90

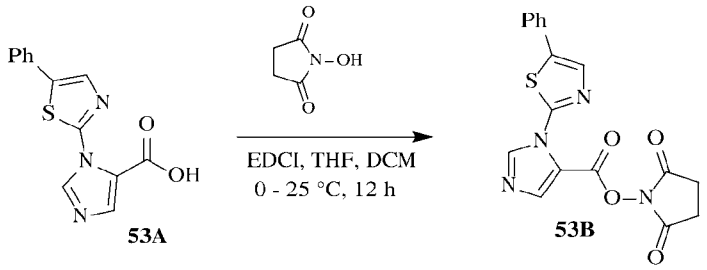
°C for 2 hours. TLC (Petroleum ether: Ethyl acetate = 2:1, R_f ~ 0.55) indicated compound **52B** was consumed completely, and one major new spot with larger polarity was detected. The reaction mixture was concentrated to give residue. The crude product was purified by silica gel chromatography eluted with Petroleum ether: Ethyl acetate = 15:1 to 5:1 to give compound **52C** (6 g, crude) as a yellow solid. MS (ESI) *m/z* $(M+H)^+$ 299.9.

[0602] To a solution of compound **52C** (3.5 g, 11.69 mmol) in THF (20 mL) and H_2O (6 mL) was added $LiOH.H_2O$ (981 mg, 23.3 mmol) in one portion. The mixture was stirred at 25 °C for 12 hours. TLC (Petroleum ether: Ethyl acetate = 1:1, R_f ~ 0.25) indicated compound **52C** was consumed completely and one new spot formed. The mixture was adjusted to pH ~ 5 by adding HCl (2M), and then white solid was precipitate out, filtered and dried under reduced pressure to give compound **52D** (1.5 g, yield: 47.3%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 8.19 (s, 1H), 7.76 - 7.70 (m, 3H), 7.53 - 7.46 (m, 2H), 7.45 - 7.38 (m, 1H).

[0603] Compound **52** (50.9 mg, yield: 43%, white solid) was prepared as in Example 5 from the corresponding intermediate carboxylic acid, compound **52D**. Compound **52**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.05 (d, J = 7.5 Hz, 1H), 8.32 (s, 1H), 8.11 (s, 2H), 7.85 (s, 1H), 7.71 - 7.66 (m, 3H), 7.48 (t, J = 7.5 Hz, 2H), 7.44 - 7.39 (m, 1H), 7.30 (d, J = 4.4 Hz, 4H), 7.23 - 7.19 (m, 1H), 5.35 - 5.25 (m, 1H), 3.21 (dd, J = 3.7, 13.8 Hz, 1H), 2.85 (dd, J = 10.3, 13.8 Hz, 1H). MS (ESI) *m/z* $(M+H)^-$ 446.0.

EXAMPLE 27

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(5-PHENYLTHIAZOL-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (53)



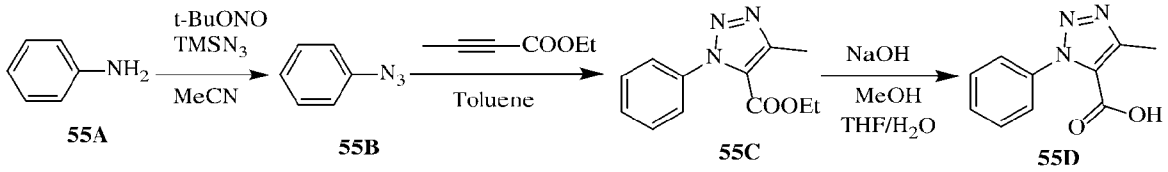
[0604] To a mixture of compound **53A** (600 mg, 2.21 mmol) and compound 1-hydroxypyrrolidine-2,5-dione (254 mg, 2.21 mmol) in THF (10 mL) at 0 °C was added a solution of EDCI (423 mg, 2.21 mmol) in DCM (5 mL) dropwise. The mixture was stirred at 25 °C for

12 hours. TLC (Petroleum ether: Ethyl acetate = 1:1, R_f ~ 0.4) indicated compound **53A** was consumed completely, and one major new spot with lower polarity was detected. The reaction mixture was concentrated to remove solvent. The residue was diluted with EtOAc (50 mL), washed with H_2O (20 mL), saturated $NaHCO_3$ (20 mL), brine (20 mL). The organics were collected, dried with Na_2SO_4, filtered, and concentrated to give desired intermediate compound **53B** (700 mg, yield: 85.9%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.20 (s, 1H), 7.86 (s, 1H), 7.57 (d, J = 6.5 Hz, 2H), 7.48 - 7.36 (m, 3H), 7.27 (s, 1H), 2.88 (s, 4H).

[0605] Compound **53** (41 mg, yield: 34.3%, white solid) was prepared as in Example **20** from the corresponding intermediate compound **53B**. Compound **53**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (d, J = 7.7 Hz, 1H), 8.82 (d, J = 5.0 Hz, 1H), 8.32 (d, J = 0.8 Hz, 1H), 8.11 (s, 1H), 7.72 - 7.64 (m, 3H), 7.52 - 7.46 (m, 2H), 7.44 - 7.39 (m, 1H), 7.30 (d, J = 4.4 Hz, 4H), 7.24 - 7.18 (m, 1H), 5.31 - 5.22 (m, 1H), 3.21 (dd, J = 13.7, 3.6 Hz, 1H), 2.90 - 2.70 (m, 2H), 0.66 - 0.54 (m, 4H). MS (ESI) m/z $(M+H)^+$ 486.1.

EXAMPLE 28

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-METHYL-1-PHENYL-1*H*-1,2,3-TRIAZOLE-5-CARBOXAMIDE (55)



55A 55B 55C 55D

[0606] A solution of compound **55A** (2.5 g, 26.8 mmol) in MeCN (50 mL) was added t-BuONO (4.15 g, 40.3 mmol) at 0 °C followed with $TMSN_3$ (4.64 g, 40.3 mmol). The reaction mixture was stirred at 20°C for 1hr. The solvent was evaporated to give intermediate compound **55B** (4 g, crude) as yellow oil.

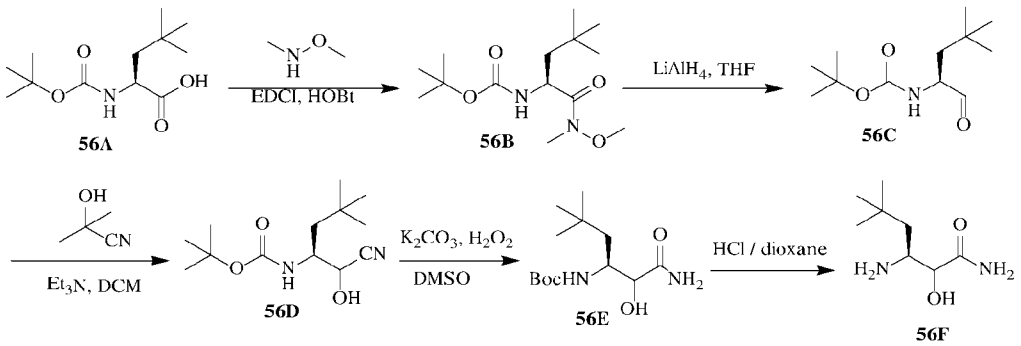
[0607] A mixture of compound **55B** (4 g, crude) and compound ethyl but-2-ynoate (1 g, 8.92 mmol) in toluene (20 mL) was stirred at 110 °C for 5hrs. The solvent was evaporated. The crude product was purified by silica gel column chromatography (Petroleum ether: Ethyl acetate = 20: 1 ~ 5: 1) to give compound **55C** (150 mg, yield: 7.27%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 - 7.49 (m, 2H), 7.44 - 7.40 (m, 2H), 7.37 (d, J = 5.1 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H).

[0608] A solution of compound **55C** (150 mg, 649 umol) in THF (2 mL) and H_2O (2 mL) was added NaOH (51.9 mg). The reaction mixture was stirred at 20 °C for 30min. TLC showed a new peak with higher polarity was generated. The solvent was evaporated and 1M HCl was added until pH ~ 6. The mixture was filtered and the cake was dried to give compound **55D** (120 mg, yield: 91.0%) as a yellow solid.

[0609] Compound **55** (46 mg, 121 umol, yield: 42.0%, yellow solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **55D**. Compound **55**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (br d, J = 7.9 Hz, 1H), 8.20 (s, 1H), 7.94 (s, 1H), 7.51 - 7.43 (m, 3H), 7.36 - 7.28 (m, 7H), 5.38 (br t, J = 7.7 Hz, 1H), 3.26 (br s, 1H), 2.82 - 2.73 (m, 1H), 2.21 (s, 3H). MS (ESI) m/z $(M+H)^+$ 378.1.

EXAMPLE 29

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-METHYL-1-PHENYL-1*H*-1,2,3-TRIAZOLE-5-CARBOXAMIDE (56)



[0610] A mixture of compound **56A** (1.0 g, 4.08 mmol), compound N,O-dimethylhydroxylamine (478 mg, 4.90 mmol, HCl) , HOBt (552 mg, 4.08 mmol) and NMM (1.24 g, 12.24 mmol, 1.35 mL) in $CHCl_3$ (20 mL) was degassed and purged with N_2 for 3 times at 0 °C, then EDCI (1.17 g, 6.12 mmol) was added in portions. The mixture was stirred at 25 °C for 20 hrs under N_2 atmosphere. The reaction mixture was quenched by addition H_2O (20 mL), and then diluted with DCM (10 mL). The combined organic layers were washed with 1N HCl (15 mL x 2), saturated aqueous $NaHCO_3$ (15 mL x 2) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the compound **56B** (1.15 g, yield: 97.7%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 6.97 (br d, J = 8.8 Hz, 1H), 4.47 (br t, J = 8.4 Hz, 1H), 3.73 - 3.64 (m, 3H), 3.06 (s, 3H), 1.51 - 1.27 (m, 11H), 0.87 (s, 9H).

[0611] To a solution of LAH (303 mg, 7.98 mmol) in THF (10 mL) was degassed and purged with N_2 for 3 times at 0 °C , and the mixture of compound **56B** (1.15 g, 3.99 mmol) in THF (20 mL) was added dropwise, and then the mixture was stirred at 0 °C for 2 hrs under N_2 atmosphere. The reaction mixture was quenched by add EtOAc (10 mL), then add 1N HCl (50 mL), and then diluted with EtOAc (20 mL), dried over Na_2SO_4, and stirred for 30 min, then filtered to give the organic layers. The combined organic layers were washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the compound **56C** (900 mg, yield: 98.4%) was obtained as a white solid. ^{1}H NMR (400MHz,$CDCl_3$) δ 9.55 (s, 1H), 4.83 (br s, 1H), 4.24 (br s, 1H), 1.86 - 1.55 (m, 2H), 1.44 (s, 9H), 1.03 - 0.91 (m, 9H).

[0612] To a solution of compound **56C** (900 mg, 3.92 mmol) in DCM (20 mL) was added compound 2-hydroxy-2-methylpropanenitrile (2.33 g, 27.32 mmol, 2.50 mL) and Et_3N (595 mg, 5.88 mmol, 815 uL). The mixture was stirred at 25 °C for 2 hrs. The reaction mixture was quenched by addition 1N HCl (20 mL), and then diluted with H_2O (20 mL) and extracted with DCM (20 mL x 2). The combined organic layers were washed with brine (20 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the compound **56D** (930 mg, yield: 92.55%) was obtained as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 5.06 - 4.66 (m, 1H), 4.55 - 4.35 (m, 1H), 4.05 - 3.73 (m, 1H), 1.80 - 1.65 (m, 2H), 1.45 (br d, J = 6.8 Hz, 9H), 1.10 - 0.80 (m, 9H).

[0613] To a solution of compound **56D** (930 mg, 3.63 mmol) and K_2CO_3 (1.00 g, 7.26 mmol) in DMSO (15 mL) was added H_2O_2 (4.12 g, 36.30 mmol, 3.49 mL, purity: 30%). The mixture was stirred at 0 °C for 2 hrs. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was stirred in DCM (0.1 mL) and PE (5 mL) for 30 min and filtered to give the compound **56E** (480 mg, yield: 48.20%) was obtained as a white solid. ^{1}H NMR (400MHz,$CDCl_3$) δ 6.83 (br s, 1H), 5.65 (br s, 1H), 5.27 - 5.06 (m, 1H), 4.99 - 4.82 (m, 1H), 4.23 - 4.00 (m, 1H), 3.88 (br t, J=8.6 Hz, 1H), 1.77 (br s, 1H), 1.60 - 1.51 (m, 1H), 1.42 (d, J = 9.3 Hz, 9H), 0.94 (d, J = 10.1 Hz, 9H).

[0614] To a solution of compound **56E** (480 mg, 1.75 mmol) in EtOAc (5 mL) was added HCl/EtOAc (4M, 5 mL). The mixture was stirred at 25 °C for 1 h. The reaction mixture

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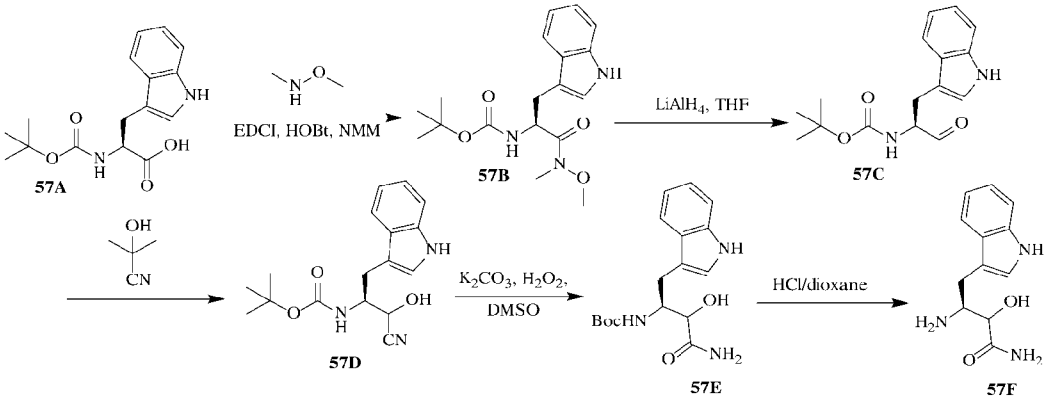
was diluted with PE (20 mL), filtered and concentrated under reduced pressure to give the compound **56F** (360 mg, yield: 97.63%, HCl) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.00 (br s, 1H), 7.92 - 7.70 (m, 1H), 7.58 - 7.41 (m, 2H), 4.21 - 3.93 (m, 1H), 3.33 (br d, J=3.5 Hz, 2H), 1.76 - 1.24 (m, 2H), 0.86 (s, 9H).

[0615] Compound **56** (94.20 mg, yield: 85.26%, white solid) was prepared as in Example **35** from the corresponding intermediate compounds, **23A** and **56F**. Compound **56**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.98 - 8.61 (m, 1H), 8.20 - 7.95 (m, 1H), 7.85 - 7.71 (m, 2H), 7.57 - 7.37 (m, 3H), 5.25 (br t, J = 6.8 Hz, 1H), 2.35 - 2.20 (m, 3H), 1.63 - 1.28 (m, 2H), 0.98 - 0.76 (m, 9H). MS (ESI) m/z $(M+H)^+$ 358.2.

EXAMPLE 30

(*S*)-*N*-(4-AMINO-1-(1*H*-INDOL-3-YL)-3,4-DIOXOBUTAN-2-YL)-3-METHYL-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (57)



[0616] A mixture of compound **57A** (5.00 g, 16.43 mmol), compound N,O-dimethylhydroxylamine (1.76 g, 18.07 mmol, HCl), HOBt (2.22 g, 16.43 mmol) and NMM (4.99 g, 49.29 mmol, 5.42 mL) in $CHCl_3$ (150 mL) was degassed and purged with N_2 for 3 times at 0 °C, then EDCI (4.72 g, 24.65 mmol) was added in portions, and then the mixture was stirred at 25 °C for 23 hrs under N_2 atmosphere. The reaction mixture was quenched by addition H_2O (100 mL), and then diluted with 1N HCl (200 mL) and extracted with $NaHCO_3$ (50 mL x 2). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 6/1 to 1/1) to give the compound **57B** (5.94 g) was obtained as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 10.79 (br s, 1H), 7.50

(d, J = 7.7 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.19 - 7.11 (m, 1H), 7.07 - 6.96 (m, 3H), 4.59 (br s, 1H), 3.70 (br s, 3H), 3.10 (s, 3H), 3.03 - 2.94 (m, 1H), 2.89 - 2.77 (m, 1H), 1.29 (s, 9H).

[0617] To a solution of LAH (330 mg, 8.64 mmol) in THF (10 mL), and then compound **57B** (2.00 g, 5.76 mmol) in THF (20 mL) was added dropwise. The mixture was stirred at 0 °C for 2 hrs. The reaction mixture was quenched by addition EtOAc (10 mL) at 0°C, and then diluted with 1N HCl (40 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with 1N HCl (40 mL) and $NaHCO_3$ (30 mL x 2) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the compound **57C** (1.55 g, yield: 93.33%) was obtained as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.02 - 10.75 (m, 1H), 9.52 (s, 1H), 7.50 (br d, J = 7.7 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.25 (br d, J = 7.3 Hz, 1H), 7.14 (d, J = 1.8 Hz, 1H), 7.05 (t, J = 7.2 Hz, 1H), 7.00 - 6.92 (m, 1H), 4.14 - 4.05 (m, 1H), 3.19 - 3.10 (m, 1H), 2.95 - 2.85 (m, 1H), 2.52 - 2.45 (m, 4H), 1.39 - 1.23 (m, 9H).

[0618] To a solution of compound **57C** (1.50 g, 5.20 mmol) in DCM (30.00 mL) was added compound N,O-dimethylhydroxylamine (885 mg, 10.40 mmol, 960 uL) and Et_3N (790 mg, 7.80 mmol, 1.08 mL). After stirred at 25 °C for 20 hrs, the reaction mixture was quenched by addition 0.5N HCl 30 mL, and then extracted with DCM (30 mL x 2). The combined organic layers were washed with brine (30 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compound **57D** (1.74 g, yellow solid): ^{1}H NMR (400MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.14 (br s, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.24 - 7.18 (m, 1H), 7.17 - 7.11 (m, 1H), 7.03 (d, J = 2.2 Hz, 1H), 5.14 (br s, 1H), 4.51 (br d, J = 6.6 Hz, 1H), 3.41 - 3.16 (m, 2H), 1.44 (s, 9H).

[0619] To a solution of compound **57D** (1.74 g, 5.52 mmol) and K_2CO_3 (1.53 g, 11.04 mmol) in DMSO (25.00 mL) was added H_2O_2 (6.43 g, 189.00 mmol, 5.45 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with H_2O (50 mL), and then quenched by addition $Na_2S_2O_3$ (50 mL) and extracted with EtOAc (50 mL x 3) and Na_2S_2O3 (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/2 to 0:1) to give the compound **57E** (689.60 mg, yield: 37.47%) was obtained as a yellow solid. ^{1}H NMR (400MHz,$CDCl_3$) δ 8.06 (br s, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.25 - 7.06

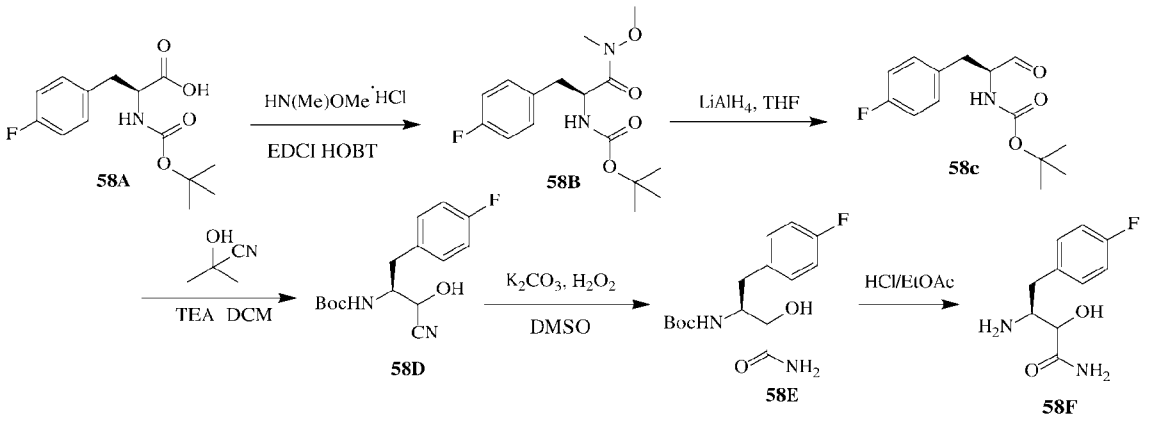
(m, 4H), 5.42 (br s, 1H), 5.19 - 5.04 (m, 1H), 4.21 - 4.08 (m, 3H), 3.30 - 3.12 (m, 2H), 1.41 (s, 9H).

[0620] To a solution of compound **57E** (680.00 mg, 2.04 mmol) in EtOAc (5.00 mL) was added HCl/EtOAc (5.00 mL). The mixture was stirred at 25 °C for 2.5 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent to give the compound **57F** (400.00 mg, yield: 72.69%, HCl) was obtained as a brown solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.01 (br s, 1H), 7.92 (br s, 2H), 7.70 - 7.46 (m, 3H), 7.39 - 7.26 (m, 2H), 7.12 - 6.95 (m, 2H), 4.01 - 3.89 (m, 1H), 3.81 - 3.64 (m, 1H), 3.14 (s, 2H), 3.08 - 2.80 (m, 2H).

[0621] Compound **57** (11.20 mg, yield: 29.41%, white solid) was prepared as in Example **15** from the corresponding intermediate compounds, **23A** and **57F**. Compound **57**: ^{1}H NMR (400MHz, DMSO-d_6) δ 10.89 (br s, 1H), 9.03 (d, J = 7.3 Hz, 1H), 8.23 (s, 1H), 7.95 (s, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 7.5 Hz, 2H), 7.48 (br d, J = 7.5 Hz, 1H), 7.39 (t, J = 7.4 Hz, 3H), 7.17 (d, J = 1.8 Hz, 1H), 7.13 - 6.96 (m, 2H), 5.56 (br s, 1H), 2.97 - 2.87 (m, 1H), 2.70 - 2.54 (m, 1H), 2.11 (s, 3H). MS (ESI) m/z $(M+H)^+$ 417.1.

EXAMPLE 31

(*S*)-*N*-(4-AMINO-1-(1*H*-INDOL-3-YL)-3,4-DIOXOBUTAN-2-YL)-3-METHYL-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (58)



[0622] To a solution of N-methoxymethanamine (1.89 g 19.42 mmol), compound **58A** (5.0 g, 17.65 mmol), HOBt (2.38 g, 17.65 mmol) and NMM (52.95 mmol, 5.8 mL) in $CHCl_3$ (100 mL) was degassed and purged with N_2 for 3 times at 0 °C, then EDCI (5.1 g, 26.48 mmol) was added in portions. The mixture was stirred at 25 °C for 16 hrs under N_2 atmosphere. The reaction mixture was washed with H_2O (100 mL). The organic layers were washed with

1mol/L HCl (100 mL x 2), saturated $NaHCO_3$ (100 mL x 2) and saturated brine (100ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®;80 g SepaFlash® Silica Flash Column, Eluent of 0 ~ 30% Ethyl acetate/Petroleum ether gradient @ 40mL/min) to afford compound **58B** (4.00 g, yield 69.4%) as white solid. ^{1}H NMR (400MHz,$CDCl_3$) δ 7.11 (dd, J=5.6, 8.3 Hz, 2H), 6.94 (t, J=8.7 Hz, 2H), 5.18 (br d, J=7.9 Hz, 1H), 4.98 - 4.80 (m, 1H), 4.13 - 4.07 (m, 2H), 3.72 - 3.64 (m, 4H), 3.14 (s, 3H), 3.08 - 2.94 (m, 1H), 2.91 - 2.70 (m, 1H), 2.02 (s, 2H), 1.78 (br s, 1H), 1.37 (s, 10H), 1.28 - 1.20 (m, 3H).

[0623] To $LiAlH_4$ (128 mg 3.37 mmol) in 100 mL of dry flask was added dropwise THF (15 mL) at 0 °C. After addition, the mixture was stirred at this temperature, and then a solution of compound **58B** (1.0 g 3.06 mmol) in THF (15 mL) was added dropwise to the above mixture at 0 °C. The resulting mixture was stirred at 0 °C for 1.5 hrs. The reaction mixture was quenched by slowly added EtOAc (20 mL) at 0 °C, and then added 1N HCl (20 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were washed with $NaHCO_3$ (30 mL x 2) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the compound **58C** (810 mg, yield 99.0%) as white solid. ^{1}H NMR (400MHz,$CDCl_3$) δ 9.65 (br s, 1H), 9.63 (br s, 1H), 7.21 - 7.08 (m, 2H), 7.00 (br d, J=8.6 Hz, 2H), 5.05 (br s, 1H), 4.42 (br s, 1H), 3.09 - 3.02 (m, 1H), 3.11 (br d, J=6.2 Hz, 1H), 1.51 - 1.38 (m, 9H).

[0624] To a solution of compound **58C** (3.2 g, 11.86 mmol) and 2-hydroxy-2-methyl-propanenitrile (2.2 mL, 23.72 mmol) in DCM (30 mL) was added TEA (2 mL, 14.23 mmol). After addition, the reaction mixture was stirred at 28 °C for 14 hrs. The reaction mixture was diluted with 30 mL of DCM and the mixture was quenched by addition 0.5N HCl 30 mL. The organic layer were washed with H_2O (30 mL) and brine (50mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give compound **58D** (3.4 g, yield 89.2%) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.15 - 7.07 (m, 2H), 7.01 - 6.90 (m, 2H), 4.94 - 4.70 (m, 1H), 4.52 - 4.36 (m, 1H), 4.16 - 3.67 (m, 1H), 3.11 - 2.78 (m, 2H), 1.57 - 1.47 (m, 2H).

[0625] To a solution of compound **58D** (3.42 g 11.62 mmol) and K_2CO_3 (3.21 g, 23.24 mmol) in DMSO (30 mL) was added H_2O_2 (395.08 mmol, 12 mL,) at 0 °C. After addition, the reaction mixture was stirred at 0 °C for 1.5 hrs. The reaction mixture was diluted with water (100 mL) and quenched with saturated aqueous $Na_2S_2O_3$ slowly into ice water. The mixture was

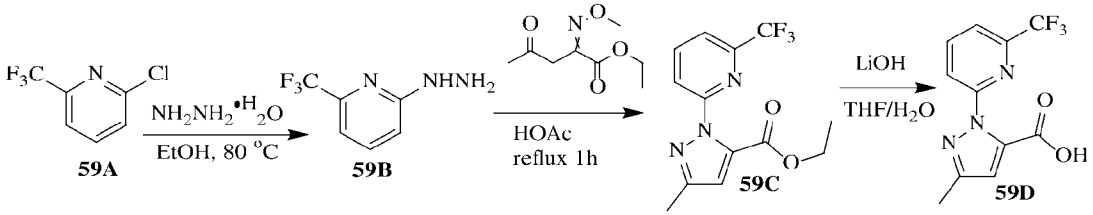
extracted with EtOAc (200 mL x 3) and the combined extracts were washed with saturated aqueous $Na_2S_2O_3$ (100 mL x 3). The organic layer was dried over Na_2SO_4, concentrated and to yield a residue. The residue was diluted with EtOAc (10 mL) and filtered to give the compound **58E** (2.25 g, yield 61.99%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.25 (br s, 6H), 6.62 - 6.03 (m, 1H), 5.75 - 5.55 (m, 1H), 4.02 - 3.67 (m, 2H), 2.80 - 2.52 (m, 2H), 2.52 - 2.51 (m, 1H), 1.26 (d, *J*=3.7 Hz, 9H). MS (ESI) *m/z* (M +Na$^+$) 334.9.

[0626] To a solution of compound **58E** (1 g 3.20 mmol) in EtOAc (10 mL) was added HCl/EtOAc (4 mmol, 20 mL). The mixture was stirred at 28 °C for 2 hrs. The reaction mixture diluted with MTBE and filtered to give the compound **58F** (750 mg, yield 94.25%) as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.25 - 7.94 (m, 3H), 7.58 - 7.43 (m, 2H), 7.41 - 7.33 (m, 1H), 7.30 - 7.23 (m, 1H), 7.41 - 7.23 (m, 1H), 7.20 - 7.05 (m, 2H), 6.90 - 6.37 (m, 1H), 6.80 - 6.25 (m, 1H), 4.24 (br s, 1H), 3.88 - 3.81 (m, 1H), 3.85 (br s, 1H), 3.68 - 3.50 (m, 1H), 2.96 - 2.76 (m, 2H). MS (ESI) *m/z* (M +H)$^+$ 213.1.

[0627] Compound **58** (130 mg, yield 78.40%, light yellow solid) was prepared as in Example **15** from the corresponding intermediate compounds, **23A** and **58F**. Compound **58**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.05 (d, *J*=7.7 Hz, 1H), 8.20 (br s, 1H), 7.93 (brs, 1H), 7.66 - 7.59 (m, 2H), 7.55 - 7.49 (m, 1H), 7.48 - 7.41 (m, 2H), 7.35 - 7.26(m, 2H), 7.17 - 7.06 (m, 2H), 5.51 - 5.40 (m, 1H), 3.28 - 3.19 (m, 1H), 2.81 - 2.69 (m, 1H), 2.11 (s, 3H). MS (ESI) *m/z* (M +H)$^+$ 396.1.

EXAMPLE 32

(*S*)-*N*-(4-AMINO-1-(1*H*-INDOL-3-YL)-3,4-DIOXOBUTAN-2-YL)-3-METHYL-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (59)



[0628] To a solution of compound **59A** (10 g, 55.08 mmol) in EtOH (30 mL) was added $NH_2NH_2.H_2O$ (32 mL, 550.80 mmol). After addition, the reaction mixture was stirred at 80 °C for 14 hrs. The reaction mixture was concentrated and the residue was dissolved into 150 mL of EtOAc, the mixture was washed with water (50 mL) and brine (50 mL), then dried over

Na_2SO_4 and concentrated in vacuum to afford compound **59B** (9.7 g, yield 99.4%) as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.71 - 7.53 (m, 1H), 7.03 - 6.79 (m, 2H), 4.23 (s, 2H).

[0629] To a solution of compound **59B** (1 g, 5.65 mmol) in AcOH (10 mL) was added ethyl 2-methoxyimino-4-oxo-pentanoate (1.1 g, 5.65 mmol). After addition, the reaction mixture was stirred at 120 °C for 14 hrs. The mixture was concentrated in vacuum and the residue was dissolved into 80 mL of EtOAc, the mixture was washed with 30 mL of saturated aqueous $NaHCO_3$ and brine (30 mL). The mixture was dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 20/1 to 10:1) to afford desired compound **59C** (1.2 g, yield: 71%) as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.34 - 8.25 (m, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 7.5 Hz, 1H), 6.86 (s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.29 (s, 3H), 1.11 (t, J = 7.1 Hz, 3H). MS (ESI) *m/z* $(M+H)^+$ 299.9.

[0630] To a solution of compound **59C** (700 mg, 2.34 mmol) in THF (10 mL) was added a solution of $LiOH.H_2O$ (393 mg, 9.36 mmol) in H_2O (10 mL) at 0 °C. After addition, the reaction mixture was stirred at 28 °C for 16 hrs, 20 mL of MTBE was added into the reaction mixture, then the mixture was separated and the aqueous layer was acidified by 1N HCl to pH ~ 4, the mixture was filtered to afford white solid which was dried to afford compound **59D** (330 mg, yield 51.95%) as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 13.48 (br s, 1H), 8.31 - 8.22 (m, 1H), 8.02- 7.89 (m, 2H), 6.81 (s, 1H), 2.27 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 271.8.

[0631] Compound **59** (50 mg, yield: 37.9%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **59D**. Compound **59**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.07 (d, J = 7.3 Hz, 1H), 8.27 - 8.16 (m, 1H),8.04 (s, 1H), 7.89 - 7.77 (m, 3H), 7.30 - 7.19 (m, 5H), 6.59 (s, 1H), 5.40 - 5.28 (m,1H), 3.15 (dd, J = 4.0, 13.8 Hz, 1H), 2.82 (dd, J = 9.5, 13.8 Hz, 1H), 2.30 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 446.1.

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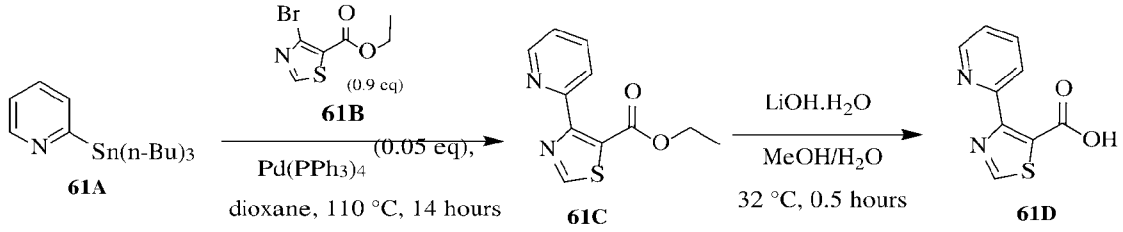
EXAMPLE 33

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (61)



[0632] A mixture of compound **61B** (500 mg, 2.12 mmol), compound **61A** (859 mg, 2.33 mmol), $Pd(PPh_3)_4$ (122 mg, 106 umol) was stirred at 105 °C for 14 hours. The mixture was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 3/1 to 1/1) to afford compound **61C** (376 mg, 74.95% yield) as yellow oil. MS (ESI) *m/z* $(M+H)^+$ 234.9.

[0633] To a solution of compound **61C** (320 mg, 1.37 mmol) in MeOH (20 mL) was added $LiOH.H_2O$ (144 mg, 3.43 mmol). The mixture was stirred at 32 °C for 0.5 h. MeOH was evaporated. To the residue was added water (20 mL). The mixture was extracted with MTBE (5 mL) and separated. The aqueous layer was acidified to pH~ 3 with 1N HCl and extracted with Ethyl Acetate (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford compound **61D** (220 mg, 77.9% yield) as white solid.

[0634] Compound **61** (21.8 mg, 21.78% yield, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **61D**. Compound **61**: ^1H NMR (400MHz, DMSO-d_6) δ 13.06 - 12.79 (m, 1H), 9.27 (s, 1H), 8.95 - 8.84 (m, 1H), 8.42 - 8.32 (m, 1H), 8.32 - 8.24 (m, 1H), 8.13 - 8.00 (m, 1H), 7.55 - 7.45 (m, 1H), 7.21 - 7.10 (m, 3H), 7.22 - 7.03 (m, 2H), 5.70 - 5.59 (m, 1H), 3.32 - 3.25 (m, 1H), 3.20 - 3.12 (m, 1H), 2.85 - 2.74 (m, 1H), 0.72 - 0.63 (m, 2H), 0.63 - 0.54 (m, 2H). MS (ESI) *m/z* $(M+H)^+$ 421.1.

EXAMPLE 34

(*S*)-*N*-(1-amino-1,2-dioxoheptan-3-yl)-3-methyl-5-phenylisoxazole-4-carboxamide (62)

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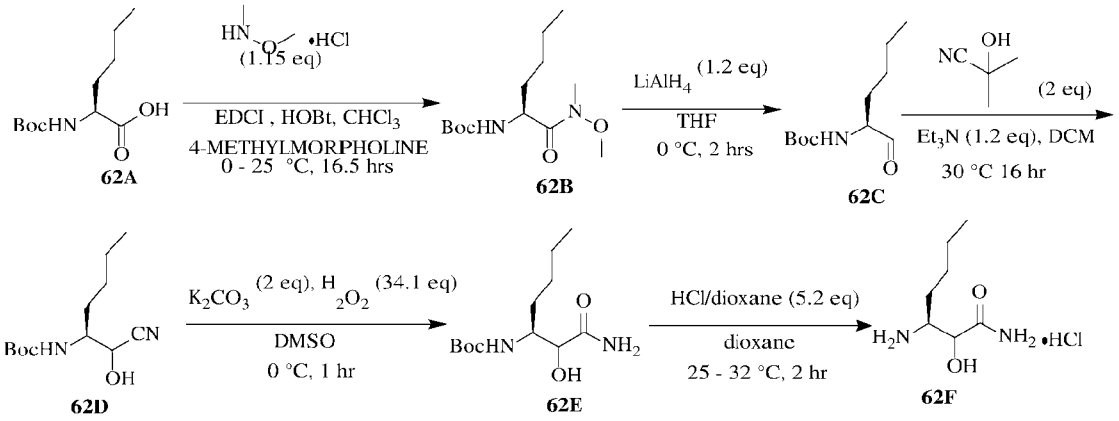

[0635] To a mixture of compound **62A** (2 g, 8.65 mmol) and compound N,O-dimethylhydroxylamine hydrochloride (970.3 mg, 9.95 mmol), HOBt (1.34g, 9.95 mmol) in $CHCl_3$ (40 mL) was added dropwise 4-methylmorpholine (2.62 g, 25.95 mmol) and EDCI (2.32 g, 12.11 mmol) in portion at 0 °C under N_2 atmosphere. The mixture was stirred at 0 °C for 30 min, and then the mixture was stirred at 25 °C for 16 hours. The reaction mixture was diluted with H_2O (5 mL). The two layers were separated and the aqueous phase was extracted with EA (5 mL x 2). The combined organic layers were washed with 0.5 N HCl (5 mL x 2) and $NaHCO_3$ (5 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give compound **62B** (1.7 g, yield 71.7%) as colorless oil. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.19 - 5.06 (m, 1H), 4.66 (br s, 1H), 3.77 (s, 3H), 3.20 (s, 3H), 1.76 - 1.66 (m, 1H), 1.55 - 1.39 (m, 10H), 1.37 - 1.28 (m, 4H), 0.93 - 0.83 (m, 3H). MS (ESI) *m/z* $(M - Boc + H)^+$ 175.0.

[0636] To a solution of $LiAlH_4$ (258.7 mg, 6.82 mmol) in THF (36 mL) was added drop wise a solution of compound **62B** (1.7 g, 6.2 mmol) in THF (18 mL) at 0 °C under N_2 atmosphere. After addition, the reaction mixture was stirred at 0 °C for 2 hours. The mixture was diluted with ethyl acetate (100 mL), washed with 1N HCl (20 mL), saturated $NaHCO_3$ (20 mL x 2), brine (15 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give compound **62C** (1.5 g, crude) as yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.58 (s, 1H), 5.03 (br s, 1H), 4.28 - 4.16 (m, 1H), 1.58 - 1.19 (m, 15H), 1.01 - 0.80 (m, 3H).

[0637] A solution of compound **62C** (1.5 g, 6.97 mmol), compound 2-hydroxy-2-methylpropanenitrile (1.3 mL, 13.94 mmol) and Et_3N (1.16 mL, 8.36 mmol) in dry DCM (30 mL) was stirred at 30 °C for 16 hours. The reaction mixture was diluted with DCM (50 mL), washed with 0.5 N HCl (20 mL), water (20 mL)and brine(20 mL). The

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organic phase was dried over Na_2SO_4, concentrated. The residue was purified by column chromatography (SiO_2, Petroleum Ether/Ethyl Acetate = 5/1 to 3:1) to afford compound **62D** (1.12 g, 66.32% yield) as white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 5.44 - 4.34 (m, 3H), 3.94 - 3.83 (m, 1H), 3.74 - 3.61 (m, 1H), 3.98 - 3.55 (m, 1H), 1.66 - 1.28 (m, 14H), 0.99 - 0.90 (m, 3H).

[0638] The mixture of compound **62D** (1.12 g, 4.62 mmol) and K_2CO_3 (1.28 g, 9.24 mmol) in DMSO (18 mL) was added H_2O_2 (4.6 mL, 158.19 mmol) at 0 °C. After addition, the reaction mixture was stirred at 0 °C for 1h. After the reaction, MTBE (20 mL) was added to the reaction mixture, and the resulting mixture was filtered and the solid was washed with MTBE (30 mL) to afford compound **62E** (1.1 g, 91.46% yield) as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.32 - 7.08 (m, 2H), 6.42 - 5.86 (m, 1H), 5.54 - 5.30 (m, 1H), 3.88 - 3.59 (m, 2H), 1.42 - 1.21 (m, 15H), 0.92 - 0.78 (m, 3H).

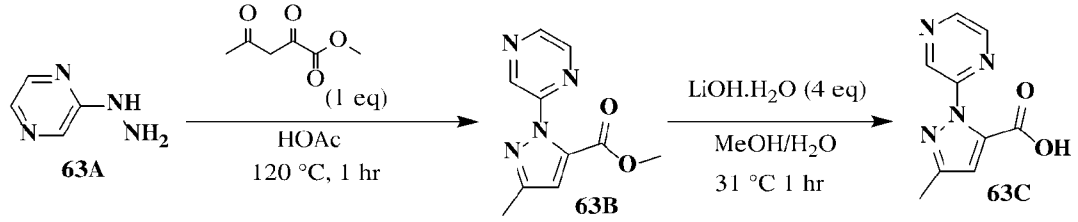
[0639] The solution of compound **62E** (600 mg, 20.82 mmol) in dioxane (10 mL) was added HCl/dioxane (3 mL, 4M) at 25 °C. The reaction mixture was stirred at 25 °C for 2 hours. The mixture was filtered to afford compound **62F** (320 mg, 70.7%, yield, HCl) was obtained as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (br s, 2H), 7.54 - 7.35 (m, 2H), 6.26 - 6.17 (m, 1H), 4.09 (br s, 1H), 1.66 - 1.37 (m, 2H), 1.37 - 1.12 (m, 5H), 0.93 - 0.72 (m, 3H)

[0640] Compound **62** (9.1 mg, yield: 38.6%, white solid) was prepared as in Example **15** from the corresponding intermediate compounds, **23A** and **62F**. Compound **62**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84-7.67 (m, 2H), 7.57 - 7.43 (m, 3H), 6.73 (s, 1H), 6.17-6.03 (m, 1H), 5.52 – 5.29 (m, 2H), 2.46 (s, 3H), 1.99 - 1.84 (m, 1H), 1.41-1.04 (m, 5H), 0.90-0.78 (m, 3H). MS (ESI) m/z (M+H)+ 344.1.

EXAMPLE 35

COMPOUNDS 63, 454

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(PYRAZIN-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (63)



AMENDED SHEET
IPEA/AU

[0641] To a solution of compound methyl 2,4-dioxopentanoate (100 mg, 693.82 umol) in AcOH (20 mL) was added compound **63A** (76.4 mg, 693.82 umol). The mixture was stirred at 120 °C for 1 hour. The mixture was in DCM (5 mL). The organic layer was washed with water (10 mL), $NaHCO_3$ to pH ~ 8~9 and dried over Na_2SO_4 and concentrated to afford compound **63B** (500 mg, 25.24% yield) as white solid.

[0642] To a solution of compound **63B** (61 mg, 279.55 umol,) in MeOH (6 mL) and H_2O (1 mL) was added $LiOH.H_2O$ (46.9 mg, 1.12 mmol). The mixture was stirred at 31 °C for 1h. MeOH was evaporated. To the residue was added water (10 mL) and the mixture was extracted with MTBE (5 mL) and separated. The aqueous layer was acidified to pH ~ 3 with 1N HCl and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford the product. (50 mg, 87.59% yield) as white solid.

[0643] Compound **63** (25.1 mg, 63.1% yield, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **63C**. Compound **63**: ^{1}H NMR (400MHz, $CDCl_3$) δ 9.16 (s, 2 H), 9.08- 8.97 (m, 1H), 8.44 (s, 1H), 7.95 (s, 1H), 7.20 (s, 3 H), 7.08 (s, 2H), 5.78 (m, 1H), 5.54 (s, 1H), 3.45 (m, 1H), 3.38 - 3.24 (m, 1H), 2.36 (s, 3H). MS (ESI) *m/z* $(M+H)^-$ 379.1.

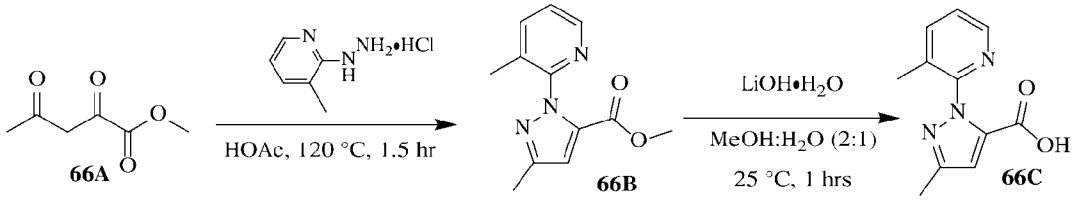
N-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(PYRAZIN-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (454)

[0644] Compound **454** (210 mg, 91.7% yield, white solid) was prepared as in compound **12** from the corresponding intermediate carboxylic acid, compound **63C** and 3-amino-*N*-cyclopropyl-2-hydroxy-4-phenylbutanamide hydrochloride. Compound **454**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.07 (d, J = 7.2 Hz, 1H), 8.84 - 8.77 (m, 2H), 8.57 (d, J = 2.8 Hz, 1H), 8.31 - 8.27 (m, 1H), 7.30 - 7.17 (m, 5H), 6.64 (s, 1H), 5.33 - 5.25 (m, 1H), 3.17 - 3.09 (m, 1H), 2.83 - 2.70 (m, 2H), 2.27 (s, 3H), 0.69 - 0.53 (m, 4H). MS (ESI) *m/z* $(M+H)^+$ 419.2.

PCT/US2017/053629
Received 4/1/2019

EXAMPLE 36

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(3-METHYLPYRIDIN-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (66)



66A 66B 66C

[0645] A mixture of compound 2-hydrazinyl-3-methylpyridine hydrochloride (2 g, 12.53 mmol) and compound **66A** (1.81 g, 12.53 mmol) in AcOH (30 mL) was degassed and purged with N_2 for 3 times, and then stirred at 120 °C for 1.5 hrs under N_2 atmosphere. The resultant mixture was concentrated under reduced pressure to remove AcOH and diluted with DCM (10 mL), neutralized with saturated aqueous $NaHCO_3$. The mixture was extracted with DCM (20 mL x 3) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (Petroleum ether : Ethyl acetate = 1:0 to 0:1) to afford compound **66B** (800.0 mg, 27.6% yield) as a white solid and compound **66B-1** (110.0 mg, 4.04% yield) as a white solid and crude **66B-1** (~ 800.0 mg).

[0646] Compound **66B**: Methyl 3-methyl-1-(3-methylpyridin-2-yl)-1H-pyrazole-5-carboxylate: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.42 - 8.37 (m, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 6.79 (s, 1H), 3.74 (s, 3H), 2.38 (s, 3H), 2.14 (s, 3H).

[0647] Compound **66B-1**: Methyl 5-methyl-1-(3-methylpyridin-2-yl)-1H-pyrazole-3-carboxylate: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.42 (d, J =3.6 Hz, 1H), 7.72 (d, J=6.8 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 6.74 (s, 1H), 3.92 (s, 3H), 2.26 (s, 3H), 2.20 (s, 3H).

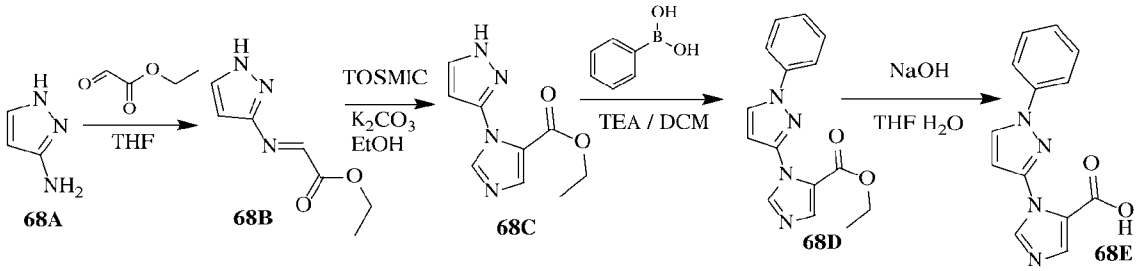
[0648] To a mixture of compound **66B** (200.0 mg, 864.86 umol) in MeOH (10 mL) and H_2O (5 mL) was added LiOH•H_2O (145.2 mg, 3.46 mmol) in one portion. After stirred at 25 °C for 1 hour, the reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was diluted with H_2O (10 mL), adjusted to pH ~ 3 with 1N HCl, and then extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give compound **66C** (150 mg, 79.84% yield, white solid). Compound **66C**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.11

(br s, 1H), 8.31 (d, J = 3.7 Hz, 1H), 7.84 (d, J = 7.3 Hz, 1H), 7.47 -7.40 (m, 1H), 6.78 (s, 1H), 2.25 (s, 3H), 2.03 (s, 3H). MS (ESI) m/z $(M+1)^+$ 218.1.

[0649] Compound **66** (24.5 mg, 54.7% yield, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **66C**. Compound **66**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, J = 3.6 Hz, 1H), 7.67 (d, J = 7.2 Hz, 1H), 7.34 (d, J = 7.2 Hz, 1H), 7.27 (br s, 1H), 7.25 - 7.21 (m, 3H), 7.04 - 6.99 (m, 2H), 6.70 (br s, 1H), 6.57 (s, 1H), 5.65 - 5.6 (m, 1H), 5.57 (br s, 1H), 3.37 - 3.29 (m, 1H), 3.2 - 3.14 (m, 1H), 2.34 (s, 3H), 2.17 (s, 3H). MS (ESI) m/z $(M+H)^+$ 392.2.

EXAMPLE 37

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(1-PHENYL-1*H*-PYRAZOL-3-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (68)



[0650] To a solution of **68A** (15 g, 181 mmol) in THF (200 mL) was added ethyl 2-oxoacetate (47.9 g, 235 mmol). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was filtered and concentrated under reduced pressure to give intermediate compound **68B** (55.3 g, crude) as brown solid. MS (ESI) m/z $(M+H)^+$ 167.8.

[0651] To a solution of **68B** (40 g, 239 mmol) in EtOH (400 mL) was added K_2CO_3 (50 g, 362 mmol) and TosMIC (40 g, 204.88 mmol). The mixture was stirred at 90 °C for 0.5 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 5: 2) to afford compound **68C** (12 g, yield: 24.3%) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.80 - 11.35 (m, 1H), 7.87 (d, J = 1.10 Hz, 1H), 7.84 (d, J = 1.10 Hz, 1 H), 7.58 (d, J = 2.43 Hz, 1H), 6.45 (d, J = 2.43 Hz, 1H), 4.25 (q, J = 7.06 Hz, 2H), 1.29 (t, J = 7.17 Hz, 3H). MS (ESI) m/z $(M+H)^+$ 207.0.

[0652] A mixture of **68C** (5 g, 24.3 mmol), phenylboronic acid (4.4 g, 36.4 mmol), $Cu(OAc)_2$ (4.4 g, 24.3 mmol), TEA (7.4 g, 72.8 mmol) in DCM (200 mL) was degassed and

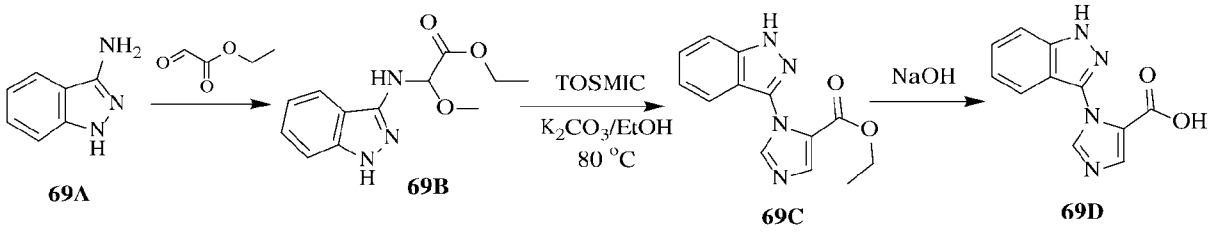
purged with O_2 for 3 times, and then the mixture was stirred at 25 °C for 10 hours under O_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 2: 1). Compound **68D** (2.3 g, yield: 33.6%) was obtained as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.04 - 7.94 (m, 2H), 7.87 (s, 1H), 7.71 (br d, J = 7.7 Hz, 2H), 7.49 (br t, J = 7.1 Hz, 2H), 7.36 (br d, J = 7.1 Hz, 1H), 7.27 (d, J = 2.0 Hz, 2H), 6.70 - 6.61 (m, 1H), 4.29 (dd, J = 2.1, 7.2 Hz, 2H), 1.38 - 1.22 (m, 3H). MS (ESI) m/z $(M+H)^+$ 282.9.

[0653] To a solution of **68D** (2.5 g, 8.86 mmol) in THF (30 mL) and H_2O (6 mL) was added NaOH (708 mg, 17.7mmol). The mixture was stirred at 80°C for 1.5 hour. The reaction mixture was concentrated under reduced pressure to remove THF, and then washed with EtOAc (20 mL). The aqueous layer was acidized with 1M HCl to pH ~ 5 and then extracted with EtOAc (30 mL x 3). The combined organic layer was washed with H_2O (40 mL), brine (40 mL), dried over Na_2SO_4, filtered and concentrated to afford crude intermediate compound **68E** (1.90 g, yield: 84.3%) as yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.62 (d, J = 2.6 Hz, 1H), 8.19 (s, 1H), 7.86 (d, J = 7.9 Hz, 2H), 7.76 (s, 1H), 7.53 (t, J = 7.9 Hz, 2H), 7.39 - 7.31 (m, 1H), 6.77 (d, J = 2.6 Hz, 1H). MS (ESI) m/z $(M+H)^+$ 254.9.

[0654] Compound **68** (33.5 mg, yield: 42.1%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **68E**. Compound **68**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (d, J = 7.7 Hz, 1 H), 8.51 (d, J = 2.6 Hz, 1 H), 8.10 (d, J = 0.9 Hz, 1 H), 8.06 (s, 1 H), 7.79 (dd, J = 8.7, 1.0 Hz, 3 H), 7.60 (d, J = 0.9 Hz, 1 H), 7.46 - 7.53 (m, 2 H), 7.30 - 7.36 (m, 1 H), 7.24 - 7.29 (m, 4 H), 7.16 - 7.23 (m, 1 H), 6.44 (d, J = 2.6 Hz, 1 H), 5.23 - 5.32 (m, 1 H), 3.17 (dd, J = 13.8, 3.9 Hz, 1 H), 2.83 (dd, J = 13.9, 10.4 Hz, 1 H). MS (ESI) m/z $(M+H)^+$ 429.1.

EXAMPLE 38

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(1*H*-INDAZOL-3-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (69)



[0655] To a solution of **69A** (8.7 g, 65.3 mmol) in MeOH (90 mL) was added ethyl 2-oxoacetate (20 g, 98.01 mmol). The mixture was stirred at 25 °C for 2 hours. The mixture was filtered and concentrated to give intermediate compound **69B** (15 g, crude) as brown solid.

[0656] To a solution of **69B** (15 g, 69.1 mmol) in EtOH (400 mL) was added K_2CO_3 (14.5 g, 104 mmol) and TosMIC (11.6 g 59.4 mmol). The mixture was stirred at 90 °C for 0.5 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1:0 to 1:1) to give compound **69C** (2.9 g, yield: 16.4%) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 11.04 (br s, 1H), 7.98 (d, J = 0.7 Hz, 1H), 7.91 (s, 1H), 7.48 - 7.41 (m, 3H), 7.25 - 7.19 (m, 1H), 4.24 - 4.14 (m, 2H), 1.14 (t, J = 7.1 Hz, 3H).

[0657] To a solution of **69C** (2.9 g, 11.3 mmol) in THF (40 mL) and H_2O (8 mL) was added NaOH (905 mg, 22.6 mmol). The mixture was stirred at 25 °C for 10 hours. The mixture was concentrated under reduced pressure to remove the organic solvent, and extracted with EtOAc (20 mL). The aqueous layer was acidized with 1M HCl to pH ~ 5 and then extracted with EtOAc (30 mL x 3). The combined organic layer was washed with H_2O (40 mL), brine (40 mL), dried over Na_2SO_4, filtered and concentrated to give **69D** (1.5 g, yield: 58.1%) as yellow solid. ^{1}HNMR (400MHz, DMSO-d_6) δ 13.35 (s, 1H), 8.16 (s, 1H), 7.83 (s, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.47 - 7.41 (m, 2H), 7.20 - 7.15 (m, 1H). MS (ESI) m/z $(M+H)^+$ 228.9.

[0658] Compound **69** (16.7 mg, yield: 20.9%, yellow solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **69D**. Compound **69**: ^{1}H NMR (400MHz, DMSO-d_6) δ 13.16 (br s, 1H), 8.84 (br d, J = 7.7 Hz, 1H), 8.08 - 7.95 (m, 2H), 7.80 - 7.70 (m, 2H), 7.52 (d, J = 8.4 Hz, 1H), 7.36 (br t, J = 7.5 Hz, 1H), 7.30 - 7.23 (m, 4H), 7.22 - 7.13 (m, 3H), 7.08 - 7.01 (m, 1H), 5.21 - 5.12 (m, 1H), 3.17 - 3.09 (m, 1H), 2.84 - 2.75 (m, 1H). MS (ESI) m/z $(M+H)^+$ 403.1.

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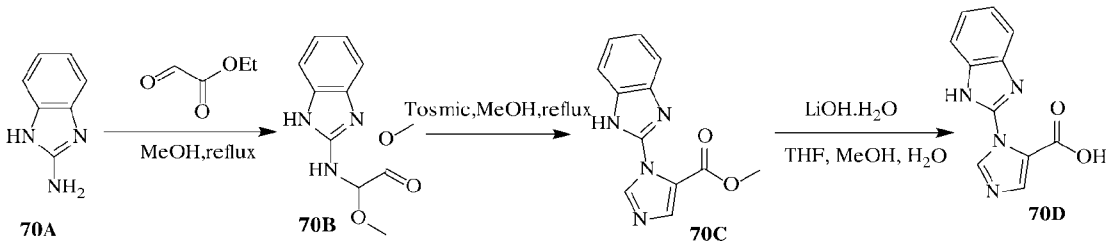
EXAMPLE 39

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(1*H*-BENZO[*d*]IMIDAZOL-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (70)



[0659] A mixture of **70A** (10 g, 75.1 mmol), ethyl 2-oxoacetate (30.6 g, 150 mmol) in MeOH (300 mL) was stirred at 70 °C for 12 hour under N_2 atmosphere. LCMS showed **70A** was consumed completely and one peak with desired MS was detected. The reaction mixture was concentrated under reduced pressure to give crude product **70B** (15 g, crude) as yellow oil. MS (ESI) *m/z* $(M+H)^+$ 235.9.

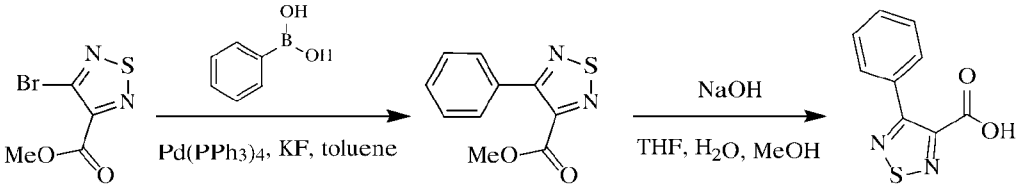
[0660] A mixture of **70B** (15 g, 63.7 mmol), K_2CO_3 (13.2 g, 95.6 mmol), TosMIC (24.9 g, 127 mmol) in MeOH (300 mL) was stirred at 70 °C for 1 hour. LCMS showed **70B** was consumed completely and one small peak with desired MS was detected. TLC (Petroleum ether : Ethyl acetate = 1:1, R_f ~ 0.3) indicated **70B** was consumed completely and one new spot formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Petroleum ether/Ethyl acetate = 10/1 to 1:1) to give **70C** (350 mg, yield: 2.3%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.52 (br s, 1 H) 8.96 (s, 1 H) 7.98 (s, 1 H) 7.69 (br d, J = 4.4 Hz, 1 H) 7.48 (br s, 1 H) 7.28 (br dd, J = 5.8, 2.8 Hz, 2 H) 3.99 (s, 3 H). MS (ESI) *m/z* $(M+H)^+$ 243.1.

[0661] A mixture of **70C** (350 mg, 1.44 mmol), LiOH.H_2O (120 mg, 2.88 mmol) in THF (5 mL), H_2O (2 mL) was stirred at 25 °C for 4 hours. LCMS showed **70C** was consumed completely and one peak with desired MS was detected. The reaction mixture was added aqueous HCl (1M) to adjust the pH ~ 5, filtered and the filtered cake was concentrated under reduced pressure. The filtered cake was washed with water. Compound **70D** (230 mg, yield: 70.1%) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (d, J = 1.3 Hz, 1 H) 7.38 - 7.63 (m, 3 H) 7.03 - 7.22 (m, 1 H) 7.03 - 7.17 (m, 1 H). MS (ESI) *m/z* $(M+H)^+$ 229.0.

[0662] Compound **70** (40 mg, yield: 46.7%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **70D**. Compound **70**: ^{1}HNMR (400MHz, DMSO-d_6) δ 12.94 (br s, 1H), 9.31 (br s, 1H), 8.38 - 8.23 (m, 1H), 8.04 (br s, 1H), 7.87 - 7.74 (m, 2H), 7.60 - 7.43 (m, 2H), 7.29 - 7.10 (m, 6H), 5.33 (br t, J = 6.6 Hz, 1H), 3.17 (br dd, J = 3.1, 13.9 Hz, 1H), 3.22 - 3.09 (m, 1H), 2.84 (br dd, J = 10.3, 13.8 Hz, 1H), 2.91 - 2.74 (m, 1H). MS (ESI) m/z $(M+H)^+$ 403.1.

EXAMPLE 40

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-PHENYL-1,2,5-THIADIAZOLE-3-CARBOXAMIDE (72)



72A **72B** **72C**

[0663] A mixture of compound **72A** (800 mg, 3.59 mmol) and phenylboronic acid (1.31 g, 10.8 mmol) in toluene (10 mL) and H_2O (500 uL) was added KF (417 mg, 7.18 mmol) and $Pd(PPh_3)_4$ (414 mg, 359 umol) under N_2. Then the reaction mixture was stirred at 100 °C under N_2 for 16hrs. The solvent was evaporated. The crude product was purified by silica gel column (petroleum ether: ethyl acetate = 20: 1 to 5: 1) to give compound **72B** (400 mg, crude) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 - 7.68 (m, 2H), 7.48 - 7.46 (m, 3H), 3.94 (s, 3H).

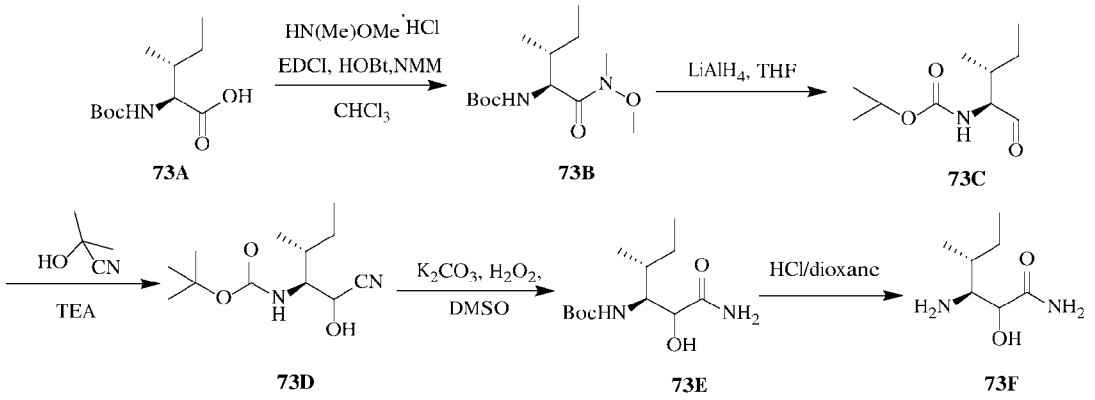
[0664] A solution of compound **72B** (500 mg, 2.27 mmol) in THF (5 mL), H_2O (5 mL) and MeOH (5 mL) was added NaOH (182 mg, 4.54 mmol). The reaction mixture was stirred at 20 °C for 1hr. 1M HCl was added to the reaction mixture until pH ~ 4. The solvent was evaporated to give a crude product **72C** (500 mg, crude) as a white solid. The crude product was used in the next step without purification.

[0665] Compound **72** (50.5 mg, yield: 43.9%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **72C**. Compound **72**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (d, J = 7.7 Hz, 1H), 8.18 (s, 1H), 7.91 (s, 1H), 7.60 - 7.55 (m, 2H), 7.48 - 7.43 (m, 1H), 7.42 - 7.36 (m, 2H), 7.31 - 7.22 (m, 5H), 5.51 (ddd, J = 3.6, 7.7,

10.0 Hz, 1H), 3.23 (dd, J = 3.6, 14.0 Hz, 1H), 2.87 (dd, J = 10.1, 14.1 Hz, 1H). MS (ESI) m/z $(M+H)^+$ 381.0.

EXAMPLE 41

N-((3*S*,4*R*)-1-AMINO-4-METHYL-1,2-DIOXOHEXAN-3-YL)-3-METHYL-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (73)



[0666] A mixture of N-methoxymethanamine (2.32 g, 23.78 mmol), compound **73A** (5.00 g, 21.62 mmol), HOBt (2.92 g, 21.62 mmol) and NMM (6.56 g, 64.86 mmol) in $CHCl_3$ (100 mL) was degassed and purged with N_2 for 3 times at 0 °C, then EDCI (6.22 g, 32.43 mmol) was added in portions. The mixture was stirred at 25 °C for 16 hrs under N_2 atmosphere. The reaction mixture was quenched by addition H_2O (100 mL). The organic layers were washed with HCl (1N, 100 mL x 2), and saturated $NaHCO_3$ (100 mL x 2), and saturated brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of 0~10% Ethyl acetate/Petroleum ether gradient) to give compound **73B** (5.0 g, yield: 84.3%) as a colorless oil. ^1H NMR (400MHz, $CDCl_3$) δ 5.10 (d, J=9.5 Hz, 1H), 4.67 - 4.53 (m, 1H), 3.76 (s, 3H), 3.20 (s, 3H), 1.70 (qt, J = 6.8, 9.9 Hz, 1H), 1.54 - 1.51 (m, 1H), 1.41 (s, 9H), 1.15 - 1.07 (m, 1H), 0.91 - 0.85 (m, 6H). MS (ESI) m/z $(M + Na^+)$ 296.9.

[0667] To a solution of $LiAlH_4$ (350 mg, 9.22 mmol) in THF (30 mL) was added a solution of compound **73B** (2.30 g, 8.38 mmol) in THF (30 mL) at 0 °C. After addition, the reaction mixture was stirred for 1hr at 5 °C. The reaction mixture was quenched by addition of ethyl acetate (10 mL) and HCl (1N, 10 mL), and extracted with EtOAc (100 mL x 2). The combined organic layers were washed with HCl (1N, 30 mL x 2), sat. $NaHCO_3$ (30 mL x 3), and brines (30mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give

compound **73C** (1.50 g, yield: 83.2%) as a colourless oil. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.45 (d, J = 1.3 Hz, 1H), 7.22 (br d, J = 7.5 Hz, 1H), 3.79 (br t, J= 6.4 Hz, 1H), 1.89 - 1.75 (m, 1H), 1.42 - 1.32 (m, 10H), 1.25 - 1.10 (m, 1H), 0.86 (d, J=6.8 Hz, 3H), 0.81 (t, J=7.4 Hz, 3H). MS (ESI) m/z $(M+H)^+$ 216.0.

[0668] To a solution of compound **73C** (1.5 g, 6.97 mmol) in DCM (10 mL) was added 2-hydroxy-2-methylpropanenitrile (1.28 mL, 13.93 mmol) and TEA (1.16 mL, 8.36 mmol), and then stirred at 25 °C for 14 hours. The reaction mixture was diluted with DCM (25 mL), washed with HCl (1N, 20 mL x 2), H_2O (30 mL), and brine (30mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give compound **73D** (1.5 g, yield: 88.8%) as a colorless liquid. ^{1}H NMR (400MHz, $CDCl_3$) δ 5.24 - 5.08 (m, 1H), 4.92 - 4.56 (m, 1H), 3.90 - 3.25 (m, 1H), 2.04 - 1.80 (m, 1H), 1.66 - 1.52 (m, 1H), 1.50 - 1.40 (m, 9H), 1.33 - 1.09 (m, 2H), 1.02 - 0.75 (m, 6H).

[0669] To a solution of compound **73D** (1.50 g, 6.19 mmol) and K_2CO_3 (1.71 g, 12.38 mmol) in DMSO (15 mL) was added H_2O_2 (7.21 g, 211.95 mmol) at 0 °C. After addition, the reaction mixture was stirred at 0 °C for 1h. The reaction mixture was diulted with water (20 mL) and quenched with saturated aqueous $Na_2S_2O_3$ slowly at ice water. The mixture was extracted with EtOAc (50 mL x 3) and the combined extracts were washed with saturated aqueous $Na_2S_2O_3$ (30 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (eluent of 0 ~ 20% Ethyl acetate/Petroleum ethergradient) to give compound **73E** (870 mg, yield: 54.0%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.31 - 6.97 (m, 2H), 6.29 - 5.87 (m, 1H), 5.44 - 5.12 (m, 1H), 3.99 - 3.80 (m, 1H), 3.71 - 3.50 (m, 1H), 1.67 - 1.41 (m, 2H), 1.39 - 1.30 (m, 9H), 1.11 - 0.92 (m, 1H), 0.89 - 0.75 (m, 6H). MS (ESI) m/z $(M + Na)^+$ 282.9.

[0670] To a solution of compound **73E** (870 mg, 3.34 mmol) in EtOAc (10 mL) was added HCl/EtOAc (4M, 16.70 mL) at 0 °C. After addition, the reaction mixture was stirred at 25 °C for 2 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was washed with MTBE (30 mL), filtered to give compound **73F** (620 mg, yield: 94.4%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.14 - 7.71 (m, 3H), 7.64 - 7.37 (m,

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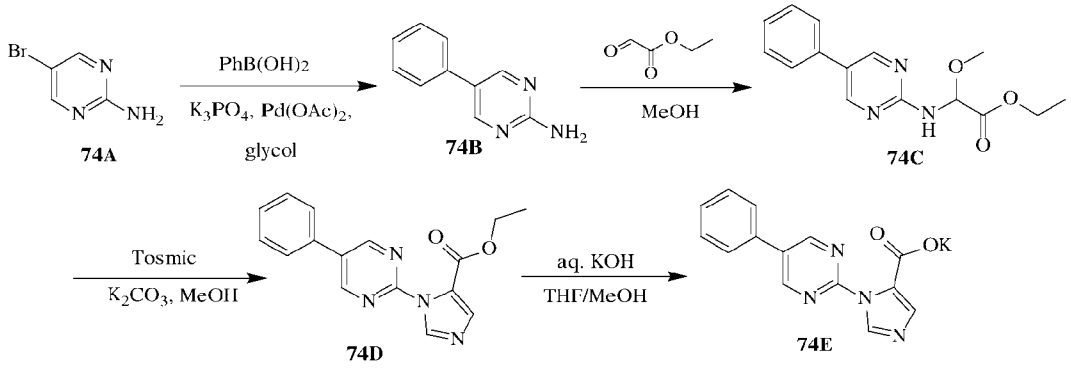
2H), 6.57 - 6.28 (m, 1H), 4.32 - 3.99 (m, 1H), 3.21 (br s, 1H), 1.82 - 1.43 (m, 2H), 1.30 - 1.03 (m, 1H), 0.99 - 0.71 (m, 6H). MS (ESI) *m/z* $(M+H)^+$ 161.1.

[0671] Compound **73** (100 mg, yield: 63.6%, white solid) was prepared as in Example **15** from the corresponding intermediate compounds, **23A** and **73F**. Compound **73**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.92 (d, J = 7.0 Hz, 1H), 8.15 (s, 1H), 7.96 - 7.65 (m, 3H), 7.62 - 7.44 (m, 3H), 5.19 (t, J = 6.5 Hz, 1H), 3.33 (br s, 1H), 2.30 (s, 3H), 2.10 - 1.94 (m, 1H), 1.36 - 1.13 (m, 2H), 0.92 (d, J = 6.8 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H). MS (ESI) *m/z* $(M+H)^+$ 344.1.

EXAMPLE 42

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(5-PHENYLPYRIMIDIN-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (74)



[0672] The mixture of compound **74A** (10.0 g, 57.47 mmol), phenylboronic acid (10.5 g, 86.21 mmol), K_3PO_4 (24.4 g, 114.94 mmol), $Pd(OAc)_2$ (1.3 g, 5.75 mmol) in ethylene glycol (200 mL) was stirred at 80 °C for 12 hrs. The reaction mixture was added to H_2O (200 mL), the insoluble substance was removed by filtration; the filtrate was extracted with ethyl acetate (200 mL x 3). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (150 mL x 3), saturated aqueous NaCl (150 mL x 3), dried over Na_2SO_4 and concentrated in vacuum. The resulting solid was treated with ethyl acetate (10 mL). The precipitate was filtered and dried in vacuum to afford compound **74B** (4.97 g, yield: 50.5%) as light yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.55 (s, 2H), 7.62 - 7.58 (m, 2H), 7.43 - 7.40 (m, 2H), 7.33 - 7.27 (m, 1H), 6.76 (br.s., 2H).

[0673] The mixture of compound **74B** (3.0 g, 17.35 mmol) and compound ethyl 2-oxoacetate (2.3 g, 22.55 mmol) in MeOH (50 mL) was stirred at 80 °C for 12 hrs. The reaction mixture was concentrated and the solid was filtered. The resulting solid was treated with MeOH

(10 mL), filtered and dried in vacuum to afford compound **74C** (3.23 g, yield: 64.8%) as light yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.71 (s, 2H), 8.24 (d, J = 8.8 Hz, 1H), 7.67 - 7.63 (m, 2H), 7.47 - 7.41 (m, 2H), 7.37 - 7.31 (m, 1H), 5.64 (d, J = 8.8 Hz, 1H), 4.19 - 4.10 (m, 2H), 3.33 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H).

[0674] The mixture of compound **74C** (500 mg, 1.74 mmol), Tosmic (680 mg, 3.48 mmol), K_2CO_3 (720 mg, 5.22 mmol) in absolute EtOH (50 mL) was stirred at 65 °C for 2 hrs. The reaction mixture was concentrated under reduced pressure; the resulting residue was added in water (30 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (SiO2, petroleum ether/ethyl acetate = 15:1 to 8:1) to afford compound **4** (293 mg, yield: 52.2%) as white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.30 (s, 2H), 8.46 (s, 1H), 7.89 (t, J = 7.2 Hz, 2H), 7.76 (s, 1H), 7.59 - 7.49 (m, 3H), 4.23 - 4.13 (m, 2H), 1.17 (t, J = 7.2 Hz, 3H). MS (ESI) m/z $(M+H)^+$ 295.1.

[0675] To the mixture of compound **74D** (1.15 g, 3.91 mmol) in THF (10 mL) and MeOH (10 mL) was added KOH (2M, 1.96 mL, 3.92 mmol) dropwise at 25 °C. The mixture was stirred at 25 °C for 23 hrs, and then concentrated under reduced pressure to afford intermediate compound **74E** (2 g, crude).

[0676] Compound **74** (14.9 mg, yield 28.2%, white solid) was prepared as in Example **5** from the corresponding intermediate compounds **74E** and **12G**. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.60 (br d, J = 6.4 Hz, 1H), 8.64 (br s, 3H), 7.82 (s, 1H), 7.59 - 7.50 (m, 6H), 7.22 - 7.11 (m, 5H), 5.83 (m, 1H), 5.61 (br s, 1H), 3.52 - 3.44 (m, 1H), 3.40 - 3.31 (m, 1H). MS (ESI) m/z $(M+H)^+$ 441.0.

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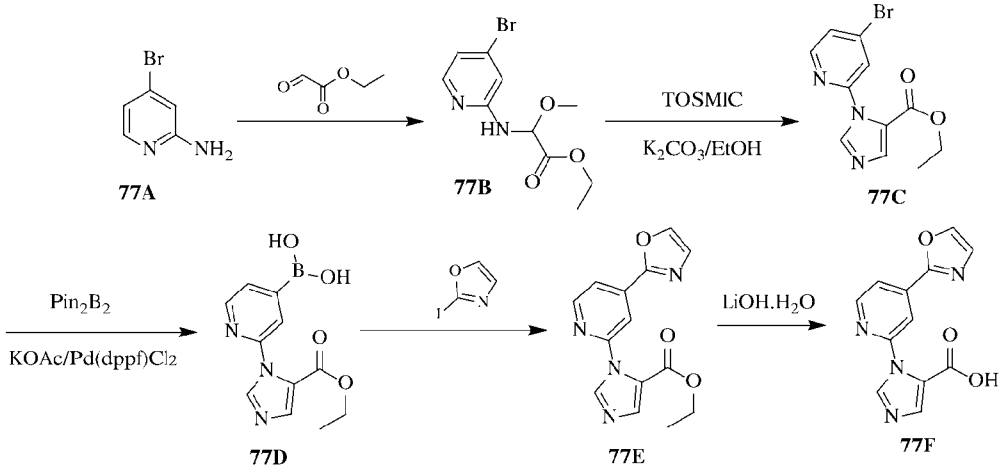
EXAMPLE 43

COMPOUNDS 77, 88

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(4-(OXAZOL-2-YL)PYRIDIN-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (77)



[0677] A mixture of **77A** (20 g, 115.60 mmol) and ethyl 2-oxoacetate (30.7g, 150.28 mmol) in MeOH (300 mL) was heated to 80 °C for 3 hrs. LCMS showed desired MS. TLC (Petroleum ether:Ethyl acetate = 3:1, R_f ~0.8) showed new point, the mixture was concentrated and residue purified by silica gel column (Petroleum ether : Ethyl acetate = 20: 1). Compound **77B** (28.9g, yield 86.5%, yellow solid): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 5.2 Hz, 1 H), 6.86 (dd, J = 5.2, 1.75 Hz, 1 H), 6.77 (d, J = 1.3 Hz, 1 H), 5.75 (br s, 1 H), 5.61 (d, J = 8.3 Hz, 1 H), 4.29 (q, J = 7.0 Hz, 2 H), 3.41 (s, 3 H), 1.37 - 1.31 (m, 3 H).

[0678] A mixture of **77B** (15 g, 51.9 mmol) and K_2CO_3 (21.5 g, 156 mmol) in EtOH (300 mL) was stirred at 80 °C for 0.5 hr, then TosMIC (15.2 g, 77.82 mmol) was added, the resulting mixture was stirred at 80 °C for another 2 hrs. LCMS showed desired MS, most of ethanol was removed and a precipitate was formed, the solid was filtered and washed with water (100 mL x 2), the solid was dried and concentrated to give **77C** (6.4 g, yield: 41.7%), as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 5.2 Hz, 1 H), 7.97 (s, 1 H), 7.85 (s, 1 H), 7.61 (s, 1 H), 7.56 (dd, J = 5.26 1.3 Hz, 1 H), 4.27 (q, J = 7.02Hz, 2 H), 1.29 (t, J = 7.02Hz, 3 H).

[0679] Compound **77C** (3 g, 10.13 mmol), Pin_2B_2 (2.57 g, 10.13 mmol), KOAc (2.98 g, 30.4 mmol) and $Pd(dppf)Cl_2$ (741 mg, 1.01 mmol) in dioxane (100 mL) was de-gassed and then heated at 70 °C for 4 hours under N_2. LCMS showed desired MS, TLC (Ethyl acetate:

Methanol = 10: 1, Rf ~ 0), the mixture was filtered and the filtrate was concentrated, the residue was purified by silica gel chromatography (DCM: Methanol = 5:1) to give **77D** (1.70 g, crude) as black solid.

[0680] Compound **77D** (300 mg, 1.15 mmol), 2-iodooxazole (157 mg, 805.00 umol), $Pd(dppf)Cl_2$ (84.1 mg, 115.00 umol) and Na_2CO_3 (244 mg, 2.30 mmol) in toluene (2 mL), EtOH (2 mL), H_2O (1 mL) was de-gassed and then heated to 120 °C for 1h under microwave condition. LCMS showed desired MS, the mixture was added water (5 mL) and extracted with ethyl acetate (10 mL x 2), the organic phases were dried and concentrated, the residue was purified by preparatory-TLC (Petroleum ether : Ethyl acetate = 1: 1) to give **77E** (80 mg, yield: 24.5%) as yellow solid.

[0681] A mixture of **77E** (80 mg, 281.42 umol) and $LiOH.H_2O$ (17.7 mg, 422.13 umol) in THF (5 mL), H_2O (1 mL) was stirred at 25 °C for 12 hrs. LCMS showed desired MS, THF was removed under vacuum, the water layer was extracted with ethyl acetate (10 mL x 2), the water layer was adjusted to pH ~ 6 with 1N HCl and lyophilized, the residue was purified by preparatory-HPLC (TFA) to give **77F** (35 mg, yield: 48.5%), as white solid. ^{1}H NMR (400MHz, methanol-d_4) δ 8.70 (d, J = 5.3 Hz, 1H), 8.25 (s, 1H), 8.16 (s, 1H), 8.11 (s, 1H), 8.08 (d, J = 5.1 Hz, 1H), 7.81 (s, 1H), 7.46 (s, 1H).

[0682] Compound **77** (38.4 mg, yield: 64.3%, white solid) was prepared as in Example **41** from the corresponding intermediate carboxylic acid, compound **77F**. Compound **77**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.93 (d, J = 7.5 Hz, 1H), 8.74 (d, J = 5.1 Hz, 1H), 8.60 (d, J = 5.7 Hz, 1H), 8.39 (d, J = 0.7 Hz, 1H), 8.22 (d, J = 0.7 Hz, 1H), 7.94 (dd, J = 1.4, 5.2 Hz, 1H), 7.82 (s, 1H), 7.65 (d, J = 0.7 Hz, 1H), 7.54 (d, J = 0.7 Hz, 1H), 7.28 (d, J = 4.4 Hz, 4H), 7.20 (qd, J = 4.2, 8.5 Hz, 1H), 5.30 - 5.22 (m, 1H), 3.16 (dd, J = 3.9, 13.8 Hz, 1H), 2.85 (dd, J = 10.1, 13.9 Hz, 1H), 2.77 - 2.68 (m, 1H), 0.67 - 0.59 (m, 2H), 0.58 - 0.50 (m, 2H). MS (ESI) m/z $(M+H)^+$ 471.1.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(4-(OXAZOL-2-YL)PYRIDIN-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (88)

[0683] Compound **88** (18.5 mg, yield: 46.5%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **77F**. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.93 (d, J = 7.5 Hz, 1H), 8.58 (d, J = 5.3 Hz, 1H), 8.37 (s, 1H), 8.21 (s,

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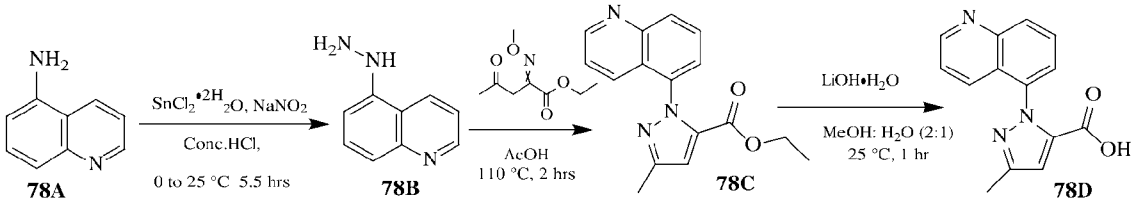
1H), 8.01 (br s, 1H), 7.91 (d, J = 5.1 Hz, 1H), 7.79 (s, 2H), 7.62 (s, 1H), 7.52 (s, 1H), 7.25 (d, J = 4.2 Hz, 4H), 7.18 (br dd, J = 4.5, 8.7 Hz, 1H), 5.25 - 5.17 (m, 1H), 3.14 (dd, J = 3.6, 14.0 Hz, 1H), 2.83 (dd, J = 10.5, 13.8 Hz, 1H). MS (ESI) m/z $(M+H)^+$ 431.1.

EXAMPLE 44

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(QUINOLIN-5-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (78)



78A 78B 78C 78D

[0684] A mixture consisting of compound **78A** (1.0 g, 6.94 mmol) in conc. HCl (4.00 mL) at 0 °C was added $NaNO_2$ (526.8 mg, 7.63 mmol) dropwise and the resultant mixture was stirred at 0 °C for 0.5 hour. The reaction mixture was warmed to 25 °C over 0.5 hour, and then cooled to 0 °C. The $SnCl_2•2H_2O$ (3.13 g, 13.88 mmol, in 1.2 mL conc. HCl) was added dropwise to the reaction mixture, and stirred at 0 °C for 0.5 hour. The resulting mixture was allowed to warm to room temperature with vigorous stirring over 4 hours and then concentrated under reduced pressure to remove solvent. The residue was filtered, and the cake was washed with ethanol (30 mL x 3), and then dried under reduced pressure to afford compound **78B** (700.0 mg, 51.55% yield) as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.95 (br s, 1H), 9.25 - 9.13 (m, 2H), 8.04 - 7.95 (m, 2H), 7.88 (d, J = 8.8 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.28 - 7.23 (m, 1H).

[0685] To a mixture of compound **78B** (500 mg, 3.14 mmol) and compound ethyl 2-(methoxyimino)-4-oxopentanoate (588 mg, 3.14 mmol) in AcOH (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 110 °C for 2 hrs under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to remove AcOH. The residue was diluted with CH_2Cl_2 (100 mL), adjusted to pH ~ 7 - 8 with saturated aqueous $NaHCO_3$, and then extracted with CH_2Cl_2 (40 mL x 2). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue, which was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1:0 to 1:0) to give compound **78C** (200 mg, 22.6% yield) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ

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8.93 (d, J = 4.0 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 6.93 (s, 1H), 4.05 (q, J = 7.2 Hz, 2H), 2.41 (s, 3H), 1.00 (t, J = 7.2 Hz, 3H). MS (ESI) m/z $(M+1)^+$ 282.0.

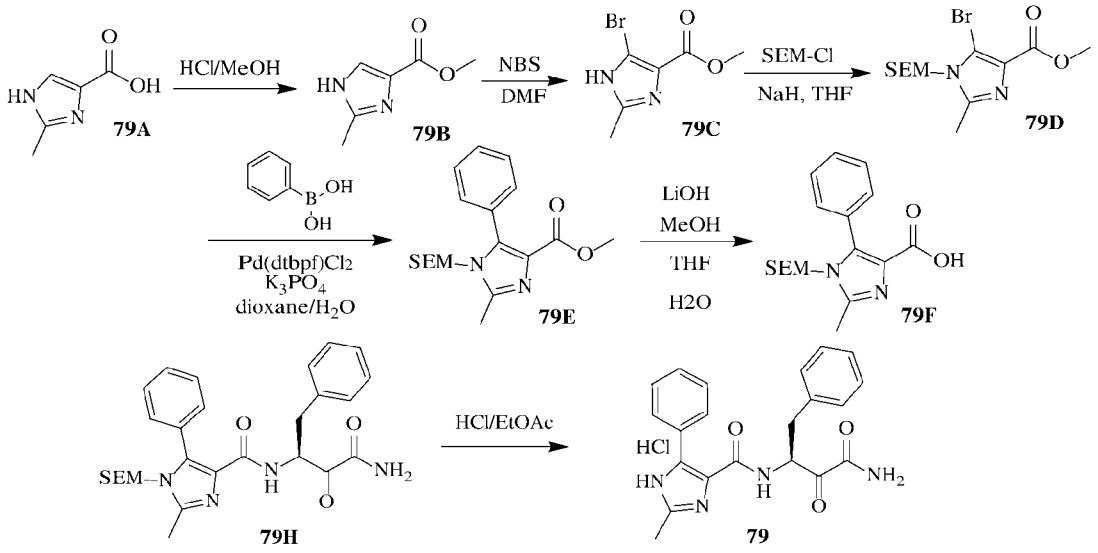
[0686] Intermediate compound **78D** (135 mg, 74.98% yield, white solid) was prepared as in Example **85** from compound **78C**. Compound **78D**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.97 (d, J = 4.0 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.89 - 7.82 (m, 1H), 7.67 - 7.52 (m, 3H), 6.97 (s, 1H), 2.32 (s, 3H). MS (ESI) m/z $(M+1)^+$ 253.9.

[0687] Compound **78** (8.8 mg, 16.77% yield, yellow solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **78D**. Compound **78**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.95 (d, J = 4.0 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.76 - 7.66 (m, 2H), 7.49 (d, J = 6.4 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.24 - 7.16 (m, 3H), 6.87 (d, J = 7.6 Hz, 2H), 6.79 (br s, 1H), 6.64 (s, 1H), 6.33 (d, J = 7.2 Hz, 1H), 5.49 - 5.42 (m, 1H), 3.27 - 3.19 (m, 1H), 3.08 - 2.98 (m, 1H), 2.78 – 2.69 (m, 1H), 0.90 - 0.83 (m, 2H), 0.61 - 0.50 (m, 2H). MS (ESI) m/z $(M+H)^+$ 468.1.

EXAMPLE 45

COMPOUNDS 79, 146, 160, 264

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-2-METHYL-5-PHENYL-1*H*-IMIDAZOLE-4-CARBOXAMIDE (79)



[0688] The solution of compound **79A** (500 mg, 3.96 mmol) in HCl/MeOH (4 M, 50 mL) was stirred at 80 °C for 12 hrs. The solvent was removed in vacuo. The residue was

adjusted to pH ~ 8 with saturated aqueous $NaHCO_3$. The solution was extracted with EtOAc (100 mL x 3). The organics were collected, dried with Na_2SO_4, filtered and concentrated. Compound **79B** (360 mg, yield: 64.87%, light yellow solid): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.90 - 7.88 (m, 1H), 7.34 - 7.31 (m, 1H), 7.15 - 7.09 (m, 2H), 5.72 - 5.63 (m, 1H), 4.87 - 4.76 (m, 2H), 2.90 - 2.86 (m, 2H), 1.92 - 1.87 (m, 2H), 1.50 - 1.47 (m, 2H), 1.26 - 1.14 (m, 8H).

[0689] To a solution of compound **79B** (360 mg, 2.57 mmol) in DMF (5 mL) at 0 °C was added NBS (550 mg, 3.08 mmol). The mixture was then warmed up to 25 °C and stirred for 12 hrs. The reaction was washed with H_2O (10 mL), extracted with DCM (20 mL). The organics were collected, dried with Na_2SO_4, filtered and concentrated to afford intermediate compound **79C** (550 mg, crude) as yellow solid. MS (ESI) *m/z* $(M+2)^+$ 220.7.

[0690] To a solution of NaH (151 mg, 3.76 mmol, 60% purity) in THF (8 mL) at 0 °C was added a solution of compound **79C** (550 mg, 2.51 mmol) in THF (2 mL) dropwise. After addition, the mixture was warmed up to 25 °C and stirred for 1h. Then SEM-Cl (0.5 mL, 2.76 mmol) was added. The mixture was stirred at 25 °C for 12 hrs. The reaction was quenched with H_2O (10 mL), extracted with EtOAc (20 mL x 2). The organics were collected and concentrated. The residue was purified by column (Petroleum Ether: Ethyl Acetate = 5:1) to afford compound **79D** (180 mg, yield: 20.51%) as colorless oil. MS (ESI) *m/z* $(M+2)^+$ 350.9.

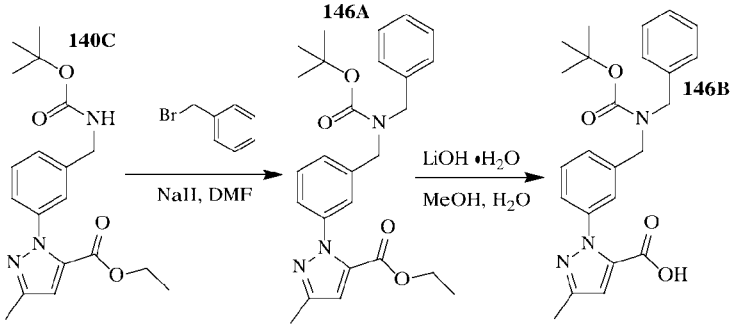
[0691] To a solution of compound **79D** (180 mg, 0.52 mmol) and phenylboronic acid (76 mg, 0.62 mmol) in dioxane (12 mL) and H_2O (4 mL) was added $Pd(dtbpf)Cl_2$ (34 mg, 0.052 mmol) and K_3PO_4 (330 mg, 1.55 mmol). The mixture was stirred at 80 °C under N_2 for 2 hrs. The reaction was washed with H_2O (10 mL), extracted with EtOAc (15 mL x 2). The organics were collected and concentrated. The residue was purified by column (Petroleum Ether: Ethyl Acetate = 5:1) to afford compound **79E** (150 mg, yield: 84.0%) as yellow oil. MS (ESI) *m/z* $(M+H)^+$ 347.0.

[0692] To a solution of compound **79E** (180 mg, 0.52 mmol) in THF (5 mL), MeOH (5 mL) and H_2O (5 mL) was added $LiOH.H_2O$ (110 mg, 2.60 mmol). The mixture was stirred at 25 °C for 12 hrs. The reaction was acidified with 1N HCl to pH ~ 3. The mixture was extracted with EtOAc (10 mL x 2). The organics were collected, dried with Na_2SO_4, filtered and concentrated to afford compound **79F** (130 mg, crude) as yellow oil. MS (ESI) *m/z* $(M+H)^+$ 333.0. Intermediate compound **79H** (65 mg, crude, yellow oil) was prepared as in Example 5

from the corresponding carboxylic acid, compound **79F**. Compound **79H**: MS (ESI) *m/z* $(M+H)^+$ 507.2.

[0693] To a solution of compound **79H** (65 mg, 0.13 mmol) in EtOAc (5 mL) was added HCl/EtOAc (4 M, 10 mL) dropwise. After addition, the mixture was stirred at 25 °C for 12 hrs. The solvent was removed in vacuo. The residue was purified by prep-HPLC (HCl) to afford compound **79** (10.00 mg, yield: 18.7%) as white solid. ^{1}H NMR (400MHz, D_2O) δ 7.45 - 7.28 (m, 3H), 7.23 - 6.97 (m, 7H), 4.46 - 4.38 (m, 1H), 3.02 - 2.93 (m, 1H), 2.48 - 2.41 (m, 3H), 2.39 - 2.29 (m, 1H). MS (ESI) *m/z* $(M+H)^+$ 377.1.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(3-((BENZYLAMINO)METHYL)PHENYL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (146)



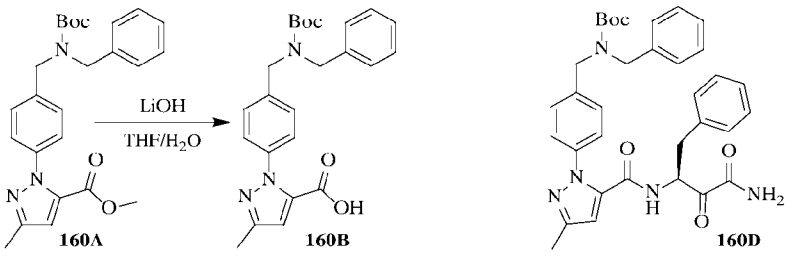
[0694] To a mixture of compound **140C** (250 mg, 0.72 mmol) and benzyl bromide (310 mg, 1.8 mmol) in DMF (10 mL) was added NaH (87 mg, 2.2 mmol, 60% purity) in batches at 0 °C under N_2. The mixture was stirred at 25 °C for 3h. The mixture was quenched with NH_4Cl (10 mL), diluted with H_2O (30 mL), extracted with ethyl acetate (20 mL x 3). The organic phase was combined and washed with brine (30 mL x 2), dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by Flash Column Chromatography (SiO2, Petroleum ether/Ethyl acetate=1/0 to 5/1) to afford compound **146A** (182 mg, yield: 57.7%) as colorless clear liquid.

[0695] To a mixture of compound **146A** (180 mg, 0.41 mmol) in MeOH (10 mL) and H_2O (2 mL) was added LiOH.H_2O (52 mg, 1.24 mmol) in one portion at 25 °C. The mixture was stirred at 25 °C for 3h. The reaction mixture was concentrated under reduced pressure to move MeOH. Then the residue was diluted with water (15 mL) and extracted with MTBE (20 mL), the aqueous phase was acidified with aqueous HCl (1M) till pH ~ 5~6 and extracted with ethyl

acetate (20 mL x 2). The combined organic layers were washed with brine (40 mL) and dried over Na_2SO_4, filtered and concentrated to afford compound **146B** (158 mg, yield: 90. 8%) as colorless liquid, which was used directly for next step without purification. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.44 - 7.39 (m, 1H), 7.37 - 7.30 (m, 3H), 7.26 (q, J = 6.9 Hz, 5H), 6.81 (s, 1H), 4.48 - 4.26 (m, 4H), 2.25 (s, 3H), 1.39 (s, 9H).

[0696] Compound **146** was prepared as in Example **45** from the intermediate compound **146B**. Compound **146** (40.0 mg, yield 74.6%, white solid): ^{1}H NMR (D_2O, 400 MHz): δ 7.51 - 7.42 (m, 6H), 7.41 - 7.36 (m, 1H), 7.36 - 7.27 (m, 5H), 7.25 (s, 1H), 6.78 (d, J = 8.6 Hz, 1H), 6.60 (s, 1H), 4.52 - 4.43 (m, 1H), 4.30 - 4.18 (m, 4H), 3.24 - 3.15 (m, 1H), 2.82 - 2.71 (m, 1H), 2.29 (s, 3H). MS (ESI) *m/z* (M-HCl+H)$^+$ 496.2.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(4-((BENZYLAMINO)METHYL)PHENYL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE HYDROCHLORIDE (160)



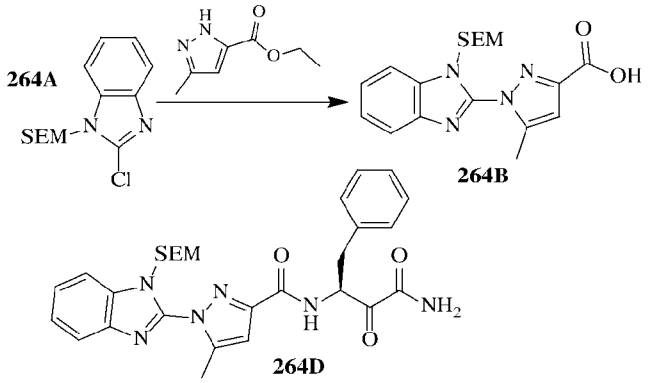
[0697] To a solution of compound **153E** (350 mg, 1.01 mmol) and benzyl bromide (432 mg, 2.53 mmol, 0.3 mL) in DMF (10 mL) was added NaH (121 mg, 3.03 mmol, 60% purity) at 0 °C. The mixture was stirred at 25 °C for 1h. The mixture was quenched with NH_4Cl (5 mL), diluted with H_2O (20 mL), extracted with ethyl acetate (20 mL x 3), the organic phase was combined, and washed with NaCl (30 mL x 2), dried over Na_2SO_4, concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 20/1 to 5/1) to give compound **160A** (400 mg, yield: 41.47%) as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.02 (dd, J = 1.1 Hz, 1H), 7.37 - 7.25 (m, 9H), 6.88 - 6.75 (m, 1H), 4.49 - 4.28 (m, 4H), 2.98 - 2.88 (m, 4H), 2.46 - 2.30 (m, 3H), 1.57 - 1.41 (m, 8H). MS (ESI) *m/z* (M-56)$^+$380.0.

[0698] To a mixture of compound **160A** (400 mg, 918.46 umol) in THF (10 mL) and H_2O (10 mL) was added LiOH.H_2O (116 mg, 2.76 mmol) in portion at 25 °C and stirred for 2.5h.

The mixture was diluted with H_2O (10 mL) and concentrated to remove THF, then the water was extracted with MTBE (30 mL x 2). The water layers were acidified to pH ~ 2 with 1N HCl, then, the solution extracted with ethyl acetate (30 mL x 3). The organic layers were dried over Na_2SO_4 and concentrated to give intermediate compound **160B** (350 mg, yield: 86.82%) as white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.40 - 7.20 (m, 9H), 6.85 (s, 1H), 4.43 (s, 2H), 4.33 (dd, J = 13.9 Hz, 2H), 2.34 (s, 3H), 1.47 (s, 8H). MS (ESI) *m/z* $(M-56)^+$366.1.

[0699] Compound **160** was prepared as in Example **79** from the corresponding carboxylic acid, compound **160B**, and then through intermediate compound **160D**. Compound **160** (30 mg, yield: 53.02%, light yellow solid): ^{1}H NMR (400MHz, DMSO-d_6) δ 9.62 - 9.57 (m, 1H), 9.15 (d, J = 7.9 Hz, 1H), 8.12 (s, 1H), 7.88 (s, 1H), 7.58 - 7.49 (m, 4H), 7.44 (dd, J = 6.8 Hz, 3H), 7.36 - 7.27 (m, 5H), 7.22 (d, J = 8.4 Hz, 2H), 6.61 (s, 1H), 5.35 - 5.28 (m, 1H), 4.18 (s, 4H), 3.25 - 3.18 (m, 1H), 2.83 (dd, J = 10.6, 13.9 Hz, 1H), 2.26 (s, 3H). MS (ESI) *m/z* $(M+H)^+$496.2.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(1*H*-BENZO[*d*]IMIDAZOL-2-YL)-5-METHYL-1*H*-PYRAZOLE-3-CARBOXAMIDE (264)



[0700] 2-chloro-1*H*-benzo[*d*]imidazole (5 g, 32.8 mmol) was added to a solution of NaH (1.31 g, 32.8 mmol, 60%) in DMF (50 mL) below 10 °C. After addition, the reaction mixture was stirred at 20 °C for 2h. Then SEM-Cl (5.46 g, 32.8 mmol,) was added to the reaction mixture. The reaction mixture was stirred at 20 °C for 16hrs. Water (150 mL) and EtOAc (150 mL) were added. The organic layer was separated and washed by brine (100 mL), concentrated to give a residue. The crude product was purified by silica gel column (petroleum ether: ethyl acetate = 20: 1~ 4: 1) to give compound **264A** (3.50 g, yield: 37.8%) as an oil. ^{1}H

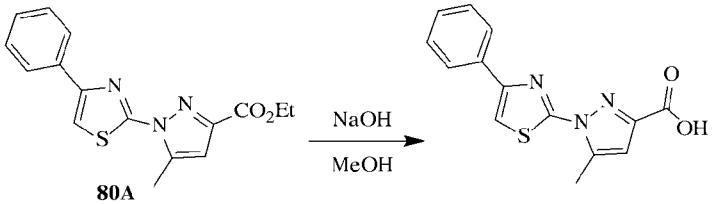
NMR (400MHz, $CDCl_3$) δ 7.78 - 7.71 (m, 1H), 7.54 - 7.48 (m, 1H), 7.41 - 7.32 (m, 2H), 5.62 (s, 2H), 3.66 - 3.59 (m, 2H), 0.99 - 0.93 (m, 2H), 0.07 (d, J = 2.0 Hz, 2H), 0.00 (s, 9H).

[0701] Compound **264** was prepared as in Example **79** from the corresponding intermediate compound **264B**, and then through intermediate compound **264D**. Compound **264** (31.8 mg, yield: 28.0%, off-white solid): ^{1}H NMR (400MHz, $CDCl_3$) δ 13.04 (br s, 1H), 8.39 (d, J = 7.6 Hz, 1H), 8.13 (br s, 1H), 7.88 (br s, 1H), 7.67 (br d, J = 7.2 Hz, 1H), 7.53 (br d, J = 7.5 Hz, 1H), 7.34 - 7.19 (m, 7H), 6.79 (s, 1H), 5.51 (dt, J = 4.0, 8.2 Hz, 1H), 3.27 (br d, J = 4.0 Hz, 1H), 3.02 (dd, J = 9.3, 13.9 Hz, 1H), 2.73 (s, 3H). MS (ESI) m/z $(M+H)^+$ 417.2.

EXAMPLE 46

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-METHYL-1-(4-PHENYLTHIAZOL-2-YL)-1*H*-PYRAZOLE-3-CARBOXAMIDE (80)

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-METHYL-1-(4-PHENYLTHIAZOL-2-YL)-1*H*-PYRAZOLE-3-CARBOXAMIDE (125)



80A **80B**

[0702] Intermediate compound **80B** (182.00 mg, 99.95% yield, white solid): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.02 (s, 1H), 7.96 (br d, J=7.5 Hz, 2H), 7.47 (br t, J=7.5 Hz, 2H), 7.41 - 7.32 (m, 1H), 6.80 (s, 1H), 2.78 (s, 3H).

[0703] Compound **80** (44 mg, 64.6% yield, white solid) was prepared as in Example **5** from the corresponding intermediate compounds **80B** and **12G**. Compound **80**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.53 (br d, J=7.3 Hz, 1H), 8.12 (br s, 1H), 8.04 - 7.94 (m, 3H), 7.86 (br s, 1H), 7.52 - 7.44 (m, 2H), 7.39 (br d, J=6.4 Hz, 1H), 7.32 - 7.17 (m, 5H), 6.76 (s, 1H), 5.43 (br s, 1H), 3.24 (br d, J=12.1 Hz, 1H), 3.12 - 3.03 (m, 1H), 2.78 (s, 3H). **MS (ESI)** m/z $(M+H)^+$ 460.1.

[0704] Compound **125** (118 mg, yield 77.6%, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic compounds **80B** and **41B**. Compound **125**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.84 (br s, 1H), 8.60 - 8.53 (m, 1H), 8.06 - 7.94 (m, 3H), 7.52 - 7.44 (m, 2H), 7.42 - 7.35 (m, 1H), 7.29 (br s, 4H), 7.21 (br s, 1H), 6.76 (s,

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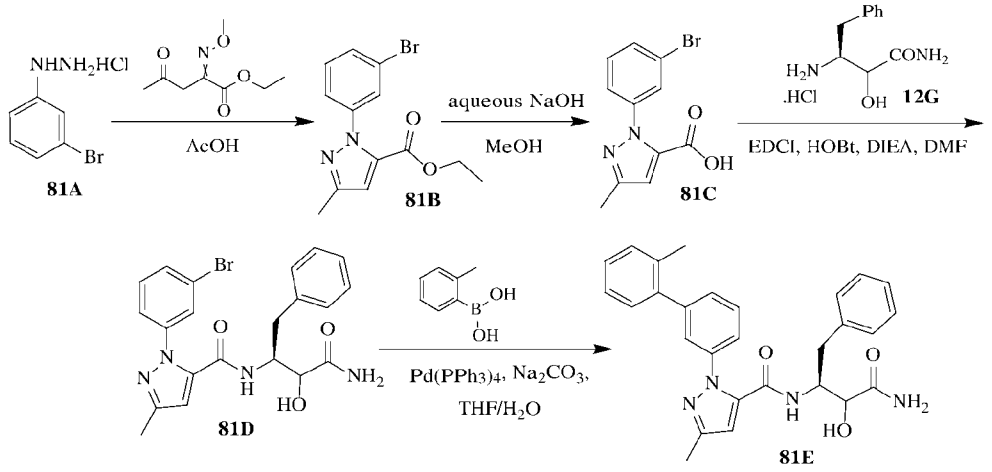
1H), 5.44 (br s, 1H), 3.27 - 3.19 (m, 1H), 3.11 - 3.02 (m, 1H), 2.78 (br s, 4H), 0.72 - 0.57 (m, 4H). MS (ESI) *m/z* $(M+H)^+$ 500.1.

EXAMPLE 47

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(2'-METHYL-[1,1'-BIPHENYL]-3-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (81)



[0705] To a mixture of compound **81A** (25 g, 111.86 mmol) and compound ethyl 2-(methoxyimino)-4-oxopentanoate (22 g, 117.45 mmol) in AcOH (150 mL) was stirred at 110 °C for 2 hrs. The reaction mixture was concentrated under reduced pressure to remove a large amount of AcOH. The residue was acidified with saturated aqueous $NaHCO_3$ till pH ~ 7-8. The precipitate was collected by filtration and the cake was triturated with petroleum ether (20 mL), filtered and dried in vacuum to afford compound **81B** (26.41 g, yield: 74.0%) as gray solid. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.71 - 7.68 (m, 1H), 7.65 (td, J = 1.5, 7.7 Hz, 1H), 7.50 - 7.38 (m, 2H), 6.95 - 6.84 (m, 1H), 4.18 (q, J = 7.0 Hz, 2H), 2.27 (s, 3H), 1.17 (t, J = 7.0 Hz, 3H). MS (ESI) *m/z* $(M+H)^+$ 310.8.

[0706] To a mixture of compound **81B** (5 g, 16.17 mmol) in MeOH (20.00 mL) was added NaOH (2M, 40 mL) in one portion at 25 °C. The mixture was stirred at 25 °C for 2 hrs. The reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was added H_2O (10 mL) and ethyl acetate (20 mL), and then the mixture was acidified with 1M HCl till the aqueous phase pH ~ 5-6. The separated aqueous layer was extracted with ethyl acetate (30 x 3 mL), the combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, filtered under reduced pressure to give crude product. The crude product was treated

with isopropyl ether (15 mL), the precipitate was filtered and dried in vacuum to afford compound **81C** (4.21 g, yield: 80.67%) as white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.65 - 7.58 (m, 2H), 7.45 - 7.36 (m, 2H), 6.83 (s, 1H), 2.23 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 282.8.

[0707] To a solution of compound **81C** (1 g, 3.56 mmol) in DMF (50 mL) was added HOBt (144 mg, 1.07 mmol), compound **12G** (903 mg, 3.92 mmol, HCl) and DIEA (1.38 g, 10.68 mmol). After stirring for 5 min, EDCI (682 mg, 3.56 mmol,) was added at 0 °C. Then the reaction mixture was stirred at 25 °C for 9 hrs. The reaction mixture was concentrated under reduced pressure to move DMF, and to the residue was added ethyl acetate (100 mL) and respectively washed with H_2O (80 mL), saturated aqueous $NaHCO_3$ (80 mL x 2), brine (80 mL x 3). The organic phase was dried over Na_2SO_4 and concentrated. The crude product was treated with *i*-propyl ether. The solid was collected and dried in vacuum to afford compound **81D** (1.3 g, yield: 79.85%) as white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.55 - 8.18 (m, 1H), 7.54 - 7.45 (m, 2H), 7.34 (br d, *J*=18.5 Hz, 1H), 7.30 - 7.14 (m, 7H), 7.00 - 6.89 (m, 1H), 6.58 (d, *J*=1.5 Hz, 1H), 5.98 - 5.73 (m, 1H), 4.44 - 4.33 (m, 1H), 4.00 - 3.89 (m, 1H), 2.93 - 2.87 (m, 0.5 H), 2.84 - 2.73 (m, 1H), 2.71 (br s, 0.6 H), 2.22 (s, 3H).

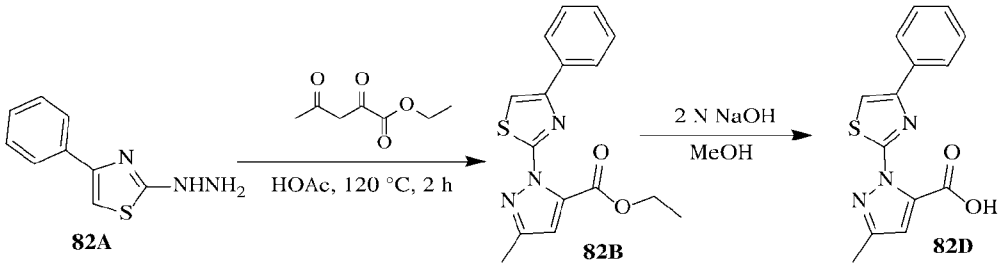
[0708] To a mixture of compound **81D** (150 mg, 328.00 umol) and compound *o*-tolylboronic acid (89.2 mg, 656.00 umol) in THF (50 mL) and H_2O (10 mL) was added Na_2CO_3 (70 mg, 656.00 umol,) and $Pd(PPh_3)_4$ (38 mg, 32.80 umol) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C for 12 hrs. Then to the reaction mixture was added H_2O (100 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (150 mL x 3), brine (150 mL x 3), dried over Na_2SO_4 and concentrated to afford compound **81E** (110 mg, yield: 71.58%) was obtained as white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.50 - 8.11 (m, 1H), 7.38 - 7.32 (m, 2H), 7.31 - 7.22 (m, 6H), 7.18 (br s, 5H), 7.10 (br d, *J* = 6.4 Hz, 1H), 7.00 (br.dd, *J* = 8.0, 16.4 Hz, 1H), 6.57 (s, 1H), 5.96 - 5.69 (m, 1H), 4.51 - 4.30 (m, 1H), 4.03 - 3.85 (m, 1H), 2.92 - 2.63 (m, 2H), 2.27 - 2.12 (m, 6H). MS (ESI) *m/z* $(M+H)^+$ 469.2.

[0709] The mixture of compound **81E** (70 mg, 149.4 umol) in DCM (10 mL) and DMSO (0.5 mL) was added DMP (190 mg, 448.2 umol) in one portion at 0 °C. The mixture was stirred at 0 °C for 5 min, then heated to 25 °C and stirred for 1.5 hours. The reaction was quenched by 20 mL of 10 % aqueous $Na_2S_2O_3$ solution and 20 mL of saturated aqueous $NaHCO_3$

solution and then extracted with DCM (30 mL x 3). The combined organic phase was washed with brine (40 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was treated with *i*-propyl ether/CH3CN (v/v = 10/1, 10 mL). The solid was collected and dried in vacuum to afford compound **81** (48.3 mg, yield: 66.3%) as white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.11 (br d, J = 8.0 Hz, 1H), 8.18 - 7.79 (m, 2H), 7.49 - 7.37 (m, 1H), 7.29 - 7.26 (m, 8H), 7.21 - 7.12 (m, 4H), 6.60 (s, 1H), 5.32 (br.s., 1H), 3.21 - 3.18 (m, 1H), 2.86 - 2.76 (m, 1H), 2.25 (br.s., 3H), 2.18 (br.s., 3H). MS (ESI) *m/z* $(M+H)^+$ 467.1.

EXAMPLE 48

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(4-PHENYLTHIAZOL-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (82)



82A 82B 82D

[0710] To a solution of compound **82A** (2.0 g, 10.46 mmol) in CH_3COOH (30.0 mL) was added compound ethyl 2,4-dioxopentanoate (1.65 g, 10.46 mmol, 1.48 mL) dropwise, then the mixture was heated to 120 °C and stirred for 2 hrs and removed the solvent under reduced pressure. The residue was dissolved in ethyl acetate (20 mL) and treated with $NaHCO_3$ until pH ~ 8, and then the organic layer was collected and evaporated under reduced pressure. The residue was purified by flash column chromatography (Petroleum Ether/Ethyl Acetate: 0 to 10/1).

[0711] Compound **82B** (660.0 mg, 2.11 mmol, 20.14% yield) was obtained as white solid. Compound **82B** (low polarity): **^{1}H NMR** ($CDCl_3$, 400 MHz,) δ 7.88 - 7.83 (m, 2H), 7.43 - 7.38 (m, 3H), 7.36 - 7.31 (m, 1H), 6.71 (s, 1H), 4.33 (q, J = 7.2 Hz, 2H), 2.37 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H).

[0712] To a solution of compound **82B** (650.0 mg, 2.07 mmol) in MeOH (10.00 mL) was added NaOH (2M, 6.00 mL) drop wise and the mixture was stirred at 25 °C for 2 hrs. The reaction was diluted with H_2O (10 mL) and extracted with MBTE(10 mL x 2). The water phase was treated with HCl (1M) until pH ~ 4, then the precipitate was filtered and dried under reduced pressure. Compound **82D** (540.0 mg, 91.3% yield) was obtained as white solid. ^{1}H NMR

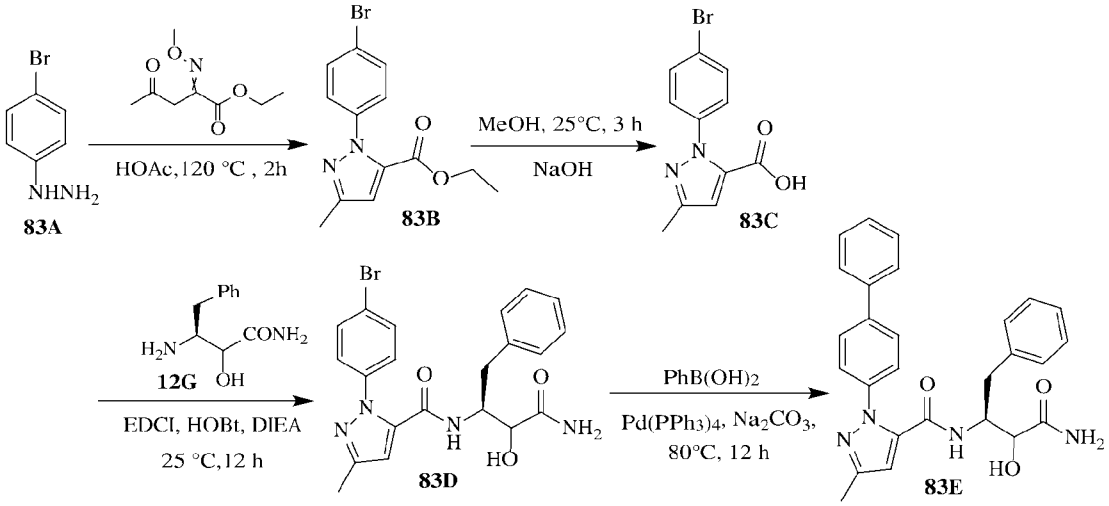
(DMSO-d_6, 400 MHz) δ 8.04 (s, 1H), 7.88 (d, J =7.1 Hz, 2H), 7.47 - 7.41 (m, 2H), 7.38 - 7.33 (m, 1H), 6.83 (s, 1H), 2.27 (s, 3H)

[0713] Compound **82** (20.0 mg, 42.74% yield, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **82D**. Compound **82**: ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.49 (d, J = 7.6 Hz, 1H), 8.12 (s, 1H), 7.94 (s, 1H), 7.88 (br s, 1H), 7.78 (br d, J = 7.2 Hz, 2H), 7.42 - 7.37 (m, 2H), 7.35 - 7.29 (m, 1H), 7.22 - 7.12 (m, 5H), 6.55 (s, 1H), 5.55 - 5.47 (m, 1H), 3.16 (m, 1H), 2.80 (m, 1H), 2.27 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 403.1.

EXAMPLE 49

COMPOUNDS 83, 126, 130

(*S*)-1-([1,1'-BIPHENYL]-4-YL)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (83)



[0714] To a solution of compound **83A** (20.0 g, 89.49 mmol, HCl) in CH_3COOH (150.0 mL) was added compound ethyl 2-(methoxyimino)-4-oxopentanoate (14.0 g, 89.49 mmol), then the mixture was heated to 120 °C and stirred for 2 hrs and removed the solvent under reduced pressure. The residue was dissolved in ethyl acetate (150 mL), treated with $NaHCO_3$ until pH ~ 7 and filtered. The solid was treated with petroleum ether. Compound **83B** (22.0g, 71.16 mmol, 79.52% yield) was obtained as yellow solid. ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.56 (d, J = 8.4 Hz, 2H), 7.31 - 7.24 (m, 2H), 6.81 (s, 1H), 4.23 (q, J = 7.2 Hz, 2H), 2.34 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H).

[0715] To a solution of compound **83B** (5.0 g, 16.17 mmol) in MeOH (40.0 mL) was added NaOH (2M, 45.0 mL) dropwise and the mixture was stirred at 25 °C for 3 hrs and removed the solvent under reduced pressure, then the mixture was diluted with H_2O (30 mL) and extracted with MTBE (60 mL x 2). Water phase was treated with HCl (1M) until pH ~ 4, and then the precipitate was filtered and dried under reduced pressure. The water phase was extracted with ethyl acetate (50 mL x 2), the organic layer (extracted with ethyl acetate) was evaporated under reduced pressure. The solid collected was compound **83C** (3.75 g, 82.5% yield) obtained as white solid. ^{1}H NMR (DMSO-d_6, 400MHz) δ 7.62 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 6.81 (s, 1H), 2.23 (s, 3H).

[0716] Compound **83** (25.0 mg, 61.24% yield, white solid) was prepared as in Example **47** from the corresponding intermediate compounds **83C**, **12G** and phenylboronic acid. Compound **83**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.49 (d, J = 7.3 Hz, 1H), 8.12 (s, 1H), 7.94 (s, 1H), 7.88 (br s, 1H), 7.78 (br d, J = 7.3 Hz, 2H), 7.48 - 7.27 (m, 4H), 7.26 - 6.96 (m, 7H), 6.55 (s, 1H), 5.55 - 5.47 (m, 1H), 3.16 (br dd, J = 4.2, 14.1 Hz, 1H), 2.80 (br dd, J = 9.7, 13.9 Hz, 1H), 2.27 (s, 3H), 2.06 (s, 1H). MS (ESI) m/z $(M+H)^+$ 453.1.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(4'-FLUORO-[1,1'-BIPHENYL]-4-YL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (126)

[0717] Compound **126** (32 mg, yield 25.5%, light yellow solid) was prepared as in Example **63** from the corresponding starting materials, compound **83D** and (4-fluorophenyl)boronic acid. Compound **126**: ^{1}H NMR (CD_3CN, 400MHz) δ 7.73 - 7.67 (m, 2H), 7.63 - 7.59 (m, 2H), 7.37 - 7.22 (m, 10H), 7.02 (br s, 1H), 6.54 (s, 1H), 6.27 (br s, 1H), 5.42 (ddd, J = 4.5, 7.8, 9.5 Hz, 1H), 3.32 (dd, J=4.5, 13.8 Hz, 1H), 2.93 (dd, J = 9.6, 14.0 Hz, 1H), 2.31 (s, 3H). MS (ESI) m/z $(M+H)^+$ 471.1.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(4'-FLUORO-[1,1'-BIPHENYL]-4-YL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (130)

[0718] Compound **130** (30 mg, yield 34.7%, light yellow solid) was prepared as in Example **105** from the corresponding starting materials, compound **83D** and p-tolylboronic acid. Compound **130**: ^{1}H NMR (DMSO-d_6,400MHz) δ 9.14 (br d, J = 7.7 Hz, 1H), 8.11 (br s, 1H), 7.87 (br s, 1H), 7.60 - 7.55 (m, 3H), 7.33 - 7.22 (m, 10H), 6.56 - 6.50 (m, 1H), 5.24 (br s, 1H),

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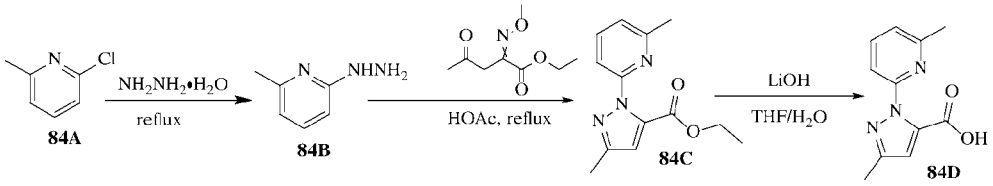
3.20 (br d, J = 13.5 Hz, 1H), 2.87 - 2.78 (m, 1H), 2.33 (s, 3H), 2.24 (s, 3H). MS (ESI) m/z $(M+H)^+$ 467.1.

EXAMPLE 50

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(6-METHYLPYRIDIN-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (84)



[0719] A mixture of compound **84A** (5 g, 39.19 mmol) and $NH_2NH_2.H_2O$ (20 g, 391.94 mmol) was heated under reflux (119 °C) for 36 hours. The reaction mixture was concentrated under reduced pressure to remove the unreacted hydrazine hydrate. The residue was diluted with H_2O (30 mL) and extracted with DCM (30 mL x 3). The combined organic layers were washed with brines (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by re-crystallization from Petroleum Ether (15 mL) at -10 °C to give compound **84B** (2.40 g, yield: 49.35%) as a black brown solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.39 - 7.29 (m, 1H), 7.25 (s, 1H), 6.51 (d, J = 8.4 Hz, 1H), 6.39 (d, J = 7.3 Hz, 1H), 4.06 (s, 2H), 2.26 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 127.8.

[0720] To a solution of compound **84B** (970 mg, 7.88 mmol) in AcOH (20 mL) was added compound ethyl 2-(methoxyimino)-4-oxopentanoate (1.36 g, 7.88 mmol). The mixture was stirred at 120 °C for 20 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H_2O (30 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (15 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography, and then by preparatory-HPLC (HCl condition) to give compound **84C** (160 mg, yield: 8.22%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.88 (t, J = 7.8 Hz, 1H), 7.50 (d, J = 8.0 Hz,1H), 7.28 (d, J = 7.5 Hz, 1H), 6.76 (s, 1H), 4.20 (d, J = 7.3 Hz, 2H), 2.43 (s, 3H), 2.28 (s, 3H), 1.14 (t, J = 7.0 Hz, 3H). MS (ESI) *m/z* $(M+H)^+$ 246.0.

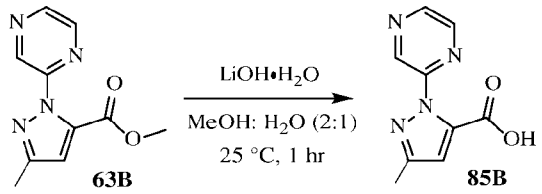
[0721] To a solution of compound **84C** (100 mg, 432.43 umol) in THF (5 mL) was added a solution of $LiOH.H_2O$ (91 mg, 2.16 mmol) in H_2O (5 mL) at 0 °C. After addition, the

reaction mixture was stirred for 14 hrs at 25 °C. The reaction mixture was diluted with H_2O (10 mL) and extracted with MTBE (30 mL). The aqueous phase was neutralized by 1N HCl to the pH ~ 4 and then was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give compound **84D** (50 mg, yield: 53.2%) as a red solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 1H), 7.89 (t, J = 8.0 Hz, 1H), 7.20 - 7.14 (m, 2H), 2.64 (s, 3H), 2.36 (s, 3H). MS (ESI) m/z $(M+H)^+$ 217.9.

[0722] Compound **84** (70 mg, yield: 54.12%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **84D**. Compound **84**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.09 (d, J = 7.3 Hz, 1H), 8.04 (s, 1H), 7.81 (s, 1H), 7.76 (t, J = 7.7 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.29 - 7.17 (m, 5H), 7.15 (d, J = 7.5 Hz, 1H), 6.44 (s, 1H), 5.37 - 5.25 (m, 1H), 3.13 (dd, J = 4.0, 13.9 Hz, 1H), 2.82 (dd, J = 9.7, 13.9 Hz, 1H), 2.24 (s, 6H). MS (ESI) m/z $(M+H)^+$ 392.1.

EXAMPLE 51

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(PYRAZIN-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (85)



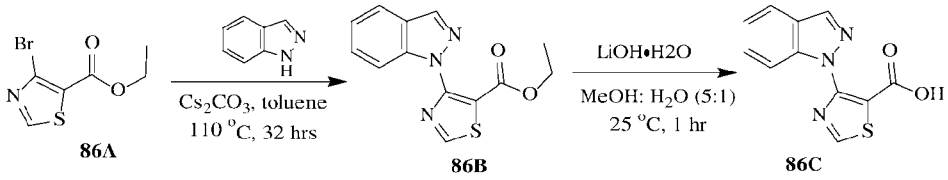
63B 85B

[0723] To a mixture of compound **63B** (200 mg, 916.55 umol) in MeOH (10 mL) and H_2O (5 mL) was added LiOH•H_2O (153.8 mg, 3.67 mmol) in one portion and the mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was diluted with H_2O (10 mL), adjusted to pH ~ 3 with 1N HCl, and then extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to afford intermediate compound **85B** (160 mg, 85.49% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (br s, 1H), 8.67 (br s, 1H), 8.32 (br s, 1H), 7.25 (br s, 1H), 2.41 (br s, 3H). MS (ESI) m/z $(M+1)^+$ 205.0.

[0724] Compound **85** (30.7 mg, 59.7% yield, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **85B**. Compound **85**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, J = 4.0 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.76 - 7.66 (m, 2H), 7.49 (d, J = 6.4 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.24 - 7.16 (m, 3H), 6.87 (d, J =7.6 Hz, 2H), 6.79 (br s, 1H), 6.64 (s, 1H), 6.33 (d, J = 7.2 Hz, 1H), 5.49 - 5.42 (m, 1H), 3.27 - 3.19 (m, 1H), 3.08 - 2.98 (m, 1H), 2.78 - 2.69 (m, 1H), 0.90 - 0.83 (m, 2H), 0.61 - 0.50 (m, 2H). MS (ESI) m/z $(M+H)^+$ 419.1.

EXAMPLE 52

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-(1*H*-INDAZOL-1-YL)THIAZOLE-5-CARBOXAMIDE (86)



[0725] A mixture consisting of compound **86A** (250 mg, 1.06 mmol), 1*H*-indazole (125.2 mg, 1.06 mmol) and Cs_2CO_3 (1.04 g, 3.18 mmol) in toluene (15 mL) was stirred at 110 °C for 32 hours. The reaction mixture was cooled to room-temperature, filtered, and concentrated under reduced pressure to give a residue, which was purified by preparatory-HPLC (HCl condition) to afford compound **86B** (20 mg, 6.90% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.87 (s, 1H), 8.19 (d, J = 0.8 Hz, 1H), 7.75 - 7.70 (m, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.41 - 7.35 (m, 1H), 7.22 - 7.17 (m, 2H), 4.17 (q, J = 7.2 Hz, 2H), 1.07 (t, J = 7.2 Hz, 3H).

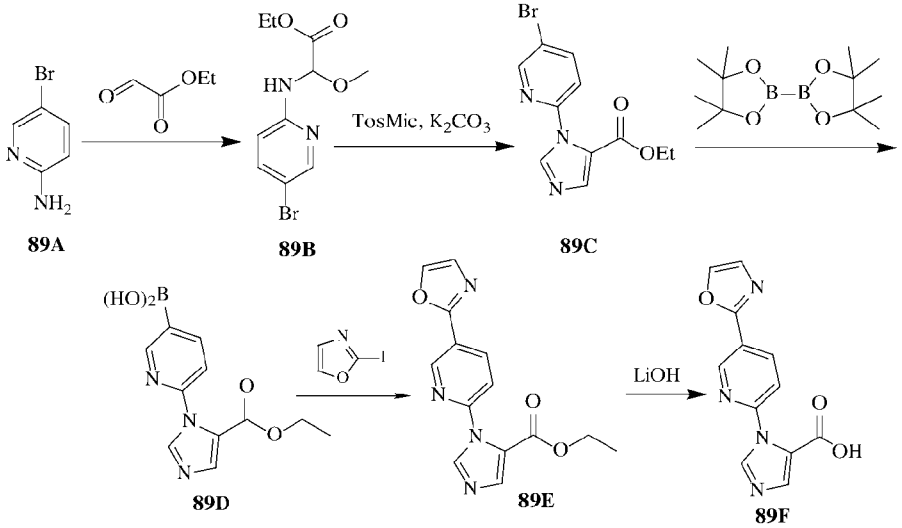
[0726] To a mixture of **86B** (40 mg, 146.35 umol) in MeOH (5 mL) and H_2O (1 mL) was added $LiOH•H_2O$ (24.6 mg, 585.40 umol) in one portion and the mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to remove MeOH and the residue was diluted with H_2O (10 mL), adjusted to pH ~ 3 with 1N HCl, and then extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford intermediate compound **86C** (30 mg, 83.58% yield) as a white solid. MS (ESI) m/z $(M+1)^+$ 245.8.

[0727] Compound **86** (5.4 mg, 10.0% yield, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **86C**. Compound **86**: ^{1}H

NMR (400 MHz, $CDCl_3$) δ 10.97 (d, J = 5.2 Hz, 1H), 8.78 (s, 1H), 8.23 (d, J =6.4 Hz, 1H), 7.82 (s, 1H), 7.71 (d, J =3.2 Hz, 1H), 7.54 - 7.44 (m, 1H), 7.32 - 7.23 (m, 1H), 7.11 - 6.96 (m, 5H), 6.85 (br s, 1H), 5.79 - 5.66 (m, 1H), 3.40 - 3.29 (m, 1H), 3.21 - 3.09 (m, 1H), 2.78 - 2.69 (m, 1H), 0.80 (d, J = 6.2 Hz, 2H), 0.55 (br s, 2H). MS (ESI) m/z $(M+H)^+$ 460.1.

EXAMPLE 53

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(5-(OXAZOL-2-YL)PYRIDIN-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (89)



[0728] To a solution of compound **89A** (40 g, 231 mmol) in MeOH (500 mL) was added ethyl 2-oxoacetate (188 g, 924 mmol) at 25 °C. The reaction mixture was stirred at 70 °C for 1hr. The reaction mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 50 : 1 to 30 : 1). Compound **89B** (70 g, crude) was obtained as yellow oil. MS (ESI) m/z $(M+H)^+$ 258.8.

[0729] To a solution of compound **89B** (35 g, 136 mmol) in EtOH (300 mL) was added TosMIC (66.4 g, 340 mmol) and K_2CO_3 (28.2 g, 204 mmol) at 25 °C. The reaction mixture was stirred at 70 °C for 1hr. The reaction mixture was filtered and the filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleumether: Ethylacetate = 20 : 1 to 3 : 1). Compound **89C** (17 g) was obtained as a yellow solid. ^1H NMR (400MHz, $CDCl_3$) δ 8.62 (d, J = 2.4 Hz, 1H), 8.00 - 7.96 (m, 2H), 7.86 (d, J = 0.9 Hz, 1H), 7.36 - 7.32 (m, 1H), 4.27 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H). MS (ESI) m/z $(M+H)^+$ 297.0.

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[0730] To a solution of compound **89C** (5g, 16.8 mmol) in dioxane (100 mL) was added bis(pinacolato)diboron (8.58 g, 33.7mmol), KOAc (16.5 g, 168 mmol) at 25 °C. The mixture was degassed and purged with N_2 for 3 times, followed by addition of $Pd(dppf)Cl_2$ (617 mg, 844 umol). The reaction mixture was degassed and purged with N_2 for 3 times and stirred at 75 °C for 4hrs. The reaction mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether : Ethyl acetate = 20 : 1 to Dichloromethane: Methanol = 5 : 1). Compound **89D** (2.7 g, yield: 61.2%) was obtained as a white solid. ^1H NMR (400MHz, methanol-d_4) δ 8.63 (br s, 1H), 8.06 (s, 2H), 7.76 (s, 1H), 7.36 (br d, J = 7.1 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H). MS (ESI) *m/z* $(M+H)^+$ 261.9.

[0731] To a solution of compound **89D** (500mg, 1.92 mmol) in dioxane (4 mL) was added 2-iodooxazole (561.48 mg, 2.88 mmol) K_2CO_3 (796.09 mg, 5.76 mmol) H_2O (1 mL) at 25 °C. The reaction mixture was degassed and purged with N_2. Then $Pd(dppf)Cl_2$ (140 mg, 192 umol) was added. The mixture was degassed and purged with N_2 and stirred at 150 °C for 1hr under microwave conditions. The reaction mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 10: 1 ~ 1.5: 1). Compound **89E** (300 mg, crude) was obtained as a grey solid. MS (ESI) *m/z* $(M+H)^+$ 285.0.

[0732] To a solution of compound **89E** (200 mg, 703 umol) in THF (2 mL) H_2O (500 uL) was added $LiOH.H_2O$ (59 mg, 1.41 mmol) and stirred at 25 °C for 12 hrs. The reaction mixture was acidified by HCl (1N) to pH ~ 5, and the precipitation was filtered to give a crude product. Compound **89F** (60 mg, crude) was obtained as a grey solid. MS (ESI) *m/z* $(M+H)^+$ 257.0.

[0733] Compound **89** (35 mg, yield: 65.4%, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **89F**. Compound **89**: ^1H NMR (400MHz, DMSO-d_6) δ 9.04 - 8.93 (m, 2H), 8.77 (br d, J = 5.1 Hz, 1H), 8.38 - 8.28 (m, 2H), 8.20 (s, 1H), 7.56 (s, 1H), 7.46 (s, 1H), 7.34 (d, J = 8.6 Hz, 1H), 7.29 - 7.22 (m, 4H), 5.32 - 5.14 (m, 1H), 3.28 (br s, 1H), 3.20 - 3.10 (m, 1H), 2.81 (br dd, J = 10.1, 13.7 Hz, 1H), 2.77 - 2.69 (m, 1H), 0.73 - 0.42 (m, 4H). MS (ESI) *m/z* $(M+H)^+$ 471.1.

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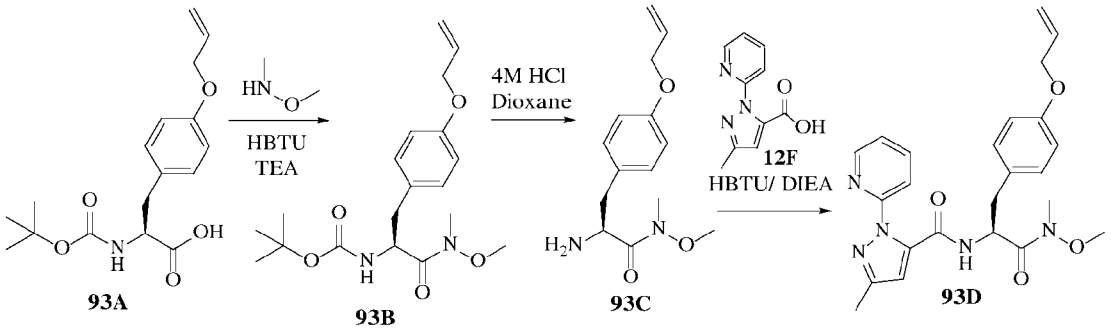
EXAMPLE 54

(*S*)-*N*-(1-(4-(ALLYLOXY)PHENYL)-3-OXOPROPAN-2-YL)-3-METHYL-1-(PYRIDIN-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (93)



[0734] Compound **93A** (1 g, 1.0 eq), N,O-dimethylhydroxylamine (607 mg, 2 eq) and HBTU (1.36 g, 1.15 eq) were combined in 10 mL DMF, the mixture was stirred at room temperature for 5 mins, and then TEA (1.3 mL, 3.0 eq) was added. The resulting mixture was stirred at room temperature for 1h. The mixture was diluted with 100 mL ethyl acetate and 20 mL Hexane, washed with 0.25N HCl, water, saturated aqueous $NaHCO_3$, and brine and concentrated in vacuo to afford intermediate compound **93B** (1 g, yield 88%) as white solid.

[0735] To a solution of compound **93B** (1 g, 1.0 eq) in 6 mLdry DCM was added 3 mL of 4M HCl in Dioxane. Resulting mixture was stirred at room temperature for 2 hrs. DCM and Dioxane were removed under vacuo, residue was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine and concentrated in vacuo to afford intermediate compound **93C** (650mg, yield 90%) as white solid.

[0736] Compound **93C** (125 mg, 1.0 eq), compound **12F** (115 mg, 1.2 eq) and HBTU (226 mg, 1.25 eq) were combined in 5 mL DMF, the mixture was stirred at room temperature for 5 mins, and then DIEA (0.23 mL, 3.0 eq) was added. The resulting mixture was stirred at room temperature for 30 mins. The mixture was diluted with 50 mL ethyl acetate and 20 mL Hexane, washed with water, saturated aqueous $NaHCO_3$ and brine and concentrated in vacuo to afford intermediate compound **93D** (180 mg, yield 85%).

[0737] Compound **6** (90 mg, 1.0 eq) was dissolved in 8 mL dry THF, cooled to -50 °C under N_2. A solution of 1N LAH in THF (0.22 mL, 1.1 eq) was added dropwise at -50 °C. The resulting mixture was stirred at -30 to -10 °C for 2 hrs. The reaction was quenched with saturated aqueous $NaHCO_3$ at -20 °C, and then extracted with 3 x 15 mL acetate. The combined

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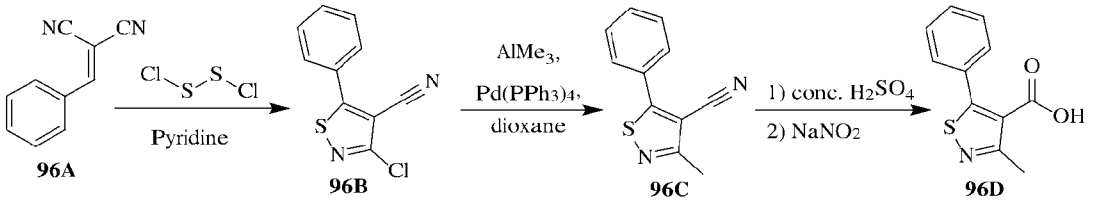
organic phase was dried over Na_2SO_4. The crude mixture was purified on silica gel column to provide compound **93** (40 mg, 51%).

EXAMPLE 55

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-5-PHENYLISOTHIAZOLE-4-CARBOXAMIDE (96)



[0738] To a solution of benzaldehyde (10.00 g, 94.23 mmol) and malononitrile (6.54 g, 98.94 mmol) in EtOH (75.00 mL) was added catalytic piperidine (80.24 mg, 942.30 umol). Then the reaction was stirred at 90°C for 2h. Yellow solid was precipitated out when the reaction mixture was cooled to room temperature, the mixture was filtered, the desired yellow solid was washed with EtOH (20 mL) and dried in vacuo to give intermediate compound **96A** (23.00 g, 79.2% yield) as yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.91 (d, J = 7.7 Hz, 2H), 7.79 (s, 1H), 7.67 - 7.60 (m, 1H), 7.58 - 7.50 (m, 2H).

[0739] To a mixture of compound **96A** (17.50 g, 113.51 mmol) and chlorosulfanyl thiohypochlorite (70.00 g, 518.36 mmol, 41.42 mL) was added pyridine (900.00 mg, 11.38 mmol). Then the reaction was stirred at 140°C for 16h. The reaction mixture was cooled to room temperature and quenched with ice/H_2O (200 mL) and EtOAc (500 mL), yellow solid was was precipitate out, filtered and the filtrate was extracted with EtOAc(100 mL x 2), the combined organic was washed with brine (100 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, eluent of 0 ~ 10% Ethyl acetate/Petroleum ether gradient @ 50 mL/min) to give compound **96B** (21.00 g, 70.4% yield) as light yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.77 (br d, J=7.1 Hz, 2H), 7.65 - 7.53 (m, 3H).

[0740] To a mixture of compound **96B** (2.00 g, 9.06 mmol) in dioxane (150.00 mL) was added $AlMe_3$ (2M, 20.00 mL) and $Pd(PPh_3)_4$ (1.05 g, 906.00 umol) under N_2, Then the reaction was stirred at 110 °C for 3h. The reaction mixture was cooled to room temperature and quenched with ice/H_2O(100 mL) and EtOAc(150 mL), yellow solid was precipitate out, filtered

and the filtrate was extracted with EtOAc(60 mL x 2), the combined organic was washed with brine (70 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash silica gel chromatography (ISCO®;40 g SepaFlash® Silica Flash Column, eluent of 0 ~ 10% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give compound **96C** (700.00 mg, 16.59% yield, 43% purity) as light yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.79 - 7.75 (m, 2H), 7.56 - 7.51 (m, 3H), 2.67 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 200.9.

[0741] To compound **96C** (490.00 mg, 2.45 mmol) was added H_2SO_4 (9.20 g, 93.81 mmol, 5.00 mL), and the reaction was stirred at 135 °C for 1.5h. Then the reaction was cooled to 0 °C and a solution of $NaNO_2$ (339.79 mg, 4.92 mmol) in H_2O (2.00 mL) was added to the above mixture and the reaction mixture was stirred at 70 °C for 1h. The reaction mixture was cooled to room temperature and poured into ice/H_2O(40 mL) and EtOAc(40 mL), extracted with EtOAc(50 mL x 2), the combined organic was extracted with 0.1N NaOH (40 mL x 2), the desired basic water phase was then added 1N HCl to pH<4, then extracted with EtOAc(40 mL x 3) and washed with brine (40 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuo to give compound **96D** (410.00 mg, 76.25% yield) as light yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.49 (s, 5H), 2.57 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 219.9.

[0742] Compound **96** (35 mg, yield: 65.86%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **96D**. Compound **96**: ^{1}H NMR (400MHz, CD_3CN) δ 7.48 - 7.33 (m, 5H), 7.29 - 7.17 (m, 3H), 7.15 - 7.06 (m, 3H), 7.01 (br s, 1H), 6.26 (br s, 1H), 5.56 (ddd, J=4.4, 7.5, 9.5 Hz, 1H), 3.23 (dd, J=4.3, 14.2 Hz, 1H), 2.77 (dd, J=9.5, 14.3 Hz, 1H), 2.28 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 394.1.

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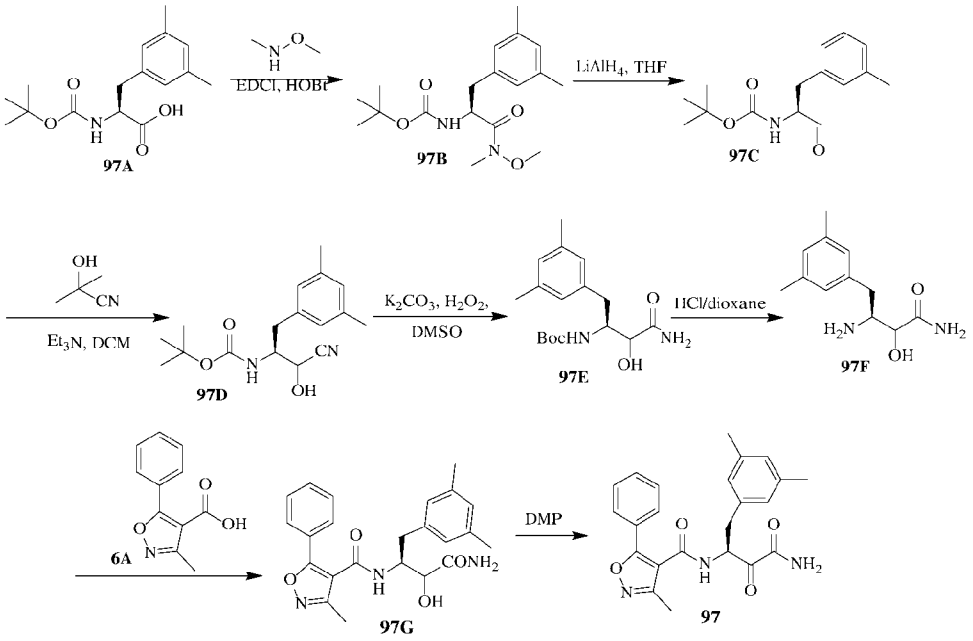
EXAMPLE 56

(*S*)-*N*-(4-AMINO-1-(3,5-DIMETHYLPHENYL)-3,4-DIOXOBUTAN-2-YL)-3-METHYL-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (97)



[0743] A mixture of compound **97A** (1.0 g, 3.41 mmol), compound N,O-dimethylhydroxylamine (400 mg, 4.09 mmol, HCl) , HOBt (460 mg, 3.41 mmol) and NMM (1.03 g, 10.23 mmol, 1.12 mL) in $CHCl_3$ (20 mL) was degassed and purged with N_2 for 3 times at 0 °C, then EDCI (980 mg, 5.12 mmol) was added in portions. The mixture was stirred at 25 °C for 20 h under N_2 atmosphere. The reaction mixture was quenched by addition H_2O (20 mL), and then diluted with DCM (10 mL). The combined organic layers were washed with 1N HCl (15 mL x 2), saturated aqueous $NaHCO_3$ (15 mL x 2) and brine (20 mL), dried over Na2SO4, filtered and concentrated under reduced pressure to give the compound **97B** (1.13 g, yield: 98.5%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.08 (br d, J = 8.2 Hz, 1H), 6.82 (s, 3H), 4.55 (br s, 1H), 3.71 (br s, 3H), 3.09 (s, 3H), 2.82 - 2.72 (m, 1H), 2.68 - 2.58 (m, 1H), 2.22 (s, 6H), 1.32 (s, 9H).

[0744] To a solution of LAH (255 mg, 6.72 mmol) in THF (10 mL) was degassed and purged with N_2 for 3 times at 0 °C , and the mixture of compound **97B** (1.13 g, 3.36 mmol) in THF (20 mL) was added dropwise, and then the mixture was stirred at 0 °C for 2 h under N_2 atmosphere. The reaction mixture was quenched by addition EtOAc (10 mL), then added 1N

HCl (50 mL), and then diluted with EtOAc (20 mL), dried over Na_2SO_4, and stirred for 30 min, then filtered to give the organic layers. The combined organic layers were washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the compound **97C** (860 mg, yield: 92.3%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.48 (s, 1H), 7.24 (br d, J = 7.7 Hz, 1H), 6.85 - 6.73 (m, 3H), 4.08 - 3.94 (m, 1H), 3.04 - 2.91 (m, 1H), 2.70 - 2.57 (m, 1H), 2.20 (s, 6H), 1.39 - 1.19 (m, 9H).

[0745] To a solution of compound **97C** (860 mg, 3.10 mmol) in DCM (10 mL) was added compound 2-hydroxy-2-methylpropanenitrile (530 mg, 6.20 mmol, 570 µL) and Et_3N (470 mg, 4.65 mmol, 650 µL). The mixture was stirred at 25 °C for 22 h. The reaction mixture was quenched by addition 1N HCl (20 mL), and then diluted with H_2O (20 mL) and extracted with DCM (20 mL x 2). The combined organic layers were washed with brine (20 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the compound **97D** (930.00 mg, yield: 98.6%) was obtained as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.19 - 6.99 (m, 1H), 6.91 - 6.78 (m, 3H), 6.77 - 6.51 (m, 1H), 4.66 - 4.34 (m, 1H), 3.84 (br s, 1H), 2.99 - 2.81 (m, 1H), 2.75 - 2.60 (m, 1H), 2.27 (br s, 6H), 1.40 - 1.20 (m, 9H).

[0746] To a solution of compound **97D** (930 mg, 3.63 mmol) and K_2CO_3 (850 mg, 6.11 mmol) in DMSO (10 mL) was added H_2O_2 (3.46 g, 30.55 mmol, 2.94 mL, purity: 30%). The mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was stirred in DCM (3 mL) and PE (25 mL) for 30 min and filtered to give the compound **5** (970 mg, yield: 98.32%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.42 - 7.08 (m, 1H), 6.86 - 6.45 (m, 3H), 6.21 - 5.49 (m, 1H), 4.06 - 3.82 (m, 1H), 3.31 (s, 1H), 2.72 - 2.52 (m, 2H), 2.26 - 2.13 (m, 6H), 1.40 - 1.18 (m, 9H).

[0747] To a solution of compound **97E** (970 mg, 3.01 mmol) in EtOAc (5 mL) was added HCl/EtOAc (4M, 5 mL). The mixture was stirred at 25 °C for 3 h. The reaction mixture was diluted with PE (20 mL), filtered and concentrated under reduced pressure to give the compound **97F** (370 mg, yield: 43.7%, HCl) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.09 - 7.89 (m, 3H), 7.58 (br s, 2H), 6.96 (br s, 2H), 6.89 (s, 1H), 4.26 (br s, 1H),

3.89 (br s, 1H), 3.69 - 3.57 (m, 1H), 2.91 - 2.73 (m, 2H), 2.30 (br s, 6H). MS (ESI) *m/z* $(M+H)^+$ 223.1.

[0748] A mixture of compound **97F** (310 mg, 1.18 mmol, HCl), compound **6A** (200 mg, 984.30 umol), HOBT (133 mg, 984.30 umol) and DIEA (520 uL, 2.95 mmol) in DCM (15 mL) was added EDCI (285 mg, 1.48 mmol), and then the mixture was stirred at 25°C for 18 h. The reaction mixture was washed with H_2O (20 mL x 2). The combined organic layers were washed with HCl (1N, 30 mL), saturated aqueous $NaHCO_3$ (30mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was stirred in Petroleum Ether (5 mL) and DCM (1 mL) for 30 min and filtered to give the compound **97G** (270 mg, yield: 61.9%) was obtained as a white solid. ^1H NMR (400MHz, DMSO-d_6) δ 8.59 - 8.24 (m, 1H), 7.64 - 7.51 (m, 2H), 7.49 - 7.28 (m, 5H), 6.89 - 6.77 (m, 3H), 5.98 - 5.63 (m, 1H), 4.61 - 4.49 (m, 1H), 4.11 - 3.86 (m, 1H), 2.86 - 2.59 (m, 2H), 2.21 - 2.03 (m, 9H). MS (ESI) *m/z* $(M+H)^+$ 408.1.

[0749] To a solution of compound **97G** (100 mg, 245.42 umol) in DCM (10 mL) was added DMP (320 mg, 736.26 umol) at 0 °C. The mixture was stirred at 25°C for 7 h. The reaction mixture was quenched by addition saturated aqueous $Na_2S_2O_3$ (15 mL) and saturated aqueous $NaHCO_3$ (15mL), the mixture was stirred for 0.2 h, and then diluted with DCM (10 mL) and extracted with H_2O (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was stirred in Petroleum Ether (15 mL) and EtOAc (1 mL) for 30 min and filtered to give the compound **97** (60 mg, yield: 60.3%) was obtained as a white solid. ^1H NMR (400MHz, DMSO-d_6) δ 9.01 (br d, J = 7.5 Hz, 1H), 8.18 (br s, 1H), 7.90 (br s, 1H), 7.64 (br d, J=7.3 Hz, 2H), 7.53 - 7.46 (m, 1H), 7.45 - 7.38 (m, 2H), 6.92 - 6.81 (m, 3H), 5.40 (br t, J = 7.3 Hz, 1H), 3.15 (br d, J=10.6 Hz, 1H), 2.72 - 2.58 (m, 1H), 2.18 (s, 6H), 2.11 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 406.1.

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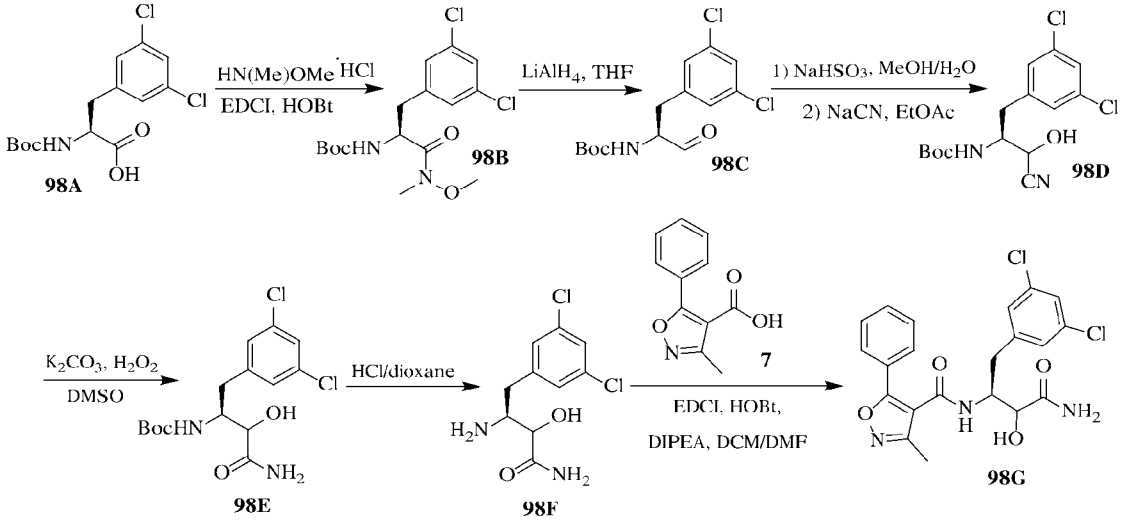
EXAMPLE 57

(*S*)-*N*-(4-AMINO-1-(3,5-DIMETHYLPHENYL)-3,4-DIOXOBUTAN-2-YL)-3-METHYL-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (98)



[0750] To a solution of compound **98A** (1.0 g, 2.99 mmol) and N-methoxymethanamine (321 mg, 3.29 mmol, HCl) in $CHCl_3$ (30 mL) was added HOBt (404 mg, 2.99 mmol,) and EDCI (803 mg, 4.19 mmol). Then NMM (1.3 mL, 11.96 mmol) was added into the reaction mixture. After addition, the reaction mixture was stirred at 28 °C for 14 h. The reaction mixture was concentrated in vacuum and the residue was dissolved into 80 mL of EtOAc. The mixture was washed with 1N HCl (30 mL x 2) and saturated aqueous $NaHCO_3$ (30 mL x 2), then brine (30 mL). The mixture was dried over Na_2SO_4 and concentrated in vacuum to afford compound **98B** (1.1 g, yield 82.9%) as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.44 (s, 1H), 7.34 - 7.19 (m, 3H), 4.55 (br s, 1H), 3.71 (br s, 3H), 3.17 - 3.00 (m, 3H), 2.90 - 2.80 (m, 1H), 2.76 - 2.67 (m, 1H), 1.29 (s, 8H). MS (ESI) *m/z* $(M-56)^+$ 320.9.

[0751] To a solution of $LiAlH_4$ (122 mg, 3.21 mmol) in THF (10 mL) was added a solution of compound **98B** (1.1 g, 2.92 mmol) in THF (20 mL) at 0 °C under N_2 atmosphere. After addition, the reaction mixture was stirred at 0 °C for 1h. 2 mL of EtOAc was added into the reaction mixture at 0 °C and the mixture was stirred for 10 min. Then 2 mL of 1N HCl was added into the reaction mixture slowly. After addition, the mixture was diluted with 80 mL of EtOAc and the mixture was washed with 1 N HCl (30 mL x 2), brine (30 mL). Then the mixture was dried over Na_2SO_4 and concentrated in vacuum to afford compound **98C** (800 mg, yield

80.9%) as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.52 (s, 1H), 7.53 - 7.17 (m, 4H), 4.20 - 4.08(m, 1H), 3.19 -3.08 (m, 1H), 2.72 - 2.63 (m, 1H), 1.37 - 1.27 (m, 9H).

[0752] To a solution of compound **98C** (800 mg, 2.51 mmol) in MeOH (10 mL) was added dropwise a solution of $NaHSO_3$ (261 mg, 2.51 mmol) in H_2O (15 mL) at 0-5 °C. After that, the reaction mixture was stirred at 25 °C for 5h. NaCN (129 mg, 2.64 mmol) in H_2O (20 mL) was added into the reaction mixture followed by EtOAc (40 mL). After that, the reaction mixture was stirred at 25 °C for 14h. The organic layer was separated and washed with brine (30 mL), then dried over Na_2SO_4.The mixture was concentrated to afford compound **98D** (800 mg, yield 92.33%) as light yellow gum. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.46 - 7.22 (m, 3H), 7.16 - 7.02 (m, 1H), 6.89 - 6.70 (m, 1H), 4.65 - 4.30 (m, 1H), 3.95 - 3.76 (m, 1H), 3.07 - 2.87 (m, 1H), 2.76 -2.55 (m, 1H), 1.32 - 1.20 (m, 8H).

[0753] To a solution of compound **98D** (800 mg, 2.32 mmol) and K_2CO_3 (641 mg, 4.64 mmol) in DMSO (8 mL) was added H_2O_2 (2 mL, 22.25 mmol, 30% purity) at 0 °C. After addition, the reaction mixture was stirred at 0 °C for 1h. The reaction mixture was diluted with ice water (20 mL) and 50 mL of saturated aqueous Na_2SO_3. The mixture was extracted with EtOAc (50 mL x 3) and the combined extracts were washed with saturated aqueous Na_2SO_3 (50 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated to afford crude compound. The crude compound was diluted with MTBE (5 mL) and filtered to afford compound **98E** (800 mg, yield 94.9%) as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.48 - 7.12 (m, 5H), 6.73 - 6.20 (m, 1H), 5.86 - 5.63 (m, 1H), 4.04 - 3.71 (m, 2H), 2.86 - 2.54 (m, 1H), 1.34 - 1.19 (m, 9H). MS (ESI) *m/z* $(M+23)^+$ 384.9.

[0754] To a solution of compound **98E** (800 mg, 2.20 mmol) in EtOAc (10 mL) was added HCl/EtOAc (4M, 55 mL). After addition, the reaction mixture was stirred at 26 °C for 1h. 20 mL of Petroleum ether was added into the reaction mixture and the mixture was filtered to afford compound **98F** (400 mg, yield 58.87%, HCl) as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.35 (br s, 1H), 8.14 (br s, 1H), 7.62 - 7.41 (m, 3H), 7.33 (d, J=1.8 Hz, 1H), 6.90 - 6.50 (m, 1H), 4.28 (br s, 1H), 3.94 - 3.84 (m, 1H), 3.77 - 3.56 (m, 1H), 3.03 - 2.80 (m, 2H).

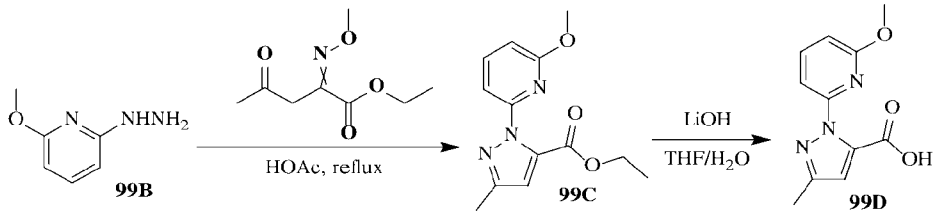
[0755] To a solution of compound **7** (100 mg, 492.15 umol) and compound **98F** (162 mg, 541.37 umol, HCl) in DMF (10 mL) was added HOBT (67 mg, 492.15 umol) and DIEA (340 uL, 1.97 mmol), then EDCI (133 mg, 689.01 umol) was added. After addition, the reaction

mixture was stirred at 26 °C for 14h. The mixture was diluted with 30 mL of EtOAc. The mixture was washed with 1N HCl (15 mL x 2) and saturated aqueous $NaHCO_3$ (15 mL x 3), then brine (20 mL). The residue was dried over Na_2SO_4 and concentrated in vacuum. The residue was diluted with 4 mL of EtOAc and filtered to afford compound **98G** (110 mg, yield 45.87%) as white solid. ^1H NMR (400MHz, DMSO-d_6) δ 8.65 - 8.26 (m, 1H), 7.60 - 7.30 (m, 9H), 7.28 - 7.17 (m, 1H), 6.04 - 5.65 (m, 1H), 4.73 - 4.56 (m, 1H), 4.11 - 4.06 (m, 0.5H), 4.01 - 3.95 (m, 0.5H), 3.01 - 2.70 (m, 2H), 2.18 - 2.09 (m, 3H). MS (ESI) *m/z* $(M+H)^+$ 448.1.

[0756] To a solution of compound **98G** (110 mg, 245.37 umol) in DCM (30 mL) and DMSO (4 mL) was added DMP (416 mg, 981.48 umol). After addition, the reaction mixture was stirred at 26 °C for 2h. 10 mL of saturated aqueous $Na_2S_2O_3$ and 10 mL of saturated aqueous $NaHCO_3$ was added into the reaction mixture, and the mixture was stirred for 20 min. Then the mixture was separated, the organic layer was washed with 10 mL of saturated aqueous $Na_2S_2O_3$ and 10 mL of saturated aqueous $NaHCO_3$, then water (20 mL) and brine (20 mL). The mixture was dried over Na_2SO_4 and concentrated in vacuum to afford compound **98** (30 mg, yield 24.66%) as light yellow solid. ^1H NMR (400MHz, DMSO-d_6) δ 9.08 (d, *J*=7.5 Hz, 1H), 8.21 (s, 1H), 7.94 (s,1H), 7.68 - 7.58 (m, 2H), 7.54 - 7.42 (m, 4H), 7.34 (d, *J*=1.8 Hz, 2H), 5.45 - 5.33 (m, 1H), 3.28 - 3.19 (m, 1H), 2.83 - 2.73 (m, 1H), 2.12 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 446.0.

EXAMPLE 58

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(6-METHOXYPYRIDIN-2-YL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (99)



99B 99C 99D

[0757] A mixture of compound 2-chloro-6-methoxypyridine (5.0 g, 34.83 mmol) in $NH_2NH_2{\cdot}H_2O$ (17.44 g, 348.30 mmol, 16.93 mL) was stirred at 120 °C for 16h. The reaction mixture was concentrated under reduced pressure to give a residue .then diluted with H_2O (30 mL) and extracted with ethyl acetate (40 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl

acetate = 5:1 to 1:1) to give compound **99B** (1.06 g, 21.87% yield) as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.41 (t, J=7.8 Hz, 1H), 6.24 - 6.08 (m, 2H), 5.73 (br s, 1H), 3.86 (s, 3H), 3.83 - 2.75 (m, 2H). MS (ESI) *m/z* $(M+H)^+$ 140.1.

[0758] A mixture of compound **99B** (1.00 g, 7.19 mmol) and ethyl 2-(methoxyimino)-4-oxopentanoate (1.35 g, 7.19 mmol) in HOAc (20.00 mL) was stirred at 120 °C for 16h. The reaction mixture was concentrated under reduced pressure to remove HOAc. The residue was diluted with H_2O (20 mL) and extracted with ethyl acetate (20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1:0 to 5:1) and further purified by preparatory-HPLC (TFA condition) to give compound **99C** (487.00 mg, 25.87% yield) was obtained as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.70 (t, *J*=7.9 Hz, 1H), 7.21 (d, *J*=7.5 Hz, 1H), 6.71 (d, *J*=8.2 Hz, 1H), 6.66 (s, 1H), 4.27 (q, *J*=7.2 Hz, 2H), 3.85 (s, 3H), 2.36 (s, 3H), 1.25 (t, *J*=7.2 Hz, 3H). MS (ESI) *m/z* $(M+H)^+$ 261.9.

[0759] To a solution of compound **99C** (487.00 mg, 1.99 mmol) in THF (15.00 mL) was added $LiOH{\cdot}H_2O$ (417.50 mg, 9.95 mmol) in H_2O (5.00 mL). The mixture was stirred at 28 °C for 16h. The reaction mixture was diluted with H_2O (10 mL) and extracted with MTBE (15 mL x 2), the water phase was added 1N HCl to pH = 3~4, extracted with EA (15 mL x 2). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give intermediate compound **99D** (396 mg, 91.61% yield) as a white solid. Compound **99D**: **^{1}H NMR** (400MHz, DMSO-d_6) δ 7.86 (t, *J*=7.8 Hz, 1H), 7.26 (d, *J*=7.5 Hz, 1H), 6.80 (d, *J*=8.2 Hz, 1H), 6.67 (s, 1H), 3.80 (s, 3H), 2.26 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 234.1.

[0760] Compound **99** (10.00 mg, 13.78% yield, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **99D**. Compound **99**: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.68 (br t, *J*=7.9 Hz, 1H), 7.26 - 7.18 (m, 4H), 7.12 - 7.01 (m, 3H), 6.73 (br s, 1H), 6.68 - 6.60 (m, 1H), 6.65 (br d, *J*=8.2 Hz, 1H), 6.50 (s, 1H), 5.73 - 5.64 (m, 1H), 5.50 (br s, 1H), 3.67 (s, 3H), 3.45 - 3.35 (m, 1H), 3.25 - 3.11 (m, 1H), 2.33 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 408.1.

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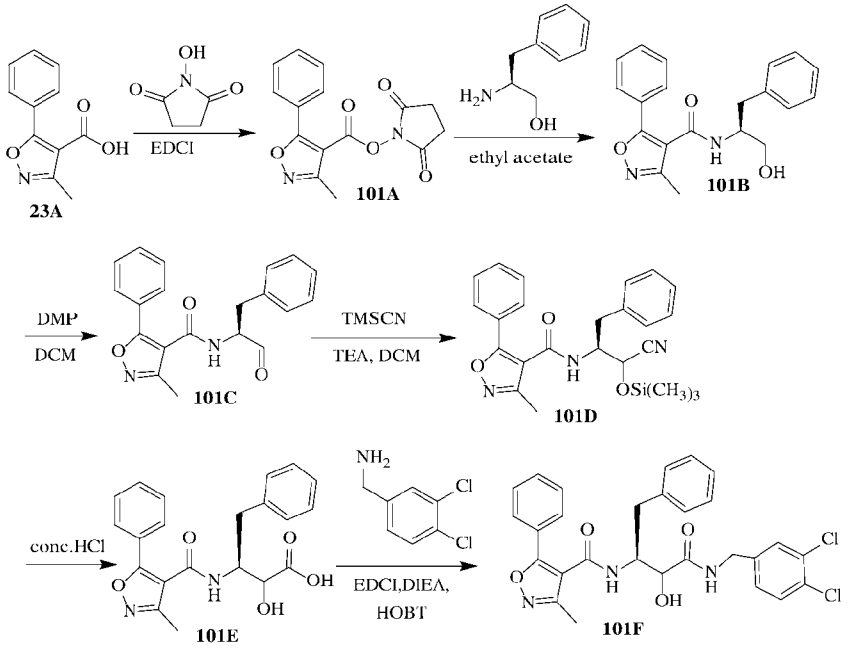
EXAMPLE 59

COMPOUNDS 101, 493

(*S*)-*N*-(4-((3,4-DICHLOROBENZYL)AMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (101)



[0761] To a solution of compound **23A** (20.00 g, 98.43 mmol) in THF (300 mL) was added 1-hydroxypyrrolidine-2,5-dione (12.46 g, 108.27 mmol) and EDCI (22.64 g, 118.12 mmol) with DCM (200 mL). The mixture was stirred at 25 °C for 12 hours. The reaction mixture was concentrated and diluted with ethyl acetate (200 mL). Then the mixture was washed with HCl (1M, 200 mL), saturated aqueous $NaHCO_3$ (200 mL), dried over Na2SO4 and concentrated. Compound **101A** (28.00 g, crude) was obtained as a yellow oil. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.94 - 7.88 (m, 2H), 7.69 - 7.63 (m, 1H), 7.62 - 7.56 (m, 2H), 2.87 (br s, 4H), 2.50 - 2.48 (m, 3H).

[0762] To a solution of compound **101A** (28.00 g, 93.25 mmol) in DMF (200 mL) was added (2S)-2-amino-3-phenyl-propan-1-ol (15.51 g, 102.57 mmol). The mixture was stirred at 25 °C for 12 hour. The mixture was diluted with H_2O (1000 mL), extracted with ethyl acetate (1000 mL), the organic layer was washed with HCl (aqueous 1000 mL), $NaHCO_3$ (aqueous 1000 mL), dried over Na_2SO_4 and concentrated. Compound **3** (20.00 g, yield 63.8%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.45 (br d, J = 8.8 Hz, 1H), 7.66 - 7.61 (m, 2H),

7.53 - 7.40 (m, 3H), 7.32 - 7.18 (m, 5H), 4.97 - 4.92 (m, 1H), 4.33 - 4.23 (m, 1H), 3.54 - 3.41 (m, 2H), 3.01 - 2.97 (m, 1H), 2.69 - 2.57 (m, 1H), 2.06 (s, 3H).

[0763] To a solution of compound **101B** (3.00 g, 8.92 mmol) in DCM (100 mL) was added DMP (5.67 g, 13.38 mmol). The mixture was stirred at 25 °C for 3 hour. The mixture quenched with 10% $Na_2S_2O_3$ (aqueous): saturated $NaHCO_3$ (aqueous) (1:1, 200 mL), extracted with DCM (200 mL) and washed with brine (200 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated. Compound **101C** (2.70 g, yield 90.5%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.66 (s, 1H), 8.91 (d, J = 8.4 Hz, 1H), 7.67 - 7.63 (m, 2H), 7.53 - 7.47 (m, 1H), 7.46 - 7.40 (m, 2H), 7.29 - 7.19 (m, 5H), 4.79 - 4.72 (m, 1H), 3.37 - 3.32 (m, 1H), 2.81 - 2.72 (m, 1H), 2.09 (s, 3H).

[0764] To a solution of compound **101C** (500.0 mg, 1.50 mmol) in DCM (20 mL) was added TMSCN (223.2 mg, 2.25 mmol, 280 uL) and TEA (15.2 mg, 150.00 umol, 20 uL). The mixture was stirred at 0 °C for 3 hours. The mixture was concentrated, diluted with ethyl acetate (20 mL), washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated to obtain compound **101D** (600.0 mg, crude) as colorless oil.

[0765] To a solution of compound **101D** (600.0 mg, 1.41 mmol) in THF (10 mL) was added HCl (10 mL). The mixture was stirred at 60 °C for 12 hours. The mixture was diluted with H_2O (200 mL), extracted with ethyl acetate (100 mL), the organic layer was washed with $NaHCO_3$ (aqueous 100 mL), the water phase was added HCl (1M) until pH ~ 1, then extracted with ethyl acetate (100 mL), the organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated. Compound **101E** (240.0 mg, crude) was obtained as a colorless oil and used in next step directly.

[0766] To a solution of compound **101E** (200.0 mg, 526 umol) in THF (10.00 mL) was added (3,4-dichlorophenyl)methanamine (92.6 mg, 525.78 umol, 70 uL), DIEA (203.85 mg, 1.58 mmol, 275.48 uL), HOBt (71.04 mg, 525.78 umol) and EDCI (120.95 mg, 630.93 umol). The mixture was stirred at 25 °C for 4 hours. The mixture was concentrated and diluted with ethyl acetate (50 mL), washed with HCl (1M, 50 mL), saturated $NaHCO_3$ (aqueous 50 mL), brine (50 mL x 3), dried over Na_2SO_4 and concentrated. The mixture was triturated with CH_3CN (5 mL) and filtered. Compound **101F** (70.0 mg, yield 24.7%) obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.63 - 8.53 (m, 1H), 8.30 (d, J = 9.2 Hz, 1H), 7.58 - 7.10 (m, 13H), 6.20

- 5.94 (m, 1H), 4.68 - 4.57 (m, 1H), 4.32 - 4.16 (m, 2H), 4.08 - 3.99 (m, 1H), 2.97 - 2.67 (m, 2H), 2.07 - 1.96 (m, 1H), 2.07 - 1.96 (m, 2H).

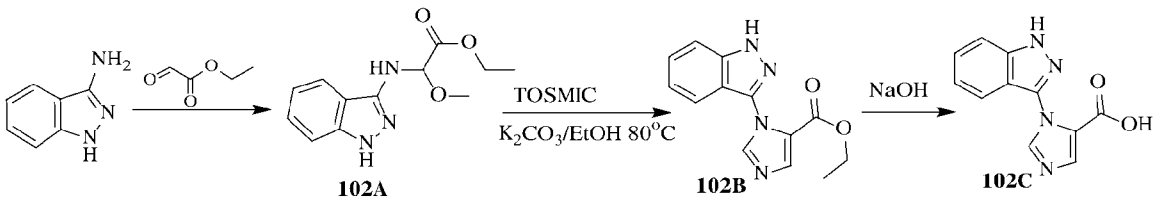
[0767] To a solution of compound **101F** (60.0 mg, 111.44 umol,) in DCM (10 mL) and DMSO (1.00 mL) was added DMP (141.8 mg, 334.32 umol). The mixture was stirred at 25 °C for 3 hours. The mixture quenched with 10% $Na_2S_2O_3$ (aqueous): saturated $NaHCO_3$ (aqueous) (1:1, 20 mL), extracted with DCM (10 mL) and washed with brine (20 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated. Compound **101** (33.2 mg, yield 55.5%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.52 - 9.43 (m, 1H), 9.12 (d, J = 7.6 Hz, 1H), 7.69 - 7.38 (m, 7H), 7.35 - 7.20 (m, 6H), 5.53 - 5.42 (m, 1H), 4.40 - 4.32 (m, 2H), 3.31 - 3.19 (m, 1H), 2.93 - 2.71 (m, 1H), 2.12 - 2.00 (m, 3H). MS (ESI) *m/z* $(M+H)^+$ 536.1.

(*S*)-*N*-(4-(((1*H*-BENZO[*d*]IMIDAZOL-5-YL)METHYL)AMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (493)

[0768] Compound **493** (20 mg, 23.4% yield, yellow solid) was prepared as in compound **101** from the corresponding intermediate carboxylic acid, compound **101E** and (1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-5-yl)methanamine followed by removal of the 2-(trimethylsilyl)ethoxy)methyl group to obtain compound **493**. Compound **493**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.67 - 7.59 (m, 3H), 7.56 (br s, 1H), 7.52 - 7.38 (m, 4H), 7.30 (br s, 1H), 7.25 - 7.14 (m, 4H), 6.89 (br d, J = 6.2 Hz, 2H), 6.12 (br d, J = 6.8 Hz, 1H), 5.72 - 5.63 (m, 1H), 4.62 (br d, J = 5.5 Hz, 2H), 3.37 (br dd, J = 4.7, 14.0 Hz, 1H), 2.99 (br dd, J = 7.9, 14.3 Hz, 1H), 2.33 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 378.1.

EXAMPLE 60

(*S*)-1-(1*H*-INDAZOL-3-YL)-*N*-(1-OXO-3-PHENYLPROPAN-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (102)



[0769] To a solution of 1*H*-indazol-3-amine (8.7 g, 65.3 mmol) in MeOH (90 mL) was added ethyl 2-oxoacetate (20 g, 98.01 mmol). The mixture was stirred at 25°C for 2 hours.

The mixture was filtered and concentrated to give crude product **102A** (15 g, crude) as brown solid, which was used for the next step without purification.

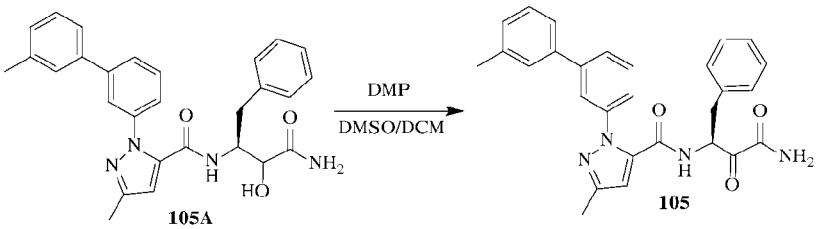
[0770] To a solution of **102A** (15 g, 69.1 mmol) in EtOH (400 mL) was added K_2CO_3 (14.5 g, 104 mmol) and TosMIC (11.6 g 59.4 mmol). The mixture was stirred at 90 °C for 0.5 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1:0 to 1:1) to give compound **102B** (2.9 g, yield: 16.4%) as yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 11.04 (br s, 1H), 7.98 (d, J = 0.7 Hz, 1H), 7.91 (s, 1H), 7.48 - 7.41 (m, 3H), 7.25 - 7.19 (m, 1H), 4.24 - 4.14 (m, 2H), 1.14 (t, J = 7.1 Hz, 3H).

[0771] To a solution of **102B** (2.9 g, 11.3 mmol) in THF (40 mL) and H_2O (8 mL) was added NaOH (905 mg, 22.6 mmol). The mixture was stirred at 25 °C for 10 hours. The mixture was concentrated under reduced pressure to remove the organic solvent, and extracted with EtOAc (20 mL). The aqueous layer was acidified with 1M HCl to pH ~ 5 and then extracted with EtOAc (30 mL x 3). The combined organic layer was washed with H_2O (40 mL), brine (40 mL), dried over Na_2SO_4, filtered and concentrated to give **102C** (1.5 g, yield: 58.1%) as yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 13.35 (s, 1H), 8.16 (s, 1H), 7.83 (s, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.47 - 7.41 (m, 2H), 7.20 - 7.15 (m, 1H). MS (ESI) m/z $(M+H)^+$ 228.9.

[0772] Compound **102** (20 mg, yield 52.9%, pale yellow solid) was prepared as in Example **6** from the corresponding intermediate compounds **102C** and **21G** ((*S*)-2-amino-3-phenylpropan-1-ol). Compound **102**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 13.22 (s, 1H), 9.48 (s, 1H), 8.95 (d, J = 8.0 Hz, 1H), 8.07 (s, 1H), 7.72 (s, 1H), 7.59 - 7.51 (m, 1H), 7.42 - 7.40 (m, 1H), 7.31 - 7.24 (m, 2H), 7.24 - 7.18 (m, 4H), 7.12 - 7.06 (m, 1H), 7.06 - 7.06 (m, 1H), 4.34 - 4.23 (m, 1H), 3.19- 3.15 (m, 1H), 2.77 - 2.74(m, 1H). MS (ESI) m/z $(M+H)^+$ 360.1.

EXAMPLE 61

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(3'-METHYL-[1,1'-BIPHENYL]-3-YL)-1H-PYRAZOLE-5-CARBOXAMIDE (105)



[0773] To a mixture of compound **103A** (150 mg, 0.33 mmol) and m-tolylboronic acid (89 mg, 0.66 mmol) in THF (50 mL) was added H_2O (10 mL), Na_2CO_3 (70 mg, 0.66 mmol) and $Pd(PPh_3)_4$ (38 mg, 0.033 mmol) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C for 12h. The reaction mixture was added H_2O (100 mL) and extracted with EA (100 mL x 3). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (150 mL x 3), brine (150 mL x 3), dried over Na_2SO_4 and concentrated. The crude product was treated with i-propyl ether/CH_3CN (10/1, 10 mL). The solid was collected and dried in vacuo to afford compound **2A** (72.7 mg, yield 42.70%) as gray solid. Compound **105A**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.51 - 8.10 (m, 1H), 7.60 - 7.52 (m, 2H), 7.47 - 7.38 (m, 2H), 7.36 - 7.28 (m, 3H), 7.26 - 7.12 (m, 7H), 7.03 - 6.93 (m, 1H), 6.57 (d, J = 3.3 Hz, 1H), 5.93 - 5.73 (m, 1H), 4.49 - 4.29 (m, 1H), 4.04 - 3.86 (m, 1H), 2.90 - 2.81 (m, 1H), 2.81 - 2.72 (m, 1H), 2.35 (s, 3H), 2.24 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 469.2.

[0774] To a mixture of compound **105A** (65 mg, 0.14 mmol) in DCM (10 mL) and DMSO (1 mL) was added DMP (177 mg, 0.42 mmol) in one portion at 0 °C. The mixture was stirred at 0 °C for 10 min, then temperature to 25 °C and stirred for 2 hours. The reaction was quenched by 20 mL of 10 % $Na_2S_2O_3$ aquoeus solution and 20 mL of saturated aqueous $NaHCO_3$ solution and then extracted with DCM (30 mL x 3). The combined organic phase was washed with brine (40 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by preparatory-HPLC (basic condition) to afford compound **105** (35.0 mg, yield 53.6%) as white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.08 (d, J = 7.7 Hz, 1H), 8.08 - 8.00 (m, 1H), 7.84 (br s, 1H), 7.60 - 7.52 (m, 2H), 7.45 - 7.37 (m, 3H), 7.36 -7.30 (m, 1H), 7.28 - 7.25 (m, 3H), 7.23 - 7.16 (m, 3H), 7.12 - 7.06 (m, 1H), 6.60 (br s, 1H), 5.29 (br s, 1H), 3.22 - 3.14 (m, 1H), 2.86 - 2.76 (m, 1H), 2.35 (s, 3H), 2.28 - 2.22 (m, 3H). MS (ESI) *m/z* $(M+H)^+$ 467.2.

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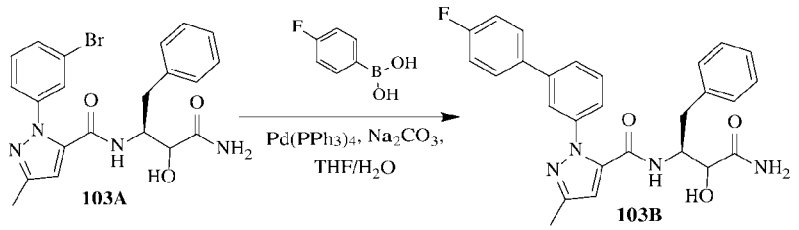
EXAMPLE 62

COMPOUNDS 103, 106, 216-218, 214

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(4'-FLUORO-[1,1'-BIPHENYL]-3-YL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (103)



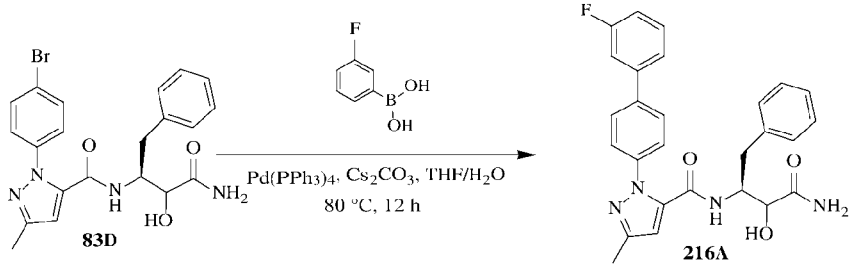
[0775] Compound **103B** (110 mg, yield 70.98%, off-white solid) was prepared as in Example **49** from the corresponding intermediate compounds **103A** and (4-fluorophenyl)boronic acid. Compound **103B**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.45 (d, J = 9.0 Hz, 0.5H), 8.15 (d, J = 9.0 Hz, 0.5H), 7.68 - 7.52 (m, 4H), 7.40 - 7.13 (m, 10H), 7.02 (br d, J = 8.4 Hz, 0.5H), 6.94 (br d, J = 7.9 Hz, 0.5H), 6.59 (d, J = 2.4 Hz, 1H), 5.93 - 5.74 (m, 1H), 4.49 - 4.32 (m, 1H), 4.02 - 3.88 (m, 1H), 2.95 - 2.66 (m, 2H), 2.26 - 2.19 (m, 3H).

[0776] Compound **103** (78 mg, yield 68.93%, pale yellow solid) was prepared as in Example **61** from the corresponding intermediate compounds **103B**. Compound **103**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.09 (d, J = 7.7 Hz, 1H), 8.09 (s, 1H), 7.86 (s, 1H), 7.65 (dd, J = 5.4, 8.7 Hz, 2H), 7.58 (br d, J = 7.7 Hz, 1H), 7.52 (s, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.32 - 7.25 (m, 6H), 7.23 - 7.19 (m, 1H), 7.11 (br d, J=7.9 Hz, 1H), 6.60 (s, 1H), 5.35 - 5.25 (m, 1H), 3.18 (dd, J = 3.5, 13.7 Hz, 1H), 2.81 (dd, J = 10.4, 13.7 Hz, 1H), 2.25 (s, 3H). MS (ESI) m/z $(M+H)^+$ 471.1.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(3'-FLUORO-[1,1'-BIPHENYL]-3-YL)-3-METHYL-1H-PYRAZOLE-5-CARBOXAMIDE (106)

[0777] Compound **106** (18.7 mg, yield 46.2%, light yellow solid) was prepared as in Example **61** from the corresponding starting materials, compound **103A** and (3-fluorophenyl)boronic acid. Compound **106**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.08 (br d, J = 7.7 Hz, 1H), 8.05 (br s, 1H), 7.85 (br s, 1H), 7.69 - 7.62 (m, 1H), 7.60 - 7.56 (m, 1H), 7.52 - 7.43 (m, 3H), 7.43 - 7.37 (m, 1H), 7.33 - 7.24 (m, 4H), 7.24 - 7.15 (m, 2H), 7.13- 7.05 (m, 1H), 6.62 (s, 1H), 5.35 - 5.25 (m, 1H), 3.20 - 3.15 (m, 1H), 2.86 - 2.76 (m, 1H), 2.28 - 2.21 (m, 3H). MS (ESI) m/z $(M+H)^+$ 471.1.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(3'-FLUORO-[1,1'-BIPHENYL]-4-YL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (216)



[0778] Compound **216** (26 mg, yield 16.7%, yellow solid) was prepared as in Example **62** from the corresponding starting materials, compound **83D** and (3-fluorophenyl)boronic acid. Compound **216**: ^{1}H NMR ($CDCl_3$,400MHz) δ 7.59 (br d, J = 7.7 Hz, 2H), 7.47 - 7.35 (m, 4H), 7.33 - 7.27 (m, 4H), 7.05 (br d, J = 6.4 Hz, 3H), 6.75 (br s, 1H), 6.49 (s, 1H), 6.42 - 6.33 (m, 1H), 5.66 - 5.50 (m, 2H), 3.39 (br dd, J = 5.0, 13.8 Hz, 1H), 3.16 (br dd, J = 7.4, 14.0 Hz, 1H), 2.40 - 2.29 (m, 3H). MS (ESI) m/z $(M+H)^+$ 471.1.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(2'-FLUORO-[1,1'-BIPHENYL]-4-YL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (217)

[0779] Compound **217** was prepared as in Example **62** from the corresponding starting materials, compound **83D** and (2-fluorophenyl)boronic acid. Compound **217** (13 mg, yield 14.49%, yellow solid): ^{1}H NMR ($CDCl_3$,400MHz) δ 7.59 (d, J = 7.3 Hz, 2H), 7.49 - 7.39 (m, 3H), 7.37 - 7.26 (m, 3H), 7.24 - 7.13 (m, 3H), 7.02 (br d, J = 6.0 Hz, 2H), 6.72 (br s, 1H), 6.49 (s, 1H), 6.37 - 6.29 (m, 1H), 5.62 - 5.49 (m, 2H), 3.36 (dd, J = 5.3, 14.1 Hz, 1H), 3.11 (dd, J = 7.4, 14.0 Hz, 1H), 2.38 - 2.29 (m, 3H). MS (ESI) m/z $(M+H)^+$ 471.2.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(3'-METHYL-[1,1'-BIPHENYL]-4-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (218)

[0780] Compound **218** was prepared as in Example **62** from the corresponding starting materials, compound **83D** and *m*-tolylboronic acid. Compound **218** (yield 36.1%, yellow solid): ^{1}H NMR ($CDCl_3$,400MHz) δ 9.16 (d, J = 7.7 Hz, 1H), 8.11 (s, 1H), 7.87 (s, 1H), 7.60 (d, J = 8.6 Hz, 2H), 7.50 - 7.43 (m, 2H), 7.38 - 7.28 (m, 5H), 7.26 - 7.21 (m, 3H), 7.18 (br d, J = 7.5 Hz, 1H), 6.54 (s, 1H), 5.28 - 5.18 (m, 1H), 3.20 (br dd, J = 3.6, 13.8 Hz, 1H), 2.83 (dd, J = 10.6, 13.7 Hz, 1H), 2.37 (s, 3H), 2.24 (s, 3H).

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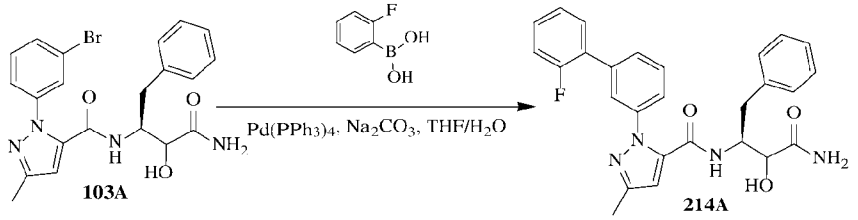
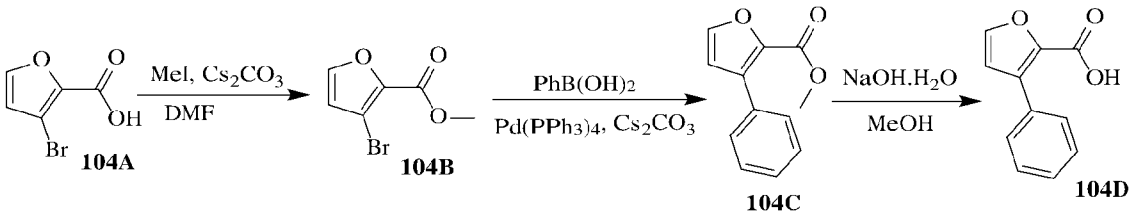
(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(2'-FLUORO-[1,1'-BIPHENYL]-3-YL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (214)



[0781] Compound **214** was prepared as in Example **62** from the corresponding starting materials, compound **103A** and (2-fluorophenyl)boronic acid. Compound **214** (20 mg, yield 29.5%, white solid): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 - 7.55 (m, 2H), 7.52 - 7.43 (m, 2H), 7.41 - 7.30 (m, 2H), 7.26 - 7.22 (m, 3H), 7.21 - 7.13 (m, 2H), 7.03 - 6.94 (m, 2H), 6.65 (br s, 1H), 6.49 (s, 1H), 6.33 - 6.26 (m, 1H), 5.56 - 5.52 (m, 1H), 5.37 (br s, 1H), 3.38 - 3.31 (m, 1H), 3.17 - 3.09 (m, 1H), 2.36 - 2.30 (m, 3H). MS (ESI) *m/z* $(M+H)^+$ 471.1.

EXAMPLE 63

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-PHENYLFURAN-2-CARBOXAMIDE (104)



[0782] To a solution of i-Pr_2NH (3 mL ,18.71 mmol) in anhydrous THF (13 mL) was added n-BuLi (7 mL,18.71 mmol) dropwise at -78 °C and stirred at 0 °C for 30 min. Then a solution of 3-bromofuran (2.5 g, 17.01 mmol) in THF (13 mL) was added to the mixture drop wise at -78 °C and the mixture was stirred at -78 °C for 30 minutes. Anhydrous CO_2 was poured into the solution at -78 °C for 30 minutes. The reaction was quenched with H_2O (20 mL) and extracted with ethyl acetate (20 mL), then water phase was treated with HCl until pH ~ 3. The precipitation was filtered and dried under reduced pressure. Compound **104A** (1.8g, crude) was obtained as yellow solid. ^{1}H NMR (DMSO-d_6, 400MHz) δ 7.96 (d, J = 1.8 Hz, 1H), 6.89 (d, J = 1.8 Hz, 1H).

[0783] Cs_2CO_3 (2.13 g, 6.55 mmol) was added to a solution of compound **104A** (500 mg, 2.62 mmol) in DMF (10 mL). Then MeI (652.43 uL, 10.48 mmol) was added to the mixture. The mixture was stirred at 25 °C for 13h. The mixture was diluted with ethyl acetate (35 mL) and H_2O (30 mL). The organic layer was separated and the aqueous layer was washed extracted with ethyl acetate (20 mL x 2). The combined organic layer was washed brine (30 mL), dried over MgSO4, filtered and concentrated. The residue was purified by Flash column chromatography (Petroleum Ether/Ethyl Acetate = 15/1). Compound **104B** (250 mg, yield 46.54%) was obtained as white solid. ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.50 (d, J = 2.0 Hz, 1H), 6.61 (d, J = 2.0 Hz, 1H), 3.94 - 3.92 (m, 3H)

[0784] To a solution of Compound **104B** (221 mg, 1.08 mmol) in THF (4 mL) and H_2O (2 mL) was added phenylboronic acid (263 mg, 2.16 mmol) and Cs_2CO_3 (553 mg, 1.70 mmol), followed by $Pd(PPh_3)_4$ (125 mg, 108.00 umol), then the mixture was heated to 80 °C and stirred for 12h. The reaction mixture was cooled to the room temperature and H_2O (6 mL) was added to quenched the reaction. The mixture was extracted with ethyl acetate (10mL x 2). The combined organic layer was washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4, filtered, evaporated under reduced pressure. The residue was purified by FCC (PE/EA: 0 to 10/1). Compound **104C** (180 mg, yield 82.42%) was obtained as yellow oil. ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.61 - 7.55 (m, 3H), 7.45 - 7.35 (m, 3H), 6.64 (d, J = 1.8 Hz, 1H), 3.86 (s, 3H)

[0785] To a solution Compound **104C** (170 mg, 840.71 umol) in MeOH (5 mL) was added NaOH (2 M, 2 mL) dropwise, then the mixture was stirred at 25 °C for 2h. The reaction was diluted with H_2O (5 mL) and removed solvent under reduced pressure, then the mixture was extracted with MTBE (5 mL). The water phase was treated with HCl (1 M) until pH ~ 3, then water phase was extracted with ethyl acetate (5 mL x 3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, evaporated under reduced pressure. Compound **104D** (120 mg, yield 75.85%) was obtained as white solid which was used directly in next step. ^{1}H NMR (DMSO-d_6, 400MHz) δ 7.90 (d, J = 1.8 Hz, 1H), 7.59 - 7.53 (m, 2H), 7.39 - 7.28 (m, 3H), 6.80 (d, J = 1.8 Hz, 1H)

[0786] Compound **104** (35 mg, yield 44.0%, yellow solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **104D**. Compound **104**: ^{1}H NMR (DMSO-d_6, 400MHz) δ 8.56 (d, J = 7.5 Hz, 1H), 8.07 (s, 1H), 7.88 (d, J = 1.8 Hz,

1H), 7.81 (s, 1H), 7.61 - 7.54 (m, 2H), 7.36 - 7.29 (m, 3H), 7.29 - 7.25 (m, 4H), 7.21 - 7.17 (m, 1H), 6.90 - 6.83 (m, 1H), 5.39 - 5.29 (m, 1H), 3.21 - 3.12 (m, 1H), 3.01 - 2.92 (m, 1H). MS (ESI) *m/z* $(M+H)^+$ 363.1

EXAMPLE 64

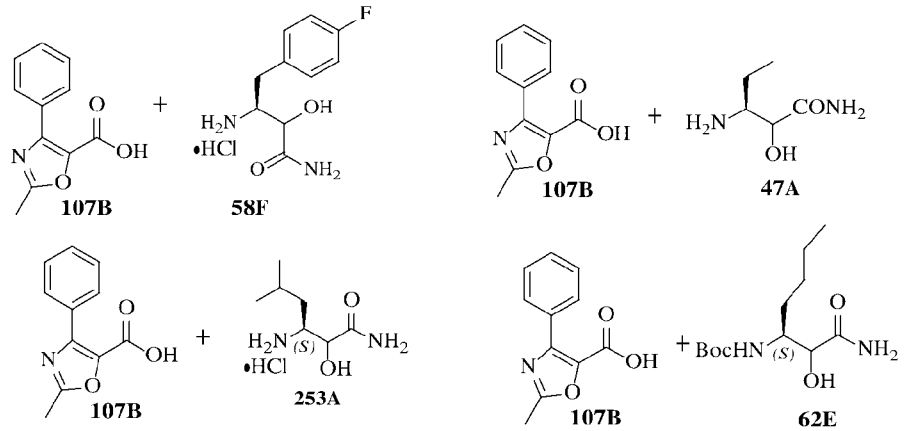
COMPOUNDS 107, 243, 253, 265, 168, 459, 460, 475

(*S*)-*N*-(4-AMINO-1-(4-FLUOROPHENYL)-3,4-DIOXOBUTAN-2-YL)-2-METHYL-4-PHENYLOXAZOLE-5-CARBOXAMIDE (107)

(*S*)-*N*-(1-AMINO-1,2-DIOXOPENTAN-3-YL)-2-METHYL-4-PHENYLOXAZOLE-5-CARBOXAMIDE (243)

(*S*)-*N*-(1-AMINO-5-METHYL-1,2-DIOXOHEXAN-3-YL)-2-METHYL-4-PHENYLOXAZOLE-5-CARBOXAMIDE (253)

(*S*)-*N*-(1-AMINO-1,2-DIOXOHEPTAN-3-YL)-2-METHYL-4-PHENYLOXAZOLE-5-CARBOXAMIDE (265)



[0787] Compounds **107**, **243**, **253** and **265** were prepared as in Example 5 from the corresponding starting materials, respectively—compound **107B** and compound **58F**, **47A**, **253A** or **62E**.

[0788] Compound **107** (77.3 mg, 51.80% yield, white solid): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 - 8.05 (m, 2H), 7.46 - 7.36 (m, 3H), 7.12 - 7.05(m, 2H), 7.00 - 6.94 (m, 2H), 6.79 - 6.70 (m, 2H), 5.72 - 5.64 (m, 1H), 5.53 (br s,1H), 5.57 - 5.47 (m, 1H), 3.46 - 3.38 (m, 1H), 3.24 - 3.16 (m,, 1H), 2.56 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 396.1.

[0789] Compound **243** (52.8 mg, 42.87% yield, yellow solid): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 6.8 Hz, 2H), 7.47 - 7.33 (m, 3H), 6.91 -6.81 (m, 1H), 6.75 (br s, 1H), 5.53

- 5.36 (m, 2H), 2.58 (s, 3H), 2.20 - 2.08 (m, 1H),1.88 - 1.76 (m, 1H), 0.99 (t, J = 7.2 Hz, 3H). MS (ESI) m/z $(M+H)^-$ 316.1.

[0790] Compound **253** (6.5 mg, 6.42% yield, white solid): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19 - 8.09 (m, 2H), 7.50 - 7.34 (m, 3H), 6.84 - 6.68 (m, 2H), 5.55 - 5.38 (m, 2H), 2.60 (s, 3H), 1.87 - 1.74 (m, 2H), 1.63 - 1.58 (m, 1H), 1.04 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.4 Hz, 3H). MS (ESI) m/z $(M+H)^+$ 344.1.

[0791] Compound **265** (79.7 mg, 94.04% purity, white solid): ^{1}H NMR (400MHz, DMSO-d_6) δ 8.73 (d, J=6.8 Hz, 1H), 8.13 - 8.03 (m, 3H), 7.79 (s, 1H), 7.45 - 7.35 (m, 3H), 5.17 - 5.10 (m, 1H), 2.56 (s, 3H), 1.87 - 1.76 (m, 1H), 1.73 - 1.60 (m, 1H), 1.45 - 1.26 (m, 4H), 0.93 - 0.83 (m, 3H). MS (ESI) m/z $(M+H)^+$ 344.1.

(*S*)-*N*-(4-AMINO-1-(4-FLUOROPHENYL)-3,4-DIOXOBUTAN-2-YL)-1-METHYL-3-PHENYL-1*H*-PYRAZOLE-4-CARBOXAMIDE (168)

[0792] Prepared as in Example **64** from the corresponding starting materials, compounds **32F** and **58F**. Compound **168** (21.3 mg, yield: 45.1%, light yellow solid): ^{1}H NMR (400MHz, DMSO-d_6) δ 8.38 (br d, J = 7.7 Hz, 1H), 8.12 - 7.99 (m, 2H), 7.81 (s, 1H), 7.54 (br d, J = 3.7 Hz, 2H), 7.36 - 7.24 (m, 5H), 7.12 (br t, J = 8.7 Hz, 2H), 5.30 - 5.20 (m, 1H), 3.89 (s, 3H), 3.19 - 3.09 (m, 1H), 2.87 - 2.74 (m, 1H). MS (ESI) m/z $(M+H)^+$ 395.1.

***N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-2-METHYL-4-PHENYLOXAZOLE-5-CARBOXAMIDE (459)**

[0793] Prepared as in compound **107** from the corresponding starting materials, compounds **107B** and 3-amino-*N*-cyclopropyl-2-hydroxy-4-phenylbutanamide hydrochloride. Compound **459** (210 mg, yield: 65.2%, white solid): ^{1}H NMR (400MHz, DMSO-d_6) δ 8.88 - 8.79 (m, 2H), 8.06 - 7.99 (m, 2H), 7.43 - 7.34 (m, 3H), 7.33 - 7.26 (m, 4H), 7.25 - 7.18 (m, 1H), 5.48 - 5.35 (m, 1H), 3.26 - 3.17 (m, 1H), 3.05 - 2.94 (m, 1H), 2.82 - 2.71 (m, 1H), 2.55 (s, 3H), 0.70 - 0.52 (m, 4H). MS (ESI) m/z $(M+H)^+$ 418.2.

***N*-(1-(CYCLOPROPYLAMINO)-1,2-DIOXOHEPTAN-3-YL)-2-METHYL-4-PHENYLOXAZOLE-5-CARBOXAMIDE (460)**

[0794] Prepared as in compound **107** from the corresponding starting materials, compounds **107B** and 3-amino-N-cyclopropyl-2-hydroxyheptanamide hydrochloride. Compound **460** (180 mg, yield: 53.3%, white solid): ^{1}H NMR (400MHz, DMSO-d_6) δ 8.76 (br s, 2H), 8.10

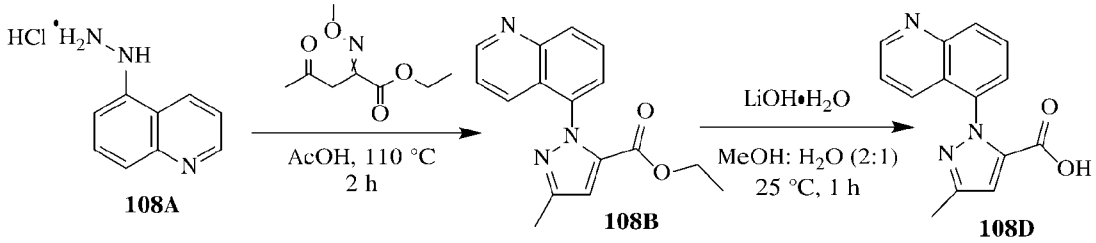
(br s, 2H), 7.40 (br s, 3H), 5.12 (br s, 1H), 2.77 (br s, 1H), 2.56 (br s, 3H), 1.81 (br s, 1H), 1.68 (br s, 1H), 1.32 (br s, 4H), 0.88 (br s, 3H), 0.70 - 0.52 (m, 4H). MS (ESI) *m/z* $(M+H)^+$ 384.2.

(*S*)-*N*-(4-FLUORO-3-OXO-1-PHENYLBUTAN-2-YL)-2-METHYL-4-PHENYLOXAZOLE-5-CARBOXAMIDE (475)

[0795] Prepared as in compound **107** from the corresponding starting materials, compounds **107B** and (2*S*,3*S*)-3-amino-1-fluoro-4-phenylbutan-2-ol hydrochloride. Compound **475** (75 mg, yield: 50.28%, white solid): ^{1}H NMR (400MHz, $CDCl_3$) δ 8.13 - 8.08 (m, 2H), 7.47 - 7.38 (m, 3H), 7.36 - 7.28 (m, 3H), 7.18 (d, *J*=6.6 Hz, 2H), 6.81 - 6.76 (m, 1H), 5.31 - 5.22 (m, 1H), 5.05 - 4.89 (m, 1H), 4.88 - 4.72 (m, 1H), 3.29 - 3.22 (m, 1H), 3.17 - 3.10 (m, 1H), 2.57 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 367.1.

EXAMPLE 65

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(QUINOLIN-5-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (108)



[0796] A mixture consisting of quinolin-5-amine (5 g, 34.68 mmol) in conc. HCl (20 mL) at 0 °C was added $NaNO_2$ (2.63 g, 38.15 mmol) dropwise and the resultant mixture was stirred at 0 °C for 0.5 hour. The reaction mixture was warmed to 25 °C over 0.5 hour, and then cooled to 0 °C. The $SnCl_2$•$2H_2O$ (15.65 g, 68.36 mmol, in 20 mL conc. HCl) was added dropwise to the reaction mixture, and stirred at 0 °C for 0.5 hour. The resulting mixture was allowed to warm to 25 °C with vigorous stirring over 4 hours. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with ethanol 90 mL (30 mL x 3), filtered and concentrated under reduced pressure to afford compound **108A** (5.2 g, 76.64% yield, HCl) as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.98 (br s, 1H), 9.26 - 9.15 (m, 2H), 8.07 - 7.97 (m, 2H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H).

[0797] To a mixture of compound **108A** (2 g, 12.56 mmol, HCl) and ethyl 2-(methoxyimino)-4-oxopentanoate (1.91 g, 10.22 mmol) in AcOH (20 mL) was degassed and

purged with N_2 for 3 times, and then the mixture was stirred at 110 °C for 2h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to remove AcOH. The residue was diluted with CH_2Cl_2 (100 mL), adjusted to pH ~ 7 - 8 with saturated aqueous $NaHCO_3$, and then extracted with CH_2Cl_2 (40 mL x 2). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue, which was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1:0 to 0:1) to give compound **108B** (1.2 g, 41.78% yield) as a yellow solid and compound **108C** (150 mg, 5.22% yield) as a yellow solid. Compound **108B**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.93 (d, J = 4.0 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 6.93 (s, 1H), 4.05 (q, J = 7.2 Hz, 2H), 2.41 (s, 3H), 1.00 (t, J = 7.2 Hz, 3H).

[0798] Compound **108C**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ ^{1}H NMR (400MHz, DMSO-d_6) δ 8.98 - 8.87 (m, 1H), 8.27 (d, J = 8.8 Hz, 1H), 7.83 - 8.77(m, 1H), 7.68 - 7.56 (m, 2H), 7.45 - 7.40 (m, 1H), 6.85 (s, 1H), 4.42 (q, J = 7.2 Hz, 2H), 2.13 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H).

[0799] To a mixture of **108B** (250 mg, 888.7 umol) in MeOH (10 mL) and H_2O (5 mL) was added $LiOH•H_2O$ (149.2 mg, 3.55 mmol) in one portion and the mixture was stirred at 25°C for 1 hour. The reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was diluted with H_2O (10 mL), adjusted to pH ~ 3 with 1N HCl, and then extracted with DCM (40 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford intermediate compound **108D** (200 mg, 88.03% yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.97 (d, J = 4.0 Hz, 1H), 8.17 (d, J = 8.8 Hz, 1H), 7.89 - 7.79 (m, 1H), 7.67 - 7.62 (m, 1H), 7.61 - 7.52 (m, 2H), 6.96 (s, 1H), 5.76 (s, 1H), 2.32 (s, 3H). MS (ESI) m/z $(M+1)^+$ 253.9.

[0800] Compound **108** (21.2 mg, 23.11 % yield, white solid) was prepared as in Example **107** from the corresponding intermediate compounds **108D** and **12G**. Compound **108**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.95 (d, J = 2.8 Hz, 1H), 8.22 (d, J = 8.8 Hz, 1H), 7.77 - 7.66 (m, 2H), 7.50 (d, J = 7.2 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.24 - 7.18 (m, 3H), 6.89 (d, J = 5.6 Hz, 2H), 6.63 (s, 2H), 6.28 (d, J = 7.2 Hz, 1H), 5.53 - 5.39 (m, 2H), 3.24 (d, J = 14.4 Hz, 1H), 3.03 (d, J = 14.4 Hz, 1H), 2.39 (s, 3H). MS (ESI) m/z $(M+H)^+$ 428.1.

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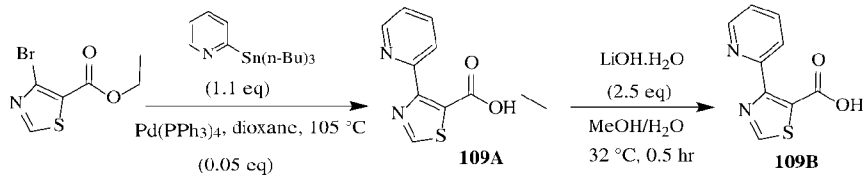
EXAMPLE 66

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-(PYRIDIN-2-YL)THIAZOLE-5-CARBOXAMIDE (109)



[0801] A mixture of ethyl 4-bromothiazole-5-carboxylate (500 mg, 2.12 mmol), 2-(tributylstannyl)pyridine (858.5 mg, 2.33 mmol), $Pd(PPh_3)_4$ (122.5 mg, 106 umol) in dioxane (15 mL) was stirred at 105 °C for 14h. The mixture was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=3:1 to 1:1) to afford compound **109A** (221 mg, 44.05% yield) as yellow oil. MS (ESI) *m/z* $(M+H)^+$ 235.0.

[0802] To a solution of compound **109A** (221 mg, 943.36 umol) in MeOH (10 mL) and water (2 mL) was added $LiOH.H_2O$ (99 mg, 2.36 mmol, 2.5 eq). The mixture was stirred at 32 °C for 0.5 hr. MeOH was evaporated. To the residue was added water (20 mL). The mixture was extracted with MTBE (5 mL) and separated. The aqueous layer was acidified to pH ~ 3 with 1N HCl and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford compound **109B** (155 mg, 79.68% yield) as white solid. ^1H NMR (400MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.84 (br d, J = 4.8 Hz, 1H), 8.57 (d, J = 8.0 Hz, 1H), 8.34 (br t, J = 7.4 Hz, 1H), 7.78 (t, J = 6.2 Hz, 1H).

[0803] Compound **109** (5.7 mg, 13.91% yield, yellow solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **109B**. Compound **109**: MS (ESI) *m/z* $(M+H)^+$ 381.0. ^1H NMR (400MHz, $CDCl_3$) δ 13.47 - 13.34 (m, 1H), 8.85 (s, 1H), 8.43 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 5.2 Hz, 1H), 7.96 - 7.79 (m, 1H), 7.26 - 7.22 (m, 1H), 7.20 - 7.06 (m, 5H), 6.81 (br s, 1H), 5.94 - 5.86 (m, 1H), 5.68 (br s, 1H), 3.49 - 3.33 (m, 2H).

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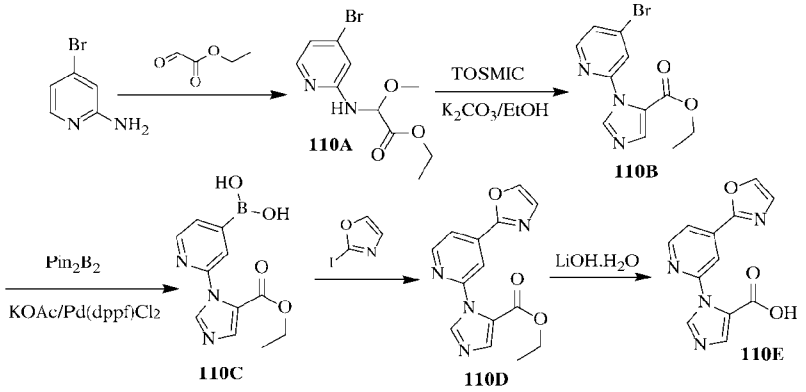
EXAMPLE 67

(*S*)-1-(4-(OXAZOL-2-YL)PYRIDIN-2-YL)-*N*-(1-OXO-3-PHENYLPROPAN-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (110)



[0804] A mixture of 4-bromopyridin-2-amine (20 g, 115.60 mmol) and ethyl 2-oxoacetate (30.7 g, 150.28 mmol) in MeOH (300 mL) was heated to 80 °C for 3 h. The mixture was concentrated, the residue was purified by silica gel column (Petroleum ether : Ethyl acetate = 20: 1). Compound **110A** (28.9 g, yield: 86.5%, yellow solid): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 5.2 Hz, 1 H), 6.86 (dd, J = 5.2, 1.75 Hz, 1 H), 6.77 (d, J = 1.3 Hz, 1 H), 5.75 (br s, 1 H), 5.61 (d, J = 8.3 Hz, 1 H), 4.29 (q, J = 7.0 Hz, 2 H), 3.41 (s, 3 H), 1.37 - 1.31 (m, 3 H).

[0805] A mixture of **110A** (15 g, 51.9 mmol) and K_2CO_3 (21.5 g, 156 mmol) in EtOH (300 mL) was stirred at 80 °C for 0.5 hr, then 1-(isocyanomethylsulfonyl)-4-methyl-benzene (15.2 g, 77.82 mmol) was added, the resulting mixture was stirred at 80 °C for another 2 h. Most of ethanol was removed and a precipitate was formed, the solid was filtered and washed with water (100 mL x 2), the solid was dried and concentrated to give **110B** (6.4 g, yield: 41.7%), as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 5.2 Hz, 1 H), 7.97 (s, 1 H), 7.85 (s, 1 H), 7.61 (s, 1 H), 7.56 (dd, J = 5.26, 1.3 Hz, 1 H), 4.27 (q, J = 7.02 Hz, 2 H), 1.29 (t, J = 7.02 Hz, 3 H).

[0806] **110B** (3 g, 10.13 mmol), Pin_2B_2 (2.57 g, 10.13 mmol), KOAc (2.98 g, 30.4 mmol) and $Pd(dppf)Cl_2$ (741 mg, 1.01 mmol) in dioxane (100 mL) was de-gassed and then heated at 70 °C for 4 hours under N_2. The mixture was filtered and the filtrate was concentrated, the residue was purified by silica gel chromatography (DCM: Methanol = 5:1) to give **110C** (1.70 g, crude) as black solid.

[0807] **110C** (300 mg, 1.15 mmol), 2-iodooxazole (157 mg, 805.00 umol), Pd(dppf)Cl_2 (84.1 mg, 115.00 umol) and Na_2CO_3 (244 mg, 2.30 mmol) in toluene (2 mL), EtOH (2 mL), H_2O (1 mL) was degassed and then heated to 120 °C for 1 hour under microwave condition. LCMS showed desired MS, the mixture was added water (5 mL) and extracted with ethyl acetate (10 mL x 2), the organic phases were dried and concentrated, the residue was purified by preparatory-TLC (Petroleum ether : Ethyl acetate = 1: 1) to give **110D** (80 mg, yield: 24.5%), as yellow solid.

[0808] A mixture of **110D** (80 mg, 281.42 umol) and LiOH.H_2O (17.7 mg, 422.13 umol) in THF (5 mL), H_2O (1 mL) was stirred at 25 °C for 12 h. LCMS showed desired MS, THF was removed under vacuum, the water layer was extracted with ethyl acetate (10 mL x 2), the water layer was adjusted to pH ~ 6 with 1N HCl and lyophilized, the residue was purified by prep-HPLC (FA) to give **110E** (35 mg, yield: 48.5%), as white solid. ^{1}H NMR (400MHz, methanol-d_4) δ 8.70 (d, J = 5.3 Hz, 1H), 8.25 (s, 1H), 8.16 (s, 1H), 8.11 (s, 1H), 8.08 (d, J = 5.1 Hz, 1H), 7.81 (s, 1H), 7.46 (s, 1H).

[0809] Compound **110** (38 mg, yield: 58.8%, white solid) was prepared as in Example **6** from the corresponding intermediate compounds **110E** and **21G** ((*S*)-2-amino-3-phenylpropan-1-ol). Compound **110**: ^{1}H NMR (400MHz, $CDCl_3$) δ 9.69 (s, 1H), 8.52 (d, J = 5.1 Hz, 1H), 7.98 (br d, J = 9.9 Hz, 2H), 7.92 (br d, J = 5.1 Hz, 1H), 7.81 (s, 1H), 7.59 (s, 1H), 7.52 (br d, J = 5.3 Hz, 1H), 7.34 (s, 1H), 7.31 - 7.17 (m, 4H), 7.13 (br d, J = 7.1 Hz, 2H), 4.84 (q, J = 6.5 Hz, 1H), 3.33 - 3.18 (m, 2H). MS (ESI) *m/z* $(M+H)^+$ 388.1.

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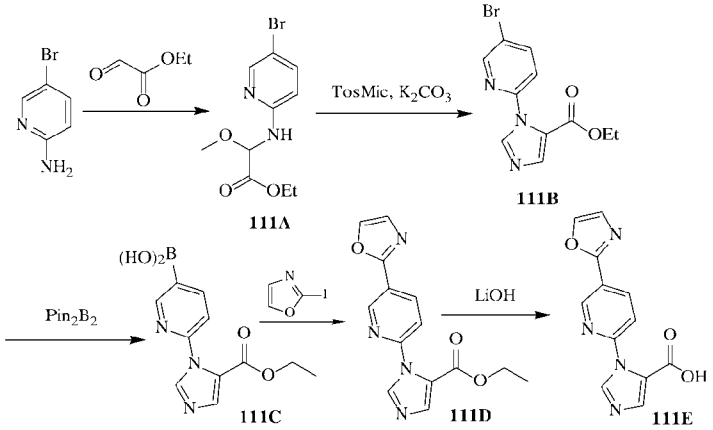
EXAMPLE 68

COMPOUNDS 111-112

(*S*)-1-(5-(OXAZOL-2-YL)PYRIDIN-2-YL)-*N*-(1-OXO-3-PHENYLPROPAN-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (111)



[0810] Compound **111E** (60 mg, crude, grey solid) was prepared as in Example **110** from the corresponding starting materials, 5-bromopyridin-2-amine. Compound **111E**: MS (ESI) *m/z* $(M+H)^+$ 257.0. Compound **111** (55 mg, yield: 76.9%, white solid) was prepared as in Example **21** from the corresponding intermediate compounds **111E** and **21G** ((*S*)-2-amino-3-phenylpropan-1-ol). Compound **111**: ^{1}H NMR (400MHz, $CDCl_3$) δ 9.71 (s, 1H), 9.05 (d, J = 1.5 Hz, 1H), 8.42 (dd, J = 2.2, 8.4 Hz, 1H), 8.02 (s, 1H), 7.79 (s, 1H), 7.57 (s, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.34 (br d, J = 6.4 Hz, 1H), 7.31 (s, 1H), 7.28 - 7.24 (m, 2H), 7.22 - 7.17 (m, 1H), 7.14 (br d, J = 7.1 Hz, 2H), 4.87 (q, J = 6.5 Hz, 1H), 3.24 (d, J = 6.4 Hz, 2H). MS (ESI) *m/z* $(M+H)^+$ 388.1.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(5-(OXAZOL-2-YL)PYRIDIN-2-YL)-1*H*-IMIDAZOLE-5-CARBOXAMIDE (112)

[0811] Compound **112** (20 mg, yield: 48.2%, white solid) was prepared as in Example **5** from the corresponding starting materials, compounds **111E** and **12G**. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.06 (d, J = 7.5 Hz, 1H), 8.99 (d, J = 1.8 Hz, 1H), 8.39 (dd, J = 2.4, 8.4 Hz, 1H), 8.34 (s, 1H), 8.26 - 8.21 (m, 1H), 8.08 (s, 1H), 7.84 (s, 1H), 7.57 (s, 1H), 7.48 (s, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.31 - 7.25 (m, 4H), 7.24 - 7.16 (m, 1H), 7.24 - 7.16 (m, 1H), 5.28 - 5.13 (m, 1H), 3.18 (dd, J = 3.7, 13.9 Hz, 1H), 2.85 (dd, J = 10.3, 13.8 Hz, 1H). MS (ESI) *m/z* $(M+H)^+$ 431.1.

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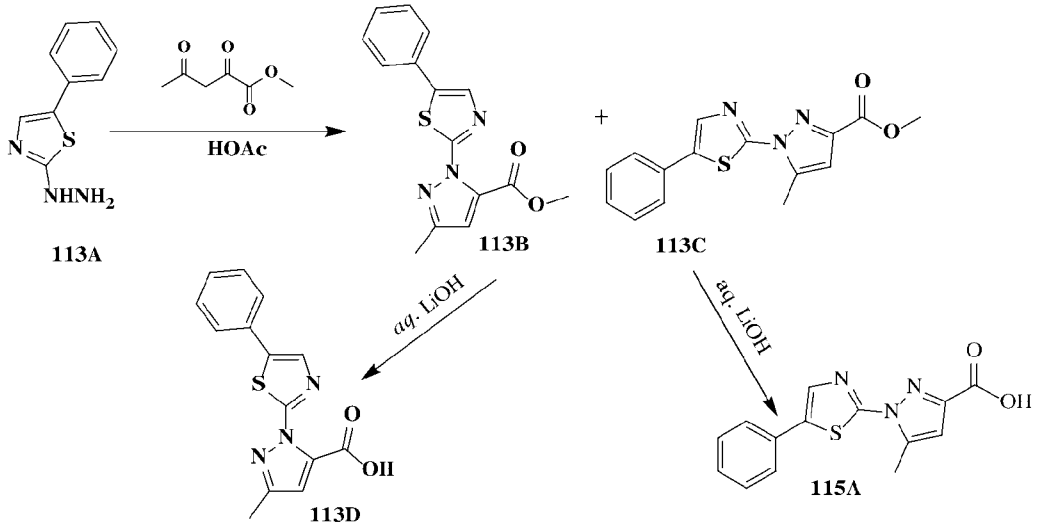
EXAMPLE 69

COMPOUNDS 113, 115



(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(5-PHENYLTHIAZOL-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (113)

[0812] 5-phenylthiazol-2-amine (850 mg, 4.82 mmol) was added to concentrated hydrochloric acid (5 mL). While being stirred at 0 °C, the aqueous solution of $NaNO_2$ (998 mg, 14.5 mmol) in H_2O (3 mL) was dropped slowly into the mixture, and the mixture was stirred for 1hr. Then hydrochloric acid solution of $SnCl_2.2H_2O$ (3.26 g, 14.4 mmol) was added drop-wise slowly, and the mixture was stirred at 25 °C for 3h. LCMS showed 5-phenylthiazol-2-amine was consumed completely and one peak with desired MS was detected. The reaction mixture was filtered. The filtered cake was wash with water (20 mL), and concentrated under reduced pressure to give the product **113A** (1 g, crude) as a yellow solid. MS (ESI) *m/z* $(M+H)^+$191.9.

[0813] A mixture of compound **113A** (1 g, 5.23 mmol), methyl 2,4-dioxopentanoate (754 mg, 5.23 mmol) in HOAc (15 mL) was stirred at 120 °C for 1hr. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure to remove the solvent, and adjusted the pH to 8 ~ 9 with the saturated aqueous $NaHCO_3$. Then the mixture was extracted with Ethyl acetate (60 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Firstly, the residue was purified by column chromatography (Petroleum ether : Ethyl acetate = 50:1 to 10:1) to give the pure compound **113C** (300 mg) and the mixture of **113B** & **113C** (300 mg). And then the mixture of

113B & **113C** (300 mg) was purified by preparatory-HPLC (TFA condition) to give **113B** (30 mg) and **113C** (120 mg) both as a yellow solid.

[0814] Compound **113B**: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.79 (br s, 1H), 7.60 - 7.51 (m, 2H), 7.46 - 7.38 (m, 2H), 7.38 - 7.29 (m, 1H), 6.75 (br s, 1H), 4.05 - 3.71 (m, 3H), 2.54 - 2.16 (m, 3H). MS (ESI) *m/z* $(M+H)^+$ 300.0.

[0815] Compound **113C**: ^{1}H NMR (400MHz, $CDCl_3$) *δ* 7.74 (s, 1H), 7.58 - 7.53 (m, 2H), 7.46 - 7.40 (m, 2H), 7.38 - 7.32 (m, 1H), 7.26 (s, 1H), 6.72 (d, *J* = 0.7 Hz, 1H), 3.96 (s, 3H), 2.75 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 300.0.

[0816] To a solution of **113B** (30 mg, 100 umol) in THF (5 mL), H_2O (1 mL) was added $LiOH.H_2O$ (6.31 mg, 150 umol). The mixture was stirred at 25 °C for 12 hours. The reaction mixture was added aqueous HCl to adjust the pH ~ 5. Then the mixture was freezed. Compound **113D** (35 mg, crude) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-*d*$_6$) *δ* 8.07 (s, 1H), 7.68 (d, *J* = 7.3 Hz, 2H), 7.49 - 7.41 (m, 2H), 7.40 - 7.32 (m, 1H), 6.79 (s, 1H), 2.25 (s, 3H).

[0817] Compound **113** (20 mg, yield: 66.4%, white solid) was prepared as in Example **5** from the corresponding intermediate compounds **113D** and **12G**. Compound **113**: ^{1}H NMR (400MHz, $CDCl_3$) *δ* 11.73 (br d, *J* = 5.5 Hz, 1H), 7.55 - 7.45 (m, 2H), 7.42 (br t, *J* = 7.3 Hz, 2H), 7.38 - 7.31 (m, 1H), 7.23 (br dd, *J* = 3.9, 8.0 Hz, 6H), 7.03 (s, 1H), 6.80 (br s, 1H), 5.87 - 5.70 (m, 1H), 5.58 (br s, 1H), 3.43 (br dd, *J* = 4.5, 14.2 Hz, 1H), 3.22 (br dd, *J* = 8.2, 14.3 Hz, 1H), 2.31 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 460.1.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-METHYL-1-(5-PHENYLTHIAZOL-2-YL)-1*H*-PYRAZOLE-3-CARBOXAMIDE (115)

[0818] Following the procedure as used for compound **113**, compound **115** (62.0 mg, yield: 68.3%, white solid) was prepared from the corresponding intermediate carboxylic acid, compound **115A**. Compound **115**: ^{1}H NMR (400MHz, $CDCl_3$) *δ* 7.71 (s, 1H), 7.56 (d, *J* = 7.3 Hz, 2H), 7.48 - 7.40 (m, 2H), 7.39 - 7.33 (m, 2H), 7.33 - 7.27 (m, 2H), 7.26 (s, 1H), 7.19 (br d, *J* = 6.8 Hz, 2H), 6.76 (br s, 1H), 6.65 (s, 1H), 5.77 - 5.62 (m, 1H), 5.52 (br s, 1H), 3.43 (dd, *J* = 5.5, 13.9 Hz, 1H), 3.26 (dd, *J* = 7.1, 13.9 Hz, 1H), 2.71 (s, 3H). MS (ESI) *m/z* $(M+23)^+$ 460.1.

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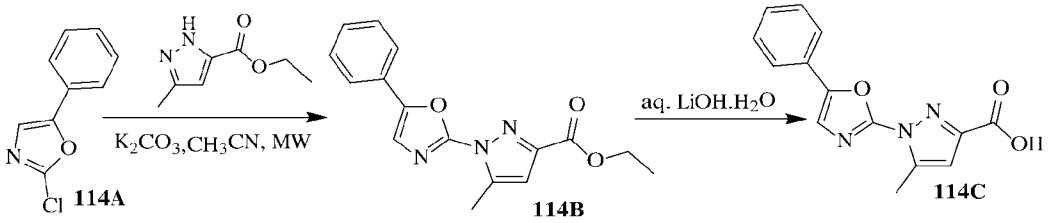
EXAMPLE 70

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-METHYL-1-(5-PHENYLOXAZOL-2-YL)-1*H*-PYRAZOLE-3-CARBOXAMIDE (114)



[0819] To a solution of 5-phenyloxazole (800 mg, 5.51 mmol) in THF (10 mL) was added n-BuLi (2.5 M, 2.76 mL) drop-wise at -78 °C and stirred for 30 min, then hexachloroethane (1.96 g, 8.27 mmol) in THF (2 mL) was added, the reaction mixture was slowly warmed to 25 °C and stirred for 12 h. The mixture was poured into ice-water (20 mL) and extracted ethyl acetate (10 mL x 2), the organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated, the residue was purified by silica gel column (Petroleum ether: Ethyl acetate = 10:1) to give **114A** (900 mg, yield: 90.9%) as yellow oil. ^1H NMR (400MHz, $CDCl_3$-*d*) δ 7.58 (d, J = 7.3 Hz, 2H), 7.45 - 7.38 (m, 2H), 7.38 - 7.31 (m, 1H), 7.27 (s, 1H).

[0820] A mixture of **114A** (90 mg, 501 umol), ethyl 3-methyl-1H-pyrazole-5-carboxylate (92.7 mg, 601 umol) and K_2CO_3 (103 mg, 752 umol) in CH_3CN (3 mL) was stirred at 120 °C for 2 hr under microwave condition. The mixture was diluted with ethyl acetate (20 mL) and water (20 mL), the organic phase was dried over Na_2SO_4, filtered and concentrated, the residue was purified by preparatory-TLC (Petroleum ether: Ethyl acetate = 5: 1) to give **114B** (0.14 g, yield: 60.4%) as yellow oil, ^1H NMR (400MHz, $CDCl_3$) δ 7.76 - 7.67 (m, 2H), 7.47 - 7.41 (m, 2H), 7.39 - 7.32 (m, 2H), 6.75 (d, J = 0.9 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 2.67 (d, J = 0.7 Hz, 3H), 1.43 (t, J = 7.2 Hz, 3H).

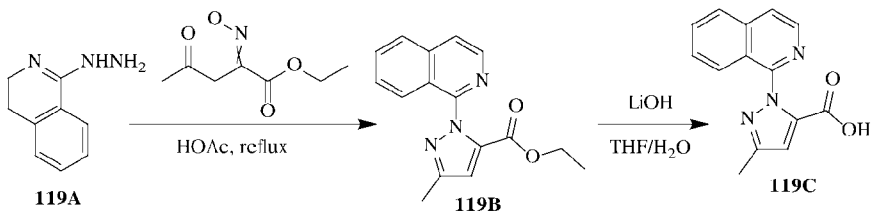
[0821] A mixture of **114B** (140 mg, 471 umol) and $LiOH.H_2O$ (39.5 mg, 942 umol) in THF (5 mL), H_2O (1 mL) was stirred at 25 °C for 2 h. The organic solvent was removed under vacuum, the water layer was adjusted to pH ~ 5 with 1N HCl and filtered, the water layer was extracted with DCM (10 mL x 3), the organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated, the residue combined the filtrate cake to give **114C** (120

mg, crude), as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.81 - 7.71 (m, 2H), 7.52 (t, J = 7.7 Hz, 2H), 7.46 - 7.40 (m, 1H), 6.81 (d, J = 0.7 Hz, 1H), 2.62 (s, 3H).

[0822] Compound **114** (53 mg, yield: 66.5%, white solid) was prepared as in Example **5** from the corresponding carboxylic acid, compound **114C**. Compound **114**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.59 (d, J = 7.7 Hz, 1H), 8.10 (s, 1H), 7.87 (s, 1H), 7.84 (s, 1H), 7.76 (d, J = 7.3 Hz, 2H), 7.52 (t, J = 7.7 Hz, 2H), 7.45 - 7.38 (m, 1H), 7.31 - 7.22 (m, 4H), 7.19 (qd, J = 4.3, 8.8 Hz, 1H), 6.72 (d, J = 0.7 Hz, 1H), 5.49 - 5.40 (m, 1H), 3.25 - 3.17 (m, 1H), 3.06 (dd, J = 9.4, 14.0 Hz, 1H), 2.57 (s, 3H). MS (ESI) m/z $(M+H)^+$ 444.1.

EXAMPLE 71

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(ISOQUINOLIN-1-YL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (119)



[0823] To a mixture of 1-chloroisoquinoline (5.0 g, 30.56 mmol) in dioxane (10.00 mL) was added $NH_2NH_2{\cdot}H_2O$ (305.62 mmol, 15 mL). The mixture was stirred at 80 °C for 16h. The reaction mixture was washed with H_2O (100 mL). The reaction mixture diluted with MTBE and filtered to give compound **119A** (4.27 g, 87.77% yield) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.16 (d, J=8.3 Hz, 1H), 7.87 (d, J=5.8 Hz, 1H), 7.72 - 7.65 (m, 1H), 7.64 - 7.56 (m, 1H), 7.48 - 7.41 (m, 1H), 6.90 (d, J=5.8 Hz, 1H). MS (ESI) m/z $(M+H)^+$ 160.1.

[0824] A mixture of compound **119A** (4.20 g, 26.38 mmol) and ethyl 2-(methoxyimino)-4-oxopentanoate (4.94 g, 26.38 mmol) in HOAc (40.00 mL) was stirred at 120 °C for 48h. The reaction mixture was concentrated under reduced pressure to remove HOAc. The residue was diluted with H_2O (20 mL) and extracted with ethyl acetate (40 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 0:1) to give compound **119B** (238.00 mg, 3.08% yield) was obtained as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.46 (br d, J=5.5 Hz, 1H),

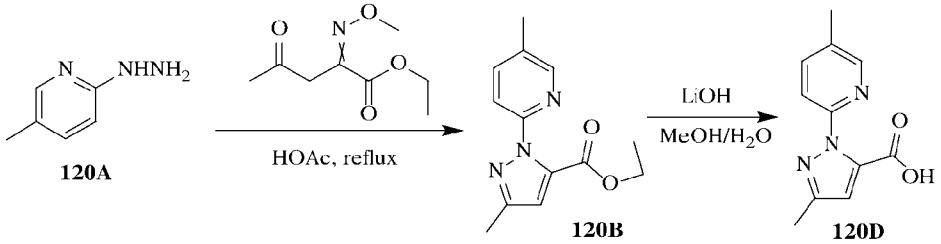
7.92 (d, *J*=8.2 Hz, 1H), 7.79 (d, *J*=5.5 Hz, 1H), 7.72 (t, *J*=7.4 Hz, 1H), 7.67 - 7.53 (m, 2H), 6.92 (s, 1H), 4.06 (q, *J*=7.1 Hz, 2H), 2.43 (s, 3H), 0.99 (t, *J*=7.2 Hz, 3H). MS (ESI) *m/z* $(M+H)^+$ 282.

[0825] To a solution of compound **119B** (238.00 mg, 846.04 umol) in THF (6.00 mL) was added $LiOH{\cdot}H_2O$ (177.50 mg, 4.23 mmol) in H_2O (2.00 mL). The mixture was stirred at 28 °C for 16h. The reaction mixture was diluted with H_2O (10 mL) and extracted with MTBE (15 mL x 2), the water phase was added 1N HCl to pH ~ 3~4, extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give intermediate compound **119C** (201.00 mg, 92.87% yield) as a yellow solid. Compound **119C**: ^1H NMR (400MHz, DMSO-d_6) δ 8.42 (d, *J*=5.5 Hz, 1H), 8.12 (d, *J*=8.2 Hz, 1H), 8.01 (d, *J*=5.7 Hz, 1H), 7.85 (t, *J*=7.2 Hz, 1H), 7.69 (t, *J*=7.4 Hz, 1H), 7.56 (d, *J*=8.4 Hz, 1H), 6.92 (s, 1H), 2.32 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 254.1.

[0826] Compound **119** (20.00 mg, 35.64% yield, light yellow solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **119C**. Compound **119**: ^1H NMR (400MHz, $CDCl_3$) δ 8.23 (br d, *J*=6.2 Hz, 1H), 7.94 - 7.85 (m, 3H), 7.75 (br t, *J*=7.8 Hz, 1H), 7.69 (br d, *J*=5.3 Hz, 1H), 7.62 (br t, *J*=7.7 Hz, 1H), 7.12 (br d, *J*=7.1 Hz, 1H), 7.09 - 7.03 (m, 2H), 6.92 (br d, *J*=7.1 Hz, 2H), 6.73 (s, 1H), 6.67 (br s, 1H), 5.65 - 5.59 (m, 1H), 5.51 (br s, 1H), 3.36 - 3.28 (m, 1H), 3.21 - 3.14 (m, 1H), 2.41 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 428.1.

EXAMPLE 72

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(5-METHYLPYRIDIN-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (120)



[0827] A mixture of 2-fluoro-5-methylpyridine (10.00 g, 89.99 mmol, 9.35 mL) in $NH_2NH_2.H_2O$ (53.00 g, 899.93 mmol, 51.5 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 120 °C for 15 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H_2O (30

mL) and extracted with ethyl acetate (20 mL x 2). The combined organic layers were washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the compound **120A** (6.09 g, yield: 54.9%) was obtained as a light pink solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.32 (dd, J = 2.0, 8.4 Hz, 1H), 6.63 (d, J = 8.4 Hz, 1H), 5.68 (br s, 1H), 2.20 (s, 3H).

[0828] A mixture of compound **120A** (2 g, 16.24 mmol), ethyl 2-(methoxyimino)-4-oxopentanoate (3.04 g, 16.24 mmol) in HOAc (20 mL) was stirred at 120 °C for 20 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H_2O (15 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic layers were washed with $NaHCO_3$ (20 mL x 3), and then washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by preparatory-HPLC (HCl condition) to give the compound **120B** (340 mg, yield: 8.5%) was obtained as a white solid. Compound **120B**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.82 (dd, J = 1.8, 8.3 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 6.77 (s, 1H), 4.19 (q, J = 7.0 Hz, 2H), 2.35 (s, 3H), 2.28 (s, 3H), 1.14 (t, J = 7.0 Hz, 3H).

[0829] To a solution of compound **120B** (340 mg, 1.39 mmol) in THF (10 mL) was added $LiOH.H_2O$ (291 mg, 6.95 mmol) in H_2O (3 mL). The mixture was stirred at 25 °C for 30 h. The reaction mixture was diluted with H_2O (15 mL) and extracted with MTBE (10 mL). The combined water layers were adjusted to pH ~ 6 by adding 1N HCl, and then extracted with ethyl acetate (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the compound **120D** (300 mg, yield: 99.4%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 13.50 (br s, 1H), 8.26 (s, 1H), 7.79 (dd, J = 1.8, 8.2 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 6.73 (s, 1H), 2.33 (s, 3H), 2.24 (s, 3H).

[0830] Compound **120** (15 mg, yield: 54.1% light yellow solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **120D**. Compound **120**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.21 (d, J = 7.3 Hz, 1H), 8.09 (s, 1H), 8.04 (s, 1H), 7.85 (s, 1H), 7.73 (dd, J = 1.6, 8.2 Hz, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.31 - 7.23 (m, 5H), 6.53 (s, 1H), 5.35 - 5.26 (m, 1H), 3.16 (dd, J = 4.0, 14.1 Hz, 1H), 2.87 (dd, J = 9.8, 14.1 Hz, 1H), 2.31 (s, 3H), 2.26 (s, 3H).

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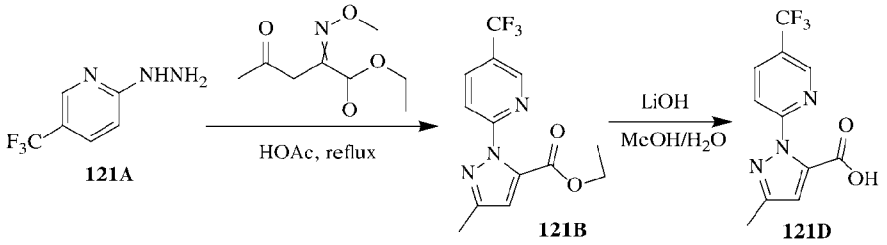
EXAMPLE 73

COMPOUNDS 121-122, 445

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(5-METHYLPYRIDIN-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (121)



[0831] Intermediate compound **121D** (650 mg, yield: 89.8%, white solid) was prepared as in Example **120** from the corresponding starting materials, compound **121A** and 2-chloro-5-(trifluoromethyl)pyridine. Compound **121A**: ^{1}H NMR (400MHz, DMSO-d_6) δ 13.55 (br s, 1H), 8.86 (s, 1H), 8.39 (dd, J = 2.3, 8.5 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 6.81 (s, 1H), 2.27 (s, 3H).

[0832] Compound **121** (35.9 mg, yield: 55.2%, white solid) was prepared as in Example **12** from the corresponding intermediate carboxylic acid, compound **121D**. Compound **121**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.15 (d, J = 7.3 Hz, 1H), 8.45 (s, 1H), 8.29 (dd, J = 2.1, 8.7 Hz, 1H), 8.11 (s, 1H), 7.88 - 7.80 (m, 2H), 7.28 - 7.24 (m, 4H), 7.22 - 7.17 (m, 1H), 6.51 (s, 1H), 5.36 - 5.28 (m, 1H), 3.14 (dd, J = 3.6, 14.0 Hz, 1H), 2.81 (dd, J = 9.9, 14.1 Hz, 1H), 2.27 (s, 3H).

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(5-(TRIFLUOROMETHYL)PYRIDIN-2-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (122)

[0833] Compound **122** (54.1 mg, yield: 87.9%, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **121D**. Compound **122**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.16 (d, J = 7.3 Hz, 1H), 8.85 (d, J = 5.1 Hz, 1H), 8.42 (s, 1H), 8.30 (dd, J = 2.1, 8.7 Hz, 1H), 7.83 (d, J = 8.6 Hz, 1H), 7.29 - 7.23 (m, 4H), 7.22 - 7.16 (m, 1H), 6.51 (s, 1H), 5.38 - 5.30 (m, 1H), 3.14 (dd, J = 3.7, 14.1 Hz, 1H), 2.86 - 2.72 (m, 2H), 2.27 (s, 3H), 0.68 - 0.55 (m, 4H).

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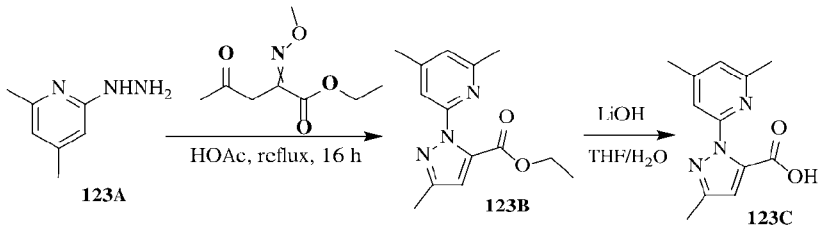
N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(5-(TRIFLUOROMETHYL)PYRIDIN-2-YL)-1H-PYRAZOLE-5-CARBOXAMIDE (445)

[0834] Compound **445** (140 mg, yield: 47.4%, white solid) was prepared as in compound **121** from the corresponding intermediates **121D** and **274D**. Compound **445**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.16 (d, J = 7.5 Hz, 1H), 8.50 - 8.43 (m, 1H), 8.31 (dd, J = 2.2, 8.8 Hz, 1H), 8.12 (s, 1H), 7.90 - 7.81 (m, 2H), 7.29 - 7.18 (m, 4H), 6.53 (s, 1H), 5.38 - 5.29 (m, 1H), 3.16 (dd, J = 4.0, 14.1 Hz, 1H), 2.83 (dd, J = 9.9, 14.1 Hz, 1H), 2.28 (s, 3H). MS (ESI) m/z $(M+H)^+$ 446.1.

EXAMPLE 74

COMPOUNDS 123-124

(S)-N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(4,6-DIMETHYLPYRIDIN-2-YL)-3-METHYL-1H-PYRAZOLE-5-CARBOXAMIDE (123)



123A 123B 123C

[0835] Intermediate compound **123C** (210 mg, yield: 78.29%, white solid) was prepared as in Example **120** from the corresponding starting materials, compound **123A** and 2-chloro-5-(trifluoromethyl)pyridine. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.38 (s, 1H), 7.14 (s, 1H), 6.77 (s, 1H), 2.40 (s, 3H), 2.37 (s, 3H), 2.26 (s, 3H). MS (ESI) m/z $(M+H)^+$ 232.0.

[0836] Compound **123** (40 mg, yield: 38.78%, light yellow solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **123C**. Compound **123**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.13 (d, J = 7.3 Hz, 1H), 8.04 (s, 1H), 7.81 (s,1H), 7.28 - 7.18 (m, 6H), 6.99 (s, 1H), 6.44 (s, 1H), 5.41 - 5.21 (m, 1H), 3.12 (dd, J = 4.0, 13.9 Hz, 1H), 2.82 (dd, J = 9.7, 13.9 Hz, 1H), 2.31 (s, 3H), 2.23 (s, 3H), 2.19 (s, 3H). MS (ESI) m/z $(M+H)^+$ 406.1.

(S)-N-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-2-METHYL-4-PHENYLTHIAZOLE-5-CARBOXAMIDE (124)

[0837] Compound **124** (40 mg, yield: 57.35%, white solid) was prepared as in Example 41 from the corresponding carboxylic acid, 2-methyl-4-phenylthiazole-5-carboxylic

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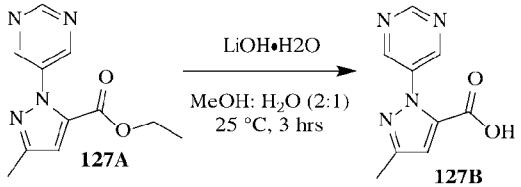
acid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.58 - 7.50 (m, 2H), 7.49 - 7.36 (m, 3H), 7.22 - 7.13 (m, 3H), 6.84 (br s, 1H), 6.80 - 6.69 (m, 2H), 6.22 (br d, J = 6.3 Hz, 1H), 5.58 - 5.46 (m, 1H), 3.26 (dd, J = 4.9, 14.2 Hz, 1H), 2.89 (dd, J = 7.5, 14.1 Hz, 1H), 2.79 (qt, J = 3.8, 7.4 Hz, 1H), 2.71 (s, 3H), 0.94 - 0.82 (m, 2H), 0.66 - 0.55 (m, 2H). MS (ESI) m/z $(M+H)^+$ 434.1.

EXAMPLE 75

(*S*)-*N*-(4-(CYCLOPROPYLAMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-METHYL-1-(4-PHENYLTHIAZOL-2-YL)-1*H*-PYRAZOLE-3-CARBOXAMIDE (127)



127A 127B

[0838] Intermediate compound **127B** (150 mg, 94.78% yield, white solid) was prepared as in Example **85** from compound **127A**. Compound **127B**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 1H), 8.99 (s, 2H), 6.94 (s, 1H), 2.27 (s, 3H).

[0839] Compound **127** (55.3 mg, 45.18% yield, white solid) was prepared as in Example **20** from the corresponding intermediate carboxylic acid, compound **127B**. Compound **127**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1H), 8.76 (s, 2H), 7.35 - 7.28 (m, 3H), 7.13 - 7.09 (m, 2H), 6.95 (br s, 1H), 6.66 - 6.60 (m, 1H), 6.47 (s, 1H), 5.60 - 5.54 (m, 1H), 3.46 - 3.38 (m, 1H), 3.20 - 3.13 (m, 1H), 2.87 - 2.77 (m, 1H), 2.35 (s, 3H), 0.92 - 0.87 (m, 2H), 0.66 - 0.61 (m, 2H). MS (ESI) m/z $(M+1)^+$ 419.1.

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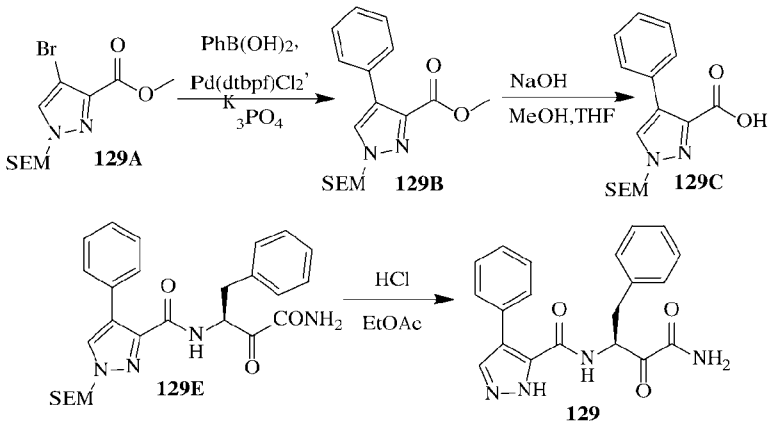
EXAMPLE 76

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-4-PHENYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (129)



[0840] To a solution of NaH (1.46 g, 36.59 mmol, 60% purity) in THF (80 mL) was added methyl 4-bromo-1*H*-pyrazole-3-carboxylate (5.00 g, 24.39 mmol) ith THF (20 mL) at 0°C. After addition, the mixture was warmed to 25°C and stirred for 2h. Then the mixture was cooled to 0°C and a solution of SEM-Cl (4.47 g, 26.83 mmol, 4.8 mL) in THF (100 mL). The mixture was stirred at 25°C for 12h. The mixture was diluted with H_2O (200 mL), the organic layer was washed with HCl (1M, 100 mL), saturated $NaHCO_3$ (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 10/1 to 3:1). Compound **129A** (3.40 g, yield 41.6%) was obtained as a colorless oil. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.39 (s, 1H), 5.51 (s, 2H), 3.87 (s, 3H), 3.62 - 3.56 (m, 2H), 0.95 - 0.81 (m, 2H), 0.07 - -0.07 (m, 9H).

[0841] A mixture of compound **2** (3.40 g, 10.14 mmol), phenylboronic acid (1.48 g, 12.17 mmol), ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (660.9 mg, 1.01 mmol), K_3PO_4 (6.46 g, 30.42 mmol) in dioxane (30 mL) and H_2O (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 70 °C for 1 hour under N_2 atmosphere. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 3:1). Compound **129B** (3.00 g, crude) was obtained as a brown oil. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.26 (s, 1H), 7.51 - 7.32 (m, 5H), 5.53 (s, 2H), 3.78 (s, 3H), 3.67 - 3.59 (m, 2H), 0.94 - 0.82 (m, 2H), 0.06 - -0.07 (m, 9H).

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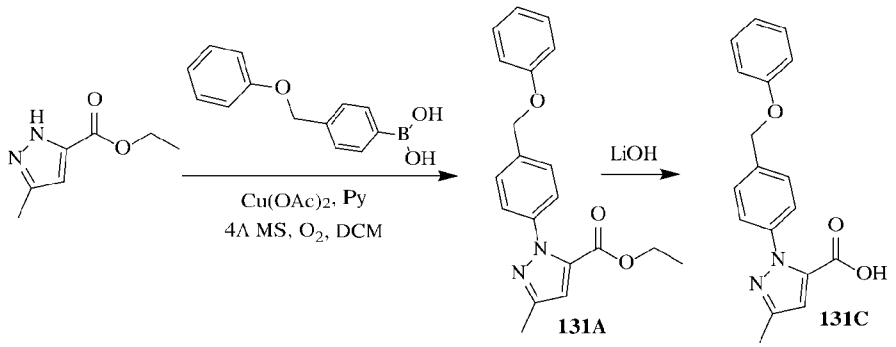
[0842] To a solution of compound **129B** (3.00 g, 9.02 mmol) in MeOH (100 mL) and THF (100 mL) was added NaOH (2M, 90 mL). The mixture was stirred at 60 °C for 1 hour. The mixture was concentrated and diluted with H_2O (200 mL), the mixture was extracted with ethyl acetate (200 mL), the water phase was added HCl (1M) until pH ~ 3, then the mixture was extracted with ethyl acetate (200 mL), the organic layer was washed with brine (200 mL), dried over Na_2SO_4 and concentrated. Compound **129C** (300.0 mg, yield 10.4%) was obtained as a brown oil. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.51 - 7.47 (m, 2H), 7.43 - 7.37 (m, 2H), 7.35 - 7.30 (m, 1H), 5.50 (s, 2H), 3.67 - 3.61 (m, 2H), 0.92 - 0.87 (m, 2H), 0.03 - -0.03 (m, 9H).

[0843] Intermediate compound **129E** (70.0 mg, crude, colorless oil) was prepared as in Example **5** from the corresponding carboxylic acid, compound **129C**. Compound **129E**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.45 (d, J = 7.6 Hz, 1H), 8.25 - 8.21 (m, 1H), 8.20 - 8.13 (m, 1H), 7.90 (s, 1H), 7.44 - 7.38 (m, 2H), 7.36 - 7.19 (m, 8H), 5.51 - 5.43 (m, 3H), 3.68 - 3.60 (m, 2H), 3.26 - 3.18 (m, 1H), 3.08 - 2.99 (m, 1H), 0.95 - 0.87 (m, 2H), 0.06 - -0.05 (m, 9H).

[0844] To a solution of compound **129E** (70.0 mg, 142.09 umol) in ethyl acetate (10 mL) was added HCl/EtOAc (4M, 710 uL). The mixture was stirred at 25 °C for 3 hours. The mixture was concentrated. The residue was purified by prep-HPLC (HCl condition). Compound **129** (20.0 mg, HCl, yield 34.4%) was obtained as a white solid. ^{1}H NMR (400MHz, D_2O) δ 7.74 - 7.61 (m, 1H), 7.41 - 7.33 (m, 2H), 7.30 - 7.09 (m, 10H), 4.54 - 4.53 (m, 1H), 3.00 - 2.92 (m, 2H). MS (ESI) m/z $(M+H)^+$ 363.1.

EXAMPLE 77

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(4-(PHENOXYMETHYL)PHENYL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (131)



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[0845] To a mixture of ethyl 3-methyl-1*H*-pyrazole-5-carboxylate (250 mg, 1.62 mmol), [4-(phenoxymethyl)phenyl]boronic acid (554.7 mg, 2.43 mmol), 4A° MS (8 g) and pyridine (141 mg, 1.78 mmol, 0.15 mL) in DCM (50 mL) was added $Cu(OAc)_2$ (383 mg, 2.11 mmol), the mixture was stirred at 25 °C for 16h under O_2 balloon (15 psi). The reaction mixture was filtered to get rid of 4A° MS and catalyst, and then the filtrate was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 5/1) and by preparatory-TLC (SiO_2, Petroleum ether/Ethyl acetate = 5/1).

[0846] Compound **131A** (69.3 mg, yield: 13.03%) was obtained as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.99 - 7.93 (m, 2H), 7.91 - 7.82 (m, 2H), 7.80 - 7.68 (m, 2H), 7.46 - 7.40 (m, 3H), 5.59 (s, 2H), 4.68 (q, J = 7.1 Hz, 2H), 2.81 (s, 3H), 2.05 (s, 1H), 1.69 (t, J = 7.2 Hz, 3H). MS (ESI) *m/z* $(M+H)^+$ 337.1.

[0847] To a solution of compound **131A** (69.3 mg, 206.02 umol), in THF (5 mL) and H_2O (3 mL) was added $LiOH.H_2O$ (26 mg, 618.06 umol).After stirred at 25 °C for 3h, the reaction mixture was added H_2O (10 mL) and extracted with MTBE (20 mL).The organic layer was washed with H_2O (10 mL). The combined aqueous layer was acidified to pH ~ 1~2 with 1N HCl, extracted with ethyl acetate (20 mL x 3), dried over Na_2SO_4, filtered and concentrated. Compound **131C** (70 mg, crude, white solid): ^{1}H NMR (400MHz, DMSO-d_6) δ 13.23 (br s, 1H), 7.57 - 7.51 (m, 2H), 7.43 (d, J = 8.3 Hz, 2H), 7.35 - 7.27 (m, 2H), 7.05 (d, J = 7.8 Hz, 2H), 6.96 (t, J = 7.3 Hz, 1H), 6.83 (s, 1H), 5.17 (s, 2H), 2.26 (s, 3H).

[0848] Compound **131** (37.2 mg, yield: 45.9%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **131C**. Compound **131**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.12 (br d, J = 7.5 Hz, 1H), 8.11 (br s, 1H), 7.86 (s, 1H), 7.39 (br d, J = 8.2 Hz, 2H), 7.33 - 7.26 (m, 6H), 7.23 (br d, J = 6.4 Hz, 1H), 7.17 (br d, J = 8.2 Hz, 2H), 7.01 (br d, J = 8.2 Hz, 2H), 6.93 (t, J = 7.4 Hz, 1H), 6.56 (s, 1H), 5.31 - 5.22 (m, 1H), 5.09 (s, 2H), 3.19 (br dd, J = 3.2, 13.8 Hz, 1H), 2.82 (br dd, J = 10.9, 13.6 Hz, 1H), 2.23 (s, 3H). MS (ESI) *m/z* $(M+H)^-$ 483.1.

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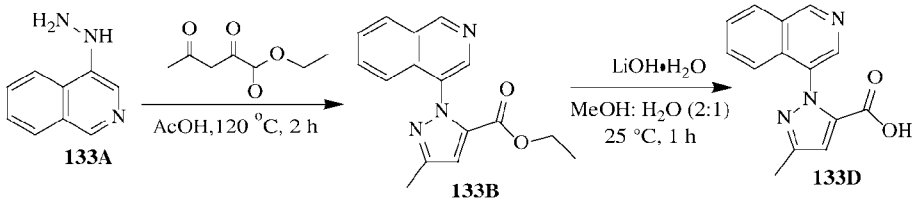
EXAMPLE 78

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(ISOQUINOLIN-4-YL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (133)



[0849] To a solution of isoquinolin-4-amine (1.4 g, 9.71 mmol) in 5N aqueous hydrochloric acid (12 mL) at 0 °C was added a solution of $NaNO_2$ (670 mg, 9.71 mmol) in deionized water (1 mL). The reaction mixture was stirred at 0 °C for 0.5h and a solution of $SnCl_2•2H_2O$ (5.48 g, 24.28 mmol) dissolved in concentrated hydrochloric acid (5 mL) was added dropwise. The mixture was stirred at 25 °C for 2h. The mixture was adjusted to pH ~ 12 - 14 with 20 % aqueous NaOH. The mixture was extracted with 2:1 $CHCl_3$/iPrOH (200 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 0:1) and then dried under reduced pressure to afford compound **133A** (720 mg, 46.55 % yield) as a brown solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.95 (br s, 1H), 9.25 - 9.13 (m, 2H), 8.04 - 7.95 (m, 2H), 7.88 (d, J = 8.8 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.28 - 7.23 (m, 1H).

[0850] To a mixture of compound **133A** (620 mg, 3.89 mmol) and ethyl 2,4-dioxopentanoate (615.9 mg, 3.89 mmol) in AcOH (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 120 °C for 2 hours under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to remove AcOH. The residue was diluted with EtOAc 10 mL and adjusted with saturated $NaHCO_3$ and then finally extracted with EtOAc (30 mL x 3). The combined organic layers were dried by Na_2SO_4, filtered and concentrated under reduced pressure to give a crude product. The reaction solution was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 0/1) to give compound **133B** (600.00 mg, 45.16% yield) as a yellow oil. Compound **133B**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.34 (s, 1H), 8.54 (s, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.72 - 7.61 (m, 2H), 7.37 (d, J = 8.0 Hz, 1H), 6.96 (s, 1H), 4.05 (q, J = 7.2 Hz, 2H), 2.42 (s, 3H), 0.98 (t, J = 7.2 Hz, 3H). MS (ESI) m/z $(M+1)^+$ 282.1.

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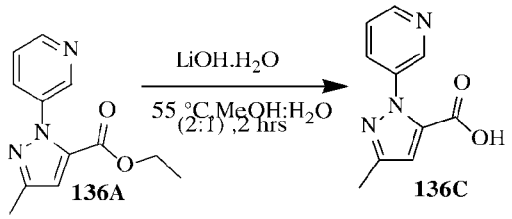
[0851] To a mixture of **133B** (200 mg, 711 umol) in MeOH (10 mL) and H_2O (5 mL) was added $LiOH•H_2O$ (119.3 mg, 2.84 mmol) in one portion and the mixture was stirred at 25°C for 1 hour. The reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was diluted with H_2O (5 mL), adjusted to pH ~ 3 with 1N HCl, and then extracted with EtOAc (40 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford intermediate compound **133D** (150 mg, 75.43% yield) as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.45 (s, 1H), 8.54 (s, 1H), 8.28 (d, J = 7.6 Hz, 1H), 7.86 - 7.73 (m, 2H), 7.27 (d, J = 8.4 Hz, 1H), 6.99 (s, 1H), 2.33 (s, 3H). MS (ESI) m/z $(M+1)^+$ 254.0.

[0852] Compound **133** (22.2 mg, 31.49% yield, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **133D**. Compound **133**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.30 (s, 1H), 8.46 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.73 - 7.63 (m, 2H), 7.47 (d, J = 8.4 Hz, 1H), 7.26 - 7.24 (m, 3H), 6.97 - 6.95 (m, 2H), 6.66 (br s, 1H), 6.59 (s, 1H), 6.48 (d, J = 7.2 Hz, 1H), 5.65 (br s, 1H), 5.41 - 5.36 (m, 1H), 3.28 - 3.24 (m, 1H), 3.11 - 3.06 (m, 1H), 2.40 (s, 3H). MS (ESI) m/z $(M+H)^+$ 428.1.

EXAMPLE 79

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(PYRIDIN-3-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (136)



136A 136C

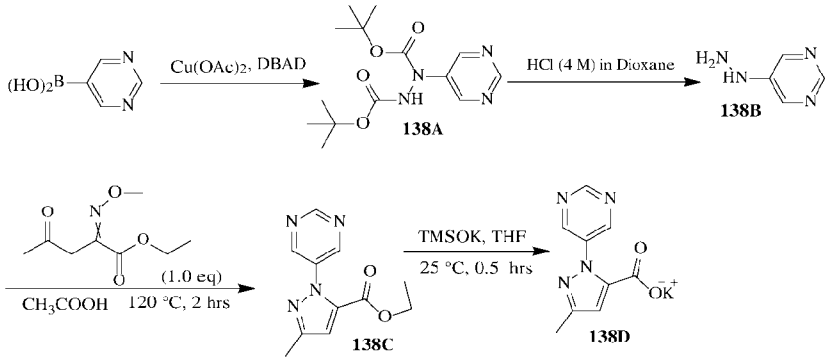
[0853] To a solution of ethyl 3-methyl-1-(pyridin-3-yl)-1H-pyrazole-5-carboxylate (2.0 g, 12.97 mmol) and pyridin-3-ylboronic acid (1.59 g, 12.97 mmol) in pyridine (30 mL) was added $Cu(OAc)_2$ (1.18 g, 6.49 mmol) .The mixture was stirred at 55 °C for 18 hrs. The mixture filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ethergradient @ 40 mL/min). Compound **136A** (850 mg, 28.34% yield, white solid): ^{1}H NMR (400MHz, $CDCl_3$): δ 8.69 (d, J = 2.0 Hz, 1H), 8.65 - 8.62 (m, 1H), 7.80 - 7.77 (m, 1H), 7.42 - 7.38 (m, 1H), 6.86 (s, 1H), 4.27 - 4.21 (m, 2H), 2.37 (s, 3H), 1.27 - 1.23 (m, 3H).

[0854] Compound **136C** (160 mg, 60.57% yield, white solid) was prepared as in Example **85**. Compound **136C**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.65 - 8.55 (m, 2H), 7.91 - 7.85 (m, 1H), 7.53 - 7.47 (m, 1H), 6.88 (s, 1H), 2.26 (s, 3H).

[0855] Compound **136** (46.2 mg, 54.66% yield, yellow solid) was prepared as in Example **5** from the corresponding intermediate compounds **136C** and **12G**. Compound **136**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 2.4 Hz, 1H), 8.58 - 8.55 (m, 1H), 7.74 - 7.69 (m, 1H), 7.36 - 7.28 (m, 4H), 7.12 - 7.07 (m, 2H), 6.79 (br s, 1H), 6.55 - 6.48(m, 1H), 6.43 (s, 1H), 5.69 (br s, 1H), 5.56 - 5.49 (m, 1H), 3.43 - 3.36 (m, 1H), 3.20 - 3.13 (m, 1H), 2.33 (s, 3H). MS (ESI) m/z $(M+H)^+$ 378.1.

EXAMPLE 80

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(PYRIMIDIN-5-YL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (138)



[0856] To a solution of pyrimidin-5-ylboronic acid (5.00 g, 40.35 mmol) in MeOH (32 mL) was added $Cu(OAc)_2$ (732.8 mg, 4.04 mmol) and DBAD (9.29 g, 40.35 mmol). The resulting mixture was stirred at 60 °C for 1 hour. The reaction mixture was cooled to 25°C, concentrated under reduced pressure, diluted with water (50 mL), and extracted with ethyl acetate (80 mL x 3). The extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the title compound as yellow oil, which was used in the next step without purification. Compound **138A** (9.00 g, 71.87% yield) was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.89 (br s, 1H), 1.53 – 1.50 (m, 18H).

[0857] To a solution of compound **138A** (9.00 g, 25.00 mmol) in 1,4-dioxane (60 mL) was added 4M HCl 1,4-dioxane (60 mL) and the mixture was stirred at room-temperature for 30 hours. The suspension was filtered, and the residue was washed with ethyl acetate (100

mL x 2) and dried under reduced pressure to afford the title compound (3.45 g, crude), which was used in the next step without purification. Compound **138B** (3.45 g, 81.17% yield, HCl) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80(s, 1H), 8.61(s, 2H).

[0858] To a solution of compound **138B** (800.0 mg, 5.46 mmol, HCl) in CH_3COOH (12 mL) was added ethyl 2-(methoxyimino)-4-oxopentanoate (1.02 g, 5.46 mmo), then the mixture was stirred at 120 °C for 2 hours. The mixture was diluted with CH_2Cl_2 (70 mL) and washed by saturated sodium bicarbonate (20 mL x 2) and saturated brine (20 mL x 2), the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash column chromatography (SiO_2, petroleum ether : ethyl acetate = 10/1 to 3/1). Compound **138C** (250.0 mg, 19.72% yield) was obtained as a white solid.

[0859] To a solution of compound **138C** (50.0 mg, 215.29 umol) in THF (3.00 mL) was added TMSOK (55.2 mg, 430.58 umol), then the mixture was stirred at 25 °C for 0.5 hour. The mixture was diluted with petroleum ethyl (20 mL) and the precipitate was filtered to give intermediate compound **138D** (45.0 mg, 86.27% yield) as a white solid. MS (ESI) *m/z* $(M+1)^+$ 204.9.

[0860] Compound **138** (10.0 mg, 14.63% yield) was prepared as in Example 5from the corresponding intermediate carboxylic acid, compound **138D**. Compound **138**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15(s, 1H), 8.78(s, 2H), 7.35-7.31(m, 3H), 7.13(d, J = 6.4 Hz, 2 H), 6.82(s, 1H), 6.58(d, J = 7.2 Hz, 1H), 6.47(s, 1H), 5.57-5.52(m, 1H), 5.46-5.58(m, 1H), 3.45-3.40(m, 1H), 3.21-3.15(m, 1H), 2.35(s, 3H). MS (ESI) *m/z* $(M+1)^+$ 379.1.

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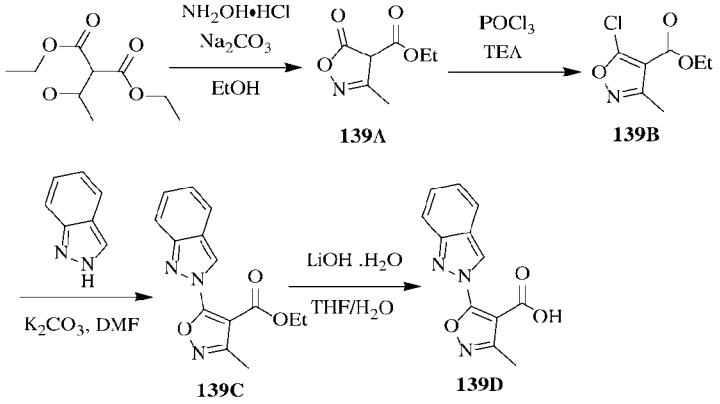
EXAMPLE 81

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-(2*H*-INDAZOL-2-YL)-3-METHYLISOXAZOLE-4-CARBOXAMIDE (139)



[0861] To a solution of diethyl 2-acetylmalonate (5 g, 24.7 mmol) in EtOH (50 mL) was added $NH_2OH.HCl$ (1.9 g, 27.2 mmol) and Na_2CO_3 (1.3 g, 12.4 mmol) in one portion, the mixture was stirred at 90 °C for 2 hours. Then the contents were poured into ice-cold water (6 mL), and then filtered to give intermediate compound **139A** (3.2 g, yield: 75.6%) as a pale yellow solid. ^1H NMR (400MHz, $CDCl_3$) δ 4.37 (q, J = 7.0 Hz, 2H), 2.43 - 2.37 (m, 3H), 1.38 (t, J = 7.2 Hz, 3H). MS (ESI) *m/z* $(M+H)^+$ 126.2.

[0862] To compound **139A** (3 g, 17.5 mmol) was added $POCl_3$ (21.5 g, 140.2 mmol, 13 mL) in one portion. Then TEA (1.8 g, 17.5 mmol) were added. The mixture was stirred at 110 °C for 24 hours under N_2. Then ice water (15 mL) was added in to the mixture, and the aqueous phase was extracted with EtOAc (25 mL x 3), the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give intermediate compound **139B** (2.6 g, 13.7 mmol, yield: 78.2%) as brown oil. ^1H NMR (400MHz, $CDCl_3$) δ 4.36 (q, J = 7.1 Hz, 2H), 2.48 (s, 3H), 1.38 (t, J = 7.2 Hz, 5H).

[0863] To a mixture of compound **139B** (400 mg, 2.1 mmol) and 2*H*-indazole (299 mg, 2.5 mmol) in DMF (3 mL) was added K_2CO_3 (1.2 g, 8.4 mmol) in one portion. The mixture was stirred at 80 °C for 12 hours. Then H_2O (9mL) was added into the mixture, and the aqueous phase was extracted with EtOAc (15 mL x 3), and the combined organic layer was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 300:1 to 40:1) to give compound **139C** (340 mg, yield: 59.4%) as a pale yellow

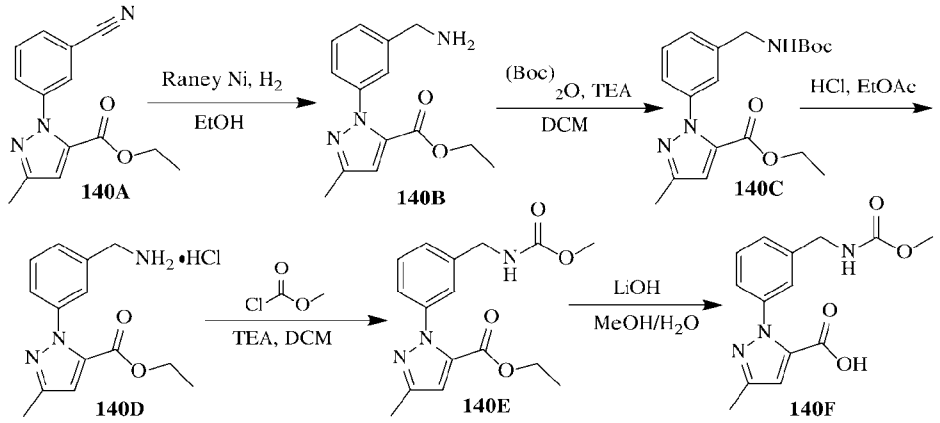
solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.57 - 7.51 (m, 1H), 7.35 (t, J = 7.7 Hz, 1H), 4.24 (q, J = 7.0 Hz, 2H), 2.56 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H).

[0864] To a solution of compound **139C** (100 mg, 368.6 umol) in THF (2 mL) and H_2O (500 uL) was added $LiOH.H_2O$ (15.5 mg, 368.6 umol) in one portion. The mixture was stirred at 25 °C for 12 hours. Then the pH of the aqueous phase was adjusted to about 5 by adding HCl (1M), and the residue concentrated on a rotary evaporator to give intermediate compound **139D** (83 mg, yield: 92.6%) as a white solid. ^{1}H NMR (400MHz, DMSO-*d6*) δ 8.62 (s, 1H), 7.94 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 3.5 Hz, 2H), 7.41 - 7.35 (m, 1H), 3.30 (br s, 3H). MS (ESI) *m/z* $(M+H)^-$ 243.9.

[0865] Compound **139** (18 mg, yield: 24.8%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **139D**. Compound **139**: ^{1}H NMR (400MHz, $CDCl_3$) δ 10.32 (br d, J = 5.7 Hz, 1H), 8.17 (d, J = 8.6 Hz, 1H), 7.93 (s, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.65 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.19 - 7.12 (m, 5H), 6.77 (br s, 1H), 5.77 - 5.69 (m, 1H), 5.49 (br s, 1H), 3.42 (dd, J = 5.1, 14.3 Hz, 1H), 3.20 (dd, J = 7.9, 14.3 Hz, 1H), 2.57 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 418.0.

EXAMPLE 82

METHYL (*S*)-(3-(5-((4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)CARBAMOYL)-3-METHYL-1*H*-PYRAZOL-1-YL)BENZYL)CARBAMATE (140)



[0866] To a solution of 3-hydrazinylbenzonitrile (30.0 g, 176.9 mmol , HCl salt) in HOAc (500 mL) was added ethyl 2-methoxyimino-4-oxo-pentanoate (33.1 g, 176.9 mmol). The mixture was stirred at 100 °C for 12 hours. The mixture was concentrated, diluted with ethyl

acetate (200 mL), washed with $NaHCO_3$ (aqueous, 200 mL), brine (200 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1:0 to 5:1). The product obtained was triturated with Petroleum ether/Ethyl acetate = 10:1 (100 mL) and filtered. Compound **140A** (20.0 g, yield 44.3%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.05 - 8.02 (m, 1H), 7.93 - 7.88 (m, 1H), 7.83 - 7.78 (m, 1H), 7.70 - 7.63 (m, 1H), 6.94 (s, 1H), 4.21 - 4.13 (m, 2H), 2.26 (s, 3H), 1.19 - 1.11 (m, 3H).

[0867] To a solution of compound **140A** (9.00 g, 35.26 mmol) in MeOH (500 mL) was added Raney-Ni (1.51 g) and $NH_3.H_2O$ (4 mL). The mixture was stirred at 25 °C under H_2 at 40 psi for 12 hours. The mixture was concentrated, diluted with ethyl acetate (500 mL), washed with HCl (500 mL), the water phase was added $NaHCO_3$ (aqueous) until pH ~ 11. Then the mixture was extracted with ethyl acetate (500 mL), washed with brine (500 mL), dried over Na_2SO_4 and concentrated to afford intermediate compound **140B** (15 g, crude) as a yellow oil.

[0868] To a solution of compound **140B** (9.6 g, 37.06 mmol) in DCM (100 mL) was added TEA (7 mL, 55.6 mmol), then Boc_2O (9 mL, 40.77 mmol) was added to the mixture and the mixture was stirred at 25°C for 12h. The reaction was washed with citric acid (10%, 100 mL), extracted with DCM (100 mL x 2), washed with H_2O (100 mL), dried over anhydrous Na_2SO_4, filtered, evaporated under reduced pressure. The crude product was purified by Flash Column Chromatography (Petroleum Ether/Ethyl Acetate =5/1) to afford compound **140C** (8.5 g, yield 63.8%) as yellow oil. ^{1}H NMR (DMSO-d_6, 400MHz) δ 7.50 - 7.44 (m, 1H), 7.43 - 7.37 (m, 1H), 7.32 - 7.24 (m, 3H), 6.88 (s, 1H), 4.20 - 4.13 (m, 4H), 2.27 (s, 3H), 1.37 (s, 9H), 1.20 - 1.14 (m, 3H).

[0869] To a suspension of compound **140C** (4.5 g, 13.03 mmol) in EA (350 mL) was added HCl/EtOAc (4 M, 35 mL) and the mixture was stirred at 25 °C for 2 h. The reaction was evaporated under reduced pressure to afford compound **140D** (3.3 g, yield 89.9%, HCl) as white solid, which was used directly in next step.

[0870] To a solution of compound **140D** (1 g, 3.4 mmol, HCl) in DCM (20 mL) was added TEA (1.4 mL, 10.1 mmol), followed by compound methylchloroformate (1.6 mL, 20.1 mmol), then the mixture was stirred at 25°C for 1h. The reaction was diluted with H_2O (10 mL), the mixture was extracted DCM (20 mL x 2). The organic layer was collected, washed with

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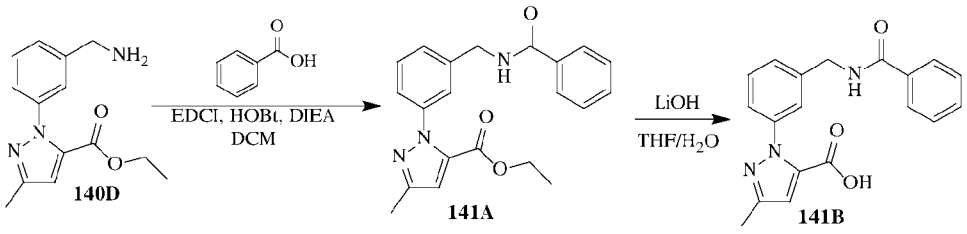
brine (20 mL x 3), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by Flash Column Chromatography (Petroleum Ether/Ethyl Acetate, 0 to 10/1) to afford compound **140E** (400 mg, yield 37.3%) was obtained as white solid. ^{1}H NMR (DMSO-d_6, 400MHz) δ 7.77 (br t, J = 6.2 Hz, 1H), 7.43 - 7.38 (m, 1H), 7.33 - 7.25 (m, 3H), 6.88 (s, 1H), 4.23 (d, J = 6.2 Hz, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.55 (s, 3H), 2.26 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H).

[0871] Compound **140F** (230 mg, yield 64.6%, white solid) was prepared as in Example **85** from the intermediate compound **140E**. ^{1}H NMR (DMSO-d_6, 400MHz) δ 7.76 (br t, J = 6.1 Hz, 1H), 7.42 - 7.35 (m, 1H), 7.31 - 7.22 (m, 3H), 6.82 (s, 1H), 4.23 (br d, J = 6.2 Hz, 2H), 3.55 (s, 3H), 2.25 (s, 3H)

[0872] Compound **140** (35 mg, yield 21.1%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **140F**. Compound **140**: ^{1}H NMR (CD_3CN, 400MHz) δ 7.40 - 7.17 (m, 10H), 7.07 (br d, J = 18.3 Hz, 2H), 6.47 (br s, 1H), 6.26 (br s, 1H), 6.09 (br s, 1H), 5.34 (br s, 1H), 4.29 (br s, 2H), 3.60 (br s, 3H), 3.27 (br d, J = 9.5 Hz, 1H), 2.99 - 2.85 (m, 1H), 2.27 (br s, 3H). MS (ESI) m/z $(M+H)^+$ 464.2.

EXAMPLE 83

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(3-(BENZAMIDOMETHYL)PHENYL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (141)



[0873] To a solution of compound **140D** (300 mg, 1.22 mmol) and benzoic acid (150 mg, 1.22 mmol) in DCM (10 mL) was added HOBt (330 mg, 2.44 mmol), DIEA (0.5 mL, 3.05 mmol) and EDCI (470 mg, 2.44 mmol). The mixture was stirred at 25°C for 12h. The solvent was removed in vacuo. The residue was dissolved in EtOAc (20 mL), washed with 1N HCl (20 mL). The organics were collected, washed with saturated $NaHCO_3$ (20 mL). The organics were collected, washed with brine (20 mL), dried with Na_2SO_4, filtered and concentrated to afford compound **141A** (400 mg, crude) as yellow oil. MS (ESI) m/z $(M+H)^+$ 364.0.

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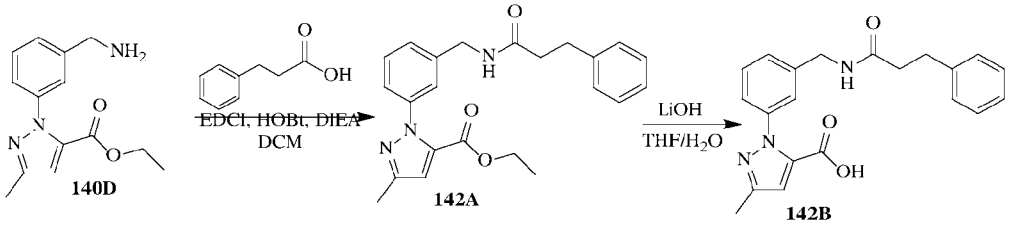
[0874] To a solution of compound **141A** (400 mg, 1.14 mmol) in THF (5 mL) and H_2O (5 mL) was added LiOH.H_2O (241 mg, 5.72 mmol). The mixture was stirred at 25°C for 12h. The reaction was acidified with 1N HCl to pH ~ 4, extracted with EtOAc (15 mL x 2). The organics were collected and concentrated. The residue was purified by preparatory-HPLC (Neutral conditions) to afford compound **141B** (100 mg, yield: 26.16%) as white solid. MS (ESI) *m/z* $(M+Na)^+$ 358.0.

[0875] Compound **141** (4.4 mg, yield: 14.40%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **141B**. Compound **141**: MS (ESI) *m/z* $(M+H)^+$ 510.0. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.86 - 8.68 (m, 2H), 7.94 - 7.88 (m, 2H), 7.84 - 7.57 (m, 2H), 7.54 - 7.20 (m, 11H), 7.11 - 6.99 (m, 1H), 6.55 (s, 1H), 5.33 - 5.24 (m, 1H), 4.56 - 4.48 (m, 2H), 3.26 - 3.18 (m, 1H), 2.95 - 2.86 (m, 1H), 2.25 (s, 3H).

EXAMPLE 84

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(3-((3-PHENYLPROPANAMIDO)METHYL)PHENYL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (142)



[0876] To a solution of compound **140D** (500 mg, 2.04 mmol) and 3-phenylpropanoic acid (310 mg, 2.04 mmol) in DCM (20 mL) was added DIEA (0.9 mL, 5.10 mmol), HOBt (552 mg, 4.08 mmol) and EDCI (783 mg, 4.08 mmol). The mixture was stirred at 25°C for 12h. The solvent was removed in vacuo. The residue was dissolved in EtOAc (30 mL), washed with 1N HCl (30 mL). The organics were collected, washed with saturated (30 mL), brine (30 mL), dried with Na_2SO_4, filtered, collected and dried in vacuo to afford intermediate compound **22** (700 mg, crude) as yellow oil. MS (ESI) *m/z* $(M+Na)^+$ 414.0.

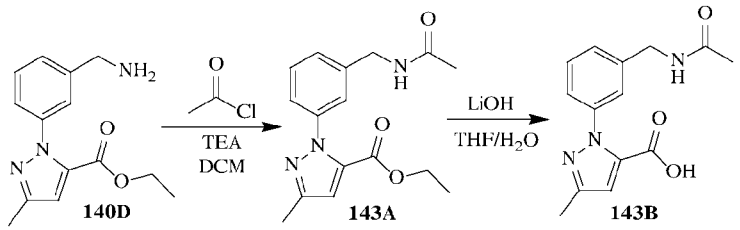
[0877] To a solution of compound **142A** (700 mg, 1.85 mmol) in THF (10 mL) and H_2O (10 mL) was added LiOH.H_2O (390 mg, 9.27 mmol). The mixture was stirred at 25°C for 12h. The residue was acidified with 1N HCl to pH ~ 4. The solution was extracted with EtOAc (20 mL x 2). The organics were collected and concentrated. The residue was purified by

preparatory-HPLC (Neutral) to afford compound **142B** (210 mg, yield: 31.24%) as white solid. **MS (ESI)** *m/z* $(M+Na)^+$ 386.0.

[0878] Compound **142** (49.5 mg, yield: 37.88%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **142B**. Compound **142**: MS (ESI) *m/z* $(M+H)^+$ 538.2. ^{1}H NMR (400MHz, DMSO-d_6) δ8.80 - 8.68 (m, 1H), 8.18 - 8.08 (m, 1H), 7.88 - 7.54 (m, 2H), 7.33 - 7.02 (m, 15H), 6.59 - 6.49 (m, 1H), 5.33 - 5.26 (m, 1H), 4.32 - 4.25 (m, 2H), 3.26 - 3.20 (m, 1H), 2.95 - 2.90 (m, 1H), 2.90 - 2.85 (m, 2H), 2.49 - 2.45 (m, 2H), 2.28 - 2.22 (m, 3H).

EXAMPLE 85

(*S*)-1-(3-(ACETAMIDOMETHYL)PHENYL)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (143)



[0879] To a solution of compound **140D** (500 mg, 2.04 mmol) and acetyl chloride (160 mg, 2.04 mmol) in DCM (20 mL) was added TEA (0.7 mL, 5.10 mmol). The mixture was stirred at 25°C for 12 h. The reaction was washed with 1N HCl (10 mL). The organics were collected, dried with Na_2SO_4, filtered and concentrated to afford intermediate compound **143A** (580 mg, crude) as yellow oil. MS (ESI) *m/z* $(M+Na)^+$ 323.9.

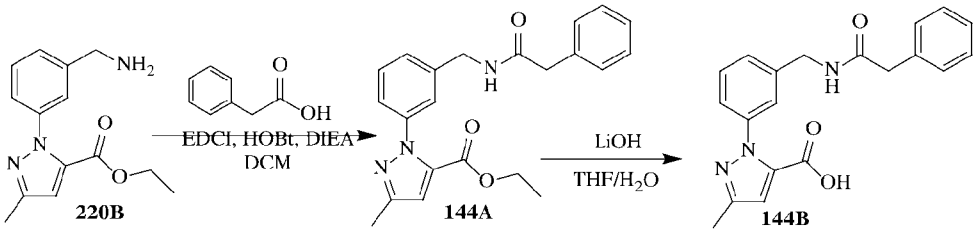
[0880] To a solution of compound **143A** (580 mg, 2.02 mmol) in THF (10 mL) and H_2O (10 mL) was added $LiOH.H_2O$ (424 mg, 10.09 mmol). The mixture was stirred at 25 °C for 12h. The reaction was acidified with 1N HCl to pH ~ 4. The solution was extracted with EtOAc (20 mL x 2). The organics were collected and concentrated. The residue was purified by preparatory-HPLC (Neutral) to afford compound **26** (100 mg, yield: 18.11%) as white solid. MS (ESI) *m/z* $(M+Na)^+$ 295.9.

[0881] Compound **143** (6.2 mg, yield: 12.26%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **143B**. Compound **143**: MS (ESI) *m/z* $(M+H)^+$ 448.1. ^{1}H NMR (400MHz, DMSO-d_6) δ8.78 - 8.67 (m, 0.6H), 8.19 - 8.05 (m, 1H), 7.85 - 7.72 (m, 1H), 7.67 - 7.53 (m, 0.6H), 7.36 - 6.87 (m, 10H), 6.59 - 6.46 (m,

1H), 6.30 - 5.89 (m, 1H), 5.33 - 5.23 (m, 0.6H), 4.52 - 4.40 (m, 0.6H), 4.32 - 4.22 (m, 2H), 3.27 - 3.19 (m, 0.5H), 2.96 - 2.85 (m,0.6H), 2.77 - 2.66 (m, 1H), 2.29 - 2.19 (m, 3H), 1.89 (s, 3H).

EXAMPLE 86

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(3-((2-PHENYLACETAMIDO)METHYL)PHENYL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (144)



[0882] To a solution of compound **140D** (500 mg, 2.04 mmol) and 2-phenylacetic acid (278 mg, 2.04 mmol) in DCM (20 mL) was added DIEA (0.9 mL, 5.10 mmol), HOBt (552 mg, 4.08 mmol) and EDCI (783 mg, 4.08 mmol). The mixture was stirred at 25 °C for 12h. The solvent was removed in vacuo. The residue was dissolved in EtOAc (30 mL), washed with 1N HCl (30 mL). The organics were collected, washed with saturated $NaHCO_3$ (30 mL). The organics were collected, washed with brine (30 mL). The organics were collected, dried with Na_2SO_4, filtered and concentrated to afford intermediate compound **144A** (700.00 mg, crude) as yellow oil. MS (ESI) *m/z* $(M+H)^+$ 378.0.

[0883] To a solution of compound **144A** (700 mg, 1.93 mmol) in THF (10 mL) and H_2O (10 mL) was added $LiOH.H_2O$ (405 mg, 9.63 mmol). The mixture was stirred at 25 °C for 12h. The reaction was acidified with 1N HCl to pH ~ 4. The solution was extracted with EtOAc (15 mL x 2). The organics were collected and concentrated. The residue was purified by preparatory-HPLC (Neutral) to give compound **144B** (260 mg, yield: 38.56%) as yellow oil. MS (ESI) *m/z* $(M+H)^+$ 349.9.

[0884] Compound **144** (36 mg, yield: 45.17%, white solid) was prepared as in Example **5** from the corresponding starting materials, compounds **144B** and **12G**. Compound **144**: MS (ESI) *m/z* $(M+H)^+$ 524.2. ^1H NMR (400MHz, DMSO-d_6) δ 9.07 (d, J = 7.6 Hz, 1H), 8.66 - 8.49 (m, 1H), 8.08 (br. s, 1H), 7.84 (br. s, 1H), 7.34 - 7.10 (m, 13H), 6.94 - 6.86 (m, 1H), 6.53 (s, 1H), 5.27 - 5.16 (m, 1H), 4.32 - 4.16 (m, 2H), 3.44 (s, 2H), 3.22 - 3.10 (m, 1H), 2.85 - 2.73 (m, 1H), 2.22 (s, 3H).

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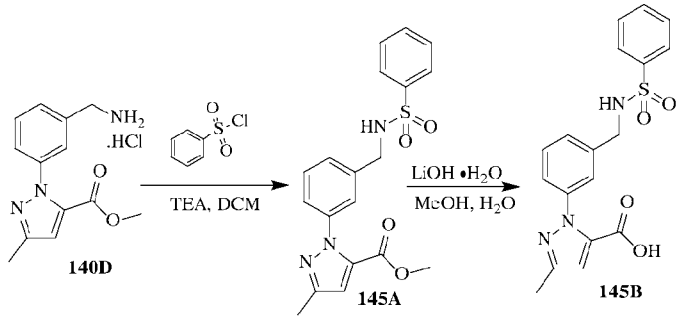
EXAMPLE 87

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(3-(PHENYLSULFONAMIDOMETHYL)PHENYL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (145)



[0885] To a mixture of compound **140D** (300 mg, 1.1 mmol, HCl salt) in DCM (20 mL) was added TEA (0.44 mL, 3.2 mmol) in one portion. Benzenesulfonyl chloride (0.15 mL, 1.2 mmol) was added dropwise to the mixture at 0 °C for 30 min and then stirred at 25 °C for 1h. The reaction mixture was washed with 0.5 N HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The separated organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was triturated with CH_3CN (2 mL). The solid was collected and dried in vacuum to afford compound **145A** (330 mg, yield 79.2%) as white solid. MS (ESI) *m/z* $(M+H)^+$ 386.0.

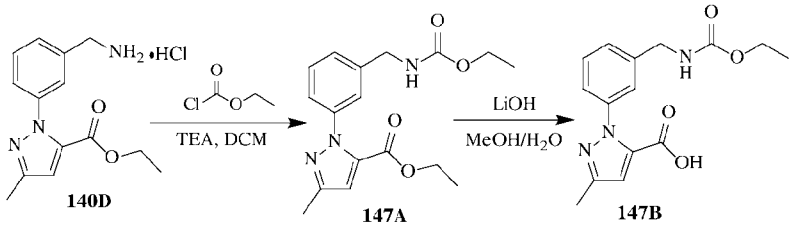
[0886] To a mixture of compound **145A** (150 mg, 0.39 mmol) in MeOH (10 mL) and H_2O (0.5 mL) was added $LiOH.H_2O$ (81.6 mg, 1.9 mmol) in one portion. The mixture was stirred at 25 °C for 12h. The reaction mixture was concentrated under reduced pressure to move MeOH. Then the residue was diluted with water (15 mL) and extracted with ethyl acetate (10 mL), the aqueous phase was acidified with aqueous HCl (1M) till pH ~ 6~7 and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (40 mL) and dried over Na_2SO_4, filtered and concentrated to afford intermediate compound **145B** (140 mg, crude) as white solid. ^1H NMR (DMSO-d_6, 400 MHz): δ 8.29 - 8.22 (m, 1H), 7.85 - 7.78 (m, 2H), 7.65 - 7.54 (m, 3H), 7.38 - 7.23 (m, 4H), 6.82 (s, 1H), 4.04 (d, J = 6.0 Hz, 2H), 2.26 (s, 3H).

[0887] Compound **145** (30 mg, yield 46.8%, white solid) was prepared as in Example **12** from the corresponding intermediate carboxylic acid, compound **145B**. Compound **145**: ^1H NMR ($CDCl_3$, 400 MHz): δ 7.86 - 7.81 (m, 2H), 7.58 - 7.46 (m, 3H), 7.37 - 7.26 (m,

5H), 7.15 - 7.06 (m, 5H), 6.41 (s, 1H), 6.24 - 6.18 (m, 1H), 6.16 - 6.10 (m, 2H), 5.38 - 5.31 (m, 1H), 4.20 - 4.08 (m, 2H), 3.34 - 3.27 (m, 1H), 3.10 - 3.03 (m, 1H), 2.30 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 546.1.

EXAMPLE 88

ETHYL (*S*)-(3-(5-((4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)CARBAMOYL)-3-METHYL-1*H*-PYRAZOL-1-YL)BENZYL)CARBAMATE (147)



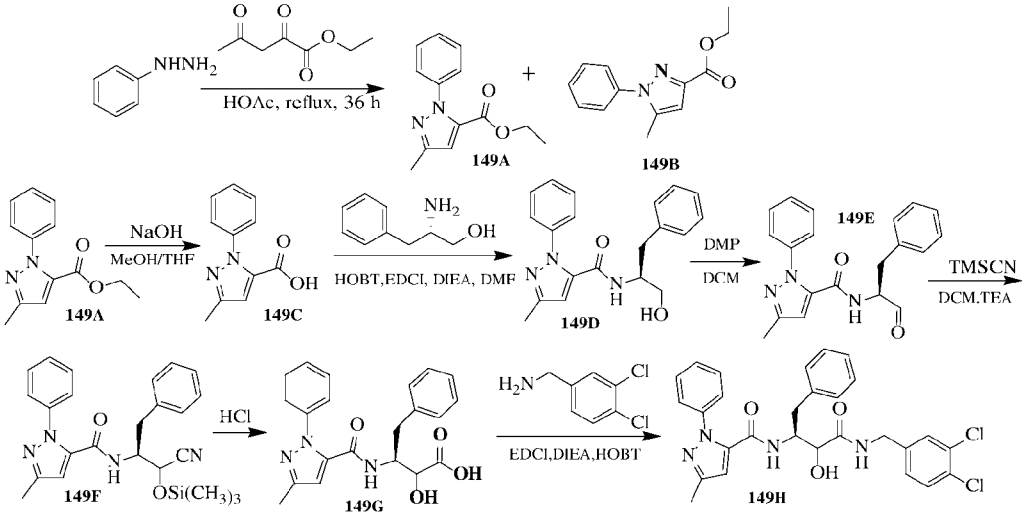
[0888] To a solution of compound **140D** (1 g, 3.38 mmol, HCl salt) in DCM (20 mL) was added TEA (1.4 mL, 10.14 mmol), ethylchloroformate (1.9 mL, 20.27 mmol,) dropwise, then the mixture was stirred at 25 °C for 1h. The reaction was diluted with H_2O (10 mL), the mixture was extracted DCM (20 mL x 2). The combined organic layer was washed with brine (20 mL x 3), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure. The product was purified by Flash Column Chromatography (Petroleum Ether/Ethyl Acetate: 0 to 10/1) to afford compound 147A (570 mg, yield 50. 9%) as white solid. ^{1}H NMR (DMSO-d_6, 400MHz) δ 7.72 (br t, J = 6.1 Hz, 1H), 7.43 - 7.37 (m, 1H), 7.32 - 7.25 (m, 3H), 6.88 (s, 1H), 4.23 (br d, J = 6.2 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 4.03 - 3.97 (m, 2H), 2.26 (s, 3H), 1.16 - 1.12 (m, 6H).

[0889] To a solution of compound **147A** (560 mg, 1.69 mmol) in MeOH (15 mL) was added LiOH (2 M, 5mL) dropwise and then the mixture was stirred at 25°C for 1h. The reaction was diluted with H_2O (10 mL) and concentrated under reduced pressure. The mixture was extracted with TBME (10 mL) and the water phase was treated with HCl (1M) until pH ~ 5. The mixture was extracted with ethyl acetate (15 mL x 3), the combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure to afford compound **147B** (420 mg, yield 81.9%) was obtained as white solid, which was used directly in next step. ^{1}H NMR (DMSO-d_6, 400MHz) δ 7.69 (br t, J = 6.2 Hz, 1H), 7.38 - 7.33 (m, 1H), 7.27 - 7.20 (m, 3H), 6.78 (s, 1H), 4.19 (br d, J = 6.2 Hz, 2H), 3.97 (q, J = 7.1 Hz, 2H), 2.22 (s, 3H), 1.16 - 1.10 (m, 3H).

[0890] Compound **147** (45mg, yield 27.4%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **147B**. Compound **147**: ^{1}H NMR (CD_3CN,400MHz) δ 7.37 - 7.22 (m, 9H), 7.10 (br d, J = 7.7 Hz, 2H), 6.49 (s, 1H), 6.33 (br s, 1H), 6.10 (br s, 1H), 5.40 - 5.31 (m, 1H), 4.31 (br d, J = 6.2 Hz, 2H), 4.08 (q, J = 7.1 Hz, 2H), 3.29 (dd, J = 4.5, 14.0 Hz, 1H), 2.93 (dd, J = 9.4, 14.0 Hz, 1H), 2.29 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H). MS (ESI) m/z $(M+H)^+$ 478.2.

EXAMPLE 89

(*S*)-*N*-(4-((3,4-DICHLOROBENZYL)AMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-PHENYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (149)



[0891] To a solution of phenylhydrazine (1.00 g, 9.25 mmol, 910 uL) in HOAc (20 mL) was added ethyl 2,4-dioxopentanoate (1.46 g, 9.25 mmol, 1.3 mL). The mixture was stirred at 100 °C for 12 hours. The mixture was concentrated and diluted with ethyl acetate (50 mL), washed with $NaHCO_3$ (aqueous, 50 mLx3), brine (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by preparatory-HPLC (TFA condition). Compound **149A** (700.0 mg, yield 32.9%) was obtained as a yellow oil. Compound **149B** (1.00 g, yield 46.9%) was obtained as a yellow oil.

[0892] Compound **149A**: ^{1}H NMR (400MHz, DMSO-d_6) δ 7.48 - 7.36 (m, 5H), 6.87 (s, 1H), 4.18 - 4.10 (m, 2H), 2.25 (s, 3H), 1.16 - 1.11 (m, 3H). **[0893]** Compound **149B**: ^{1}H NMR (400MHz, DMSO-d_6) δ 7.61 - 7.44 (m, 5H), 6.75 (s, 1H), 4.31 - 4.23 (m, 2H), 2.31 (s, 3H), 1.30 - 1.24 (m, 3H).

[0894] To a solution of compound **149A** (700.0 mg, 3.04 mmol) in THF (20 mL) and MeOH (20mL) was added NaOH (2M, 30) .The mixture was stirred at 25 °C for 12 hours. The mixture was concentrated, diluted with H_2O (20 mL), extracted with ethyl acetate (20 mL), the water phase was added HCl (1M) until pH ~ 1, then the mixture was extracted with ethyl acetate (20 mL), the organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated. Compound **149C** (600.0 mg, yield 97.6%) was obtained as a colorless oil. ^{1}H NMR (400MHz, DMSO-d_6) δ 13.21 (br s, 1H), 7.49 - 7.31 (m, 5H), 6.81 (s, 1H), 2.24 (s, 3H).

[0895] To a solution of compound **149C** (600.0 mg, 2.97 mmol) in THF (20 mL) was added DIEA (1.54 g, 11.88 mmol, 2 mL), (2*S*)-2-amino-3-phenyl-propan-1-ol (448.7 mg, 2.97 mmol), HOBt (401.3 mg, 2.97 mmol) and EDCI (683.2 mg, 3.56 mmol). The mixture was stirred at 25 °C for 12 hours. The mixture was concentrated and diluted with ethyl acetate (50 mL), washed with HCl (1M, 50 mL), saturated $NaHCO_3$ (aqueous, 50 mL), brine (50 mLx3), dried over Na_2SO_4 and concentrated. Compound **149D** (600.0 mg, yield 60.2%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.38 (d, J = 8.8 Hz, 1H), 7.32 - 7.17 (m, 8H), 7.12 - 7.07 (m, 2H), 6.50 (s, 1H), 4.89 - 4.83 (m, 1H), 4.10 - 3.99 (m, 1H), 3.48 - 3.35 (m, 2H), 2.95 - 2.87 (m, 1H), 2.68 - 2.59 (m, 1H), 2.21 (s, 3H).

[0896] To a solution of compound **149D** (600.0 mg, 1.79 mmol) in DCM (200 mL) was added DMP (1.14 g, 2.69 mmol). The mixture was stirred at 25 °C for 2 hours. The mixture quenched with 10% $Na_2S_2O_3$ (aqueous): saturated NaHCO3 (aqueous) (1:1, 200 mL), extracted with DCM (100 mL) and washed with brine (20 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated. Compound **149E** (500.0 mg, yield 83.8%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.03 (d, J = 8.0Hz, 1H), 7.36 - 7.13 (m, 10H), 6.57 (s, 1H), 4.56 - 4.49 (m, 1H), 3.28 - 3.21 (m, 1H), 2.81 - 2.72 (m, 1H), 2.25 - 2.17 (m, 3H).

[0897] To a solution of compound **149E** (500.0 mg, 1.50 mmol) in DCM (10 mL) was added TEA (15.2 mg, 150.00 umol, 20 uL) and TMSCN (223.2 mg, 2.25 mmol, 280 uL). The mixture was stirred at 0 °C for 3 hours. The mixture was washed with H_2O (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated to obtain intermediate compound **149F** (600.0 mg, crude) as a colorless oil.

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[0898] To a solution of compound **149F** (600.0 mg, 1.39 mmol) in THF (30 mL) was added HCl (10 mL). After stirred at 60 °C for 12 hours, the mixture was diluted with H_2O (100 mL), extracted with ethyl acetate (50 mL). The organic layer was washed with $NaHCO_3$ (aq, 50 mL). The water phase was added HCl (1M) until pH ~ 1, and then extracted with ethyl acetate (500 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated to obtain intermediate compound **149G** (500.0 mg, crude) as colorless oil.

[0899] To a solution of compound **149G** (500.0 mg, 1.32 mmol) in THF (10 mL) was added (3, 4-dichlorophenyl)methanamine (255.6 mg, 1.45 mmol, 190 uL), HOBt (178.4 mg, 1.32 mmol), DIEA (682.4 mg, 5.28 mmol, 920 uL) and EDCI (303.7 mg, 1.58 mmol) with DCM (10 mL). The mixture was stirred at 25 °C for 12 hours. The mixture was concentrated and diluted with ethyl acetate (30 mL), washed with HCl (1M, 30 mL), saturated $NaHCO_3$ (aqueous, 30 mL), brine (30 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by preparatory-HPLC (TFA condition). The product obtained (70 mg) was triturated with CH_3CN (5 mL) and filtered. Compound **149H** (30.0 mg, 4.23%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.67 - 8.50 (m, 1H), 8.11 (d, J = 9.6 Hz, 1H), 7.50 - 7.41 (m, 1H), 7.39 - 7.34 (m, 1H), 7.32 - 7.14 (m, 9H), 7.07 - 6.96 (m, 2H), 6.47 - 6.36 (m, 1H), 4.46 - 4.36 (m, 1H), 4.34 - 4.10 (m, 2H), 4.06 - 3.99 (m, 1H), 2.95 - 2.71 (m, 2H), 2.26 - 2.13 (m, 2H), 2.26 - 2.13 (m, 1H).

[0900] To a solution of compound **149H** (30.0 mg, 55.82 umol) in DCM (10 mL) and DMSO (1 mL) was added DMP (47.4 mg, 111.64 umol). The mixture was stirred at 25 °C for 48 hours. The mixture was quenched with 10% $Na_2S_2O_3$ (aqueous): saturated $NaHCO_3$ (aqueous) (1:1, 20 mL), extracted with DCM (10 mL) and washed with brine (20 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was triturated with CH_3CN (3 mL) and filtered. Compound **149** (15.0 mg, yield 40.0%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.36 - 9.30 (m, 1H), 9.11 (br d, J = 7.6 Hz, 1H), 7.54 - 7.48 (m, 2H), 7.33 - 7.19 (m, 9H), 7.13 (br d, J=6.6 Hz, 2H), 6.52 (s, 1H), 5.29 - 5.22 (m, 1H), 4.34 - 4.28 (m, 2H), 3.22 - 3.15 (m, 1H), 2.89 - 2.80 (m, 1H), 2.26 - 2.18 (m, 3H). MS (ESI) *m/z* $(M+H)^+$ 535.1.

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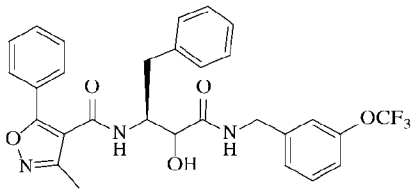
EXAMPLE 90

COMPOUNDS 150-152

(*S*)-*N*-(3,4-DIOXO-1-PHENYL-4-((3-(TRIFLUOROMETHOXY)BENZYL)AMINO)BUTAN-2-YL)-3-METHYL-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (150)



150A

[0901] To a solution of compound **101E** (500.0 mg, 1.31 mmol) in THF (10 mL) was added [3-(trifluoromethoxy)phenyl]methanamine (251.3 mg, 1.31 mmol), DIEA (509.6 mg, 3.94 mmol, 690 uL), HOBt (177.6 mg, 1.31 mmol) and EDCI (302.4 mg, 1.58 mmol) with DCM (5 mL). After stirred at 25 °C for 12 hours, the mixture was concentrated and diluted with ethyl acetate (50 mL), washed with HCl (1M, 50 mL), saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL x 3), dried over Na_2SO_4 and concentrated. The crude product (0.30 g) was triturated with CH_3CN (5 mL) and filtered. Compound **150A** (140.0 mg, yield 19.3%, white solid): ^{1}H NMR (400MHz, DMSO-d_6) δ 8.75 - 8.53 (m, 1H), 8.31 (d, J = 9.6 Hz, 1H), 7.59 - 7.08 (m, 14H), 6.21 - 5.91 (m, 1H), 4.71 - 4.56 (m, 1H), 4.40 - 4.24 (m, 2H), 4.22 - 4.01 (m, 1H), 2.98 - 2.67 (m, 2H), 2.09 - 1.96 (m, 3H).

[0902] To a solution of compound **150A** (60.0 mg, 108.40 umol) in DCM (10 mL) and DMSO (1 mL) was added DMP (137.9 mg, 325.20 umol). After stirred at 25 °C for 4 hour, the mixture was quenched with 10% $Na_2S_2O_3$ (aqueous): saturated aq. $NaHCO_3$ (1:1, 20 mL), extracted with DCM (10 mL) and washed with brine (20 mLx3). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was triturated with CH_3CN (3 mL) and filtered. Compound **150** (50.0 mg, yield 82.8%, white solid): ^{1}H NMR (400MHz, DMSO-d_6) δ 9.54 - 9.45 (m, 1H), 9.11 (d, J = 7.6 Hz, 1H), 7.67 - 7.57 (m, 2H), 7.54 - 7.36 (m, 4H), 7.34 - 7.18 (m, 8H), 5.52 - 5.43 (m, 1H), 4.40 (br d, J = 6.0 Hz, 2H), 3.27 - 3.18 (m, 1H), 2.84 - 2.72 (m, 1H), 2.04 (s, 3H). MS (ESI) m/z $(M+H)^+$ 552.1.

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(*S*)-3-METHYL-*N*-(4-((4-(METHYLSULFONYL)BENZYL)AMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (151)

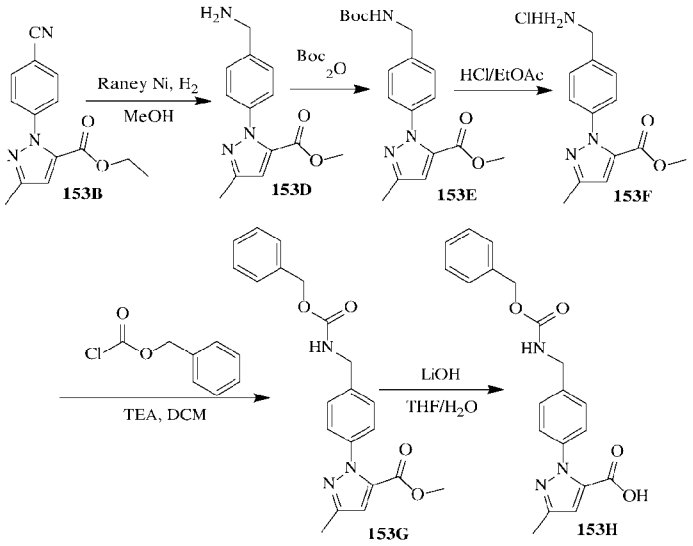
(*S*)-3-METHYL-*N*-(4-((3-(METHYLSULFONYL)BENZYL)AMINO)-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-5-PHENYLISOXAZOLE-4-CARBOXAMIDE (152)

[0903] Compounds **151** and **152** were prepared as in Example **150** from compound **101E** and the corresponding amine, respectively. Compound **151** (40.0 mg, 63.6% yield, white solid): ^{1}H NMR (400MHz, DMSO-d_6) δ 9.58 - 9.51 (m, 1H), 9.12 (d, J = 7.2 Hz, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.65 - 7.59 (m, 2H), 7.56 - 7.38 (m, 5H), 7.31 - 7.19 (m, 5H), 5.53 - 5.44 (m, 1H), 4.48 - 4.42 (m, 2H), 3.29 - 3.21 (m, 1H), 3.20 - 3.10 (m, 3H), 2.83 - 2.73 (m, 1H), 2.08 - 1.96 (m, 3H). MS (ESI) *m/z* (M+H)$^+$ 546.1.

[0904] Compound **152** (42.0 mg, 68.8% yield, white solid): ^{1}H NMR (400MHz, DMSO-d_6) δ 9.59 - 9.51 (m, 1H), 9.11 (d, J = 7.6 Hz, 1H), 7.91 - 7.78 (m, 2H), 7.67 - 7.57 (m, 4H), 7.53 - 7.37 (m, 3H), 7.34 - 7.17 (m, 5H), 5.53 - 5.45 (m, 1H), 4.46 (br d, J = 6.4 Hz, 2H), 3.29 - 3.21 (m, 1H), 3.20 - 3.10 (m, 3H), 2.83 - 2.72 (m, 1H), 2.09 - 1.98 (s, 3H). MS (ESI) *m/z* (M+H)$^+$ 546.1

EXAMPLE 91

BENZYL (*S*)-(4-(5-((4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)CARBAMOYL)-3-METHYL-1*H*-PYRAZOL-1-YL)BENZYL)CARBAMATE (153)



[0905] To a solution of 4-hydrazinylbenzonitrile (20 g, 117.92 mmol, HCl) in HOAc (200 mL) was added ethyl 2-methoxyimino-4-oxo-pentanoate (23.18 g, 123.82 mmol), then the

mixture was heated to 110 °C and stirred for 12h and then removed the solvent under reduced pressure. The residue was dissolved in ethyl acetate (200 mL) and treated with $NaHCO_3$ until pH ~ 8 and then the organic layer was collected and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 15/1 to 3/1) to give compound **153B** (5 g, yield: 16.61%) as a white solid. Compound **153B**: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.71 (dd, J = 7.9 Hz, 2H), 7.53 (br d, J = 7.5 Hz, 2H), 6.84 (s, 1H), 4.23 (q, J = 7.0 Hz, 2H), 2.33 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H). MS (ESI) *m/z* $(M+H)^+$ 255.9.

[0906] To a solution of compound **153B** (6.5 g, 25.46 mmol) in MeOH (70 mL) was added Raney-Ni (1.09 g, 12.73 mmol) and $NH_3.H_2O$ (2.68 g, 76.38 mmol, 3 mL) under argon. The suspension was degassed under vacuum and purged with H_2 3 times. The mixture was stirred at 30 °C for 16h under H_2 (40 psi). The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give intermediate compound **153D** (6.6 g, crude) as a yellow oil. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.46 - 7.36 (m, 2H), 7.35 - 7.29 (m, 2H), 6.87 (s, 1H), 3.77 (s, 2H), 3.71 (s, 3H), 2.26 (s, 3H).

[0907] To a mixture of compound **153D** (3.3 g, 13.45 mmol) in DCM (40 mL) was added Et_3N (2.04 g, 20.17 mmol, 2.8 mL) and Boc_2O (3.52 g, 16.14 mmol, 3.7 mL) in portion at 25 °C under N_2. The mixture was stirred at 25 °C for 1.5h. The reaction mixture was diluted with DCM (20 mL), and washed with H_2O (50 mL). The organic layer was separated and the aqueous layer was extracted with DCM (20 mL x 2). The combined organic layers was washed with brine (30 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 5/1 to 2/1) to give compound **153E** (3.3 g, yield: 64.86%) as yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.37 (s, 4H), 6.80 (s, 1H), 4.38 (dd, J = 5.1 Hz, 2H), 3.78 (s, 3H), 2.36 (s, 3H), 1.47 (s, 9H). MS (ESI) *m/z* $(M+H)^+$ 346.1.

[0908] To a mixture of compound **153E** (3.3 g, 9.55 mmol) in ethyl acetate (20 mL) was added HCl/EtOAc (4M, 20 mL) dropwise at 0 °C. The reaction mixture was stirred at 25 °C for 2h. The mixture was concentrated to give intermediate compound **153F** (2.7 g, crude, HCl) as white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.63 (dd, J = 7.9 Hz, 2H), 7.40 (dd, J = 7.5 Hz, 2H), 6.80 (s, 1H), 4.16 (s, 2H), 3.74 (s, 3H), 2.34 (s, 3H).

[0909] To a mixture of compound **153F** (300 mg, 1.06 mmol, HCl) in DCM (20 mL) was added Et_3N (268.15 mg, 2.65 mmol, 0.4 mL) and benzyl carbonochloridate (181 mg, 1.06 mmol, 0.2 mL) in portion at 25 °C and stirred for 1.5h. The reaction mixture was treated with DCM (20 mL), added with H_2O (30 mL). The organic layer was separated and washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 5/1 to 1/1) to give compound **153G** (350 mg, yield: 87.03%) as off-white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.42 - 7.29 (m, 9H), 6.82 - 6.78 (m, 1H), 5.16 (s, 2H), 4.45 (dd, J = 6.2 Hz, 2H), 3.80 - 3.77 (m, 3H), 2.39 - 2.34 (m, 3H). MS (ESI) *m/z* $(M+H)^+$380.0.

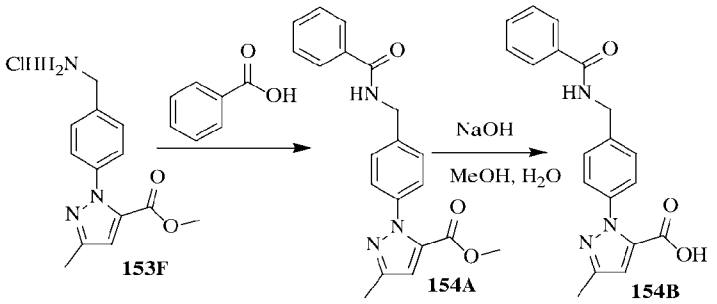
[0910] To a mixture of compound **153G** (350 mg, 922.48 umol) in THF (10 mL) and H_2O (10 mL) was added $LiOH.H_2O$ (116 mg, 2.77 mmol) in portion at 25 °C and stirred for 1.5h. The mixture was diluted with H_2O (10 mL) and concentrated to remove THF, then, the water was extracted with MTBE (30 mL x 2). The water layers were acidified to pH ~ 2 with 1N HCl, then, the solution extracted with ethyl acetate (30 mL x 3). The organic layers were dried over Na_2SO_4 and concentrated to give intermediate compound **153H** (300 mg, yield: 89.04%) as white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.35 (dd, J = 5.3, 8.2 Hz, 6H), 7.30 - 7.16 (m, 2H), 7.14 - 6.98 (m, 1H), 6.90 - 6.82 (m, 1H), 5.15 (s, 2H), 4.47 - 4.30 (m, 2H), 2.46 - 2.28 (m, 3H). MS (ESI) *m/z* $(M+H)^+$366.1.

[0911] Compound **153** (35 mg, yield: 50.19%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **153H**. Compound **153**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.04 (d, J = 7.7 Hz, 1H), 8.09 (s, 1H), 7.84 (br s, 2H), 7.38 - 7.17 (m, 12H), 7.09 (d, J = 8.2 Hz, 2H), 6.53 (s, 1H), 5.27 (t, J = 7.5 Hz, 1H), 5.04 (s, 2H), 4.20 (d, J = 6.0 Hz, 2H), 3.19 (dd, J = 3.3, 14.1 Hz, 1H), 2.86 - 2.75 (m, 1H), 2.22 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 540.2.

EXAMPLE 92

COMPOUNDS 154-159, 496

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(4-(BENZAMIDOMETHYL)PHENYL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (154)



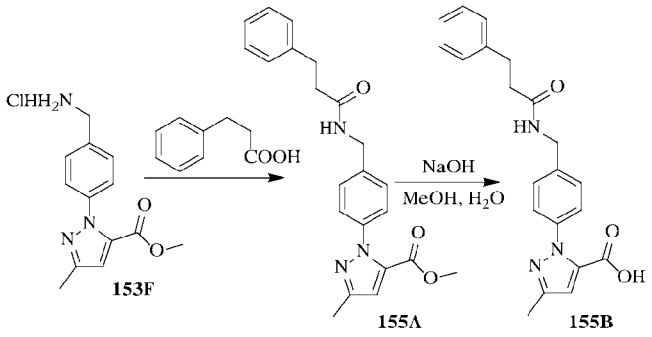
[0912] To a mixture of compound **153F** (300 mg, 1.06 mmol, HCl), benzoic acid (155 mg, 1.27 mmol, 0.2 mL), HOBt (286 mg, 2.12 mmol) and DIEA (343 mg, 2.65 mmol, 0.5 mL) in DCM (20 mL) was added EDCI (406 mg, 2.12 mmol) in portion at 25 °C and stirred for 4h. The reaction mixture was treated with DCM (10 mL), washed with H_2O (20 mL). The organic layer was separated and the aqueous layer was extracted with DCM (10 mL x 2). The combined organic layer was washed with 0.5N HCl (20 mL x 2), $NaHCO_3$ (20 mL x 2) and brine (30 mL), dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 5/1 to 1/1) to give compound **154A** (280 mg, yield: 75.61%) as offwhite solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.81 (dd, J = 6.4 Hz, 2H), 7.58 - 7.40 (m, 7H), 6.85 - 6.78 (m, 1H), 6.48 (br s, 1H), 4.72 (br d, J = 5.1 Hz, 2H), 3.84 - 3.77 (m, 3H), 2.41 - 2.34 (m, 4H). MS (ESI) *m/z* $(M+Na)^+$ 372.0.

[0913] To a mixture of compound **154A** (280 mg, 801.42 umol) in MeOH (10 mL) and H_2O (10 mL) was added NaOH (2M, 2 mL) in portion at 25 °C and stirred for 3h. The mixture was concentrated to remove MeOH and then the water was extracted with MTBE (30 mL x 2). The water layer were acidized to pH ~ 2 with 1N HCl, then the solution extracted with ethyl acetate (20 mL x 2). The organic layers were dried over Na_2SO_4 and concentrated to give intermediate compound **154B** (200 mg, yield: 74.41%) as white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.79 (dd, J = 8.2 Hz, 2H), 7.50 - 7.31 (m, 7H), 6.78 (s, 1H), 4.62 (s, 2H), 2.31 (s, 3H). MS (ESI) *m/z* $(M+H)^-$336.0.

[0914] Compound **154** (20 mg, yield: 29.53%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **154B**. Compound **154**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.11 - 9.04 (m, 2H), 8.11 (s, 1H), 7.96 - 7.91 (m, 2H), 7.86 (s, 1H), 7.56 - 7.47 (m, 3H), 7.30 (d, J = 4.4 Hz, 3H), 7.27 (d, J = 8.6 Hz, 2H), 7.23 - 7.19

(m, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.55 (s, 1H), 5.32 - 5.26 (m, 1H), 4.51 (br d, *J* = 5.7 Hz, 2H), 3.21 (dd, *J* = 3.5, 13.9 Hz, 1H), 2.86 - 2.78 (m, 1H), 2.25 (s, 3H). MS (ESI) *m/z* $(M+H)^+$510.1.

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(4-((3-PHENYLPROPANAMIDO)METHYL)PHENYL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (155)



[0915] Following the procedure as used for compound **154B**, intermediate compound **155B** (200 mg, yield: 74.41%, white solid) was prepared from compound **153F** through **155A**. Compound **155B**: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.28 - 7.12 (m, 8H), 6.94 (s, 1H), 6.78 (s, 1H), 4.42 - 4.31 (m, 2H), 2.94 (t, *J* = 7.5 Hz, 2H), 2.50 (t, *J* = 7.2 Hz, 2H), 2.31 (s, 3H). MS (ESI) *m/z* $(M+H)^+$364.1.

[0916] Compound **155** (20 mg, yield: 27.16%, light yellow solid) was prepared as in Example **12** from the corresponding intermediate carboxylic acid, compound **155B**. Compound **155**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.06 (d, *J* = 7.7 Hz, 1H), 8.38 (t, *J* = 5.8 Hz, 1H), 8.11 (s, 1H), 7.87 (s, 1H), 7.33 - 7.29 (m, 4H), 7.27 (d, *J* = 7.5 Hz, 2H), 7.24 - 7.18 (m, 3H), 7.13 - 7.07 (m, 4H), 6.56 (s, 1H), 5.30 (dd, *J* = 2.6 Hz, 1H), 4.27 (d, *J* = 5.7 Hz, 2H), 3.25 - 3.19 (m, 1H), 2.87 - 2.83 (m, 2H), 2.53 (d, *J* = 2.0 Hz, 1H), 2.49 - 2.44 (m, 2H), 2.25 (s, 3H). MS (ESI) *m/z* $(M+H)^+$538.2.

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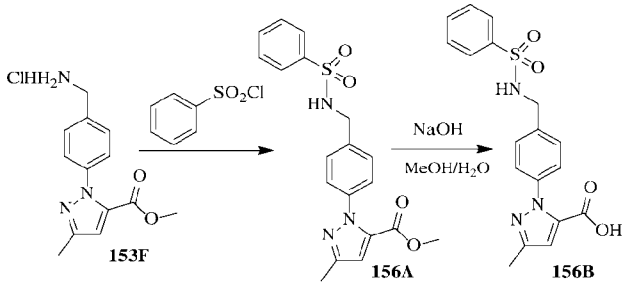
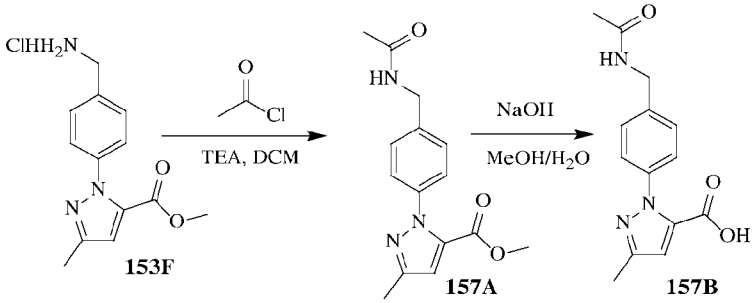
(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(4-(PHENYLSULFONAMIDOMETHYL)PHENYL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (156)



[0917] Following the procedure as used for compound **154B**, intermediate compound **156B** (250 mg, yield: 86.48%, white solid) was prepared from compound **153F** through **156A**. Compound **156B**: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.85 (dd, J = 7.7 Hz, 2H), 7.61 - 7.43 (m, 3H), 7.29 - 7.20 (m, 4H), 6.78 (s, 1H), 4.09 (s, 2H), 2.30 (s, 3H). MS (ESI) *m/z* $(M+H)^+$372.0.

[0918] Compound **156** (45 mg, yield: 78.05%, white solid) was prepared as in Example **12** from the corresponding intermediate carboxylic acid, compound **156B**. Compound **156**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.10 - 9.01 (m, 1H), 8.19 (br s, 1H), 8.09 (s, 1H), 7.86 - 7.79 (m, 3H), 7.63 - 7.56 (m, 3H), 7.32 - 7.25 (m, 5H), 7.19 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 6.52 (s, 1H), 5.26 (br s, 1H), 3.97 (d, J = 5.3 Hz, 2H), 3.23 - 3.13 (m, 1H), 2.87 - 2.75 (m, 1H), 2.22 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 546.1.

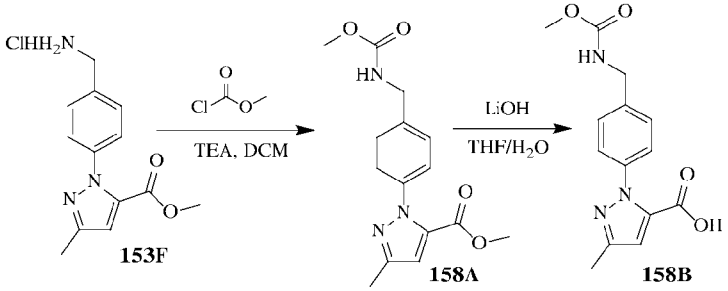
(*S*)-1-(4-(ACETAMIDOMETHYL)PHENYL)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1*H*-PYRAZOLE-5-CARBOXAMIDE (157)



[0919] Following the procedure as used for compound **154B**, intermediate compound **157B** (162 mg, yield: 94.62%, white solid) was prepared from compound **153F** through **157A**. Compound **157B**: ^{1}H NMR (400MHz, DMSO-d_6) δ 13.20 (br s, 1H), 8.43 (br t, J = 5.8 Hz, 1H), 7.37 - 7.25 (m, 4H), 6.79 (s, 1H), 4.29 (d, J = 6.0 Hz, 2H), 2.23 (s, 3H), 1.88 (s, 3H).

[0920] Compound **157** (17 mg, yield: 33.13%, gray solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **157B**. Compound **157**: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.71 (br d, J = 7.5 Hz, 1H), 8.12 (br s, 1H), 7.83 - 7.54 (m, 2H), 7.31 - 7.18 (m, 9H), 6.55 (s, 1H), 5.35 - 5.27 (m, 1H), 4.28 (d, J = 6.0 Hz, 2H), 3.25 (d, J = 4.3 Hz, 0.5H), 3.21 (d, J = 4.0 Hz, 0.5H), 2.94 (s, 0.5H), 2.91 (d, J=4.3 Hz, 0.5H), 2.25 (s, 3H), 1.91 (s, 3H). MS (ESI) m/z $(M+H)^+$ 448.1.

METHYL (*S*)-(4-(5-((4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)CARBAMOYL)-3-METHYL-1*H*-PYRAZOL-1-YL)BENZYL)CARBAMATE (158)



[0921] Following the procedure as used for compound **154B**, intermediate compound **158B** (150 mg, yield: 62.91%, white solid) was prepared from compound **153F** through **158A**. Compound **158B**: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.36 - 7.28 (m, 4H), 6.78 (s, 1H), 4.36 (s, 2H), 3.67 (s, 3H), 2.34 - 2.30 (m, 3H). MS (ESI) m/z $(M+H)^+$289.9.

[0922] Compound **158** (12 mg, yield: 22.68%, light yellow solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **158B**. Compound **158**: ^{1}H NMR (400MHz, DMSO-d_6) δ 9.08 (dd, J = 7.5 Hz, 1H), 8.13 (s, 1H), 7.87 (br s, 1H), 7.74 (s, 1H), 7.35 - 7.17 (m, 7H), 7.16 - 7.07 (m, 2H), 6.54 (s, 1H), 5.34 - 5.24 (m, 1H), 4.19 (dd, J = 6.0 Hz, 2H), 3.57 (s, 3H), 3.28 - 3.18 (m, 1H), 2.82 (dd, J = 10.9, 13.3 Hz, 1H), 2.24 (s, 3H). MS (ESI) m/z $(M+H)^-$464.1.

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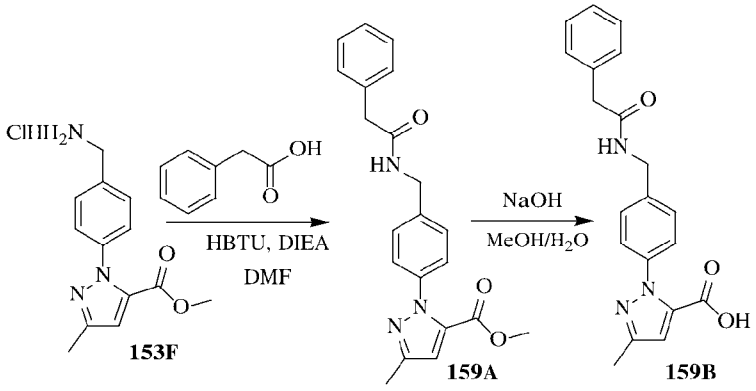
(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-3-METHYL-1-(4-((2-PHENYLACETAMIDO)METHYL)PHENYL)-1*H*-PYRAZOLE-5-CARBOXAMIDE (159)



[0923] To a mixture of compound **153F** (300 mg, 1.06 mmol, HCl) and 2-phenylacetic acid (173 mg, 1.27 mmol, 0.16 mL) in DMF (10 mL) was added DIEA (548 mg, 4.24 mmol, 0.75 mL) and HBTU (603 mg, 1.59 mmol) in one portion at 25 °C. The mixture was stirred at 25 °C for 1.5h. The mixture was diluted with 30 mL ethyl acetate and 20 mL H_2O, the organic layer was separated and washed with 1N HCl (20 mL x 2), saturated $NaHCO_3$ (20 mL x2) and brine (20 mL), the organic layer was dried with over Na_2SO_4, and filtered and organic layer was concentrated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 4/1). Compound **159A** (190 mg, yield: 49.32%) was obtained as a yellow oil. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.62 (br t, J = 5.8 Hz, 1H), 7.36 - 7.14 (m, 9H), 6.91 - 6.78 (m, 1H), 4.31 (d, J = 6.0 Hz, 2H), 3.69 (s, 3H), 3.48 (s, 2H), 2.24 (s, 3H).

[0924] To a solution of compound **159A** (190 mg, 522.83 umol) in MeOH (8 mL) and H_2O (5 mL) was added NaOH (84 mg, 2.09 mmol). The mixture was stirred at 25 °C for 2h. The reaction mixture was concentrated and added 10 mL of water and the mixture was extracted with MTBE (10 mL x 2), the aqueous layer was acidified by 1N HCl to pH ~ 2~3 at 0 °C, and extracted with EtOAc (10 mL x 2), the organic phase was dried over Na_2SO_4, and concentrated to give a residue. Compound **159B** (143 mg, yield: 78.28%) was obtained as a white solid, which was used for next step directly. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.62 (br t, J = 5.7 Hz, 1H), 7.34 - 7.24 (m, 8H), 7.24 - 7.19 (m, 1H), 6.76 (s, 1H), 4.30 (d, J = 5.7 Hz, 2H), 3.48 (s, 2H), 2.22 (s, 3H).

[0925] Compound **159** (25 mg, yield: 33.34%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **159B**. Compound

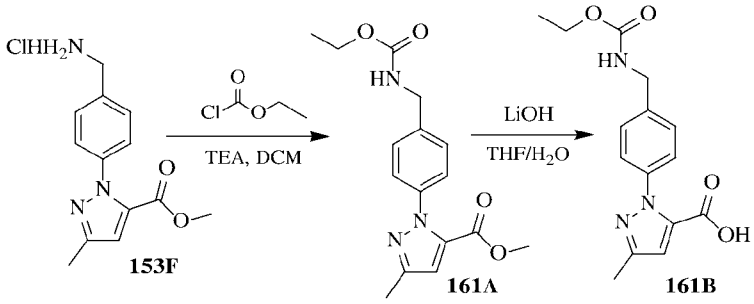
159: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.31 (br s, 1H), 7.40 - 7.05 (m, 17H), 6.56 (s, 1H), 5.31 (dd, J = 4.3, 9.8 Hz, 1H), 4.31 (d, J = 4.3 Hz, 2H), 3.52 (s, 2H), 3.23 (dd, J = 4.3, 14.1 Hz, 1H), 2.91 (dd, J = 10.0, 13.8 Hz, 1H), 2.25 (s, 3H). MS (ESI) m/z $(M+H)^+$ 524.2.

N-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-(4-((4-FLUOROBENZAMIDO)METHYL)PHENYL)-3-METHYL-1H-PYRAZOLE-5-CARBOXAMIDE (496)

[0926] Compound **496** (246.9 mg, yield: 80.2%, white solid) was prepared as in compound **154** using intermediate **153F** and 4-fluorobenzoyl chloride and the resulting product was subjected to reactions as in compound **12** to obtain compound **496**. Compound **496**: ^{1}H NMR (400MHz, DMSO-d_6) δ 99.20 - 9.05 (m, 2H), 8.13 (s, 1H), 8.05 - 7.96 (m, 2H), 7.87 (s, 1H), 7.40 - 7.16 (m, 9H), 7.16 - 7.08 (m, 2H), 6.54 (s, 1H), 5.32 - 5.22 (m, 1H), 4.55 - 4.45 (m, 2H), 3.22 - 3.14 (m, 1H), 2.83 -2.73 (m, 1H), 2.24 (s, 3H). MS (ESI) m/z $(M+H)^+$ 526.2.

EXAMPLE 93

METHYL (*S*)-(4-(5-((4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)CARBAMOYL)-3-METHYL-1H-PYRAZOL-1-YL)BENZYL)CARBAMATE (161)



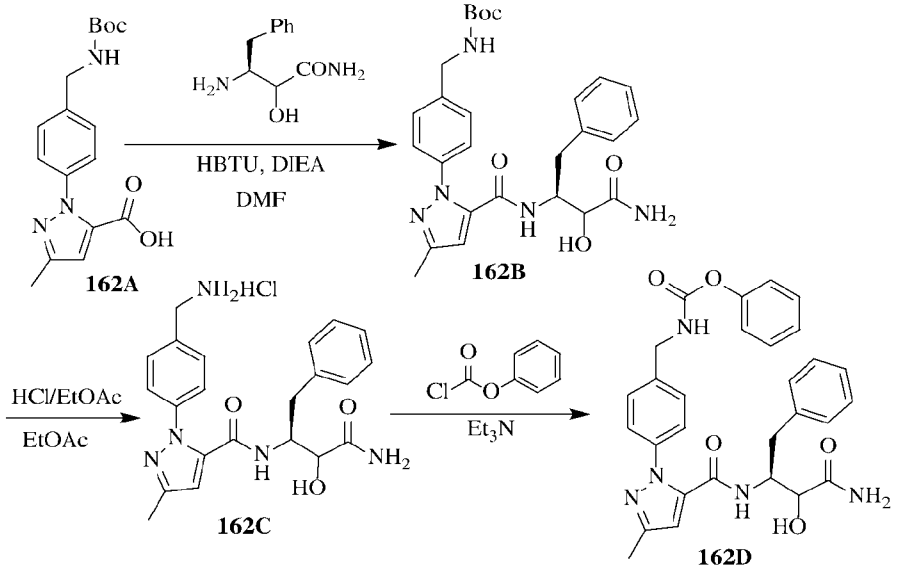
[0927] To a mixture of compound **153F** (450 mg, 1.60 mmol, HCl) in DCM (15.00 mL) was added TEA (485 mg, 4.79 mmol, 0.7mL) and ethyl carbonochloridate (452 mg, 4.17 mmol, 0.4 mL) in portion at 25 °C and stirred for 2h. The reaction mixture was treated with DCM (20 mL), washed with H_2O (30 mL). The organic layer was separated and washed with brine (30 mL), dried over anhydrous $NaSO_4$, filtered and concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 5/1 to 1/1) to give compound **161A** (400 mg, yield: 52.81%) as offwhite solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.37 (br s, 4H), 6.80 (dd, J = 3.5 Hz, 1H), 4.43 (s, 2H), 4.20 - 4.09 (m, 2H), 3.79 (d, J = 3.7 Hz, 3H), 2.36 (dd, J = 3.5 Hz, 3H), 1.27 (td, J = 3.5, 7.1 Hz, 3H). MS (ESI) m/z $(M+H)^+$318.0.

[0928] To a mixture of compound **161A** (400 mg, 1.26 mmol) in THF (10 mL) and H_2O (10 mL) was added $LiOH.H_2O$ (159 mg, 3.78 mmol) in portion at 25 °C and stirred for 0.5h. The mixture was diluted with H_2O (10 mL) and concentrated to remove THF, then, the water was extracted with MTBE (30 mL x 2). The water layers were acidified to pH ~ 2 with 1N HCl, then, the solution extracted with ethyl acetate (30 mL x 3). The organic layers were dried over Na_2SO_4 and concentrated to give intermediate compound **161B** (300 mg, yield: 78.50%) as white solid. ^1H NMR (400MHz, $CDCl_3$) δ 7.33 (s, 4H), 6.79 (s, 1H), 4.35 (s, 2H), 4.23 - 4.03 (m, 2H), 2.38 - 2.27 (m, 3H), 1.41 - 1.19 (m, 4H). MS (ESI) *m/z* $(M+H)^+$304.0.

[0929] Compound **161** (25 mg, yield: 22.8%, white solid) was prepared as in Example **5** from the corresponding intermediate carboxylic acid, compound **161B**. Compound **161**: ^1H NMR (400MHz, DMSO-d_6) δ 9.07 (dd, J = 8.2 Hz, 1H), 8.12 (s, 1H), 7.87 (s, 1H), 7.69 (s, 1H), 7.42 - 7.27 (m, 5H), 7.20 (dd, J = 7.9 Hz, 2H), 7.16 - 7.06 (m, 2H), 6.54 (s, 1H), 5.34 - 5.24 (m, 1H), 4.18 (dd, J = 5.5 Hz, 2H), 4.02 (q, J = 7.1 Hz, 2H), 3.21 (dd, J = 2.9, 13.2 Hz, 1H), 2.92 - 2.77 (m, 1H), 2.24 (s, 3H), 1.18 (br t, J = 7.1 Hz, 3H). MS (ESI) *m/z* $(M+H)^+$478.1.

EXAMPLE 94

PHENYL (S)-(4-(5-((4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)CARBAMOYL)-3-METHYL-1H-PYRAZOL-1-YL)BENZYL)CARBAMATE (162)



[0930] To a mixture of compound **153E** (300 mg, 868.58 umol) in THF (10 mL) and H_2O (10 mL) was added $LiOH.H_2O$ (109 mg, 2.61 mmol) in portion at 25 °C and stirred for 12h.

The mixture was diluted with H_2O (10 mL) and concentrated to remove THF, then, the water was extracted with MTBE (30 mL x 2). The water layers were acidified to pH ~ 2 with 1N HCl, then, the solution extracted with ethyl acetate (30 mL x 3). The organic layers were dried over Na_2SO_4 and concentrated to give intermediate compound **162A** (250 mg, yield: 86.86%) as white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.41 - 7.30 (m, 2H), 7.27 - 7.04 (m, 2H), 6.86 (s, 1H), 4.43 - 4.26 (m, 2H), 2.46 - 2.32 (m, 3H), 1.60 - 1.40 (m, 9H). MS (ESI) *m/z* $(M+H)^+$332.0.

[0931] To a mixture of compound **12G** (209 mg, 905.33 umol, HCl) and compound **162A** (250 mg, 754.44 umol) in DMF (10 mL) was added DIEA (244 mg, 1.89 mmol, 0.3 mL) and HBTU (343 mg, 905.33 umol) in portion at 25 °C and stirred for 1.5h. The reaction mixture was treated with ethyl acetate (40 mL), washed with H_2O (50 mL x 2). The organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was triturated in DCM (2 mL) and petroleum ether (10 mL), the solid was collected and was dried in vacuo to give compound **162B** (300 mg, yield: 75.76%) as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.72 - 8.41 (m, 1H), 7.95 (s, 1H), 7.45 - 7.20 (m, 7H), 7.12 (dd, J = 8.4 Hz, 2H), 7.02 - 6.91 (m, 2H), 6.70 - 6.48 (m, 1H), 6.08 (d, J = 5.5 Hz, 1H), 4.45 (s, 1H), 4.12 - 3.98 (m, 2H), 2.89 (s, 1H), 2.87 - 2.80 (m, 1H), 2.73 (s, 1H), 2.28 - 2.14 (m, 3H), 1.52 - 1.33 (m, 9H). MS (ESI) *m/z* $(M-56)^+$452.1.

[0932] To a mixture of compound **162B** (300 mg, 591.04 umol) in EA (10 mL) was added HCl/EtOAc (4M, 10 mL) dropwise at 0 °C. The reaction mixture was stirred at 25 °C for 2h. The mixture was concentrated to give intermediate compound **162C** (250 mg, yield: 95.28%, HCl) as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.71 - 8.64 (m, 2H), 7.53 - 7.35 (m, 3H), 7.34 - 7.17 (m, 7H), 7.03 (dd, J = 8.4 Hz, 2H), 6.65 (s, 1H), 4.59 - 4.30 (m, 1H), 4.15 (s, 2H), 2.88 (s, 1H), 2.83 (dd, J = 11.9 Hz, 1H), 2.72 (s, 1H), 2.22 (s, 3H).

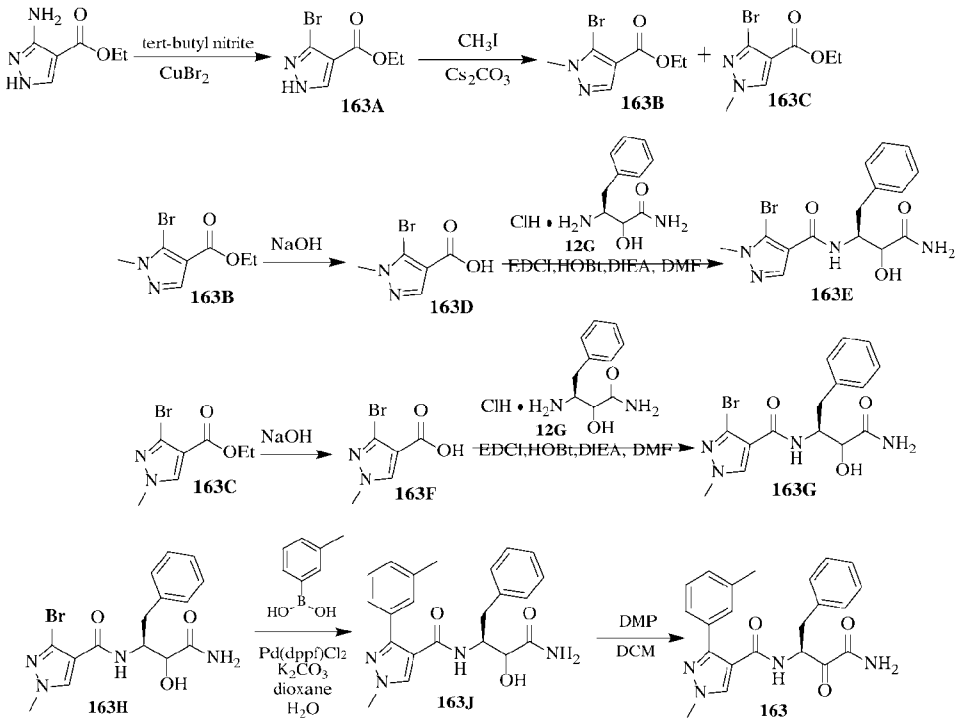
[0933] To a mixture of compound **162C** (120 mg, 270.31 umol, HCl) in DCM (10 mL) was added Et_3N (68 mg, 675.78 umol, 0.1 mL) and phenyl carbonochloridate (51 mg, 324.38 umol, 0.1 mL) in portion at 25 °C and stirred for 1h. The reaction mixture was treated with DCM (20 mL), added with H_2O (30 mL). The organic layer was separated and washed with brine (30 mL), dried over anhydrous $NaSO_4$, filtered and concentrated. The residue was purified by preparatory-HPLC (HCl condition) to give compound **162D** (70 mg, yield: 47.71%) as off-white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.50 (dd, J = 9.0 Hz, 1H), 7.41 - 7.11

(m, 14H), 7.08 (s, 1H), 7.02 (dd, J = 8.4 Hz, 1H), 6.99 (dd, J = 8.4 Hz, 1H), 6.78 - 6.72 (m, 2H), 6.57 - 6.50 (m, 1H), 4.43 (s, 1H), 4.31 - 4.22 (m, 2H), 3.99 (s, 1H), 2.87 - 2.75 (m, 2H), 2.74 - 2.65 (m, 2H), 2.27 - 2.20 (m, 3H). MS (ESI) m/z $(M+H)^+$528.1.

[0934] To a mixture of compound **162D** (40 mg, 75.82 umol) in DMSO (3 mL) and DCM (15 mL) was added DMP (96 mg, 227.46 umol) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 1.5h. The reaction mixture was diluted with DCM (10 mL), $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (10 mL), then stirred for 10 min and layers were separated. The organic layers were washed with water (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was triturated in DCM (2 mL) and petroleum ether (10 mL), the solid was collected and was dried in vacuo to give compound **162** (25 mg, yield: 51.13%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.15 (d, J = 8.0 Hz, 1H), 8.39 (t, J = 6.0 Hz, 1H), 8.14 (s, 1H), 7.88 (s, 1H), 7.41 - 7.19 (m, 11H), 7.14 (dd, J = 8.0 Hz, 3H), 6.68 - 6.51 (m, 1H), 5.41 - 5.22 (m, 1H), 4.29 (dd, J = 6.0 Hz, 2H), 3.21 (dd, J = 3.5, 13.6 Hz, 1H), 2.85 (dd, J = 10.8, 13.8 Hz, 1H), 2.25 (s, 3H). MS (ESI) m/z $(M+H)^+$526.1.

EXAMPLE 95

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-METHYL-3-(*m*-TOLYL)-1*H*-PYRAZOLE-4-CARBOXAMIDE (163)



[0935] To a solution of *t*-BuONO (3.8 mL, 30.94 mmol) in CH_3CN (60 mL) was added $CuBr_2$ (6.91 g, 30.94 mmol). The mixture was stirred at 25 °C for 1h under N_2. Then ethyl 3-amino-1H-pyrazole-4-carboxylate (4 g, 25.78 mmol) was added in portions. The mixture was then heated to 70 °C and stirred for 12h. The reaction was washed with H_2O (100 mL), extracted with EtOAc (100 mL x 2). The organics were collected, dried with Na_2SO_4, filtered and concentrated to afford intermediate compound **163A** (6 g, crude) as black oil. MS (ESI) *m/z* $(M+2)^+$ 220.9.

[0936] To a solution of compound **163A** (10 g, 45.65 mmol) and Cs_2CO_3 (29.75 g, 91.30 mmol) in DMF (250 mL) was added MeI (19.44 g, 136.95 mmol, 8.53 mL). The mixture was stirred at 25 °C for 16h. The mixture was filtered, the filtrate was diluted with H_2O (500 mL), and extracted with ethyl acetate (100 mL x 3), dried over Na_2SO_4, concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 5/1). Compound **163B** (2.5 g, yield: 23.50%) was obtained as a yellow oil, and Compound **163C** (5.5 g, yield: 51.70%) was obtained as a white solid.

[0937] Compound **163B**: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.93 (s, 1H), 4.31 (q, J = 7.1 Hz, 2H), 3.95 - 3.87 (m, 3H), 1.36 (t, J = 7.1 Hz, 3H).

[0938] Compound **163C**: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.82 (s, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.99 - 3.77 (m, 3H), 1.35 (t, J = 7.2 Hz, 3H).

[0939] To a solution of compound **163B** (600 mg, 2.57 mmol) in MeOH (10 mL) and H_2O (10 mL) was added NaOH (514 mg, 12.85 mmol). The mixture was stirred at 25 °C for 3h. The reaction mixture was concentrated and added 20 mL of water, the mixture was extracted with MTBE (10 mL x 2), the aqueous layer was acidified by 1N HCl to pH ~ 2~3 at 0 °C, and extracted with EtOAc (20 mL x 2), the organic phase was dried over Na_2SO_4, concentrated to give a residue. Compound **163D** (480 mg, yield: 91.05%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 12.65 (s, 1H), 8.13 (s, 1H), 3.82 (s, 3H).

[0940] To a solution of Compound **163D** (450 mg, 2.20 mmol), (3*S*)-3-amino-2-hydroxy-4-phenyl-butanamide **12G** (761 mg, 3.30 mmol, HCl) and HOBT (445 mg, 3.30 mmol) in DCM (20 mL) was added DIEA (1.14 g, 8.80 mmol, 1.54 mL) and EDCI (843 mg, 4.40 mmol). The mixture was stirred at 25 °C for 16h. The mixture was diluted with $CHCl_3$: *i*PrOH = 3: 1 (50 mL), washed with 1N HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL) and brine (30

mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The solid was triturated in ethyl acetate (30 mL), filtered. Compound **163E** (550 mg, yield: 61.64%) was obtained as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.09 - 7.95 (m, 1H), 7.78 (d, J = 8.8 Hz, 0.6H), 7.46 (d, J = 9.0 Hz, 0.4H), 7.38 - 7.07 (m, 6H), 6.01 - 5.86 (m, 1H), 4.54 - 4.33 (m, 1H), 4.00 (dd, J = 3.4, 5.2 Hz, 1H), 3.85 - 3.74 (m, 4H), 2.93 - 2.67 (m, 1H), 2.62 (dd, J = 2.3, 13.8 Hz, 1H). MS (ESI) *m/z* $(M+H)^+$381.0.

[0941] To a solution of compound **163C** (2.6 g, 11.16 mmol) in MeOH (10 mL) and H_2O (10 mL) was added LiOH.H_2O (2.34 g, 55.80 mmol). The mixture was stirred at 25 °C for 12h. The reaction mixture was concentrated and added 20 mL of water and the mixture was extracted with MTBE (20 mL x 2), the aqueous layer was acidified by 1N HCl to pH ~ 2~3 at 0 °C, and extracted with EtOAc (30 mL x 2), the organic phase was dried over Na_2SO_4 and concentrated to give a residue. Compound **163F** (2.2 g, yield: 96.16%) was obtained as a gray solid, which was used for next step directly. ^{1}H NMR (400MHz, DMSO-d_6) δ 12.55 (br s, 1H), 8.24 (s, 1H), 3.81 (s, 3H).

[0942] To a mixture of compound **163F** (2.2 g, 10.73 mmol) and compound **12G** (2.97 g, 12.88 mmol HCl) in DMF (20 mL) and HOBt (2.17 g, 16.10 mmol) and DIEA (4.16 g, 32.19 mmol, 5.62 mL) and EDCI (4.11 g, 21.46 mmol) in one portion at 25 °C. The mixture was stirred at 25 °C for 12h. The reaction mixture was diluted with H_2O (40 mL) and extracted with $CHCl_3$: isopropanol (v: v = 3: 1; 30 x 3 mL), then the organic phase was washed with 1N HCl (20 mL x 2) and saturated aqueous $NaHCO_3$ (20 mL x 2). The mixture was dried over Na_2SO_4 and concentrated. The residue was diluted with EtOAc (15 mL) the solid was collected and dried in vacuo. Compound **163G** (2.9 g, yield: 68.06%) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.61 (br d, J = 8.8 Hz, 1H), 7.31 (br d, J = 2.4 Hz, 2H), 7.24 - 7.13 (m, 5H), 5.89 (d, J = 5.7 Hz, 1H), 4.51 - 4.40 (m, 1H), 4.00 - 3.97 (m, 1H), 3.79 (s, 3H), 2.80 - 2.76 (m, 1H), 2.65 - 2.58 (m, 1H). MS (ESI) *m/z* $(M+H)^+$381.0.

[0943] Compound **163G** (200 mg, 525 umol), m-tolylboronic acid (85.6 mg, 629 umol), Pd(dppf)Cl_2 (38.4 mg, 52.5 umol) and K_2CO_3 (145 mg, 1.05 mmol) in dioxane (5 mL) was de-gassed and then heated to 100 °C for 12 hours under N_2. The mixture was filtered and concentrated, the residue was purified by prep-TLC (Dichloromethane: Methanol = 10: 1) to give compound **163H** (100 mg, yield: 48.6%), as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.99

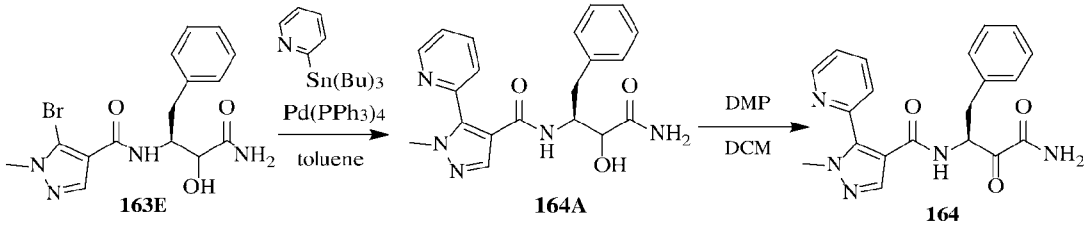
(d, J = 19.4 Hz, 1H), 7.37 (br s, 1H), 7.31 - 7.06 (m, 11H), 5.76 (br s, 1H), 4.52 - 4.31 (m, 1H), 3.98 (br s, 1H), 3.83 (s, 3H), 3.80 (br s, 1H), 2.87 - 2.72 (m, 1H), 2.71 - 2.56 (m, 1H), 2.26 (d, J = 6.8 Hz, 3H).

[0944] A mixture of compound **163H** (100 mg, 255 umol) and DMP (432 mg, 1.02 mmol) in DCM (10 mL), DMSO (2 mL) was stirred at 25°C for 1 hr. The mixture was diluted DCM (20 mL), quenched with saturated aqueous $NaHCO_3$ (20 mL), saturated aqueous $Na_2S_2O_3$ (20 mL) and stirred for 20 min, the mixture was extracted with DCM (20 mL x 2), the combined organic phase was washed with water (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated, the residue was stirred in DCM and n-hexane for 20 min, the solid was filtered and dried to give **163** (43.5 mg, yield: 43.7%) as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.23 (br d, J = 7.3 Hz, 1H), 8.08 - 7.97 (m, 2H), 7.78 (s, 1H), 7.38 (s, 1H), 7.31 (br d, J = 7.5 Hz, 1H), 7.28 - 7.13 (m, 6H), 7.11 - 7.05 (m, 1H), 5.31 - 5.21 (m, 1H), 3.85 (s, 3H), 3.12 (dd, J = 3.7, 13.9 Hz, 1H), 2.79 (dd, J = 9.7, 13.9 Hz, 1H), 2.25 (s, 3H). MS (ESI) m/z $(M+H)^+$ 391.1.

EXAMPLE 96

COMPOUNDS 164, 169, 480-488, 498-518, 530, 548, 567-573, 585, 587, 591, 593, 597, 601-605, 607, 611, 613-617, 620-621, 624-629

(*S*)-*N*-(4-AMINO-3,4-DIOXO-1-PHENYLBUTAN-2-YL)-1-METHYL-5-(PYRIDIN-2-YL)-1*H*-PYRAZOLE-4-CARBOXAMIDE (164)



[0945] To the mixture of **163E** (200 mg, 527 umol) and tributyl(2-pyridyl)stannane (388 mg, 1.05 mmol) in toluene (5 mL) was added $Pd(PPh_3)_4$ (60.9 mg, 52.7 umol) under N_2 (15 psi). After stirred at 110 °C for 10 h, the mixture was concentrated in vacuum to get residue. The residue was purified by preparatory-HPLC (acid) to get compound **164A** (85 mg, yield: 42.5%) as light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ 8.97 (br d, J = 7.06 Hz, 1H), 8.72 (br d, J = 7.28 Hz, 1H), 8.55 (dd, J = 17.64, 4.85 Hz, 1H), 8.03 – 7.95 (m, 1H), 7.88 - 7.79 (m, 1H), 7.43 - 7.31 (m, 2H), 7.13 - 6.99 (m, 6H), 5.49 (br d, J = 10.14 Hz, 1H), 4.27 - 4.17 (m, 2H), 3.89 (d, J = 3.53 Hz, 3H), 3.26 - 2.91 (m, 2H).

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
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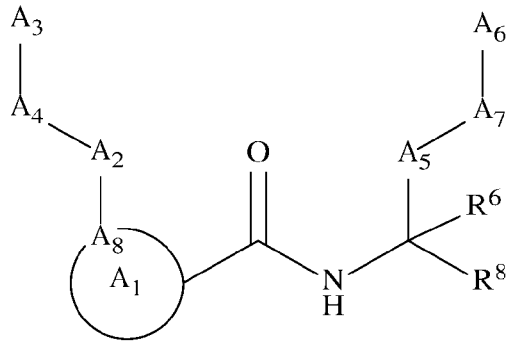
International Patent Application No.: PCT/US2017/053629
Knobbe Ref.: BLADT.004WO
Received 4/1/2019

APPENDIX

January 3, 2019 Marked up Article 34 Amendment

WHAT IS CLAIMED IS:

1. A compound having the structure of the formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

A_1 is selected from the group consisting of optionally substituted 5-10 membered heterocyclyl provided the 6-10-membered heterocyclyl is not substituted with oxo; optionally substituted 5- or 8- membered heteroaryl; and optionally substituted C_{3-10} carbocyclyl;

A_2 is selected from the group consisting of optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted C_{3-10} carbocyclyl, -S-, -S(=O)-, -SO_2-, -C(=S)-, -CH=CH-, -C≡C-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(S)NH-, -NHC(S)O-, -NHC(S)-, and single bond;

A_4 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, -$(CR_2)_n$-S-$(CR_2)_n$-, -$(CR_2)_n$-S(=O)-$(CR_2)_n$-, -$(CR_2)_n$-SO_2-$(CR_2)_n$-, -$(CR_2)_n$-O-$(CR_2)_n$-, -$(CR_2)_n$-C(=S)-$(CR_2)_n$-, -$(CR_2)_n$-C(=O)-$(CR_2)_n$-, -$(CR_2)_n$-CH=CH-$(CR_2)_n$-, -$(CR_2)_n$-OC(O)NH-$(CR_2)_n$-, -$(CR_2)_n$-NHC(O)NH-$(CR_2)_n$-, -$(CR_2)_n$-NHC(O)O-$(CR_2)_n$-, -$(CR_2)_n$-NHC(S)NH-$(CR_2)_n$-, -$(CR_2)_n$-NHC(S)O-$(CR_2)_n$-, -$(CR_2)_n$-NHC(S)-$(CR_2)_n$-, and single bond;

when A_2 and A_4 are single bond, A_3 is directly attached to A_8;

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A_3 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, and optionally substituted C_{3-10} carbocyclyl, or if A_2 is selected from optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted C_{3-10} carbocyclyl, then A_3 is selected from the group consisting of hydrogen, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, -C≡CH, and optionally substituted 2- to 5-membered polyethylene glycol;

A_5 is selected from the group consisting of optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-8} alkyl, -S-, -S(=O)-, $-SO_2-$, -O-, -C(=S)-, -C(=O)-, -NR-, -CH=CH-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(O)-, -NHC(S)NH-, -NHC(S)O-, -NHC(S)-, and single bond;

A_6 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted –O-C_{1-6} alkyl, optionally substituted –O C_{2-6} alkenyl, $-OSO_2CF_3$, and any natural or non-natural amino acid side chain;

A_7 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-8} alkyl, -S-, S(=O)-, $-SO_2-$, -O-, -C(=S)-, -C(=O)-, -NR-, -CH=CH-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(O)-, -NHC(S)NH-, -NHC(S)O-, -NHC(S)-, and single bond;

when A_5 and A_7 are single bond, A_6 is directly attached to the carbon to which R^8 is attached;

A_8 is a ring member of A_1 and is selected from the group consisting of C and N;

R^8 is selected from the group consisting of $-COR^1$, [[-CN,]]-CH=$CHSO_2R$, and $-CH_2NO_2$;

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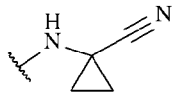
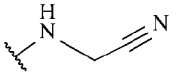
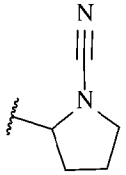
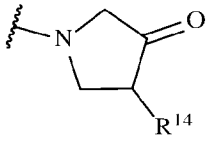
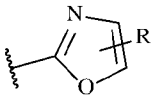
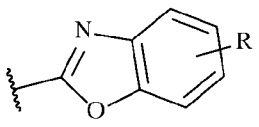
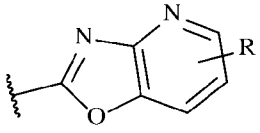
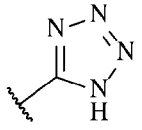
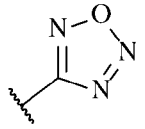
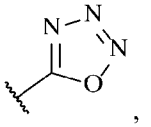
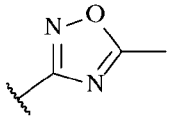
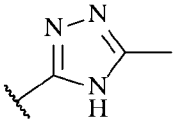
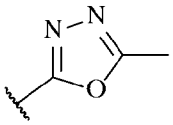
R^1 is selected from the group consisting of H, [[-OH,]]C_{1-4} haloalkyl, -COOH, -CH_2NO_2, -C(=O)NOR, [[-NH_2,]]-$CONR^2R^3$, -$CH(CH_3)=CH_2$, -$CH(CF_3)NR^2R^3$,

-C(F)=$CHCH_2CH_3$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ;

R^{14} is halo;

each R, R^2, and R^3 are independently selected from –H, optionally substituted C_{1-4} alkyl, optionally substituted C_{1-8} alkoxyalkyl, optionally substituted 2- to 5-membered polyethylene glycol, optionally substituted C_{3-7} carbocyclyl, optionally substituted 5-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted C_{6-10} aryl(C_1-C_6)alkyl, and optionally substituted 5-10 membered heteroaryl;

R^6 is independently selected from –H and optionally substituted C_{1-4} alkyl; and each n is independently selected to be an integer from 0 to 3.

2. The compound of claim 1, wherein:

A_1 is selected from the group consisting of optionally substituted 6-10 membered heterocyclyl provided the 6-10-membered heterocyclyl is not substituted with oxo; optionally substituted 5- or 8- membered heteroaryl; and optionally substituted C_{3-10} carbocyclyl;

A_2 is selected from the group consisting of optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted C_{3-10} carbocyclyl, -S-, -S(=O)-, -SO_2-, -C(=S)-, -CH=CH-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(S)NH-, -NHC(S)O-, -NHC(S)-, and single bond;

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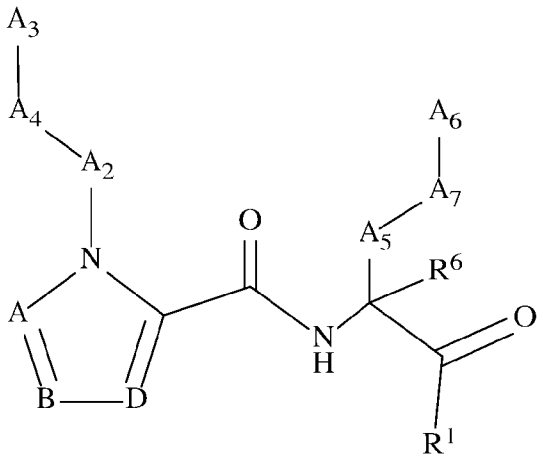
A_4 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, -S-, S(=O)-, $-SO_2-$, -O-, -C(=S)-, -C(=O)-, -CH=CH-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(S)NH-, -NHC(S)O-, -NHC(S)-, and single bond;

A_3 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, and optionally substituted C_{3-10} carbocyclyl;

A_6 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-8} alkyl, optionally substituted $-O-C_{1-6}$ alkyl, optionally substituted $-O$ C_{2-6} alkenyl, and any natural or non-natural amino acid side chain; and

each R, R^2, and R^3 are independently selected from –H, optionally substituted C_{1-4} alkyl, optionally substituted C_{3-7} carbocyclyl, optionally substituted 5-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, and optionally substituted 5-10 membered heteroaryl.

3. The compound of any one of claims 1 and 2 having the structure of formula **I-a**:



I-a

or a pharmaceutically acceptable salt thereof, wherein:

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A, B, and D are each independently selected from the group consisting of $C(R^4)$ and N; and

each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy.

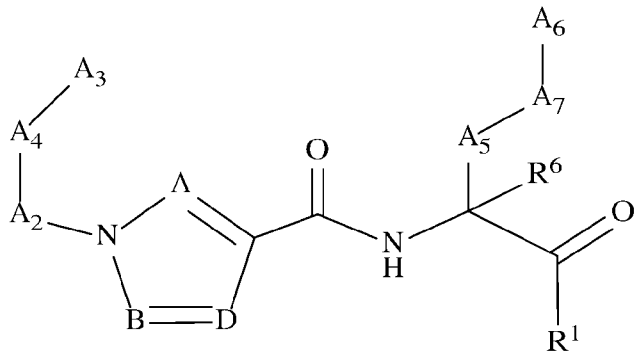
4. The compound of claim 3, wherein A, B, and D are independently selected from the group consisting of CH and N.

5. The compound of claim 4, wherein A is N, B is CH, and D is CH.

6. The compound of claim 4, wherein A is CH, B is N, and D is CH.

7. The compound of claim 4, wherein A is N, B is N, and D is N.

8. The compound of any one of claims 1 and 2 having the structure of formula **I-b**:



I-b

or a pharmaceutically acceptable salt thereof, wherein:

A, B, and D are each independently selected from the group consisting of $C(R^4)$ and N; and

each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy.

9. The compound of claim 8, wherein A, B, and D are independently selected from the group consisting of CH and N.

10. The compound of any one of claims 1 and 2 having the structure of formula **I-c**:

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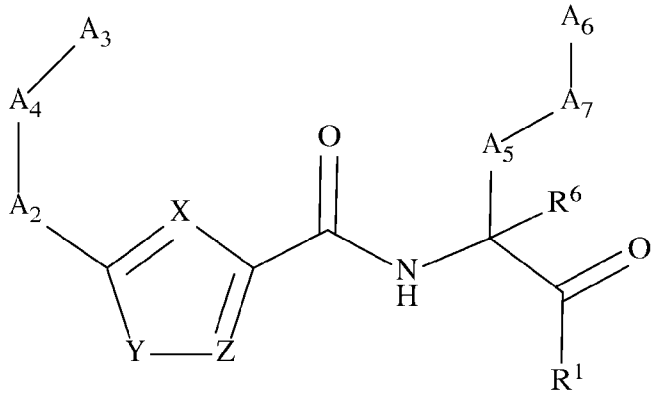


I-c

or a pharmaceutically acceptable salt thereof, wherein:

Y is selected from the group consisting of NR^5, O, S, and SO_2;

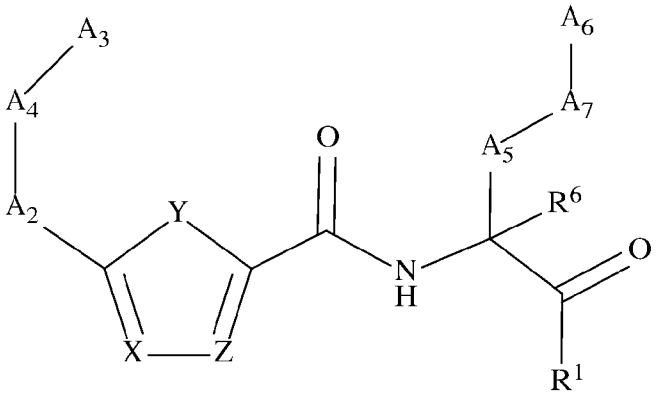
X and Z are each independently selected from the group consisting of $C(R^4)$ and N;

each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy; and

R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy).

11. The compound of claim 10, wherein X and Z are independently selected from the group consisting of CH and N.

12. The compound of any one of claims 1 and 2 having the structure of formula **I-d**:



I-d

or a pharmaceutically acceptable salt thereof, wherein:

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Y is selected from the group consisting of NR^5, O, S, and SO_2;

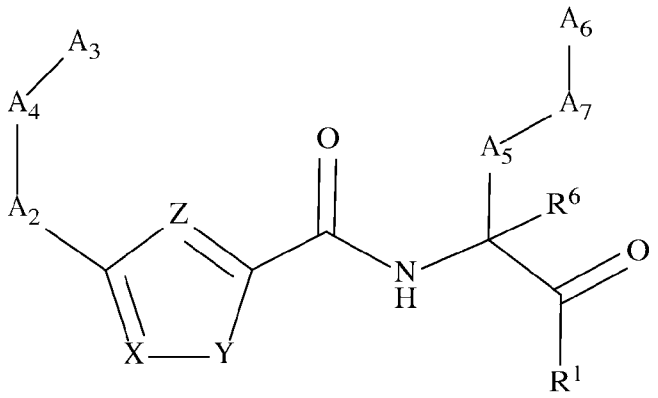
X and Z are each independently selected from the group consisting of $C(R^4)$ and N;

each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy; and

R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy).

13. The compound of claim 12, wherein X and Z are independently selected from the group consisting of CH and N

14. The compound of any one of claims 1 and 2 having the structure of formula **I-e**:



I-e

or a pharmaceutically acceptable salt thereof, wherein:

Y is selected from the group consisting of NR^5, O, S, and SO_2;

X and Z are each independently selected from the group consisting of $C(R^4)$ and N;

each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy; and

R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, and

C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy).

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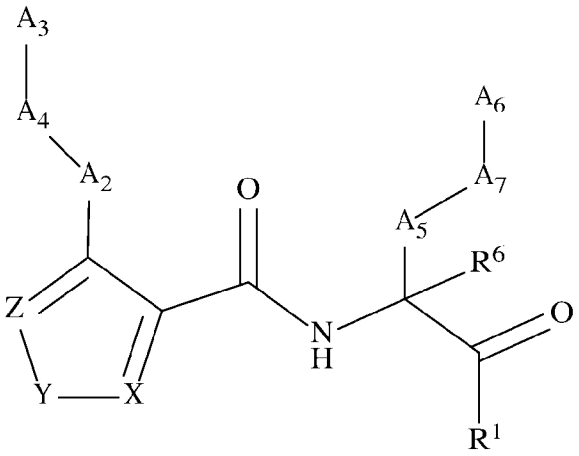
15. The compound of claim 14, wherein X and Z are independently selected from the group consisting of CH and N.

16. The compound of any one of claims 1 and 2 having the structure of formula **I-f**:



I-f

or a pharmaceutically acceptable salt thereof, wherein:

Y is selected from the group consisting of NR^5, O, S, and SO_2;

X and Z are each independently selected from the group consisting of $C(R^4)$ and N;

each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy; and

R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy).

17. The compound of claim 16, wherein Z is N, Y is NR^5, and X is CH.

18. The compound of claim 17, wherein R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_1-C_4 haloalkyl, and cyclopropyl.

19. The compound of claim 16, wherein Z is N, Y is O, and X is $C(R^4)$.

20. The compound of claim 16, wherein Z is N, Y is S, and X is $C(R^4)$.

21. The compound of claim 16, wherein Z is $C(R^4)$, Y is S, and X is $C(R^4)$.

22. The compound of claim 16, wherein Z is $C(R^4)$, Y is O, and X is $C(R^4)$.

23. The compound of claim 16, wherein Z is N, Y is S, and X is N.

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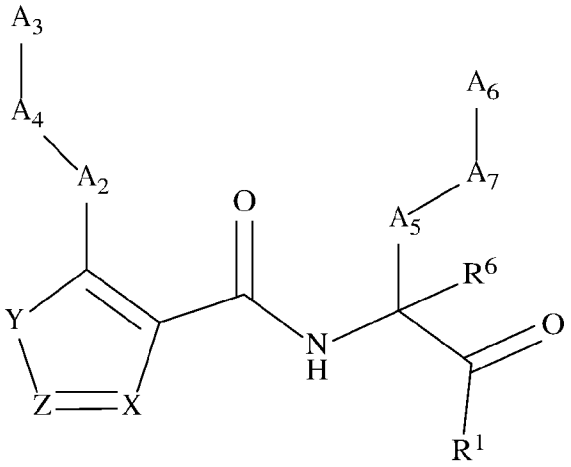
24. The compound of claim 16, wherein Z is N, Y is O, and X is N.

25. The compound of any one of claims 1 and 2 having the structure of formula **I-g**:



I-g

or a pharmaceutically acceptable salt thereof, wherein:

Y is selected from the group consisting of NR^5, O, S, and SO_2;

X and Z are each independently selected from the group consisting of $C(R^4)$ and N;

each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy; and

R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy).

26. The compound of claim 25, wherein X and Z are independently selected from the group consisting of CH and N.

27. The compound of claim 25, wherein Y is NR^5, Z is N, and X is CH.

28. The compound of any one of claims 1 and 2 having the structure of formula **I-h**:

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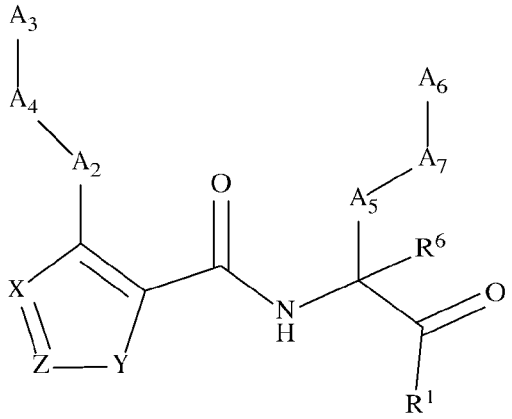

I-h

or a pharmaceutically acceptable salt thereof, wherein:

Y is selected from the group consisting of NR^5, O, S, and SO_2;

X and Z are each independently selected from the group consisting of $C(R^4)$ and N;

each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy; and

R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy).

29. The compound of claim 28, wherein X and Z are independently selected from the group consisting of CH and N.

30. The compound of claim 28, wherein X is CH, Z is N, and Y is NR^5.

31. The compound of claim 28, wherein X is N, Z is $C(R^4)$, and Y is O.

32. The compound of claim 31, wherein R^4 is selected from –H and C_{1-4} alkyl.

33. The compound of claim 28, wherein X is N, Z is $C(R^4)$, and Y is S.

34. The compound of claim 28, wherein X is N, Z is N, and Y is S.

35. The compound of any one of claims 1 and 2 having the structure of formula **I-j**:

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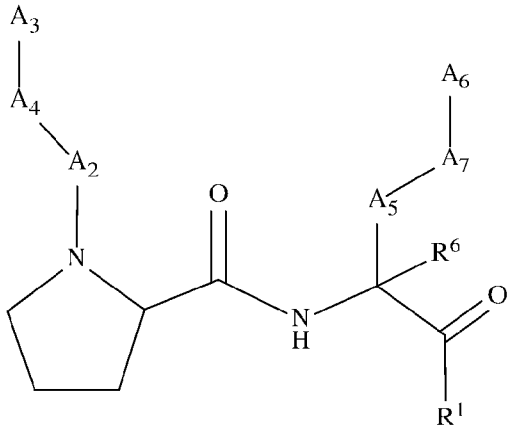
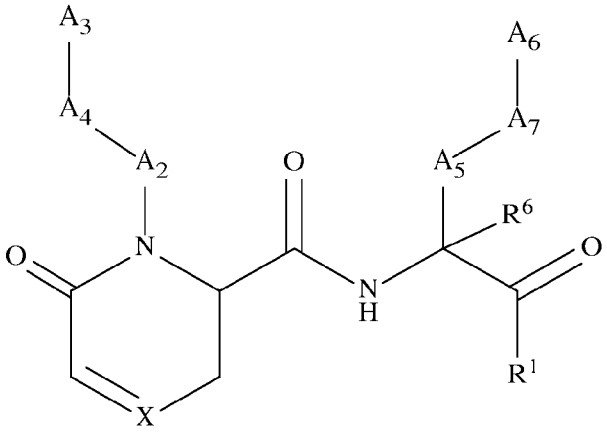


I-j

or a pharmaceutically acceptable salt thereof.

36. A compound having the structure of formula **I-k**:



I-k

or a pharmaceutically acceptable salt thereof, wherein:

A_2 is selected from the group consisting of optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted C_{3-10} carbocyclyl, -S-, -S(=O)-, -SO_2-, -C(=S)-, -CH=CH-, -C≡C-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(S)NH-, -NHC(S)O-, -NHC(S)-, and single bond;

A_4 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, -$(CR_2)_n$-S-$(CR_2)_n$-, -$(CR_2)_n$-S(=O)-$(CR_2)_n$-, -$(CR_2)_n$-SO_2-$(CR_2)_n$-, -$(CR_2)_n$-O-$(CR_2)_n$-, -$(CR_2)_n$-C(=S)-$(CR_2)_n$-, -$(CR_2)_n$-C(=O)-$(CR_2)_n$-, -$(CR_2)_n$-CH=CH-$(CR_2)_n$-, -$(CR_2)_n$-OC(O)NH-$(CR_2)_n$-, -$(CR_2)_n$-NHC(O)NH-$(CR_2)_n$-, -$(CR_2)_n$-

$NHC(O)O-(CR_2)_n-$, $-(CR_2)_n-NHC(S)NH-(CR_2)_n-$, $-(CR_2)_n-NHC(S)O-(CR_2)_n-$, $-(CR_2)_n-NHC(S)-(CR_2)_n-$, and single bond;

when A_2 and A_4 are single bond, A_3 is directly attached to the ring nitrogen;

A_3 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, and optionally substituted C_{3-10} carbocyclyl, or if A_2 is selected from optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted C_{3-10} carbocyclyl, then A_3 is selected from the group consisting of hydrogen, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, $-C \equiv CH$, and optionally substituted 2- to 5-membered polyethylene glycol;

A_5 is selected from the group consisting of optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-8} alkyl, -S-, -S(=O)-, $-SO_2-$, -O-, -C(=S)-, -C(=O)-, -NR-, -CH=CH-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(O)-, -NHC(S)NH-, -NHC(S)O-, -NHC(S)-, and single bond;

A_6 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted –O-C_{1-6} alkyl, optionally substituted –O C_{2-6} alkenyl, $-OSO_2CF_3$, and any natural or non-natural amino acid side chain;

A_7 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-8} alkyl, -S-, S(=O)-, $-SO_2-$, -O-, -C(=S)-, -C(=O)-, -NR-, -CH=CH-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(O)-, -NHC(S)NH-, -NHC(S)O-, -NHC(S)-, and single bond;

when A_5 and A_7 are single bond, A_6 is directly attached to the carbon to which COR^1 is attached;

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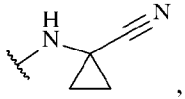
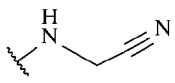
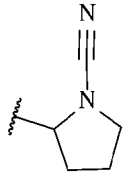
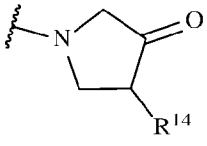
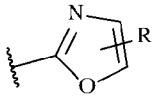
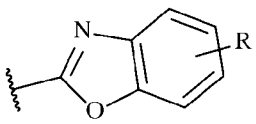
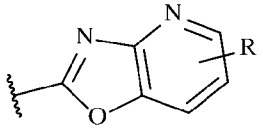
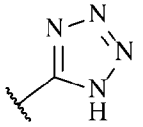
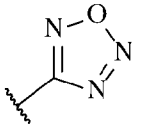
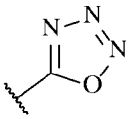
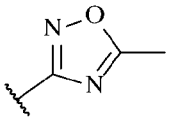
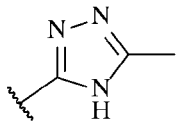
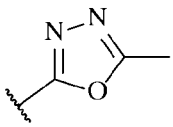
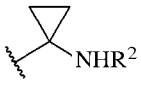
R^1 is selected from the group consisting of H, [[-OH,]]C_{1-4} haloalkyl, -COOH, -CH_2NO_2, -C(=O)NOR, [[-NH_2,]]-$CONR^2R^3$, -$CH(CH_3)=CH_2$, -$CH(CF_3)NR^2R^3$, -C(F)=$CHCH_2CH_3$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ;

R^{14} is halo;

each R, R^2, and R^3 are independently selected from –H, optionally substituted C_{1-4} alkyl, optionally substituted C_{1-8} alkoxyalkyl, optionally substituted 2- to 5-membered polyethylene glycol, optionally substituted C_{3-7} carbocyclyl, optionally substituted 5-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted C_{6-10} aryl(C_1-C_6)alkyl, and optionally substituted 5-10 membered heteroaryl;

R^6 is independently selected from –H and optionally substituted C_{1-4} alkyl; and

each n is independently selected to be an integer from 0 to 3;

X is selected from the group consisting of $C(OR^5)$, $C(R^4)$, and N;

R^4 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy; and

R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy).

37. The compound of claim 36, wherein X is independently selected from the group consisting of CH and N.

38. The compound of any one of claims 1 and 2 having the structure of formula **I-m**:

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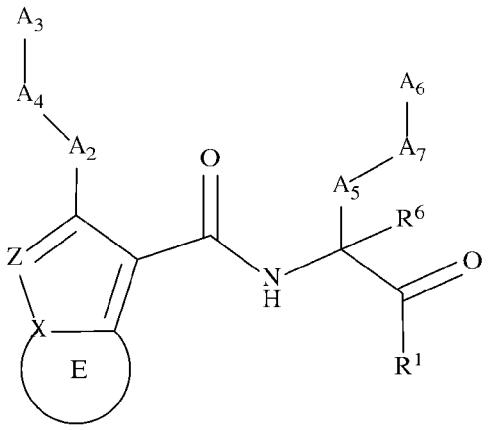


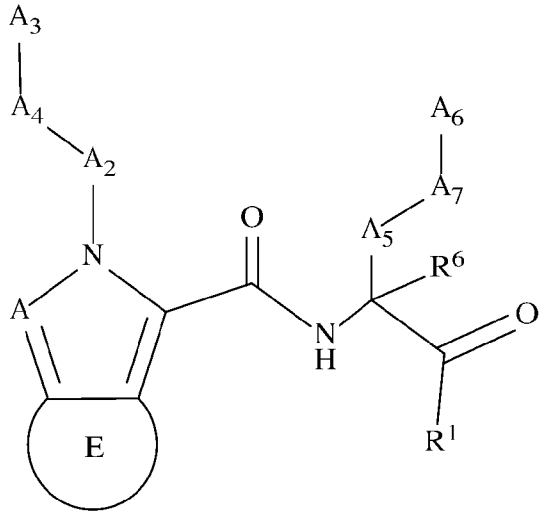
I-m

or a pharmaceutically acceptable salt thereof, wherein X and Z are independently selected from the group consisting of $C(R^4)$ and N;

E is selected from the group consisting of an optionally substituted C_{5-6} carbocyclyl and an optionally substituted 5- to 6-membered heterocyclyl; and

each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy.

39. The compound of any one of claims 1 and 2 having the structure of formula **I-n**:



I-n

or a pharmaceutically acceptable salt thereof, wherein A is selected from the group consisting of $C(R^4)$ and N;

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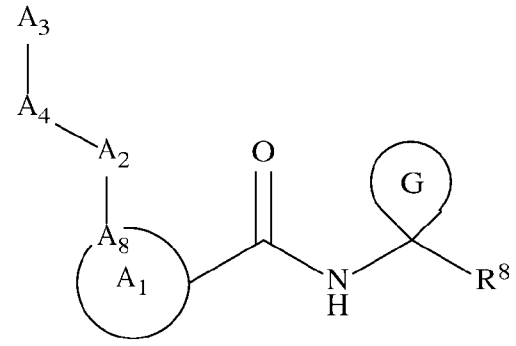
E is selected from the group consisting of an optionally substituted C_{5-6} carbocyclyl, an optionally substituted 5- to 6-membered heterocyclyl, an optionally substituted 5- to 6-membered heteroaryl, and an optionally substituted phenyl; and

each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl, halo, hydroxy, and C_1-C_6 alkoxy.

40. A compound having the structure of formula **III**:



III

or a pharmaceutically acceptable salt thereof, wherein:

A_1 is selected from the group consisting of optionally substituted 5-10 membered heterocyclyl provided the 6-10-membered heterocyclyl is not substituted with oxo; optionally substituted 5-, 8-, or 9- membered heteroaryl; and optionally substituted C_{3-10} carbocyclyl;

A_2 is selected from the group consisting of optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted C_{3-10} carbocyclyl, -S-, -S(=O)-, -SO_2-, -C(=S)-, -CH=CH-, -C≡C-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(S)NH-, -NHC(S)O-, -NHC(S)-, and single bond;

A_4 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, -$(CR_2)_n$-S-$(CR_2)_n$-, -$(CR_2)_n$-S(=O)-$(CR_2)_n$-, -$(CR_2)_n$-SO_2-$(CR_2)_n$-, -$(CR_2)_n$-O-$(CR_2)_n$-, -$(CR_2)_n$-C(=S)-$(CR_2)_n$-, -$(CR_2)_n$-C(=O)-$(CR_2)_n$-, -$(CR_2)_n$-CH=CH-$(CR_2)_n$-, -$(CR_2)_n$-OC(O)NH-$(CR_2)_n$-, -$(CR_2)_n$-NHC(O)NH-$(CR_2)_n$-, -$(CR_2)_n$-NHC(O)O-$(CR_2)_n$-, -$(CR_2)_n$-NHC(S)NH-$(CR_2)_n$-, -$(CR_2)_n$-NHC(S)O-$(CR_2)_n$-, -$(CR_2)_n$-NHC(S)-$(CR_2)_n$-, and single bond;

when A_2 and A_4 are single bond, A_3 is directly attached to A_8;

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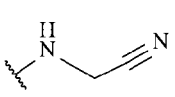
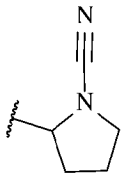
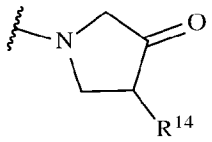
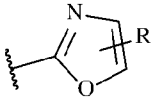
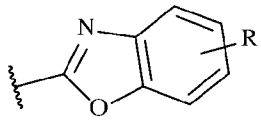
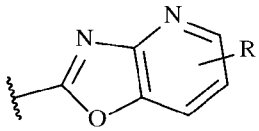
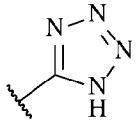
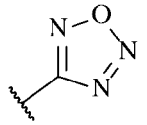
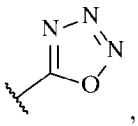
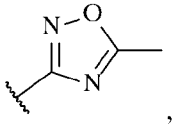
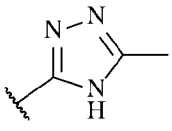
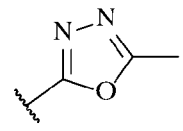
A_3 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, and optionally substituted C_{3-10} carbocyclyl, or if A_2 is selected from optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted C_{3-10} carbocyclyl, then A_3 is selected from the group consisting of hydrogen, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, -C≡CH, and optionally substituted 2- to 5-membered polyethylene glycol;

G is an optionally substituted C_3 to C_7 carbocyclyl or an optionally substituted 4- to 7-membered heterocyclyl;

A_8 is a ring member of A_1 and is selected from the group consisting of C and N;

R^8 is selected from the group consisting of $-COR^1$, $-CH=CHSO_2R$, $-CH_2NO_2$;

R^1 is selected from the group consisting of H, [[-OH,]]C_{1-4} haloalkyl, -COOH, $-CH_2NO_2$, -C(=O)NOR, [[$-NH_2$,]]$-CONR^2R^3$, $-CH(CH_3)=CH_2$, $-CH(CF_3)NR^2R^3$, $-C(F)=CHCH_2CH_3$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ;

R^{14} is halo; and

each R, R^2, and R^3 are independently selected from –H, optionally substituted C_{1-4} alkyl, optionally substituted C_{1-8} alkoxyalkyl, optionally substituted 2- to 5-membered polyethylene glycol, optionally substituted C_{3-7} carbocyclyl, optionally substituted 5-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted C_{6-10} aryl(C_1-C_6)alkyl, and optionally substituted 5-10 membered heteroaryl;

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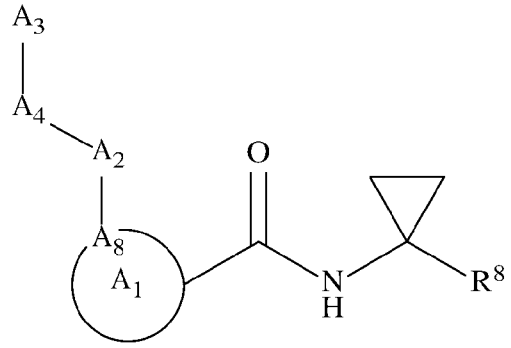
R^6 is independently selected from –H and optionally substituted C_{1-4} alkyl; and each n is independently selected to be an integer from 0 to 3.

41. The compound of claim 40, having the structure of formula (**III-a**):



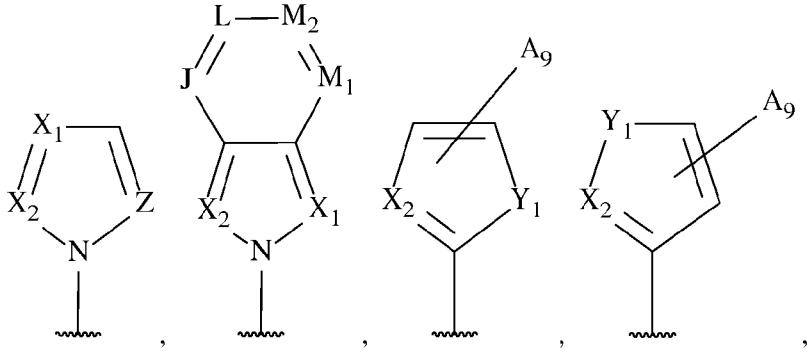
III-a

or a pharmaceutically acceptable salt thereof.

42. The compound of any one of claims 1-41, wherein at least one of the optionally substituted moieties of A_2, A_4, and A_3 is substituted with ^{18}F

43. The compound of any one of claims 1-42, wherein at least one of the optionally substituted moieties of A_2, A_4, and A_3 is substituted with C_1-C_6 alkyl containing one or more ^{11}C.

44. The compound of any one of claims claim 1-43, wherein A_3 is selected from the group consisting of



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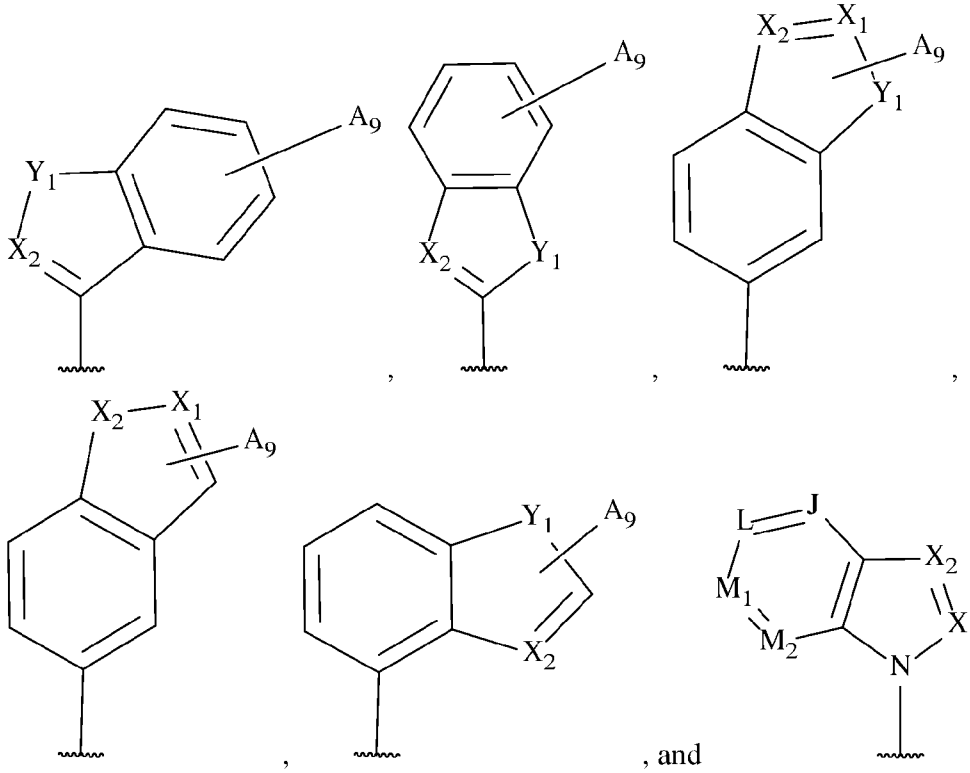

A_9 is selected from the group consisting of H, C_{6-10} aryl, 5-10 membered heteroaryl, 3-10 membered heterocyclyl, and C_{3-10} carbocyclyl, C_{1-4} alkyl;

X_2, X_1, and Z are each independently selected from the group consisting of $C(R^4)$ and N;

Y_1 is selected from the group consisting of NR^5, O, and S;

J, L, M_1 and M_2 are each independently selected from the group consisting of $C(R^4)$ and N;

R^4 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy;

R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy).

45. The compound of any one of the claims 1-43, wherein A_3 is optionally substituted C_{6-10} aryl.

46. The compound of claim 45, wherein A_3 is phenyl.

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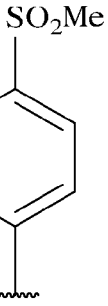
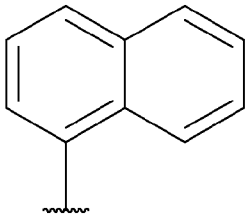
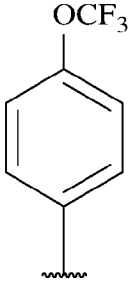
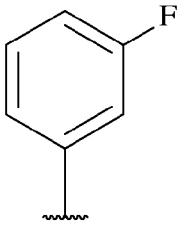
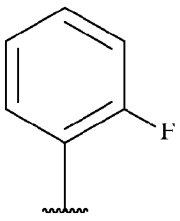
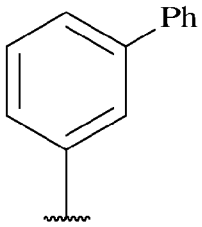
47. The compound of claim 45, wherein A_3 is selected from the group consisting of 

,  , 

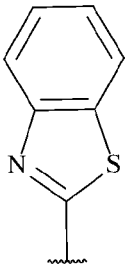
, 

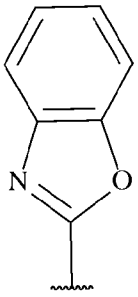
, 

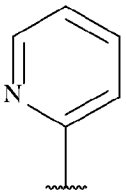
, and 

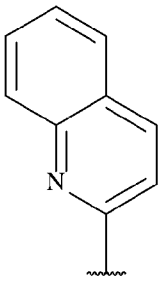
.

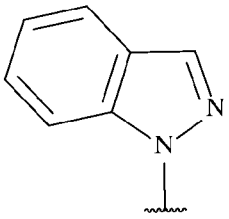
48. The compound of any one of the claims 1-43, wherein A_3 is optionally substituted 5-10 membered heteroaryl.

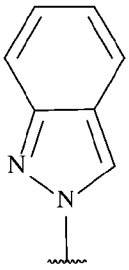
49. The compound of claim 48, wherein A_3 is selected from the group consisting of 

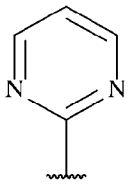
, 

, 

, 

, 

, 

, and 

.

50. The compound of any one of claims 1-49 wherein A_2 is single bond.

51. The compound of any one of the claims 1-49, wherein A_2 is –CH=CH-.

52. The compound of any one of the claims 1-49, wherein A_2 is –S-.

53. The compound of any one of claims 1-49, wherein A_2 is phenyl.

54. The compound of any one of claims 1-49, wherein A_2 is selected from the group consisting of optionally substituted 3-10 membered heterocyclyl, optionally substituted

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C_{6-10} aryl, optionally substituted 5- or 7-10 membered heteroaryl, optionally substituted C_{3-10} carbocyclyl, -S-, -S(=O)-, -SO_2-, -C(=S)-, -CH=CH-, -C≡C-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(S)NH-, -NHC(S)O-, and -NHC(S)-.

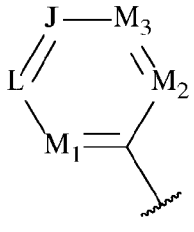
55. The compound of any one of claims 1-49, wherein A_2 is selected from the group consisting of optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted C_{3-10} carbocyclyl, and -C=C-.

56. The compound of any one of claims 1-49, wherein A_2 is selected from the group consisting of optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted C_{3-10} carbocyclyl.

57. The compound of any one of claims 1-56, wherein A_4 is single bond.

58. The compound of any one of claims 1-43, wherein A_2 is a single bond, A_4 is a single bond, and A_3 is an optionally substituted C_{6-10} aryl or an optionally substituted 5-10 membered heteroaryl.

59. The compound of claim 58, wherein A_3 has the structure:



, wherein

J, L, M_1, M_2, and M_3 are each independently selected from the group consisting of $C(R^4)$ and N; and

each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy.

60. The compound of claim 59, wherein each of J, L, M_1, M_2, and M_3 are $C(R^4)$.

61. The compound of claim 60, wherein each R^4 is independently selected from –H and halo.

62. The compound of claim 59, wherein M_1 is $C(R^4)$; R^4 is halo and each of J, L, M_2, and M_3 are CH.

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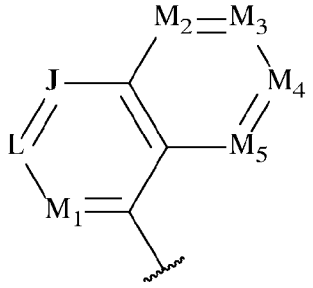
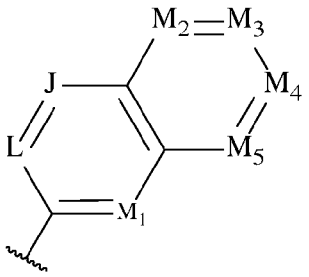
63. The compound of claim 59, wherein L is $C(R^4)$; R^4 is halo and each of J, M_1, M_2, and M_3 are CH.

64. The compound of claim 58, wherein A_3 has a structure selected from the group consisting of:



and

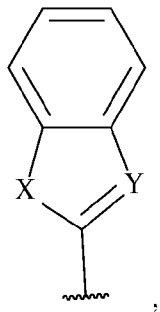


, wherein

J, L, M_1, M_2, M_3, M_4, and M_5 are each independently selected from the group consisting of $C(R^4)$ and N; and

each R^4 is independently selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy.

65. The compound of claim 58, wherein A_3 has the structure:



, wherein

X is selected from the group consisting of $C(R^4)$ and N;

Y is selected from O and S; and

R^4 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy.

66. A compound having the structure of formula **I-o**:

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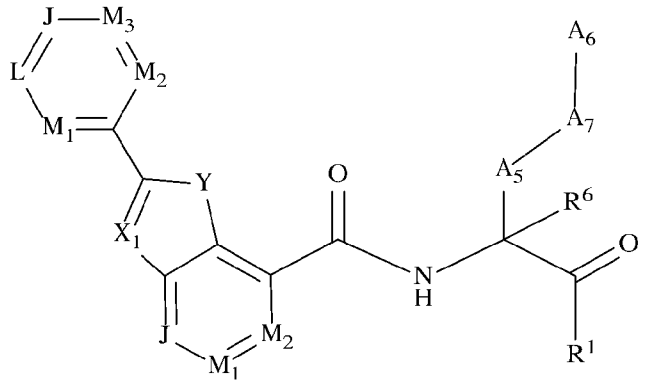

I-o

or a pharmaceutically acceptable salt thereof, wherein:

Y is selected from the group consisting of NR^5, O, S, and SO_2;

X_1 is selected from the group consisting of $C(R^4)$ and N;

J, L, M_1, M_2, and M_3 are each independently selected from the group consisting of $C(R^4)$ and N;

A_5 is selected from the group consisting of optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-8} alkyl, -S-, -S(=O)-, $-SO_2-$, -O-, -C(=S)-, -C(=O)-, -NR-, -CH=CH-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(O)-, -NHC(S)NH-, -NHC(S)O-, -NHC(S)-, and single bond;

A_6 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted –O-C_{1-6} alkyl, optionally substituted –O C_{2-6} alkenyl, $-OSO_2CF_3$, and any natural or non-natural amino acid side chain;

A_7 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-8} alkyl, -S-, S(=O)-, $-SO_2-$, -O-, -C(=S)-, -C(=O)-, -NR-, -CH=CH-, -OC(O)NH-, -NHC(O)NH-, -NHC(O)O-, -NHC(O)-, -NHC(S)NH-, -NHC(S)O-, -NHC(S)-, and single bond;

when A_5 and A_7 are single bond, A_6 is directly attached to the carbon to which R^6 is attached;

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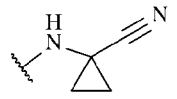
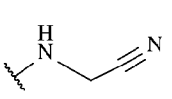
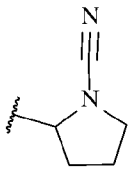
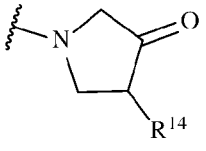
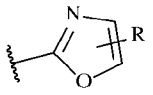
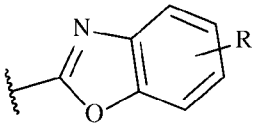
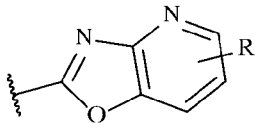
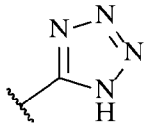
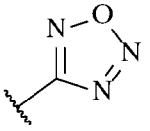
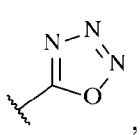
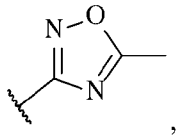
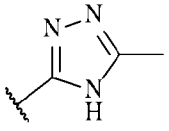
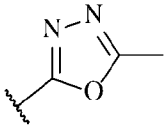
R^4 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, hydroxy, and C_1-C_6 alkoxy;

R^5 is selected from the group consisting of –H, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy);

R^1 is selected from the group consisting of H, [[-OH,]]C_{1-4} haloalkyl, -COOH, -CH_2NO_2, -C(=O)NOR, [[-NH_2,]]-$CONR^2R^3$, -$CH(CH_3)$=CH_2, -$CH(CF_3)NR^2R^3$,

-C(F)=$CHCH_2CH_3$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ;

R^{14} is halo;

each R, R^2, and R^3 are independently selected from –H, optionally substituted C_{1-4} alkyl, optionally substituted C_{1-8} alkoxyalkyl, optionally substituted 2- to 5-membered polyethylene glycol, optionally substituted C_{3-7} carbocyclyl, optionally substituted 5-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted C_{6-10} aryl(C_1-C_6)alkyl, and optionally substituted 5-10 membered heteroaryl;

R^6 is independently selected from –H and optionally substituted C_{1-4} alkyl; and each n is independently selected to be an integer from 0 to 3.

67. The compound of claim 66, wherein J, L, M_1, M_2, and M_3 are independently selected from the group consisting of CH and N.

68. The compound of any one of claims 1-39 and 42-67, wherein at least one of the optionally substituted moieties of A_5, A_7, and A_6 is substituted with ^{18}F.

69. The compound of any one of claims 1-39 and 42-67, wherein at least one of the optionally substituted moieties of A_5, A_7, and A_6 is substituted with C_1-C_6 alkyl containing one or more ^{11}C.

70. The compound of any one of the claims 1-39 and 42-67, wherein A_6 is phenyl.

71. The compound of anyone of claims 1-39 and 42-67, wherein A_6 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{1-8} alkyl, optionally substituted –O-C_{1-6} alkyl, and optionally substituted –O C_{2-6} alkenyl.

72. The compound of any one of the claims 1-39 and 42-67, wherein A_7 is –CH_2-.

73. The compound of any one of the claims 1-39 and 42-67, wherein A_7 is O.

74. The compound of any one of the claims 1-39 and 42-67, wherein A_7 is –CH=CH-.

75. The compound of any one of the claims 1-39 and 42-67, wherein A_7 is S.

76. The compound of any one of the claims 1-39 and 42-67, wherein A_7 is single bond.

77. The compound of any one of the claims 1-39 and 42-67, wherein A_7 is optionally substituted C_{6-10} aryl.

78. The compound of claim 77, wherein A_7 is phenyl.

79. The compound of any one of claims 1-78, wherein A_5 is -CH_2-.

80. The compound of any one of claims 1-39 and 42-67, wherein A_5 is -CH_2- or -CH_2CH_2-; A_7 is a single bond; and A_6 is selected from the group consisting of C_1-C_4 alkyl, optionally substituted phenyl, optionally substituted 5-10 membered heteroaryl.

81. The compound of claim 80, wherein A_6 is optionally substituted phenyl.

82. The compound of claim 80, wherein A_6 is unsubstituted phenyl.

83. The compound of claim 80, wherein A_6 is phenyl optionally substituted with one or more C_1-$_4$ alkyl, C_{3-7} carbocyclyl, halo, hydroxy, and C_1-C_6 alkoxy.

84. The compound of claim 80, wherein A_6 has the structure:

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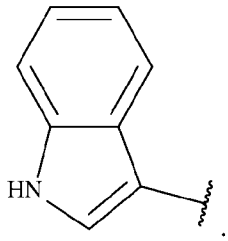


85. The compound of any one of claims 1-39 and 42-67, wherein A_5 is a single bond, A_7 is a single bond; and A_6 is C_1-C_5 alkyl.

86. The compound of claim 85, wherein A_6 is selected from the group consisting of ethyl, n-propyl, isopropyl, isobutyl, 2,2-dimethylpropyl, and 1,2-dimethylpropyl.

87. The compound of any one of the claims 1-86, wherein R^1 is $CONR^2R^3$.

88. The compound of claim 87, wherein R^2 is –H and R^3 is optionally substituted C_{1-4} alkyl.

89. The compound of claim 87, wherein R^2 is –H and R^3 is selected from the group consisting of –H, C_1-C_4 alkyl optionally substituted with C-amido, and C_3-C_6 cycloalkyl.

90. The compound of claim 89, wherein R^3 is selected from ethyl or cyclopropyl.

91. The compound of claim 89, wherein R^3 is methyl substituted with C-amido.

92. The compound of claim 89, wherein R^3 is –H.

93. The compound of claim 87, wherein R^3 is optionally substituted C_{1-4} alkyl.

94. The compound of claim 87, wherein R^3 is benzyl.

95. The compound of any one of claims 1-39 and 42-94, wherein R^6 is –H and optionally substituted C_{1-4} alkyl.

96. The compound of claim 95, wherein R^6 is optionally substituted C_{1-4} alkyl.

97. The compound of claim 96, wherein R^6 is methyl.

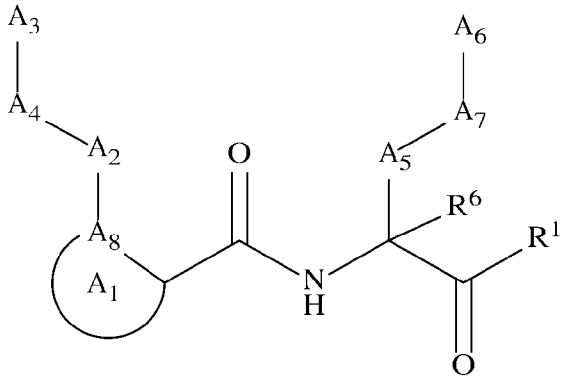
98. The compound of any one of claims 1-2, wherein A_1 is selected from the group consisting of optionally substituted 6-10 membered heterocyclyl; 5-membered heterocyclyl optionally substituted with one or more C_{1-4} alkyl, C_{3-7} carbocyclyl, halo, hydroxy, or C_1-C_6 alkoxy; optionally substituted 5-, or 8- membered heteroaryl; and optionally substituted C_{3-10} carbocyclyl.

99. The compound of any one of claims 1-2, wherein A_1 is selected from the group consisting of 5-membered heterocyclyl optionally substituted with one or more C_{1-4}

alkyl, C_{3-7} carbocyclyl, halo, hydroxy, or C_1-C_6 alkoxy and optionally substituted 5-membered heteroaryl.

100. The compound of any one of claims 1-2, wherein A_1 is optionally substituted 5-membered heteroaryl.

101. The compound of any one of claims 1-2, having the structure of formula **I-p**:



I-p

or a pharmaceutically acceptable salt thereof.

102. A compound having the structure selected from the group consisting of: compounds 1 to 90, compound 93, compound 94, compounds 96 to 195, compounds 197 to 235, compounds 238 to 273, compounds 276 to 281, compounds 283 to 299, compounds 303 to 306, compound 308, compound 309, compounds 313 to 363, compound 365, compounds 367 to 410, compounds 413 to 424, compounds 428 to 445, compound 447, compound 448, compounds 454 to 532, compound 540, compounds 546 to 588, compounds 591 to 605, compounds 607 to 611, compounds 613 to 630, and pharmaceutically acceptable salts thereof.

103. A compound having the structure selected from the group consisting of: compounds 91, 92, 196, 274, 282, 307, 310 to 312, 364, 366, 411, 541, and pharmaceutically acceptable salts thereof.

104. A compound having the structure of the formula II:

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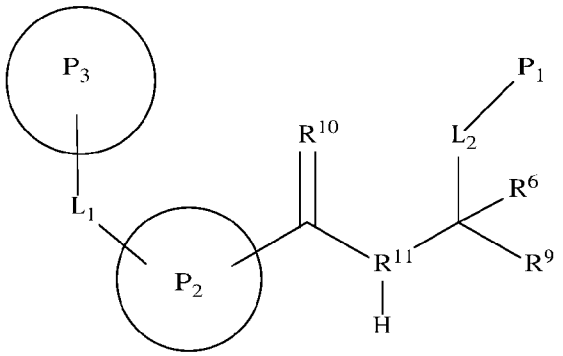

II

or a pharmaceutically acceptable salt thereof, wherein:

P_2 is an optionally substituted cyclic moiety having a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 9 P2 pocket moiety selected from the group consisting of Gly190, Phe233, Gly253, His254, and Ala255;

L_1 is a bond or a moiety consisting of from 1 to 25 atoms selected from the group consisting of carbon, oxygen, nitrogen, hydrogen, and sulfur;

P_3 is an optionally substituted cyclic moiety positioned by L_1 and having a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_3 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 9 P3 pocket moiety selected from the group consisting of Gly189, Gly190, Ser191, Thr236, and Gly253;

R^{10} is oxo and is positioned by P_2 such that, upon binding of the compound to calpain 9, R^{10} forms a polar interaction with, and is within 4 Å or less of, calpain 9 Gly190 amide;

R^{11} is nitrogen and is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 9, R^{11} forms a polar interaction with, and is within 4 Å or less of, calpain 9 Gly253 carbonyl;

L_2 is a bond or a moiety consisting of from 1 to 25 atoms selected from the group consisting of carbon, oxygen, nitrogen, hydrogen, and sulfur;

P_1 is a moiety positioned by L_2 and having a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_1 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 9 P1 pocket moiety selected from the group consisting of Gly95, Lys188, Gly189, and Ser242;

R^9 is a moiety positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 9, at least one atom of R^9 forms a polar interaction with, and is within 4 Å or less of, at least one calpain 9 moiety selected from the group consisting of Gln91, Cys97, and His254; and

R^6 is selected from –H and optionally substituted C_{1-4} alkyl.

105. The compound of claim 104, wherein:

R^9 is $–(C=R^{12})(C=R^{13})NR^2R^3$;

R^{12} is oxo and is positioned such that, upon binding of the compound to calpain 9, R^{12} forms a polar interaction with, and is within 4 Å or less of, calpain 9 His254 imidazole;

R^{13} is oxo and is positioned such that, upon binding of the compound to calpain 9, R^{13} forms a polar interaction with, and is within 4 Å or less of, at least one calpain 9 moiety selected from the group consisting of Gln91 side chain carboxamide and Cys97 backbone amide; and

R^2 and R^3 are independently selected from –H, optionally substituted C_{1-4} alkyl, optionally substituted C_{3-7} carbocyclyl, optionally substituted 5-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted C_{6-10}aryl(C_1-C_6)alkyl, and optionally substituted 5-10 membered heteroaryl.

106. The compound of claim 105, wherein R^{12} is positioned such that, upon binding of the compound to calpain 9, R^{12} is within 2.6 to 3.2 Å or less of, calpain 9 His254 imidazole.

107. The compound of claim 106, wherein R^{12} is positioned such that, upon binding of the compound to calpain 9, R^{12} is within 2.6 to 3.0 Å or less of, calpain 9 His254 imidazole.

108. The compound of any one of claims 105 to 107, wherein R^{13} is positioned such that, upon binding of the compound to calpain 9, R^{13} is within 2.6 to 3.5 Å to the calpain 9 moieties including both Gln91 side chain carboxamide and Cys97 backbone amide.

109. The compound of claim 108, wherein R^{13} is positioned such that, upon binding of the compound to calpain 9, R^{13} is within 2.6 to 3.2 Å to the calpain 9 moieties including both Gln91 side chain carboxamide and Cys97 backbone amide.

110. The compound of claim 104, wherein R^9 is positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 9, at least one atom of R^9 forms a polar interaction with, and is within 3.6 Å or less of, at least one calpain 9 moiety selected from the group consisting of Gln91, Cys97, and His254.

111. The compound of claim 110 wherein R^9 is positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 9, at least one atom of R^9 is within 2.6 to 3.6 Å to the calpain 9 moieties including both Gln91 side chain carboxamide and Cys97 backbone amide.

112. The compound of claim 111, wherein R^9 is positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 9, at least one atom of R^9 is within 2.9 to 3.2 Å to the calpain 9 moieties including both Gln91 side chain carboxamide and Cys97 backbone amide.

113. The compound of claim 104, wherein a carbon atom in R^9 at its point of attachment forms a covalent bond with Cys97

114. The compound of claim 76, wherein the covalent bond length is between 1.7 and 1.9 Å.

115. The compound of any one of claims 104 to 114, wherein P_2 is an optionally substituted 5-membered heteroaryl.

116. The compound of any one of claims 104 to 115, wherein R^{11} is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 9, R^{11} forms a polar interaction with, and is within 3.6 Å or less of, calpain 9 Gly253 carbonyl.

117. The compound of any one of claims 104 to 116, wherein:

P_2 has a size and configuration such that, upon binding of the compound to calpain 1, at least one atom of P_2 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 1 P2 pocket moiety selected from the group consisting of Gly208, Ser251, Gly271, His272, and Ala273;

P_3 is positioned by L_1 and has a size and configuration such that, upon binding of the compound to calpain 1, at least one atom of P_3 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 1 P3 pocket moiety selected from the group consisting of Gly207, Gly208, Ser209, Ile254, and Gly271;

R^{10} is positioned by P_2 such that, upon binding of the compound to calpain 1, R^{10} forms a polar interaction with, and is within 4 Å or less of, calpain 1 Gly208 amide;

R^{11} is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 1, R^{11} forms a polar interaction with, and is within 4 Å or less of, calpain 1 Gly271 carbonyl;

P_1 is positioned by L_2 and has a size and configuration such that, upon binding of the compound to calpain 1, at least one atom of P_1 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 1 P1 pocket moiety selected from the group consisting of Gly113, Ser206, Gly207, and Met260; and

R^9 is positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 1, at least one atom of R^9 forms a polar interaction with, and is within 4 Å or less of, at least one calpain 1 moiety selected from the group consisting of Gln109, Cys115, and His272.

118. The compound of any one of claims 104 to 117, wherein:

P_2 has a size and configuration such that, upon binding of the compound to calpain 2, at least one atom of P_2 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 2 P2 pocket moiety selected from the group consisting of Gly198, Ser241, Gly261, His262, and Ala263;

P_3 is positioned by L_1 and has a size and configuration such that, upon binding of the compound to calpain 2, at least one atom of P_3 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 2 P3 pocket moiety selected from the group consisting of Gly197, Gly198, Ala199, Ile244, and Gly261;

R^{10} is positioned by P_2 such that, upon binding of the compound to calpain 2, R^{10} forms a polar interaction with, and is within 4 Å or less of, calpain 2 Gly198 amide;

R^{11} is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 2, R^{11} forms a polar interaction with, and is within 4 Å or less of, calpain 2 Gly261 carbonyl;

P_1 is positioned by L_2 and has a size and configuration such that, upon binding of the compound to calpain 2, at least one atom of P_1 forms a non-polar interaction with, and is

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within 5 Å or less of, at least one calpain 2 P1 pocket moiety selected from the group consisting of Gly103, Ser196, Gly197, and Ser250; and

R^9 is positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 2, at least one atom of R^9 forms a polar interaction with, and is within 4 Å or less of, at least one calpain 2 moiety selected from the group consisting of Gln99, Cys105, and His262.

119. The compound of any one of claims 65 to 118, wherein P_2 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 is within 2.6 to 3.6 Å of Gly190 carbonyl oxygen.

120. The compound of claim 119, wherein P_2 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 is within 2.9 to 3.3 Å of Gly190 carbonyl oxygen.

121. The compound of any one of claims 65 to 120, wherein P_2 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 is within 2.8 to 4.8 Å of a carbon atom in Phe233.

122. The compound of claim 121, wherein P_2 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 is within 2.9 to 3.3 Å of a carbon atom in Phe233.

123. The compound of any one of claims 65 to 122, wherein P_2 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 is within 2.6 to 3.7 Å of Gly253 carbonyl oxygen.

124. The compound of claim 123, wherein P_2 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 is within 2.9 to 3.3 Å of Gly253 carbonyl oxygen.

125. The compound of any one of claims 65 to 124, wherein P_2 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 is within 2.9 to 4.8 Å of Ala255 nitrogen.

126. The compound of claim 125, wherein P_2 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_2 is within 3.2 to 4.0 Å of Ala255 nitrogen.

127. The compound of any one of claims 65to 126, wherein P_3 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_3 is within 3.1 to 4.3 Å of Gly189 C-alpha.

128. The compound of claim 127, wherein P_3 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_3 is within 3.2 to 4.0 Å of Gly189 C-alpha.

129. The compound of any one of claims 65to 128, wherein P_3 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_3 is within 3.0 to 4.3 Å of Gly190 carbonyl oxygen.

130. The compound of claim 129, wherein P_3 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_3 is within 3.2 to 4.0 Å of Gly190 carbonyl oxygen.

131. The compound of any one of claims 65 to 130, wherein P_3 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_3 is within 3.2 to 4.8 Å of Ser191 nitrogen.

132. The compound of claim 131, wherein P_3 has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_3 is within 3.2 to 4.0 Å of Ser191 nitrogen.

133. The compound of any one of claims 1 to 132, wherein R^{10} is positioned by P_2 such that, upon binding of the compound to calpain 9, R^{10} is within 2.6 to 3.5 Å of, calpain 9 Gly190 amide.

134. The compound of claim 133, wherein R^{10} is positioned by P_2 such that, upon binding of the compound to calpain 9, R^{10} is within 2.9 to 3.3 Å of, calpain 9 Gly190 amide.

135. The compound of any one of claims 65 to 134, wherein R^{11} is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 9, R^{11} is within 2.6 to 3.6 Å or less of, calpain 9 Gly253 carbonyl.

136. The compound of claim 135, wherein R^{11} is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 9, R^{11} is within 2.9 to 3.3 Å or less of, calpain 9 Gly253 carbonyl.

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137. The compound of any one of claims 65 to 136, wherein P_1 is positioned by L_2 and has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_1 is within 3.2 to 4.4 Å Gly95 carbonyl oxygen.

138. The compound of claim 137, wherein P_1 is positioned by L_2 and has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_1 is within 3.2 to 4.0 Å Gly95 carbonyl oxygen.

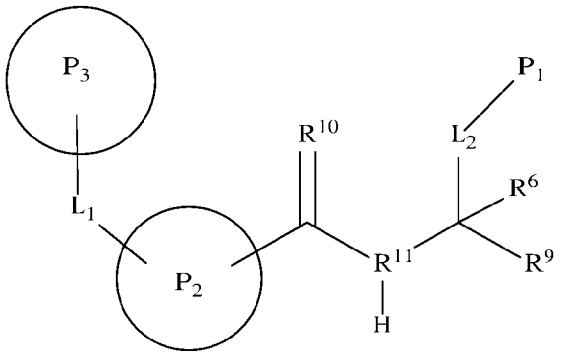
139. The compound of any one of claims 65 to 138, wherein P_1 is positioned by L_2 and has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_1 is within 3.2 to 4.7 Å of Lys188 carbonyl carbon.

140. The compound of claim 139, wherein P_1 is positioned by L_2 and has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_1 is within 2.6 to 4.0 Å of Lys188 carbonyl carbon.

141. The compound of any one of claims 65 to 140, wherein P_1 is positioned by L_2 and has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_1 is within 3.0 to 4.1 Å of Gly189 C-alpha.

142. The compound of claim 141, wherein P_1 is positioned by L_2 and has a size and configuration such that, upon binding of the compound to calpain 9, at least one atom of P_1 is within 3.2 to 4.0 Å of Gly189 C-alpha.

143. A compound having the structure of the formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:

P_2 is an optionally substituted cyclic moiety having a size and configuration such that, upon binding of the compound to calpain 1, at least one atom of P_2 forms a non-polar

interaction with, and is within 5 Å or less of, at least one calpain 1 P2 pocket moiety selected from the group consisting of Gly208, Ser251, Gly271, His272, and Ala273;

L_1 is a bond or a moiety consisting of from 1 to 25 atoms selected from the group consisting of carbon, oxygen, nitrogen, hydrogen, and sulfur;

P_3 is an optionally substituted cyclic moiety positioned by L_1 and having a size and configuration such that, upon binding of the compound to calpain 1, at least one atom of P_3 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 1 P3 pocket moiety selected from the group consisting of Gly207, Gly208, Ser209, Ile254, and Gly271;

R^{10} is oxo and is positioned by P_2 such that, upon binding of the compound to calpain 1, R^{10} forms a polar interaction with, and is within 4 Å or less of, calpain 1 Gly208 amide;

R^{11} is nitrogen and is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 1, R^{11} forms a polar interaction with, and is within 4 Å or less of, calpain 1 Gly271 carbonyl;

L_2 is a bond or a moiety consisting of from 1 to 25 atoms selected from the group consisting of carbon, oxygen, nitrogen, hydrogen, and sulfur;

P_1 is a moiety positioned by L_2 and having a size and configuration such that, upon binding of the compound to calpain 1, at least one atom of P_1 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 1 P1 pocket moiety selected from the group consisting of Gly113, Ser206, Gly207, and Met260;

R^9 is a moiety positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 1, at least one atom of R^9 forms a polar interaction with, and is within 4 Å or less of, at least one calpain 1 moiety selected from the group consisting of Gln109, Cys115, and His272; and

R^6 is selected from –H and optionally substituted C_{1-4} alkyl.

144. The compound of claim 143, wherein:

R^9 is $-(C{=}R^{12})(C{=}R^{13})NR^2R^3$;

R^{12} is oxo and is positioned such that, upon binding of the compound to calpain 1, R^{12} forms a polar interaction with, and is within 4 Å or less of, calpain 1 His272 imidazole;

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R^{13} is oxo and is positioned such that, upon binding of the compound to calpain 1, R^{13} forms a polar interaction with, and is within 4 Å or less of, at least one calpain 1 moiety selected from the group consisting of Gln109 side chain carboxamide and Cys115 backbone amide; and

R^2 and R^3 are independently selected from –H, optionally substituted C_{1-4} alkyl, optionally substituted C_{3-7} carbocyclyl, optionally substituted 5-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted C_{6-10}aryl(C_1-C_6)alkyl, and optionally substituted 5-10 membered heteroaryl.

145. The compound of claim 143, wherein R^9 is positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 1, at least one atom of R^9 forms a polar interaction with, and is within 3.5 Å or less of, at least one calpain 1 moiety selected from the group consisting of Gln109, Cys115, and His272.

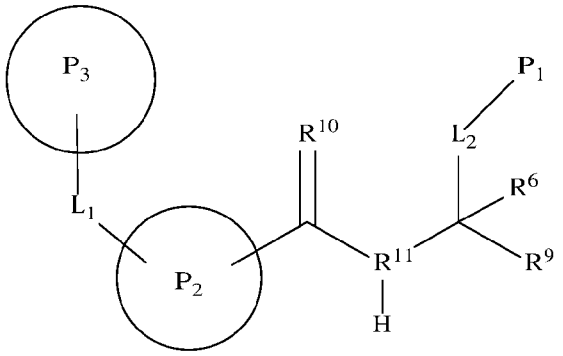
146. The compound of claim 145, wherein a carbon atom in R^9 at its point of attachment forms a covalent bond with Cys115.

147. The compound of claim 146, wherein the covalent bond length is between 1.7 and 1.9 Å.

148. The compound of claim 143 or 147, wherein P_2 is an optionally substituted 5-membered heteroaryl.

149. The compound of any one of claims 143 to 148, wherein R^{11} is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 1, R^{11} forms a polar interaction with, and is within 3.5 Å or less of, calpain 1 Gly271 carbonyl.

150. A compound having the structure of the formula II:



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or a pharmaceutically acceptable salt thereof, wherein:

P_2 is an optionally substituted cyclic moiety having a size and configuration such that, upon binding of the compound to calpain 2, at least one atom of P_2 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 2 P2 pocket moiety selected from the group consisting of Gly198, Ser241, Gly261, His262, and Ala263;

L_1 is a bond or a moiety consisting of from 1 to 25 atoms selected from the group consisting of carbon, oxygen, nitrogen, hydrogen, and sulfur;

P_3 is an optionally substituted cyclic moiety positioned by L_1 and having a size and configuration such that, upon binding of the compound to calpain 2, at least one atom of P_3 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 2 P3 pocket moiety selected from the group consisting of Gly197, Gly198, Ala199, Ile244, and Gly261;

R^{10} is oxo and is positioned by P_2 such that, upon binding of the compound to calpain 2, R^{10} forms a polar interaction with, and is within 4 Å or less of, calpain 2 Gly198 amide;

R^{11} is nitrogen and is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 2, R^{11} forms a polar interaction with, and is within 4 Å or less of, calpain 2 Gly261 carbonyl;

L_2 is a bond or a moiety consisting of from 1 to 25 atoms selected from the group consisting of carbon, oxygen, nitrogen, hydrogen, and sulfur;

P_1 is a moiety positioned by L_2 and having a size and configuration such that, upon binding of the compound to calpain 2, at least one atom of P_1 forms a non-polar interaction with, and is within 5 Å or less of, at least one calpain 2 P1 pocket moiety selected from the group consisting of Gly103, Ser196, Gly197, and Ser250;

R^9 is a moiety positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 2, at least one atom of R^9 forms a polar interaction with, and is within 4 Å or less of, at least one calpain 2 moiety selected from the group consisting of Gln99, Cys105, and His262; and

R^6 is selected from –H and optionally substituted C_{1-4} alkyl.

151. The compound of claim 150, wherein:

R^9 is $-(C{=}R^{12})(C{=}R^{13})NR^2R^3$;

R^{12} is oxo and is positioned such that, upon binding of the compound to calpain 2, R^{12} forms a polar interaction with, and is within 4 Å or less of, calpain 2 His262 imidazole;

R^{13} is oxo and is positioned such that, upon binding of the compound to calpain 2, R^{13} forms a polar interaction with, and is within 4 Å or less of, at least one calpain 2 moiety selected from the group consisting of Gln99 side chain carboxamide and Cys105 backbone amide; and

R^2 and R^3 are independently selected from –H, optionally substituted C_{1-4} alkyl, optionally substituted C_{3-7} carbocyclyl, optionally substituted 5-10 membered heterocyclyl, optionally substituted C_{6-10} aryl, optionally substituted C_{6-10}aryl(C_1-C_6)alkyl, and optionally substituted 5-10 membered heteroaryl.

152. The compound of claim 150, wherein R^9 is positioned by the carbon to which it is attached such that, upon binding of the compound to calpain 2, at least one atom of R^9 forms a polar interaction with, and is within 3.5 Å or less of, at least one calpain 2 moiety selected from the group consisting of Gln99, Cys105, and His262.

153. The compound of claim 150, wherein a carbon atom in R^9 at its point of attachment forms a covalent bond with Cys195.

154. The compound of claim 116, wherein the covalent bond length is between 1.7 and 1.9 Å.

155. The compound of any one of claims 150 to 154, wherein P_2 is an optionally substituted 5-membered heteroaryl.

156. The compound of any one of claims 150 to 155, wherein R^{11} is positioned by the carbons to which it is bonded such that, upon binding of the compound to calpain 2, R^{11} forms a polar interaction with, and is within 3.5 Å or less of, calpain 2 Gly261 carbonyl.

157. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1-156 and a pharmaceutically acceptable excipient.

158. A method of treating fibrotic disease or a secondary disease state or condition thereof, comprising administering to a subject in need thereof, a compound according to any one of claims 1-156.

159. The method of claim 158, wherein the disease is selected from the group consisting of liver fibrosis, renal fibrosis, lung fibrosis, hypersensitivity pneumonitis,

interstitial fibrosis, systemic scleroderma, macular degeneration, pancreatic fibrosis, fibrosis of the spleen, cardiac fibrosis, mediastinal fibrosis, myelofibrosis, endomyocardial fibrosis, retroperitoneal fibrosis, progressive massive fibrosis, nephrogenic systemic fibrosis, fibrotic complications of surgery, chronic allograft vasculopathy and/or chronic rejection in transplanted organs, ischemic-reperfusion injury associated fibrosis, injection fibrosis, cirrhosis, diffuse parenchymal lung disease, post-vasectomy pain syndrome, and rheumatoid arthritis.

160. The method of claim 158, wherein the treatment decreases the expression level and/or activity of a calpain.

161. The method of claim 160, wherein the calpain is CAPN1, CAPN2, or CAPN9.

162. The method of claim 158 wherein the treatment inhibits myofibroblast differentiation or treats a disease associated with myofibroblast differentiation.

163. The method of claim 158, wherein the treatment inhibits Fibroblast-to-Myofibroblast Transition (FMT).

164. The method of claim 158, wherein the treatment inhibits Epithelial to Mesenchymal Transition or Endothelial to Mesenchymal Transition.

165. The method of claim 164, wherein the myofibroblast differentiation is a TGFβ-mediated myofibroblast differentiation.

166. The method of claim 158, wherein the fibrotic disease is a cancer.

167. The method of claim 166, wherein the cancer is a cancer of epithelial origin.

168. The method of claim 167, wherein the cancer of epithelial origin is selected from the group consisting of breast cancer, basal cell carcinoma, adenocarcinoma, gastrointestinal cancer, lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, brain, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, skin cancer, prostate cancer, and renal cell carcinoma.

169. The method of claim 158, wherein the fibrotic disease is stiff skin syndrome (SKS).

170. The method of claim 158, wherein the compound is of Formula I.

171. The method of claim 158, wherein the subject is a mammal.

172. The method of claim 158, wherein the subject is a human.

173. The method of claim 158, wherein the route of administration is selected from the group consisting of: enteral, intravenous, oral, intraarticular, intramuscular, subcutaneous, intraperitoneal, epidural, transdermal, and transmucosal.

174. The method of claim 158, wherein the administration is intravenous.

175. A method of inhibiting myofibroblast differentiation comprising contacting a cell with a compound of anyone of claims 1-156.

176. The method of claim 175, wherein the cell is in a fibrotic tissue.

177. The method of claim 175, wherein the cell is in a cancerous tissue.

178. The method of claim 175, wherein the cell is in a tissue with high TGFβ signaling.

179. A method for inhibiting calpain, the method comprising contacting a compound of any one of claims 1-156 with a CAPN1, CAPN2, and/or CAPN9 enzyme residing inside a subject.

180. A method of competitive binding with calpastatin (CAST), the method comprising contacting a compound of anyone of claims 1-156 with CAPN1, CAPN2, and/or CAPN9 enzymes residing inside a subject.