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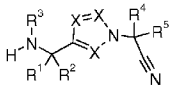
(54) Title: HETEROARYL NITRILE COMPOUNDS USEFUL AS INHIBITORS OF CATHEPSIN-S



(I)

(57) Abstract: Disclosed are Cathepsin-S reversible inhibitor compounds of the formula (I) which are useful in the treatment of autoimmune and other diseases. Also disclosed are pharmaceutical compositions containing the same, and methods of making and using the same.

WO 2011/109470 A1

Heteroaryl Nitrile Compounds Useful as Inhibitors of Cathepsin-S.

APPLICATION DATA

This application claims benefit to US provisional application serial no. 61/310,827 filed March 5, 2010.

BACKGROUND OF THE INVENTION

1. TECHNICAL FIELD

This invention relates reversible inhibitors of the Cathepsin-S which are useful in the treatment of autoimmune and other diseases.

2. BACKGROUND INFORMATION

Cathepsin-S, and compounds active as inhibitors of the Cathepsin-S have been described elsewhere. See for example WO2004083182. A step thought to be critical in autoimmune diseases is the display of self-antigen on the surface of antigen presenting cells (e.g. B-cells) by MHCII. Before presenting antigens to the $CD4^+$ T cells, the antigen binding groove of MCHII is occupied by a protein called P10. Apparently critical to allowing the self-antigen to be displayed on the B-cell surface, the protease Cathepsin-S is involved in cleaving P10 to a lower affinity peptide called CLIP, which can be displaced by the antigenic peptides. Thus by blocking Cathepsin-S with a small-molecule inhibitor may prevent the display of self-antigen, and ameliorate the disease or symptoms of autoimmune or inflammatory diseases. There is presently a large unmet medical need for treatments of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, psoriasis, atherosclerosis, and inflammatory diseases such as chronic obstructive pulmonary disease.

BRIEF SUMMARY OF THE INVENTION

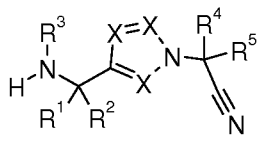
The work cited above supports the principle that by blocking Cathepsin-S, a small-molecule inhibitor can ameliorate the disease or symptoms of autoimmune diseases.

It is therefore an object of the invention to provide a novel class of potent inhibitors of Cathepsin-S for treatments of autoimmune diseases, and their pharmaceutical compositions.

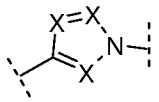
It is a further object of the invention to provide methods of making and methods of using such compounds.

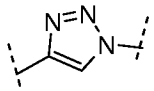
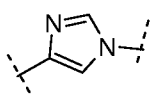
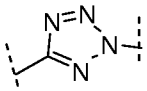
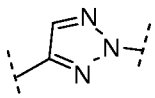
DETAILED DESCRIPTION OF THE INVENTION

In the broadest generic embodiment, there is provided a compound of the formula (I):



(I)

wherein the  ring is chosen from:

 (i),  (ii),  (iii) or  (iv) each optionally substituted by C_{1-3} alkyl;

R^1 is C_{1-7}alkyl, C_{3-7}cycloalkyl, aryl, heterocyclyl or heteroaryl each optionally substituted by one or more R^c;

R^2 is hydrogen or C_{1-7}alkyl;

or R^1 and R^2 taken together form a C_{3-7}cycloalkyl or C_{3-7} heterocyclyl ring optionally substituted by one or more halogen or C_{1-7}alkyl;

R^3 is -C(O)C_{1-7}alkyl, -C(O)C_{3-7}cycloalkyl, -C(O)aryl, -C(O)heteroaryl, -C(O)heterocyclyl, -C(O)NR^aR^b, -C(O)OR^a, -CH(R_f)-heteroaryl, -CH(R_f)-aryl, -CH(R_f)-heterocyclyl, aryl, C_{3-7}cycloalkyl or heteroaryl, each ring is optionally substituted by one or more R^d;

R^4 and R^5 are each independently hydrogen, C_{1-7}alkyl, aryl, or heteroaryl, or R^4 and R^5 taken together may form a C_{3-7}cycloalkyl or C_{3-7} heterocyclyl ring each ring being optionally substituted by C_{1-5}alkyl;

R^a, R^b each independently are hydrogen, C_{1-7}alkyl, aryl or heteroaryl, or may be taken together to form a saturated or unsaturated C_{3-7}cycloalkyl or C_{3-7} heterocyclyl ring;

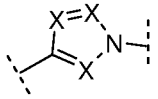
R^c is C_{1-7}alkyl, C_{1-7}alkoxy, C_{3-7}cycloalkyl, aryl, benzyl, halogen or -C(O)-O-benzyl;

R^d each is independently chosen from C_{1-7}alkyl, C_{1-7}alkoxy, C_{1-7}acyl, -C(O)NR^aR^b, -NH-C(O)-C_{1-7}alkyl, halogen, -CN, -$S(O)_m$-R_e, -NH-$S(O)_m$-R_e;

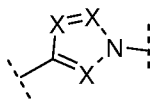
R_e is chosen from C_{1-7}alkyl and amino;

R^f each is independently chosen from hydrogen or C_{1-7}alkyl;

m is 0-2;

wherein one or more hydrogens on any one or more of R^1, R^2, R^3, R^2, R^4, R^5, R^a, R^b, R^c, R^d, R^e, R^f or  may be replaced by a halogen or deuterium atom;

with the proviso that

when  is (i), and

neither R^1 nor R^2 is hydrogen, and

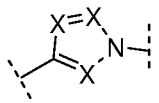
R^3 is -C(O)C_{1-7}alkyl, -C(O)C_{3-7}cycloalkyl, -C(O)aryl, -C(O)heteroaryl, -C(O)heterocyclyl,-CH(R^f)-heteroaryl, -CH(R^f)-aryl, -CH(R^f)-heterocyclyl, aryl, C_{3-7}cycloalkyl or heteroaryl

then R^4 and R^5 must either both be hydrogen or they must form a ring.

or a pharmaceutically acceptable salt thereof.

In another embodiment of the invention there is provided a compound of the formula (I) according the embodiments immediately above and wherein

R^2 = hydrogen or C_{1-7}alkyl if

a)  is (i), or

b) R^4 and R^5 are hydrogen, or

c) R^4 and R^5 form a ring, or

d) R^3 is -C(O)N$R^a$$R^b$ or - C(O)OR^a,

or a pharmaceutically acceptable salt thereof.

In another embodiment of the invention there is provided a compound of the formula (I) according any of the embodiments above and wherein

R^1 is C_{1-7}alkyl, C_{3-7}cycloalkyl, cyclohexyl-D11, phenyl, oxiranyl, azepanyl, diazepanyl, azetidinyl, pyrrolidinyl, pyrrolinyl, thiomorpholinyl, dioxalanyl, piperazinyl, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxanyl, piperidinonyl, tetrahydropyrimidonyl, piperidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,1-dioxo-hexahydro-1λ6-thiopyranyl, 1-oxo-hexahydro-1λ4-thiopyranyl, aziridinyl, thiadiazolyl, tetrazolyl, pyrrolyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyranyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzothienyl, quinolinyl, quinazolinyl, naphthyridinyl, indazolyl, triazolyl, purinyl, benzofuranyl, thiazolyl, isothiazolyl, imidazolyl, oxazolyl, isoxazolyl, thienyl, furanyl, pyrazolyl and pyridinyl, each optionally substituted by an R^c;

R^2 is hydrogen or C_{1-5}alkyl;
or R^1 and R^2 taken together form a C_{3-7}cycloalkyl;

R^3 = -C(O)C_{1-7}alkyl, -C(O)C_{3-6}cycloalkyl, -C(O)phenyl, -C(O)heterocyclyl wherein the heterocyclyl is chosen from oxiranyl, azepanyl, diazepanyl, azetidinyl, pyrrolidinyl, pyrrolinyl, thiomorpholinyl, dioxalanyl, piperazinyl, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxanyl, piperidinonyl, tetrahydropyrimidonyl, piperidinyl, tetrahydrothiopyranyl, morpholinyl, piperidinyl, tetrahydrofuranyl and tetrahydropyranyl, -C(O)heteroaryl wherein the heteroaryl is chosen from benzofuranyl, imidazo[2,1-b]thiazolyl, imidazo[1,2-a]pyrazinyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, thiazolyl, isothiazolyl, imidazolyl, oxazolyl, isoxazolyl, thienyl, furanyl, pyrazolyl and pyridinyl,
-C(O)NH-phenyl, heterocyclyl chosen from oxiranyl, azepanyl, diazepanyl, azetidinyl, pyrrolidinyl, pyrrolinyl, thiomorpholinyl, dioxalanyl, piperazinyl, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxanyl, piperidinonyl, tetrahydropyrimidonyl, piperidinyl, tetrahydrothiopyranyl, morpholinyl, piperidinyl, tetrahydropyranyl 1,1-Dioxo-1λ6-thiomorpholine, tetrahydrofuranyl, 1,1-dioxo-hexahydro-1λ6-thiopyranyl, piperidinyl and 2-oxo-imidazolidinyl, phenyl, C_{3-7}cycloalkyl, -CH_2-2-oxo-imidazolidinyl and -$CH(R_f)$-heteroaryl wherein the heteroaryl is chosen from thiazolyl, isothiazolyl, imidazolyl, oxazolyl, isoxazolyl, thienyl, furanyl, pyrazolyl and pyridinyl, each ring is optionally substituted by one or more R^d;

R^4 and R^5 are each independently hydrogen or C_{1-7}alkyl,or
R^4 and R^5 taken together may form a C_{3-6}cycloalkyl, oxiranyl, azepanyl, diazepanyl, azetidinyl, pyrrolidinyl, pyrrolinyl, thiomorpholinyl, dioxalanyl, piperazinyl, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxanyl, piperidinonyl, tetrahydropyrimidonyl, piperidinyl, tetrahydrothiopyranyl, morpholinyl, piperidinyl or tetrahydropyranyl each ring being optionally substituted by C_{1-3}alkyl;

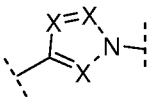
R^a, R^b are each independently hydrogen, C_{1-5}alkyl or phenyl;

R^c is C_{1-5}alkyl, C_{1-5}alkoxy, C_{3-6}cycloalkyl, phenyl, benzyl, fluoro or -C(O)-O-benzyl;

R^d is independently chosen from C_{1-5}alkyl, C_{1-5}alkoxy, C_{1-5}acyl, -C(O)NR^aR^b, -NH-C(O)-C_{1-5}alkyl, halogen, -CN, -$S(O)_2$-R_e, -NH-$S(O)_2$-R_e;

R_e is chosen from C_{1-5}alkyl and amino;

R^f is independently chosen from hydrogen and C_{1-5}alkyl;

wherein one or more hydrogens on any one or more of R^1, R^2, R^3, R^2, R^4, R^5, R^a, R^b, R^c, R^d, R^e, R^f or  may be replaced by a halogen or deuterium atom;

or a pharmaceutically acceptable salt thereof.

In another embodiment of the invention there is provided a compound of the formula (I) according to any of the embodiments above and wherein

R^1 is t-butyl, sec-butyl, 3-pentyl, cyclohexyl, -CH_2-cyclohexyl, cyclopentyl, cyclopropyl, phenyl, cyclohexyl-D11, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,1-dioxo-hexahydro-1λ6-thiopyranyl or 1-oxo-hexahydro-1λ4-thiopyranyl, each optionally substituted by an R^c;

R^2 is hydrogen or methyl;
or R^1 and R^2 taken together form a cyclohexyl;

R^3 is -C(O)C_{1-7}alkyl, -C(O) cyclopropyl, -C(O)cyclopentyl, -C(O)phenyl, -C(O)heterocyclyl wherein the heterocyclyl is chosen from morpholinyl, piperidinyl, tetrahydrofuranyl and tetrahydropyranyl, -C(O)heteroaryl wherein the heteroaryl is chosen from benzofuranyl, imidazo[2,1-b]thiazolyl, imidazo[1,2-a]pyrazinyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, thiazolyl, isothiazolyl, imidazolyl, oxazolyl, isoxazolyl, thienyl, furanyl, pyrazolyl and pyridinyl,

-C(O)NH-phenyl, heterocyclyl chosen from 1,1-Dioxo-1λ6-thiomorpholine, tetrahydrofuranyl, 1,1-dioxo-hexahydro-1λ6-thiopyranyl, piperidinyl and 2-oxo-imidazolidinyl, phenyl, cyclohexyl and $-CH_2$-thienyl;

R^4 and R^5 are each independently hydrogen, methyl or n-butyl or
R^4 and R^5 taken together may form cyclopropyl, piperidinyl, tetrahydropyranyl or 1-methyl-piperidinyl;

R^a, R^b are each independently hydrogen, methyl or phenyl;

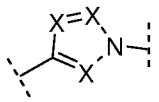
R^c is methyl, methoxy, cyclohexyl, phenyl, benzyl, fluoro or -C(O)-O-benzyl;

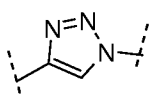
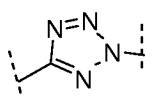
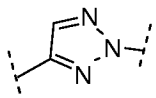
R^d is independently chosen from methyl, $-CF_3$, $-CH_2CF_3$, methoxy, acetyl, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, -NH-C(O)-methyl, $-S(O)_2-CH_3$, $-S(O)_2-NH_2$, $-NH-S(O)_2-CH_3$, F, Cl and –CN;

R^f is independently chosen from hydrogen, methyl and CF_3;

or a pharmaceutically acceptable salt thereof.

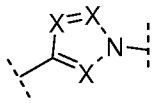
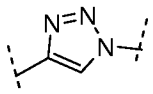
In another embodiment of the invention there is provided a compound of the formula (I) according to any of the embodiments above and wherein

wherein the  ring is chosen from:

 (i),  (iii) or  (iv);

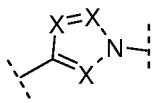
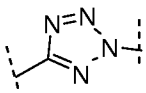
or a pharmaceutically acceptable salt thereof.

In another embodiment of the invention there is provided a compound of the formula (I) according to any of the embodiments above and wherein

wherein the  ring is  (i)

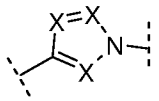
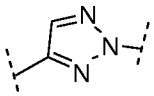
or a pharmaceutically acceptable salt thereof.

In another embodiment of the invention there is provided a compound of the formula (I) according to any of the embodiments above and wherein

wherein the  ring is  (iii)

or a pharmaceutically acceptable salt thereof.

In another embodiment of the invention there is provided a compound of the formula (I) according to any of the embodiments above and wherein

wherein the  ring is:  (iv)

or a pharmaceutically acceptable salt thereof.

In another embodiment of the invention there is provided a compound of the formula (I) according to any of the embodiments above and wherein

R^1 is cyclohexyl, -CH_2-cyclohexyl, 4,4-difluorocyclohexyl, 3-methoxycyclohexyl, 4-methylcyclohexyl, 4-trifluoromethylcyclohexyl, cyclohexyl-D11, cyclopentyl,3-pentyl, sec-butyl, tetrahydropyranyl, or tetrahydrothiopyranyl.

In another embodiment of the invention there is provided a compound of the formula (I) according to any of the embodiments above and wherein

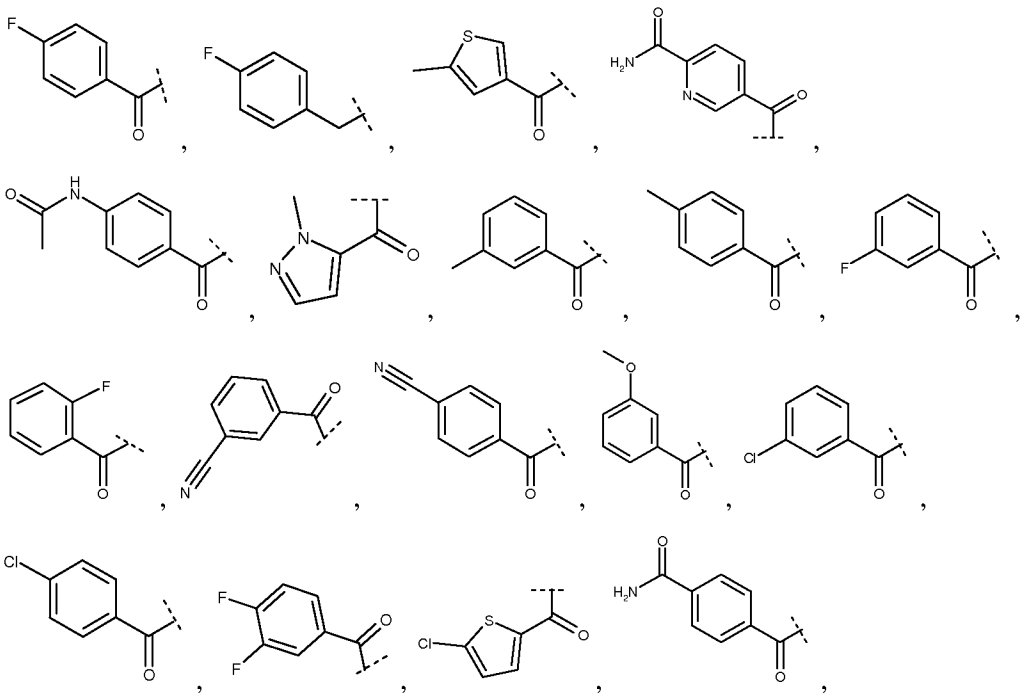
R^2 is hydrogen or methyl;

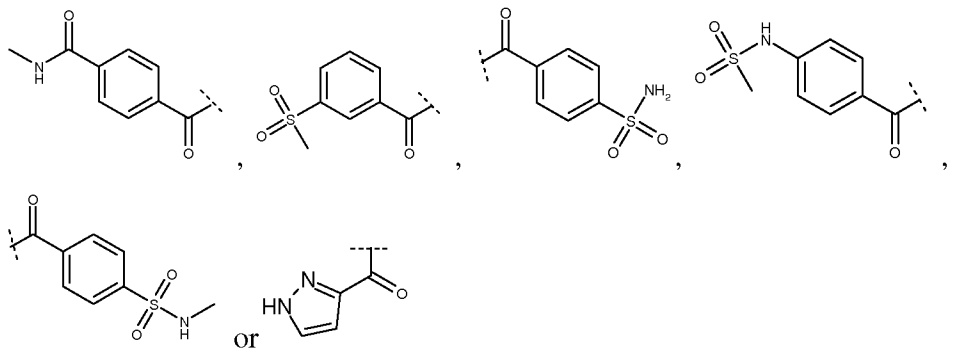
or R^1 and R^2 taken together form a cyclohexyl.

In another embodiment of the invention there is provided a compound of the formula (I) according to any of the embodiments above and wherein

R^3 is -C(O)cyclopropyl, -C(O)phenyl, -C(O)heterocyclyl wherein the heterocyclyl is chosen from morpholinyl and piperidinyl, -C(O)heteroaryl wherein the heteroaryl is chosen from imidazo[2,1-b]thiazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, thienyl, furanyl, pyrazolyl and pyridinyl,

or R^3 is



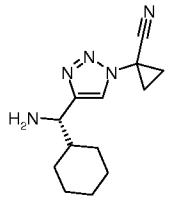
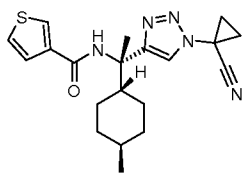
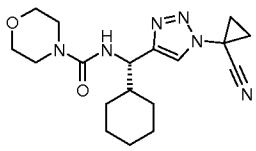


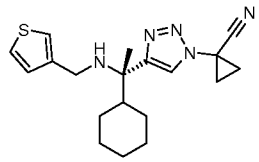
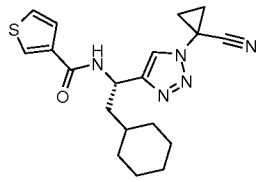
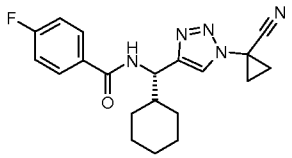
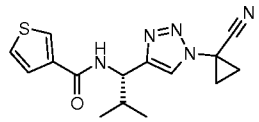
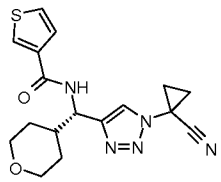
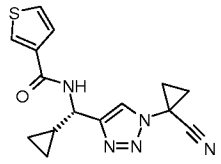
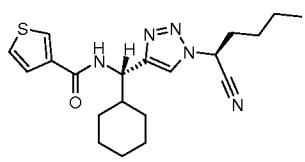
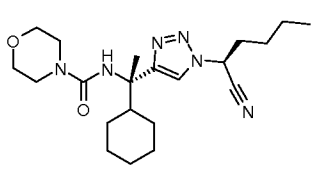
In another embodiment of the invention there is provided a compound of the formula (I) according to any of the embodiments above and wherein

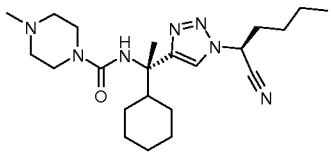
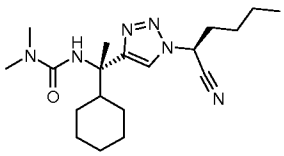
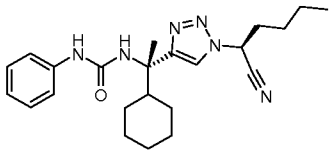
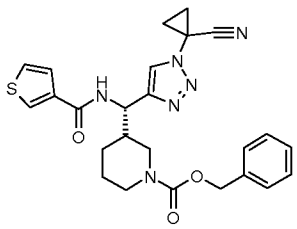
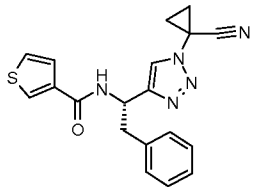
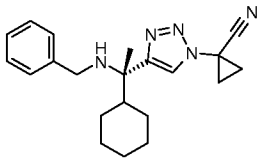
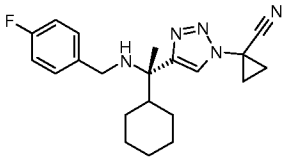
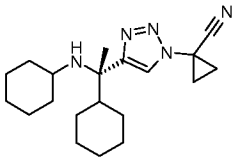
R^4 and R^5 are each independently hydrogen, methyl or n-butyl or

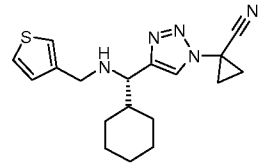
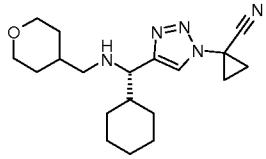
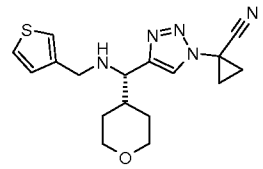
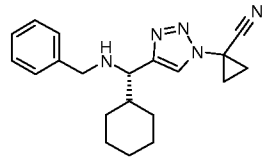
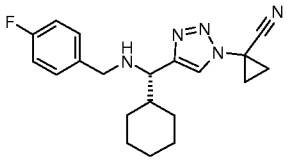
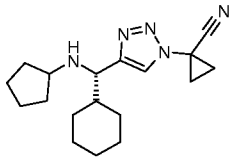
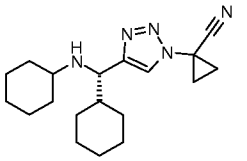
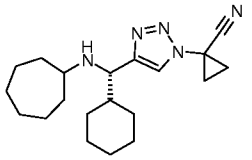
R^4 and R^5 taken together may form cyclopropyl, piperidinyl, or tetrahydropyranyl.

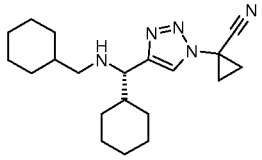
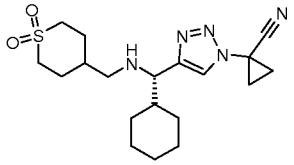
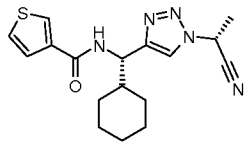
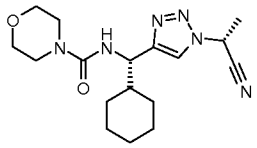
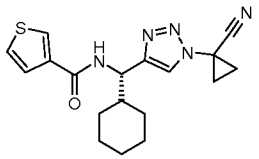
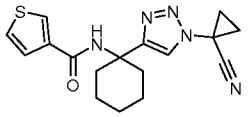
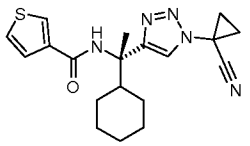
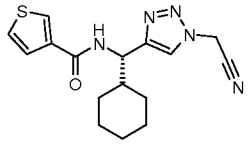
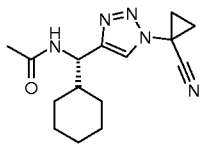
In another embodiment, the invention provides compounds in Table I which can be made in view of the general schemes, examples and methods known in the art.

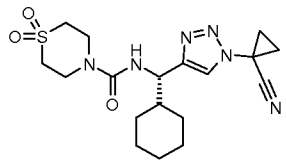
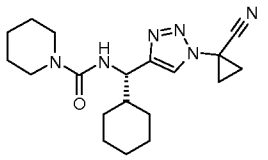
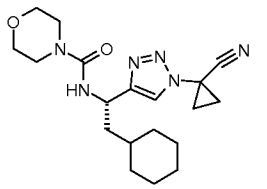
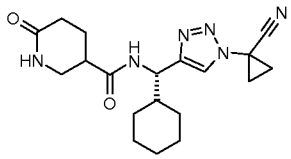
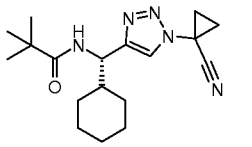
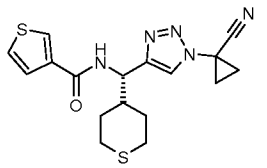
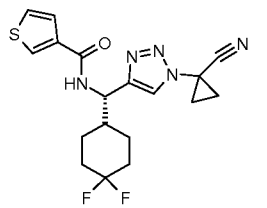
Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
1		1-[4-((S)-Amino-cyclohexyl-methyl)-[1,2,3]triazol-1-yl]-cyclopropanecarbonitrile	E 0.51 246.1
2		Thiophene-3-carboxylic acid [(S)-1-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-1-(4-methyl-cyclohexyl)-ethyl]-amide	A 1.75 384.8
3		Morpholine-4-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	A 1.35 359.4

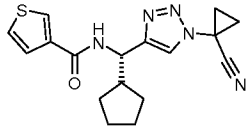
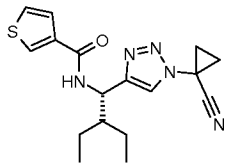
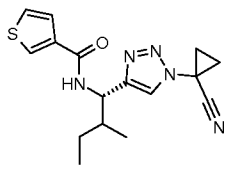
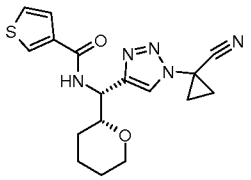
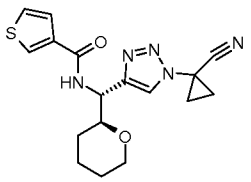
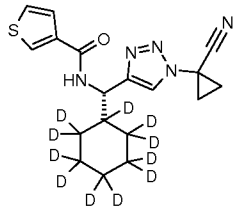
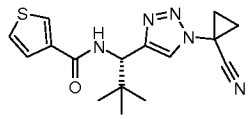
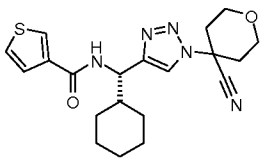
Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
4		1-(4-{(S)-1-Cyclohexyl-1-[(thiophen-3-ylmethyl)-amino]-ethyl}-[1,2,3]triazol-1-yl)-cyclopropanecarbonitrile	E 0.67 356.5
5		Thiophene-3-carboxylic acid {(S)-1-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-2-cyclohexyl-ethyl}-amide	F 2.24 370.3
6		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-4-fluoro-benzamide	A 1.65 368.6
7		Thiophene-3-carboxylic acid {(S)-1-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-2-methyl-propyl}-amide	F 1.38 316.3
8		Thiophene-3-carboxylic acid [(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-(tetrahydro-pyran-4-yl)-methyl]-amide	F 1.05 358.2
9		Thiophene-3-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclopropyl-methyl}-amide	F 1.18 314.2
10		Thiophene-3-carboxylic acid {(S)-[1-((S)-1-cyano-pentyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	C 1.49 386.2
11		Morpholine-4-carboxylic acid {(S)-1-[1-((S)-1-cyano-pentyl)-1H-[1,2,3]triazol-4-yl]-1-cyclohexyl-ethyl}-amide	A 1.65 403.8

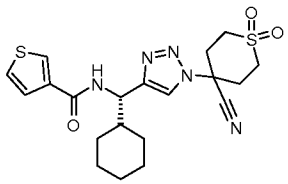
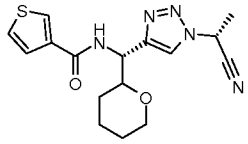
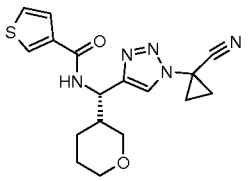
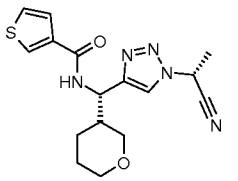
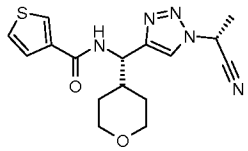
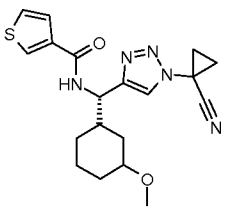
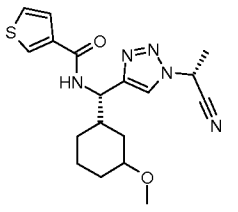
Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
12		4-Methyl-piperazine-1-carboxylic acid {(S)-1-[1-((S)-1-cyano-pentyl)-1H-[1,2,3]triazol-4-yl]-1-cyclohexyl-ethyl}-amide	A 1.41 416.8
13		3-{(S)-1-[1-((S)-1-Cyano-pentyl)-1H-[1,2,3]triazol-4-yl]-1-cyclohexyl-ethyl}-1,1-dimethyl-urea	A 1.69 361.7
14		1-{(S)-1-[1-((S)-1-Cyano-pentyl)-1H-[1,2,3]triazol-4-yl]-1-cyclohexyl-ethyl}-3-phenyl-urea	A 1.88 409.8
15		3-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-[(thiophene-3-carbonyl)-amino]-methyl}-piperidine-1-carboxylic acid benzyl ester	B 6.17 491.7
16		Thiophene-3-carboxylic acid {(S)-1-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-2-phenyl-ethyl}-amide	B 5.8 364.5
17		1-[4-((S)-1-Benzylamino-1-cyclohexyl-ethyl)-[1,2,3]triazol-1-yl]-cyclopropanecarbonitrile	E 0.59 350.3
18		1-{4-[(S)-1-Cyclohexyl-1-(4-fluoro-benzylamino)-ethyl]-[1,2,3]triazol-1-yl}-cyclopropanecarbonitrile	E 0.7 368.5
19		1-[4-((S)-1-Cyclohexyl-1-cyclohexylamino-ethyl)-[1,2,3]triazol-1-yl]-cyclopropanecarbonitrile	E 0.71 342.3

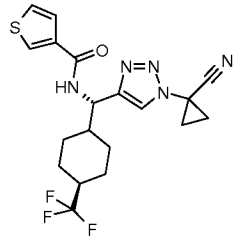
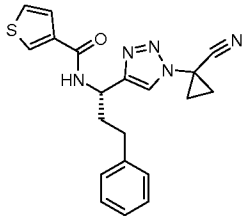
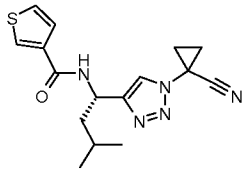
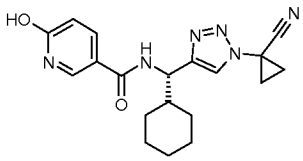
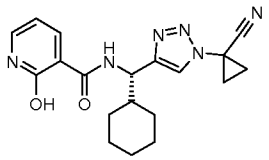
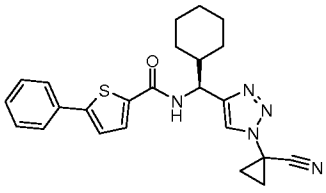
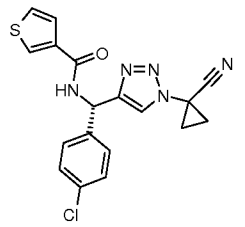
Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
20		1-(4-{(S)-Cyclohexyl-[(thiophen-3-ylmethyl)-amino]-methyl}-[1,2,3]triazol-1-yl)-cyclopropanecarbonitrile	E 0.64 342.2
21		1-(4-{(S)-Cyclohexyl-[(tetrahydro-pyran-4-ylmethyl)-amino]-methyl}-[1,2,3]triazol-1-yl)-cyclopropanecarbonitrile	E 0.57 344.2
22		1-(4-{(S)-(Tetrahydro-pyran-4-yl)-[(thiophen-3-ylmethyl)-amino]-methyl}-[1,2,3]triazol-1-yl)-cyclopropanecarbonitrile	E 0.47 344.1
23		1-[4-((S)-Benzylamino-cyclohexyl-methyl)-[1,2,3]triazol-1-yl]-cyclopropanecarbonitrile	E 0.65 336.2
24		1-{4-[(S)-Cyclohexyl-(4-fluoro-benzylamino)-methyl]-[1,2,3]triazol-1-yl}-cyclopropanecarbonitrile	E 0.68 354.1
25		1-[4-((S)-Cyclohexyl-cyclopentylamino-methyl)-[1,2,3]triazol-1-yl]-cyclopropanecarbonitrile	E 0.65 314.1
26		1-[4-((S)-Cyclohexyl-cyclohexylamino-methyl)-[1,2,3]triazol-1-yl]-cyclopropanecarbonitrile	E 0.70 328.2
27		1-[4-((S)-Cycloheptylamino-cyclohexyl-methyl)-[1,2,3]triazol-1-yl]-cyclopropanecarbonitrile	E 0.71 342.2

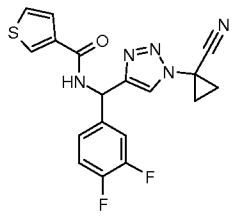
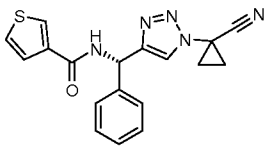
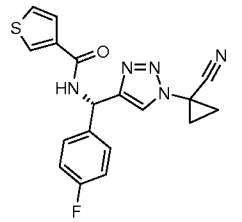
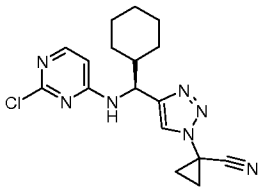
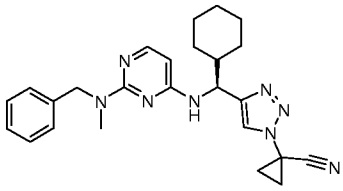
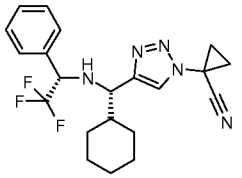
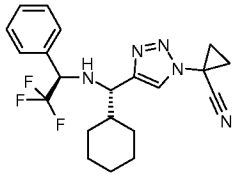
Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
28		1-{4-[(S)-Cyclohexyl-(cyclohexylmethyl-amino)-methyl]-[1,2,3]triazol-1-yl}-cyclopropanecarbonitrile	E 0.73 342.2
29		1-(4-{(S)-Cyclohexyl-[(1,1-dioxo-hexahydro-1l6-thiopyran-4-ylmethyl)-amino]-methyl}-[1,2,3]triazol-1-yl)-cyclopropanecarbonitrile	E 0.53 392.2
30		Thiophene-3-carboxylic acid {(S)-[1-((R)-cyano-methyl-methyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	A 1.87 344.1
31		Morpholine-4-carboxylic acid {(S)-[1-((R)-cyano-methyl-methyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	F 1.37 347.2
32		Thiophene-3-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	A 1.58 356.6
33		Thiophene-3-carboxylic acid {1-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl}-amide	A 1.47 342.3
34		Thiophene-3-carboxylic acid {(S)-1-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-1-cyclohexyl-ethyl}-amide	F 2.11 370.2
35		Thiophene-3-carboxylic acid [(S)-(1-cyanomethyl-1H-[1,2,3]triazol-4-yl)-cyclohexyl-methyl]-amide	F 1.78 330.1
36		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-	F 1.33 288.1

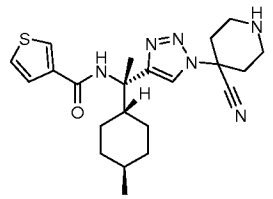
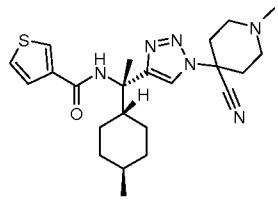
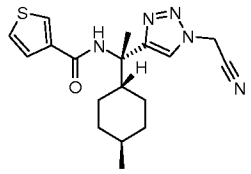
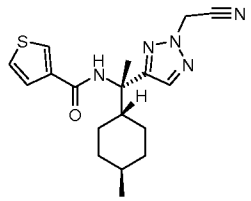
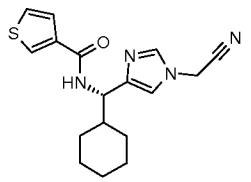
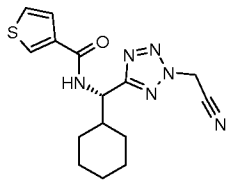
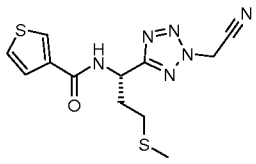
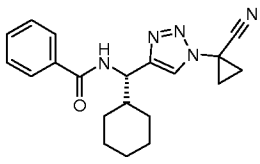
Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
		acetamide	
37		1,1-Dioxo-1l6-thiomorpholine-4-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	A 1.34 407.3
38		Piperidine-1-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	A 1.57 357.3
39		Morpholine-4-carboxylic acid {(S)-1-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-2-cyclohexyl-ethyl}-amide	F 1.74 373.2
40		6-Oxo-piperidine-3-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.72 371.2
41		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-2,2-dimethyl-propionamide	F 2.07 330.2
42		Thiophene-3-carboxylic acid [(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-(tetrahydro-thiopyran-4-yl)-methyl]-amide	A 1.43 374.3
43		Thiophene-3-carboxylic acid [(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-(4,4-difluoro-cyclohexyl)-methyl]-amide	F 1.72 392.1

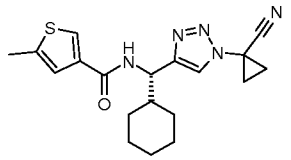
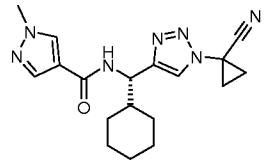
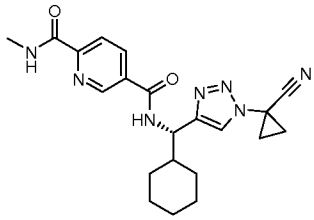
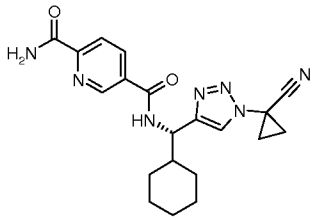
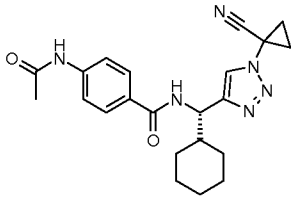
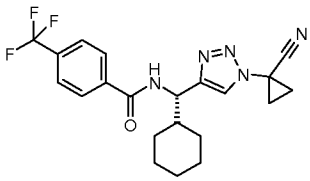
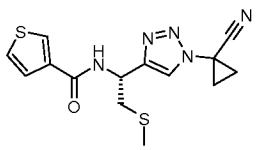
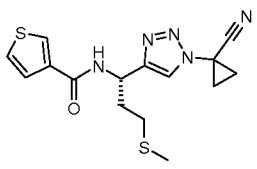
Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
44		Thiophene-3-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclopentyl-methyl}-amide	F 1.72 342.3
45		Thiophene-3-carboxylic acid {(S)-1-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-2-ethyl-butyl}-amide	F 1.93 344.1
46		Thiophene-3-carboxylic acid {(S)-1-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-2-methyl-butyl}-amide	F 1.71 330.1
(R,R) -47		Thiophene-3-carboxylic acid {(R)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-(R)-tetrahydro-pyran-2-yl-methyl}-amide	F 1.48 358.1
(R,S) -47		Thiophene-3-carboxylic acid {(R)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-(S)-tetrahydro-pyran-2-yl-methyl}-amide	F 1.51 358.1
48		Thiophene-3-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-D11-methyl}-amide	C 1.26 367.2
49		Thiophene-3-carboxylic acid {(S)-1-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-2,2-dimethyl-propyl}-amide	F 1.65 330.3
50		Thiophene-3-carboxylic acid {(S)-[1-(4-cyano-tetrahydro-pyran-4-yl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	F 1.94 400.1

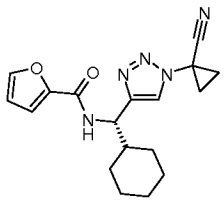
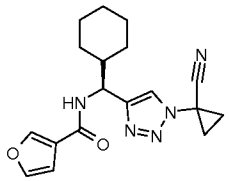
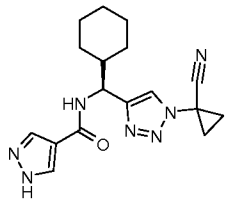
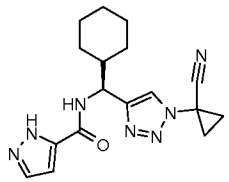
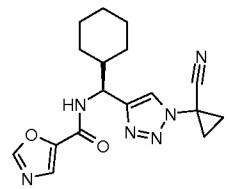
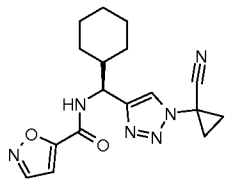
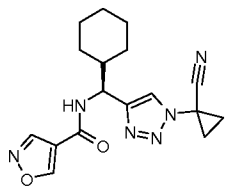
Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
51		Thiophene-3-carboxylic acid {(S)-[1-(4-cyano-1,1-dioxo-hexahydro-1l6-thiopyran-4-yl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	F 1.96 448.1
52		Thiophene-3-carboxylic acid [(R)-[1-((R)-cyano-methyl-methyl)-1H-[1,2,3]triazol-4-yl]-(tetrahydro-pyran-2-yl)-methyl]-amide	F 1.31 346.1
53		Thiophene-3-carboxylic acid [(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-(tetrahydro-pyran-3-yl)-methyl]-amide	F 1.12 358.1
54		Thiophene-3-carboxylic acid [(S)-[1-((R)-cyano-methyl-methyl)-1H-[1,2,3]triazol-4-yl]-(tetrahydro-pyran-3-yl)-methyl]-amide	E 1.03 & 1.09 346.0 & 346.0
55		Thiophene-3-carboxylic acid [(S)-[1-((R)-cyano-methyl-methyl)-1H-[1,2,3]triazol-4-yl]-(tetrahydro-pyran-4-yl)-methyl]-amide	F 1.05 346.1
56		Thiophene-3-carboxylic acid [(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-(3-methoxy-cyclohexyl)-methyl]-amide	F 1.44&1.46 3.86.1 & 386.1
57		Thiophene-3-carboxylic acid [(S)-[1-((R)-cyano-methyl-methyl)-1H-[1,2,3]triazol-4-yl]-(3-methoxy-cyclohexyl)-methyl]-amide	F 1.40/1.47 374.1/374.1

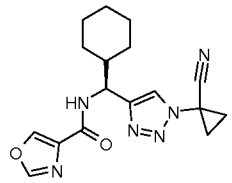
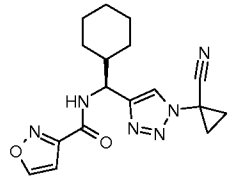
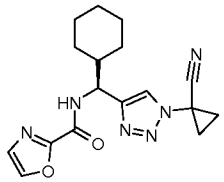
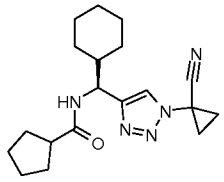
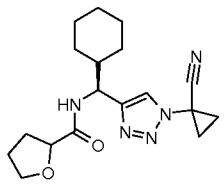
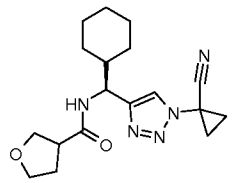
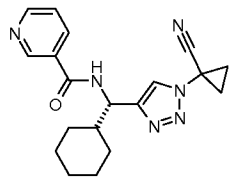
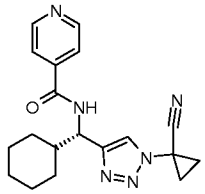
Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
58		Thiophene-3-carboxylic acid [(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-(4-trifluoromethyl-cyclohexyl)-methyl]-amide	D 1.31 424.2
59		Thiophene-3-carboxylic acid {(S)-1-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-3-phenyl-propyl}-amide	F 1.93 378.2
60		Thiophene-3-carboxylic acid {(S)-1-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-3-methyl-butyl}-amide	F 1.57 330.2
61		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-6-hydroxy-nicotinamide	E 0.74 367.0
62		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-2-hydroxy-nicotinamide	E 0.78 367.1
64		5-Phenyl-thiophene-2-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	F 2.73 432.2
65		Thiophene-3-carboxylic acid {(S)-(4-chloro-phenyl)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-methyl}-amide	C 1.25 384.2

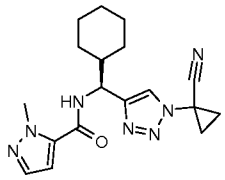
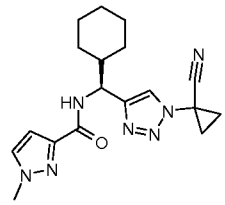
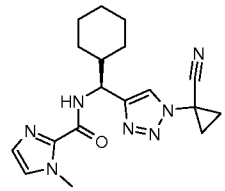
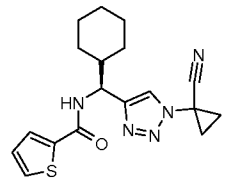
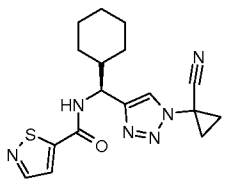
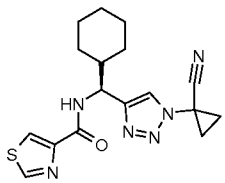
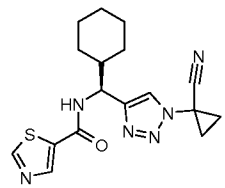
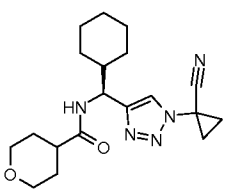
Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
66		Thiophene-3-carboxylic acid [[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-(3,4-difluoro-phenyl)-methyl]-amide	C 1.55 386.2
67		Thiophene-3-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-phenyl-methyl}-amide	C 1.15 350.2
68		Thiophene-3-carboxylic acid [(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-(4-fluoro-phenyl)-methyl]-amide	C 1.17 368.2
69		1-{4-[(S)-(2-Chloro-pyrimidin-4-ylamino)-cyclohexyl-methyl]-[1,2,3]triazol-1-yl}-cyclopropanecarbonitrile	F 1.97 358.1
70		1-(4-{(S)-[2-(Benzyl-methyl-amino)-pyrimidin-4-ylamino]-cyclohexyl-methyl}-[1,2,3]triazol-1-yl)-cyclopropanecarbonitrile	F 1.39 461.0
71		1-{4-[(S)-Cyclohexyl-((S)-2,2,2-trifluoro-1-phenyl-ethylamino)-methyl]-[1,2,3]triazol-1-yl}-cyclopropanecarbonitrile	A 1.97 404.4
72		1-{4-[(S)-Cyclohexyl-((R)-2,2,2-trifluoro-1-phenyl-ethylamino)-methyl]-[1,2,3]triazol-1-yl}-cyclopropanecarbonitrile	A 2 404.4

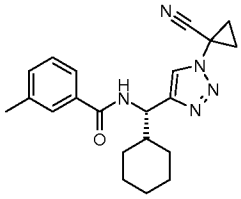
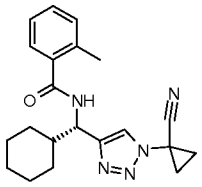
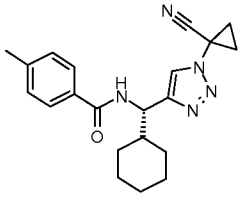
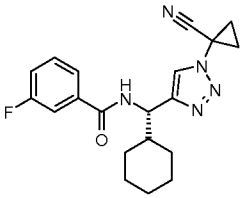
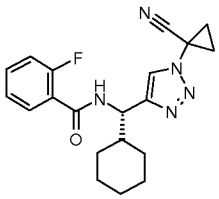
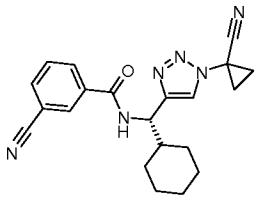
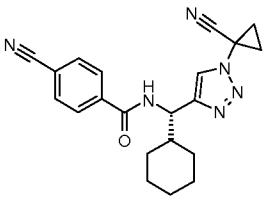
Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
73		Thiophene-3-carboxylic acid [(S)-1-[1-(4-cyano-piperidin-4-yl)-1H-[1,2,3]triazol-4-yl]-1-(4-methyl-cyclohexyl)-ethyl]-amide	F 1.43 427.7
74		Thiophene-3-carboxylic acid [(S)-1-[1-(4-cyano-1-methyl-piperidin-4-yl)-1H-[1,2,3]triazol-4-yl]-1-(4-methyl-cyclohexyl)-ethyl]-amide	F 1.43 441.4
75		Thiophene-3-carboxylic acid [(S)-1-(1-cyanomethyl-1H-[1,2,3]triazol-4-yl)-1-(4-methyl-cyclohexyl)-ethyl]-amide	A 1.61 358.2
76		Thiophene-3-carboxylic acid [(S)-1-(2-cyanomethyl-2H-[1,2,3]triazol-4-yl)-1-(4-methyl-cyclohexyl)-ethyl]-amide	A 1.71 358.2
77		Thiophene-3-carboxylic acid [(S)-(1-cyanomethyl-1H-imidazol-4-yl)-cyclohexyl-methyl]-amide	C 1.3 329.6
78		Thiophene-3-carboxylic acid [(S)-(2-cyanomethyl-2H-tetrazol-5-yl)-cyclohexyl-methyl]-amide	D 2.32 331.2
79		Thiophene-3-carboxylic acid [(S)-1-(2-cyanomethyl-2H-tetrazol-5-yl)-3-methylsulfanyl-propyl]-amide	
80		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-benzamide	E 0.98 350.2

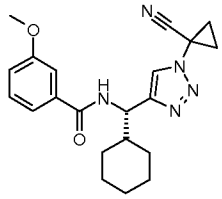
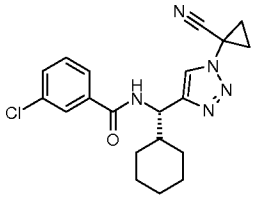
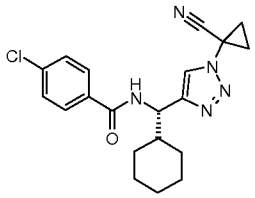
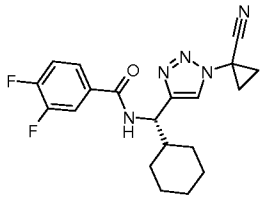
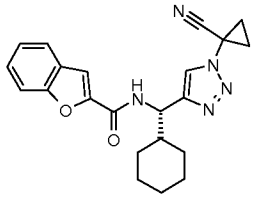
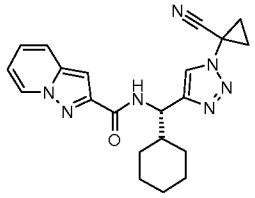
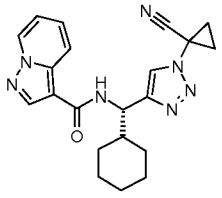
Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
81		5-Methyl-thiophene-3-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 1.02 370.1
82		1-Methyl-1H-pyrazole-4-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.72 354.4
83		Pyridine-2,5-dicarboxylic acid 5-({(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide) 2-methylamide	C 1.4 408.3
84		Pyridine-2,5-dicarboxylic acid 2-amide 5-({(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide)	C 1.09 394.2
85		4-Acetylamino-N-{(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-benzamide	E 0.77 407.21
86		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-4-trifluoromethyl-benzamide	E 1.12 418.2
87		Thiophene-3-carboxylic acid {(R)-1-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-2-methylsulfanyl-ethyl}-amide	F 1.33 334.2
88		Thiophene-3-carboxylic acid {(S)-1-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-3-methylsulfanyl-propyl}-	F 1.36 348.3

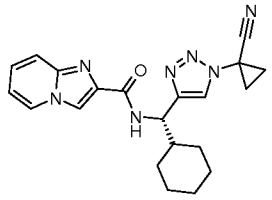
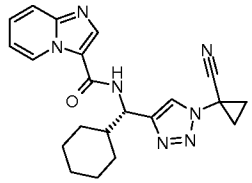
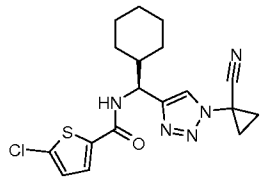
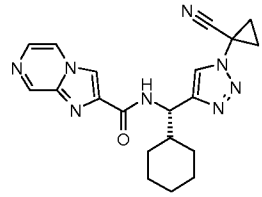
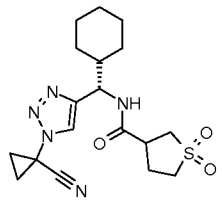
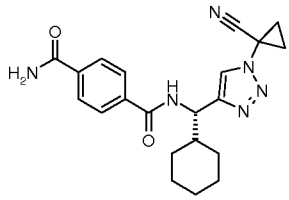
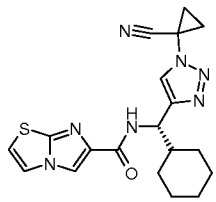
Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
		amide	
89		Furan-2-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	F 1.62 340.1
90		Furan-3-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.83 340.19
91		1H-Pyrazole-4-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.67 340.18
92		2H-Pyrazole-3-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.72 340.18
93		Oxazole-5-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.73 341.15
94		Isoxazole-5-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.8 341.17
95		Isoxazole-4-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.79 341.16

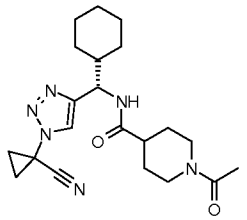
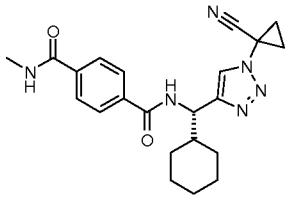
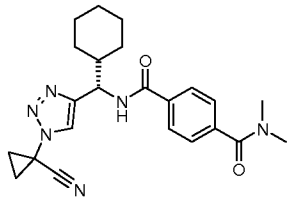
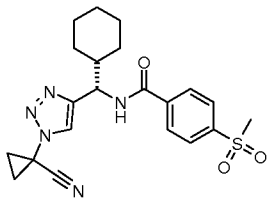
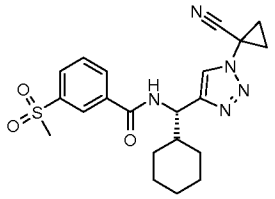
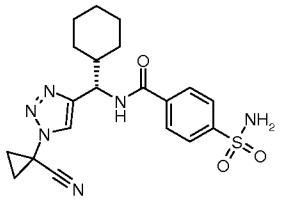
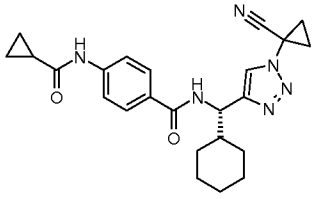
Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
96		Oxazole-4-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.78 341.17
97		Isoxazole-3-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.84 341.19
98		Oxazole-2-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.8 341.19
99		Cyclopentanecarboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.92 342.26
100		Tetrahydro-furan-2-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.82 344.21
101		Tetrahydro-furan-3-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.73 344.19
102		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-nicotinamide	E 0.72 351.72
103		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-isonicotinamide	E 0.7 351.94

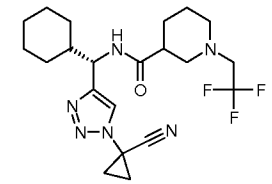
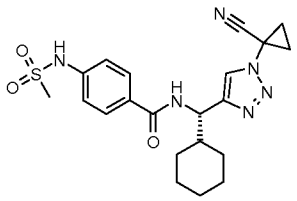
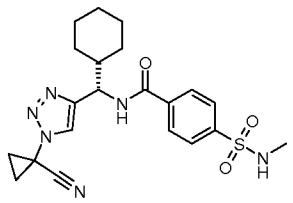
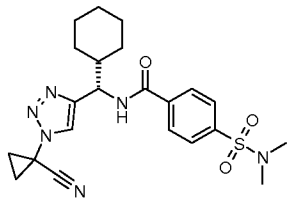
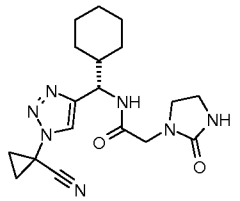
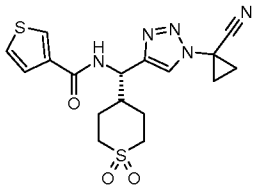
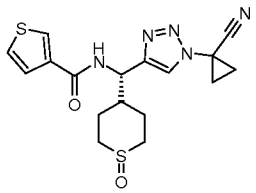
Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
104		2-Methyl-2H-pyrazole-3-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.81 354.26
105		1-Methyl-1H-pyrazole-3-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.8 354.21
106		1-Methyl-1H-imidazole-2-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.81 354.96
107		Thiophene-2-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.9 356.16
108		Isothiazole-5-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.85 357.13
109		Thiazole-4-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.84 357.16
110		Thiazole-5-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.78 357.17
111		Tetrahydro-pyran-4-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.75 358.21

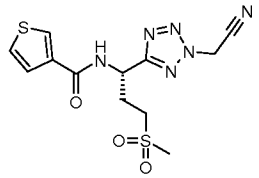
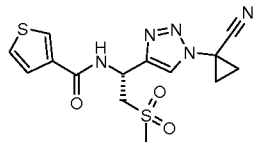
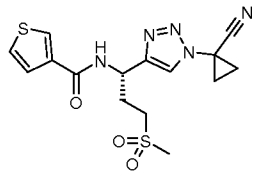
Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
112		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-3-methyl-benzamide	E 0.98 364.26
113		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-2-methyl-benzamide	E 0.94 364.07
114		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-4-methyl-benzamide	E 0.98 364.24
115		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-3-fluoro-benzamide	E 0.96 368.93
116		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-2-fluoro-benzamide	E 0.95 368.19
117		3-Cyano-N-{(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-benzamide	E 0.91 375.18
118		4-Cyano-N-{(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-benzamide	E 0.9 375.19

Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
119		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-3-methoxy-benzamide	E 0.94 380.21
120		3-Chloro-N-{(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-benzamide	E 1.02 384.18
121		4-Chloro-N-{(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-benzamide	E 1.01 384.13
122		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-3,4-difluoro-benzamide	F 1.47 386.2
123		Benzofuran-2-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 1.02 390.2
124		Pyrazolo[1,5-a]pyridine-2-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.92 390.22
125		Pyrazolo[1,5-a]pyridine-3-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.84 390.2

Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
126		Imidazo[1,2-a]pyridine-2-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	F 1.47 390.2
127		Imidazo[1,2-a]pyridine-3-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.68 390.01
128		5-Chloro-thiophene-2-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 1.03 390.11
129		Imidazo[1,2-a]pyrazine-2-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.76 391.56
130		1,1-Dioxo-tetrahydro-1lambda*6*-thiophene-3-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.71 392.16
131		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-terephthalamide	E 0.71 393.18
132		Imidazo[2,1-b]thiazole-6-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.84 396.11

Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
133		1-Acetyl-piperidine-4-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.7 399.25
134		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-N'-methyl-terephthalamide	E 0.75 407.21
135		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-N',N'-dimethyl-terephthalamide	E 0.8 421.24
136		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-4-methanesulfonyl-benzamide	E 0.81 428.17
137		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-3-methanesulfonyl-benzamide	E 0.83 428.19
138		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-4-sulfamoyl-benzamide	E 0.75 429.18
139		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-4-(cyclopropanecarbonyl-amino)-benzamide	E 0.87 433.23

Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
140		1-(2,2,2-Trifluoro-ethyl)-piperidine-3-carboxylic acid {(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-amide	E 0.96 439.59
141		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-4-methanesulfonylamino-benzamide	E 0.8 443.21
142		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-4-methylsulfamoyl-benzamide	E 0.83 443.18
143		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-4-dimethylsulfamoyl-benzamide	E 0.9 457.22
144		N-{(S)-[1-(1-Cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-cyclohexyl-methyl}-2-(2-oxo-imidazolidin-1-yl)-acetamide	E 0.64 372.21
145		Thiophene-3-carboxylic acid [(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-(1,1-dioxo-hexahydro-1λ6-thiopyran-4-yl)-methyl]-amide	A 1.19 406.2
146		Thiophene-3-carboxylic acid [(S)-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-(1-oxo-hexahydro-1λ4-thiopyran-4-yl)-methyl]-amide	B 4.01 390.2

Compound	Structure	Name	LCMS Method, RT (min), $[M+H]^+$
147		Thiophene-3-carboxylic acid [(S)-1-(2-cyanomethyl-2H-tetrazol-5-yl)-3-methanesulfonyl-propyl]-amide	C 1.12 355.2
148		Thiophene-3-carboxylic acid {(R)-1-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-2-methanesulfonyl-ethyl}-amide	F 1.14 366.3
149		Thiophene-3-carboxylic acid {(S)-1-[1-(1-cyano-cyclopropyl)-1H-[1,2,3]triazol-4-yl]-3-methanesulfonyl-propyl}-amide	F 1.16 380.2

or the pharmaceutically acceptable salts thereof.

In another aspect the invention relates to compounds – or the pharmaceutically acceptable salts – of the formula (I) as medicaments.

In another aspect the invention relates to pharmaceutical preparations, containing as active ingredient one or more compounds of the formula (I) or the pharmacologically acceptable salts thereof, optionally in combination with conventional excipients and/or carriers.

In another aspect the invention relates to the use of compounds of the formula (I) for preparing a pharmaceutical composition for the treatment of autoimmune diseases.

In another aspect the invention relates to the a method of treating autoimmune diseases by administering a therapeutically effective amount of a compound of the formula (I).

In another aspect the invention relates to a pharmaceutical preparation comprising a compound of the formula (I), while the formula (I) compounds are optionally also in the

form of the tautomers, the racemates, the enantiomers, the diastereomers, the mixtures thereof, or as pharmaceutically acceptable salts of all the above-mentioned forms.

In another aspect the invention relates to compounds of the invention which also include their isotopically-labelled forms. An isotopically-labelled form of an active agent of a combination of the present invention is identical to said active agent but for the fact that one or more atoms of said active agent have been replaced by an atom or atoms having an atomic mass or mass number different from the atomic mass or mass number of said atom which is usually found in nature. Examples of isotopes which are readily available commercially and which can be incorporated into an active agent of a combination of the present invention in accordance with well established procedures, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, *e.g.*, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

In another aspect the invention relates to the compounds of the formula (I) which may be used in combination with other active substances which are used in the treatments of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, psoriasis, atherosclerosis, and chronic obstructive pulmonary disease. Such combinations can be administered either separately or in combination in a pharmaceutical composition.

Definitions

All terms as used herein in this specification, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. Other more specific definitions are as follows:

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts

thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. For example, such salts include acetates, ascorbates, benzenesulfonates, benzoates, besylates, bicarbonates, bitartrates, bromides/hydrobromides, Ca-edetates/edetates, camsylates, carbonates, chlorides/hydrochlorides, citrates, edisylates, ethane disulfonates, estolates esylates, fumarates, gluceptates, gluconates, glutamates, glycolates, glycollylarsnilates, hexylresorcinates, hydrabamines, hydroxymaleates, hydroxynaphthoates, iodides, isothionates, lactates, lactobionates, malates, maleates, mandelates, methanesulfonates, mesylates, methylbromides, methylnitrates, methylsulfates, mucates, napsylates, nitrates, oxalates, pamoates, pantothenates, phenylacetates, phosphates/diphosphates, polygalacturonates, propionates, salicylates, stearates subacetates, succinates, sulfamides, sulfates, tannates, tartrates, teoclates, toluenesulfonates, triethiodides, ammonium, benzathines, chloroprocaines, cholines, diethanolamines, ethylenediamines, meglumines and procaines. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

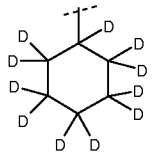
The term "C_{1-n}-alkyl", wherein n is an integer from 2 to n, either alone or in combination with another radical denotes an acyclic, saturated, branched or linear hydrocarbon radical with 1 to n C atoms. For example the term C_{1-5}-alkyl embraces the radicals H_3C-, H_3C-CH_2-, H_3C-CH_2-CH_2-, H_3C-$CH(CH_3)$-, H_3C-CH_2-CH_2-CH_2-, H_3C-CH_2-$CH(CH_3)$-, H_3C-$CH(CH_3)$-CH_2-, H_3C-$C(CH_3)_2$-, H_3C-CH_2-CH_2-CH_2-CH_2-, H_3C-CH_2-CH_2-$CH(CH_3)$-, H_3C-CH_2-$CH(CH_3)$-CH_2-, H_3C-$CH(CH_3)$-CH_2-CH_2-, H_3C-CH_2-$C(CH_3)_2$-, H_3C-$C(CH_3)_2$-CH_2-, H_3C-$CH(CH_3)$-$CH(CH_3)$- and H_3C-CH_2-$CH(CH_2CH_3)$-.

Alkoxy shall be understood to be a C_{1-n}-alkyl with an oxygen atom wherein the point of attachment is via the oxygen, for example methoxy: H_3CO-.

Acyl shall be understood to be a C_{1-n}-alkyl with an carbonyl group wherein the point of attachment is via the carbonyl, for example acetyl: $H_3CC(O)$-.

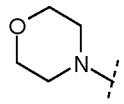
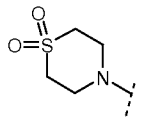
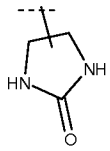
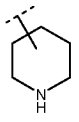
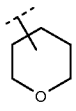
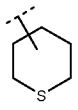
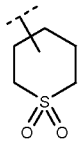
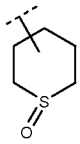
The term "C_{3-n}-cycloalkyl", wherein n is an integer 4 to n, either alone or in combination with another radical denotes a cyclic, saturated hydrocarbon radical with 3 to n C atoms. For example the term C_{3-7}-cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The structures of the above will be apparent to one skilled in the art, other specific examples include

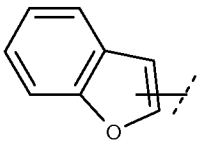
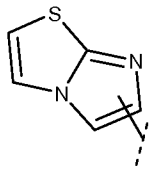
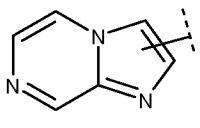
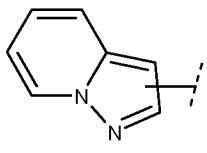
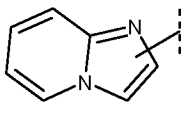
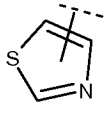
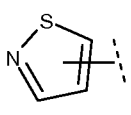
the deuterated form of cyclohexyl: cyclohexyl-D11  .

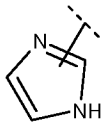
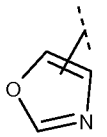
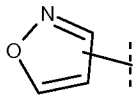
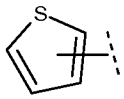
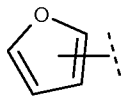
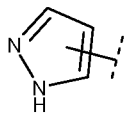
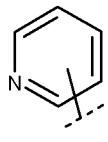
The term "aryl" as used herein, either alone or in combination with another radical, denotes a carbocyclic aromatic monocyclic group containing 6 carbon atoms which may be further fused to a second 5- or 6-membered carbocyclic group which may be aromatic, saturated or unsaturated. Aryl includes, but is not limited to, phenyl, indanyl, indenyl, naphthyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl and dihydronaphthyl. The term "aryl" is intended to include all the possible hydrogenated forms.

The term "heterocyclyl" means a saturated or unsaturated mono- or polycyclic-ring systems including aromatic ring system containing one or more heteroatoms selected from N, O or $S(O)_r$ with r=0, 1 or 2 wherein none of the heteroatoms is part of the aromatic ring. The term "heterocycle" is intended to include all the possible isomeric forms. Unless otherwise stated, heterocycles include but are not limited to, for example oxiranyl, azepanyl, diazepanyl, azetidinyl, pyrrolidinyl, pyrrolinyl, thiomorpholinyl, dioxalanyl, piperazinyl, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxanyl, piperidinonyl, tetrahydropyrimidonyl. The structures of the above will be apparent to one skilled in the art, other specific examples include

morpholinyl  , 1,1-Dioxo-1λ6-thiomorpholine  , 2-oxo-imidazolidinyl  , piperidinyl  , tetrahydropyranyl  , tetrahydrofuranyl  , tetrahydrothiopyranyl  , 1,1-dioxo-hexahydro-1λ6-thiopyranyl  , 1-oxo-hexahydro-1λ4-thiopyranyl  .

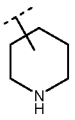
The term "heteroaryl" means a mono- or polycyclic-ring systems containing one or more heteroatoms selected from N, O or S(O)r with r =0, 1 or 2 wherein the heteroatom(s) is part of aromatic ring. The term “heteroaryl” is intended to include all the possible isomeric and hydrogenated forms. Unless otherwise stated, such heteroaryls include but are not limited to, for example: aziridinyl, thiadiazolyl, tetrazolyl, pyrrolyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyranyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzothienyl, quinolinyl, quinazolinyl, naphthyridinyl, indazolyl, triazolyl and purinyl. The structures of the above will be apparent to one skilled in the art, other specific examples include:

benzofuranyl  , imidazo[2,1-b]thiazolyl  , imidazo[1,2-a]pyrazinyl  , pyrazolo[1,5-a]pyridinyl  , imidazo[1,2-a]pyridinyl  , thiazolyl  , isothiazolyl  ,

imidazolyl  , oxazolyl  , isoxazolyl  , thienyl  , furanyl  , pyrazolyl  and pyridinyl  , and all the possible hydrogenated forms thereof.

Halogen encompasses fluorine, chlorine, bromine and/or iodine atoms.

Each of the above alkyl, cycloalkyl, aryl, heteroalkyl, heterocyclyl or heteroaryl, or any other substituent recited in this application, shall be understood to be optionally fully or partially halogenated where possible, preferably by Cl, F or Br.

Any ring structure which has shown this bond  , such bond shall be understood to be covalently attached to another moiety at the dashed line and covalently attached at any point in the ring (floating) that will replace a hydrogen atom and result in a stable bond, for example  represent piperidinyl attached at the 1, 2, 3 or 4 position.

Features and advantages of the present invention will become apparent from the following detailed Examples, which illustrate the fundamentals of the invention by way of example, without restricting its scope.

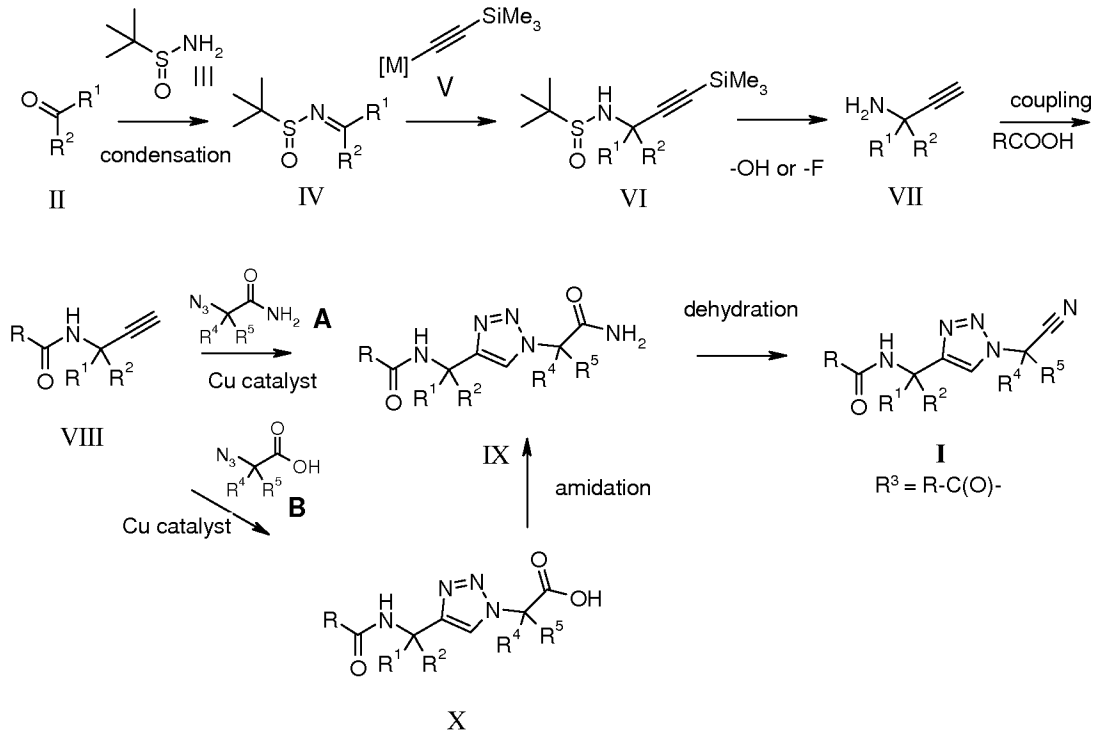
GENERAL SYNTHETIC METHODS

The invention also provides processes for making compounds of Formula (I). In all methods, unless specified otherwise, R^1, R^2, R^3, R^4, R^5 and X in the formulas below shall have the meaning of R^1, R^2, R^3, R^4, R^5 and X in Formula (I) of the invention described herein above.

Optimum reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures, and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Typically, reaction progress may be monitored by thin layer chromatography (TLC), if desired, and intermediates and products may be purified by chromatography on silica gel and/or by recrystallization.

The examples which follow are illustrative and, as recognized by one skilled in the art, particular reagents or conditions could be modified as needed for individual compounds without undue experimentation. Starting materials and intermediates used, in the methods below, are either commercially available or easily prepared from commercially available materials by those skilled in the art.

Compounds of Formula (I) may be synthesized by the method illustrated in Scheme 1

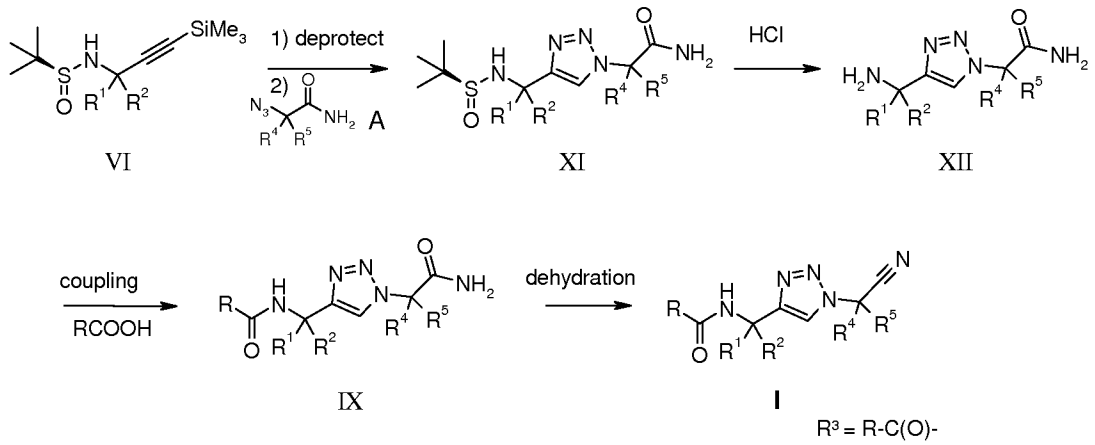


Scheme 1

As illustrated in scheme 1, reaction of a carbonyl compound of formula II with sulfinamide of formula III, in a suitable solvent, provides an imine of formula IV. Reaction of the compound of formula IV with a trimethylsilyl alkyne of formulaV, in a suitable solvent, in the presence of a suitable base , provides an alkyne of formula VI. Removal of the silyl group, under standard conditions, provides an alkyne and deprotection of the amine nitrogen provides an amino compound of the formula VII. Coupling of the free amino group in compound VII with an acid RCOOH, under standard coupling conditions, provides an amide of formula VIII. Standard peptide coupling reactions known in the art (see for example M. Bodanszky, 1984, The Practice of Peptide Synthesis, Springer-Verlag) may be employed in these syntheses. An example of suitable coupling conditions is treatment of a solution of the carboxylic acid in a suitable solvent such as DMF with EDC, HOBT, and a base such as diisopropylethylamine, followed by the desired amine. Alternatively, the acid may be converted to its corresponding acid chloride by reaction with reagents such as thionyl chloride or oxalyl chloride, the acid chloride is then reacted with a suitable amine, in a suitable solvent to provide the corresponding amide. Reaction of the alkyne of formula VIII with an azide A, in the presence of a copper catalyst, provides a triazole of formula IX. Dehydration of the triazole of formula IX under standard conditions, using standard reagents such as cyanuric chloride, provides a compound of formula (I).

Alternatively reaction of the alkyne of formula VIII with an azide B, in the presence of a copper catalyst, provides a triazole of formula X. Amidation of the acid of formula X, under standard conditions, provides a compound of formula IX which may be dehydrated to afford a compound of formula (I)

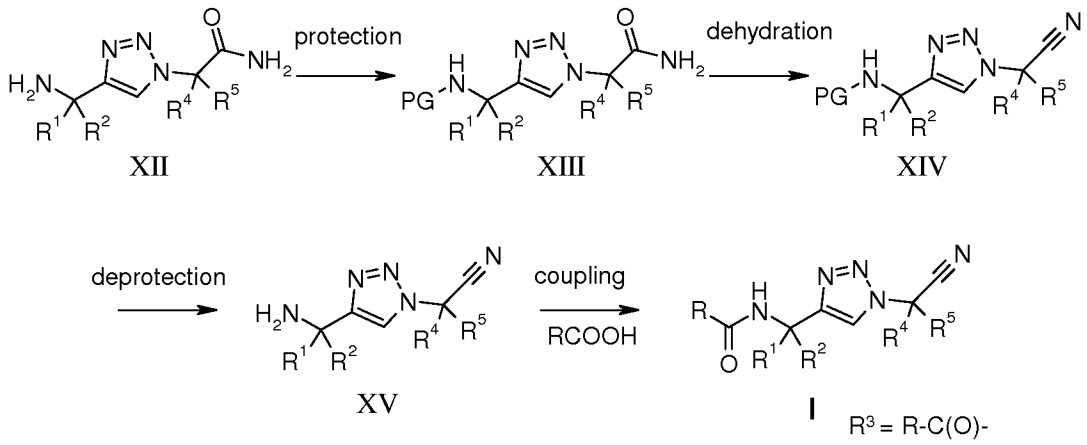
Compounds of Formula (I) may be synthesized by the method outlined in Scheme 2



Scheme 2

As outlined in scheme 2, deprotection of the alkyne of formula VI, in a suitable solvent, in the presence of a suitable base, followed by reaction with an azide A, in the presence of a copper catalyst, provides a triazole of formula XI. Reaction of triazole XI with an acid provides the free amine of formula XII. Coupling of the amine as in scheme 1, followed by dehydration, under standard conditions, provides a compound of formula (I).

Compounds of Formula (I) may also be prepared according to scheme 3.

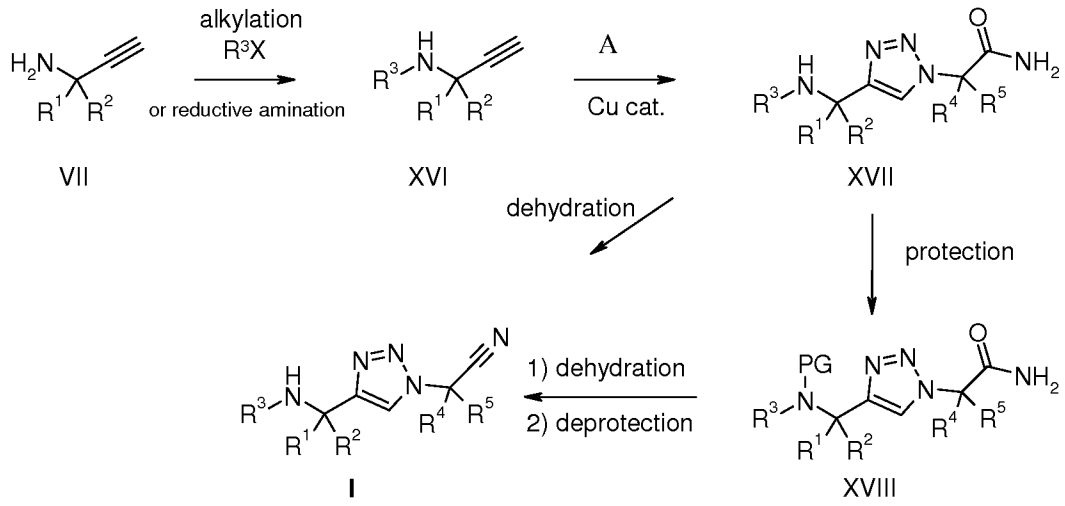


Scheme 3

As shown in scheme 3, protection of the amino group in a compound of formula XII provides the corresponding protected amine of formula XIII, wherein PG = protecting group such as BOC. Dehydration of the amide in compound XIII, provides the

corresponding nitrile of formula XIV. Deprotection of the amino group of compound XIV, under standard conditions, followed by coupling as in scheme 1, provides a compound of formula (I).

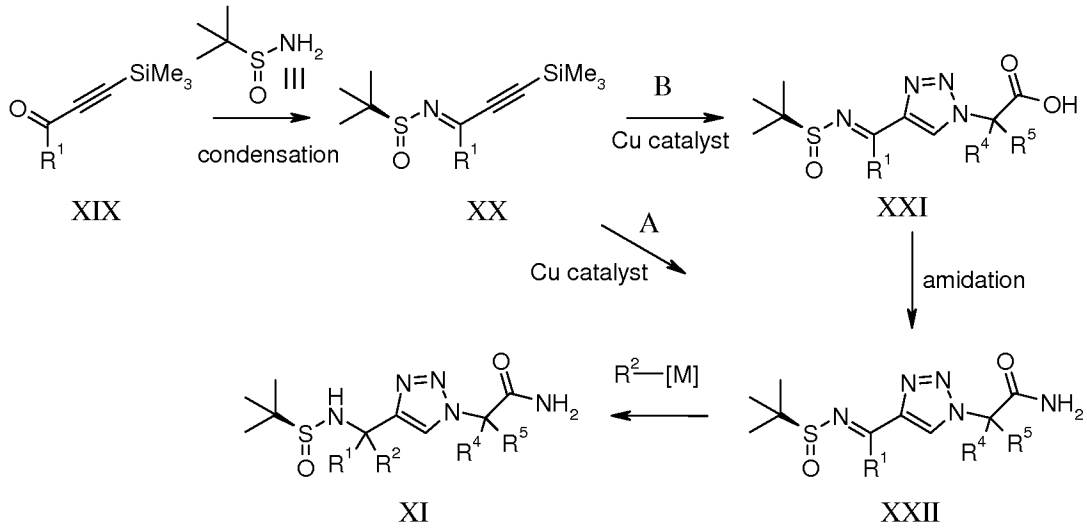
Compounds of Formula (I) may be made according to scheme 4



Scheme 4

As outlined in scheme 4, reaction of an amine of formula VII with an alkylating agent R^3X, in a suitable sovent, provides the corresponding alkylated compound of formula XVI. X = halide or –OTf. Compound XVI can alternatively be prepared by the reaction of the amine VII with a carbonyl compound R^3=O under reducing conditions. Reaction of compound XVI with azide A as in scheme 1, provides a triazole of formula XVII. Dehydration of the amide group in compound XVII, under standard conditions, provides a compound of formula (I). Alternatively, the amino group in compound XVII may be protected prior to dehydration as shown in the scheme above.

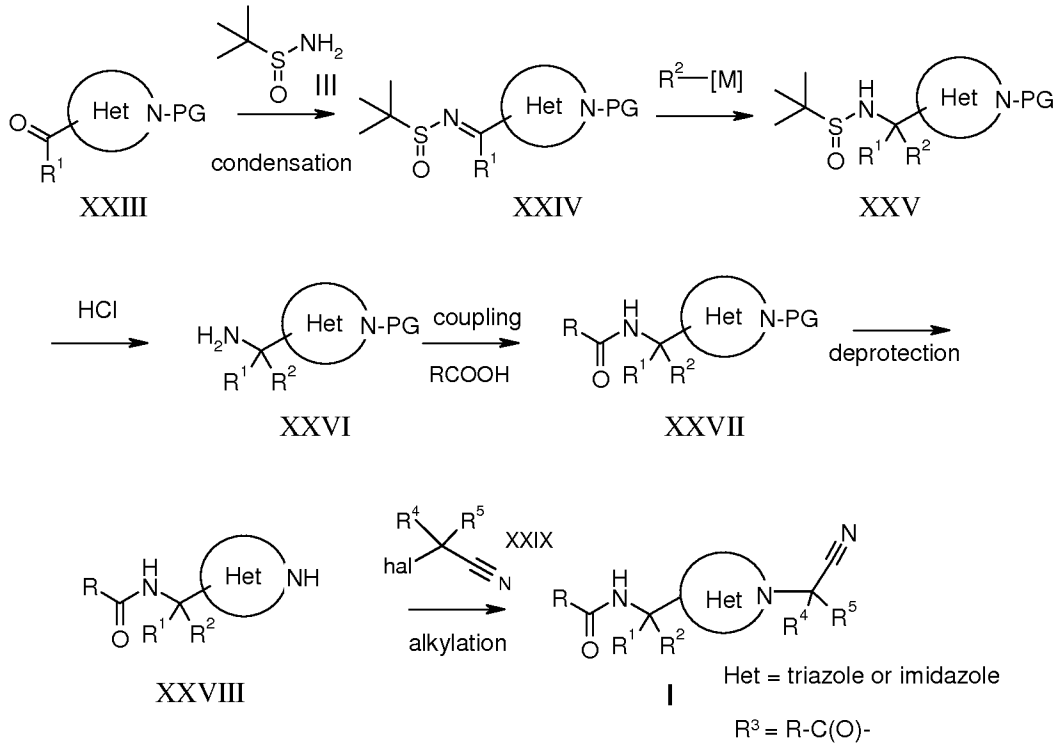
Compounds of Formula (I) may be synthesized as outlined in scheme 5



Scheme 5

As illustrated in scheme 5, reaction of a compound of formula XIX with compound III, in a suitable solvent, provides a trimethylsilyl alkyne of formula XX. Removal of the silyl group and reaction with azide A or B, in the presence of a copper catalyst, provides the corresponding triazoles XXI or XXII respectively. Compound XXI may be converted to compound XXII under standard amidation conditions known in the literature. Alkylation of compound of formula XXII with R^2-M, where M is a metal such as Li or Mg, provides a compound of formula XI which may be converted to a compound of formula (I) as outlined in scheme 2.

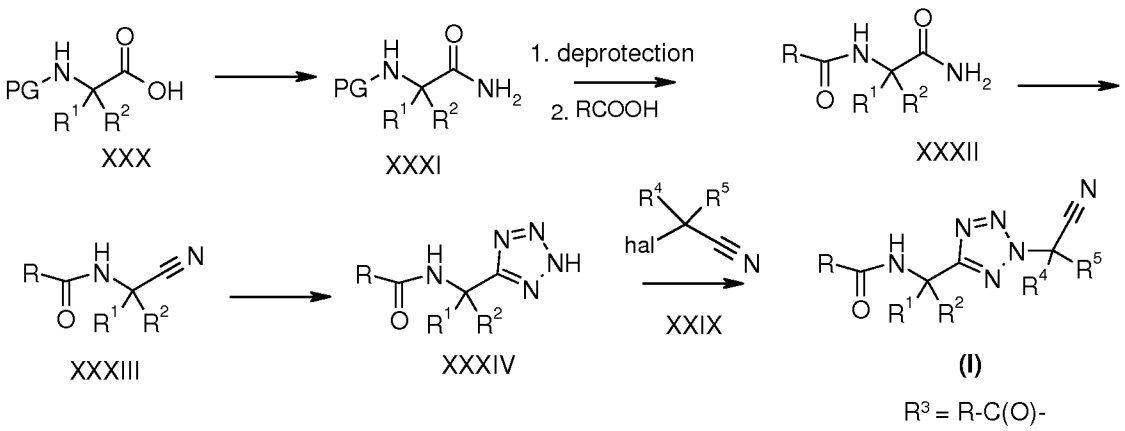
Compounds of Formula (I) may be prepared by the method outlined in scheme 6



Scheme 6

As shown in scheme 6, reaction of a compound of formula XXIII with compound III, in a suitable solvent, provides an imime of formula XXIV. Het = triazole or imidazole and PG = protecting group. Alkylation of compound of formula XXIV with R^2-M, where M is a metal such as Li or Mg, provides a compound of formula XXV. Reaction of compound XXV with an acid such as hydrochloric acid , provides the free amine of formula XXVI. Coupling of the free amine XXVI as in scheme 1, provides a compound of formula XXVIII. Deprotection of the amine nitrogen followed by alkylation with an appropriate alkylating agent XXIX, provides a compound of formula (I).

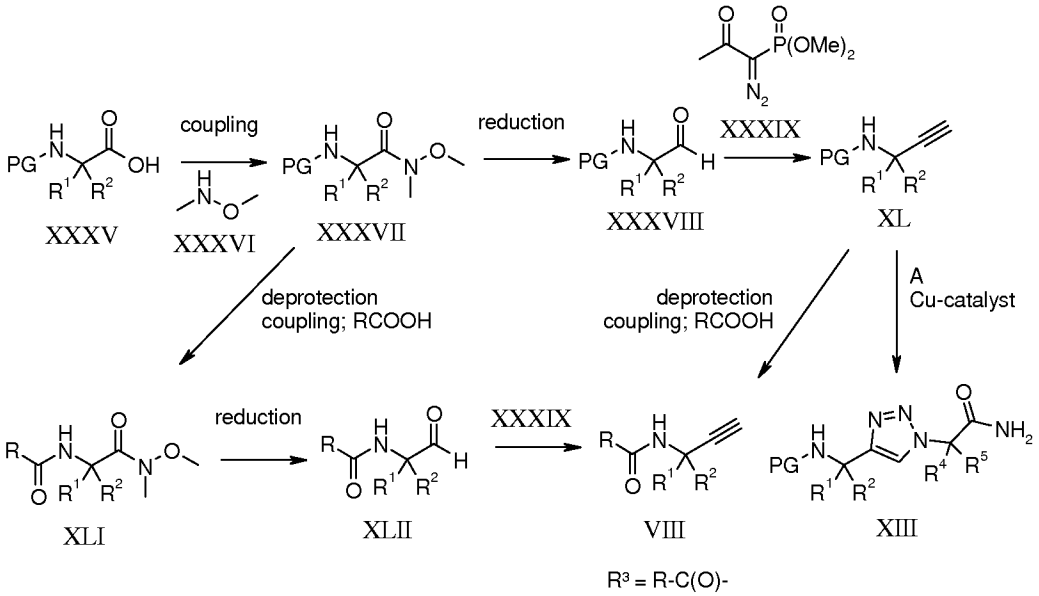
Compounds of Formula (I) may be made by the method shown in scheme 7.



Scheme 7

As illustrated in scheme 7, amidation of an N-protected amino acid of formula XXX provides an amide of formula XXXI. PG is an amine protecting group such as BOC. Deprotection of the amine under standard reaction conditions followed by coupling of the free amine with an acid RCOOH or its corresponding acid chloride provides a coupled product of formula XXXII. Dehydration of the amide group of compound XXXII, provides a nitrile of formula XXXIII. Reaction of nitrile XXXIII with sodium azide, in a suitable solvent, provides the tetrazole of formula XXXIV. Alkylation of the tetrazole with an alkylating agent of formula XXIX, in suitable solvent, provides a compound of formula (I)

Compounds of Formula (I) may be made by the method shown in scheme 8.



Scheme 8

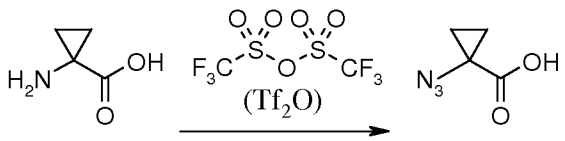
As illustrated in Scheme 8, amino aldehydes of formula XXXVIII can be prepared from protected amino acids of formula XXXV by first coupling with amine XXXVI under standard conditions followed by reduction using a reducing agent such as diisobutylaluminum hydride. Reaction of the aldehyde of formula XXXVIII with the Ohira-Bestman reagent XXXIX in standard solvents and in the presence of a base such as K_2CO_3, provides an alkyne of formula XL. Deprotection of the amino group in XL, under standard conditions, followed by standard coupling with an acid RCOOH provides a compound of formula VIII, which can be transformed into a compound of formula (I) as illustrated in Scheme 1. The compound of formula XL can react with an azide A in the presence of a copper catalyst to provide a compound of structure XIII (Scheme 3). Alternatively, the amides of formula XLI may be similarly reduced to XLII and then reacted with XXXIX to provide compounds of formula VIII. Amides of structure XLI can be prepared, for example from XXXVII via standard deprotection followed by coupling with RCOOH.

Further modification of the initial product of formula (I) by methods known in the art and illustrated in the Examples below, may be used to prepare additional compounds of this invention.

Examples:

The following intermediates are used in the preparation of the Examples.

Synthesis of I-001

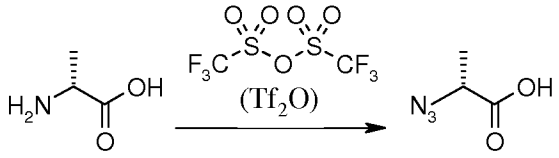


(ACPC) I-001

Tf_2O (3.3 mL, 20 mmol) is added to a mixture of NaN_3 (6.33 g, 97.3 mmol), H_2O (16 mL), and CH_2Cl_2 (26 mL) at 0 C. The mixture is stirred at 0 C for 2h, then the layers are separated. The aqueous layer is extracted with CH_2Cl_2 (2 x 15 mL). The combined extracts are washed with saturated aqueous Na_2CO_3, then added to a stirring mixture of ACPC (1.0 mg, 9.9 mmol), K_2CO_3 (2.05 g, 14.8 mmol), $CuSO_4 \cdot 5H_2O$ (24 mg), H_2O (30 mL), and methanol (50 mL). The resulting mixture is stirred for 16 h, then evaporated, diluted with H_2O (150 mL), and concentrated HCl is added until the pH reaches 6. Phosphate buffer (pH 7, 150 mL) is added, and the mixture is washed with EtOAc (3 x

100 mL). Concentrated HCl is added to until the pH reaches 2. The mixture is extracted with EtOAc (3 x 150 mL). The extracts are combined, dried over Na_2SO_4, filtered, and concentrated to provide **I-001** as an oil.

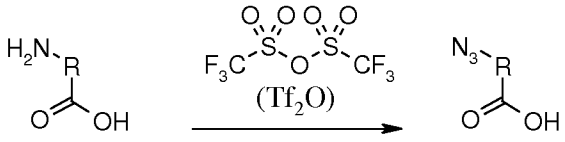
Synthesis of I-002



D-Ala I-002

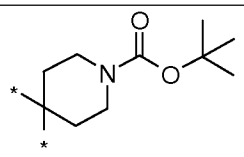
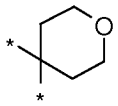
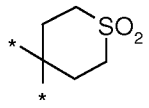
Tf_2O (2.78 mL, 16.7 mmol) is added to a mixture of NaN_3 (5.35 g, 82.4 mmol), H_2O (14 mL), and CH_2Cl_2 (22 mL) at 0 C. The mixture is stirred at 0 C for 2h, then the layers are separated. The aqueous layer is extracted with CH_2Cl_2 (2 x 10 mL). The combined extracts are washed with saturated aqueous Na_2CO_3, then added to a stirring mixture of D-Ala (745 mg, 8.37 mmol), K_2CO_3 (1.74 g, 12.6 mmol), $CuSO_4 \cdot 5H_2O$ (21 mg), H_2O (27 mL), and MeOHl (45 mL). The resulting mixture is stirred for 16 h, then evaporated, and diluted with H_2O (50 mL). Concentrated HCl is added until the pH is 6. Phosphate buffer (pH 7, 50 mL) is added, and the mixture is washed with EtOAc (3 x 25 mL). The aqueous layer is acidified to pH 2 with concentrated HCl, and extracted with EtOAc (3 x 30 mL). The extracts are combined, dried over Na_2SO_4, filtered, and concentrated to provide **I-002** as an oil.

The following azides are prepared from the appropriate amino acid in the same manner as **I-001** and **I-002**.

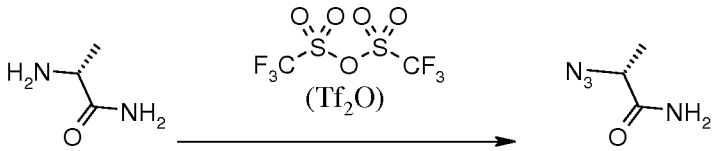


amino acid azido acid

Azido Acid	R

I-003	
I-004	
I-006	

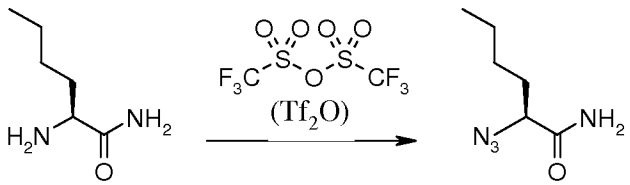
Synthesis of I-007



D-Ala-NH_2 I-007

Tf_2O (12 mL, 71 mmol) is added to a mixture of NaN_3 (23 g, 350 mmol), H_2O (100 mL), and CH_2Cl_2 (200 mL) at 0 C. The mixture is stirred at 0 C for 2h, then the layers are separated. The aqueous layer is extracted with CH_2Cl_2 (2 x 50 mL). The combined extracts are added to a stirring mixture of D-Ala-NH_2 (4.4 g, 35 mmol), K_2CO_3 (7.3 g, 53 mmol), 0.3 M $CuSO_4 \cdot 5H_2O$ (1.2 mL, 0.35 mmol), H_2O (200 mL), and MeOH (400 mL). The resulting mixture is stirred for 16 h, then evaporated, and diluted with H_2O (50 mL). The mixture is concentrated, H_2O (100 mL) is added, and the mixture is extracted with EtOAc (3 x 100 mL). The extracts are combined, washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated to provide **I-007** as a solid.

Synthesis of I-009

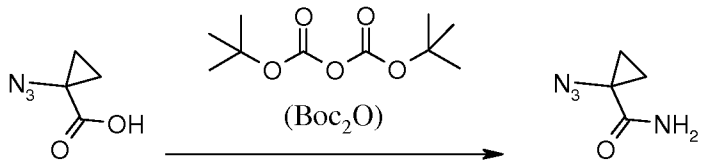


I-008 I-009

Tf_2O (5.0 mL, 30 mmol) is added to a mixture of NaN_3 (10 g, 160 mmol), H_2O (20 mL), and CH_2Cl_2 (20 mL) at 0 C. The mixture is stirred at 0 C for 2h, then the layers are

separated. The aqueous layer is extracted with CH_2Cl_2 (2 x 20 mL). The combined extracts are washed with saturated Na_2CO_3, then added to a stirring mixture of **I-008** (2.0 g, 15 mmol), K_2CO_3 (33 g, 240 mmol), $CuSO_4 \cdot 5H_2O$ (40 mg, 0.163 mmol), H_2O (40 mL), and MeOH (80 mL). The resulting mixture is stirred for 16 h, then evaporated to 60 mL and extracted with EtOAc (2 x 70 mL). The extracts are combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated to provide **I-009**.

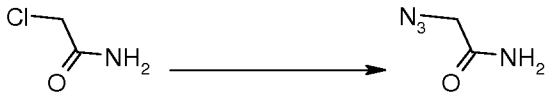
Synthesis of I-010



I-001 I-010

Boc_2O (11.5 g, 52.7 mmol) is added to **I-001** (7.92 mg, 49.9 mmol), pyridine (2.5 mL, 31 mmol), $(NH_4)HCO_3$ (4.75 g, 60.1 mmol), and MeCN (50 mL). The mixture is stirred for 16 h, then concentrated by half, diluted with EtOAc (40 mL), washed with H_2O (20 mL), $NaHCO_3$ (20 mL), and brine (20 mL). The washes are extracted with EtOAc (40 mL), the extracts are combined, dried over Na_2SO_4, filtered, and concentrated. The product is recrystallized from iPrOH to provide **I-010** as a solid.

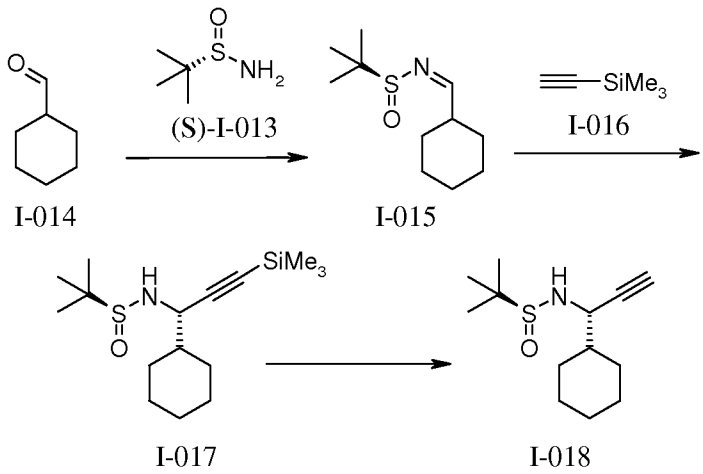
Synthesis of I-012



I-011 I-012

I-011 (2.0 g, 21.4 mmol), NaN_3 (7.0 g, 110 mmol), Bu_4NI (0.79 g, 2.1 mmol), and DMF (30 mL) are stirred at 50 °C for 6h, then at rt for 72 h. This mixture is combined with EtOAc (25 mL) and H_2O (25 mL). The extract is washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to provide **I-012** in a mixture with **I-011**.

Synthesis of I-018

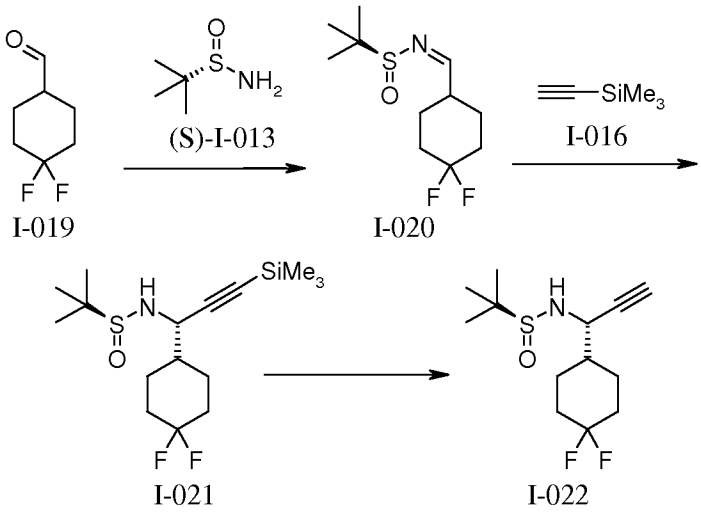


(S)-I-013 (8.0 g, 66 mmol) and $Ti(OEt)_4$ (28 mL, 230 mmol) are added to **I-014** (8.8 mL, 73 mmol) and CH_2Cl_2 (100 mL). The mixture is stirred overnight, then poured over a stirring mixture of celite (150 g), H_2O (90 mL), and CH_2Cl_2 (60 mL). The mixture is shaken, then filtered, and the solids washed with CH_2Cl_2 (600 mL). The filtrate is washed with brine (60 mL), dried over $MgSO_4$, filtered, and concentrated to provide **I-015** as an oil.

1.67 M BuLi in hexane (77 mL, 120 mmol) is added to **I-016** (19 mL, 140 mmol) and toluene (100 mL) at -78 C. The mixture is stirred for 15 min, and a -78 C mixture of Me_3Al (34 mL, 67 mmol), **I-015** (14 g, 61 mmol), and toluene (100 mL) prepared at -78 C is added. The resulting mixture is stirred at -78 C for 2h, then is poured over a stirring mixture of celite (30 g), $NaHCO_3$ (20 mL), H_2O (10 mL), and EtOAc (240 mL). The mixture is stirred for 20 min, dried with $MgSO_4$, then filtered, washed with EtOAc, concentrated, and purified by silica chromatography (5-50% EtOAc in heptane gradient) to provide **I-017** as an oil.

4 M NaOH in H_2O (11 mL, 44 mmol) is added to **I-017** (15 g, 42 mmol) and MeOH (50 mL). The resulting mixture is stirred overnight, and EtOAc (40 mL) is added and stirred for 4 h. EtOAc is added (80 mL), and the mixture is washed with half saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to provide **I-018** as a solid.

Synthesis of I-022

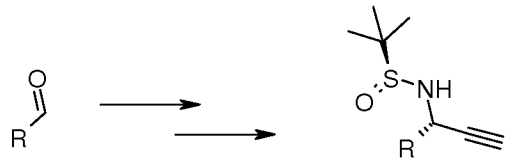


(S)-I-013 (1.1 g, 8.8 mmol), $Ti(OiPr)_4$ (4.0 mL, 14 mmol), **I-019** (1.0 g, 6.8 mmol; Evans, K. *et al.*, US patent application US2007/0249670, 2007) and THF (100 mL) are stirred at 60 C for 12 h. The mixture is poured over stirring saturated aqueous $NaHCO_3$ (130 mL), and filtered through celite. The filtrate is washed with brine, dried over $MgSO_4$, and purified by silica chromatography (0-60% MTBE in heptane) to provide **I-020** as an oil.

1.67 M BuLi in hexane (0.87 mL, 2.2 mmol) is added to **I-016** (0.26 mL, 1.0 mmol) and toluene (30 mL) at -78 C. The mixture is stirred for 15 min, and a -78 C mixture of 2.0 Me_3Al in toluene (0.57 mL, 1.1 mmol), **I-020** (0.26 g, 1.0 mmol), and toluene (30 mL) prepared at -78 C is added. The mixture is stirred for 2 h at -78 C and 4 h at rt. Saturated aqueous Na_2SO_4 (25 mL) is added, and the mixture is extracted by EtOAc (3 x 75 mL). The extracts are combined, washed with brine, dried over $MgSO_4$ filtered, and concentrated to provide **I-021** as an oil.

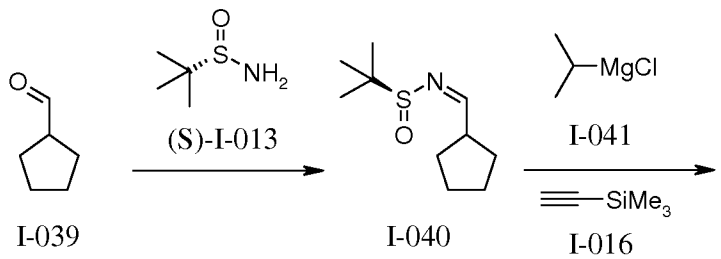
4 M NaOH in H_2O (0.26 mL, 1.0 mmol) is added to **I-021** (0.36 g, 1.0 mmol) and MeOH (2 mL). The resulting mixture is stirred for 2 h. Saturated aqueous NH_4Cl (20 mL) is added, and the mixture is extracted with EtOAc (2 x 20 mL). The extracts are combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide **I-022** as an oil.

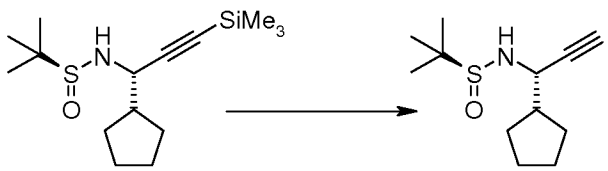
The following intermediates are prepared from the corresponding aldehydes in the same manner as **I-018** and **I-022**.



Intermediate	R
I-023	cyclohexylmethyl
I-024	tetrahydropyran-2-yl
I-025	tetrahydropyran-3-yl
I-026	tetrahydropyran-4-yl
I-027	cyclopropyl
I-028	*N*-Cbz-piperidin-3-yl
I-029	benzyl
I-030	cyclohexan-D11-yl
I-031	2-phenylethyl
I-032	3-methoxycyclohexyl
I-033	*trans*-(4-CF_3)-cyclohexyl
I-034	t-butyl
I-035	isobutyl
I-036	3-pentyl
I-037	sec-butyl
I-038	thiocyclohexan-4-yl

Synthesis of I-043



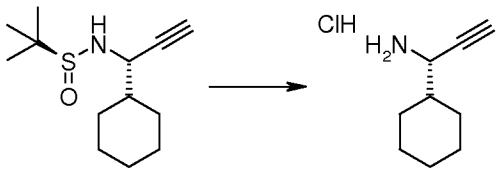


(S)-I-013 (0.5 g, 4.9 mmol) and $Ti(OEt)_4$ (1.8 mL, 8.7 mmol) are added to **I-039** (0.60 mL, 4.9 mmol) and $ClCH_2CH_2Cl$ (100mL). The mixture is stirred for 2h at 60 C, then poured over a stirring mixture of celite (30 mL) and H_2O (10 mL). The mixture is stirred for 30 min, filtered through $MgSO_4$, and concentrated to provide **I-040** as an oil.

I-016 (1.3 mL, 9.3 mmol) is added to 2.0 M **I-041** in Et_2O (4.1 mL) at 0 C and stirred for 4h at rt. The resulting mixture is added to stirring **I-040** (0.83 g, 4.1 mmol) and CH_2Cl_2 (20 mL) at -48 C. The mixture warms to rt, and is stirred for 5 days. H_2O (5 mL) and saturated aqueous NH_4Cl (5 mL) are added. The organic phase is separated, washed with brine, dried over $MgSO_4$, filtered, concentrated, and purifed by silica chromatography (5-50% EtOAc in heptane) to provide **I-042** as an oil.

4 M NaOH in H_2O (0.56 mL, 2.2 mmol) is added to **I-042** (0.64 g, 2.1 mmol) in MeOH (2 mL). The resulting mixture is stirred for 2h. EtOAc (10 mL) is added and the mixture stirred for 14 h. The mixture is washed with half saturated $NaHCO_3$ (5 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to provide **I-043** as an oil.

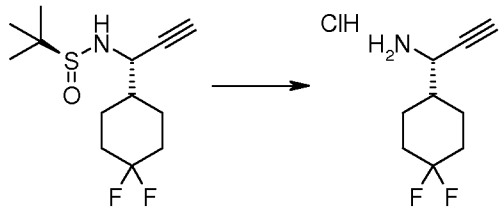
Synthesis of I-044



I-018 I-044

4M HCl in dioxane (11 mL, 44 mmol) is added to **I-018** (5.3 g, 20 mmol) and MeOH (44 mL). The mixture is stirred at 0 C for 2 h, then concentrated, and stirred in 10:1 MTBE/iPrOH (22 mL) for 30 min. The mixture is filtered, and the solids washed with MTBE and dried to provide **I-044**.

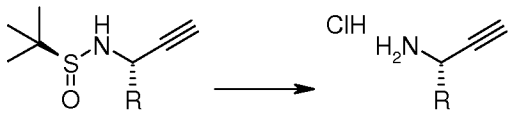
Synthesis of I-045



I-020 I-042

4M HCl in dioxane (3 mL, 12 mmol) is added to **I-022** (0.31 g, 1.1 mmol) and MeOH (10 mL). The mixture is stirred for 2 h, then concentrated, and washed with Et_2O to provide **I-045** as a solid.

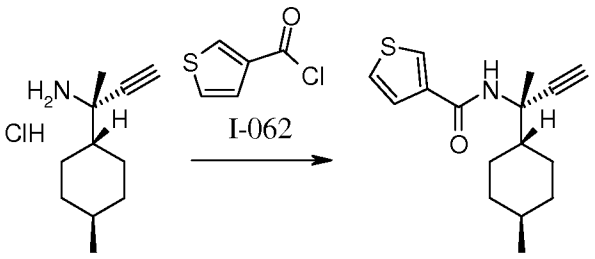
The following intermediates are prepared from the corresponding sulfinamides in the same manner as **I-044** and **I-045**.



sulfinamide pdt (intermediate)

Intermediate	Sulfinamide	R
I-046	**I-025**	tetrahydropyran-3-yl
I-047	**I-023**	cylcohexylmethyl
I-048	**I-030**	cyclohexy-D11-yl
I-049	**I-034**	t-butyl
I-050	**I-035**	isobutyl
I-051	**I-043**	cyclopentyl
I-052	**I-032**	3-methoxylcyclohexyl
I-053	**I-033**	4-CF_3-cyclohexyl
I-054	**I-031**	2-phenylethyl
I-055	**I-028**	*N*-Cbz-piperidin-3-yl
I-056	**I-029**	benzyl
I-057	**I-024**	tetrahydropyran-3-yl
I-058	**I-026**	tetrahydropyran-4-yl
I-059	**I-027**	cyclopropyl
I-060	**I-036**	3-pentyl
I-061	**I-037**	sec-butyl

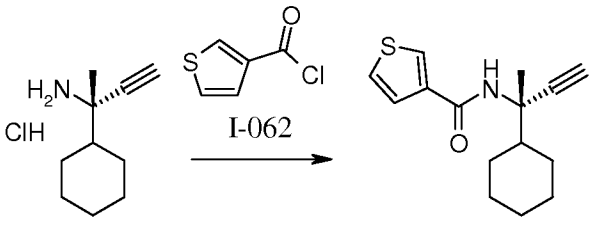
Synthesis of I-064



I-063 I-064

I-062 (0.80 g, 5.5 mmol) and THF (3 mL) is added to **I-063** (1.0 g, 5.0 mmol; Patterson, A. W., *et al.*, *J. Med. Chem.*, **2006**, *49*, 6298.), Et_3N (1.5 mL, 11 mmol), and THF (10 mL). The mixture is stirred for 16h, then filtered through celite, concentrated, and purified by silica chromatography (10-60% EtOAc in heptane gradient) to provide **I-064** as a solid.

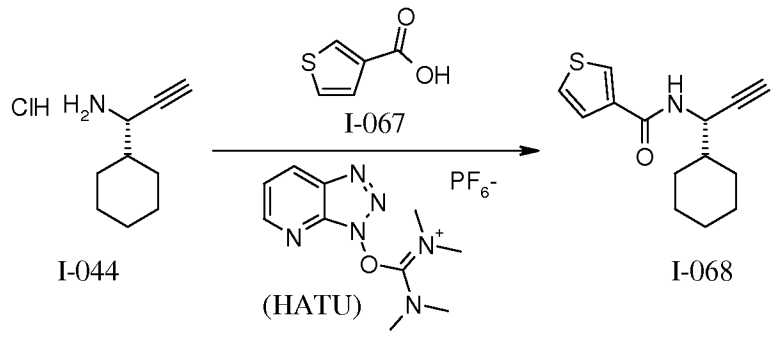
Synthesis of I-066



I-065 I-066

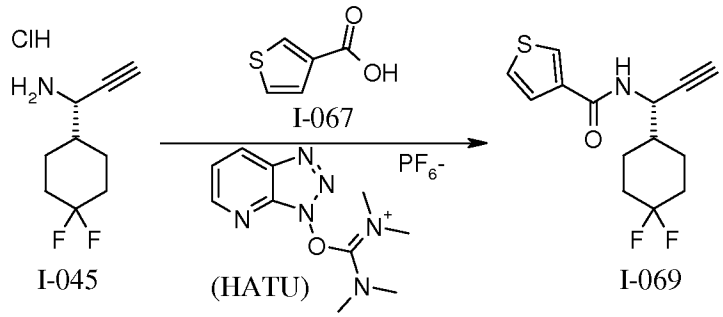
I-062 (0.80 g, 5.5 mmol) and THF (3 mL) is added to **I-065** (1.0 g, 5.0 mmol; Patterson, A. W., *et al.*, *J. Med. Chem.*, **2006**, *49*, 6298.), Et_3N (1.5 mL, 11 mmol), and THF (10 mL). The mixture is stirred for 16h, then filtered through celite, concentrated, and purified by silica chromatography (10-60% EtOAc in heptane gradient) to provide **I-066** as a solid.

Synthesis of I-068



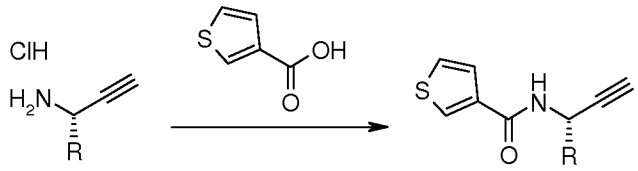
HATU (1.36 g, 3.6 mmol) is added to **I-044** (560 mg, 3.3 mmol), **I-067** (1.4 g, 3.6 mmol), Et_3N (4.5 mL, 32 mmol), and THF (16 mL). The resulting mixture is stirred for 16 h, then concentrated and purified by silica chromatography (5-60% EtOAc in heptane gradient) to provide **I-068** as a solid.

Synthesis of I-069



HATU (0.43 g, 1.1 mmol) and **I-045** (0.21 g, 1.0 mmol) are added to **I-067** (0.14 g, 1.1 mmol), Et_3N (0.71 mL, 5 mmol), and DMF (3 mL). The resulting mixture is stirred for 2 h, then directly purified by C18 semi-preparative HPLC (5-95% MeCN in H_2O gradient with 0.1% TFA) provide **I-069** as a solid.

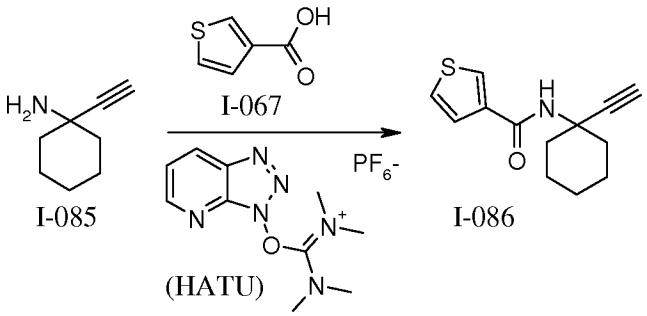
The following intermediates are prepared from the appropriate propargylamine in the same manner as **I-068** and **I-069**.



Intermediate	amine	R

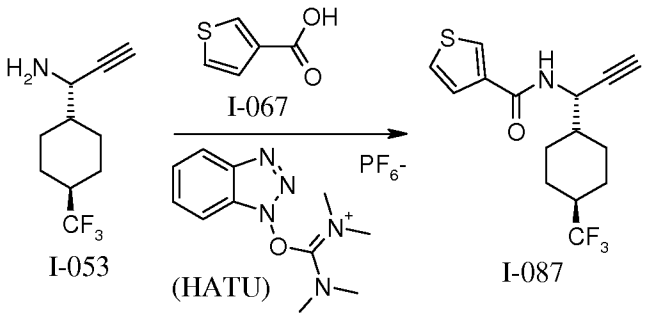
Intermediate	amine	R
I-070	**I-047**	cyclohexylmethyl
I-071	**I-048**	cyclohexan-D11-yl
I-072	**I-049**	t-butyl
I-073	**I-051**	cyclopentyl
I-074	**I-057**	tetrahydropyran-2-yl
I-075	**I-046**	tetrahydropyran-3-y
I-076	**I-058**	tetrahydropyran-4-yl
I-077	**I-052**	3-methoxycyclohexyl
I-078	**I-050**	isobutyl
I-079	**I-054**	2-phenylethyl
I-080	**I-055**	*N*-Cbz-piperidin-3-yl
I-081	**I-056**	benzyl
I-082	**I-059**	cyclopropyl
I-083	**I-060**	3-pentyl
I-084	**I-061**	sec-butyl

Synthesis of I-086



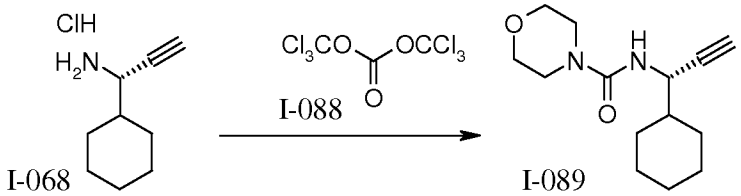
HATU (2.0 g, 5.4 mmol) and Et_3N (2.0 mL, 3.0 mmol) are added to **I-085** (0.60 g, 4.9 mmol), **I-067** (0.69 g, 5.4 mmol), and THF (24 mL). The mixture is stirred for 16 h, concentrated, and purified by silica chromatography (5-60% EtOAc in heptane gradient) to provide **I-086** as a solid.

Synthesis of I-087



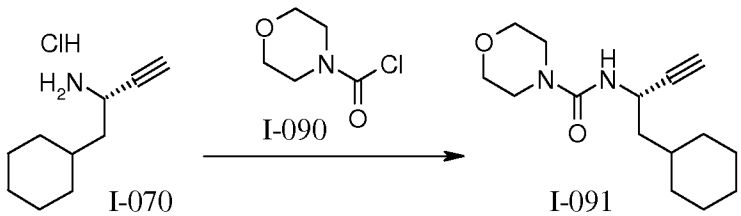
TBTU (0.37 g, 1.1 mmol) and Et_3N (0.43 mL, 3.1 mmol) are added to **I-053** (0.25 g, 1.0 mmol), **I-067** (0.15 g, 1.1 mmol), and DMF (3 mL). The mixture is stirred for 16 h, mixed with EtOAc, and washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated to provide **I-087**.

Synthesis of I-089



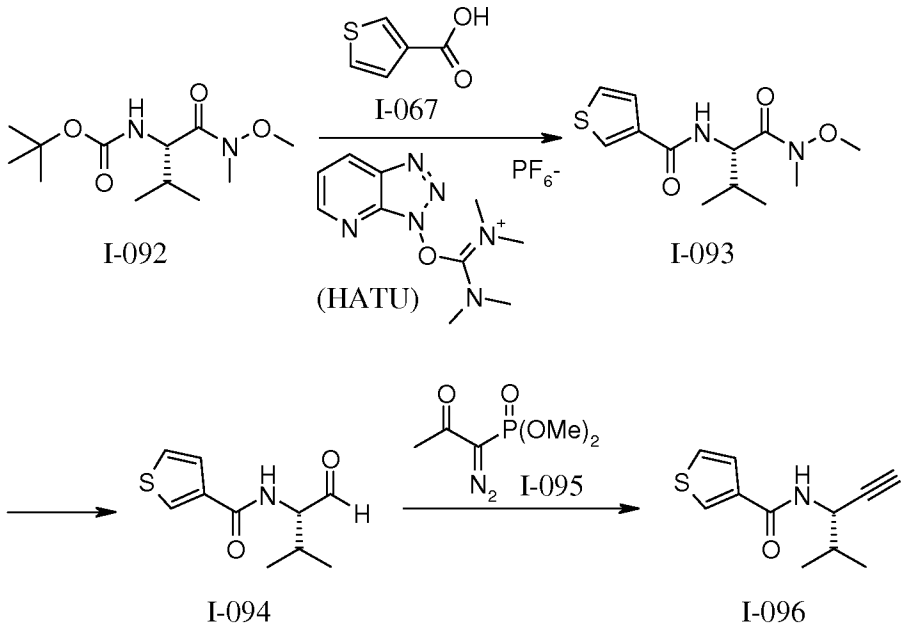
I-088 (0.33 g, 1.1 mmol) and CH_2Cl_2 (10 mL) are added to **I-068** (0.50 g, 2.9 mmol), iPr_2NEt (2.0 mL, 12 mmol), and CH_2Cl_2 (5 mL). The mixture is stirred for 10 min and morpholine (0.32 mg, 3.7 mmol) is added. After 12 h, EtOAc (40 mL) is added. The mixture is washed with brine, dried over Na_2SO_4, filtered, concentrated and purified first by silica chromatography (2-10% MeOH in CH_2Cl_2 gradient), then by C18 semi-preparative HPLC (5-95% MeCN in H_2O gradient with 0.1% TFA) provide **I-089** as a solid.

Synthesis of I-091



I-090 (87 mg, 0.59 mmol) is added to **I-070** (0.10 g, 0.53 mmol), Et_3N (0.37 mL, 2.7 mmol), and DMF (3 mL). The mixture is stirred for 2 h and concentrated to provide **I-091** as an oil.

Synthesis of I-096



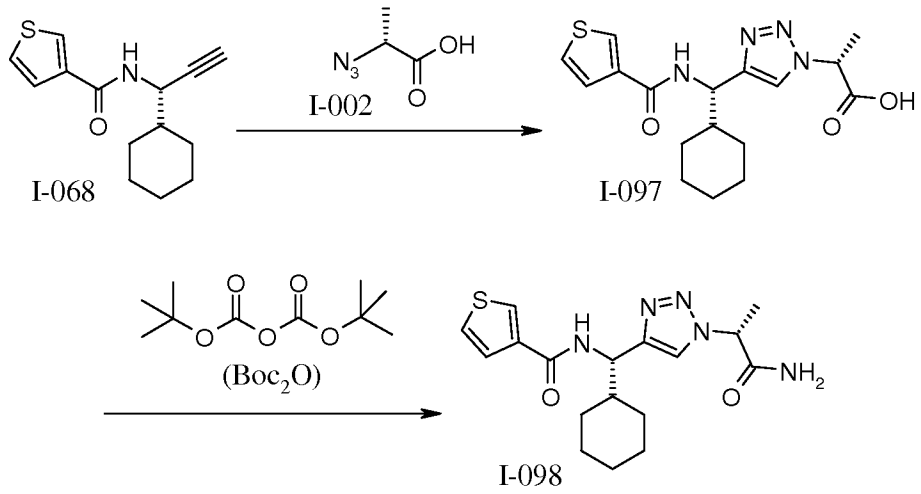
4.0 M HCl in dioxane (5.0 mL, 20 mmol) is added to **I-092** (0.84 g, 3.2 mmol). The mixture is stirred for 12 h, then concentrated. THF (12 ml), Et_3N (1.8 mL, 13 mmol), **I-067** (0.41 g, 3.2 mmol), and HATU (1.8 g, 4.8 mmol) are added. The mixture is stirred for 12 h. EtOAc (20 mL) is added and the mixture is washed with $NaHCO_3$ (10 mL). Th wash is extracted with EtOAc (10 mL), and the extracts are combined, washed with $NaHCO_3$ (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered, concentrated, and purified by silica chromatography (30-70% EtOAc in heptane gradient) to provide **I-093** as an oil.

1.0 M (iBu)$_2$AlH (3.3 mL, 3.3 mmol) is added dropwise to **I-093** (0.41 g, 1.5 mmol) and CH_2Cl_2 (10 mL) at -78 C. The mixture is stirred at -78 C for 40 min, MeOH (3.5 mL) is added, and the mixture is warmed to rt. The mixture is stirred for 15 min with celite (0.84 g) wet with water (0.33 mL) and 1 M $NaHSO_4$ (0.33 mL) and additional CH_2Cl_2 (4 mL). The mixture is filtered, and the filtrate is dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (20-66% EtOAc in heptane gradient) to provide **I-094** as an oil.

I-095 (0.12 g, 0.63 mmol) is added to **I-094** (65 mg, 0.31 mmol), K_2CO_3 (0.13 g, 0.94 mmol), and MeOH (5 mL) at 0 C. The mixture is stirred for 14 h and concentrated.

EtOAc (50 mL) is added, and the mixture is washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (5-50% EtOAc in heptane gradient) to provide **I-096** as a solid.

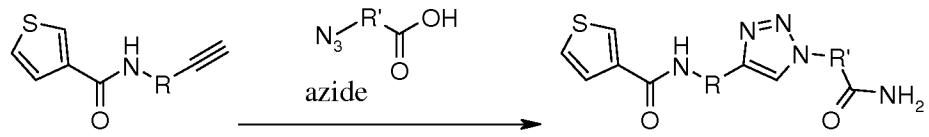
Synthesis of I-098

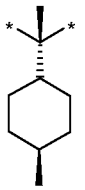
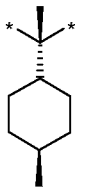
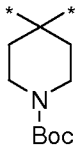
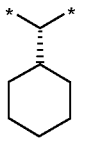
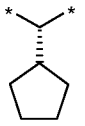


iPr_2NEt (0.33 mL, 1.9 mmol) and CuI (550 mg, 2.9 mmol) are added to **I-068** (240 mg, 0.96 mmol), **I-002** (130 mg, 1.1 mmol), and THF (30 mL). The mixture is stirred for 72 h, then concentrated, diluted with EtOAc (200 mL), and washed with saturated aqueous NH_4Cl (2 x 100 mL), and H_2O (2 x 100 mL). The organic layer is extracted with saturated aqueous $NaHCO_3$ (3 x 100 mL), and concentrated HCl is added until the pH reaches 2. The resulting mixture is extracted with EtOAc (3 x 100 mL). Extracts are combined, dried over $MgSO_4$, filtered, and concentrated to provide **I-097** as a solid.

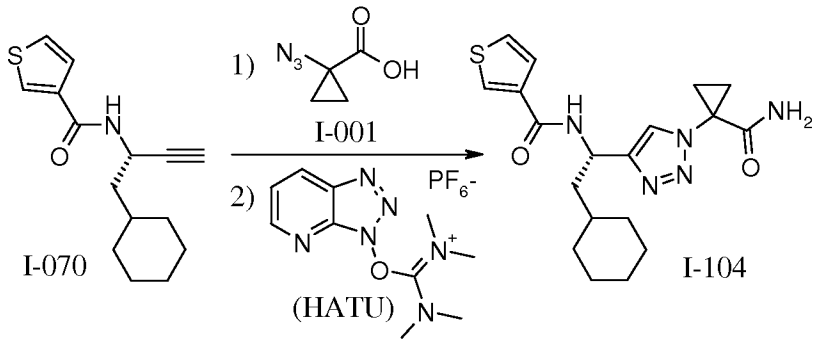
Boc_2O (270 mg, 1.2 mmol) and MeCN (0.5 mL) is added to **I-097** (350 mg, 0.95 mmol), pyridine (47 µL, 0.57 mmol), $(NH_4)HCO_3$ (91 mg, 1.2 mmol), and MeCN (1.5 mL). The mixture is stirred for 16 h, Boc_2O (270 mg, 1.2 mmol) is added again, the mixture is stirred for 16 h, then concentrated and purified by silica chromatography (twice by 5-20% MeOH in CH_2Cl_2 gradient) to provide **I-098** as a solid.

The following intermediates are prepared from the appropriate alkynes and azides in the same manner as **I-098**.



Intermediate	Alkyne	Azide	R	R'
I-099	**I-064**	**I-001**		
I-100	**I-064**	**I-003**		
I-101	**I-068**	**I-102** (Patterson, A. W., 2006)		
I-103	**I-073**	**I-001**		

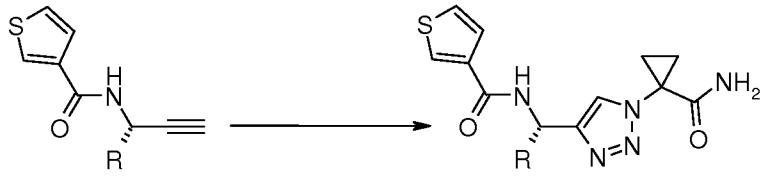
Synthesis of I-104



Sodium ascorbate (0.16 g, 0.81 mmol) in H_2O (0.4 mL) is added to a stirring mixture of **I-070** (0.21 g, 0.81 mmol), **I-001** (0.10 g, 0.79 mmol), 0.5 M $CuSO_4$ (0.16 mL, 0.08 mmol), 2M NaOH (0.20 mL, 0.80 mmol), and EtOH (3 mL). The mixture is stirred for

16 h and diluted with H_2O (10 mL). 2N HCl is added until the pH falls between 4 and 5, and the mixture is extracted with EtOAc (2 x 15 mL). The extracts are combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide a solid. This solid is combined with HATU (0.33 g, 0.86 mmol), DMF (2 mL), and NH_3 is bubbled through for 5 minutes. The resulting mixture is stirred for 1 h, diluted with EtOAc (20 mL), washed with brine. The extract is dried over $MgSO_4$, filtered, concentrated, and purified by C18 semi-preparative HPLC (5-90% MeCN in H_2O gradient with 0.1% TFA) to provide **I-104** as a solid.

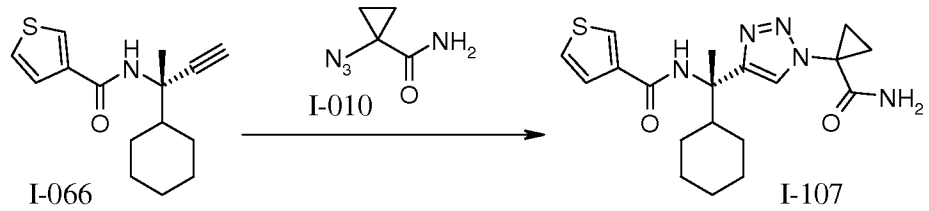
The following intermediates are is prepared from the appropriate propargylamine in the same manner as **I-104**.



alkyne pdt (intermediate)

Intermediate	Alkyne	R
I-105	**I-076**	tetrahydropyran-4-yl
I-106	**I-082**	cyclopropyl

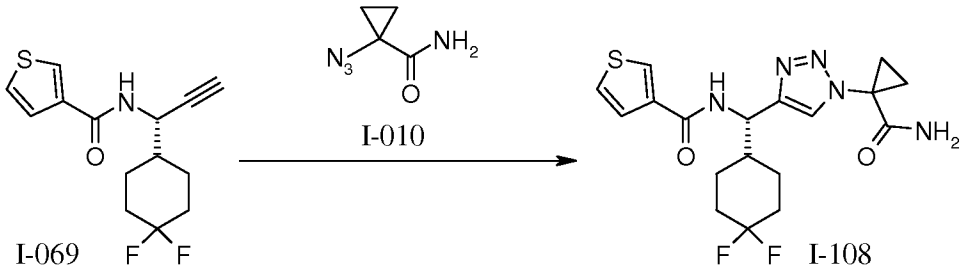
Synthesis of I-107



I-066 I-010 I-107

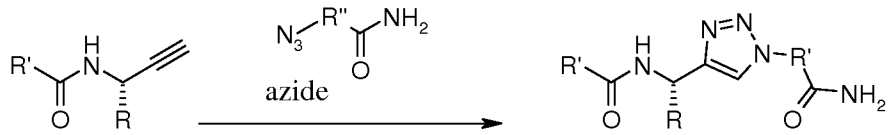
Sodium ascorbate in H_2O (1 M; 2.3 mL, 2.3 mmol) is added to a stirring mixture of **I-066** (0.30 g, 1.2 mmol), **I-010** (0.29 g, 2.3 mmol), $CuSO_4$ (0.3 M; 0.77 mL, 0.23 mmol), and 1:1 H_2O/t-BuOH. The mixture is stirred for 16 h, diluted with H_2O and saturated $NaHCO_3$, and extracted with EtOAc (3x 20 mL). The extracts are combined, washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by silica chromatography (1-20% MeOH in CH_2Cl_2 gradient) to provide **I-107** as an oil.

Synthesis of I-108



Sodium ascorbate in H_2O (1 M; 2.05 mL, 2.05 mmol) is added to a stirring mixture of **I-069** (0.29 g, 1.0 mmol), **I-010** (0.14 g, 1.1 mmol), $CuSO_4$ (0.3 M; 0.35 mL, 0.1 mmol), and 1:1 H_2O/t-BuOH (5 mL). The mixture is stirred for 16 h, diluted with EtOAc (60 mL), and washed with saturated $NaHCO_3$. The wash is extracted with EtOAc (20 mL). The extract is washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (1-20% MeOH in CH_2Cl_2 gradient) to provide **I-108** as a solid.

The following intermediates are prepared from the appropriate alkynes and azides in the same manner as **I-107** and **I-108**.

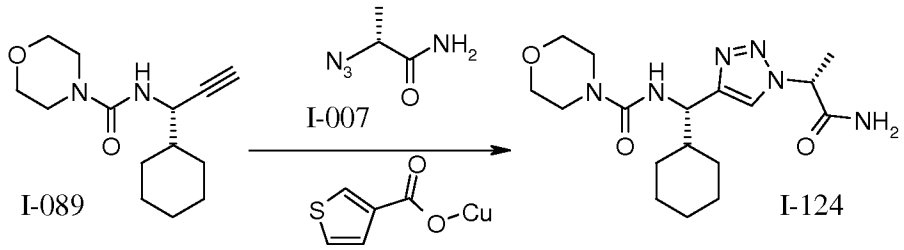


alkyne pdt (intermediate)

Intermediate	alkyne	azide	R	R'	R''
I-109	**I-091**	**I-010**	cyclohexylmethyl	1-morpholine	1,1-cPr
I-110	**I-080**	**I-010**	*N*-Cbz-piperidin-3-yl	2-thiophene	1,1-cPr
I-111	**I-096**	**I-010**	isopropropyl	2-thiophene	1,1-cPr
I-112	**I-081**	**I-010**	benzyl	2-thiophene	1,1-cPr
I-113	**I-072**	**I-010**	t-butyl	2-thiophene	1,1-cPr
I-114	**I-084**	**I-010**	sec-butyl	2-thiophene	1,1-cPr
I-115	**I-075**	**I-010**	tetrahydropyran-3-yl	2-thiophene	1,1-cPr
I-116	**I-074**	**I-007**	tetrahydropyran-2-yl	2-thiophene	*R*-CH(Me)-
I-117	**I-025**	**I-007**	tetrahydropyran-3-yl	2-thiophene	*R* -CH(Me)-
I-118	**I-077**	**I-010**	3-methoxycyclohexyl	2-thiophene	1,1-cPr
I-119	**I-077**	**I-007**	3-methoxycyclohexyl	2-thiophene	*R* -CH(Me)-

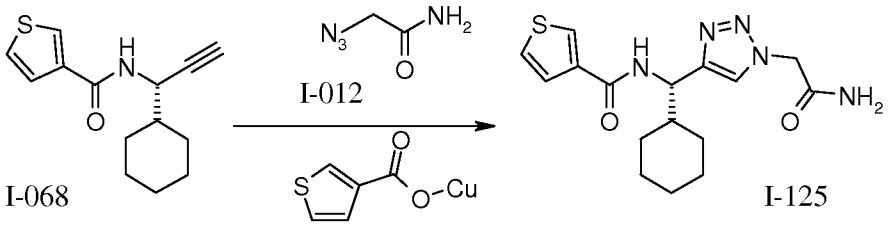
Intermediate	alkyne	azide	R	R'	R''
I-120	**I-074**	**I-010**	tetrahydropyran-2-yl	2-thiophene	1,1-cPr
I-121	**I-078**	**I-010**	isobutyl	2-thiophene	1,1-cPr
I-122	**I-079**	**I-010**	2-phenylethyl	2-thiophene	1,1-cPr
I-123	**I-083**	**I-010**	3-pentyl	2-thiophene	1,1-cPr

Synthesis of I-124



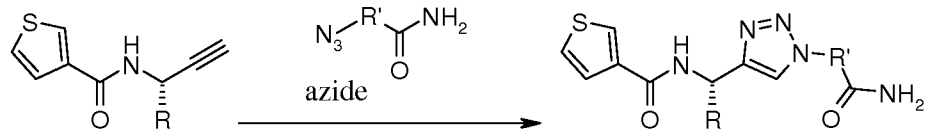
A mixture of **I-089** (0.17 g, 0.68 mmol), **I-007** (0.10 g, 0.88 mmol), CuTC (39 mg. 0.20 mmol), 2,6-lutidine (0.16 mL, 1.4 mmol), and $CHCl_3$ (5 mL) is stirred for 2h at 40 C. MeOH (10 mL) is added, the mixture is cooled to rt, filtered, and the filtrate is concentrated. The resulting residue is washed with MeCN and dried to provide **I-124** as a solid.

Synthesis of I-125

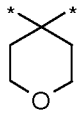
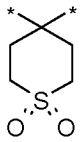
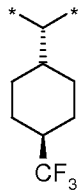
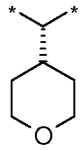


A mixture of **I-068** (0.20 g, 0.81 mmol), **I-012** (0.16 g, 1.6 mmol), CuTC (46 mg. 0.24 mmol), 2,6-lutidine (0.19 mL, 1.6 mmol), and $CHCl_3$ (5 mL) is stirred for 4h at 40 C. MeOH (10 mL) is added, the mixture is cooled to rt, filtered, and the filtrate is concentrated. The resulting residue is washed with MeCN and dried to provide **I-125** as a solid.

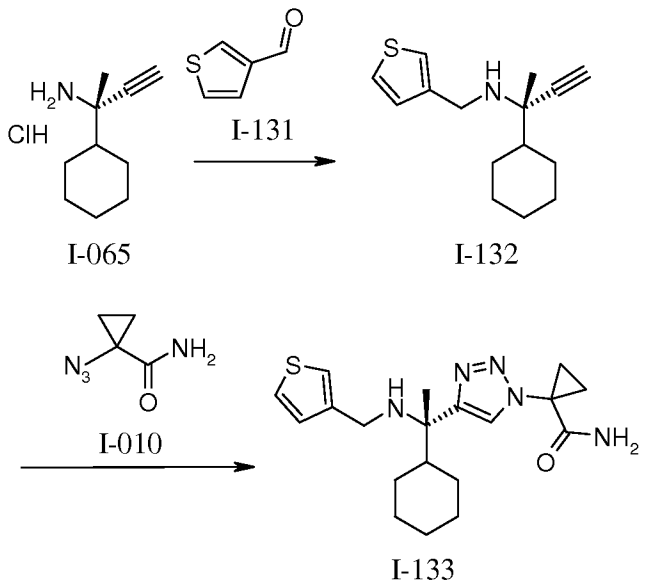
The following compounds are prepared from the appropriate alkyne in the same manner as **I-124** and **I-125**.



alkyne pdt (intermediate)

Intermediate	alkyne	azide	R	R'
I-126	**I-071**	**I-010**	cyclohexyl-D11	1,1-cPr
I-127	**I-068**	**I-004**	cyclohexyl	
I-128	**I-068**	**I-006**	cyclohexyl	
I-129	**I-087**	**I-010**		1,1-cPr
I-130	**I-076**	**I-007**		

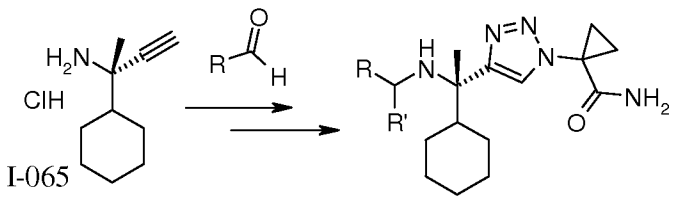
Synthesis of I-133



1 N NaOH (1.1 mL, 1.1 mmol) is added to **I-065** (0.20 g, 1.1 mmol; Patterson, A. W., *et al.*, *J. Med. Chem.*, **2006**, *49*, 6298.) and H_2O (2 mL). The mixture is extracted with toluene (3 mL). The extract is dried over Na_2SO_4, filtered, and added to activated 4Å molecular sieves (0.20 g). **I-131** (0.12 g, 1.1 mmol) and toluene (0.5 mL) are added, and the mixture is stirred for 16 h. The mixture is filtered through celite, concentrated, and combined with MeOH (5.3 mL) at 0 C. $NaBH_4$ (80 mg, 2.1 mmol) is added, and the mixture is stirred for 2h, diluted with H_2O, and extracted with CH_2Cl_2 (3x). The extracts are combined, dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (5-40% EtOAc in heptane gradient) to provide **I-132** as an oil.

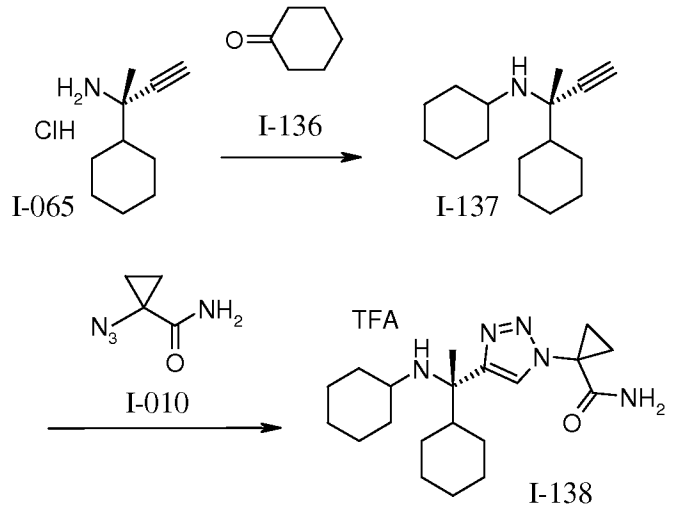
Sodium ascorbate in H_2O (1 M; 0.44 mL, 0.44 mmol) is added to a stirring mixture of **I-132** (55 mg, 0.22 mmol), **I-010** (72 mg, 0.44 mmol), $CuSO_4$ (0.3 M; 74 µL, 0.02 mmol), and 1:1 H_2O/t-BuOH (1 mL). The mixture is directly purified by C18 semi-preparative HPLC (5-75% MeCN in H_2O gradient with 0.1% TFA). Product fractions are concentrated, diluted with saturated aqueous $NaHCO_3$, extracted with EtOAc. The extract is dried over $MgSO_4$, filtered, and concentrated to provide **I-133** as an oil.

The following intermediates are prepared with the appropriate aldehydes in the same manner as **I-133**.



Intermediate	R
I-134	phenyl
I-135	4-fluorophenyl

Synthesis of I-138

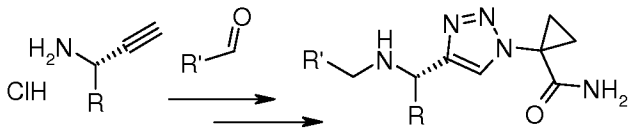


A mixture of **I-065** (0.10 g, 0.53 mmol) , **I-136** (59 mg, 0.60 mmol), NaOAc (49 mg, 0.60 mmol), and $ClCH_2CH_2Cl$ (3 mL) is stirred for 0.5 h. $NaBH(OAc)_3$ (0.25 g, 1.2 mmol) is added. The mixture is stirred for 16 h, washed with sat $NaHCO_3$, and extracted three times with CH_2Cl_2. The extracts are combined, washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (5-50% EtOAc in heptane gradient) to provide **I-137** as an oil.

Sodium ascorbate in H_2O (1 M; 0.86 mL, 0.86 mmol) is added to a stirring mixture of **I-137** (100 mg, 0.43 mmol), **I-010** (80 mg, 0.63 mmol), $CuSO_4$ (0.3 M; 290 µL, 0.09 mmol), and 1:1 H_2O/t-BuOH (2.1 mL). The mixture is stirred for 2h, diluted with H_2O, and extracted with EtOAc (3 x 20 mL). The extracts are combined, washed with brine,

dried over $MgSO_4$, filtered, concentrated, and purified by C18 semi-preparative HPLC (10-95% MeCN in H_2O gradient with 0.1% TFA) to provide **I-138** as an oil.

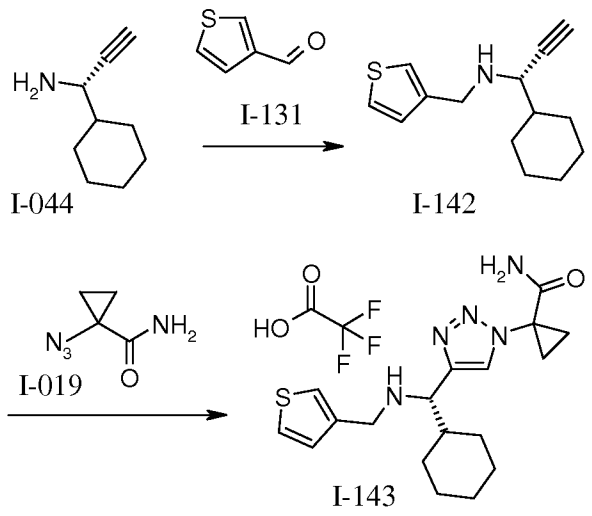
The following intermediates are prepared with the appropriate aldehydes and propargyl amines in the same manner as **I-138**.



amine pdt (intermediate)

Intermediate	amine	R	R'
I-139	**I-044**	cyclohexyl	tetrahydropyran-4-yl
I-140	**I-058**	tetrahydropyran-4-yl	thiophen-3-yl
I-141	**I-044**	cyclohexyl	thiomorphonlin-1-yl

Synthesis of I-143

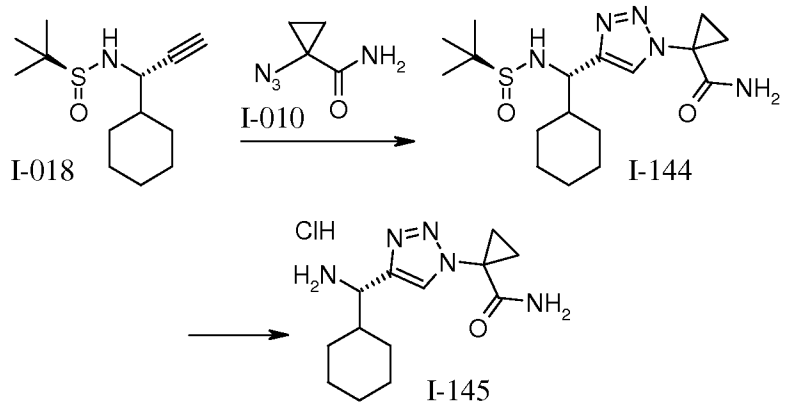


I-044 I-131 I-142 I-019 I-143

Activated 4Å molecular sieves (0.10 g) is added to **I-044** (79 mg, 0.57 mmol) and **I-131** (70 mg, 0.63 mmol) and toluene (2.4 mL). The mixture is stirred for 16 h, filtered through celite, and concentrated. MeOH (2.6 mL) and then $NaBH_4$ (39 mg, 1.0 mmol) are added at 0 C, and the mixture is stirred for 2h, diluted with H_2O, extracted with CH_2Cl_2 (3x). The extracts are combined, dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (5-40% EtOAc in heptane gradient) to provide **I-142** as an oil.

Sodium ascorbate (1 M; 0.86 mL, 0.86 mmol) is added to a stirring mixture of **I-142** (0.10 g, 0.43 mmol), **I-010** (80 mg, 0.63 mmol), 0.3 M $CuSO_4$ (0.29 mL, 0.09 mmol), and 1:1 H_2O/t-BuOH (2.1 mL). The mixture is stirred for 2 h and diluted with saturated aqueous $NaHCO_3$, then extracted with EtOAC (3x 20 mL). The extracts are combined, dried over $MgSO_4$, filtered, concentrated, and purified by C18 semi-preparative HPLC (10-95% MeCN in H_2O gradient with 0.1% TFA) to provide **I-143** as an oil.

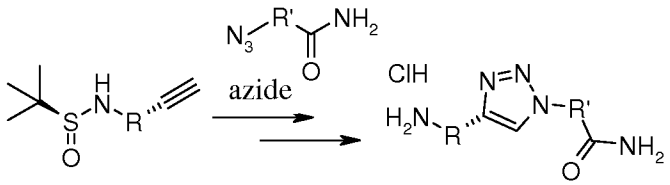
Synthesis of I-145

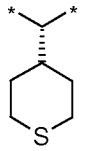
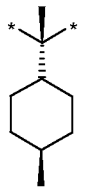


Sodium ascorbate (5.6 g, 28 mmol) in H_2O (39 mL) is added to a stirring mixture of **I-018** (3.78 g, 14.1 mmol), **I-010** (1.87 g, 14.8 mmol), 0.5 M $CuSO_4$ (2.82 mL, 1.41 mmol), and ethanol (43 mL). The mixture is stirred for 16 h, then concentrated, diluted with EtOAc (120 mL), and washed with aqueous $NaHCO_3$ (30 mL saturated solution diluted with 50 mL of H_2O). The EtOAc layer is washed with saturated aqueous NH_4Cl (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to provide **I-144**.

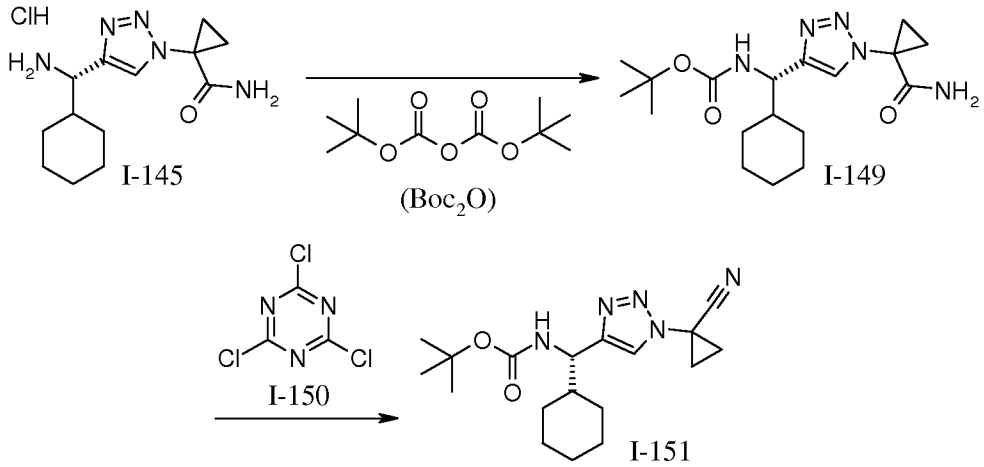
4M HCl in dioxane (7 mL, 28 mmol) is added to **I-144** (5.85 g, 14.0 mmol) and MeOH (25 mL). The mixture is stirred for 1 h, concentrated, and triturated with 95:5 MTBE/iPrOH and MTBE to provide **I-145** as a solid.

The following intermediates are prepared in the same manner as **I-145**.



Intermediate	sulfinamide	azide	R	R'
I-146	**I-038**	**I-010**		1,1-cPr
I-147	**I-148** (Patterson, A. W., 2006)	**I-009**		*S* -CH(Bu)-

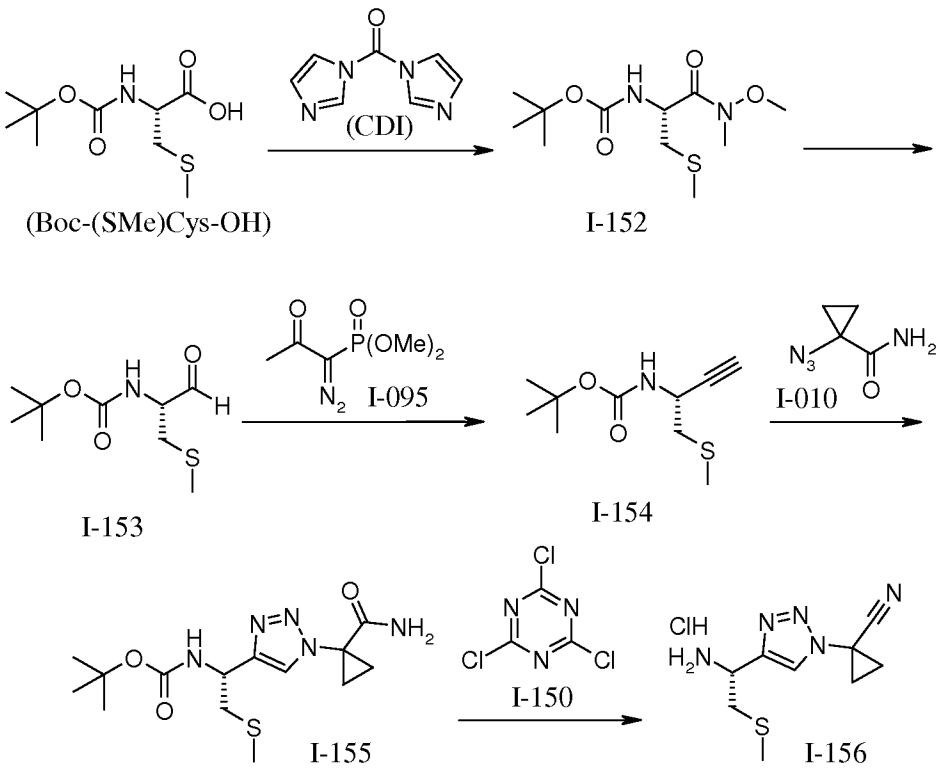
Synthesis of I-151



To **I-145** (0.20 g, 0.67 mmol) in CH_2Cl_2 (2.2 mL) is added Et_3N (93 μL, 0.67 mmol) and Boc_2O (0.15 g, 0.67 mmol). The mixture is stirred for 1 h, diluted with CH_2Cl_2, washed with H_2O and brine, dried, and concentrated to provide **I-149** as a solid.

I-150 (1.1 g, 6.1 mmol) is added to **I-149** (2.2 g, 6.1 mmol) and DMF (20 mL). The mixture is stirred for 1 h, and diluted with saturated $NaHCO_3$. The aqueous phase is extracted with EtOAc (3x). The extracts are combined, washed with H_2O and brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (5-50% EtOAc in heptane gradient) to provide **I-151** as a solid.

Synthesis of I-156



CDI (0.63 g, 3.9 mmol)is added to a mixture of Boc-(SMe)Cys-OH (0.83 g, 3.5 mmol), MeONHMe-HCl (0.38 g, 3.9 mmol), and CH_2Cl_2 (10 mL). The mixture is stirred overnight, washed with 1M $NaHSO_4$ and brine, dried over Na_2SO_4, filtered, concentrated and purified by silica chromatography (25-50% EtOAc in heptane gradient) to provide **I-152** as an oil.

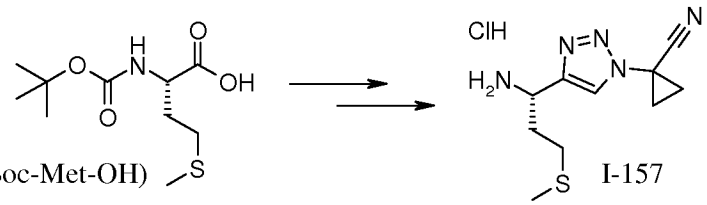
1M $(i\text{Bu})_2AlH$ (5.2 mL, 5.2 mmol) is added slowly to **I-152** (0.65 g, 2.3 mmol) and CH_2Cl_2 (10 mL) at -78 C. The mixture is stirred at -78 for 40 min, 1M $NaHSO_4$ (5 mL) is added, the mixture is warmed to rt, and CH_2Cl_2 (60 mL) and brine (10 mL) are added. The mixture is filtered through celite. The organic phase of the filtrate is dried over Na_2SO_4, filtered, and concentrated to provide **I-153** as an oil.

I-095 (0.82 g, 4.3 mmol) is added to **I-153** (0.48 g, 2.2 mmol), K_2CO_3 (0.90 g, 6.5 mmol), and MeOH (5 mL) at 0 C. The mixture is stirred at rt for 14 h and EtOAc (50 mL) is added. The mixture is washed with brine (10 mL), dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (5-50% EtOAc in heptane gradient) to provide **I-154** as an oil.

Sodium ascorbate (0.40 g, 2.0 mmol) and H_2O (5 mL) is added to a stirring mixture of **I-154** (0.21 g, 0.98 mmol), **I-010** (0.15 g, 1,2 mmol), 0.3 M $CuSO_4$ (0.35 mL, 0.11 mmol), and EtOH (5 mL). The mixture is stirred for 12 h, concentrated, and diluted with EtOAc (60 mL). The mixture is washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (0-8% MeOH in CH_2Cl_2 gradient) to provide **I-155** as a solid.

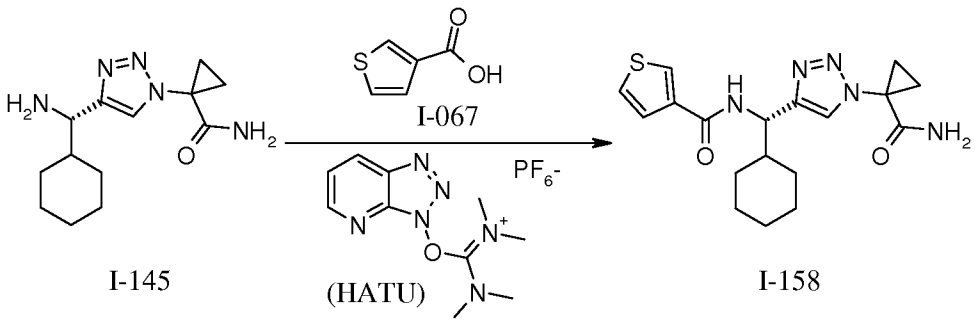
I-150 (86 mg, 0.47 mmol) is added to **I-155** (0.16 g, 0.47 mmol) and DMF (2 mL) at 0 C. The mixture is stirred for 14 h, and diluted with EtOAc (40 mL). The mixture is washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (2-10% MeOH in CH_2Cl_2 gradient). The resulting material is stirred in 4.0 M HCl in dioxane (0.5 mL) for 1h, then concentrated and triturated with MTBE to provide **I-156** as a solid.

Synthesis of I-157



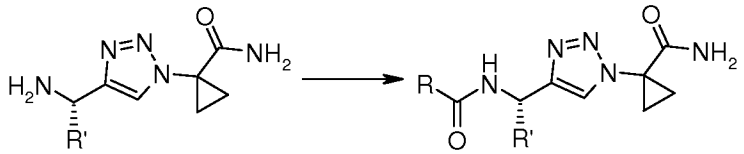
I-157 is prepared from Boc-Met-OH in the same manner as **I-156**.

Synthesis of I-158



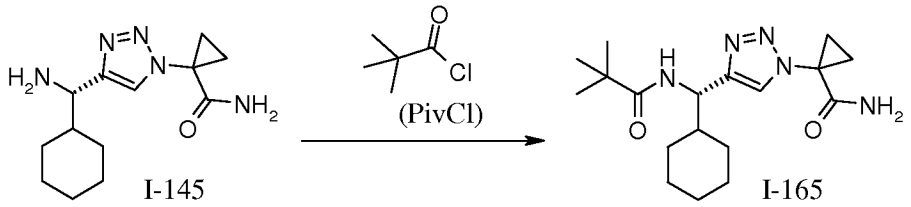
A mixture of **I-145** (36 mg, 0.14 mmol), **I-067** (20 mg, 0.16 mmol), Et_3N (0.05 mL, 0.4 mmol), HATU (75 mg, 0.20 mmol), and DMF (1 mL) is stirred for 3 days, then diluted with EtOAc (30 mL) and washed with H_2O (20 mL) and brine (25 mL). The extract is dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (20-100% EtOAc in heptane) to provide **I-158**.

The following intermediates are prepared in the same manner as **I-158**.



Intermediate	amine	R	R'
I-159	**I-146**	thiophen-3-yl	thiocyclohexan-4-yl
I-160	**I-145**	5-phenylthiophen-2-yl	cyclohexyl
I-161	**I-145**	4-fluorophenyl	cyclohexyl
I-162	**I-145**	pyridon-5-yl	cyclohexyl
I-163	**I-145**	pyridon-3-yl	cyclohexyl
I-164	**I-145**	6-oxopiperidin-3-yl	cyclohexyl

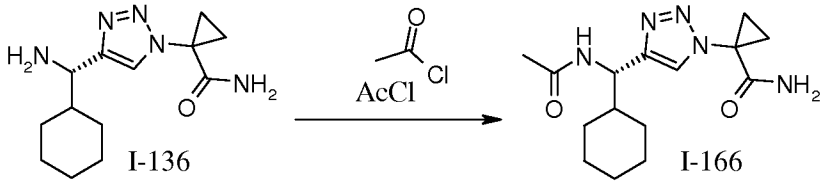
Synthesis of I-165



PivCl (45 μL, 0.37 mmol) is added to **I-145** (0.10 g, 0.33 mmol), Et_3N (0.14 mL, 1.0 mmol), and THF (1.7 mL). The mixture is stirred for 4h, concentrated, and purified by

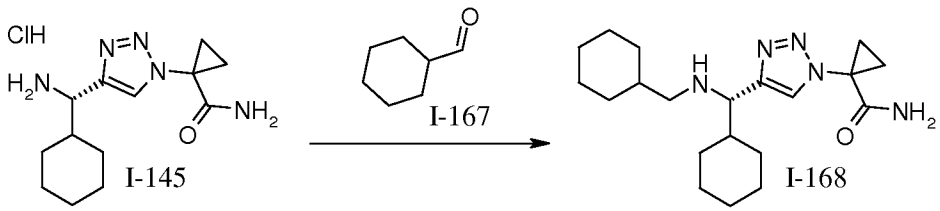
C18 semi-preparative HPLC (5-95% MeCN in H_2O gradient with 0.1% TFA) to provide **I-165** as a solid.

Synthesis of I-166



AcCl (30 μL, 0.37 mmol) is added to **I-145** (0.10 g, 0.33 mmol), Et_3N (0.14 mL, 1.0 mmol), and THF (1.7 mL). The mixture is stirred for 4h, concentrated, and purified by C18 semi-preparative HPLC (5-95% MeCN in H_2O gradient with 0.1% TFA) to provide **I-166** as a solid.

Synthesis of I-168



A mixture of **I-145** (50 mg, 0.17 mmol) , **I-167** (19 mg, 0.17 mmol), NaOAc (14 mg, 0.17 mmol), HOAc (50 μL), and $ClCH_2CH_2Cl$ (5 mL) is stirred for 0.5 h. $NaBH(OAc)_3$ (68 mg, 0.32 mmol) is added. The mixture is stirred for 1 h, washed with sat $NaHCO_3$, and extracted three times with CH_2Cl_2. The extracts are combined, washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (0-30% EtOAc in heptane gradient) to provide **I-168** as a solid.

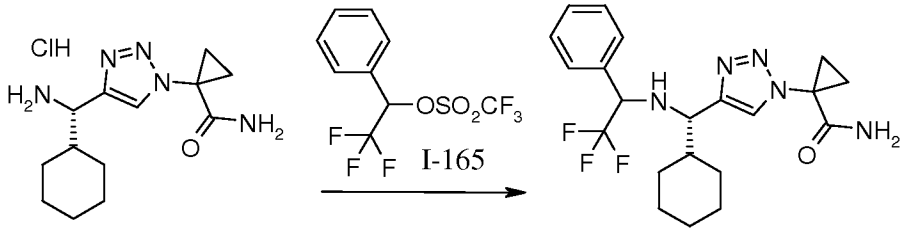
The following intermediates are prepared from the appropriate amines and carbonyl compounds in the same manner as **I-168**.

amine pdt (intermediate)

Intermediate	amine	R	R'

Intermediate	amine	R	R'
I-169	**I-145**	cyclopentyl	cyclohexyl
I-170	**I-145**	cylclohexane	cyclohexyl
I-171	**I-145**	cycloheptyl	cyclohexyl
I-172	**I-145**	benzyl	cyclohexyl
I-173	**I-145**	4-fluorobenzyl	cyclohexyl

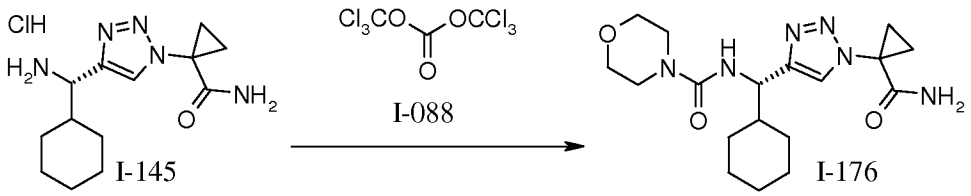
Synthesis of I-175



I-136 I-166

I-174 (0.16 g, 0.50 mmol) is added to **I-145** (0.10 g, 0.33 mmol), iPr_2NEt (0.20 mL, 1.2 mmol), and THF (2 mL). The mixture is stirred at 60 C for 4 h. EtOAc (40 mL) is added, and the mixture is washed with 0.5 N HCl (15 mL), saturated aqueous $NaHCO_3$, and brine. The extract is dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (1-10% MeOH in CH_2Cl_2 gradient) to provide **I-175** as a mixture of diastereomers.

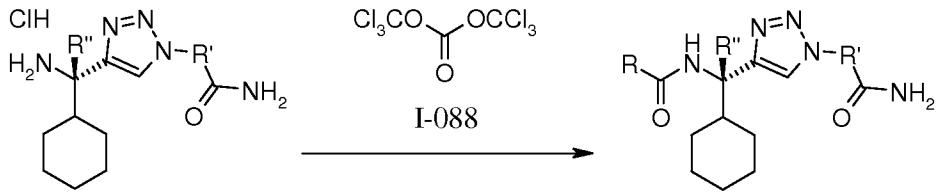
Synthesis of I-176



I-145 I-176

A mixture of **I-145** (70 mg, 0.23 mmol) and iPr_2NEt (0.16 mL, 1.0 mmol) is added to **I-088** (26 mg, 0.09 mmol) and CH_2Cl_2 (2 mL). The mixture is stirred for 30 min, morpholine (26 mg, 0.30 mmol) is added, and the resulting mixture is stirred overnight, diluted with EtOAc (40 mL), and washed with brine. The extract is dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (2-10% MeOH in CH_2Cl_2 gradient) to provide **I-176** as a solid.

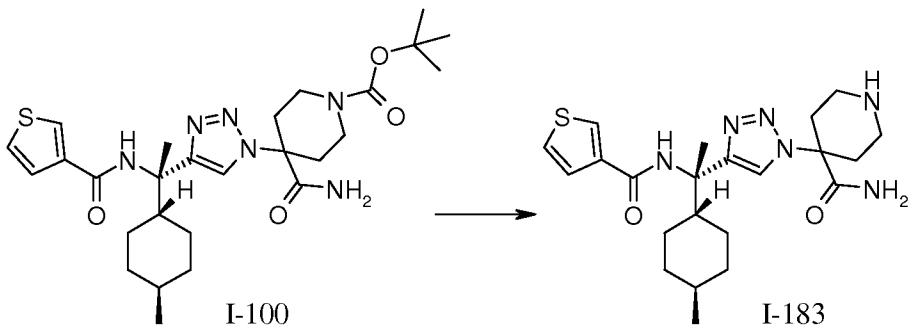
The following intermediates are prepared from the designated amines and the appropriate amines R in the same manner as **I-176**.



amine pdt (intermediate)

Intermediate	amine	R	R'	R''
I-177	**I-145**	1-dioxthiomorpholine	1,1-cPr	H
I-178	**I-145**	1-piperidine	1,1-cPr	H
I-179	**I-147**	1-morpholine	*S* -CH(Bu)-	Me
I-180	**I-147**	1-(4-Me-piperidine)	*S* -CH(Bu)-	Me
I-181	**I-147**	Me_2N-	*S* -CH(Bu)-	Me
I-182	**I-147**	PhNH-	*S* -CH(Bu)-	Me

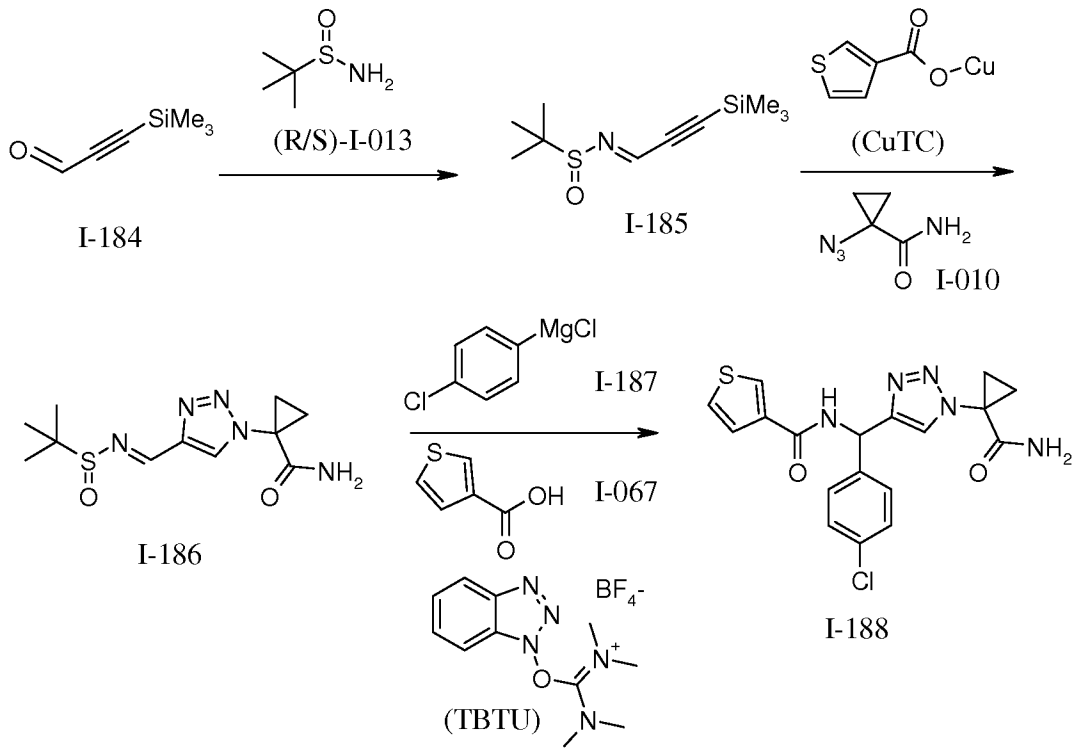
Synthesis of I-183



I-100 I-183

TFA (0.5 mL, 6.7 mmol) is added to **I-100** (240 mg, 0.44 mmol) and CH_2Cl_2 (2 mL). The mixture is stirred for 72 h, concentrated, and purified directly by C18 semi-preparative HPLC (5-95% MeCN in H_2O gradient with 0.1% TFA). Product fractions are diluted with $NaHCO_3$ and extracted with EtOAc (3 x 30 mL). The extracts are combined, dried over $MgSO_4$, filtered, and concentrated to provide **I-183** as a solid.

Synthesis of I-188



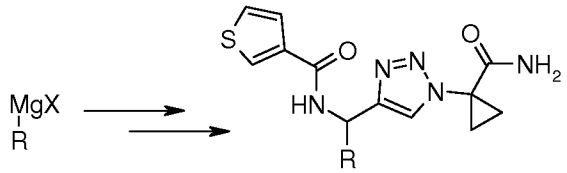
A mixture of **I-184** (2.8 g, 22 mmol), $Ti(OEt)_4$ (7.7 mL, 26 mmol), **(R/S)-I-013** (4.0 g, 33 mmol), and THF (100 mL) are stirred for 1 h. The mixture is poured into a stirring mixture of H_2O (100 mL) and EtOAc (100 mL). The resulting mixture is filtered through celite. The EtOAc phase is separated, dried, filtered, concentrated, mixed with CH_2Cl_2, filtered, and concentrated to provide **I-185** as an oil.

2,6-Lutidine (0.91 mL, 7.9 mmol) is added to CuTC (0.22 g, 1.2 mmol) **I-185** (0.90 g, 3.92 mmol), **I-010** (0.64 g, 5.1 mmol), and $CHCl_3$ (10 mL). The mixture is stirred for 16 h at 40 C. The mixture is filtered, concentrated, and purified by silica chromatography (50-100% EtOAc in heptane gradient) to provide **I-186**.

1 M **I-187** in THF (2.2 mL, 2.2 mmol) is added to **I-186** (0.20 g, 0.72 mmol) and THF (5 mL). After stirring for 1 h, saturated aqueous NH_4Cl is added and the mixture is extracted with EtOAc. The extract is dried, filtered, concentrated, dissolved in CH_2Cl_2, filtered, and concentrated. The resulting residue is combined with MeOH (1 mL) and 4 M HCl in dioxane (1 mL) is added. The resulting mixture is combined with DMF (3 mL) and added to Et_3N (0.30 mL, 2.2 mmol), **I-067** (0.11 g, 0.86 mmol), and TBTU (0.25 g, 0.79 mmol). The mixture is stirred for 2 h, diluted with MeOH and purified by

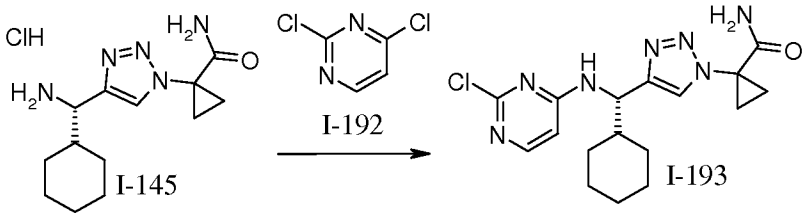
C18 semi-preparative HPLC (5-100% MeCN in H_2O gradient with 0.1% TFA) to provide **I-188** as a solid.

The following intermediates are prepared using **I-186** and the appropriate Grignard reagent (RMgX) in the same manner as **I-188**.



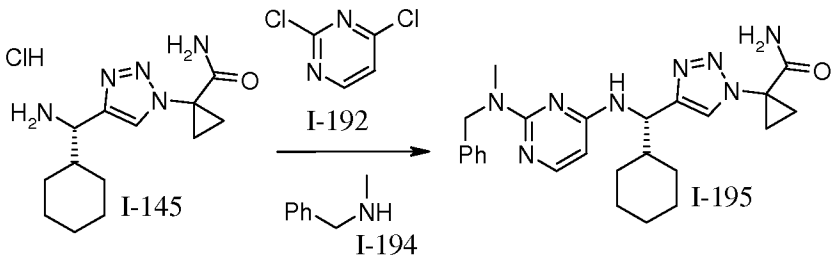
Intermediate	R
I-189	3,4-difluorophenyl
I-190	phenyl
I-191	4-fluorophenyl

Synthesis of I-193



A mixture of **I-192** (49 mg, 0.33 mmol), **I-145** (99 mg, 0.33 mmol), *i*Pr_2NEt (0.2 mL), and DMF (2.0 mL) is stirred at 75 C for 6 h. The mixture is directly purified by C18 semi-preparative HPLC (10-95% MeCN in H_2O gradient with 0.1% TFA) to provide **I-193** as a solid.

Synthesis of I-195

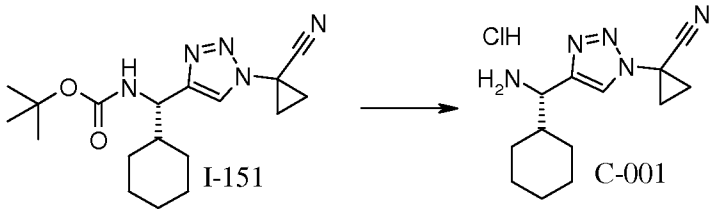


A mixture of **I-192** (49 mg, 0.33 mmol), **I-145** (99 mg, 0.33 mmol), *i*Pr_2NEt (0.2 mL), and DMF (2.0 mL) is stirred at 75 C for 6 h. **I-194** (48 mg, 0.40 mmol) is added and the mixture is stirred at 150 C for 4 h. The mixture is directly purified by C18 semi-

preparative HPLC (10-95% MeCN in H_2O gradient with 0.1% TFA) to provide **I-195** as a solid.

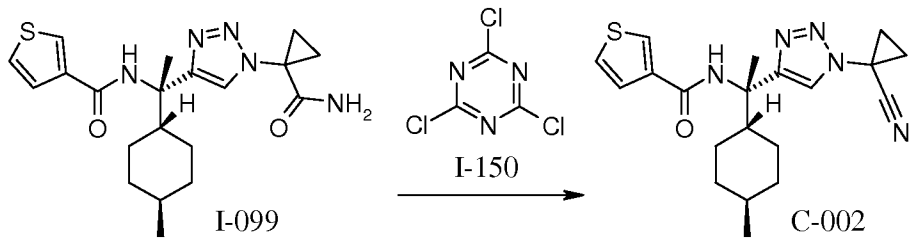
The following intermediates are used in the preparation of the Examples.

Example 1: Synthesis of C-001



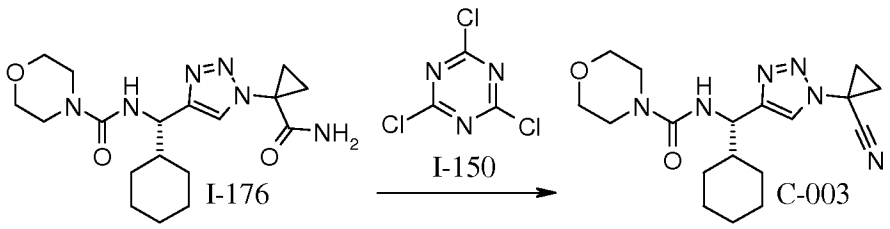
4M HCl in dioxane (3.6 mL, 14 mmol) is added to **I-151** (1.7 g, 4.8 mmol) and CH_2Cl_2 (3.5 mL). The mixture is stirred for 1 h, concentrated, and triturated with MTBE to provide **C-001** as a solid.

Example 2: Synthesis of C-002



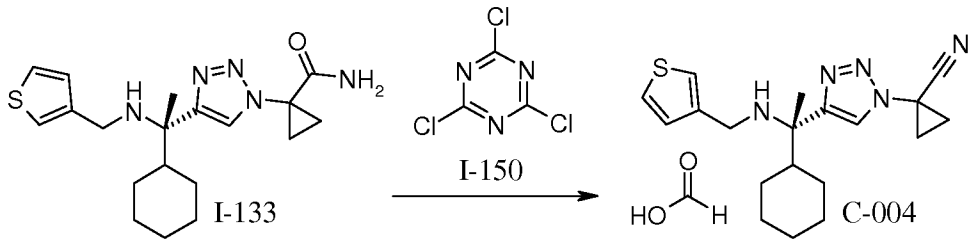
I-150 (70 mg, 0.38 mmol) is added to **I-099** (220 mg, 0.55 mmol) and DMF (2 mL) at 0 C. The mixture is stirred at 0 C for 1h then at rt for 16 h. **I-150** (70 mg, 0.38 mmol) is added and the mixture is stirred for 24 h. **I-150** (70 mg, 0.38 mmol) is added and the mixture is stirred overnight, cooled to 5 C, and H_2O (5 mL) is added. The mixture is extracted with EtOAc (3 x 5 mL). The extracts are combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated, then purified by C18 semi-preparative HPLC (5-95% MeCN in H_2O gradient with 0.1% TFA) provide **C-002** as a solid.

Example 3: Synthesis of C-003



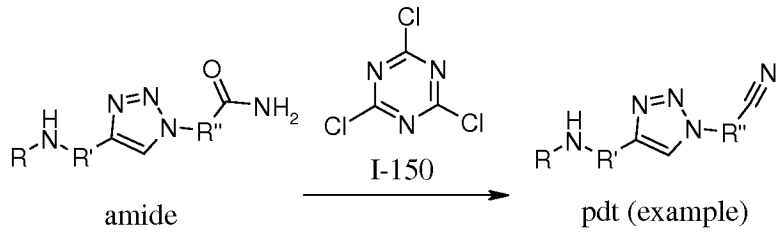
I-150 (16 mg, 0.09 mmol) is added to **I-176** (32 mg, 0.09 mmol) and DMF (1 mL). The mixture is stirred for 14 h, diluted with EtOAc (40 mL), washed with saturated aqueous $NaHCO_3$ and brine. The extract is dried over Na_2SO_4, concentrated, and purified by silica chromatography (2-10% MeOH with 0.5% NH_4OH in CH_2Cl_2 gradient) to provide **C-003** as a solid.

Example 4: Synthesis of C-004

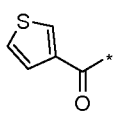
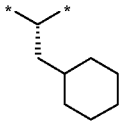
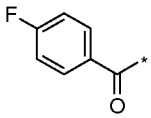
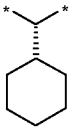
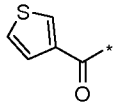
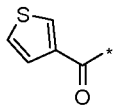
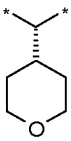
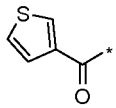
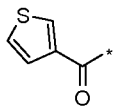
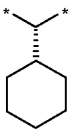
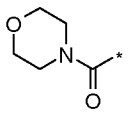
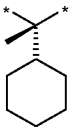
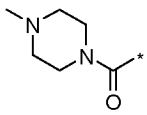
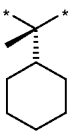
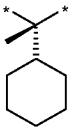
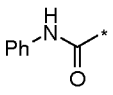
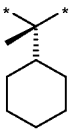
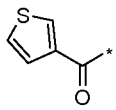
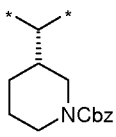


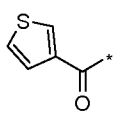
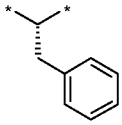
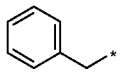
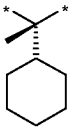
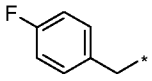
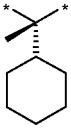
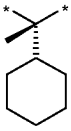
I-150 (52 mg, 0.28 mmol) is added to **I-133** (58 mg, 0.14 mmol) and DMF (1 mL) at 0 C. The mixture is stirred for 30 min at 4 C, and 3 h at rt. The mixture is diluted with H_2O (5 mL) at 5 C, and extracted with EtOAc (3 x 5 mL). The extracts are combined, washed with brine, dried over Na_2SO_4, filtered, and purified by C18 semi-preparative HPLC (10-80% MeCN in H_2O gradient with 0.1% HCO_2H) to provide **C-004** as a solid.

The following Examples are prepared via dehydration of the appropriate amide in the same manner as **C-002, C-003, C-004**.

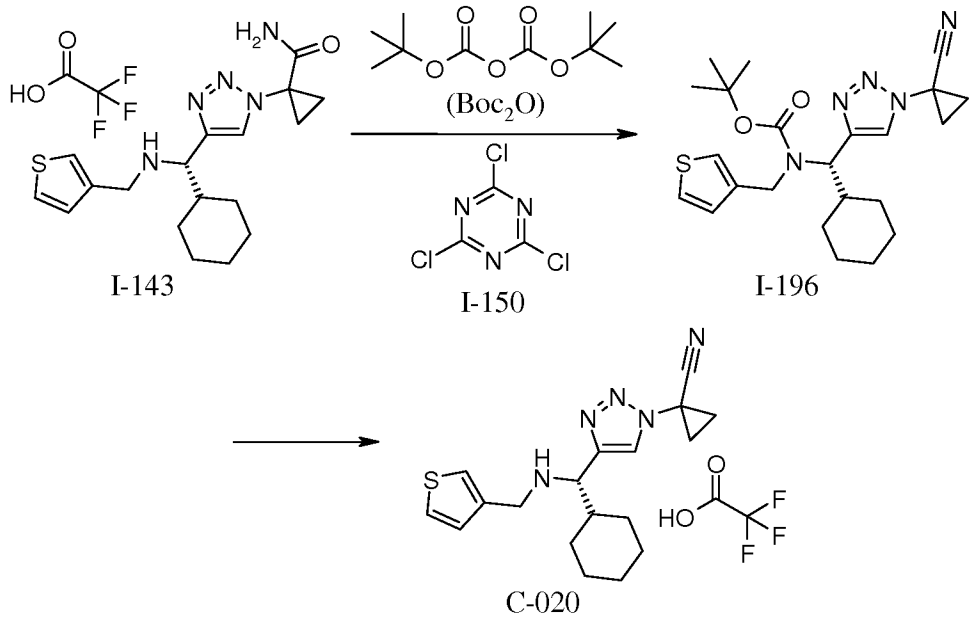


Example	Amide	R	R'	R''

Example	Amide	R	R'	R''
C-005	I-104			
C-006	I-161			
C-007	I-111			
C-008	I-105			
C-009	I-106			
C-010	I-101			
C-011	I-179			
C-012	I-180			
C-013	I-181			
C-014	I-182			
C-015	I-110			

Example	Amide	R	R'	R''
C-016	I-112			
C-017	I-134			
C-018	I-135			
C-019	I-138			

Example 5: Synthesis of C-020

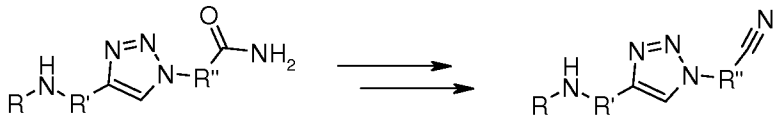


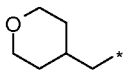
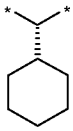
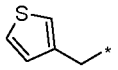
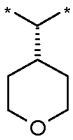
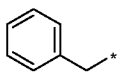
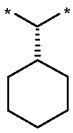
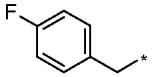
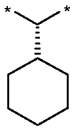
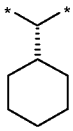
Boc_2O (33 mg, 0.15 mmol) is added to **I-143** (55 mg, 0.12 mmol), Et_3N (27 μL, 0.20 mmol), and CH_2Cl_2 (0.5 mL). The mixture is stirred for 1 h, CH_2Cl_2 is added and the mixture is washed with H_2O and brine, dried, filtered, and concentrated. To this residue and DMF (1 mL) is added **I-150** (18 mg, 0.10 mmol). The mixture is stirred for 1 h, and then is diluted with EtOAc and saturated aqueous $NaHCO_3$ (1 mL). The mixture is stirred for 15 min, then extracted with EtOAc (3x). The extracts are combined, washed

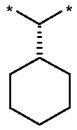
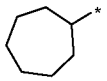
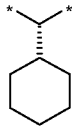
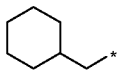
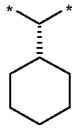
with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated to provide **I-196** as a solid.

4N HCl in dioxane (0.14 mL, 0.56 mmol) is added to **I-196** (43 mg, 0.10 mmol) and CH_2Cl_2 (0.5 mL). The mixture is stirred at rt for 2h, at 4 C for 60 h, and at rt for 2h. The mixture is directly purified by C18 semi-preparative HPLC (5-75% MeCN in H_2O gradient with 0.1% TFA) provide **C-020** as a solid

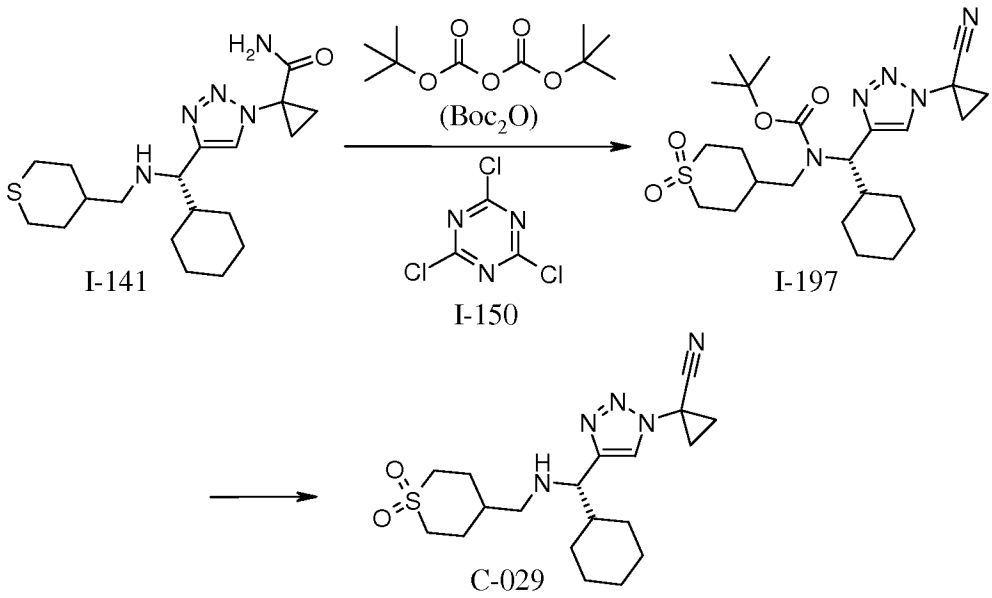
The following Examples are prepared from the appropriate intermediates in the same manner as **C-020**.



Example	Intermediate	R	R'	R''
C-021	**I-139**			
C-022	**I-140**			
C-023	**I-172**			
C-024	**I-173**			
C-025	**I-169**			

Example	Intermediate	R	R'	R''
C-026	I-170			
C-027	I-171			
C-028	I-168			

Example 6: Synthesis of C-029

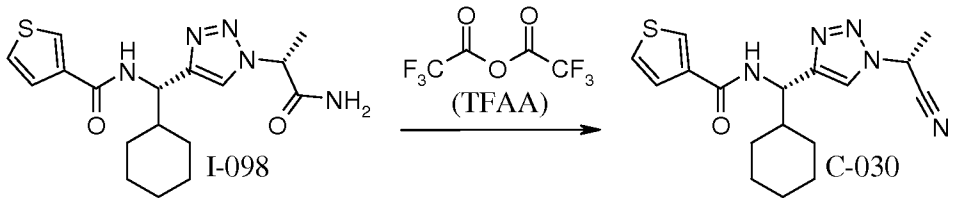


Boc_2O (57 mg, 0.26 mmol) is added to **I-141** (97 mg, 0.26 mmol), Et_3N (42 μL, 0.30 mmol), and CH_2Cl_2 (0.9 mL). The mixture is stirred for 1 h, CH_2Cl_2 is added and the mixture is washed with H_2O and brine, dried, filtered, and concentrated. To this residue and THF(1 mL) is added oxone (0.20 g, 0.32 mmol). This mixture is stirred for 1h and filtered and the solids washed with EtOAc. The filtrate is washed with 10% $Na_2S_2O_3$, water, and brined, then dried over Na_2SO_4, filtered, and concentrated. To this residue and DMF (1 mL) is added **I-150** (22 mg, 0.12 mmol). The mixture is stirred for 1 h, and then is diluted with EtOAc and saturated aqueous $NaHCO_3$ (1 mL). The mixture is stirred for 15 min, then extracted with EtOAc (3x). The extracts are combined, washed

with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated to provide **I-197** as a solid.

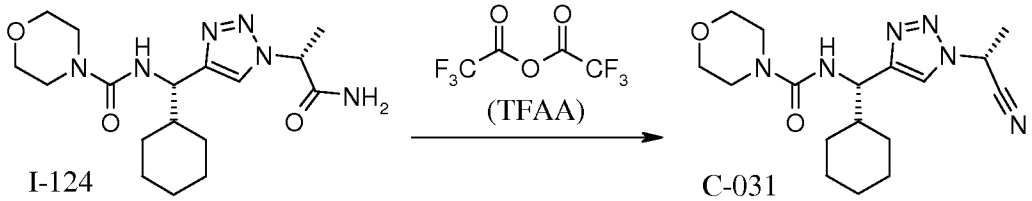
4N HCl in dioxane (0.090 mL, 0.36 mmol) is added to **I-197** (57 mg, 0.10 mmol) and CH_2Cl_2 (0.5 mL). The mixture is stirred at rt for 2h, at 4 C for 60 h, and at rt for 2h. The mixture is directly purified by C18 semi-preparative HPLC (5-60% MeCN in H_2O gradient with 0.1% TFA) to provide **C-029** as a solid

Example 7: Preparation of C-030



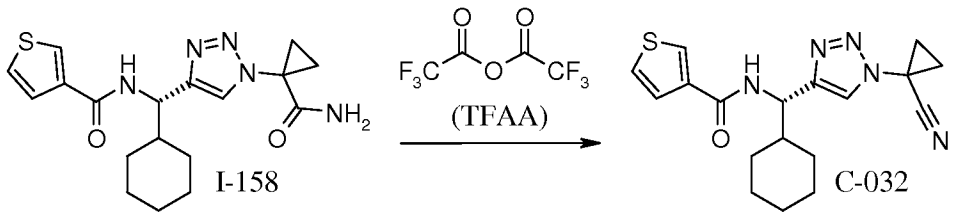
TFAA is added in three portions (each 15 µL; 0.11 mmol) to **I-098** (36 mg, 0.10 mmol) and pyridine (0.5 mL). The mixture is stirred for 3.5 h. Direct purification by reverse phase C18 semi-preparative HPLC (5-95% MeCN in H_2O gradient with 0.1% TFA) provides **C-030** as a solid.

Example 8: Synthesis of C-031



TFAA (42 µL, 0.30 mmol) is added to **I-124** (210 mg, 0.52 mmol), and pyridine (1.4 mL). After 1 h, MeOH (1 mL) is added, and the mixture is directly purified by C18 semi-preparative HPLC (5-95% MeCN in H_2O gradient with 0.1% TFA) to provide **C-031** as a solid.

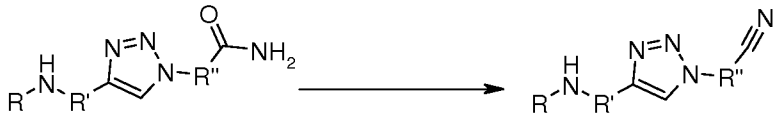
Example 9: Synthesis of C-032

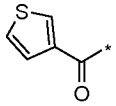
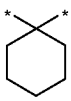
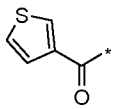
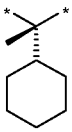
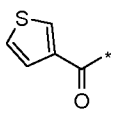
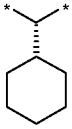
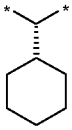
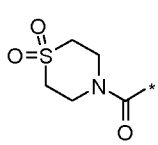
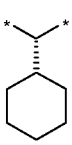


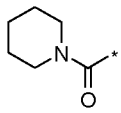
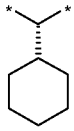
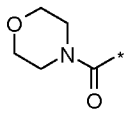
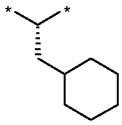
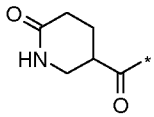
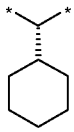
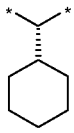
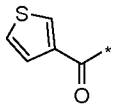
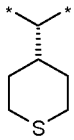
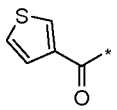
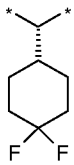
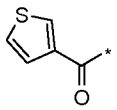
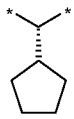
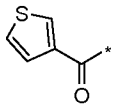
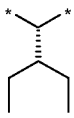
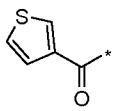
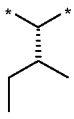
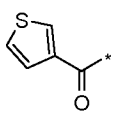
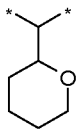
I-158 C-032

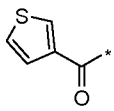
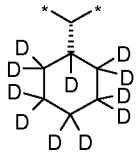
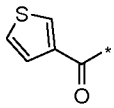
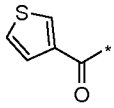
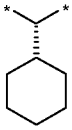
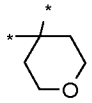
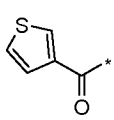
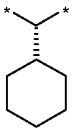
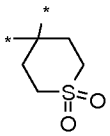
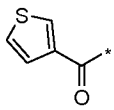
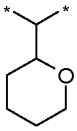
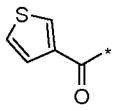
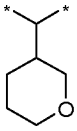
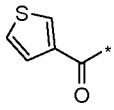
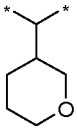
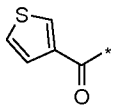
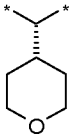
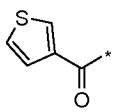
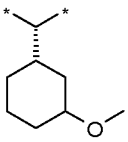
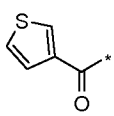
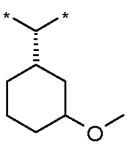
TFAA (17 μL; 0.12 mmol) is added in portions to a mixture of **I-158** (39 mg, 0.10 mmol), THF (1 mL), and Et_3N (30 μL, 0.22 mmol). The mixture is stirred for 1 h. The mixture is diluted with EtOAc (40 mL), and washed with brine. The extract is dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (10-70 % EtOAc in heptane gradient) to provide **C-032** as a solid.

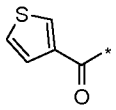
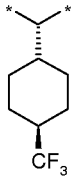
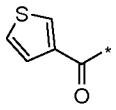
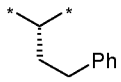
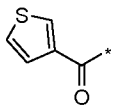
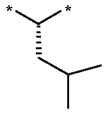
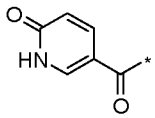
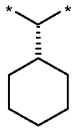
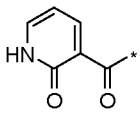
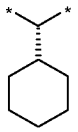
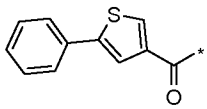
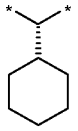
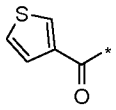
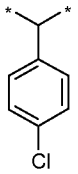
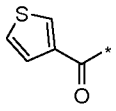
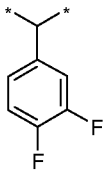
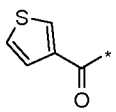
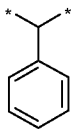
The following Examples are prepared via dehydration of the appropriate amide in the same manner as **C-030, C-031,** and **C-032**.

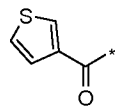
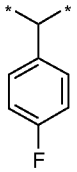
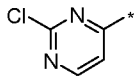
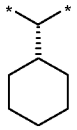
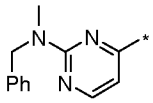
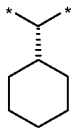


Example	Amide SM	R	R'	R''
C-033	**I-086**			
C-034	**I-107**			
C-035	**I-125**			
C-036	**I-166**			
C-037	**I-177**			

Example	Amide SM	R	R'	R''
C-038	I-178			
C-039	I-109			
C-040	I-164			
C-041	I-165			
C-042	I-159			
C-043	I-108			
C-044	I-103			
C-045	I-123			
C-046	I-114			
(R,R/R,S)-C-047	I-120			

Example	Amide SM	R	R'	R''
C-048	I-126			
C-049	I-113			
C-050	I-127			
C-051	I-128			
C-052	I-116			
C-053	I-115			
C-054	I-117			
C-055	I-130			
C-056	I-118			
C-057	I-119			

Example	Amide SM	R	R'	R''
C-058	I-129			
C-059	I-122			
C-060	I-121			
C-061	I-162			
C-062	I-163			
C-064	I-160			
C-065	I-188			
C-066	I-189			
(R/S)-C-067	I-190			

Example	Amide SM	R	R'	R''
(R/S)-C-068	I-191			
C-069	I-193			
C-070	I-195			

Example 10: Isolation of (S)-C-067

(R/S)-C-067 is separated by chiral semi-preparative HPLC (Chiralcel AD-H; 40% iPrOH in heptane) to provide **(S)-C-067** as a solid.

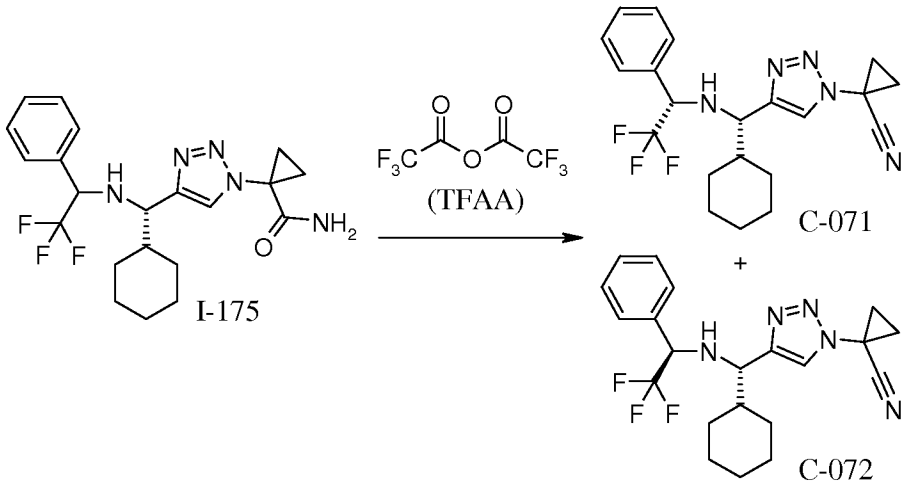
Example 11: Isolation of (S)-C-068

(R/S)-C-068 is separated by chiral semi-preparative HPLC (Chiralcel AD-H; 40% iPrOH in heptane) to provide **(S)-C-068** as a solid.

Example of 12: Isolation of (R,R)- and (R,S)-C-047

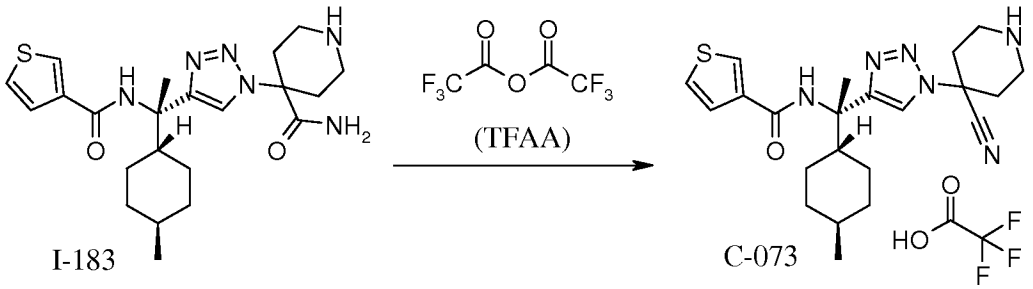
(R,R/R,S)-C-047 is separated by chiral semi-preparative HPLC (Luna C18, 33% MeCN in H_2O with 0.1% TFA) to provide its two diastereomers, each as solids.

Example 13: Synthesis of C-071 and C-072



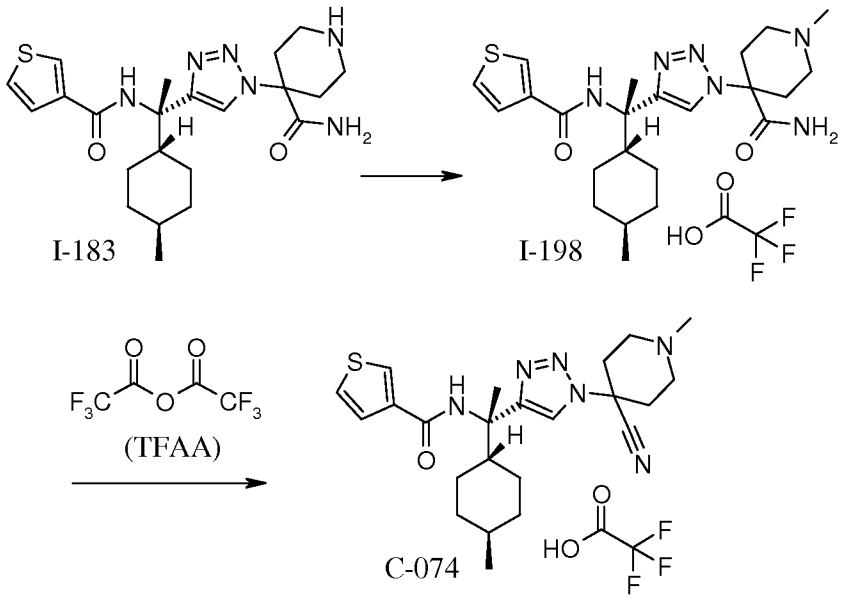
TFAA (0.03 mL, 0.15 mmol) is added to **I-175** (30 mg, 0.07 mmol) and pyridine (1 mL). The mixture is stirred for 14 h, concentrated, and purified by C18 semi-preparative HPLC (50-95% MeCN in H_2O gradient with 0.1% HCO_2H) to provide **C-071** and **C-072** as solids.

Example 14: Synthesis of C-073



TFAA (0.15 mL, 0.11 mmol) is added to **I-183** (0.45 g, 0.10 mmol), Et_3N (31 uL, 0.22 mmol), and THF (1 mL). The mixture is stirred for 4 h and concentrated. H_2O (0.5 mL), MeOH (0.5 mL), and K_2CO_3 (50 mg) are added. The resulting mixture is stirred for 16 h, then directly purified by C18 semi-preparative HPLC (5-95% MeCN in H_2O gradient with 0.1% TFA) to provide **C-073** as a solid.

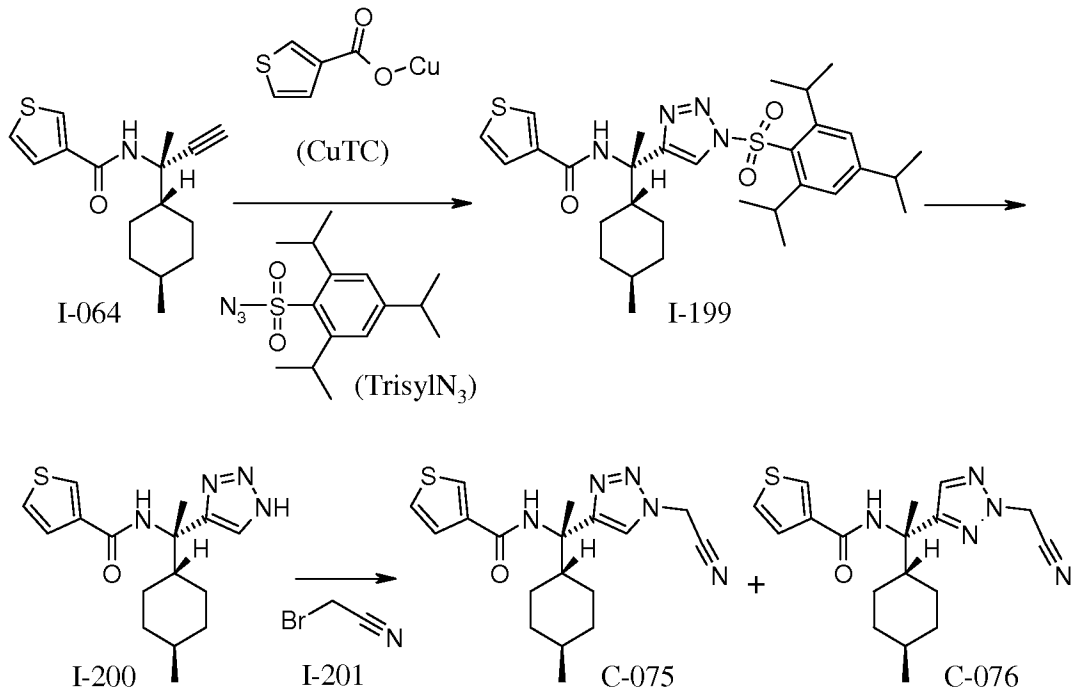
Example 15: Synthesis of C-074



$NaCNBH_3$ (32 mg, 0.51 mmol) is added to a mixture of **I-183** (45 mg, 0.10 mmol), 37% aqueous formaldehyde (75 μL, 1.0 mmol), and MeOH (1 mL). The mixture is stirred for 16 h, concentrated, and directly purified by C18 semi-preparative HPLC (5-95% MeCN in H_2O gradient with 0.1% TFA) to provide **I-198** as a solid.

TFAA (4 μL, 0.03 mmol) is added to **I-198** (12 mg, 0.03 mmol), Et_3N (8 μL, 0.06 mmol), and THF (1 mL). The mixture is stirred for 16 h and concentrated, then directly purified by C18 semi-preparative HPLC (5-95% MeCN in H_2O gradient with 0.1% TFA) to provide **C-074** as a solid.

Example 16: Preparation of C-075 and C-076

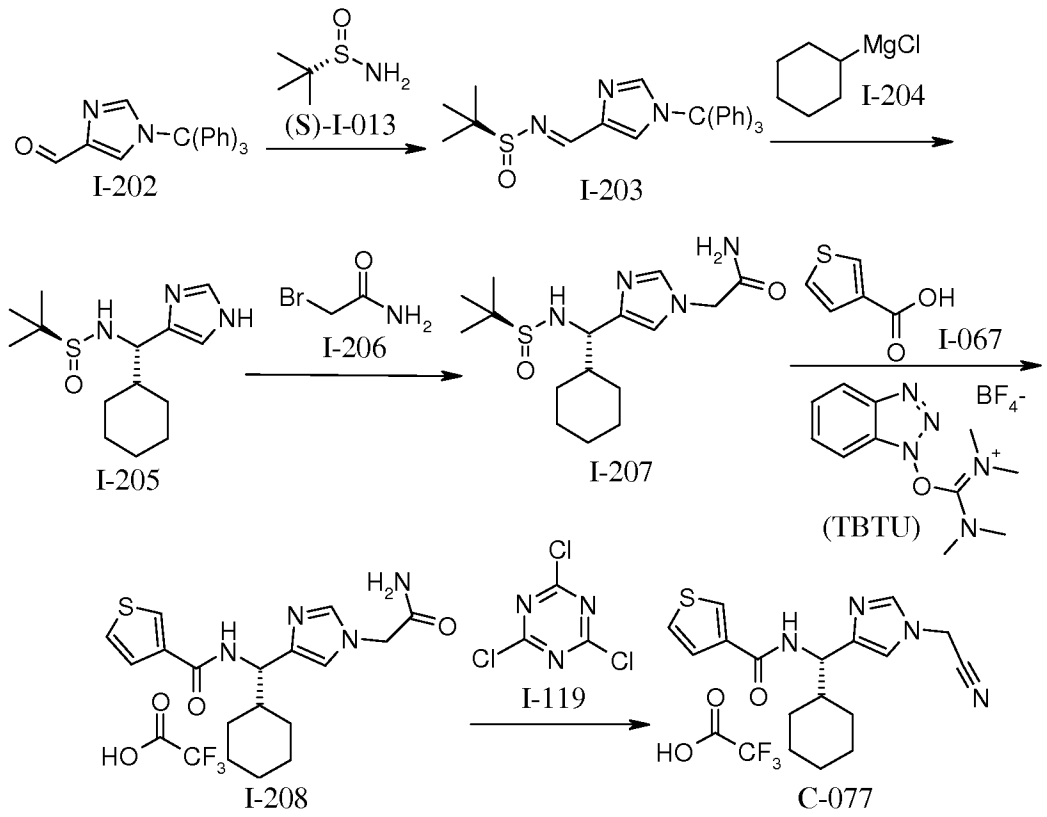


I-064 (275 mg, 1.00 mmol) and TrisylN$_3$ (310 mg, 1.00 mmol) are added to CuTC (19 mg, 0.10 mmol) and toluene (5 mL). The mixture is stirred for 2 days, filtered, concentrated, and purifed first by silica chromatography (0-25% EtOAc in heptane gradient), and then by C18 semi-preparative HPLC (60-100% MeCN in H_2O gradient with 0.1% TFA) to provide **I-199** as a solid.

I-199 (120 mg, 0.21 mmol), Me_3SiCN (0.08 mL, 0.63 mmol), and $CHCl_3$ (1 mL) are heated in a microwave at 140 C for 20 min, then concentrated, and purified by C18 semi-preparative HPLC (5-100% MeCN in H_2O gradient with 0.1% TFA) to provide **I-200**.

NaH (60% in mineral oil; 16 mg, 0.41 mmol) is added to **I-200** (65 mg, 0.20 mmol) and DMF (1 mL) at 0 C. The mixture is stirred for 30 min, **I-201** (15 uL, 0.22 mmol) is added, and the mixture is stirred at rt for 2 h. Direct purification by reverse phase C18 semi-preparative HPLC (5-95% MeCN in H_2O gradient with 0.1% TFA) provides **C-075** and **C-076** both as solids.

Example 17: Synthesis of C-077



(S)-I-013 (3.2 g, 26 mmol) and $Ti(OiPr)_4$ (5.8 mL, 20 mmol) are added to **I-202** (4.5 mL, 23 mmol) and THF (20 mL). The mixture is stirred for 3 h at 45 C, then poured into stirring EtOAc (300 mL) and H_2O (300 mL). The mixture is filtered, the extract is separated, dried, filtered, concentrated, and purified by silica chromatography (0-70% EtOAc in heptane gradient) to provide **I-203** as a solid.

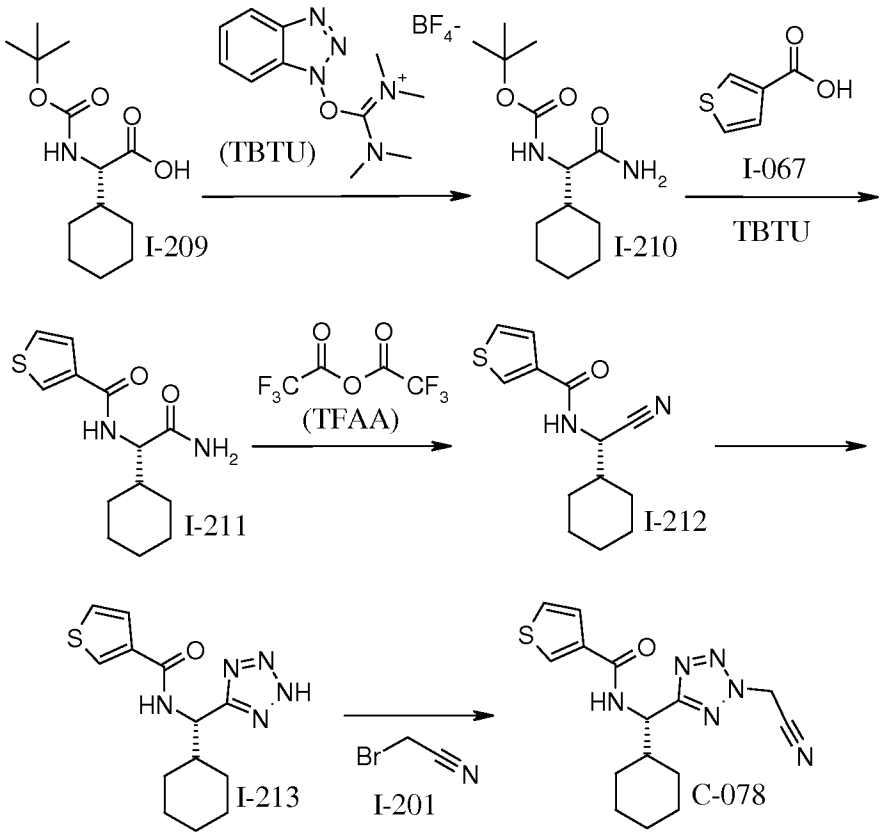
2.0 M **I-204** in Et_2O(8.5 mL, 17 mmol) is added slowly to **I-203** (3.0 g, 6.8 mmol) and THF (40 mL) at -78 C. The mixture is stirred for 30 min and saturated aqueous NH_4Cl is added. The mixture is extracted with EtOAc. The extract is concentrated to provide a solid. A portion of this material (1.0 g) is stirred with AcOH (12 mL) and H_2O (1 mL) at 60 C for 2 h. The mixture is concentrated and purified by silica chromatography (0-10% MeOH in CH_2Cl_2 gradient) to provide **I-205** as a solid.

60% NaH in mineral oil (64 mg, 1.6 mmol) is added to **I-205** (0.42 g, 1.5 mmol) in DMF (10 mL). When gas evolution subsides, **I-206** (0.22 g, 1.6 mmol) is added. The mixture is stirred for 16 h. EtOAc is added, and the mixture is washed with brine, dried, filtered, concentrated, and purified by silica chromatography (0-15% MeOH in CH_2Cl_2 gradient) to provide **I-207** as a solid.

4 M HCl in dioxane (0.5 mL, 2 mmol) is added to **I-207** (240 mg, 0.70 mmol) and MeOH (3 mL). The mixture is stirred for 3 h, then concentrated. The resulting mixture is combined with DMF (3 mL), Et_3N (0.39 mL, 2.8 mmol), **I-067** (0.11 g, 0.85 mmol), and TBTU (0.27 g, 0.85 mmol). The mixture is stirred for 1 h, concentrated, and purified by C18 semi-preparative HPLC (5-65% MeCN in H_2O gradient with 0.1% TFA) to provide **I-208** as a solid.

I-150 (19 mg, 0.10 mmol) is added to **I-208** (60 mg, 0.13 mmol) and DMF (1 mL). The mixture is stirred for 3 h. Direct purification by reverse phase C18 semi-preparative HPLC (5-95% MeCN in H_2O gradient with 0.1% TFA) provides **C-077** as a solid.

Example 18: Synthesis of C-078



A mixture of **I-209** (1.0 g, 3.9 mmol), Et_3N (0.65 mL, 4.7 mmol), TBTU (1.4 g, 4.3 mmol), and DMF (20 mL) is saturated with NH_3 and stirred for 1 h. It is then diluted with saturated aqueous $NaHCO_3$. The mixture is filtered to provide **I-210**.

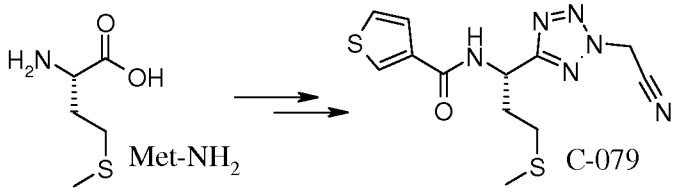
I-210 (480 mg, 1.9 mmol) is stirred in 4N HCl in dioxane (8 mL) for 15 min. The mixture is concentrated and DMF (10 mL), Et_3N (0.79 mL, 5.7 mmol), **I-067** (360 mg, 2.8 mmol), and TBTU (0.73 g, 2.3 mmol) are added. The resulting mixture is stirred for 16 h and diluted with saturated aqueous $NaHCO_3$. The mixture is filtered, and the solids are triturated with MeCN to provide **I-211** as a solid.

TFAA (0.26 mL, 1.7 mmol) is added dropwise to **I-211** (300 mg, 1.1 mmol) in pyridine (6 ml). After 30 min, MeOH is added and the mixture is concentrated, diluted with EtOAc, washed with brine, dried, filtered, and evaporated to provide **I-212**.

A mixture of **I-212** (230 mg, 0.93 mmol), NaN_3 (240 mg, 3.7 mmol), NH_4Cl (200 mg, 3.7 mmol), and DMF (6 mL) is stirred at 100 C for 16 h. It is cooled to rt, filtered, and purified directly by reverse phase C18 semi-preparative HPLC (5-70% MeCN in H_2O gradient with 0.1% TFA) provides **I-213** as a solid.

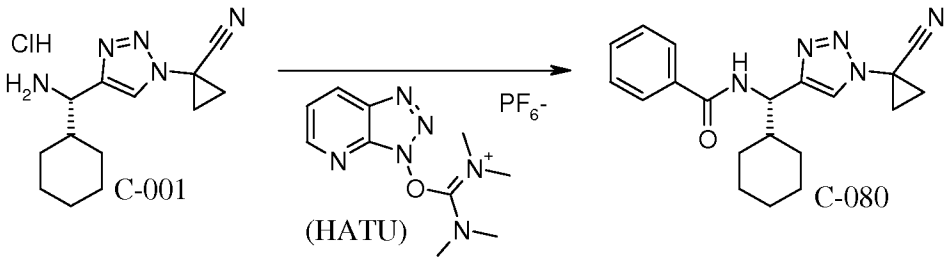
NaH (60% in mineral oil; 22 mg, 0.54 mmol) is added to **I-213** (150 mg, 0.51 mmol) in DMF (3 mL) at 0 C and stirred for 10 min. **I-201** (38 µL, 0.54 mmol) is added, and the mixture is stirred overnight. The mixture is directly purified by reverse phase C18 semi-preparative HPLC (5-80% MeCN in H_2O gradient with 0.1% TFA), then by silica chromatography (0-50% EtOAc in heptane) to provide **C-078** as a solid.

Example 19: Synthesis of C-079



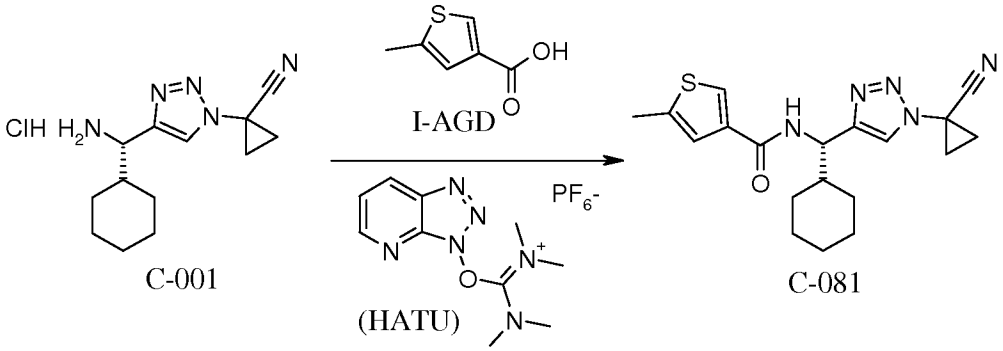
C-079 is prepared from Met-NH_2 in the same manner as **C-078**.

Example 20: synthesis of C-080



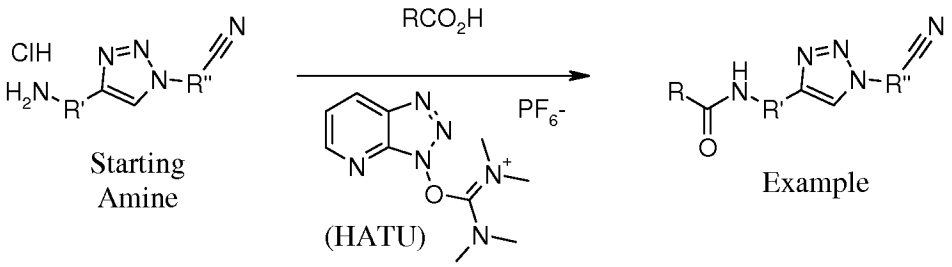
A mixture of **C-001** (20 mg, 0.07 mmol), Et_3N (20 µL, 0.15 mmol), and DMAc (0.5 mL) is added to a stirring mixture of benzoic acid (9 mg, 0.07 mmol), HATU (38 mg, 0.10 mmol), and DMAc (0.5 mL). The resulting mixture is stirred for 16 h, concentrated, and purified by C18 semi-preparative HPLC (5-85% MeCN in H_2O gradient with 0.1% TFA) to provide **C-080** as a solid.

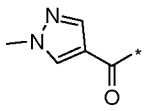
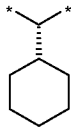
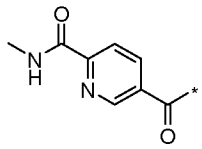
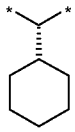
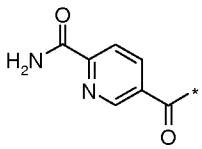
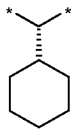
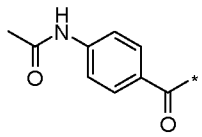
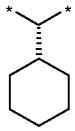
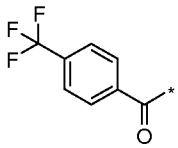
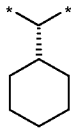
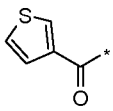
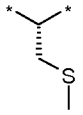
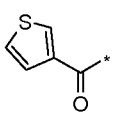
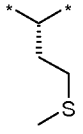
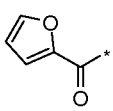
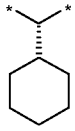
Example 21: Synthesis of C-081

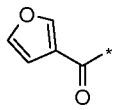
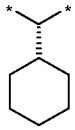
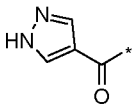
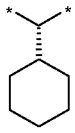
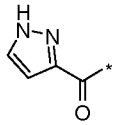
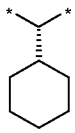
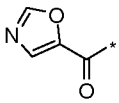
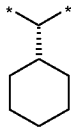
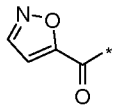
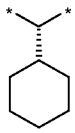
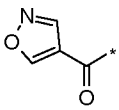
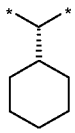
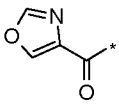
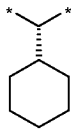
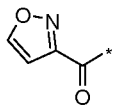
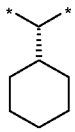
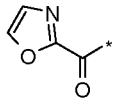
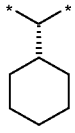
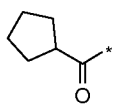
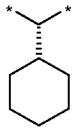


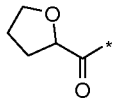
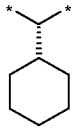
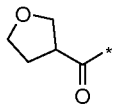
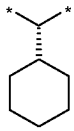
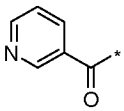
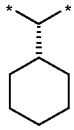
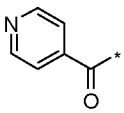
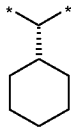
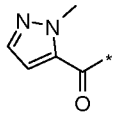
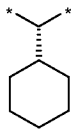
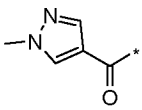
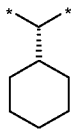
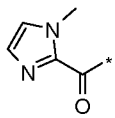
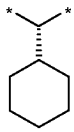
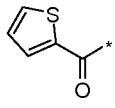
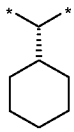
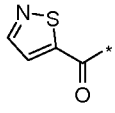
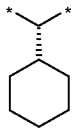
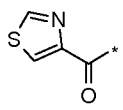
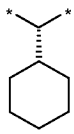
A mixture of **C-001** (38 mg, 0.11 mmol), Et_3N (30 µL, 0.23 mmol), and DMF (0.5 mL) is added to a stirring mixture of I-AGD (16 mg, 0.11 mmol), HATU (64 mg, 0.17 mmol), and DMF (0.5 mL). The resulting mixture is stirred for 16 h, concentrated, and purified by C18 semi-preparative HPLC (5-85% MeCN in H_2O gradient with 0.1% TFA) to provide **C-081** as a solid.

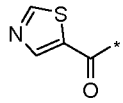
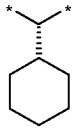
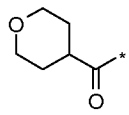
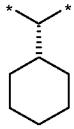
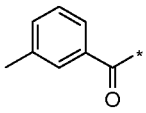
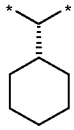
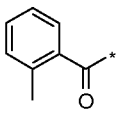
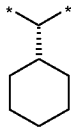
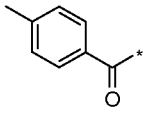
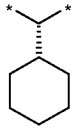
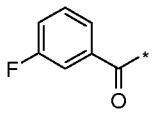
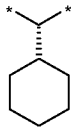
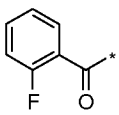
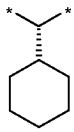
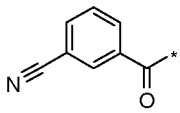
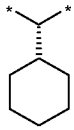
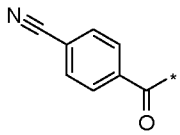
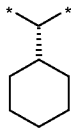
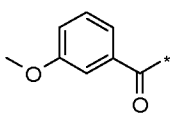
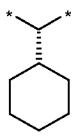
The following Examples are prepared from the appropriate carboxylic acid is the same manner as **C-080** and **C-081**.

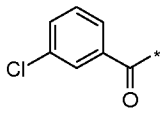
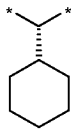
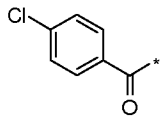
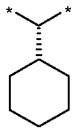
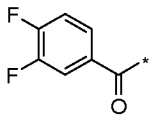
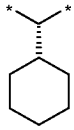
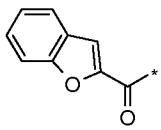
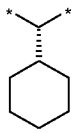
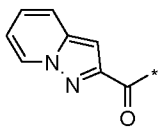
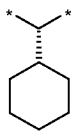
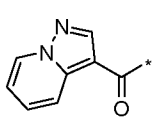
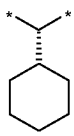
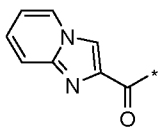
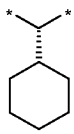
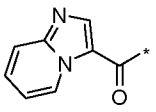
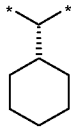
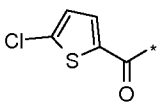
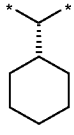
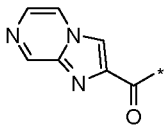
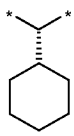


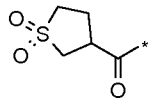
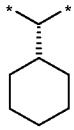
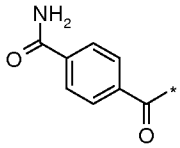
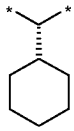
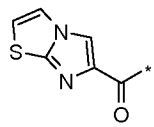
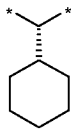
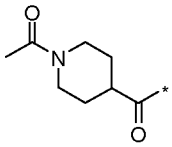
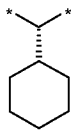
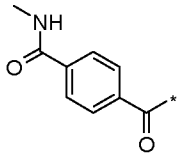
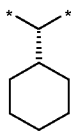
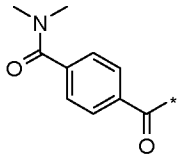
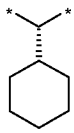
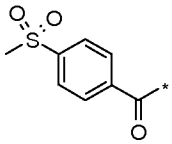
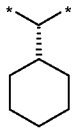
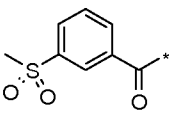
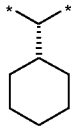
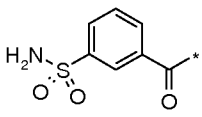
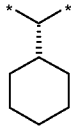
Example	Starting Amine	R	R'	R''
C-082	C-001			
C-083	C-001			
C-084	C-001			
C-085	C-001			
C-086	C-001			
C-087	I-156			
C-088	I-157			
C-089	C-001			

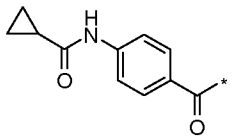
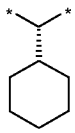
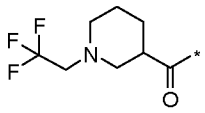
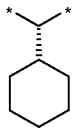
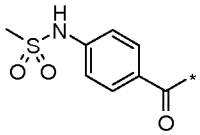
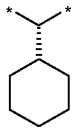
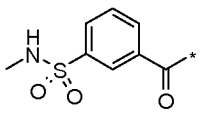
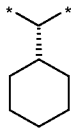
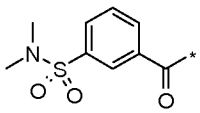
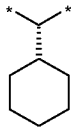
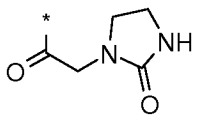
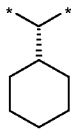
Example	Starting Amine	R	R'	R''
C-090	C-001			
C-091	C-001			
C-092	C-001			
C-093	C-001			
C-094	C-001			
C-095	C-001			
C-096	C-001			
C-097	C-001			
C-098	C-001			
C-099	C-001			

Example	Starting Amine	R	R'	R''
C-100	C-001			
C-101	C-001			
C-102	C-001			
C-103	C-001			
C-104	C-001			
C-105	C-001			
C-106	C-001			
C-107	C-001			
C-108	C-001			
C-109	C-001			

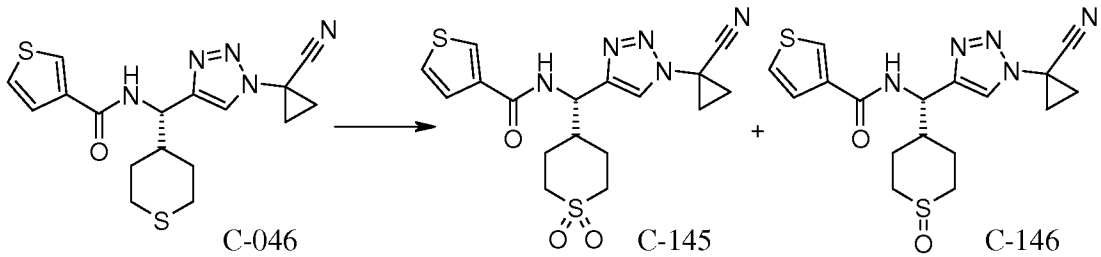
Example	Starting Amine	R	R'	R''
C-110	C-001			
C-111	C-001			
C-112	C-001			
C-113	C-001			
C-114	C-001			
C-115	C-001			
C-116	C-001			
C-117	C-001			
C-118	C-001			
C-119	C-001			

Example	Starting Amine	R	R'	R''
C-120	C-001			
C-121	C-001			
C-122	C-001			
C-123	C-001			
C-124	C-001			
C-125	C-001			
C-126	C-001			
C-127	C-001			
C-128	C-001			
C-129	C-001			

Example	Starting Amine	R	R'	R''
C-130	C-001			
C-131	C-001			
C-132	C-001			
C-133	C-001			
C-134	C-001			
C-135	C-001			
C-136	C-001			
C-137	C-001			
C-138	C-001			

Example	Starting Amine	R	R'	R''
C-139	C-001			
C-140	C-001			
C-141	C-001			
C-142	C-001			
C-143	C-001			
C-144	C-001			

Example 22: Synthesis of C-145 and C-146

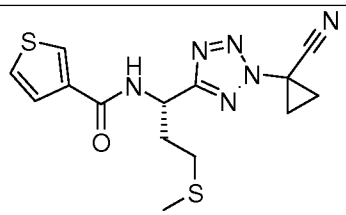
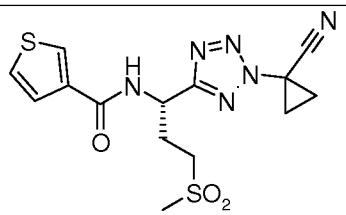
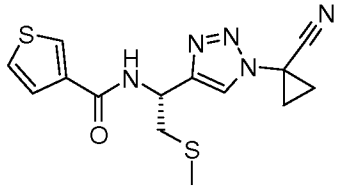
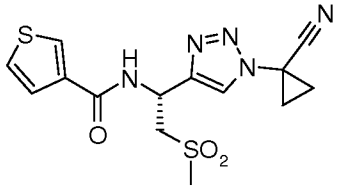
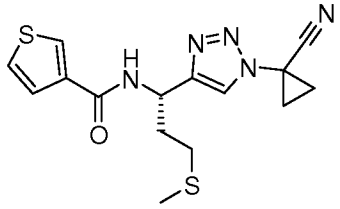
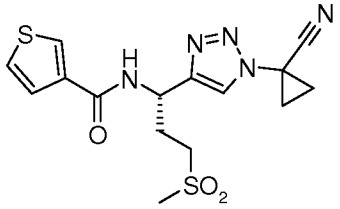


C-046 C-145 C-146

H_2O_2 (30%; 0.04 mL, 0.4 mmol) is added to **C-042** (50 mg, 0.13 mmol), $Na_2WO_4 \cdot (H_2O)_2$ (1 mg), $Bu_4N(HSO_4)$ (3 mg, 0.01 mmol), and EtOAc (5 mL). The mixture is stirred for 3 h, EtOAc (70 mL) is added, and the mixture is stirred with saturated aqueous Na_2SO_3 (10 mL) for 10 min. The organic phase is separated and washed with brine (15 mL), dried over Na_2SO_4, filtered, concentrated, and purified by

C18 semi-preparative HPLC (10-85% MeCN in H_2O gradient with 0.1% TFA) to provide **C-145** and **C-146** both as a solids.

The following sulfones are prepared from their corresponding thiol ethers in the same manner as **C-145**.

Thiol Ether		Sulfone Product	
C-079		**C-147**	
C-087		**C-148**	
C-088		**C-149**	

Analytical methods:

Method A: Agilent Zorbax C18 SB 3.5um 4.6x30mm cartridge, 2.5 mL/min

Time (min)	Water 0.1% formic acid (%)	Acetonitrile 0.1% formic acid (%)
0	95	5
1.7	5	95
2	5	95
2.1	95	5
2.3	95	5
2.5	95	5

Method B: Agilent Zorbax C18 SB 3.5um 4.6x30mm cartridge, 1.5 mL/min

Time	Water 0.1%	Acetonitrile 0.1%

(min)	formic acid (%)	formic acid (%)
0	95	5
7	5	95
9	5	95
9.3	95	5
10	95	5

Method C: Agilent SB-C18 1.8um 3x50mm column, 1.5 mL/min

Time (min)	Water 0.1% formic acid (%)	Acetonitrile 0.1% formic acid (%)
0	88	12
0.25	70	30
0.3	60	40
1.19	5	95
1.75	0	100
2.00	0	100

Method D: Agilent SB-C18 1.8um 3x50mm column, 1.5 mL/min

Time (min)	Water 0.1% formic acid (%)	Acetonitrile 0.1% formic acid (%)
0	95	5
3.8	10	90
4.5	0	100
5.0	0	100

Method E: Waters BEH 2.1x50mm C18 1.7um column, 0.8 mL/min

Time (min)	Water 0.1% formic acid (%)	Acetonitrile 0.1% formic acid (%)
0	90	10
1.19	5	95
1.7	5	95
2.0	5	95

Method F: Waters BEH 2.1x50mm C18 1.7um column, 0.8 mL/min

Time (min)	Water 0.1% formic acid (%)	Acetonitrile 0.1% formic acid (%)
0	90	10
4.5	5	95
4.58	5	95
5.0	5	95

Assays:

Cathepsin mediated hydrolysis of FR-Rhodamine110 substrate (Invitrogen R6502) is measured as the reduction in fluorescence with inhibitor compared to uninhibited controls. The final assay concentrations are 0.5nM Cat S and 4.2μM FR-Rhodamine110 in assay buffer. The assay buffer consists of 50 mM NaOAc, 2.5 mM EDTA, 10 mM $MgSO_4$, 0.1% CHAPS pH 4.8, and 500 μM TCEP. Inhibitors are serially diluted in DMSO, then diluted further with assay buffer, and 2 μL aliquots transferred to assay plates. The reaction takes place at 28 C for 1 hour. Data is plotted as POC vs. inhibitor concentration. The IC_{50} is defined as the concentration necessary to inhibit 50% of Cathepsin S activity. Preferred compound will have an IC_{50} of less than nM.

Method of Treatment

The present invention is directed to compounds of the formula (I) which are useful in the treatment of a disease and condition wherein the activity of inhibiting Cathepsin-S is of therapeutic benefit, including but not limited to the treatment of autoimmune diseases

These encompass autoimmune diseases and other diseases involving inappropriate antigen specific immune responses including, but not limited to, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, multiple sclerosis, Guillain-Barre syndrome, psoriasis, Grave's disease, myasthenia gravis, scleroderma, glomerulonephritis, dermatitis including contact and atopic dermatitis, insulin-dependent diabetes mellitus, endometriosis, and chronic obstructive pulmonary disease and asthma including allergic asthma. The compounds of the invention can also be used to treat other disorders associated with extracellular proteolysis such as Alzheimer's disease and atherosclerosis. The compounds of the invention can also be used to treat other disorders associated with inappropriate autoimmune responses, T-cell mediated immune responses, or extracellular proteolysis mediated by cathepsin S. Therefore, the invention also provides methods of modulating an autoimmune disease comprising administering to a patient in need of such treatment a pharmaceutically effect amount of a compound according to the invention.

Furthermore, the present invention relates to the use of a compound of the formula (I) for the treatment of multiple sclerosis, rheumatoid arthritis, psoriasis, atherosclerosis, and chronic obstructive pulmonary disease.

In a further aspect of the present invention the present invention relates to methods for the treatment of above mentioned diseases and conditions, which method comprises the administration of an effective amount of a compound of the formula (I) to a human being.

Dosage levels and requirements are well-recognized in the art and may be selected by those of ordinary skill in the art from available methods and techniques suitable for a particular patient. In some embodiments, dosage levels range from about 10-1000 mg/dose for a 70 kg patient. Although one dose per day may be sufficient, up to 5 doses per day may be given. For oral doses, up to 2000 mg/day may be required. As the skilled artisan will appreciate, lower or higher doses may be required depending on particular factors. For instance, specific dosage and treatment regimens will depend on factors such as the patient's general health profile, the severity and course of the patient's disorder or disposition thereto, and the judgment of the treating physician.

The compounds of the formula (I) may be used on their own or in combination with other active substances according to the invention, optionally also in combination with other pharmaceutically active substances.

Pharmaceutical Compositions:

The instant invention provides a bulk composition comprised of a CAT-S inhibitor of the formula (I) having desirable stability and purity wherein the purity is greater than 90%, 95% or 99%. The composition may additionally comprise in varying percentage, salts, solvates, hydrates, polymorphic forms, and the like, is intended to equally apply to the salt, solvate, hydrates, polymorphic forms of enantiomers, diastereomers, tautomers, racemates of the compounds of the formula (I).

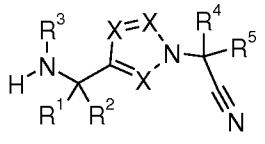
The bulk composition comprised of a CAT-S inhibitor of the formula (I) may be a pharmaceutical composition comprising as an effective amount of the active ingredient which is at least one compound of formula (I). The pharmaceutical composition of formula (I) additionally comprising at least one pharmaceutically acceptable carrier and/or adjuvant.

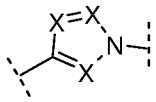
Suitable preparations for administering the compounds of formula will be apparent to those with ordinary skill in the art and include for example tablets, pills, capsules, suppositories, lozenges, troches, solutions, syrups, elixirs, sachets, injectables, inhalatives and powders etc. Methods for preparing such dosage forms are known. The content of the pharmaceutically active compound(s) should be in the range from contain at least about 15%, but more preferably at least about 20%, of a compound of the invention (w/w) or a combination thereof.

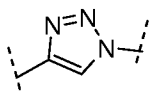
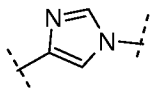
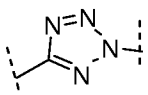
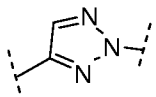
Suitable tablets may be obtained, for example, by mixing one or more compounds according to formula (I) with known excipients, for example inert diluents, carriers, disintegrants, adjuvants, surfactants, binders and/or lubricants . The tablets may also consist of several layers.

CLAIMS

1. A compound of the formula (I):


(I)

wherein the  ring is chosen from:

 (i),  (ii),  (iii) or  (iv) each optionally substituted by C_{1-3} alkyl;

R^1 is C_{1-7}alkyl, C_{3-7}cycloalkyl, aryl, heterocyclyl or heteroaryl each optionally substituted by one or more R^c;

R^2 is hydrogen or C_{1-7}alkyl;
or R^1 and R^2 taken together form a C_{3-7}cycloalkyl or C_{3-7} heterocyclyl ring optionally substituted by one or more halogen or C_{1-7}alkyl;

R^3 is -C(O)C_{1-7}alkyl, -C(O)C_{3-7}cycloalkyl, -C(O)aryl, -C(O)heteroaryl, -C(O)heterocyclyl, -C(O)NR^aR^b, -C(O)OR^a, -CH(R_f)-heteroaryl, -CH(R_f)-aryl, -CH(R_f)-heterocyclyl, aryl, C_{3-7}cycloalkyl or heteroaryl, each ring is optionally substituted by one or more R^d;

R^4 and R^5 are each independently hydrogen, C_{1-7}alkyl, aryl, or heteroaryl, or R^4 and R^5 taken together may form a C_{3-7}cycloalkyl or C_{3-7} heterocyclyl ring each ring being optionally substituted by C_{1-5}alkyl;

R^a, R^b each independently are hydrogen, C_{1-7}alkyl, aryl or heteroaryl, or may be taken together to form a saturated or unsaturated C_{3-7}cycloalkyl or C_{3-7} heterocyclyl ring;

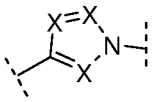
R^c is C_{1-7}alkyl, C_{1-7}alkoxy, C_{3-7}cycloalkyl, aryl, benzyl, halogen or -C(O)-O-benzyl;

R^d each is independently chosen from C_{1-7}alkyl, C_{1-7}alkoxy, C_{1-7}acyl, -C(O)NR^aR^b, -NH-C(O)-C_{1-7}alkyl, halogen, -CN, -$S(O)_m$-R_e, -NH-$S(O)_m$-R_e;

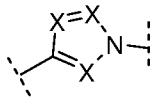
R_e is chosen from C_{1-7}alkyl and amino;

R^f each is independently chosen from hydrogen or C_{1-7}alkyl;

m is 0-2;

wherein one or more hydrogens on any one or more of R^1, R^2, R^3, R^2, R^4, R^5, R^a, R^b, R^c, R^d, R^e, R^f or  may be replaced by a halogen or deuterium atom;

with the proviso that

when  is (i), and

neither R^1 nor R^2 is hydrogen, and

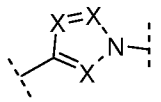
R^3 is -C(O)C_{1-7}alkyl, -C(O)C_{3-7}cycloalkyl, -C(O)aryl, -C(O)heteroaryl, -C(O)heterocyclyl,-CH(R^f)-heteroaryl, -CH(R^f)-aryl, -CH(R^f)-heterocyclyl, aryl, C_{3-7}cycloalkyl or heteroaryl

then R^4 and R^5 must either both be hydrogen or they must form a ring.

or a pharmaceutically acceptable salt thereof.

2. The compound of the formula (I) according claim 1 and wherein

R^2 = hydrogen or C_{1-7}alkyl if



a) is (i), or

b) R^4 and R^5 are hydrogen, or

c) R^4 and R^5 form a ring, or

d) R^3 is $-C(O)NR^aR^b$ or $-C(O)OR^a$,

or a pharmaceutically acceptable salt thereof.

3. The compound of the formula (I) according claim 2 and wherein

R^1 is C_{1-7}alkyl, C_{3-7}cycloalkyl, cyclohexyl-D11, phenyl, oxiranyl, azepanyl, diazepanyl, azetidinyl, pyrrolidinyl, pyrrolinyl, thiomorpholinyl, dioxalanyl, piperazinyl, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxanyl, piperidinonyl, tetrahydropyrimidonyl, piperidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,1-dioxo-hexahydro-1λ6-thiopyranyl, 1-oxo-hexahydro-1λ4-thiopyranyl, aziridinyl, thiadiazolyl, tetrazolyl, pyrrolyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyranyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzothienyl, quinolinyl, quinazolinyl, naphthyridinyl, indazolyl, triazolyl, purinyl, benzofuranyl, thiazolyl, isothiazolyl, imidazolyl, oxazolyl, isoxazolyl, thienyl, furanyl, pyrazolyl and pyridinyl, each optionally substituted by an R^c;

R^2 is hydrogen or C_{1-5}alkyl;
or R^1 and R^2 taken together form a C_{3-7}cycloalkyl;

R^3 = $-C(O)C_{1-7}$alkyl, $-C(O)C_{3-6}$cycloalkyl, -C(O)phenyl, -C(O)heterocyclyl wherein the heterocyclyl is chosen from oxiranyl, azepanyl, diazepanyl, azetidinyl, pyrrolidinyl, pyrrolinyl, thiomorpholinyl, dioxalanyl, piperazinyl, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxanyl, piperidinonyl, tetrahydropyrimidonyl, piperidinyl, tetrahydrothiopyranyl, morpholinyl, piperidinyl, tetrahydrofuranyl and tetrahydropyranyl, -C(O)heteroaryl wherein the heteroaryl is chosen from benzofuranyl, imidazo[2,1-b]thiazolyl, imidazo[1,2-a]pyrazinyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, thiazolyl, isothiazolyl, imidazolyl, oxazolyl, isoxazolyl, thienyl, furanyl, pyrazolyl and pyridinyl,

-C(O)NH-phenyl, heterocyclyl chosen from oxiranyl, azepanyl, diazepanyl, azetidinyl, pyrrolidinyl, pyrrolinyl, thiomorpholinyl, dioxalanyl, piperazinyl, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxanyl, piperidinonyl, tetrahydropyrimidonyl, piperidinyl, tetrahydrothiopyranyl, morpholinyl, piperidinyl, tetrahydropyranyl 1,1-Dioxo-1λ6-thiomorpholine, tetrahydrofuranyl, 1,1-dioxo-hexahydro-1λ6-thiopyranyl, piperidinyl and 2-oxo-imidazolidinyl, phenyl, C_{3-7}cycloalkyl, -CH_2-2-oxo-imidazolidinyl and -$CH(R_f)$-heteroaryl wherein the heteroaryl is chosen from thiazolyl, isothiazolyl, imidazolyl, oxazolyl, isoxazolyl, thienyl, furanyl, pyrazolyl and pyridinyl, each ring is optionally substituted by one or more R^d;

R^4 and R^5 are each independently hydrogen or C_{1-7}alkyl,or
R^4 and R^5 taken together may form a C_{3-6}cycloalkyl, oxiranyl, azepanyl, diazepanyl, azetidinyl, pyrrolidinyl, pyrrolinyl, thiomorpholinyl, dioxalanyl, piperazinyl, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxanyl, piperidinonyl, tetrahydropyrimidonyl, piperidinyl, tetrahydrothiopyranyl, morpholinyl, piperidinyl or tetrahydropyranyl each ring being optionally substituted by C_{1-3}alkyl;

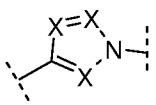
R^a, R^b are each independently hydrogen, C_{1-5}alkyl or phenyl;

R^c is C_{1-5}alkyl, C_{1-5}alkoxy, C_{3-6}cycloalkyl, phenyl, benzyl, fluoro or -C(O)-O-benzyl;

R^d is independently chosen from C_{1-5}alkyl, C_{1-5}alkoxy, C_{1-5}acyl, -$C(O)NR^aR^b$, -NH-C(O)-C_{1-5}alkyl, halogen, -CN, -$S(O)_2$-R_e, -NH-$S(O)_2$-R_e;

R_e is chosen from C_{1-5}alkyl and amino;

R^f is independently chosen from hydrogen and C_{1-5}alkyl;

wherein one or more hydrogens on any one or more of R^1, R^2, R^3, R^2, R^4, R^5, R^a, R^b, R^c, R^d, R^e, R^f or  may be replaced by a halogen or deuterium atom;

or a pharmaceutically acceptable salt thereof.

4. The compound of the formula (I) according claim 3 and wherein

R^1 is t-butyl, sec-butyl, 3-pentyl, cyclohexyl, -CH_2-cyclohexyl, cyclopentyl, cyclopropyl, phenyl, cyclohexyl-D11, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,1-dioxo-hexahydro-1λ6-thiopyranyl or 1-oxo-hexahydro-1λ4-thiopyranyl, each optionally substituted by an R^c;

R^2 is hydrogen or methyl;
or R^1 and R^2 taken together form a cyclohexyl;

R^3 is -C(O)C_{1-7}alkyl, -C(O) cyclopropyl, -C(O)cyclopentyl, -C(O)phenyl, -C(O)heterocyclyl wherein the heterocyclyl is chosen from morpholinyl, piperidinyl, tetrahydrofuranyl and tetrahydropyranyl, -C(O)heteroaryl wherein the heteroaryl is chosen from benzofuranyl, imidazo[2,1-b]thiazolyl, imidazo[1,2-a]pyrazinyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, thiazolyl, isothiazolyl, imidazolyl, oxazolyl, isoxazolyl, thienyl, furanyl, pyrazolyl and pyridinyl, -C(O)NH-phenyl, heterocyclyl chosen from 1,1-Dioxo-1λ6-thiomorpholine, tetrahydrofuranyl, 1,1-dioxo-hexahydro-1λ6-thiopyranyl, piperidinyl and 2-oxo-imidazolidinyl, phenyl, cyclohexyl and –CH_2-thienyl;

R^4 and R^5 are each independently hydrogen, methyl or n-butyl or
R^4 and R^5 taken together may form cyclopropyl, piperidinyl, tetrahydropyranyl or 1-methyl-piperidinyl;

R^a, R^b are each independently hydrogen, methyl or phenyl;

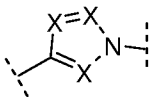
R^c is methyl, methoxy, cyclohexyl, phenyl, benzyl, fluoro or -C(O)-O-benzyl;

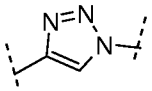
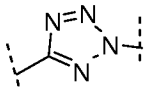
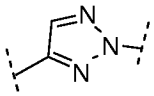
R^d is independently chosen from methyl, -CF_3, -CH_2CF_3, methoxy, acetyl, -C(O)NH_2, -C(O)$NHCH_3$, -C(O)$N(CH_3)_2$, -NH-C(O)-methyl, -S(O)$_2$-CH_3, -S(O)$_2$-NH_2, -NH-S(O)$_2$-CH_3, F, Cl and –CN;

R^f is independently chosen from hydrogen, methyl and CF_3;

or a pharmaceutically acceptable salt thereof.

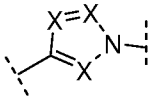
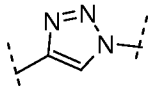
5. The compound of the formula (I) according claim 4 and wherein

wherein the  ring is chosen from:

 (i),  (iii) or  (iv);

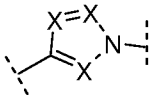
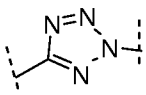
or a pharmaceutically acceptable salt thereof.

6. The compound of the formula (I) according claim 5 and wherein

wherein the  ring is  (i)

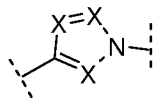
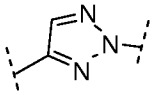
or a pharmaceutically acceptable salt thereof.

7. The compound of the formula (I) according claim 5 and wherein

wherein the  ring is  (iii)

or a pharmaceutically acceptable salt thereof.

8. The compound of the formula (I) according claim 5 and wherein

wherein the  ring is:  (iv)

or a pharmaceutically acceptable salt thereof.

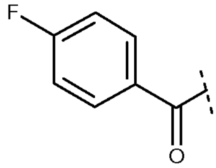
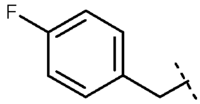
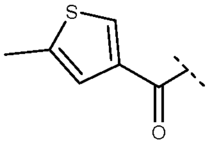
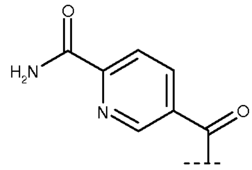
9. The compound of the formula (I) according claim 5 and wherein

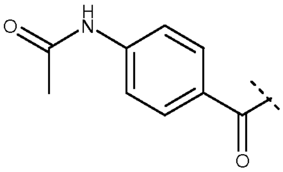
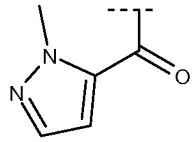
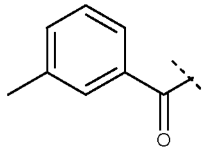
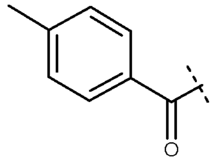
R^1 is cyclohexyl, -CH_2-cyclohexyl, 4,4-difluorocyclohexyl, 3-methoxycyclohexyl, 4-methylcyclohexyl, 4-trifluoromethylcyclohexyl, cyclohexyl-D11, cyclopentyl,3-pentyl, sec-butyl, tetrahydropyranyl, or tetrahydrothiopyranyl;
or a pharmaceutically acceptable salt thereof.
.

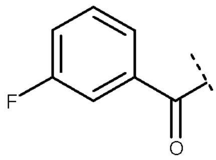
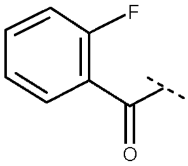
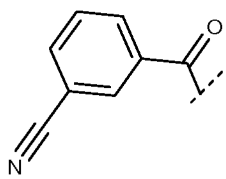
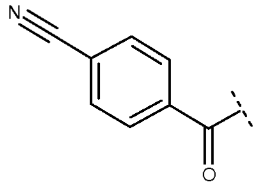
10. The compound of the formula (I) according claim 9 and wherein
R^2 is hydrogen or methyl;
or R^1 and R^2 taken together form a cyclohexyl;
or a pharmaceutically acceptable salt thereof.

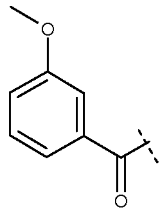
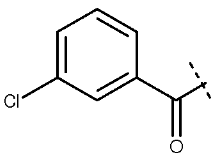
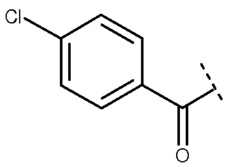
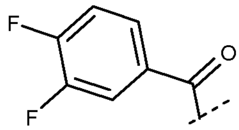
11. The compound of the formula (I) according claim 10 and wherein

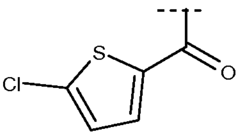
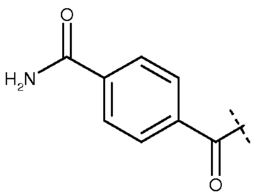
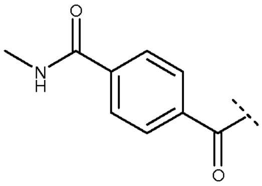
R^3 is -C(O)cyclopropyl, -C(O)phenyl, -C(O)heterocyclyl wherein the heterocyclyl is chosen from morpholinyl and piperidinyl, -C(O)heteroaryl wherein the heteroaryl is chosen from imidazo[2,1-b]thiazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, thienyl, furanyl, pyrazolyl and pyridinyl,
or R^3 is

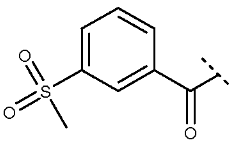
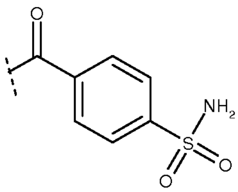
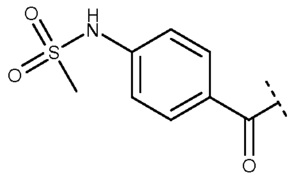
 ,  ,  ,  ,

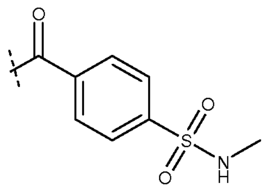
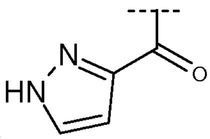
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 or  ;

or a pharmaceutically acceptable salt thereof.

.

12. The compound of the formula (I) according claim 11 and wherein

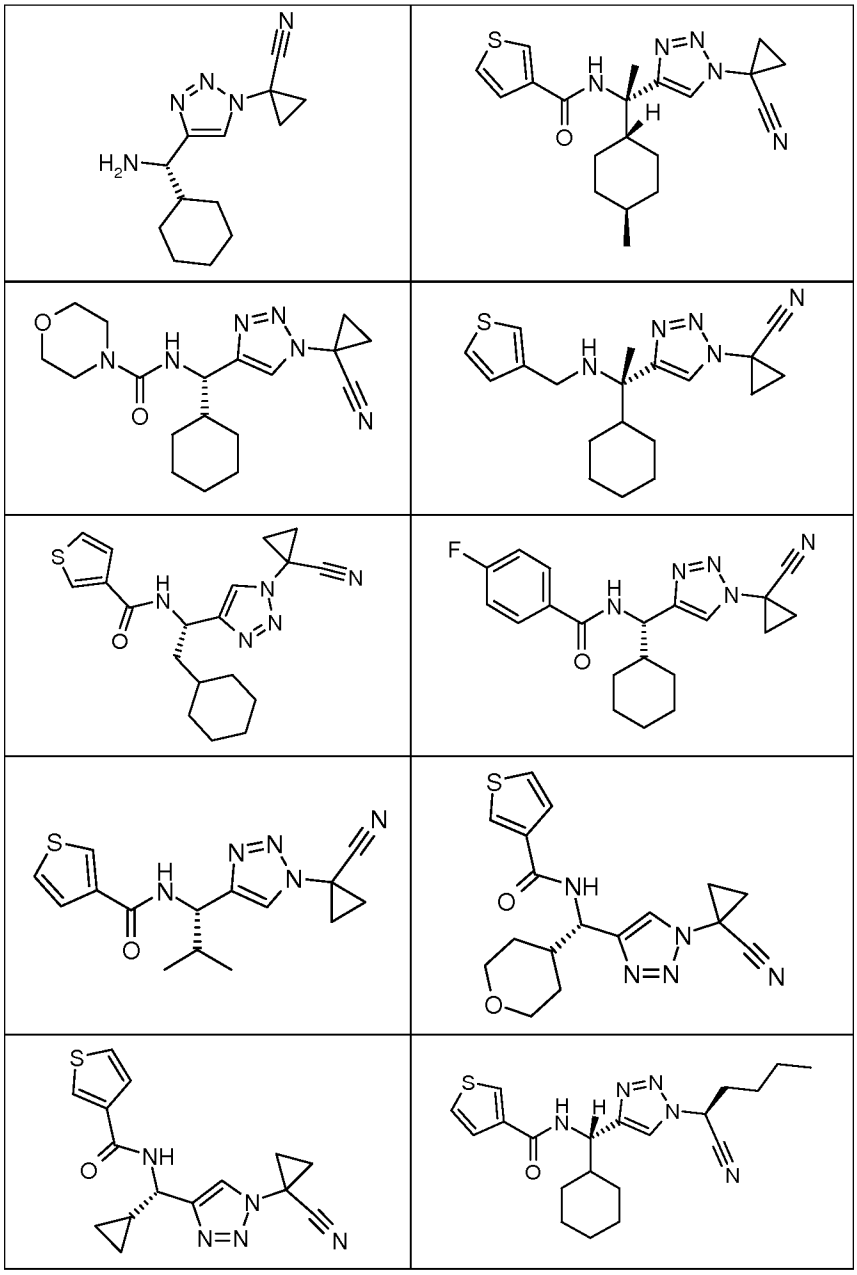
R^4 and R^5 are each independently hydrogen, methyl or n-butyl or

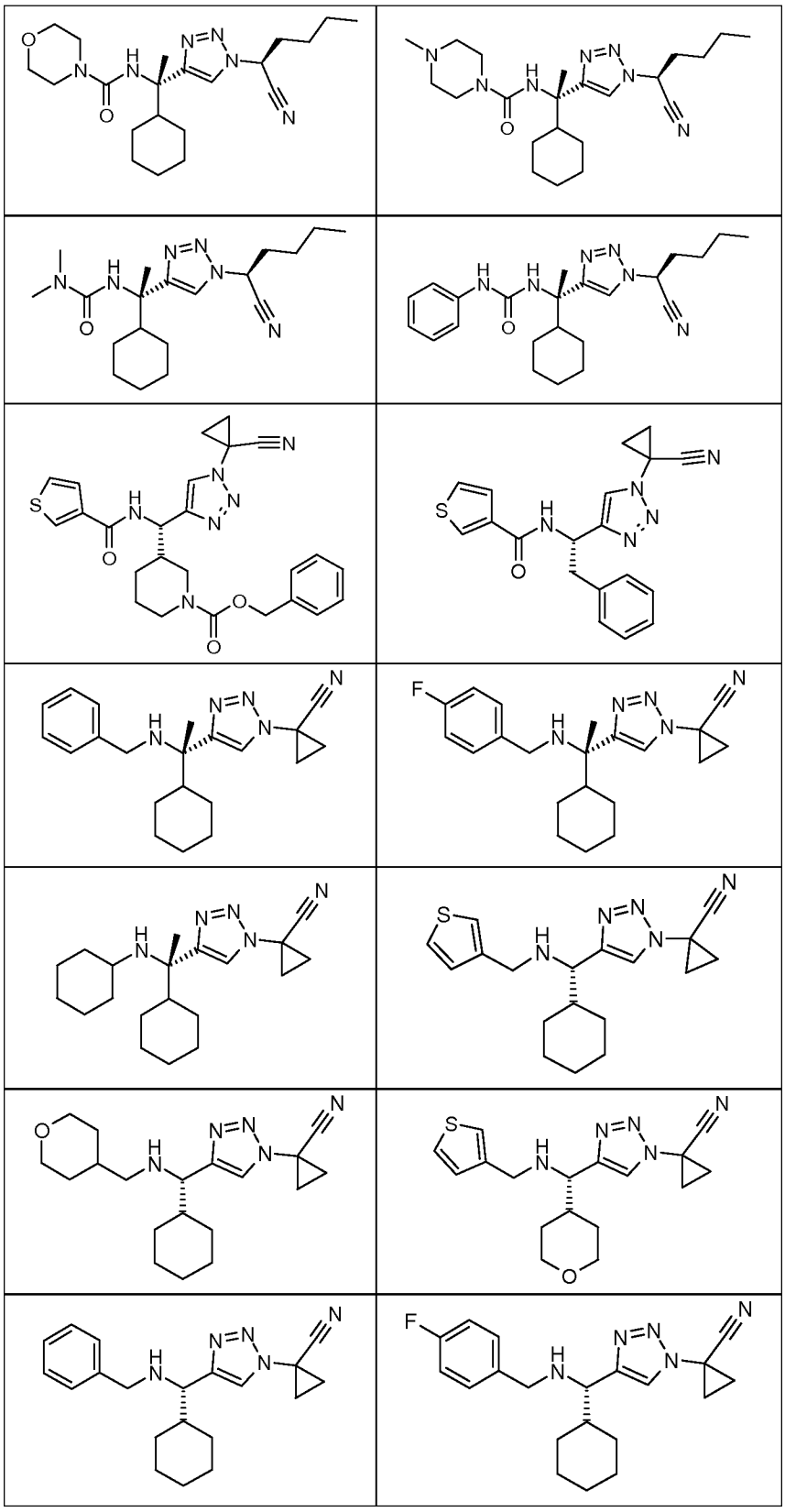
R^4 and R^5 taken together may form cyclopropyl, piperidinyl, or tetrahydropyranyl;

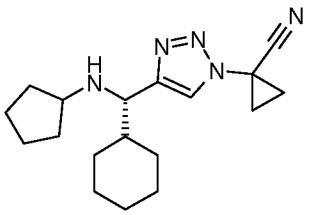
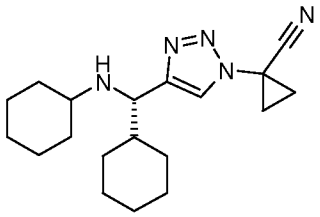
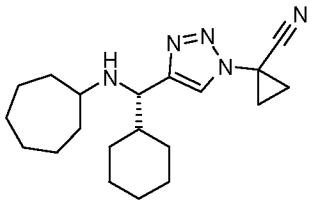
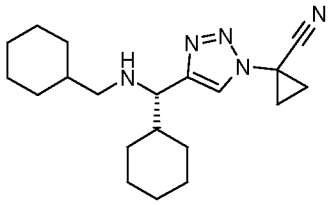
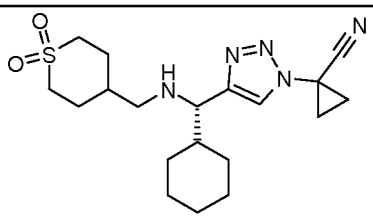
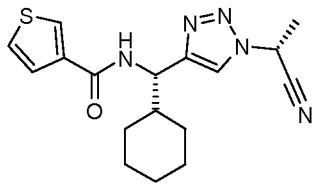
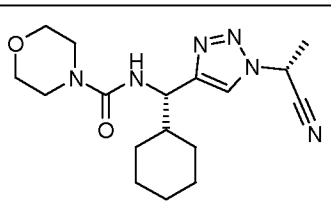
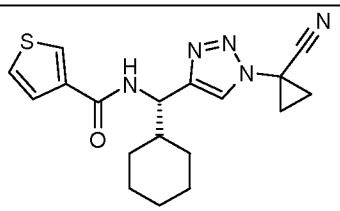
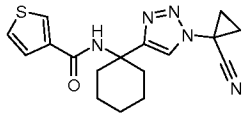
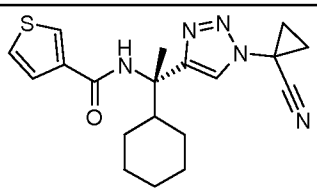
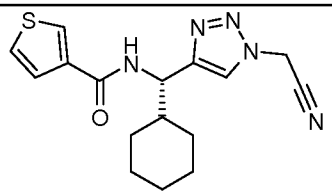
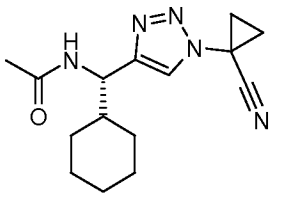
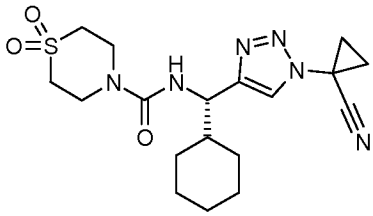
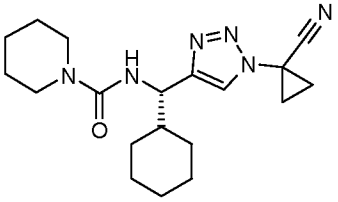
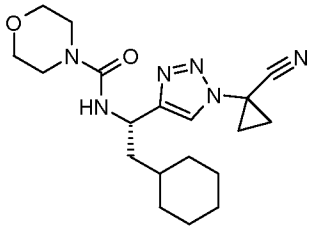
or a pharmaceutically acceptable salt thereof.

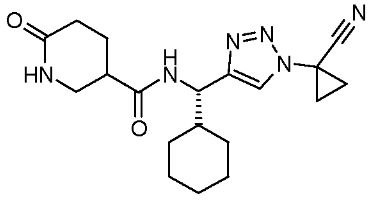
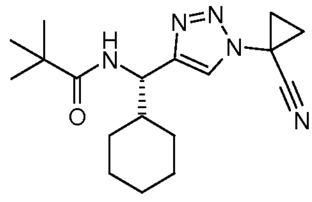
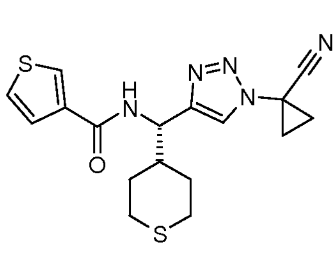
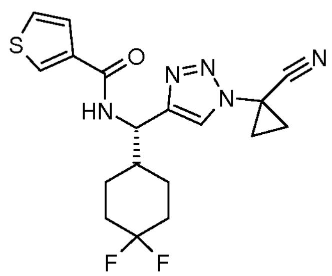
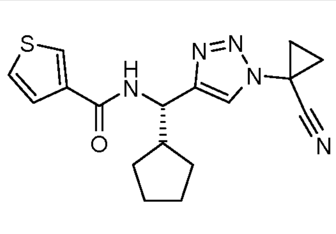
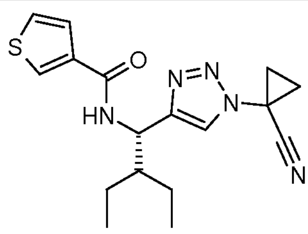
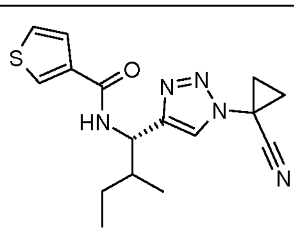
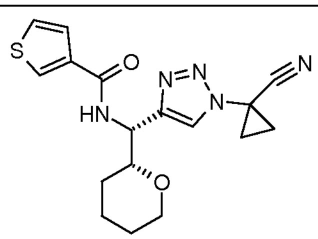
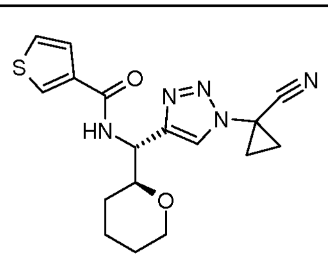
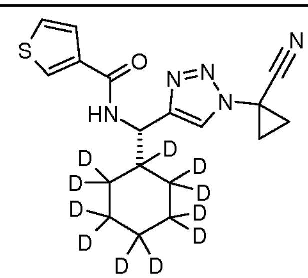
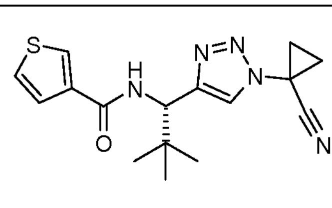
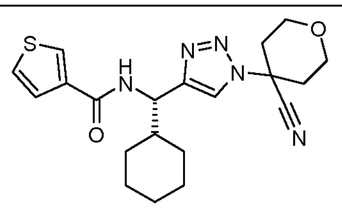
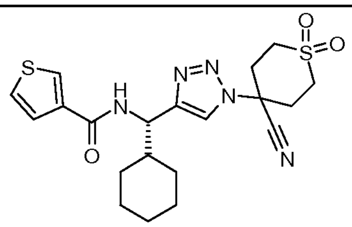
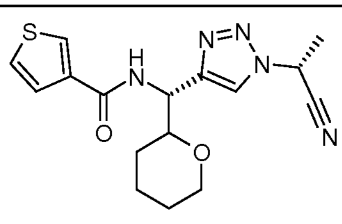
.

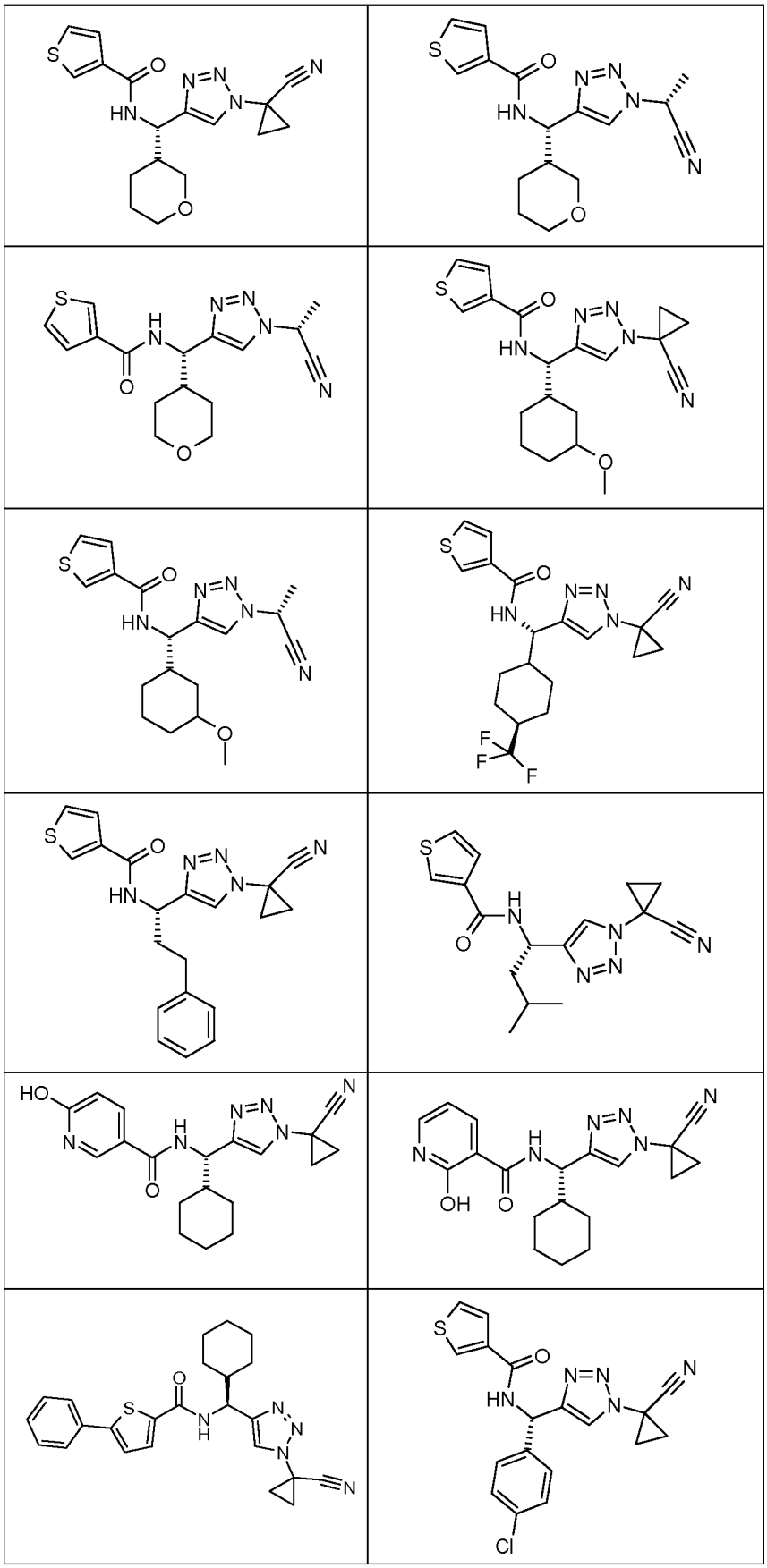
13. A compound chosen from

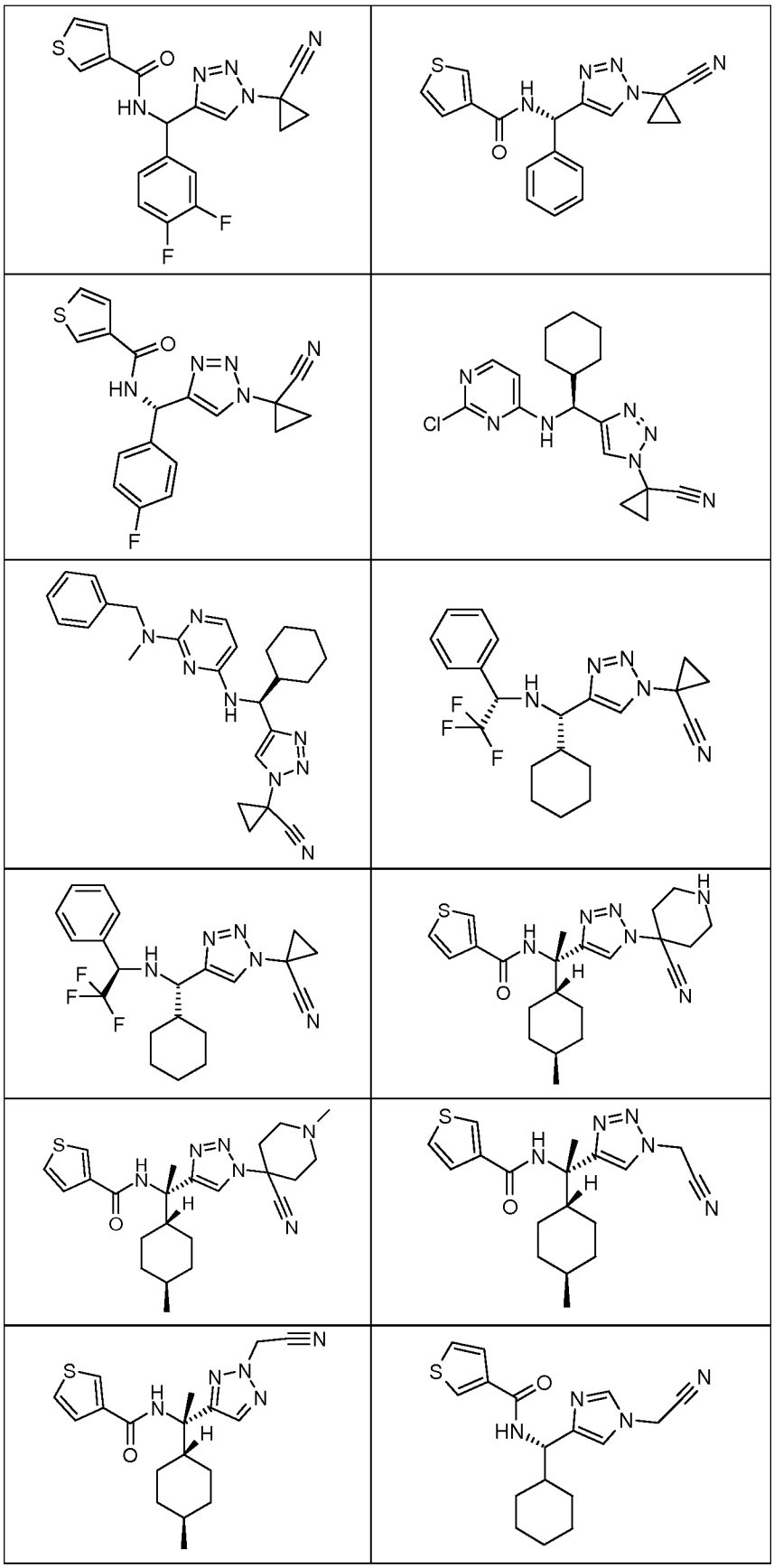


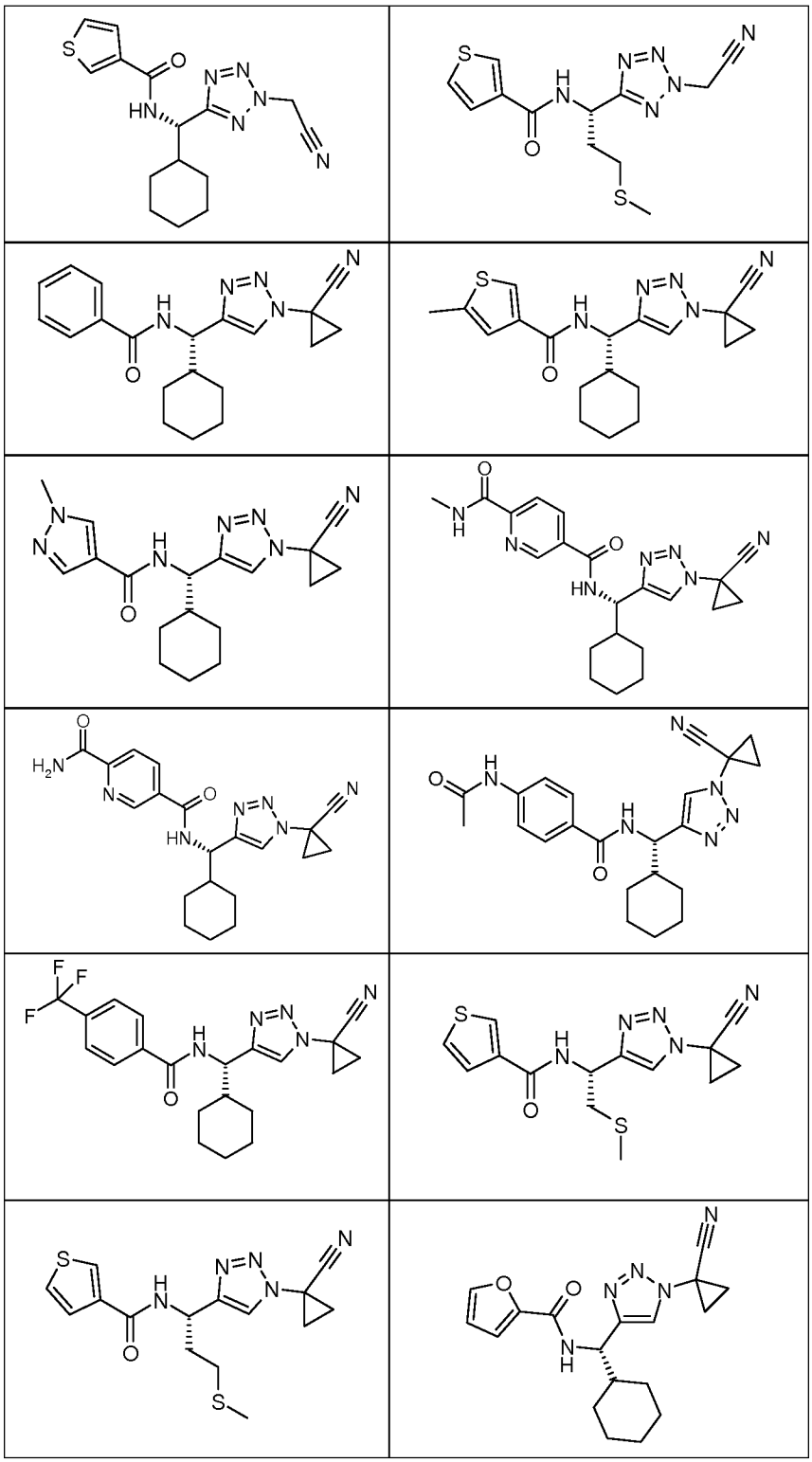


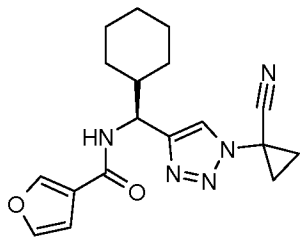
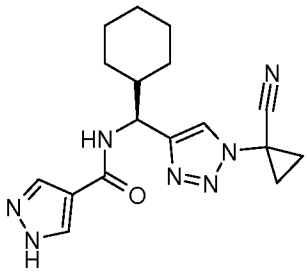
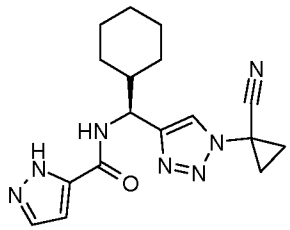
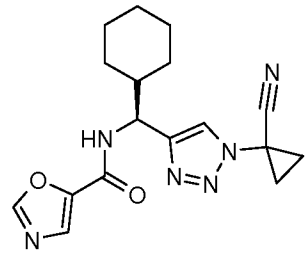
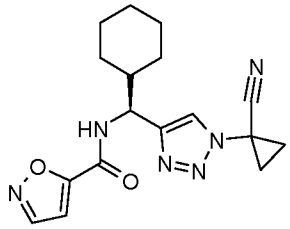
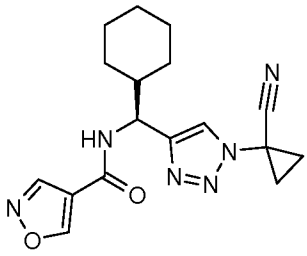
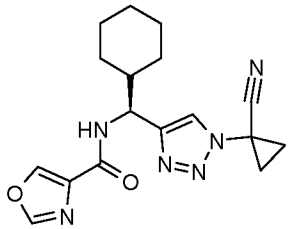
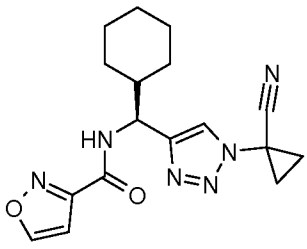
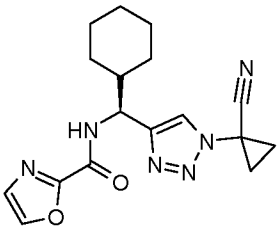
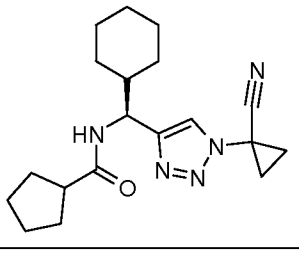
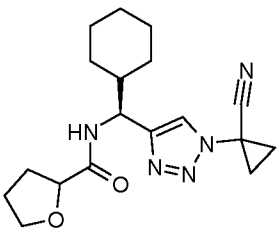
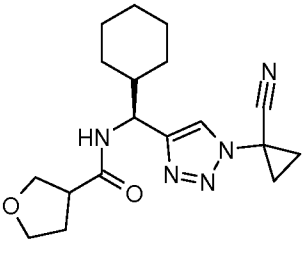
	
	
	
	
	
	
	
	

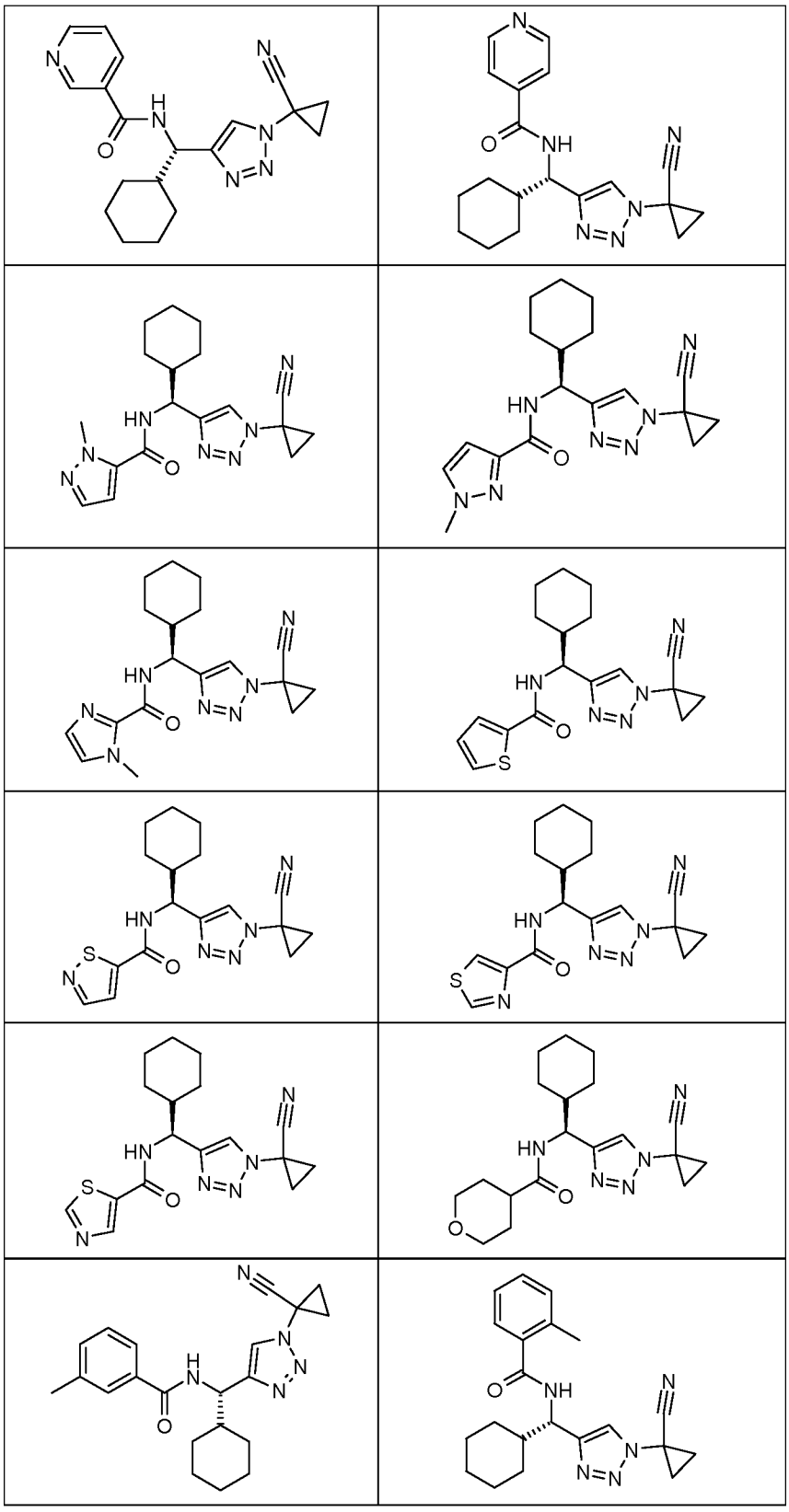
	
	
	
	
	
	
	

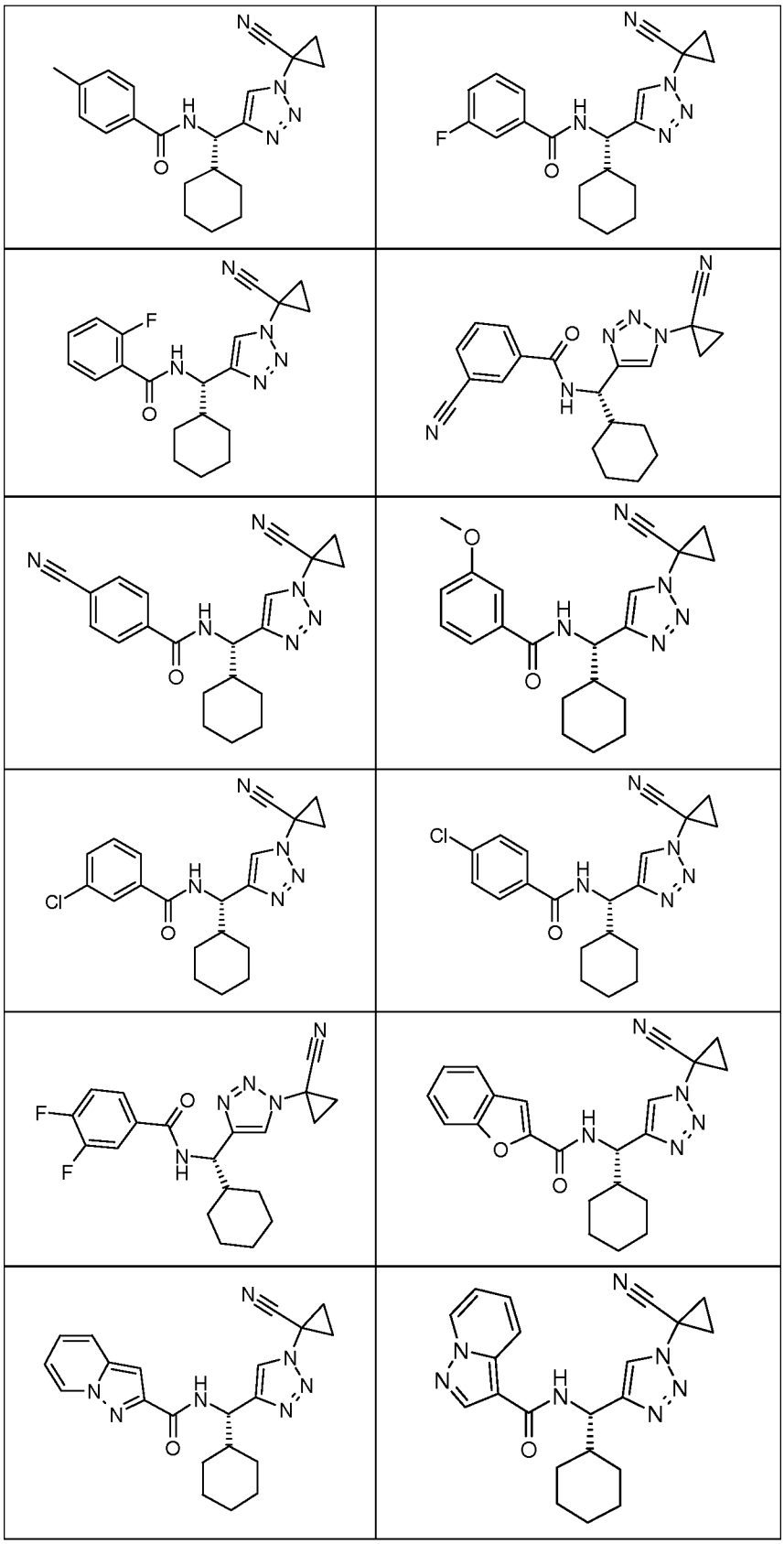


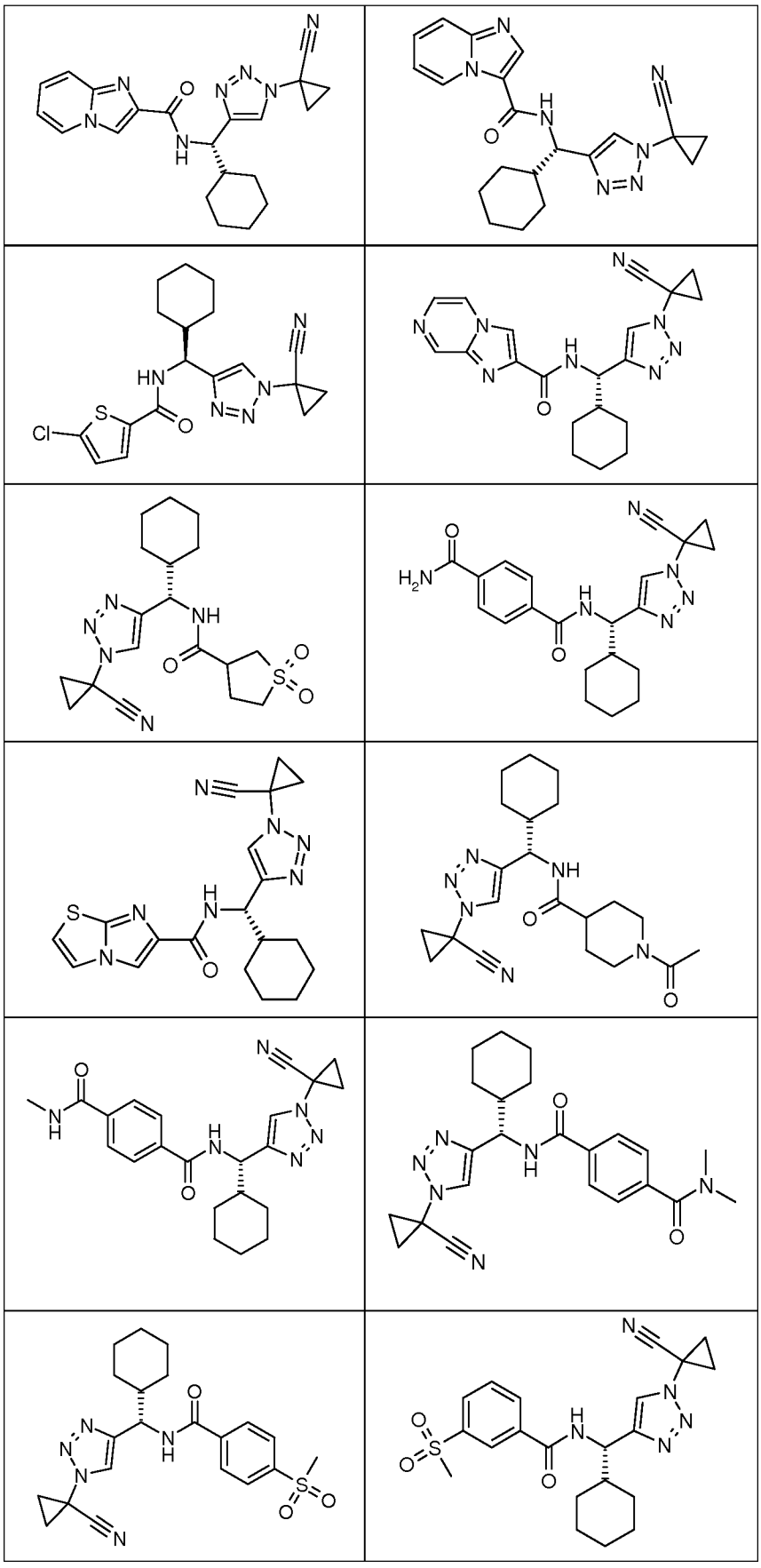


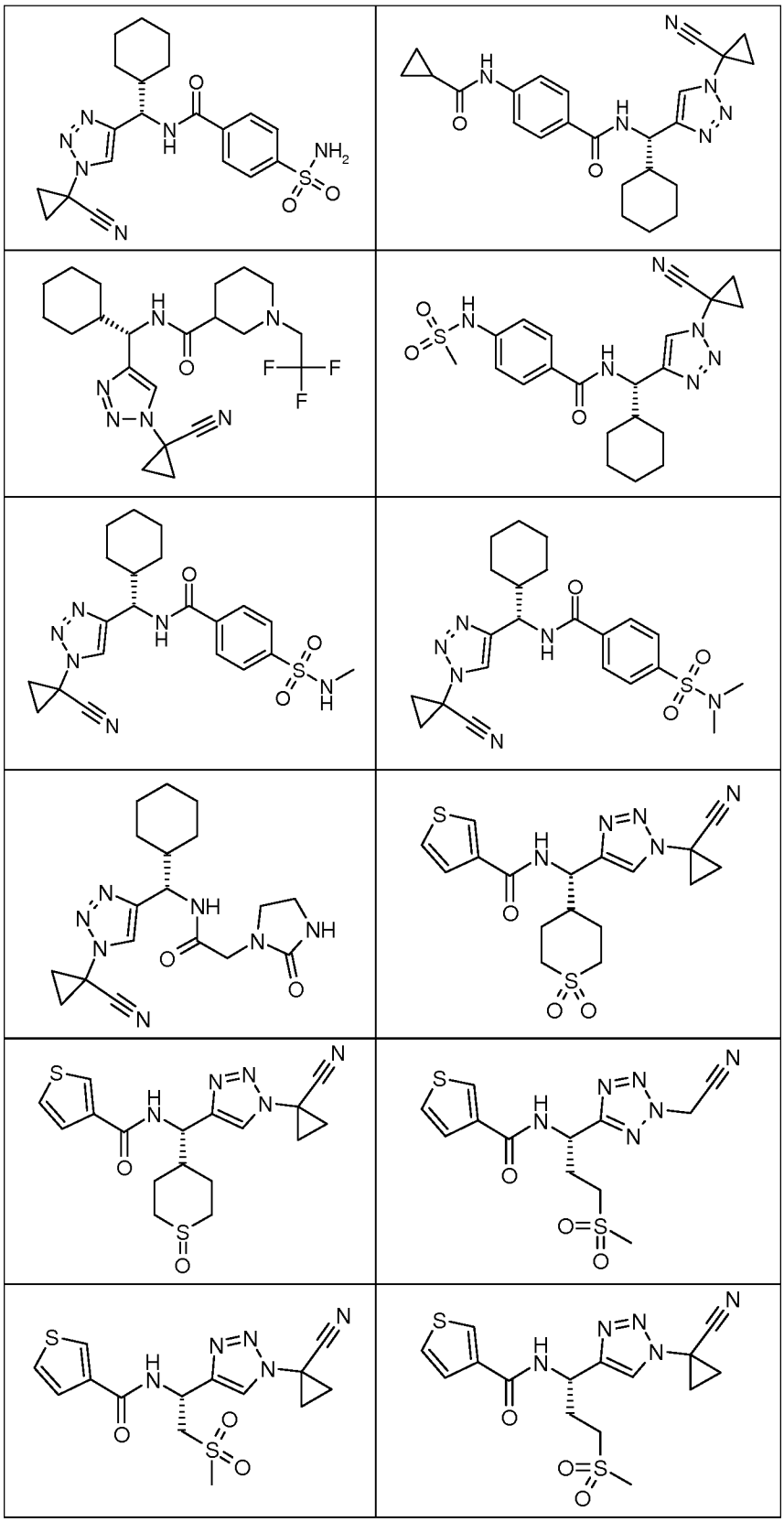










or the pharmaceutically acceptable salts thereof.

14. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 and one or more pharmaceutically acceptable carriers and/or adjuvants.

15. A method of treating a diease or condition chosen from rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, multiple sclerosis, Guillain-Barre syndrome, psoriasis, Grave's disease, myasthenia gravis, scleroderma, glomerulonephritis, dermatitis including contact and atopic dermatitis, insulin-dependent diabetes mellitus, endometriosis, chronic obstructive pulmonary disease, asthma,Alzheimer's disease and atherosclerosis comprising administering to a patient in need of such treatment a pharmaceutically effect amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/026805

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D249/04 C07D401/12 C07D403/12 C07D405/12 C07D409/12
C07D409/14 C07D413/12 C07D417/12 C07D471/04 C07D487/04
C07D513/04 A61K31/4192 A61P17/00 A61P25/28 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATTERSON A W ET AL: "Identification of selective, nonpeptidic nitrile inhibitors of cathepsin S using the substrate activity screening method", JOURNAL OF MEDICINAL CHEMISTRY, vol. 49, no. 21, October 2006 (2006-10), pages 6298-6307, XP002630675, ISSN: 0022-2623, DOI: 10.1021/JM060701S page 6302; table 5 -----	1-15
A	WO 2004/083182 A1 (BOEHRINGER INGELHEIM PHARMA [US]; HICKEY EUGENE R [US]; LIU WIEMEN [US) 30 September 2004 (2004-09-30) cited in the application the whole document -----	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 March 2011	08/04/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Duval, Eric

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/026805

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-15(partially)

   compounds of formula (I) where R2=H

   ---

2. claims: 1-15(partially)

   compounds of formula (I) where R2=alkyl and R4=R5=H

   ---

3. claims: 1-15(partially)

   compounds of formula (I) where R2=alkyl and one of R4/R5 is H while the other is different from H.

   ---

4. claims: 1-15(partially)

   compounds of formula (I) where R2=alkyl and both R4 and R5 are different from H (or R4/R5 form together a cycle)

   ---

5. claims: 1-8, 10-15(all partially)

   compounds of formula (I) where R1 and R2 together form a ring

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/026805

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004083182 A1	30-09-2004	AR 043563 A1	03-08-2005
		AU 2004221860 A1	30-09-2004
		BR PI0408299 A	07-03-2006
		CA 2518728 A1	30-09-2004
		CN 1761652 A	19-04-2006
		EP 1606258 A1	21-12-2005
		JP 4455506 B2	21-04-2010
		JP 2006519768 T	31-08-2006
		KR 20050109553 A	21-11-2005
		MX PA05008240 A	05-10-2005
		NZ 542905 A	30-04-2009
		PE 03122005 A1	14-06-2005
		ZA 200505418 A	31-01-2007