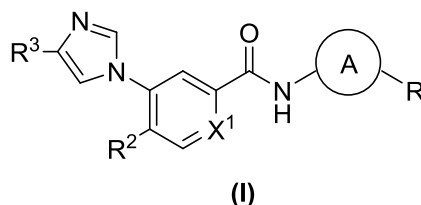


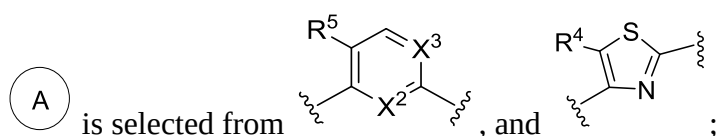
CLAIMS

WHAT IS CLAIMED:

1. A compound represented by Formula (I) or a pharmaceutically acceptable salt, or ester thereof:



wherein;

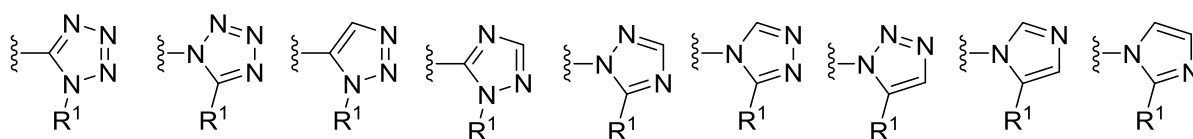


X¹, X² and X³ are each independently selected from N or C(R⁵);

R³, R⁴ and R⁵ are each independently selected from the group consisting of:

- 1) Hydrogen;
- 2) Halogen;
- 3) -NO₂;
- 4) Cyano;
- 5) Optionally substituted -C₁-C₈ alkyl;
- 6) Optionally substituted -C₃-C₈ cycloalkyl;
- 7) Optionally substituted 3- to 8- membered heterocycloalkyl; and
- 8) Optionally substituted -C₁-C₈ alkoxyl;

R is selected from:

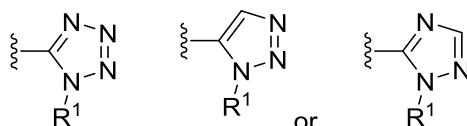


, each of which is optionally substituted when possible;

R¹ is selected from the group consisting of:

- 1) Hydrogen;
- 2) Optionally substituted -C₁-C₈ alkyl;
- 3) Optionally substituted -C₂-C₈ alkenyl;
- 4) Optionally substituted -C₂-C₈ alkynyl;
- 5) Optionally substituted -C₃-C₈ cycloalkyl;

- 6) Optionally substituted aryl;
- 7) Optionally substituted arylalkyl;
- 8) Optionally substituted 3- to 8- membered heterocycloalkyl;
- 9) Optionally substituted heteroaryl;
- 10) Optionally substituted heteroarylalkyl; and
- 11) $-N(R^6)(R^7)$;



provided that when R is , or , R^1 is not $-N(R^6)(R^7)$;

R^2 is selected from the group consisting of:

- 1) Hydrogen;
- 2) Halogen;
- 3) $-NO_2$;
- 4) Cyano;
- 5) Optionally substituted $-C_1-C_8$ alkyl;
- 6) Optionally substituted $-C_2-C_8$ alkenyl;
- 7) Optionally substituted $-C_2-C_8$ alkynyl;
- 8) Optionally substituted $-C_3-C_8$ cycloalkyl;
- 9) Optionally substituted aryl;
- 10) Optionally substituted arylalkyl;
- 11) Optionally substituted 3- to 8- membered heterocycloalkyl;
- 12) Optionally substituted heteroaryl;
- 13) Optionally substituted heteroarylalkyl;
- 14) $-N(R^6)(R^7)$;
- 15) $-S(O)_2N(R^6)(R^7)$;
- 16) $-N(R^6)C(O)(R^7)$; and
- 17) $-N(R^6)S(O)_2(R^7)$;

wherein R^6 and R^7 are independently selected from the group consisting of hydrogen, $-C_1-C_{15}$ alkyl, preferably C_1-C_8 -alkyl; cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is optionally substituted with 1-3 substituents independently selected from halo, alkyl, alkylamino, dialkylamino, alkylC(O)NH-, arylC(O)NH-, heteroarylC(O)-NH, $-CN$, alkoxy, $-CF_3$, aryl, and heteroaryl,

5

Chemical structures of various cyclic and branched molecules, including alcohols, fluorides, and perfluorinated compounds, with stereochemical indicators.

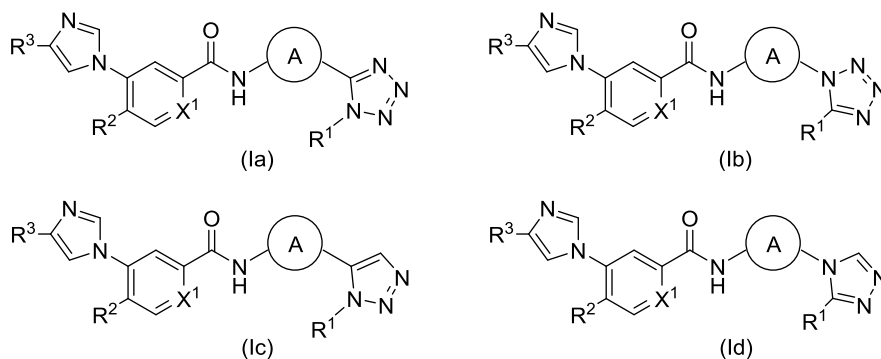
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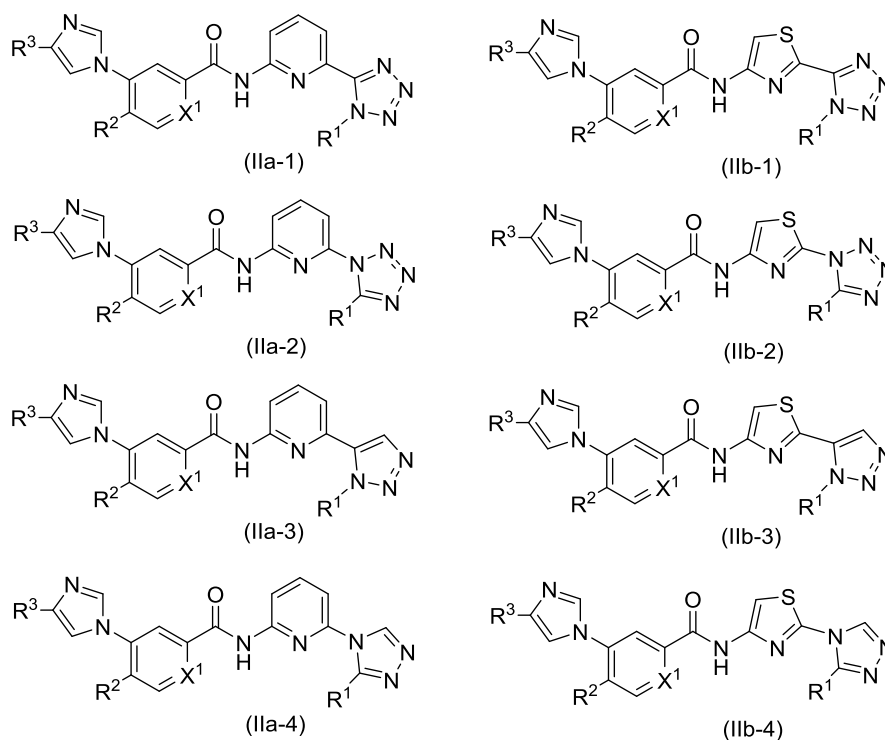
5. The compound of claim 1, which is selected from compounds of Formula **(Ia)**, **(Ib)**, **(Ic)**, or **(Id)**, or a pharmaceutically acceptable salt thereof:



wherein $\textcircled{\text{A}}$, R^1 , R^2 , R^3 and X^1 are as defined claim 1.

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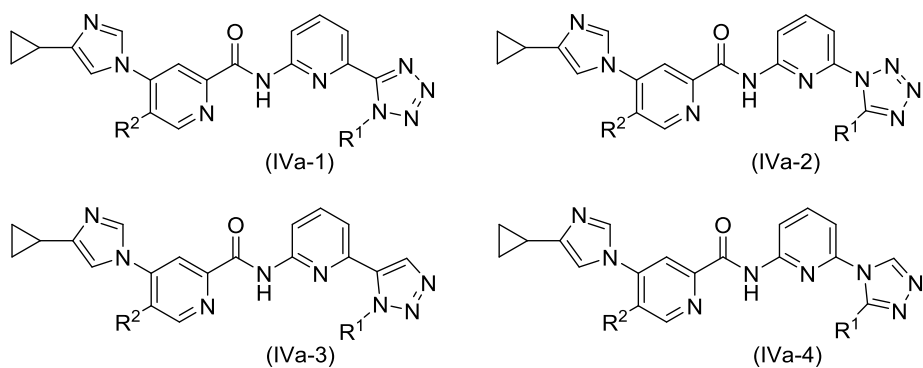
6. The compound of claim 1, which is selected from compounds of FormulaE **(IIa-1)~(IIa-4)**, or **(IIb-1)~(IIb-4)**, or a pharmaceutically acceptable salt thereof:



wherein R^1 , R^2 , R^3 , and X^1 are as defined claim 1.

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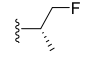
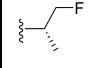
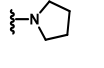
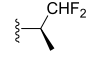
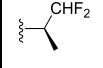
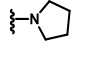
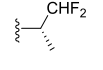
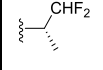
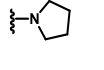
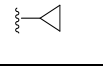
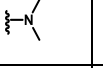
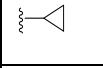
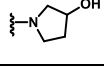
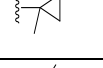
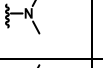
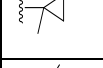
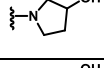
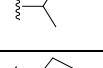
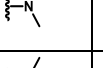
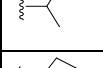
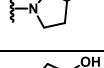
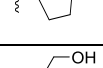
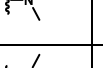
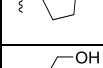
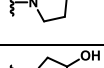
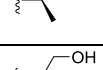
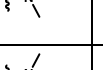
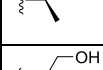
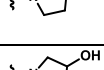
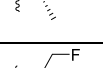
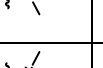
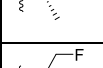
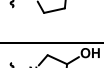
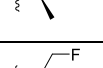
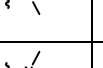
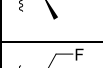
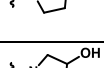
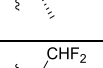
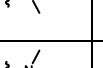
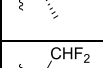
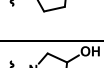
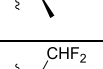
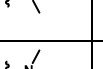
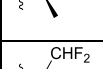
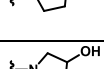
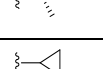
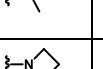
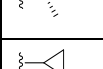
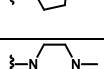
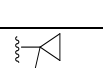
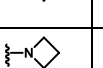
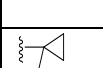
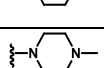
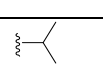
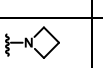
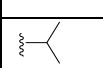
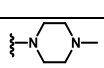
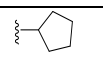
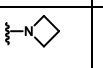
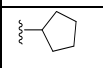
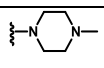
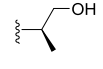
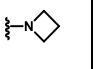
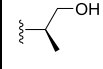
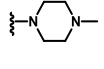
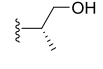
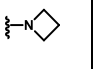
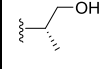
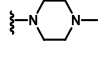
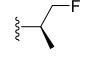
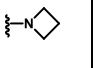
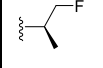
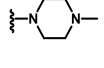
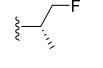
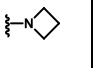
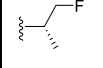
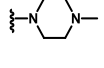
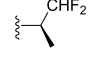
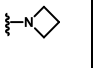
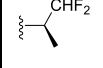
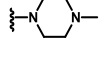
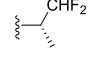
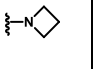
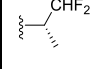
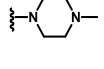
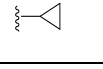
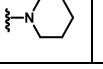
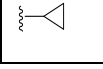
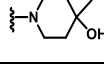
7. The compound of claim 1, which is selected from compounds of Formula **(IVa-1)**, **(IVa-2)**, **(IVa-3)**, or **(IVa-4)**, or a pharmaceutically acceptable salt thereof:



wherein R¹ and R² are delineated for each compound in Table 1,

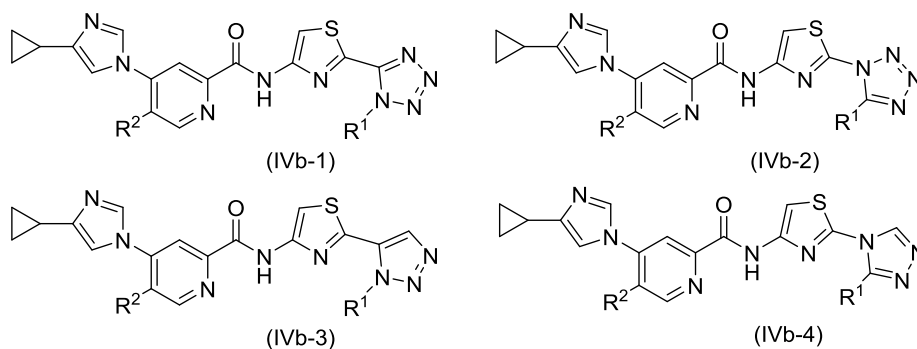
Table 1

Entry	R ¹	R ²	Entry	R ¹	R ²
1		Me	51		
2		Me	52		
3		Me	53		
4		Me	54		
5		Me	55		
6		Me	56		
7		Me	57		
8		Me	58		
9		Me	59		
10		Me	60		
11		CF ₃	61		
12		CF ₃	62		
13		CF ₃	63		
14		CF ₃	64		
15		CF ₃	65		
16		CF ₃	66		
17		CF ₃	67		

18		CF ₃	68		
19		CF ₃	69		
20		CF ₃	70		
21			71		
22			72		
23			73		
24			74		
25			75		
26			76		
27			77		
28			78		
29			79		
30			80		
31			81		
32			82		
33			83		
34			84		
35			85		
36			86		
37			87		
38			88		
39			89		
40			90		
41			91		

42			92		
43			93		
44			94		
45			95		
46			96		
47			97		
48			98		
49			99		
50			100		

8. The compound of claim 1, which is selected from compounds of Formula (IVb-1), (IVb-2), (IVb-3), or (IVb-4), or a pharmaceutically acceptable salt thereof:



wherein R¹ and R² are delineated for each compound in Table 2,

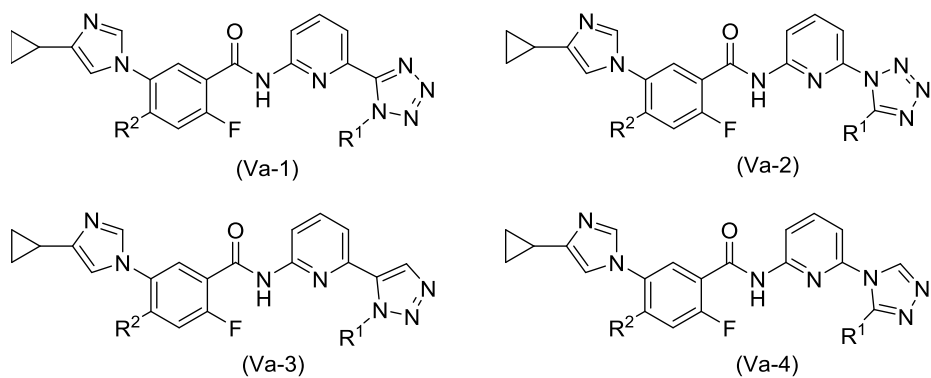
Table 2

Entry	R ¹	R ²	Entry	R ¹	R ²
101		Me	151		
102		Me	152		
103		Me	153		
104		Me	154		
105		Me	155		

106		Me	156		
107		Me	157		
108		Me	158		
109		Me	159		
110		Me	160		
111		CF ₃	161		
112		CF ₃	162		
113		CF ₃	163		
114		CF ₃	164		
115		CF ₃	165		
116		CF ₃	166		
117		CF ₃	167		
118		CF ₃	168		
119		CF ₃	169		
120		CF ₃	170		
121			171		
122			172		
123			173		
124			174		
125			175		
126			176		
127			177		
128			178		
129			179		

130			180		
131			181		
132			182		
133			183		
134			184		
135			185		
136			186		
137			187		
138			188		
139			189		
140			190		
141			191		
142			192		
143			193		
144			194		
145			195		
146			196		
147			197		
148			198		
149			199		
150			200		

9. The compound of claim 1, which is selected from compounds of Formula (Va-1), (Va-2), (Va-3), or (Va-4), or a pharmaceutically acceptable salt thereof:



wherein R^1 and R^2 are delineated for each compound in Table 3,

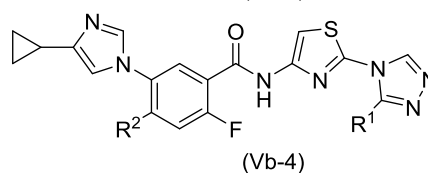
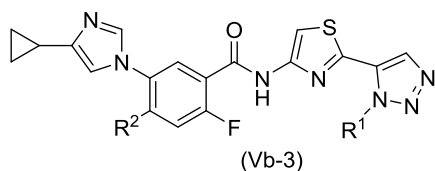
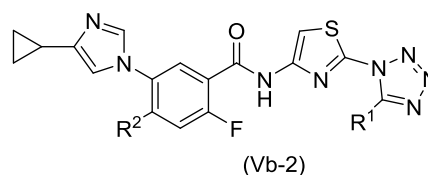
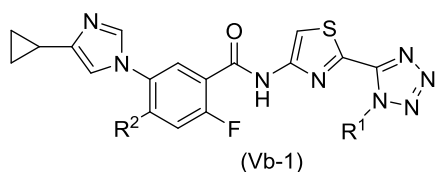
Table 3

Entry	R^1	R^2	Entry	R^1	R^2
201		Me	251		
202		Me	252		
203		Me	253		
204		Me	254		
205		Me	255		
206		Me	256		
207		Me	257		
208		Me	258		
209		Me	259		
210		Me	260		
211		CF ₃	261		
212		CF ₃	262		
213		CF ₃	263		
214		CF ₃	264		
215		CF ₃	265		
216		CF ₃	266		
217		CF ₃	267		

218		CF ₃	268		
219		CF ₃	269		
220		CF ₃	270		
221			271		
222			272		
223			273		
224			274		
225			275		
226			276		
227			277		
228			278		
229			279		
230			280		
231			281		
232			282		
233			283		
234			284		
135			285		
236			286		
237			287		
238			288		
239			289		
240			290		
241			291		

242			292		
243			293		
244			294		
245			295		
246			296		
247			297		
248			298		
249			299		
250			300		

10. The compound of claim 1, which is selected from compounds of Formula (Vb-1), (Vb-2), (Vb-3), or (Vb-4), or a pharmaceutically acceptable salt thereof:

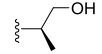
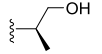
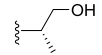
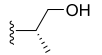
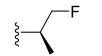
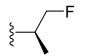
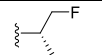
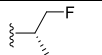
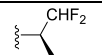
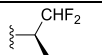
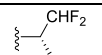
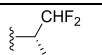
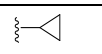
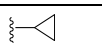
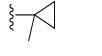
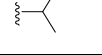
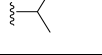
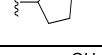
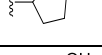
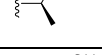
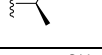
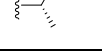
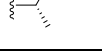
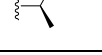
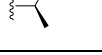
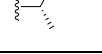
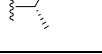
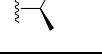
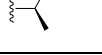
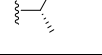
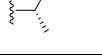
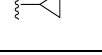
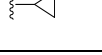
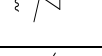
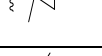
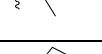
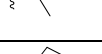
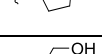
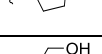
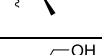
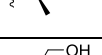
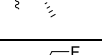
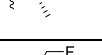
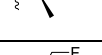
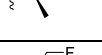
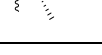
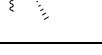


5

wherein R¹ and R² are delineated for each compound in Table 4,

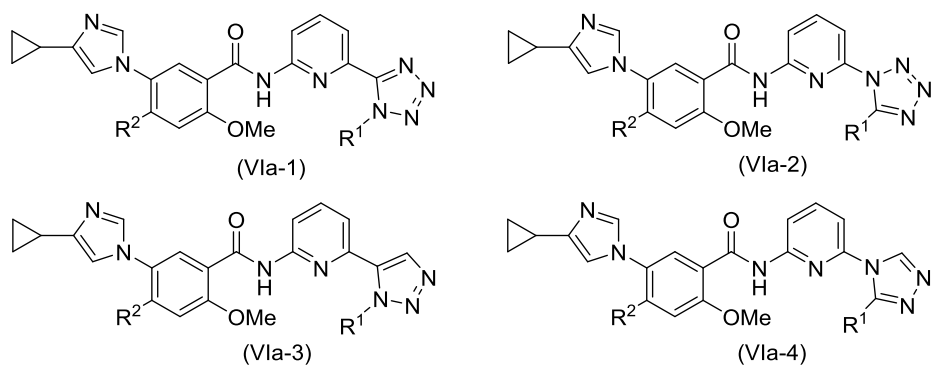
Table 4

Compound	R ¹	R ²	Compound	R ¹	R ²
301		Me	151		
302		Me	352		
303		Me	353		
304		Me	354		

305		Me	355		
306		Me	356		
307		Me	357		
308		Me	358		
309		Me	359		
310		Me	360		
311		CF ₃	361		
312		CF ₃	362		
313		CF ₃	363		
314		CF ₃	364		
315		CF ₃	365		
316		CF ₃	366		
317		CF ₃	367		
318		CF ₃	368		
319		CF ₃	369		
320		CF ₃	370		
321			371		
322			372		
323			373		
324			374		
325			375		
326			376		
327			377		
328			378		

329			379		
330			380		
331			381		
332			382		
333			383		
334			384		
335			385		
336			386		
337			387		
338			388		
339			389		
340			390		
341			391		
342			392		
343			393		
344			394		
345			395		
346			396		
347			397		
348			398		
349			399		
350			400		

11. The compound of claim 1, which is selected from compounds of Formula (VIa-1), (VIa-2), (VIa-3), or (VIa-4), or a pharmaceutically acceptable salt thereof:



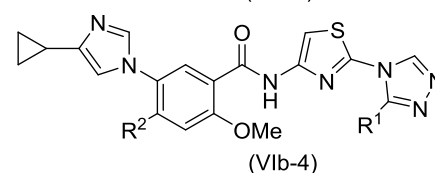
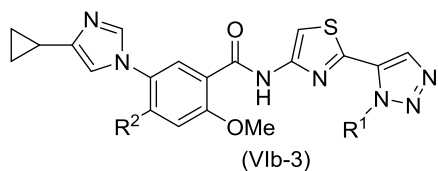
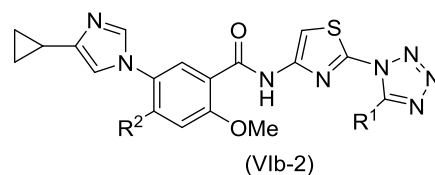
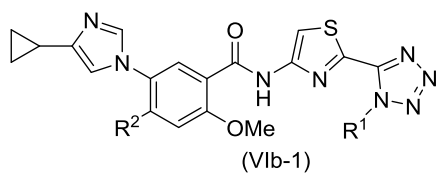
wherein R¹ and R² are delineated for each compound in Table 5,

Table 5

Entry	R ¹	R ²	Entry	R ¹	R ²
401		Me	451		
402		Me	452		
403		Me	453		
404		Me	454		
405		Me	455		
406		Me	456		
407		Me	457		
408		Me	458		
409		Me	459		
410		Me	460		
411		CF ₃	461		
412		CF ₃	462		
413		CF ₃	463		
414		CF ₃	464		
415		CF ₃	465		
416		CF ₃	466		
417		CF ₃	467		
418		CF ₃	468		
419		CF ₃	469		
420		CF ₃	470		

421			471		
422			472		
423			473		
424			474		
425			475		
426			476		
427			477		
428			478		
429			479		
430			480		
430			481		
432			482		
433			483		
434			484		
435			485		
436			486		
437			487		
438			488		
439			489		
440			490		
441			491		
442			492		
443			493		
444			494		
445			495		
446			496		
447			497		
448			498		
449			499		
450			500		

12. The compound of claim 1, which is selected from compounds of Formula (VIb-1), (VIb-2), (VIb-3), or (VIb-4), or a pharmaceutically acceptable salt thereof:



wherein R¹ and R² are delineated for each compound in Table 6,

5

Table 6

Entry	R ¹	R ²	Entry	R ¹	R ²
501		Me	551		
502		Me	552		
503		Me	553		
504		Me	554		
505		Me	555		
506		Me	556		
507		Me	557		
508		Me	558		
509		Me	559		
510		Me	560		
511		CF ₃	561		
512		CF ₃	562		
513		CF ₃	563		
514		CF ₃	564		
515		CF ₃	565		
516		CF ₃	566		
517		CF ₃	567		
518		CF ₃	568		
519		CF ₃	569		

520		CF ₃	570		
521			571		
522			572		
523			573		
524			574		
525			575		
526			576		
527			577		
528			578		
529			579		
530			580		
531			581		
532			582		
533			583		
534			584		
535			585		
536			586		
537			587		
538			588		
539			589		
540			590		
541			591		
542			592		
543			593		
544			594		
545			595		
546			596		
547			597		
548			598		
549			599		
550			600		

13. The compound of claim 1, selected from the compounds set forth below or a pharmaceutically acceptable salt thereof:

Compound	Structure
1a	
2a	
3a	
4a	
5a	
6a	
7a	
8a	
9a	
10a	

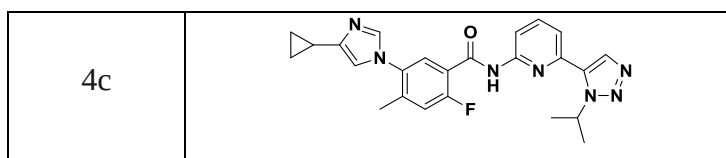
11a	
12a	
13a	
14a	
15a	
16a	
17a	
18a	
19a	
20a	

21a	
22a	
23a	
24a	
25a	
26a	
27a	
28a	
29a	
30a	

31a	
32a	
33a	
34a	
35a	
36a	
37a	
38a	
39a	
40a	
41a	
42a	
43a	
44a	

45a	
46a	
47a	
48a	
49a	
50a	
51a	
52a	
53a	
54a	
55a	
56a	
57a	

58a	
59a	
60a	
61a	
1b	
2b	
3b	
4b	
5b	
6b	
1c	
2c	
3c	



14. A pharmaceutical composition comprising an effective amount of one or more compounds of Formula (I) according to any one of claims 1-13 with a pharmaceutically acceptable carrier or excipient.
15. Use of one or more compounds of Formula (I) according to any one of claims 1-13 for the preparation of pharmaceutical compositions for the treatment of an ASK-1 mediated disease or condition.
16. The use according to claim 15, wherein the ASK-1 mediated disease or condition is selected from the group consisting of an autoimmune disorder, a neurodegenerative disorder, an inflammatory disease, chronic kidney disease, renal disease, cardiovascular disease, a metabolic disease, or an acute or chronic liver disease.
17. The use according to claim 16, wherein the chronic liver disease is selected from the group consisting of primary biliary cirrhosis (PBC), cerebrotendinous xanthomatosis (CTX), primary sclerosing cholangitis (PSC), drug induced cholestasis, intrahepatic cholestasis of pregnancy, parenteral nutrition associated cholestasis (PNAC), bacterial overgrowth or sepsis associated cholestasis, autoimmune hepatitis, chronic viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), liver transplant associated graft versus host disease, living donor transplant liver regeneration, congenital hepatic fibrosis, choledocholithiasis, granulomatous liver disease, intra- or extrahepatic malignancy, Sjogren's syndrome, Sarcoidosis, Wilson's disease, Gaucher's disease, hemochromatosis, or alpha 1-antitrypsin deficiency.
18. The use according to claim 16, wherein the renal disease is selected from the group consisting of diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), hypertensive nephrosclerosis, chronic glomerulonephritis, chronic transplant

glomerulopathy, chronic interstitial nephritis, kidney fibrosis and polycystic kidney disease.

19. The use according to claim 16, wherein the cardiovascular disease is selected from the group consisting of atherosclerosis, arteriosclerosis, reperfusion/ischemia in stroke, cardiac hypertrophy, respiratory diseases, heart attacks, myocardial ischemia.

20. The use according to claim 16, wherein the metabolic disease is selected from the group consisting of insulin resistance, Type I and Type II diabetes, and obesity.

21. The use according to claim 16, wherein chronic kidney disease is selected from the group consisting of polycystic kidney disease, pyelonephritis, kidney fibrosis and glomerulonephritis.

22. Use of a compound according to any one of claims 1-13 for the preparation of pharmaceutical compositions for the treatment of a disease selected from the group consisting of, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, Sjogren's syndrome, organ hypoxia, vascular hyperplasia, , hepatic ischemia, congestive heart failure, pathologic immune responses such as that caused by T cell activation, thrombin-induced platelet aggregation, osteoporosis, osteoarthritis and multiple myeloma-related bone disorder, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), epilepsy, seizures, Huntington's disease, polyglutamine diseases, traumatic brain injury, ischemic and hemorrhaging stroke, cerebral ischemias or neurodegenerative disease, including apoptosis-driven neurodegenerative disease, caused by traumatic injury, acute hypoxia, ischemia or glutamate neurotoxicity.