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(54) Title: TASK CHANNEL ANTAGONISTS

(57) Abstract: This invention relates to TASK-1 and/or TASK-3 antagonists and/or their pharmaceutically acceptable salts, compositions and methods for treating and preventing disorders which are caused by activation or by an activated TASK-1 and/or TASK-3, and disorders which have TASK-1 and/or TASK-3-related damage as a secondary cause.



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TASK CHANNEL ANTAGONISTS

FIELD OF THE INVENTION

5 The invention relates generally to compounds which act as modulators, e.g., antagonists of TASK channels, particularly, TASK-1 and/or TASK-3, compositions and therapeutic uses thereof.

BACKGROUND OF THE INVENTION

10 Potassium channels are membrane proteins that play an important role in many physiological processes. There are three major families of potassium channel proteins each with structural and functional distinctions characterized by the number of transmembrane domains (2, 4 or 6). The first and second families of potassium channels are the voltage-dependent potassium channels (K_v) and the inwardly rectifying potassium channel (K_{ir}). The members of the third
15 family are known as the KCNK, or K_{2p} (Coetzee W. J. et al; New York Acad Sci. 1999 (868), 233-285) proteins to which the TASK (TWIK-related acid-sensitive potassium) belongs. The TASK channels are generally referred to as TASK-1 (which is also known as (aka) KCNK3 or $K_{2p3.1}$), TASK-2 (aka KCNK5 or $K_{2p5.1}$), TASK-3 (aka KCNK9 or $K_{2p9.1}$), TASK-4 (aka KCNK17 or $K_{2p17.1}$ or TALK-2) and TASK-5 (aka KCNK15 or $K_{2p15.1}$). TASK-1 and TASK-
20 3 channels have the greatest homology within this family with a greater than 50% amino acid identity. For background discussion see Goldstein, S.A.N., et al., Nat. Rev. Neurosci. 2, 175-184 (2001); Lesage, F., et al., Am. J. Physiol. Renal Physiol. 279, F793-F801 (2000); Lesage, F., et al., Neuropharmacology 44, 1-7 (2003); and Talley, E.M., Neuroscientist 9, 46-56 (2003).

25 The TASK channels are sensitive to extracellular pH within physiological range displaying inhibition at acidic pH and activated at alkaline pH (Duprat F., et al., EMBO J. 1997 (16), 5464-5471). TASK-1 is expressed in the brain, spinal ganglia, peripheral tissues such as pancreas, placenta, uterus, lung, heart, kidney, small intestine and stomach, and have been detected in motor neurons of the locus coeruleus and hypoglossal nerve (a motor cranial nerve which is integrally involved in the maintenance of the upper respiratory pathways). TASK-3
30 channels are primarily expressed in the cerebellum (Medhurst, A.D., et al., Mol. Brain Res. 2001 (86), 101-114).

35 TASK-1 channels have been shown to be involved in respiratory regulation in respiratory neurons of the brainstem, in carotid bodies and motor neurons of the hypoglossal nerve, and also in neuroepithelial cells of the lung. The lowering of the pH and resultant blockage of the pH-dependent TASK-1 channels that occur from inadequate respiration (e.g., hypoxia, hindered breathing, excessive physical stress) leads to depolarization of the cells, which leads to

the activation of the neurons involved in the respiratory regulation [Buckler K.J., et al., J. Physiol. 2000 (525), 135-142; Bayliss, D.A., et al., Respiration Physiology 2001 (129), 159-174).

Blocking TASK channels, by increasing the activity of chemosensitive neurons in conjunction with activation of the motor neurons of the hypoglossal nerve, can stimulate respiration, stabilize the upper respiratory pathways and protect the pathways from collapse and occlusion. Stabilization of the upper respiratory pathways can also help eliminate or inhibit snoring. Thus, blocking TASK-1 channels can be beneficial in the treatment of respiratory disorders such as sleep apnea. TASK-1 channels have also been found in smooth muscle cells of mesenteric and pulmonary arteries, and are suggested to be involved in acidosis-induced pulmonary vasoconstriction (Gurney A.M., et al., Circ. Res. 2003 (93), 957-964).

It has been shown that TASK-1 channels are responsible for programmed cell death (apoptosis) in granulosa cells, and that the cell death can be prevented by blocking the TASK-3 (Patel A.J., Pflugers Arch, 2004 (448), 261-273). Thus, developing inhibitors of TASK channels, particularly specific inhibitors of TASK-1 and/or TASK-3 channels, could lead to therapeutic treatment of neurodegenerative disorders.

The TASK-3 gene has been found in several human carcinoma tissues (e.g., breast cancer, colon cancer, lung cancer), which leads to the belief that TASK-3 inhibitors may be useful as an anticancer drug. See Mu D., et al., Cancer Cell 2003 (3), 297-302; and Pei, L., et al., Proc. Natl. Acad. Sci. USA 2003 (100), 7803-7807. In addition to being an anticancer agent (e.g., breast cancer, lung cancer, colon cancer, prostate cancer), TASK-3 antagonists may also be useful for the treatment of respiratory disorders (e.g., Cheyne-Stokes respiration, disrupted central respiratory drive, muscle-related respiratory disorders, acute and chronic lung disorders with hypoxia and hypercapnia), sleep disorders, excessive daytime sleepiness, sleep apneas, snoring, neurodegenerative disorders, cognitive impairment (e.g., dementia, Alzheimer's disease) or major depressive disorder, Parkinson's disease, Huntington's disease.

SUMMARY OF THE INVENTION

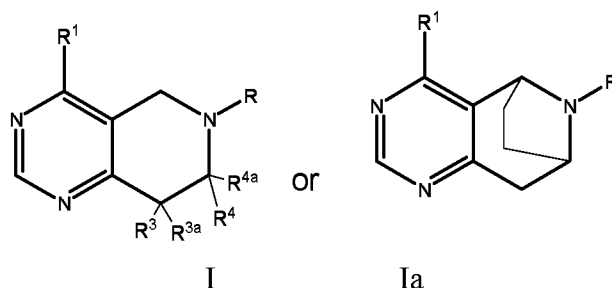
One aspect of the present invention relates to TASK-1 and/or TASK-3 antagonists and/or their pharmaceutically acceptable salts, compositions and methods for treating and preventing disorders which are caused by activation or by an activated TASK-1 and/or TASK-3, and disorders which have TASK-1 and/or TASK-3-related damage as a secondary cause.

Another aspect of this invention is use of the TASK-1 and/or TASK-3 antagonists and/or their pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment or prevention of cancer disorders (e.g., breast cancer, lung cancer, colon cancer, prostate cancer), respiratory disorders (e.g., Cheyne-Stokes respiration, disrupted central

respiratory drive, muscle-related respiratory disorders, acute and chronic lung disorders with hypoxia and hypercapnia), sleep disorders, excessive daytime sleepiness, sleep apneas, snoring, neurodegenerative disorders, cognitive impairment (e.g., dementia, Alzheimer's disease) or major depressive disorder, atypical depression, Parkinson's disease, and Huntington's disease.

5

More particularly, the present invention relates to TASK-1 and/or TASK-3 antagonist of structural formula I or Ia:



10 or pharmaceutically acceptable salts and individual enantiomers and diastereomers thereof wherein:

R¹ represents C₁₋₆ alkylC(O)OC₁₋₆alkyl, (CH₂)_nC₆₋₁₀aryl, (CH₂)_nC₅₋₁₀heterocycle, (CH₂)_nC₃₋₁₀cycloalkyl, N(CH₃)(CH₂)_nC(O)NHC₆₋₁₀aryl, and N(CH₃)(CH₂)_nC₅₋₁₀heterocycle; said cycloalkyl, aryl and heterocycle optionally substituted with 1 to 3 groups of R^a;

15

R represents H, C₁₋₆ alkyl, C(O)(CH₂)_nC₆₋₁₀aryl, C(O)O(CH₂)_nC₆₋₁₀aryl, C(O)(CH₂)_nC₅₋₁₀heterocycle, (CH₂)_nC₆₋₁₀aryl, SO₂C₆₋₁₀ aryl, SO₂C₅₋₁₀ heterocycle, C(O)NHC₆₋₁₀aryl, C(O)C₂₋₄alkynyl, CNC₆₋₁₀aryl, (CH₂)_nC₅₋₁₀heterocycle, or C(O)CH(CH₃)N(CH₃)CH₂C₆₋₁₀ aryl, said alkynyl, aryl, alkyl, and heterocycle optionally substituted with 1 to 3 groups of R^a;

20

R^a represents (CH₂)_nOH, (CH₂)_nCN, C(OH)CN, C₁₋₆ alkyl, CH(OH)(CH₂)_nC₆₋₁₀ aryl, CH(OH)(CH₂)_nC₃₋₁₀ cycloalkyl, OC₁₋₆ alkyl, O(CH₂)_nC₂₋₆ alkenyl, C(O)OC₁₋₆ alkyl, C(O)C₁₋₆ alkyl, (CH₂)_nC(O)(CH₂)_nC₃₋₁₀ cycloalkyl, (CH₂)_nC(O)(CH₂)_nC₅₋₁₀ aryl, (CH₂)_nC(O)(CH₂)_nC₅₋₁₀ heterocyclyl, (CH₂)_nC(O)O(CH₂)_nC₃₋₁₀ cycloalkyl, (CH₂)_nC(O)O(CH₂)_nC₅₋₁₀ aryl, (CH₂)_nC(O)O(CH₂)_nC₅₋₁₀ heterocyclyl, halo, (CH₂)_nC₆₋₁₀aryl, O(CH₂)_nC₆₋₁₀aryl, (CH₂)_nC₅₋₁₀heterocycle, -N(CH₃)CH₂C(O)NHC₆₋₁₀aryl, -NH(CH₂)_nC₆₋₁₀aryl, -N(CH₃)CH₂C₆₋₁₀aryl, -NH(C₁₋₆alkyl), (CH₂)_nSO₂C₁₋₆alkyl, (CH₂)_nSO₂C₆₋₁₀aryl, -O-, C₃₋₁₀ cycloalkyl, -SC₁₋₆ alkyl, CF₃, OCF₃, CHF₂, CH₂F, CF₃OC₁₋₆alkyl, NH₂, C(O)N(C₁₋₆ alkyl)(CH₂)_nC₅₋₁₀heterocyclyl, C(O)N(C₁₋₆alkyl)₂, (CH₂)_nOC(O)C₁₋₆alkyl, (CH₂)_nOC(O)C₆₋₁₀aryl, (CH₂)_nOC(O)C₅₋₁₀heterocyclyl, (CH₂)_nOC(O)C₃₋₁₀cycloalkyl, said alkyl, cycloalkyl, aryl and heterocycle optionally substituted with 1 to 3 groups of R^{aa};

30

R^{aa} represents C(O)OC₁₋₆ alkyl, O(CH₂)_nphenyl, OH, OCH₃, SCH₃, OCH₂CH₃, OCH₂CF₃, CF₃, OCF₃, CN, C₁₋₆ alkyl, halo, NHC(O)OC₁₋₆ alkyl, =NOC₁₋₆alkyl, O(CH₂)_nC₆₋₁₀aryl;

5 R³, R^{3a}, R⁴ R^{4a} independently represent hydrogen or C₁₋₆ alkyl; and

n represents 0 to 4.

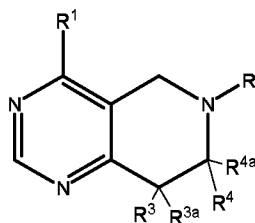
This invention also relates to compositions and methods for using the compounds
10 disclosed herein. These and other embodiments of the present invention will readily occur to those of ordinary skill in the art in view of the disclosure herein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to TASK-1 and/or TASK-3 antagonists and/or their
15 pharmaceutically acceptable salts, compositions and methods for treating and preventing disorders which are caused by activation or by an activated TASK-1 and/or TASK-3, such as cancer disorders (e.g., breast cancer, lung cancer, colon cancer, prostate cancer), respiratory disorders (e.g., Cheyne-Stokes respiration, disrupted central respiratory drive, muscle-related respiratory disorders, acute and chronic lung disorders with hypoxia and hypercapnia), sleep disorders,
20 excessive daytime sleepiness, sleep apneas, snoring, neurodegenerative disorders, cognitive impairment (e.g., dementia, Alzheimer's disease) or major depressive disorder, Parkinson's disease, and Huntington's disease.

An embodiment of this invention is realized when n in R and R¹ is 0-2, preferably 0-1 and more preferably 0.

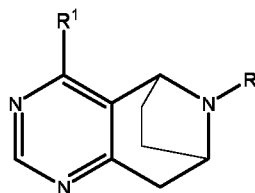
25 An embodiment of the present invention is represented by structural formula I:



I

wherein R¹, R, R³, R^{3a}, R⁴, and R^{4a} are as previously described.

30 Another embodiment of the present invention is represented by structure formula Ia:

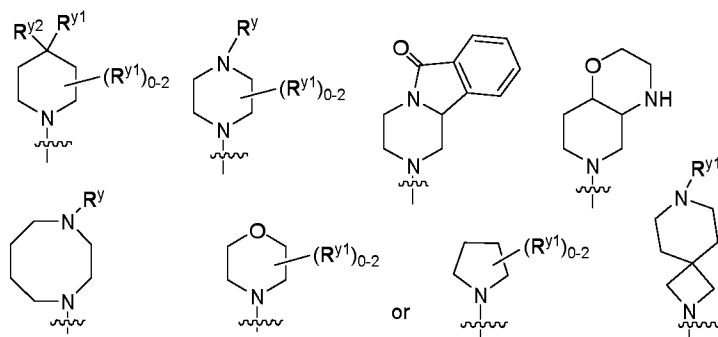


Ia

wherein R^1 , and R are as previously described.

Another embodiment of the present invention is realized when R^1 is

5



wherein:

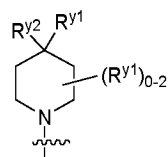
R^Y represents H, C₁₋₆alkyl, C(O)C₁₋₆alkyl, C(O)C₃₋₁₀cycloalkyl, C(O)(CH₂)_nC₆₋₁₀aryl, C(O)(CH₂)_nC₅₋₁₀heterocycle, C(O)OC₁₋₆alkyl, (CH₂)_nC₆₋₁₀aryl, (CH₂)_nC₅₋₁₀heterocycle, said
10 alkyl, aryl, cycloalkyl, and heterocycle optionally substituted with 1 to 3 groups of R^a ;

R^1 is the same as R^a ;

or when two R^1 are present they may combined to form a C₃₋₁₀ cyclic group optionally having 1-2
15 heteroatoms selected from N, O, and S, said cyclic group optionally substituted with 1 to 3 groups of R^a ;
and R^{y2} is H, halo, or OH and all other variables are as described herein.

Another embodiment of the present invention is realized when n in R^1 is 0-1, preferably 0.

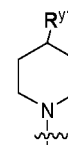
Still another embodiment of the present invention is realized when R^1 is

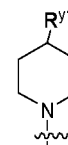


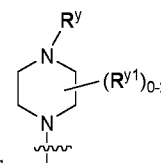
and all other variables are as originally described. A subembodiment of this invention is

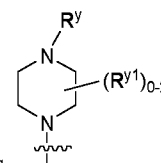
20 realized when R^1 is C₁₋₆alkyl, C(O)OC₁₋₆alkyl, C(O)C₁₋₆alkyl, C₃₋₆cycloalkyl, C(O)C₃₋₆cycloalkyl, C₅₋₁₀ heterocycle, said alkyl, heterocyclyl, and cycloalkyl optionally substituted with 1 to 3 groups of R^a .

Another subembodiment of this invention is realized when only 1 R^1 is present.



Another embodiment of the present invention is realized when R¹ is  and all other variables are as originally described. A subembodiment of this invention is realized when R^{Y1} is C₁-6alkyl, C(O)OC₁-6alkyl, C(O)C₁-6alkyl, C₃-6cycloalkyl, C(O)C₃-6cycloalkyl, C₅-10 heterocycle, said alkyl, cycloalkyl, heterocycle optionally substituted with 1 to 3 groups of R^a. Another subembodiment of this invention is realized when R^{Y1} is C(O)OCH₂CH₃, C(O)CH₂CH₃, C(O)CH₃, C(O)(CH₂)₂CH₃, C(O)cyclopropyl, C(OH)(CH₃)₂, cyclopropylOH, and optionally substituted oxadiazolyl, preferably C(O)OCH₂CH₃, or C(O)CH₂CH₃.



Yet another embodiment of the present invention is realized when R¹ is  and all other variables are as originally described. A subembodiment of this invention is realized when R^Y is C(O)C₁-6alkyl, C(O)(CH₂)_nC₆₋₁₀aryl, C(O)(CH₂)_nC₅₋₁₀heterocycle, (CH₂)_nC₆₋₁₀aryl, or (CH₂)_nC₅₋₁₀heterocycle, said alkyl, aryl, cycloalkyl, and heterocycle optionally substituted with 1 to 3 groups of R^a, and R^{Y1} is C₁-6alkyl, CF₃, CH₂F, said alkyl optionally substituted with 1 to 3 groups of R^a.



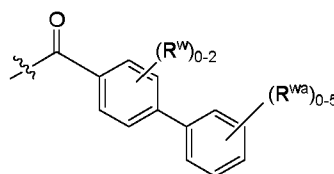
Still another embodiment of the present invention is realized when R¹ is  and all other variables are as originally described.

Another embodiment of the present invention is realized when R³, R^{3a}, R⁴ and R^{4a} are all hydrogen and all other variables are as originally described.

Still another embodiment of this invention is realized when R is C(O)(CH₂)_nC₆₋₁₀aryl, C(O)(CH₂)_nC₅₋₁₀heterocycle, SO₂C₆₋₁₀aryl, or SO₂C₅₋₁₀heterocycle, said aryl and heterocycle optionally substituted with 1 to 3 groups of R^a. A subembodiment of this invention is realized when R is C(O)(CH₂)_nC₆₋₁₀aryl substituted with 1 to 3 groups of R^a. Still another embodiment of this invention is realized when R is C(O)phenyl and the R^a substitution is an optionally substituted phenyl group, substituted with 1 to 3 groups of R^{aa}. Yet another subembodiment of this invention is realized when R is SO₂C₆₋₁₀aryl substituted with 1 to 3 groups of R^a.

Another embodiment of the present invention is realized when R is represented by formula

II:

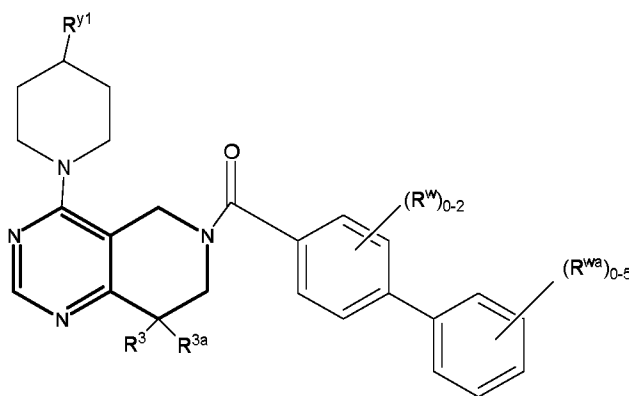


II

wherein R^W and R^{Wa} are independently selected from the group consisting of H, $OC_{1-6}alkyl$,
 5 $O(CH_2)_n C_{6-10}aryl$, $SC_{1-6}alkyl$, CF_3 , OCF_3 , CN , $C_{1-6}alkyl$, and halo. A subembodiment of this invention is realized when R^W and R^{Wa} are both hydrogen.

Another embodiment of the present invention is realized when R is phenyl or pyridyl optionally substituted by 1 to 3 groups of R^a . A subembodiment of this invention is realized when R is optionally substituted biphenyl.

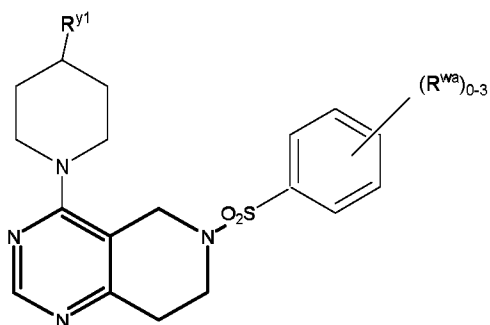
10 Another embodiment of the present invention is represented by structural formula III:



III

wherein R^3 , R^{3a} , R^{Y1} , R^W and R^{Wa} is as previously described. A subembodiment of formula III is
 15 realized when R^{Y1} is $C_{1-6}alkyl$, $C(O)OC_{1-6}alkyl$, $C(O)C_{1-6}alkyl$, $C_{3-6}cycloalkyl$, $C(O)C_{3-6}cycloalkyl$, said alkyl and cycloalkyl optionally substituted with 1 to 3 groups of R^a . Another subembodiment of formula III is realized when R^{Y1} is $C(O)OCH_2CH_3$, $C(O)CH_2CH_3$, $C(O)(CH_2)_2CH_3$, $C(O)cyclopropyl$, $C(OH)(CH_3)_2$, cyclopropylOH. Still another subembodiment of formula III is realized when R^W and R^{Wa} are both hydrogen.

20 Yet another embodiment of this invention is represented by structural IV:

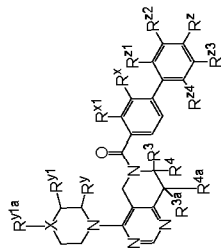


IV

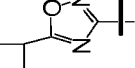
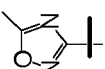
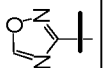
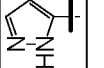
wherein R^{y1} and R^{wa} are previously described herein.

5 Non-limiting examples of the compounds of this invention are found in Tables 1-4:

Table 1



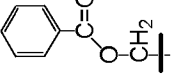
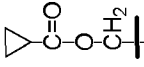
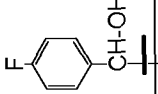
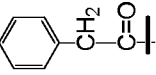
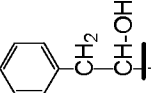
	1	X	R ^{1a}	R ³	R ^{3A}	R ⁴	R ^{4A}	R ^X	R ^{X1}	R ^Y	R ^{Y1}	R ^Z	RZ1	RZ2	RZ ³	RZ ⁴	LCMS M+1
	2	CH	C(O)OCH ₂ CH ₃	CH ₃	H	CH ₃	H	H	H	H	H	H	H	H	H	H	499.6
	3	N															478.6
	4	N	C(O)CH ₂ CH ₃	H	H	H	H	H	H	H	H	H	H	H	H	H	456.6
	5	N	C(O)CH ₃	H	H	H	H	H	H	H	H	H	H	H	H	H	442.6
	6	CH	C(O)OCH ₂ CH ₃	H	H	H	H	Cl	H	H	H	H	H	H	H	H	506
	7	CH	C(O)OCH ₂ CH ₃	H	H	H	H	F	H	H	H	H	H	H	H	H	489.5
	8	CH	C(O)CH ₂ CH ₃	H	H	H	H	H	H	CH ₃	H	H	H	H	H	H	469.6
	9	N	C(O)OCH ₂ CH ₃	H	H	H	H	H	CH	CH ₂ O	H	H	H	H	H	H	502.6
	10	CH	C(O)OCH ₂ CH ₃	H	H	H	H	H	CH ₃	H	H	H	H	H	H	H	455.6
	11	CH	H	H	H	H	H	H	H	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	471.6
	12	CH	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	CH ₃	H	H	H	H	H	H	477.6
	13	CH	SO ₂ CH ₃	H	H	H	H	H	H	H	H	H	H	H	H	H	477.6
	14	CH	H	H	H	H	H	H	H	H	F	H	H	H	H	H	417.5
	15	N	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	CH ₂ OH	H	H	H	H	H	H	502.6
	16	CH	C(O)cyclopropyl	H	H	H	H	H	H	H	H	F	OCH ₃	H	H	H	515.6
	17	CH	C(O)CH ₂ CH ₃	H	CH ₃	H	CH ₃	H	H	H	H	H	H	H	H	H	499.6
	18	CH	C(O)cyclopropyl	H	H	H	H	H	H	H	H	H	CN	F	H	H	510.6
	19	CH	C(O)cyclopropyl	H	H	H	H	H	H	H	H	F	CN	H	H	H	510.6
	20	CH	C(O)cyclopropyl	H	H	H	H	H	H	H	H	F	H	F	H	H	503.5
	21	CH	C(O)cyclopropyl	H	H	H	H	H	H	H	H	F	H	H	H	H	485.6

22	CH	-C((CH ₂) ₂ CH ₃) =NOCH ₂ CH ₃)	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	512.7
23	CH	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	519.6
24	CH	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	
26	N	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	22.6
27	N	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	514.6
28	N	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	504.6
29	CH	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	501.6
30	C- OH	CF ₃	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	483.5
31	CH	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	531.6
32	CH	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	507.8
			H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	509.5
33	CH		H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	481.6
34	CH		H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	467.5
35	CH	C(CH ₃) ₂ OH	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	560.2
36	CH	C(CH ₃) ₂ OH	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	489.5
37	CH	C(CH ₃) ₂ OH	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	465.6
38	CH		H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	465.6
39	CH		H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	465.6

[illegible]

[illegible]

[illegible]

92	CH	$\text{C}(\text{O})\text{OCCH}_2\text{CH}_3$		H	H	H	H	H	H	565.7
93	CH			H	H	H	H	H	H	533.7
94	CH			H	H	H	H	H	H	497.6
95	CH	$\text{CH}_2\text{OC}(\text{O})\text{CH}_2\text{CH}_3$		H	H	H	H	H	H	485
96	CH	$\text{CH}_2\text{OC}(\text{O})\text{CH}_3$		H	H	H	H	H	H	471
97	CH			H	H	H	H	H	H	469.6
98	CH			H	H	H	H	H	H	509.6
100	CH			H	H	H	H	H	H	517.6
101	CH			H	H	H	H	H	H	505.6

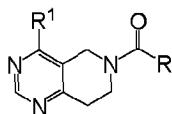
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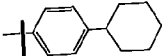
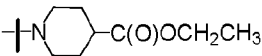
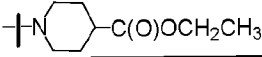
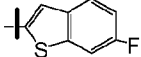
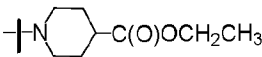
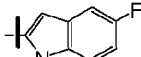
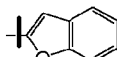
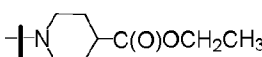
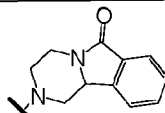
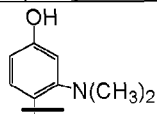
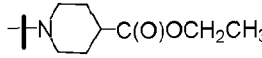
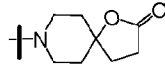
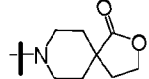
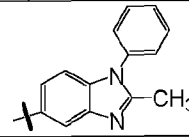
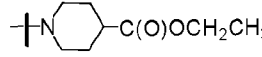
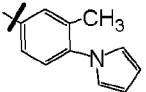
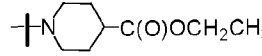
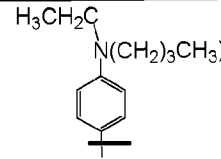
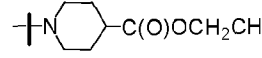
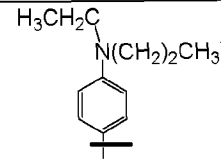
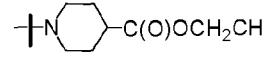
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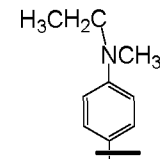
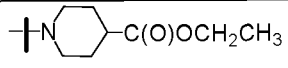
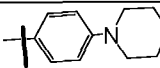
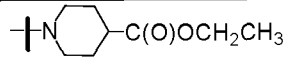
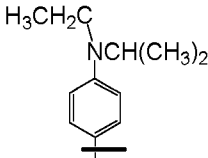
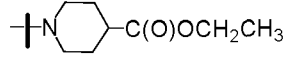
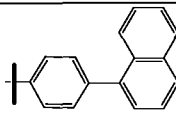
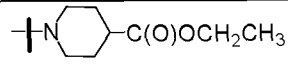
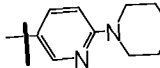
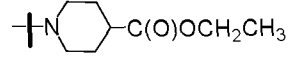
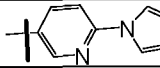
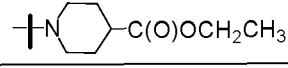
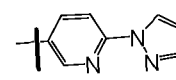
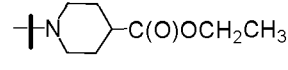
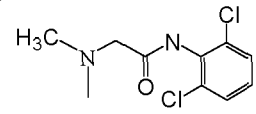
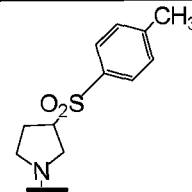
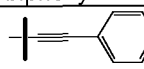
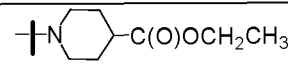
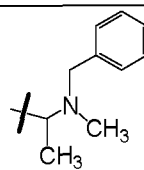
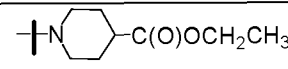
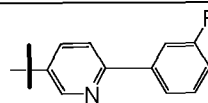
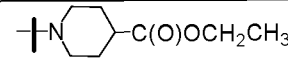
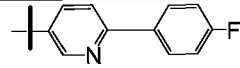
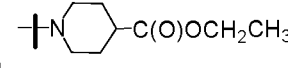
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163	CH	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	H	H	Cl	H	H	H	506
165	CH	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	H	H	H	OCH ₃	H	H	501.7
166	CH	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	H	H	H	CH ₃	H	H	485.8
167	CH	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	H	H	H	Cl	H	H	506
168	CH	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	H	H	H	F	H	H	489.6
169	CH	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	H	H	OCH ₃	H	H	H	501.6
170	CH	C(O)OCH ₂ CH ₃	H	H	H	H	H	H	H	H	Cl	H	H	H	506
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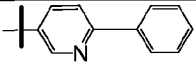
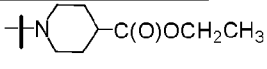
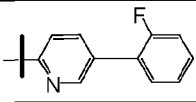
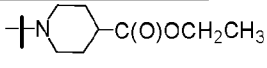
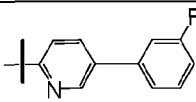
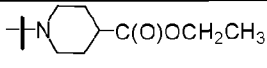
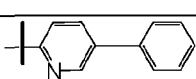
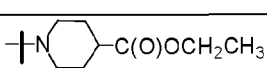
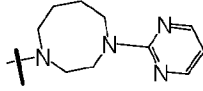
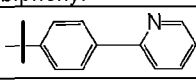
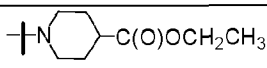
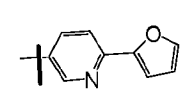
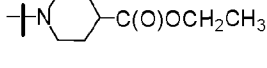
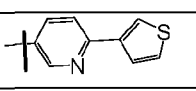
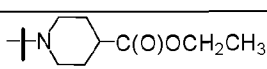
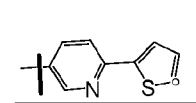
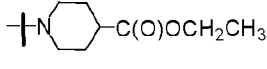
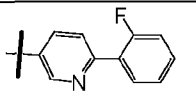
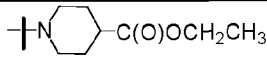
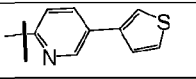
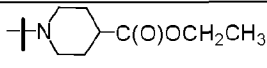
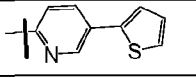
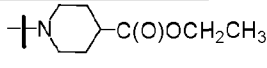
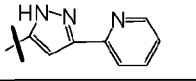
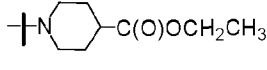
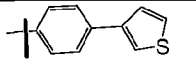
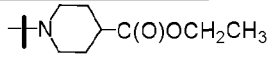
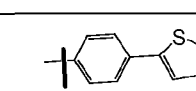
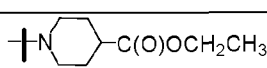
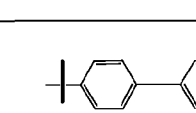
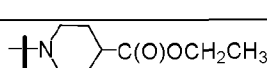
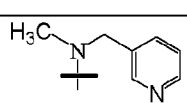
Table 2



	<u>R</u>	<u>R¹</u>	<u>LCMS</u> <u>(M+1)</u>
1	biphenyl		477.6
2	biphenyl		462.6
3	biphenyl		456.6
4	biphenyl		540.6
5	biphenyl		440.6
6	biphenyl		540.7
7			470.3
8			474.6
9			434.5
10			462.6

11			477.6
12	naphthyl		445.5
13			469.6
14			466.5
15			435.5
16	biphenyl		435.5
17	biphenyl		502.6
18			
19	biphenyl		469.6
20	biphenyl		469.6
21			525.6
22			474.6
23			494.7
24			479.6

25			452.5
26			478.6
27			480.6
28			521.6
29			479.8
30			461.5
31			462.5
32	biphenyl		547.5
33	biphenyl		539.7
34			419.5
35			466.6
36			472.6
37			472.6

38			472.6
39			490.5
40			490.5
41			472.6
42	biphenyl		492.6
43			472.6
44			462.5
45			478.6
46			478.6
47			490.5
48			478.6
49			478.6
50			462.5
51			477.6
52			477.6
53			472.5
54	biphenyl		466.6

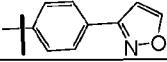
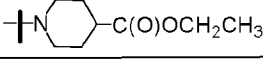
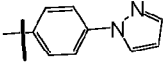
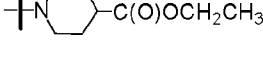
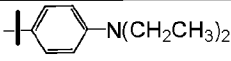
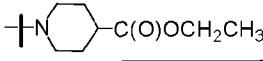
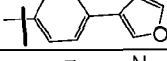
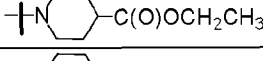
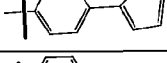
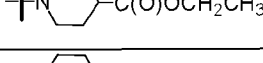
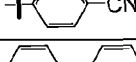
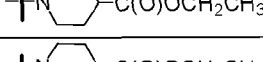
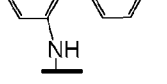
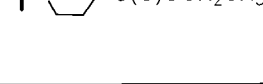
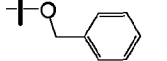
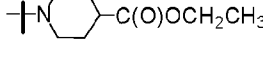
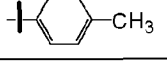
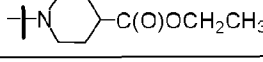
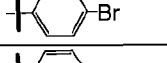
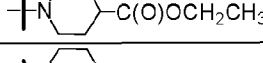
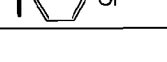
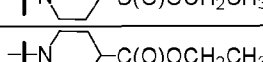
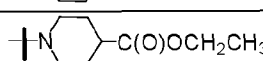
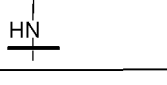
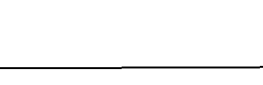
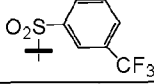
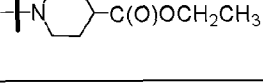
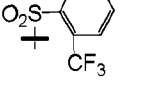
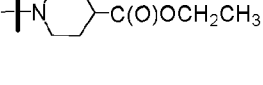
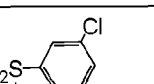
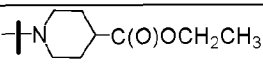
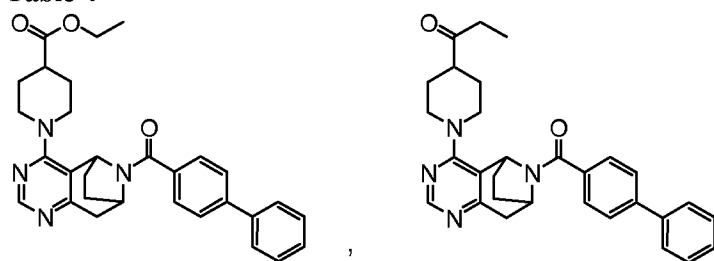
55			462.5
56			461.5
57			466.6
58			461.5
59			460.5
60			420.5
61			486.6
62			425.5
63			409.5
64			474.3
65			429.9
66	biphenyl		471.5
67			460.5

Table 3

	R	R1	LCMS (M+1)
1			499.5
2			499.5
3			466

4			466
5			445.6
6			480.6
7			481.6
8			445.6
9	H		291.3

Table 4



or pharmaceutically acceptable salts and individual enantiomers and diastereomers thereof.

- 5 When any variable (e.g. aryl, heterocycle, R^1 , R^5 etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

- 10 When for example, R^a is $-O-$ and attached to a carbon it is referred to as a carbonyl group and when it is attached to a nitrogen (e.g., nitrogen atom on a pyridyl group) or sulfur atom it is referred to a N-oxide and sulfoxide group, respectively.

- 15 As used herein, "alkyl" encompasses groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, and alkynyl and means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, and heptyl. "Alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 10 carbon atoms and at least one carbon

to carbon double bond. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. Preferably, alkenyl is C₂-C₆ alkenyl. Preferred alkynyls are C₂-C₆ alkynyl.

"Alkenyl," "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond. In the case of alkenyl it has a double bond and in the case of alkynyl a triple bond is expected.

As used herein, "fluoroalkyl" refers to an alkyl substituent as described herein containing at least one fluorine substituent.

The term "cycloalkyl" refers to a saturated hydrocarbon containing one ring having a specified number of carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The term "C₁₋₆" includes alkyls containing 6, 5, 4, 3, 2, or 1 carbon atoms

The term "alkoxy" as used herein, alone or in combination, includes an alkyl group connected to the oxygen connecting atom. The term "alkoxy" also includes alkyl ether groups, where the term 'alkyl' is defined above, and 'ether' means two alkyl groups with an oxygen atom between them. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, methoxymethane (also referred to as 'dimethyl ether'), and methoxyethane (also referred to as 'ethyl methyl ether').

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, or biphenyl.

The term heterocycle, heterocyclyl, or heterocyclic, as used herein, represents a stable 4- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. The term heterocycle or heterocyclic includes heteroaryl moieties. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl,

pyrrolyl, quinazolinyl, quinolinyl, quinoxalyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, thienyl and triazolyl.

In certain embodiments, the heterocyclic group is a heteroaryl group. As used herein, the term "heteroaryl" refers to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, between one and about three heteroatoms selected from the group consisting of N, O, and S. heteroaryl groups include, without limitation, thienyl, benzothienyl, furyl, benzofuryl, dibenzofuryl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indolyl, quinolyl, isoquinolyl, quinoxalyl, tetrazolyl, oxazolyl, thiazolyl, and isoxazolyl.

In certain other embodiments, the heterocyclic group is fused to an aryl or heteroaryl group. Examples of such fused heterocycles include, without limitation, tetrahydroquinolinyl and dihydrobenzofuranyl.

The term "heteroaryl", as used herein except where noted, represents a stable 5- to 7-membered monocyclic- or stable 9- to 10-membered fused bicyclic heterocyclic ring system which contains an aromatic ring, any ring of which may be saturated, such as piperidinyl, partially saturated, or unsaturated, such as pyridinyl, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heteroaryl groups include, but are not limited to, benzimidazole, benzisothiazole, benzisoxazole, benzofuran, benzothiazole, benzothiophene, benzotriazole, benzoxazole, carboline, cinnoline, furan, furazan, imidazole, indazole, indole, indolizine, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinazoline, quinoline, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazine, triazole, and N-oxides thereof.

Examples of heterocycloalkyls include azetidyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, imidazolyl, pyrrolidin-2-one, piperidin-2-one, and thiomorpholinyl.

The term "heteroatom" means O, S or N, selected on an independent basis.

A moiety that is substituted is one in which one or more hydrogen atoms have been independently replaced with another chemical substituent. As a non-limiting example, substituted phenyls include 2-fluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2,4-fluoro-3-propylphenyl. As another non-limiting example, substituted n-octyls include 2,4-dimethyl-5-ethyl-octyl and 3-cyclopentyl-octyl.

Included within this definition are methylenes ($-\text{CH}_2-$) substituted with oxygen to form carbonyl ($-\text{CO}-$).

Unless otherwise stated, as employed herein, when a moiety (e.g., cycloalkyl, hydrocarbyl, aryl, alkyl, heteroaryl, heterocyclic, urea, etc.) is described as "optionally substituted" it is meant that the group optionally has from one to four, preferably from one to three, more preferably one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo (e.g., an annular -CH- substituted with oxo is -C(O)-), nitro, halohydrocarbyl, hydrocarbyl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, acyl, carboxy, hydroxyalkyl, , alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups. Preferred substituents, which are themselves not further substituted (unless expressly stated otherwise) are:

- (a) halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino, guanidino, and
- (b) C₁-C₆ alkyl or alkenyl or arylalkyl imino, carbamoyl, azido, carboxamido, mercapto, hydroxy, hydroxyalkyl, alkylaryl, arylalkyl, C₁-C₈ alkyl, SO₂CF₃, CF₃, SO₂Me, C₁-C₈ alkenyl, C₁-C₈ alkoxy, C₁-C₈ alkoxycarbonyl, aryloxycarbonyl, C₂-C₈ acyl, C₂-C₈ acylamino, C₁-C₈ alkylthio, arylalkylthio, arylthio, C₁-C₈alkylsulfinyl, arylalkylsulfinyl, arylsulfinyl, C₁-C₈ alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, C₀-C₆ N-alkylcarbamoyl, C₂-C₁₅ *N,N* dialkylcarbamoyl, C₃-C₇ cycloalkyl, aroyl, aryloxy, arylalkyl ether, aryl, aryl fused to a cycloalkyl or heterocycle or another aryl ring, C₃-C₇ heterocycle, or any of these rings fused or spiro-fused to a cycloalkyl, heterocycle, or aryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above.

"Halogen" refers to fluorine, chlorine, bromine and iodine.

The term "mammal" "mammalian" or "mammals" includes humans, as well as animals, such as dogs, cats, horses, pigs and cattle.

All patents, patent applications and publications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety and are deemed representative of the prevailing state of the art.

As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise. Thus, for example, reference to "a primer" includes two or more such primers, reference to "an amino acid" includes more than one such amino acid, and the like.

The phrases "effective amount" or "therapeutically effective amount" mean a concentration of TASK-1 and/or TASK-3 receptor complex modulator sufficient to inhibit or enhance the effect of the TASK-1 and/or TASK-3 receptor complex.

Compounds described herein may contain one or more double bonds and may thus give rise to cis/trans isomers as well as other conformational isomers. The present invention includes all such possible isomers as well as mixtures of such isomers unless specifically stated otherwise.

The compounds of the present invention may contain one or more asymmetric centers and may thus occur as racemates, racemic mixtures, single enantiomers, diastereomeric mixtures, and individual diastereomers.

In the compounds of generic Formula I, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula I. For example, different isotopic forms of hydrogen (H) include protium (^1H) and deuterium (^2H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic Formula I can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

It will be understood that, as used herein, references to the compounds of structural formula I are meant to also include the pharmaceutically acceptable salts, and also salts that are not pharmaceutically acceptable when they are used as precursors to the free compounds or in other synthetic manipulations.

The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N, N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine,

lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, and tromethamine.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like.

The pharmaceutical compositions of the present invention comprise compounds of the invention (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. Such additional therapeutic agents can include, for example, i) opiate agonists or antagonists, ii) calcium channel antagonists, iii) 5HT receptor agonists or antagonists, iv) sodium channel antagonists, v) NMDA receptor agonists or antagonists, vi) COX-2 selective inhibitors, vii) NK1 antagonists, viii) non-steroidal anti-inflammatory drugs ("NSAID"), ix) selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"), x) tricyclic antidepressant drugs, xi) norepinephrine modulators, xii) lithium, xiii) valproate, xiv) neurontin (gabapentin), xv) pregabalin, and xvi) sodium channel blockers. The instant compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

The instant compounds have clinical uses for the treatment of epilepsy and partial and generalized tonic seizures. They are also useful for neuroprotection under ischaemic conditions caused by stroke or neural trauma and for treating multiple sclerosis. The present compounds are useful for the treatment of tachy-arrhythmias. Additionally, the instant compounds are useful for the treatment of neuropsychiatric disorders, including mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders, dysthymic disorders and atypical depression, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalised anxiety disorders. Thus, another aspect of this invention is the use of the

compounds of formula I in the manufacture of a medicament to treat diseases associated with TASK-1 and/or TASK-3 receptor complex.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats guinea pigs, or other bovine, ovine, equine, canine, feline, rodent such as mouse, species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

It will be appreciated that for the treatment of depression or anxiety, a compound of the present invention may be used in conjunction with other anti-depressant or anti-anxiety agents, such as norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), α -adrenoreceptor antagonists, atypical anti-depressants, benzodiazepines, 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, neurokinin-1 receptor antagonists, corticotropin releasing factor (CRF) antagonists, and pharmaceutically acceptable salts thereof.

Further, it is understood that compounds of this invention can be administered at prophylactically effective dosage levels to prevent the above-recited conditions and disorders, as well as to prevent other conditions and disorders associated with calcium channel activity.

Creams, ointments, jellies, solutions, or suspensions containing the instant compounds can be employed for topical use. Mouth washes and gargles are included within the scope of topical use for the purposes of this invention.

Dosage levels from about 0.01 mg/kg to about 140 mg/kg of body weight per day are useful in the treatment of neuropsychiatric disorders, or alternatively about 0.5 mg to about 7 g per patient per day. For example, neuropsychiatric disorders may be effectively treated by the administration of from about 0.01mg to about 75 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day neuropsychiatric disorders may be effectively treated by the administration of from about 0.01 mg to about 125 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 5.5 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.5 mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1

mg to about 1000 mg of the active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg or 1000 mg.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors. Such patient-related factors include the age, body weight, general health, sex, and diet of the patient. Other factors include the time and route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

In practice, the compounds of the invention, or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds of the invention, or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt. The compounds of the invention, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas.

Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

As described previously, in preparing the compositions for oral dosage form, any of the usual pharmaceutical media can be employed. For example, in the case of oral liquid preparations such as suspensions, elixirs and solutions, water, glycols, oils, alcohols, flavoring agents, preservatives,

coloring agents and the like may be used; or in the case of oral solid preparations such as powders, capsules and tablets, carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be included.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. In addition to the common dosage forms set out above, controlled release means and/or delivery devices may also be used in administering the instant compounds and compositions.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are advantageous oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants.

Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet advantageously contains from about 0.1 mg to about 500 mg of the active ingredient and each cachet or capsule advantageously containing from about 0.1 mg to about 500 mg of the active ingredient. Thus, a tablet, cachet, or capsule conveniently contains 0.1 mg, 1 mg, 5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, or 500 mg of the active ingredient taken one or two tablets, cachets, or capsules, once, twice, or three times daily.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the

form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage, and thus should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, and dusting powder.

Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented of the invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid, such as, for example, where the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, and preservatives (including anti-oxidants). Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient.

Compositions containing a compound of the invention, or pharmaceutically acceptable salts thereof, can also be prepared in powder or liquid concentrate form.

Further, as described above, the instant compounds can be utilized in combination with one or more therapeutically active compounds. In particular, the inventive compounds can be advantageously used in combination with i) opiate agonists or antagonists, ii) other calcium channel antagonists, iii) 5HT receptor agonists or antagonists, including 5-HT_{1A} agonists or antagonists, and 5-HT_{1A} partial agonists, iv) sodium channel antagonists, v) N-methyl-D-aspartate (NMDA) receptor agonists or antagonists, vi) COX-2 selective inhibitors, vii) neurokinin receptor 1 (NK1) antagonists, viii) non-steroidal anti-inflammatory drugs (NSAID), ix) selective serotonin reuptake inhibitors (SSRI) and/or selective serotonin and norepinephrine reuptake inhibitors

(SSNRI), x) tricyclic antidepressant drugs, xi) norepinephrine modulators, xii) lithium, xiii) valproate, xiv) norepinephrine reuptake inhibitors, xv) monoamine oxidase inhibitors (MAOIs), xvi) reversible inhibitors of monoamine oxidase (RIMAs), xvii) alpha-adrenoreceptor antagonists, xviii) atypical anti-depressants, xix) benzodiazepines, xx) corticotropin releasing factor (CRF) antagonists, xxi) neurontin (gabapentin) and xxii) pregabalin.

The abbreviations used herein have the following meanings (abbreviations not shown here have their meanings as commonly used unless specifically stated otherwise): Ac (acetyl), AcOH (acetic acid), Bn (benzyl), Boc (tertiary-butoxycarbonyl), Bop reagent (benzotriazol-1-yloxy)tris(dimethylamino)phosonium hexafluorophosphate, DCM (dichloromethane or methylene chloride), DIEA (diisopropylethyl amine), DMAP (4-(dimethylamino)pyridine), DMF (N,N-dimethylformamide), DMSO (dimethyl sulfoxide), DPPF (1,1'-bis(diphenylphosphino)ferrocene), EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride), Et₃N (triethylamine), EA or EtOAc (ethyl acetate), HCOOH (formic acid), HOBT (1-hydroxybenzotriazole), iPrOH (isopropanol), K₂CO₃ (potassium carbonate), LAH (lithium aluminum hydride), MeOH (methanol), Ms (methanesulfonyl; mesyl; or SO₂Me), MsO (methanesulfonate or mesylate), NaHCO₃ (sodium bicarbonate), MgSO₄ (magnesium sulfate), MS (molecular sieves), MsCl (methanesulfonyl chloride), NaH (sodium hydride), Na₂SO₄ (sodium sulfate), Pd(OH)₂ (palladium hydroxide, 20% on carbon), PE (petroleum ether), Ph (Phenyl), POCl₃ (phosphorous oxychloride), r.t. or RT (room temperature), Rac (Racemic), SOCl₂ (thionyl chloride), TFA (trifluoroacetic acid), THF (Tetrahydrofuran), TLC (thin layer chromatography), Me (methyl), Et (ethyl), n-Pr (normal propyl), i-Pr (isopropyl), n-Bu (normal butyl), i-Butyl (isobutyl), s-Bu (secondary butyl), t-Bu (tertiary butyl), c-Pr (cyclopropyl), c-Bu (cyclobutyl), c-Pen (cyclopentyl), c-Hex (cyclohexyl).

The present compounds can be prepared according to the procedures provided in the Examples. The following Examples further describe, but do not limit, the scope of the invention.

Unless specifically stated otherwise, the experimental procedures were performed under the following conditions: All operations were carried out at room or ambient temperature; that is, at a temperature in the range of 18-25 °C. Inert gas protection was used when reagents or intermediates were air and moisture sensitive. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm Hg) with a bath temperature of up to 60 °C. The course of reactions was followed by thin layer chromatography (TLC) or by high-pressure liquid chromatography-mass spectrometry (HPLC-MS), and reaction times are given for illustration only. The structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data. When given, yields are for

illustration only. When given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz, 400 MHz or 500 MHz using the indicated solvent. Conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. Broad; etc. In addition, "Ar" signifies an aromatic signal. Chemical symbols have their usual meanings; the following abbreviations are used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

The procedures described herein for synthesizing the compounds may include one or more steps of protecting group manipulations and of purification, such as, re-crystallization, distillation, column chromatography, flash chromatography, thin-layer chromatography (TLC), radial chromatography and high-pressure chromatography (HPLC). The products can be characterized using various techniques well known in the chemical arts, including proton and carbon-13 nuclear magnetic resonance (^1H and ^{13}C NMR), infrared and ultraviolet spectroscopy (IR and UV), X-ray crystallography, elemental analysis and HPLC and mass spectrometry (HPLC-MS). Methods of protecting group manipulation, purification, structure identification and quantification are well known to one skilled in the art of chemical synthesis.

Appropriate solvents are those which will at least partially dissolve one or all of the reactants and will not adversely interact with either the reactants or the product. Suitable solvents are aromatic hydrocarbons (e.g, toluene, xylenes), halogenated solvents (e.g, methylene chloride, chloroform, carbontetrachloride, chlorobenzenes), ethers (e.g, diethyl ether, diisopropylether, tert-butyl methyl ether, diglyme, tetrahydrofuran, dioxane, anisole), nitriles (e.g, acetonitrile, propionitrile), ketones (e.g, 2-butanone, diethyl ketone, tert-butyl methyl ketone), alcohols (e.g, methanol, ethanol, n-propanol, iso-propanol, n-butanol, t-butanol), N,N-dimethyl formamide (DMF), dimethylsulfoxide (DMSO) and water. Mixtures of two or more solvents can also be used. Suitable bases are, generally, alkali metal hydroxides, alkaline earth metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide, barium hydroxide, and calcium hydroxide; alkali metal hydrides and alkaline earth metal hydrides such as lithium hydride, sodium hydride, potassium hydride and calcium hydride; alkali metal amides such as lithium amide, sodium amide and potassium amide; alkali metal carbonates and alkaline earth metal carbonates such as lithium carbonate, sodium carbonate, cesium carbonate, sodium hydrogen carbonate, and cesium hydrogen carbonate; alkali metal alkoxides and alkaline earth metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and magnesium ethoxide; alkali metal alkyls such as methyllithium, n-butyllithium, sec-butyllithium, t-butyllithium, phenyllithium, alkyl magnaesium halides, organic bases such as trimethylamine, triethylamine, triisopropylamine, N,N-diisopropylethyl amine, piperidine, N-methyl piperidine,

morpholine, N-methyl morpholine, pyridine, collidines, lutidines, and 4-dimethylaminopyridine; and bicyclic amines such as DBU and DABCO.

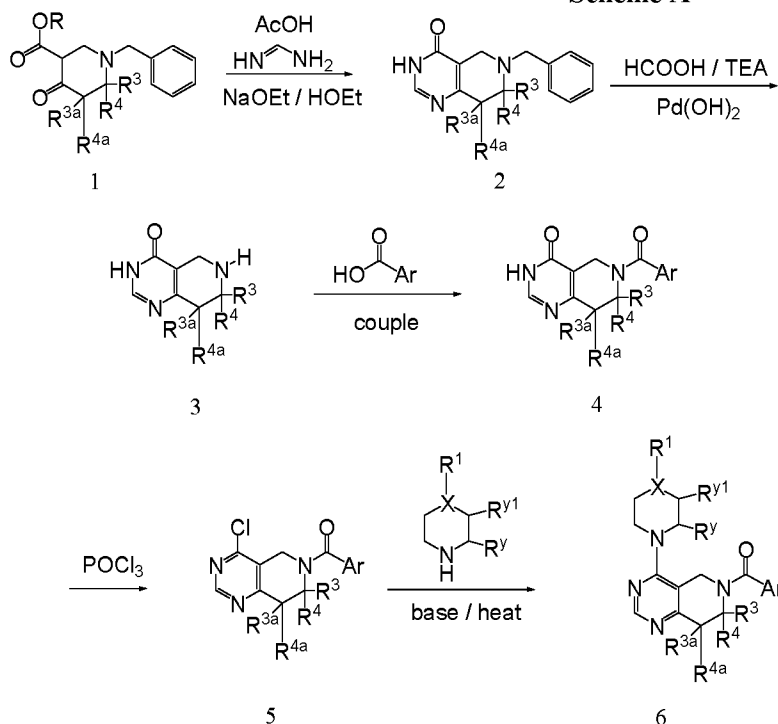
It is understood that the functional groups present in compounds described in the examples below can be further manipulated, when appropriate, using the standard functional group transformation techniques available to those skilled in the art, to provide desired compounds described in this invention.

It is also understood that compounds of this invention contain one or more stereocenters that may be prepared as single enantiomers or diastereomers, or as mixtures containing two or more enantiomers or diastereomers in any proportion.

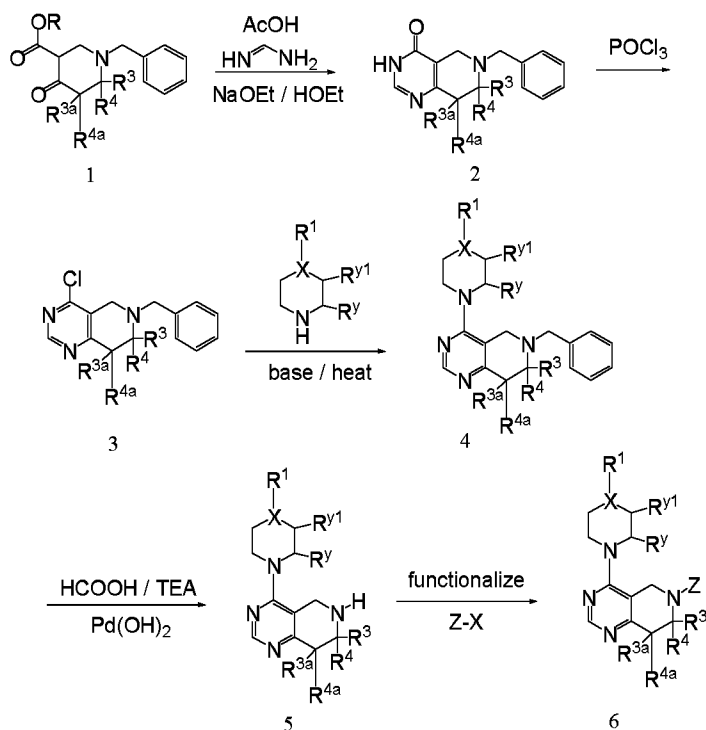
Other variations or modifications, which will be obvious to those skilled in the art, are within the scope and teachings of this invention. This invention is not to be limited except as set forth in the following claims.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made according to procedures known in the art or as illustrated herein.

Scheme A



Scheme B



The compounds of the present invention can be prepared readily according to the following Schemes and specific examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art but are not mentioned in greater detail. The general procedures for making the compounds claimed in this invention can be readily understood and appreciated by one skilled in the art from viewing the following Schemes.

The synthesis of the compounds in this invention can be synthesized using one of the methods described in schemes A or B. Cyclocondensation of an appropriately substituted keto ester 1 using formamidine and a base catalyst such as sodium methoxide can provide bicyclic structure 2 which can subsequently be deprotected using catalytic hydrogenation to afford amine 3. Amine 3 can then be coupled using an appropriately substituted carboxylic acid and an amide coupling agent to give intermediate pyrazinone 4 which can be converted the the corresponding chloropyrimidine 5. The penultimate compounds 5 can then be heated with a cyclic amine in the presence of an acid scavenger to afford the final compounds 6 which could be functionalized further depending on the structure of the target.

Scheme B represents an alternative procedure for the synthesis of the claimed compounds and begins with the bicyclic pyrazinone 2 from scheme A above. Chloropyrimidine formation can be effected by the action of an electrophilic halogenating agent such as phosphorous oxychloride to afford intermediate 3.

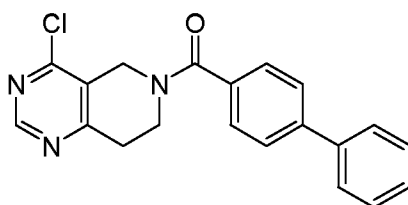
Nucleophilic aromatic substitution with an appropriately substituted cyclic amine can provide intermediate

4 which can then be deprotected using hydrogenating conditions. The resulting amine can then be functionalized using a variety of acylating or sulfonylating agents to provide the desired targets 6.

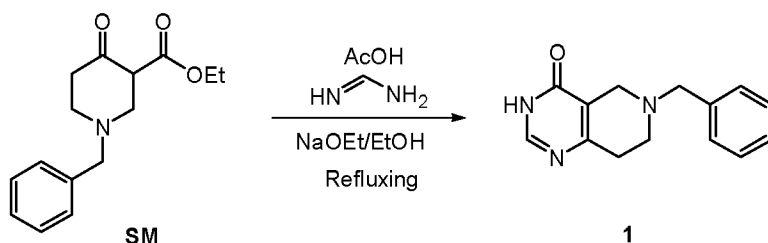
INTERMEDIATES AND EXAMPLES

5 The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

INTERMEDIATE 1 **Biphenyl-4-yl(4-chloro-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl) methanone**

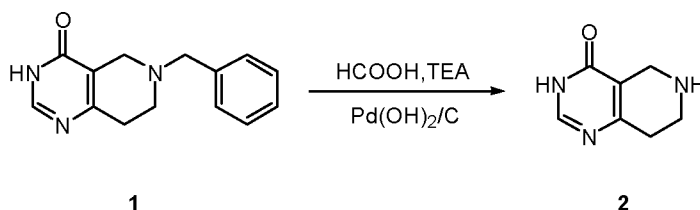


10 **Step A:**



1-Benzyl-3-ethoxycarbonyl-4-piperidone hydrochloride (12.89 g, 43.3 mmol) was suspended in a sodium methoxide solution in methanol (25 % wt/wt, 50 mL, 216.2 mmol) and formamidine acetate (5.4 g, 51.9 mmol) was added to the mixture. The reaction mixture was refluxed until all of the starting material was consumed (2 h). The methanol was removed under reduced pressure, and the resulting white solid was dissolved in a 3/1 mixture of chloroform / isopropanol. The mixture was washed with water and brine, dried over Na₂SO₄, filtered and evaporated to give the desired product as a white solid (9.4 g). **MS (ESI):** 242.1 [M+1]⁺

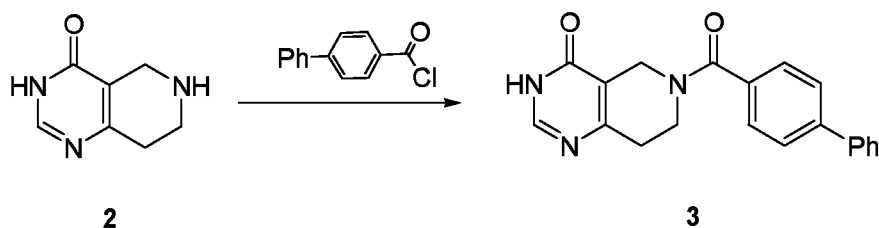
Step B:



To a solution of compound 1 (100 g, 0.415 mol), Pd(OH)₂ (23 g), and TEA (200 g, 2.07 mol) in MeOH (1500 mL) was added HCOOH (50 mL) dropwise at 60°C over 30 mins and after addition, the mixture was stirred at 60°C for additional 5 hours. The reaction mixture was cooled to room temperature and

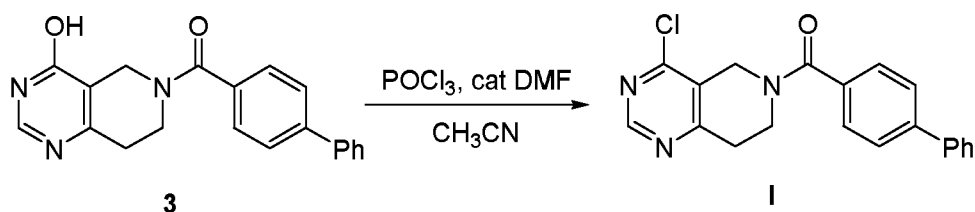
filtered over Celite. The filtrate was concentrated to yield the title compound **2** (65 g) as a yellow solid which was used directly in the next reaction. **MS (ESI)**: 152 ($M+H$)⁺.

Step C:



- 5 To a stirred suspension of compound **2** (50 g, 0.3 mol) and NaHCO₃ (70 g, 0.8 mol) in THF (250 mL) and H₂O (80 mL) was added a solution of 4-biphenylcarbonyl chloride (19 g, 0.33 mol) in THF (50 mL) at 0°C over 15 min and the resulting mixture was allowed to stir at rt for additional 3 hrs. A large amount of white solid formed and the mixture was filtered then washed with cool ethanol to give 75 g of compound **3** after drying. **MS (ESI)**: 332 [$M+1$]⁺

10 **Step D:**

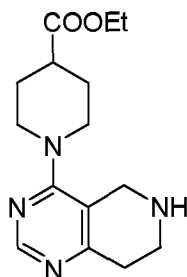


- A mixture of compound **3** (50 g, 0.15 mol), phosphoryl chloride (100 mL, 1.0 mol) and acetonitrile (500 mL) and DMF (2 mL) was heated to reflux at 70°C for 5 hour. After cooling, the mixture was evaporated to give the remaining black residue, which was taken up in DCM (600 mL) and poured into 200 mL of ice-water. The mixture was carefully neutralized with the addition of solid NaHCO₃ to pH~9. The organic layer was separated and the aqueous layer was washed with DCM twice. The combined organic phase was washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was then purified on silica gel column (MeOH/DCM (0-5%)) to yield the title compound **4** as a brown solid (31 g). **MS (ESI)**: 351.0 [$M+1$]⁺

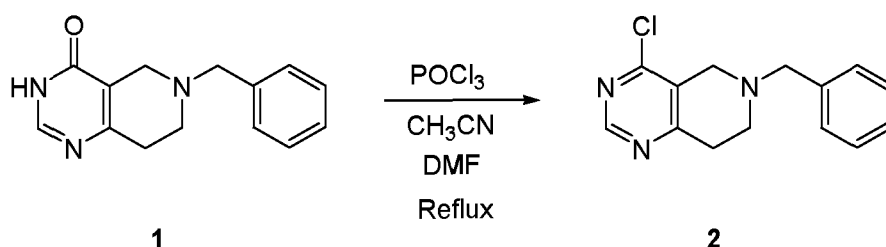
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INTERMEDIATE II

Ethyl 1-(5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl) piperidine-4-carboxylate

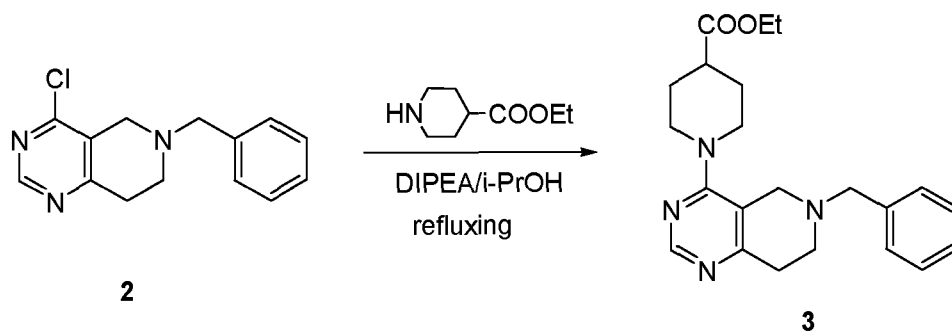


Step A



A mixture of 6-benzyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4(3H)-one **1** from Intermediate I, step A (5.0 g, 0.02 mol), phosphorous oxychloride (3.30 mL, 0.035 mol) and acetonitrile (80 mL) and DMF (catalytic amount) was heated at reflux for 3 hours. Then the solvents were reduced in vacuum and the remaining black residue was taken up in dichloromethane (250 mL) and poured over ice. The mixture was carefully neutralized with the addition of solid sodium bicarbonate to pH~8. The layers were separated and the organic was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by column chromatography to yield compound **2** as a yellow oil (3 g). **MS (ESI)**: 242.1 $[M+1]^+$ 1H NMR (DMSO- d_6): δ 8.80 (s, 1H), 7.40-7.24 (m, 5H), 3.76 (s, 2H), 3.57 (s, 2H), 2.92 (t, 2H), 2.80 (t, 2H).

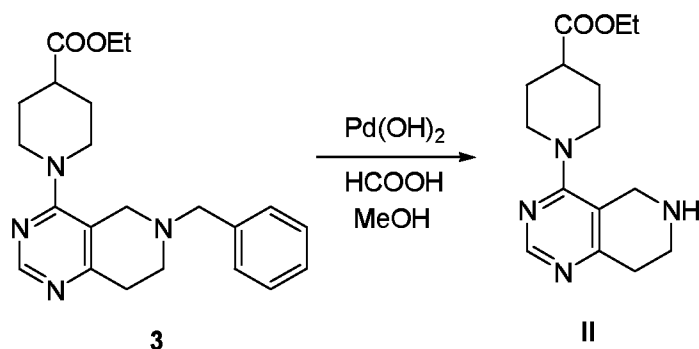
Step B:



To the solution of compound **2** (5.4g, 20.8mmol) and ethyl isonipecotate (3.92 g, 24.95 mmol) in 100 mL of ethanol was added DIEA (4.02g, 31.2mmol) and the mixture was heated to reflux for 4 hours. TLC (DCM: MeOH=15: 1) indicated that the reaction completed. The reaction mixture was then concentrated

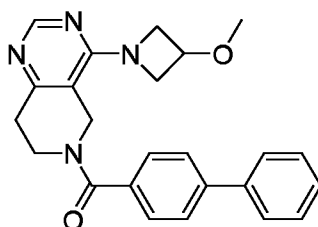
and purified by chromatography over silica gel to give compound **3** as pale brown solid (7.2 g) **MS (ESI)**: 381.4 $[M+1]^+$

Step C:

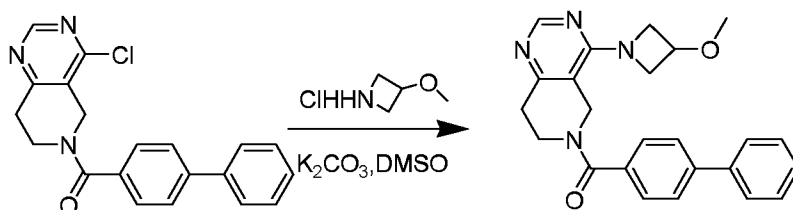


- 5 A mixture of **3** (4 g, 10.5 mmol), ammonium formate (6.64 g, 105 mmol), palladium hydroxide (1.0 g) in methanol (50 mL) was heated at reflux for 3h. The mixture was cooled to rt and filtered over Celite. The filtrate was concentrated under reduced pressure to yield the crude compound as a yellow oil (3.6 g) which could be stored and used directly without further purification. **MS (ESI)**: 291.2 $[M+1]$.

10 **Example 1: Biphenyl-4-yl[4-(3-methoxyazetidin-1-yl)-7,8-dihydropyrido [4,3-d]pyrimidin-6(5H)-yl]methanone**



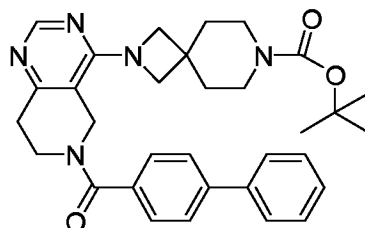
Step A



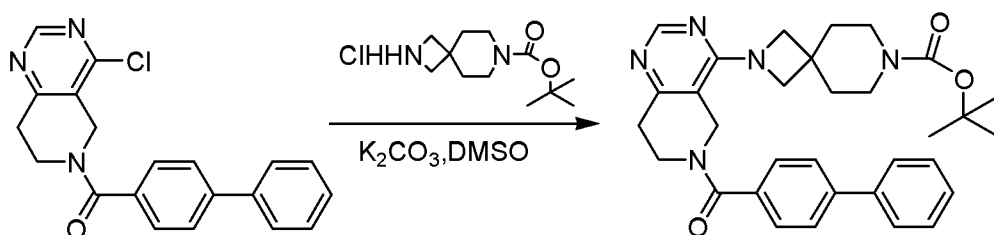
- 15 To a solution of Intermediate I (100 mg, 0.29 mmol) in anhydrous DMSO (6 mL) was added 3-methoxyazetidine (176.72 mg, 1.43 mmol) and K_2CO_3 (197.50 mg, 1.43 mmol), then the mixture was heated to 90 °C for 4 hrs. The reaction mixture was cooled to rt and filtered. The filtrate was evaporated

and purified by HPLC to yield the desired compound (50 mg). ^1H NMR (CDCl_3) δ 8.44 (br, 1H), 7.40 ~ 7.69 (m, 9H), 4.81 (br, 3H), 4.36 (br, 4H), 3.80 (s, 2H), 3.35 (s, 3H), 2.72 (br, 2H).

Example 2: tert-butyl 2-[6-(biphenyl-4-ylcarbonyl)-5,6,7,8-tetrahydropyrido [4,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate

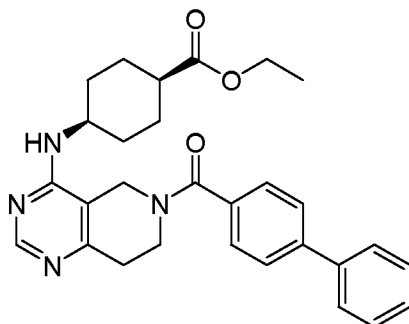
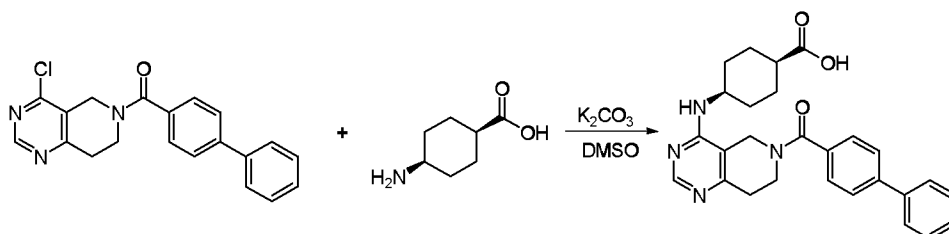


Step A

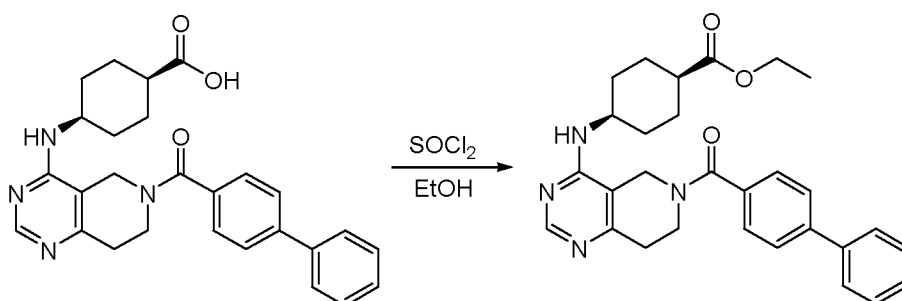


- 10 To a solution of Intermediate I (300 mg, 0.87 mmol) in anhydrous DMSO (15 mL) was added t-butyl 2, 7-diazaspiro [3.5] nonane-7-carboxylate (685 mg, 2.61 mmol) and K_2CO_3 (360 mg, 2.61 mmol). The mixture was heated to 90°C for 4 hrs. The reaction mixture was filtered and the filtrate was evaporated and purified by HPLC to yield compound (350 mg) ^1H NMR (MeOD) δ 8.05 (br, 1H), 7.40 ~ 7.69 (m, $J = 8.0$ Hz, 2H), 7.23 (d, $J = 7.3$ Hz, 2H), 7.15 (d, $J = 7.8$ Hz, 2H), 7.02 (t, $J = 7.6$ Hz, 1H), 6.95 (t, $J = 7.4$ Hz, 2H), 5.04 (s, 1H), 4.02 ~ 4.21 (m, 2H), 3.22 ~ 3.66 (m, 9H), 2.50 (s, 2H), 1.36 ~ 1.68 (m, 4H), 1.01 (s, 9H).

Example 3: ethyl cis-4-{[6-(biphenyl-4-ylcarbonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl]amino}cyclohexanecarboxylate

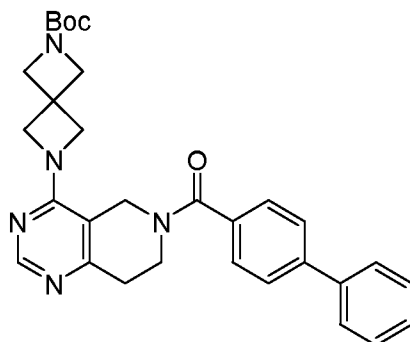
**Step A**

- 5 To a solution of Intermediate I (150 mg, 0.44 mmol) and 4-aminocyclohexane carboxylic acid (123 mg, 0.86 mmol) in 2 mL of DMSO was added K_2CO_3 (178 mg, 1.29 mmol), then the mixture was stirred at $80^\circ C$ for 4hrs. The cooled reaction mixture was neutralized with 2N HCl to pH~7 and solid deposited, then filtered. The filtered cake was dried in vacuo to give the crude product (150 mg) which was used to next reaction directly. MS (m/z): 457 (M+H)⁺.

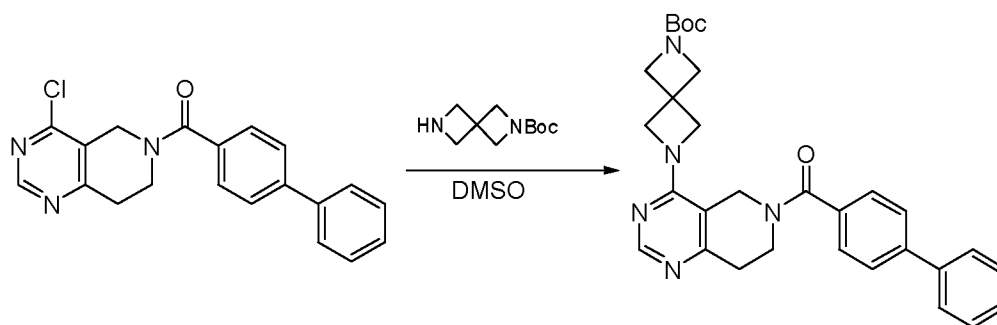
10 **Step B:**

- SOCl₂ was added to 2 mL of EtOH dropwise at $0^\circ C$ then the compound from step A above (150 mg, 0.33 mmol) was added to the solution and stirring was continued overnight at rt. The reaction mixture was concentrated and the residue was purified by HPLC to give pure product (60 mg). ¹H NMR (MeOD): δ 8.56 (s, 1H), 7.73 (d, J=7.1Hz, 2H), 7.63 (d, J=7.1Hz, 2H), 7.55 (d, J=7.3Hz, 2H), 7.44 (t, J=6.9Hz, 2H), 7.34~7.37 (m, 1H), 4.50~4.60 (m, 2H), 4.33 (s, 1H), 3.78~4.13 (m, 4H), 2.92 (s, 2H), 2.63 (s, 1H), 2.19 (s, 2H), 1.64~1.81 (m, 6H), 1.24 (s, 3H). MS (m/z): 485 (M+H)⁺.

Example 4: tert-butyl 6-[6-(biphenyl-4-ylcarbonyl)-5,6,7,8- tetrahydropyrido[4,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.3]heptane-2-carboxylate

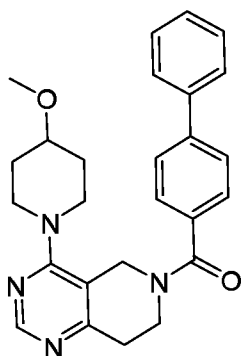
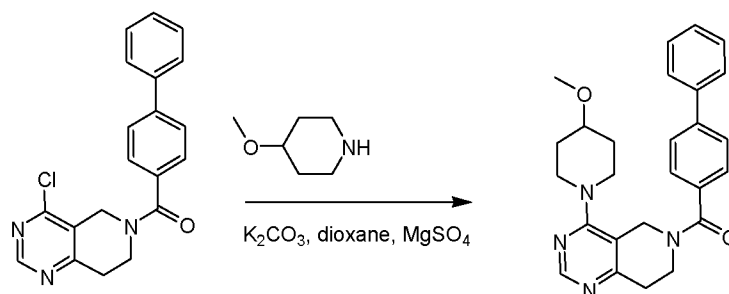


5 Step A



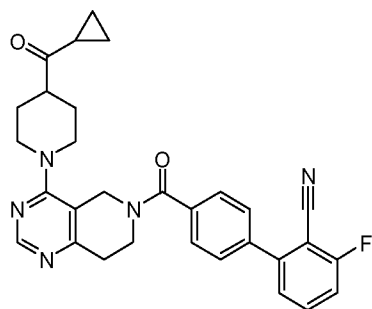
To a solution of Intermediate 1 (300 mg, 0.86 mmol) and the amine (371 mg, 1.29 mmol) in 4 mL of DMSO was added K_2CO_3 (593 mg, 4.29 mmol), then the mixture was stirred at 80°C for 4 hours. The cooled reaction mixture was purified by HPLC to give the desired product (300 mg). 1H NMR (MeOD): δ 8.45 (s, 1H), 7.75 (d, $J=7.4$ Hz, 2H), 7.66 (d, $J=7.5$ Hz, 2H), 7.56 (d, $J=5.6$ Hz, 2H), 7.45 (t, $J=7.6$ Hz, 2H), 7.37 (t, $J=7.3$ Hz, 1H), 4.8 (br, 3H), 4.01~4.46 (m, 7H), 3.60~3.75(m, 2H), 2.89 (s, 2H), 1.42 (s, 9H). MS (m/z): 512 (M+H) $^+$.

Example 5: Biphenyl-4-yl[4-(4-methoxypiperidin-1-yl)-7,8-dihydropyrido [4,3-d]pyrimidin-6(5H)-yl]methanone

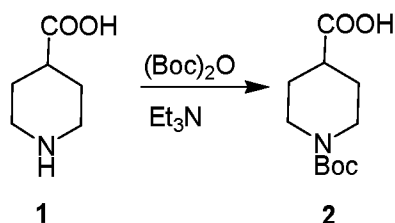
**Step A:**

To a solution of Intermediate I (100 mg, 0.286 mmol) in dioxane (3 mL) was added 4-methoxy-piperidine (66 mg, 0.572 mmol), K_2CO_3 (79 mg 0.572 mmol) and $MgSO_4$ (86 mg, 0.716 mmol). The resulting mixture was heated to 70°C and stirred overnight. After cooling to rt, the reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by HPLC to give 63.6 mg of the desired product. MS (ESI) m/e 429 (M+H). 1H NMR (CD_3OD) δ 8.46 (s, 1H), 7.66 (d, $J=8.4$ Hz, 2H), 7.57 (d, $J=8.4$ Hz, 2H), 7.46 (d, $J=8.0$ Hz, 2H), 7.37 (t, $J=7.2$ Hz, 2H), 7.20-7.30 (m, 1H), 4.60-4.70 (m, 1H), 3.50-4.15 (m, 1H), 3.20-3.38 (m, 3H), 2.80-3.02 (m, 2H), 1.50-2.10 (m, 7H).

Example 6: 4'-({4-[4-(cyclopropylcarbonyl)piperidin-1-yl]-7,8-dihydropyrido [4,3-d]pyrimidin-6(5H)-yl}carbonyl)-3-fluorobiphenyl-2-carbonitrile

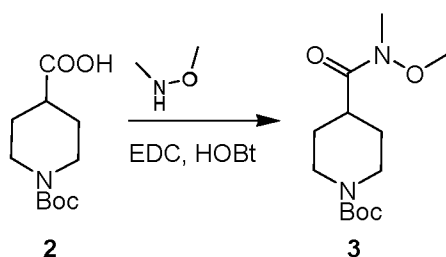


15 **Step A**



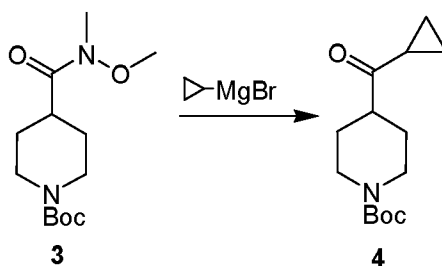
To a mixture of compound **1** (25 g, 194 mmol) and (Boc)₂O (50.7 g, 232 mmol) in 150 mL CH₂Cl₂ was added, Et₃N (58.8 g, 582 mmol). The solution was stirred at rt overnight. The solvent was removed under reduced pressure to give the crude compound (42 g).

5 Step B



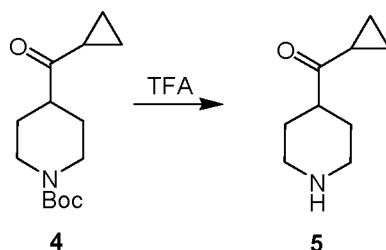
A mixture of compound **2** (40 g, 0.175 mol), O,N-Dimethyl hydroxylamine (17 g, 0.175 mol), HOBT (11.8 g, 0.088 mol), EDCI (50 g, 0.263 mol), and Et₃N (53 g, 0.525 mol) in 300 mL CH₂Cl₂ was stirred at rt overnight. The solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography (PE/EtOAc (3:1)) to give an off-white solid compound **3** (41 g).

Step C



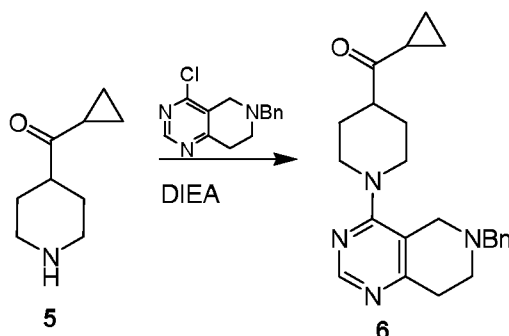
To a solution of compound **3** (10 g, 36.8 mmol) in 50 mL dry THF was added c-PrMgBr (80.8 mL, 40.4 mmol, 0.5 M) dropwise at 0 °C. The mixture was allowed to stir at rt for another one hour. The mixture was concentrated under reduced pressure. Added 100 mL of water, extracted with EtOAc. The organic layer was washed with an aqueous solution of NaCl (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure give the crude product compound **4** (5.91 g).

20 Step D



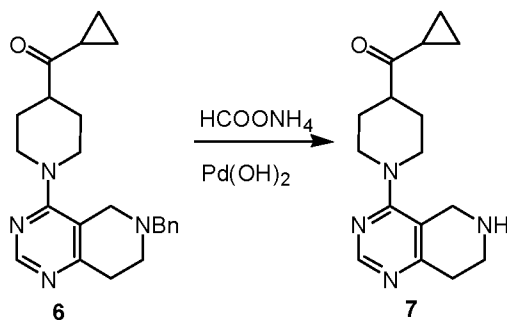
Compound **4** (5 g, 19.7 mmol) in 30 ml CH_2Cl_2 was added 10 mL of CF_3COOH . The mixture was stirring at rt for 2 hours. 10% NaOH (50 ml) was added to quench the solution. The residue extracted with EtOAc. Organic layer was dried on MgSO_4 . The solvent was removed under reduced pressure to give the crude product compound **5** without further purification (2.33 g).

Step E



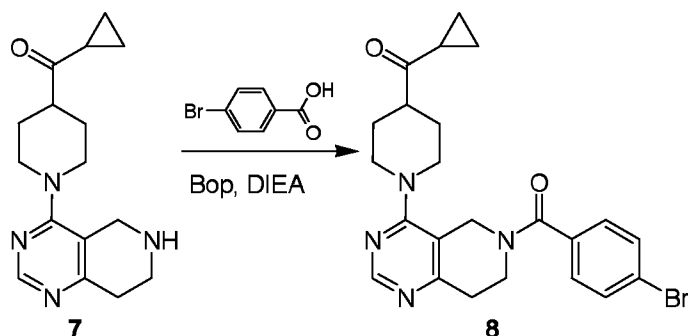
To a solution of 6-benzyl-4-chloro-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine (3.9 g, 15.0 mmol) in EtOH (50 mL) was added compound **5** (2.3 g, 15.0 mmol) and DIEA (3.87 g, 30 mmol). The mixture was stirred at 80 °C for 3 hours then the mixture was evaporated to dryness. The crude product was purified by silica gel chromatography eluted with PE: EA = (5:1) to give the desired product (4.08 g)

Step F



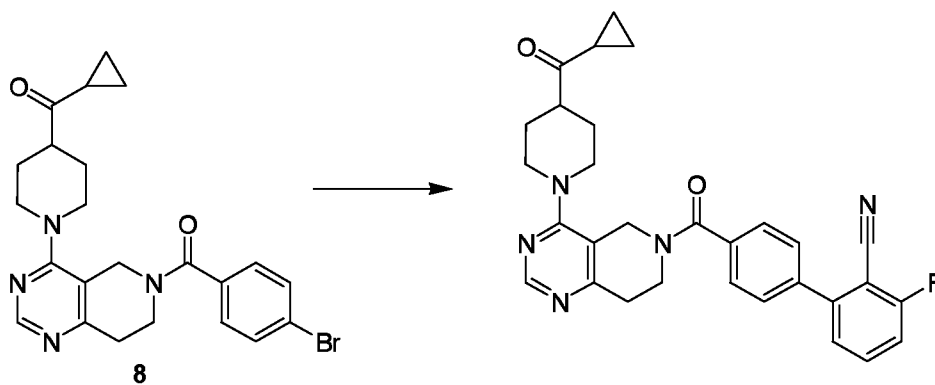
A mixture of compound **6** (2.04 g, 5.41 mmol), ammonium formate (3.4 g, 54.1 mmol) and Pd(OH)_2 (0.6 g) in 20 mL MeOH was heated to reflux for 3 hours, then the mixture was filtered. The solvent was removed under reduced pressure to give desired product (1.35 g).

Step G



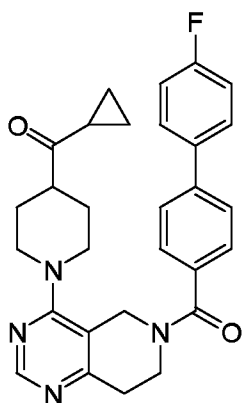
To a solution of compound **7** (200 mg, 0.7 mmol) in 8 ml CH_2Cl_2 was added 4-Bromobenzoic acid (140 mg, 0.7 mmol), Bop (340 mg, 0.77 mmol) and DIEA (361 mg, 2.8 mmol). The mixture was stirred at r.t. for 3 hours and the mixture was evaporated to dryness. The crude product was purified by silica gel chromatography eluted with PE: EA = (5:1) to give desired product (315 g).

Step H

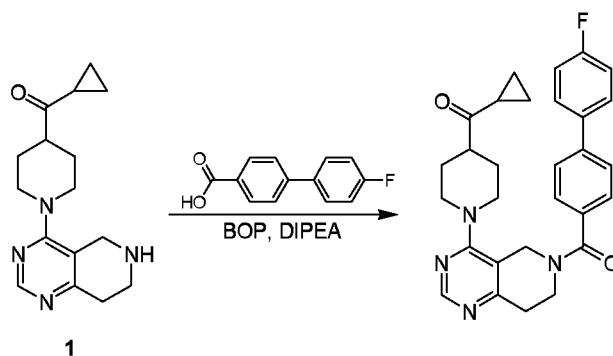


To a solution of compound **8** (418 mg, 0.89 mmol) in toluene and dioxane (8 mL/2 mL) was added dioxaborolan (220 mg, 0.89 mmol), Cs_2CO_3 (580 mg, 1.78 mmol), Pd(dppf)Cl_2 (33 mg, 0.0445 mmol). The mixture was stirring at 80 °C overnight under N_2 . The mixture was evaporated to dryness and the crude product was purified by HPLC to give the desired target (287 mg).

Example 7: cyclopropyl(1-{6-[(4'-fluorobiphenyl-4-yl)carbonyl]-5,6,7,8- tetra- hydropyrido[4,3-d]pyrimidin-4-yl}piperidin-4-yl)methanone

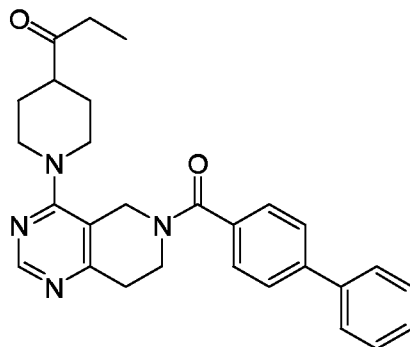
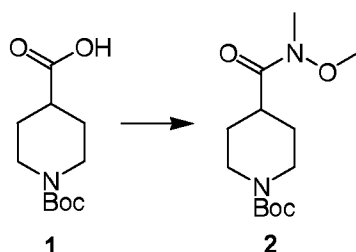


Step A

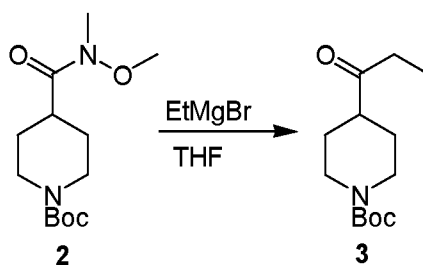


A mixture of compound 7 from step F in Example 5 (100 mg, 0.349 mmol), 4'-fluorobiphenyl-4-carboxylic acid (75.5 mg, 0.349 mmol), BOP (185 mg, 0.419 mmol) and DIPEA (180 mg, 1.396 mmol) in DCM (10 mL) was stirred at RT for 3 hours. After the reaction was complete, solvent was removed under reduced pressure; the residue was extracted with DCM, washed with water and brine, dried over MgSO_4 . DCM was removed under reduced pressure to give the desired product (140 mg). **MS (m/z) :** 485 ($\text{M}+\text{H}^+$) **^1H NMR** (MeOD, 400 MHz): δ 8.56 (s, 1H), 7.65-7.72 (m, 4H), 7.53-7.55 (d, $J=7.6$ Hz, 2H), 7.16-7.21 (t, $J=8.4$ Hz, $J=8.8$ Hz, 2H), 4.33-4.46 (m, 2H), 3.89-4.03 (m, 2H), 3.46-3.53 (t, $J=10.8$ Hz, $J=18.4$ Hz, 2H), 2.84-3.11 (m, 4H), 1.96-2.13 (m, 4H), 0.80-1.49 (m, 6H).

Example 8: 1-{1-[6-(biphenyl-4-ylcarbonyl)-5,6,7,8-tetrahydropyrido[4,3-d]-pyrimidin-4-yl]piperidin-4-yl}propan-1-one

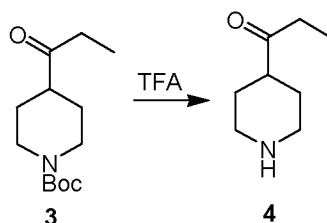
**Step A**

A mixture of compound **1** (4 g, 1.75 mol), O,N-Dimethyl-hydroxylamine (1.7 g, 1.75 mol), HOBt (1.18 g, 8.8 mmol), EDCI (5 g, 26.3 mmol), and Et₃N (5.3 g, 52.5 mmol) in 30 mL CH₂Cl₂ was stirred at r.t. overnight. Solvent was removed under reduced pressure. The crude product was purified by silica gel chromatography eluted with PE/EtOAc (3:1) to give an off-white solid compound **2** (4.1 g).

Step B

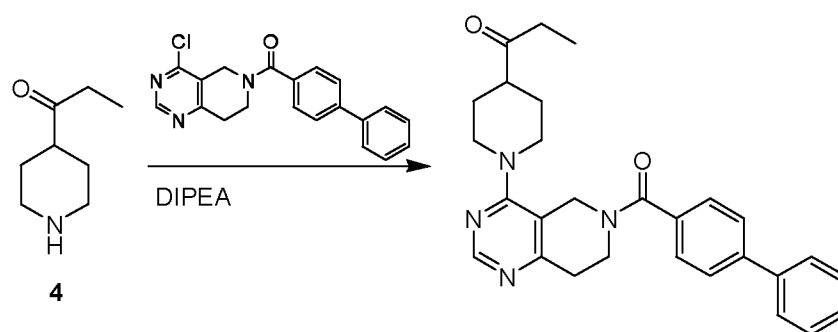
To a solution of compound **2** (4 g, 14.7 mmol) in dry THF (20 mL) was added EtMgBr (32.3 mL, 16.2 mmol, 0.5 M) dropwise at 0 °C. The mixture was allowed to stir at r.t. for another one hour. The mixture was concentrated under reduced pressure. 40 mL of water was added and the mixture was extracted with EA. The organic layer was washed with an aqueous solution of NaCl (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure give the crude product compound **3** (2.36 g).

Step C



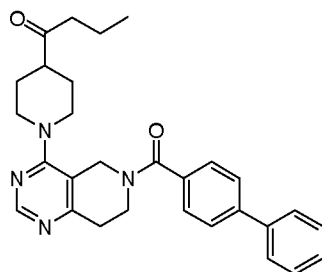
Compound **3** (2 g, 7.88 mmol) in 12 ml CH_2Cl_2 was added 4 mL of CF_3COOH . The mixture was stirred at r.t. for 2 hours. 10% NaOH (20 ml) was added to quench the solution. The residue extracted with EtOAc and the organic layer was dried over MgSO_4 . The solvent was removed under reduced pressure to give the crude product compound **4** (0.93 g).

Step D

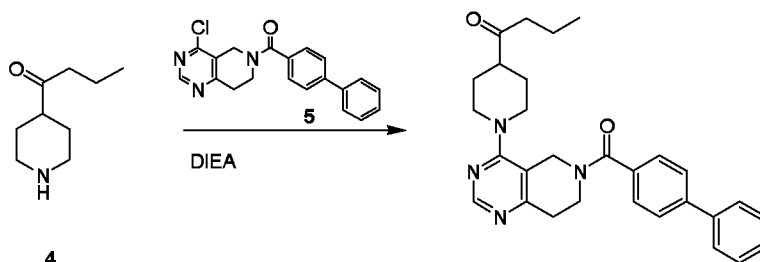


To a solution of Intermediate I (1.1 g, 3.1 mmol) in EtOH (15 mL) was added 1-Piperidin-4-yl-propan-1-one (437 mg, 3.1 mmol) and DIEA (1.55 g, 12 mmol). The mixture was stirred at 80 °C for 3 hours then the mixture was evaporated to dryness. The crude product was purified by silica gel chromatography eluted with PE: EA =(10:1) to give desired product (0.95 g). MS (m/e): 454 ($\text{M} + \text{H}$)⁺ ¹H NMR (MeOD) δ , 8.55 (s, 1H), 7.65-7.74 (m, 2H), 7.56-7.63 (m, 2H), 7.46-7.54 (m, 2H), 7.42-7.44 (m, 2H), 7.36-7.38 (m, 1H), 4.50-4.80 (m, 2H), 4.23-4.60 (m, 2H), 3.64-4.12 (m, 2H), 3.36-3.60 (m, 1H), 2.70-3.12 (m, 3H), 2.23-2.69 (m, 2H), 1.64-2.17 (m, mH), 1.16-1.56 (m, 1H), 0.64-1.15 (m, 3H).

Example 9: 1-{1-[6-(biphenyl-4-ylcarbonyl)-5,6,7,8- tetrahydropyrido[4,3-d]pyrimidin-4-yl]piperidin-4-yl}butan-1-one

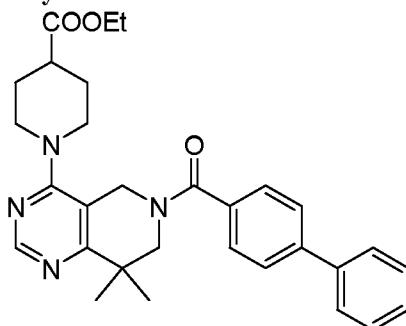


Step A

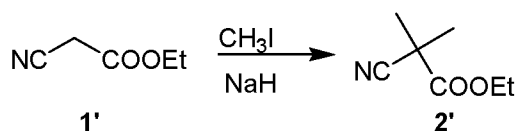


To a solution of compound **4** (831 mg, 5.3 mmol) in EtOH (50 mL) was added Intermediate I (1.7 g, 4.87 mmol) and DIEA (1.25 g, 9.74 mmol). The resulting mixture was stirred at 80 °C for 3 hours. After cooling to r.t., the reaction mixture was concentrated and the residue was purified by HPLC. MS (ESI) m/e 469 (M+H) ^1H NMR (CD_3OD) δ , 8.56 (s, 1H), 7.72-7.75 (m, 2H), 7.67-7.69 (m, 2H), 7.56-7.63 (m, 2H), 7.43-7.49 (m, 2H), 7.36-7.38 (m, 1H), 4.46-4.83 (m, 2H), 3.90-4.07 (m, 2H), 3.21-3.72 (m, 2H), 2.95-3.15 (m, 2H), 2.21-2.94 (m, 3H), 1.84-2.19 (m, 2H), 1.63-1.84 (m, 1H), 1.13-1.64 (m, 3H), 0.58-1.13 (m, 3H).

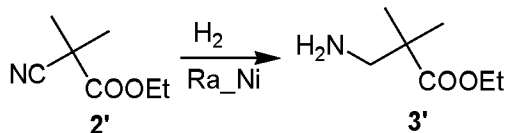
Example 10: ethyl 1-[6-(biphenyl-4-ylcarbonyl)-8,8-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl]piperidine-4-carboxylate



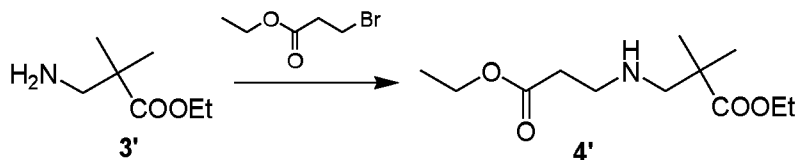
Step A



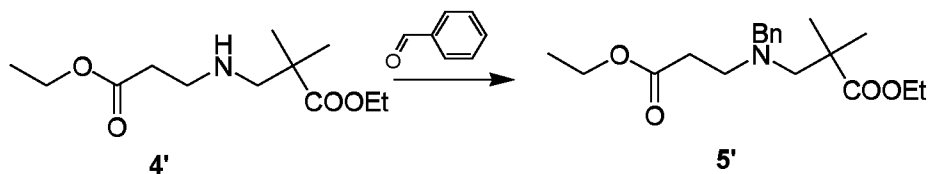
To a solution of NaH (31 g, 0.795 mol) in THF (200 mL), was added compound **1'** (30 g, 0.265 mol) was added dropwise at 0°C under N_2 . The solution was stirred at this temperature for 30 minutes, then iodomethane (94.11 g, 0.663 mol) was added into the mixture and stirring was continued as the solution warmed slowly to room temperature overnight. Water (300 mL) was added and the aqueous layer was extracted with EA (200 mL) twice. The organic layer was washed with an aqueous solution of NaCl (150 mL) and dried over Na_2SO_4 . The organic layer was concentrated under reduced pressure to give compound **2'** (32.1 g) as slight yellow liquid.

Step B

The mixture of compound **2'** (0.5 g, 3.54 mmol) and Ra_Ni (0.1 g) in MeOH was stirred at r.t. under H_2 atmosphere for 3 hour. The reaction mixture was filtered and concentrated to give the crude product (484 mg) without further purification.

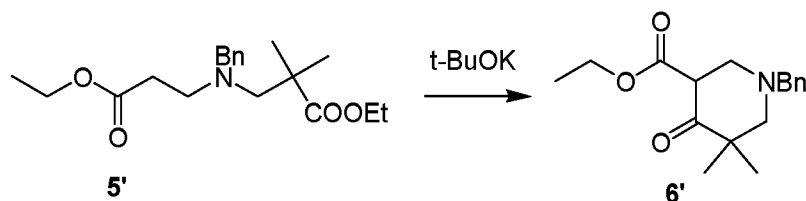
Step C

- 10 To a solution of compound **3'** (20 mg, 0.138 mmol) in EtOH (3 mL) was added 3-Bromo-propionic acid ethyl ester (30 g, 0.165 mmol) and triethylamine (28 mg, 0.276 mmol). The mixture was stirring at 80 °C for 3 hours then the mixture was evaporated to dryness under depress. The crude product was purified by silica gel chromatography eluted with PE: EA =(5:1) to give desired product (30 mg).

Step D

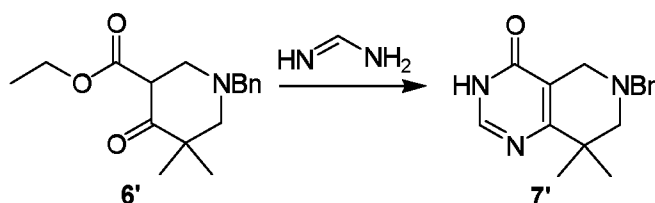
- 15 Compound **4'** (7 g, 28.5 mmol) was dissolved with 30 mL of MeOH, then two drops of glacial acetic acid followed by benzaldehyde (3.6 g, 34.1 mmol) were added into the mixture, and the mixture was heated to reflux for 30 min. $NaBH_3CN$ (5.37 g, 85.5 mmol) was added into the mixture at 0°C and the mixture was stirred at r.t for 3 hour. The mixture was concentrated and water was added (30 mL) then the mixture was extracted with EA. The organic layer was washed with an aqueous solution of NaCl (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluted with PE: EA = (4:1) to give desired product (6.5 mg).

Step E



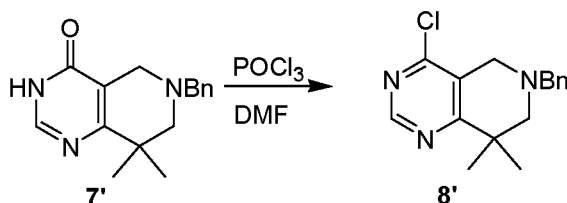
To a solution of t-BuOK (1.6 g, 14.3 mmol) in 20 mL dry THF was added Compound **5'** (2.4 g, 7.16 mmol) dropwise at 0 °C. The mixture was allowed to stir at r.t. for another one hour. The mixture was concentrated under reduced pressure. Added 30 mL of water, extracted with EA. The organic layer was washed with an aqueous solution of NaCl (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure give the crude product compound **6'** (1.1 g).

Step F



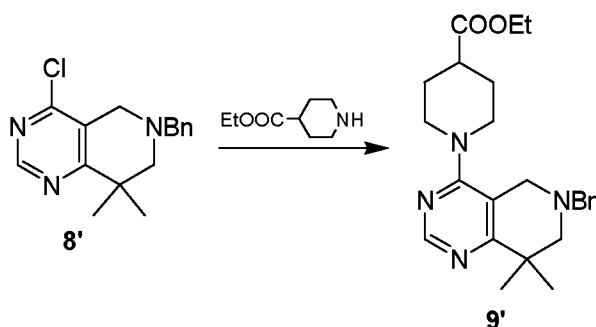
A mixture of compound **6'** (1.1 g, 3.8 mmol), formamidine acetate (368 mg, 4.57 mmol) and sodium methoxide (1.03 g, 19 mmol) in 5 mL MeOH was heated to reflux for 3 hours, then the mixture was filtrated. Solvent was removed under reduced pressure, then extracted with EA while PH=7. The organic layer was washed with an aqueous solution of NaCl (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure give the crude product compound **7'** (0.81 g).

Step G

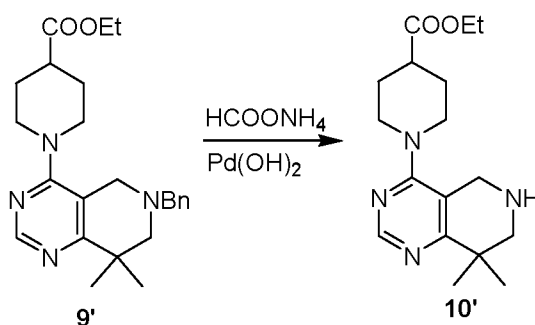


A mixture of compound **7'** (0.1 g, 0.372 mmol), POCl₃ (569 mg, 3.72 mmol) and two drops of DMF in 5 mL CH₃CN was heated to reflux for 3 hours. Reduced the solvents and the residue was taken up in CH₂Cl₂ and poured over ice. The mixture was carefully neutralized with the addition of solid sodium bicarbonate to pH = 8. The organic layer was washed with brine, dried over MgSO₄, and concentrated to give the desired product (72.5 mg).

Step H

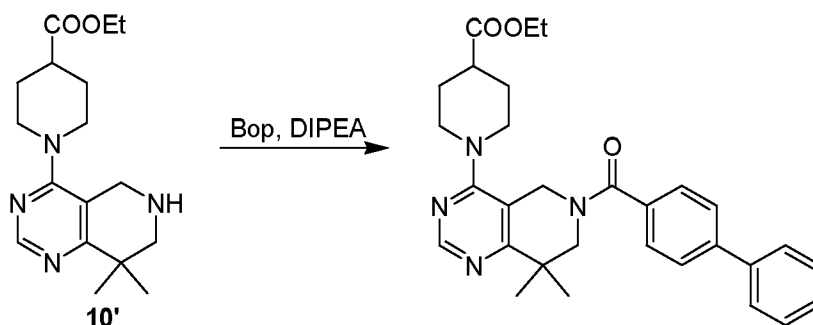


To a solution of compound **8'** (580 mg, 2.02 mmol) in EtOH (30 mL) was added piperidine-4-carboxylic acid ethyl ester (317 mg, 2.02 mmol) and DIEA (1.04 g, 8.08 mmol). The mixture was stirring at 80 °C for 3 hours then the mixture was evaporated to dryness under depress. The crude product was purified by silica gel chromatography eluted with DCM: MeOH = (20:1) to give desired product (0.68 g). **Step I**



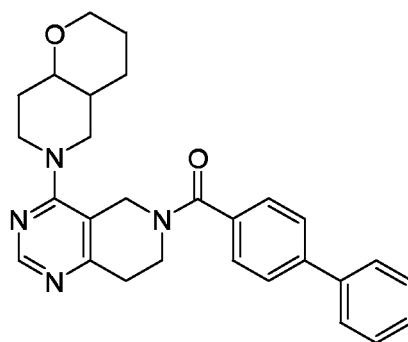
A mixture of compound **9'** (0.4 g, 0.98 mmol), ammonium formate (0.62 g, 9.8 mmol) and Pd(OH)₂ (0.2 g) in 10 mL MeOH was heated to reflux for 3 hours, then the mixture was filtered. The solvent was removed under reduced pressure to give desired product (285 mg).

Step J

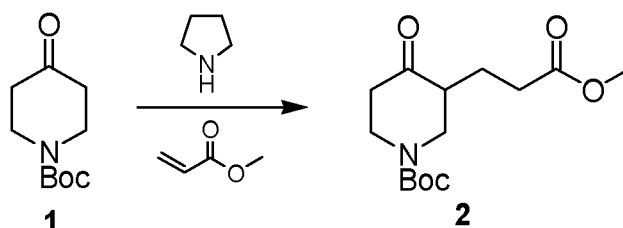


To a solution of compound **10'** (285 mg, 0.448 mmol) in 10 ml CH₂Cl₂ was added biphenyl-4-carboxylic acid (89 mg, 0.448 mmol), Bop (218 mg, 0.493 mmol) and DIEA (231 mg, 1.79 mmol). The mixture was stirring at r.t. for 3 hours then the mixture was evaporated to dryness under depress. The crude product was purified by HPLC to give (175 mg).

Example 11: cis and trans Biphenyl-4-yl{4-[(8aR)-hexahydro-2H-pyrano [3,2-c]pyridin-6(5H)-yl]-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl}methanone

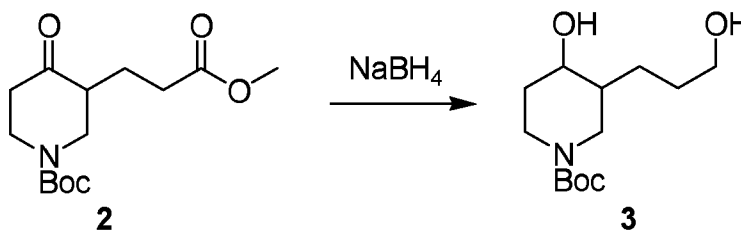


5 Step A



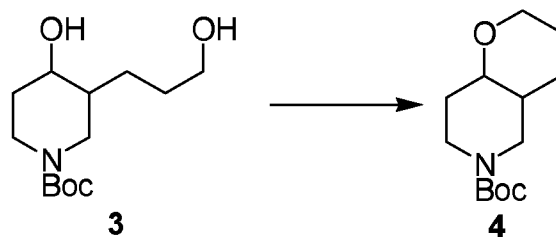
A mixture of compound **1** (4.0 g, 20 mmol), pyrrolidine (2.8 g, 40 mmol) and 4 Å MS (5 g) in EtOH 20 mL was refluxed for 16hrs. Acrylic acid methyl ester (1.72 g, 20 mmol) was added to the mixture, and the mixture was refluxed for 4 hrs. After cooled to r.t., the reaction mixture was filtered and concentrated in vacuo. H₂O (10 mL) was added to the residue, extracted with EtOAc (20 mL × 2). The combined organic layers were dried over Na₂SO₄, concentrated, and purified by chromatography on silica (CH₂Cl₂ : MeOH = 50:1) to give product **2** (5.05 g).

Step B



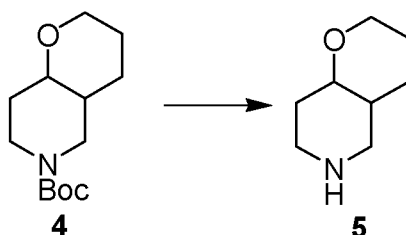
To a stirred solution of compound **2** (2.85 g, 10 mmol) in EtOH (20 mL) was added NaBH₄ (3.8 g, 100 mmol). The resulting mixture was stirred at r.t. for 4h, quenched with H₂O (20 mL) and concentrated in vacuum then extracted with EtOAc (20 mL × 3). The combined organic layer was dried over Na₂SO₄, concentrated in vacuum to give product **3** (2.03 g) MS (ESI) m/e 260 (M+H).

Step C



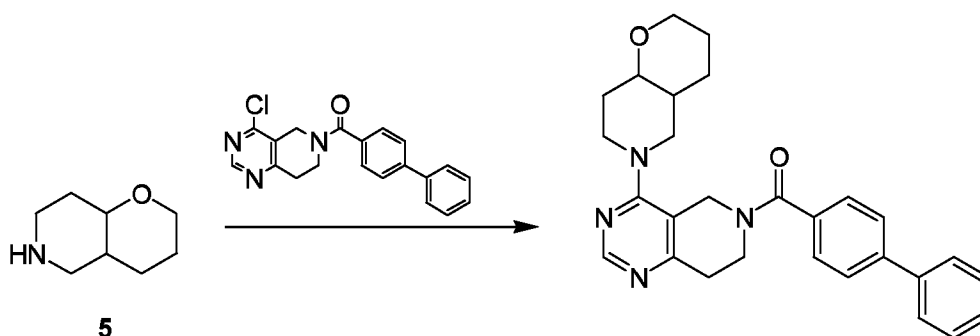
To a stirred solution of compound **3** (1.3 g, 5 mmol) and Et₃N (0.5 g, 5 mmol) in CH₂Cl₂ (10 mL) was added MsCl (570 mg, 5 mmol) and the mixture was stirred at 0 °C for 30 min. The mixture was concentrated in vacuum and 10 mL toluene and K₂CO₃ (1.38 g, 10 mmol) were added to the residue. The resulting mixture was stirred at 100 °C for 4 h. After cooled to r.t., H₂O (10 mL) was added and the mixture was extracted with EA (20 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated and purified by chromatography on silica (PE : EA = 2:1) to give product **4** (705 mg).

Step D



To a stirred solution of compound **4** (705 mg, 2.9 mmol) in CH₂Cl₂ (5 mL) was added 3 mL of CF₃COOH. The mixture was stirred at r.t. for 6 hours and concentrated in vacuum to give product **5** (400 mg). MS (ESI) m/e 142 (M+H).

Step E



A mixture of compound **5** (141 mg, 1.0 mmol), Intermediate I (175 mg, 0.5 mmol) and K_2CO_3 (414 mg, 3.0 mmol) in anhydrous DMSO (6 mL) was stirred at 120 °C for 5 hrs. After cooling to r.t., the reaction mixture was filtered. The filtrate was purified by Prep-HPLC to yield **trans isomer A** (82 mg, 36%) and **cis isomer B** (125 mg, 55%), respectively.

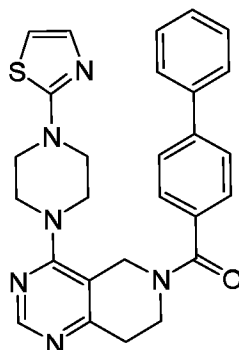
5

trans: MS (ESI) m/e 455 (M+H). 1H NMR ($CDCl_3$) δ 8.50 (s, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 7.2 Hz, 2H), 7.33-7.44 (m, 5H), 4.70 (s, 2H), 4.49 (d, J = 7.6 Hz, 1H), 4.28 (d, J = 8.0 Hz, 1H), 3.96 (d, J = 10.0 Hz, 1H), 3.81 (s, 2H), 3.45 (t, J = 10.8 Hz, 1H), 3.12-3.26 (m, 4H), 2.84 (t, J = 12.0 Hz, 1H), 2.01-2.05 (m, 1H), 1.46-1.77 (m, 5H).

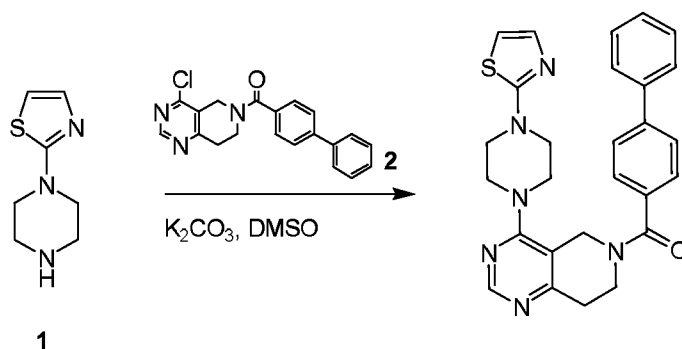
10

cis: MS (ESI) m/e 455 (M+H). 1H NMR ($CDCl_3$) δ 8.50 (s, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 7.6 Hz, 2H), 7.32-7.43 (m, 5H), 4.69 (s, 2H), 3.99-4.13 (m, 3H), 3.67-3.79 (m, 4H), 3.47 (t, J = 10.8 Hz, 2H), 3.14 (s, 2H), 1.67-1.94 (m, 6H), 1.16-1.18 (m, 1H).

15 **Example 12: Biphenyl-4-yl{4-[4-(1,3-thiazol-2-yl)piperazin-1-yl]-7,8-dihydro- pyrido [4,3-d]pyrimidin-6(5H)-yl}methanone**



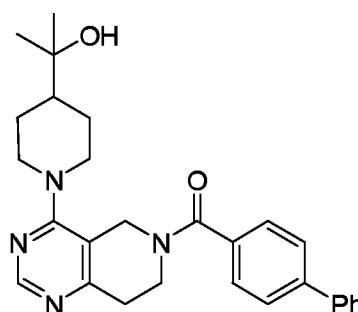
Step A:



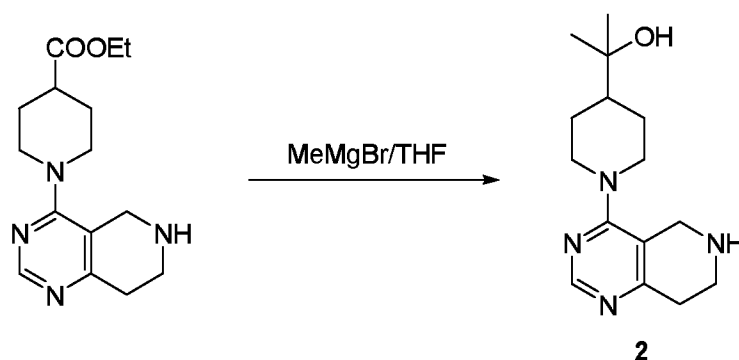
20 A mixture of compound **1** (96.7 mg, 0.572 mmol), chloropyrimidine intermediate **2** (100 mg, 0.286 mmol), K_2CO_3 (158 mg, 1.14 mmol) in DMSO (3 mL) was heated to 90°C and stirred overnight. After cooling to

r.t., the mixture was filtered, water was added, and extracted with EtOAc (5 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuum. The residue was purified by preparative HPLC to afford the desired compound (30 mg). MS (ESI) m/e 483 (M+H). ¹H NMR (CD₃OD) δ 8.65 (s, 1H), 7.73 (d, J= 8.0 Hz, 2H), 7.65-7.50 (m, 4H), 7.42 (d, J= 6.4 Hz, 2H), 7.37-7.20 (m, 2H), 6.92 (s, 1H), 4.14-3.50 (m, 12H), 3.07 (s, 2H).

Example 13: Biphenyl-4-yl{4-[4-(2-hydroxypropan-2-yl) piperidin-1-yl]-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl}methanone

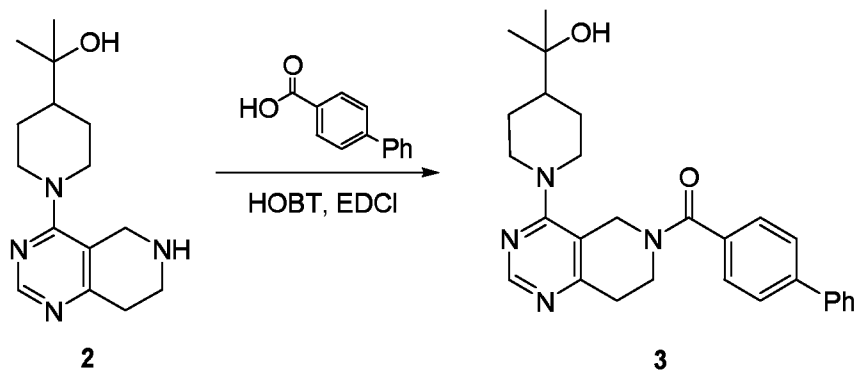


Step A:



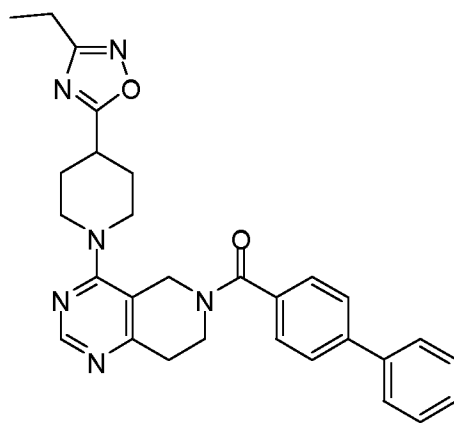
To a solution of Intermediate II (580 mg, 2 mmol) in 20 mL of anhydrous THF at -78 °C was added a solution of CH₃MgBr (1.3 mL, 3.0 M in ether, 4 mmol) in ether dropwise under N₂. After the addition, the mixture was stirred at -78 °C for additional 1 h and then slowly warmed to 0°C. TLC showed the starting material was consumed and the mixture was quenched with saturated NH₄Cl solution carefully. The aqueous layer was extracted with DCM twice. The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated to give crude 2 as a brown oil (550 mg), which was used in next step without further purification. MS (m/z): 277 (M+H)⁺

Step B:

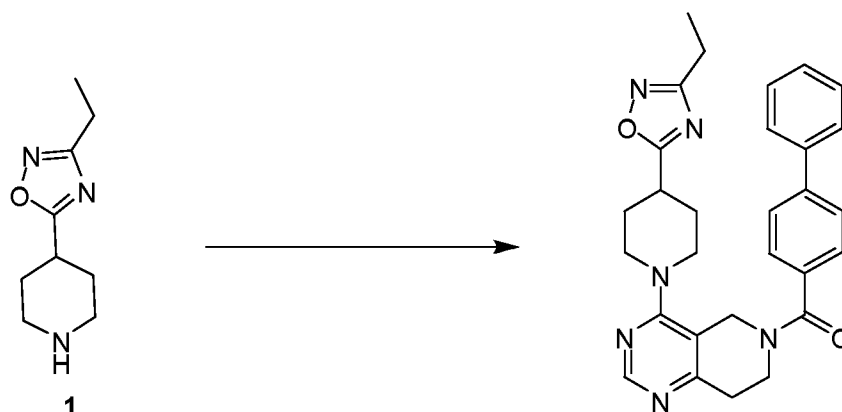


To a stirred solution of compound **2** (550 mg, 2 mmol) and acid biphenylcarboxylic acid (2.4 mmol) in DCM (10 mL) was added HOBT (331 mg, 2.4 mmol) and EDCI (5 mmol) at room temperature and the reaction mixture was allowed to stir overnight. The mixture was diluted with 20 mL of DCM and the combined organic layers were washed with water and brine, dried over Na₂SO₄, concentrated. The crude residue was purified on silica gel column eluting with DCM/MeOH (100/1~30/1) to give 410 mg of the desired compound. **MS (m/z):** 457 (**M+H**)⁺ **¹H NMR (CD₃OD)** δ8.561(s, 1H), 7.73 (d, 2H, *J*=7.2 Hz), 7.69 (d, 2H, *J*=6.8 Hz), 7.59 (d, 2H, *J*=7.6 Hz), 7.41-7.49 (m, 3H), 4.42 (br, 2H), 3.93-4.13 (m, 3H), 2.69-3.19 (m, 5H), 1.90-2.03 (m, 3H), 1.49-1.71 (m, 2H), 0.94-1.19 (m, 8H).

Example 14: Biphenyl-4-yl{4-[4-(3-ethyl-1,2,4-oxadiazol-5-yl) piperidin-1-yl]-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl}methanone



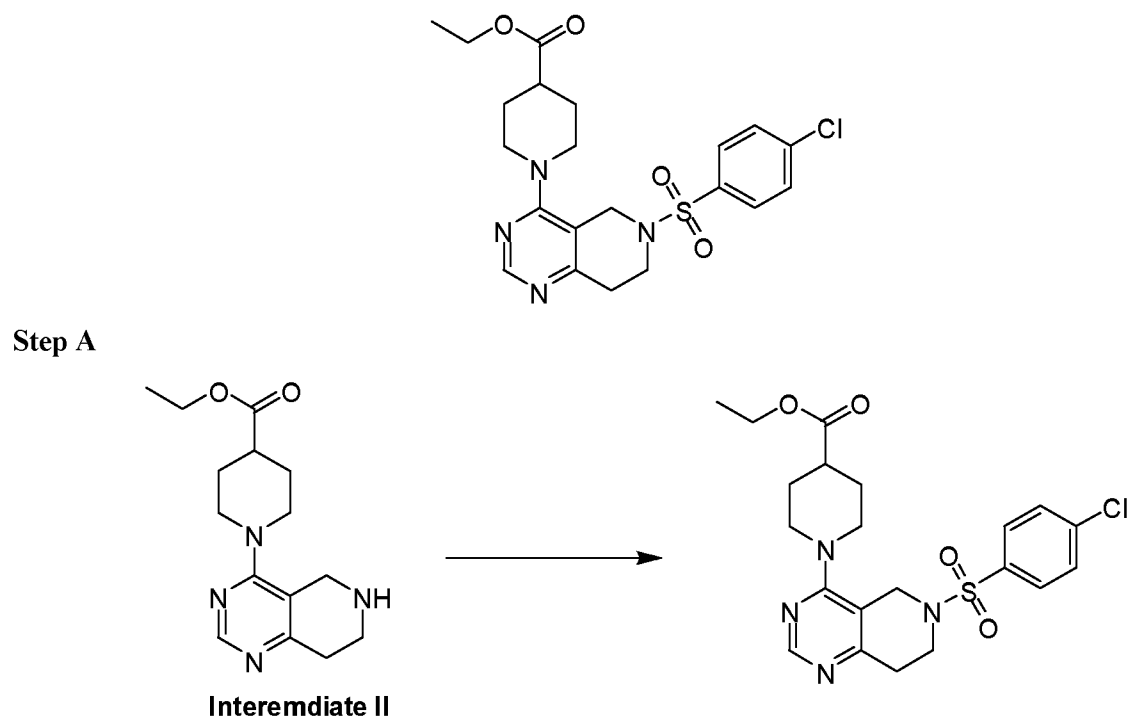
Step A



To a solution of intermediate I (50.0 mg, 0.14 mmol) in anhydrous dioxane (3 mL) was added compound **1** (50 mg, 0.28 mmol), K_2CO_3 (58.00 mg, 0.42 mmol) and $MgSO_4$ (14 mg, 0.14 mmol). The resulting mixture was heated to 100°C for 6 hrs. The reaction mixture was cooled to r.t., filtered and the filtrate was concentrated in vacuum. The residue was purified by preparative HPLC to yield title compound (9 mg).

MS (m/z) : 495 ($M+H^+$) **1H NMR** (CD_3OD) δ 8.51 (s, 1H), 7.64-7.66 (d, $J=7.2$ Hz, 2H), 7.46-7.53 (m, 4H), 7.37 (t, $J=7.2$ Hz, 2H), 7.27-7.29 (m, 1H), 5.41 (s, 1H), 4.20-4.37 (m, 2H), 3.81-3.99 (m, 2H), 3.48-3.58 (m, 2H), 2.90-3.00 (m, 2H), 2.59-2.65 (m, 4H), 1.91-2.20 (m, 4H), 1.12-1.21 (m, 3H).

Example 15: Ethyl 1-(6-(4-chlorophenylsulfonyl)-5,6,7,8-tetrahydropyrido- [4,3-d]pyrimidin-4-yl)piperidine-4-carboxylate



To a solution of Intermediate II (50 mg, 0.172 mmol) and Et₃N (52 mg, 0.516 mmol) in DCM (3 mL) was added 4-chlorophenylsulfonyl chloride (54 mg, 0.258 mmol). The resulting mixture was stirred at room temperature for 3h. The mixture was concentrated at r.t. in vacuum and the residue was purified by preparative HPLC to afford the desired compound (20 mg). **MS (m/z)** : 465 (M+H⁺) **¹H NMR (CD₃OD) δ**

8.47(s, 1H), 7.82 (d, J=7.38 Hz, 2H), 7.61 (d, J=7.15 Hz, 2H), 4.27(s, 2H), 4.23~ 4.10(m, 4H), 3.64~ 3.53 (m, 4H), 3.41(t, J=12.4 Hz, 2H), 2.93 (s, 2H), 2.82~ 2.72 (m, 1H), 2.16~ 2.02 (m, 3H), 1.84~ 1.71 (m, 2H).

Assay

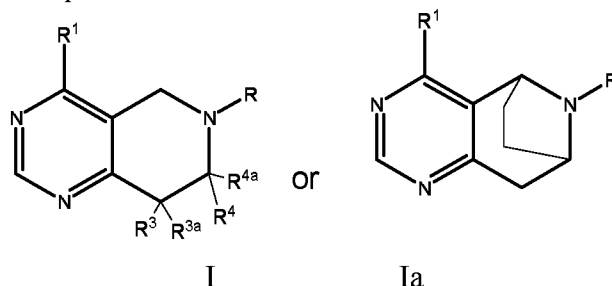
Determination of compound activity on the TASK-3 channel by electrophysiology. The TASK-3 antagonist assay was designed to determine the inhibition of compounds on the human TASK-3 current. To produce the TASK-3 cell line, the human TASK-3/pENTR221 clone was ordered from Invitrogen (Cat #IOH45737, accession #NM_016601) and was subcloned into the pcDNA5/FRT/TO vector (Invitrogen #V6520-20). The clone was transfected with Lipofectamine 2000 reagent into TRex-Flp-In-CHO cells. Cells were induced with 10ng/ml tetracycline overnight before recording and cultured in F-12 (Invitrogen #31765), 10% Tet approved FBS (BD#631101 Lot#041-05-016), 100 U/ml Pen-Strep (Invitrogen #15140-122), 500 ug/ml Hygromycin B (Invitrogen #10687-010), and 15 ug/ml Blasticidin. The TASK-3 Antagonist Assay was developed using the IonWorks®Quattro™ system from Molecular Devices (Sunnyvale, CA). In this electrophysiology platform cells are sealed on a Population Patch Plate™ (PPC) technology. Electrical access is obtained using the Nystatin (Sigma, #N6261). Currents are recorded using a 200ms depolarization to +50 mV followed by a 200 ms ramp from -110 - +70 mV for both the pre- and post-compound recordings. The compounds of formula I have an IC₅₀ activity of 100 μM or less for the TASK receptor. Many of the compounds of formula I have an IC₅₀ of less than 200 nM. For example, the compounds below have IC₅₀ < 3000nM in the "TASK-3 antagonist assay". In particular, the compounds of Examples 2, 5, 7, 8, 10, 12, and 14 exhibited the following IC₅₀ (nM) values:

Example	IUPAC Name	IC ₅₀ (nM)
2	tert-Butyl 2-[6-(biphenyl-4-ylcarbonyl)-5,6,7,8-tetrahydropyrido [4,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate	2408 ± 191
5	Biphenyl-4-yl[4-(4-methoxypiperidin-1-yl)-7,8-	135 ± 37

	dihydropyrido [4,3-d]pyrimidin-6(5H)-yl]methanone	
7	Cyclopropyl(1-{6-[(4'-fluorobiphenyl-4-yl)carbonyl]-5,6,7,8-tetra-hydropyrido[4,3-d]pyrimidin-4-yl}piperidin-4-yl)methanone	67 ± 6
8	1-{1-[6-(Biphenyl-4-ylcarbonyl)-5,6,7,8-tetrahydropyrido[4,3-d]-pyrimidin-4-yl]piperidin-4-yl}propan-1-one	35 ± 10
10	Ethyl 1-[6-(biphenyl-4-ylcarbonyl)-8,8-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl]piperidine-4-carboxylate	567 ± 34
12	Biphenyl-4-yl{4-[4-(1,3-thiazol-2-yl)piperazin-1-yl]-7,8-dihydro-pyrido [4,3-d]pyrimidin-6(5H)-yl}methanone	71 ± 4
14	Biphenyl-4-yl{4-[4-(3-ethyl-1,2,4-oxadiazol-5-yl) piperidin-1-yl]-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl}methanone	46 ± 5

CLAIMS

1. A compound of structural formula I and Ia:



or pharmaceutically acceptable salts and individual enantiomers and diastereomers thereof wherein:

R^1 represents C_{1-6} alkyl, $C(O)OC_{1-6}$ alkyl, $(CH_2)_n C_{6-10}$ aryl, $(CH_2)_n C_{5-10}$ heterocycle, $(CH_2)_n C_{3-10}$ cycloalkyl, $N(CH_3)(CH_2)_n C(O)NHC_{6-10}$ aryl, and $N(CH_3)(CH_2)_n C_{5-10}$ heterocycle; said cycloalkyl, aryl and heterocycle optionally substituted with 1 to 3 groups of R^a ;

R represents H, C_{1-6} alkyl, $C(O)(CH_2)_n C_{6-10}$ aryl, $C(O)O(CH_2)_n C_{6-10}$ aryl, $C(O)(CH_2)_n C_{5-10}$ heterocycle, $(CH_2)_n C_{6-10}$ aryl, $SO_2 C_{6-10}$ aryl, $SO_2 C_{5-10}$ heterocycle, $C(O)NHC_{6-10}$ aryl, $C(O)C_{2-4}$ alkynyl, CNC_{6-10} aryl, $(CH_2)_n C_{5-10}$ heterocycle, or $C(O)CH(CH_3)N(CH_3)CH_2 C_{6-10}$ aryl, said alkynyl, aryl, alkyl, and heterocycle optionally substituted with 1 to 3 groups of R^a ;

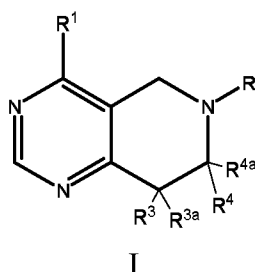
R^a represents $(CH_2)_n OH$, $(CH_2)_n CN$, $C(OH)CN$, C_{1-6} alkyl, $CH(OH)(CH_2)_n C_{6-10}$ aryl, $CH(OH)(CH_2)_n C_{3-10}$ cycloalkyl, OC_{1-6} alkyl, $O(CH_2)_n C_{2-6}$ alkenyl, $C(O)OC_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl, $(CH_2)_n C(O)(CH_2)_n C_{3-10}$ cycloalkyl, $(CH_2)_n C(O)(CH_2)_n C_{5-10}$ aryl, $(CH_2)_n C(O)(CH_2)_n C_{5-10}$ heterocycle, $(CH_2)_n C(O)O(CH_2)_n C_{3-10}$ cycloalkyl, $(CH_2)_n C(O)O(CH_2)_n C_{5-10}$ aryl, $(CH_2)_n C(O)O(CH_2)_n C_{5-10}$ heterocycle, halo, $(CH_2)_n C_{6-10}$ aryl, $O(CH_2)_n C_{6-10}$ aryl, $(CH_2)_n C_{5-10}$ heterocycle, $-N(CH_3)CH_2 C(O)NHC_{6-10}$ aryl, $-NH(CH_2)_n C_{6-10}$ aryl, $-N(CH_3)CH_2 C_{6-10}$ aryl, $-NH(C_{1-6}$ alkyl), $(CH_2)_n SO_2 C_{1-6}$ alkyl, $(CH_2)_n SO_2 C_{6-10}$ aryl, $-O-$, C_{3-10} cycloalkyl, $-SC_{1-6}$ alkyl, CF_3 , OCF_3 , CHF_2 , CH_2F , $CF_3 OC_{1-6}$ alkyl, NH_2 , $C(O)N(C_{1-6}$ alkyl) $(CH_2)_n C_{5-10}$ heterocycle, $C(O)N(C_{1-6}$ alkyl) $_2$, $(CH_2)_n OC(O)C_{1-6}$ alkyl, $(CH_2)_n OC(O)C_{6-10}$ aryl, $(CH_2)_n OC(O)C_{5-10}$ heterocycle, $(CH_2)_n OC(O)C_{3-10}$ cycloalkyl, said alkyl, cycloalkyl, aryl and heterocycle optionally substituted with 1 to 3 groups of R^{aa} ;

R^{aa} represents $C(O)OC_{1-6}$ alkyl, $O(CH_2)_n$ phenyl, OH , OCH_3 , SCH_3 , OCH_2CH_3 , OCH_2CF_3 , CF_3 , OCF_3 , CN , C_{1-6} alkyl, halo, $NHC(O)OC_{1-6}$ alkyl, $=NOC_{1-6}$ alkyl, $O(CH_2)_n C_{6-10}$ aryl;

R³, R^{3a}, R⁴ R^{4a} independently represent hydrogen or C₁₋₆ alkyl; and

n represents 0 to 4.

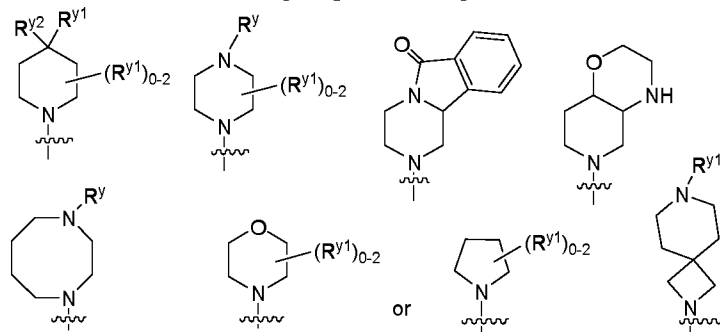
2. The compound according to claim 1 represented by structural formula I:



or pharmaceutically acceptable salts and individual enantiomers and diastereomers thereof.

3. The compound according to claim 1 or pharmaceutically acceptable salts and individual enantiomers and diastereomers thereof wherein:

R^1 is selected from the group consisting of:

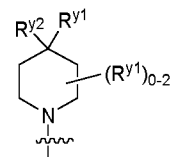


wherein:

RY represents H, C₁₋₆alkyl, C(O)C₁₋₆alkyl, C(O)C₃₋₁₀cycloalkyl, C(O)(CH₂)_nC₆₋₁₀aryl, C(O)(CH₂)_nC₅₋₁₀heterocycle, C(O)OC₁₋₆alkyl, (CH₂)_nC₆₋₁₀aryl, (CH₂)_nC₅₋₁₀heterocycle, said alkyl, aryl, cycloalkyl, and heterocycle optionally substituted with 1 to 3 groups of Ra;

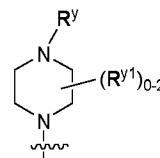
Ry¹ is the same as Ra;

or when two R^{y1} are present they may combined to form a C₃₋₁₀ cyclic group optionally having 1-2 heteroatoms selected from N, O, and S, said cyclic group optionally substituted with 1 to 3 groups of R^a; and R^{y2} is H, halo, or OH.



4. The compound according to claim 3 wherein R¹ is , R^{Y2} is hydrogen, R^{Y1} is independently selected from the group consisting of hydrogen, C₁-6alkyl, C(O)OC₁-6alkyl, C(O)C₁-6alkyl, C₃-6cycloalkyl, C(O)C₃-6cycloalkyl, C₅-10heterocycle, said alkyl, cycloalkyl, heterocyclyl optionally substituted with 1 to 3 groups of R^a, and R³, R^{3a}, R⁴ and R^{4a} are all hydrogen.

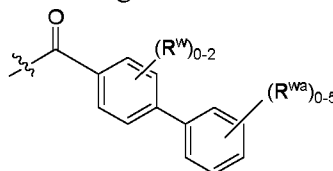
5



5. The compound according to claim 1 wherein R¹ is , R^Y is C(O)C₁-6alkyl, C(O)(CH₂)_nC₆-10aryl, C(O)(CH₂)_nC₅-10heterocycle, (CH₂)_nC₆-10aryl, or (CH₂)_nC₅-10heterocycle, said alkyl, aryl, cycloalkyl, and heterocycle optionally substituted with 1 to 3 groups of R^a, R^{Y1} is independently selected from the group consisting of hydrogen, C₁-6alkyl, CF₃, CH₂F, said alkyl optionally substitute with 1 to 3 groups of R^a, and R³, R^{3a}, R⁴ and R^{4a} are all hydrogen.

10

6. The compound according to claim 1 wherein R is represented by formula II:



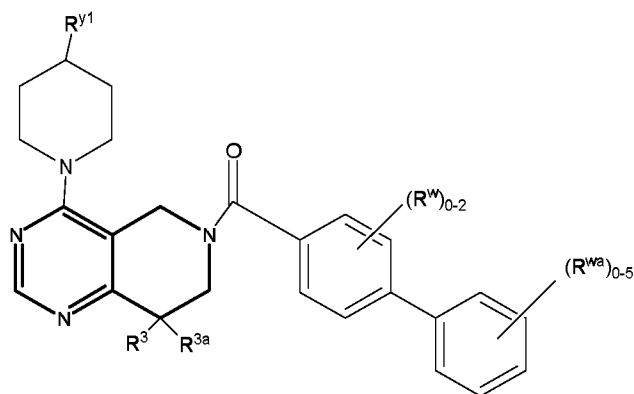
II

15

or pharmaceutically acceptable salts and individual enantiomers and diastereomers thereof wherein: and R^W and R^{Wa} are independently selected from the group consisting of H, OC₁-6alkyl, O(CH₂)_nC₆-10aryl, SC₁-6alkyl, CF₃, OCF₃, CN, C₁-6 alkyl, and halo.

20

7. The compound according to claim 1 represented by structural formula III:



III

or pharmaceutically acceptable salts and individual enantiomers and diastereomers thereof wherein:

R^3 , R^{3a} , R^{Y1} is as previously described and R^W and R^{Wa} are independently selected from the group consisting of H, $OC_{1-6}alkyl$, $O(CH_2)_n C_{6-10}aryl$, $SC_{1-6}alkyl$, CF_3 , OCF_3 , CN, $C_{1-6}alkyl$, and halo.

8. The compound according to claim 7 wherein R^{Y1} is $C_{1-6}alkyl$, $C(O)OC_{1-6}alkyl$, $C(O)C_{1-6}alkyl$, $C_{3-6}cycloalkyl$, $C(O)C_{3-6}cycloalkyl$, C_{5-10} heterocycle, said alkyl, cycloalkyl and heterocycle optionally substituted with 1 to 3 groups of R^a , and R^W and R^{Wa} are both hydrogen.

9. A compound according to claim 1 represented by Tables 1 through 4 or pharmaceutically acceptable salts and individual enantiomers and diastereomers thereof.

10. A compound which is:
 tert-Butyl 2-[6-(biphenyl-4-ylcarbonyl)-5,6,7,8-tetrahydropyrido [4,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate;
 Biphenyl-4-yl[4-(4-methoxypiperidin-1-yl)-7,8-dihydropyrido [4,3-d]pyrimidin-6(5H)-yl]methanone;
 Cyclopropyl(1-{6-[(4'-fluorobiphenyl-4-yl)carbonyl]-5,6,7,8-tetra- hydropyrido[4,3-d]pyrimidin-4-yl}piperidin-4-yl)methanone;
 1-{1-[6-(Biphenyl-4-ylcarbonyl)-5,6,7,8- tetrahydropyrido[4,3-d]- pyrimidin-4-yl]piperidin-4-yl}propan-1-one;
 Ethyl 1-[6-(biphenyl-4-ylcarbonyl)-8,8-dimethyl-5,6,7,8- tetrahydropyrido[4,3-d]pyrimidin-4-yl]piperidine-4-carboxylate;
 Biphenyl-4-yl{4-[4-(1,3-thiazol-2-yl)piperazin-1-yl]-7,8-dihydro- pyrido [4,3-d]pyrimidin-6(5H)-yl}methanone;
 Biphenyl-4-yl{4-[4-(3-ethyl-1,2,4-oxadiazol-5-yl) piperidin-1-yl]-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl}methanone,

or pharmaceutically acceptable salts and individual enantiomers and diastereomers thereof.

11. A pharmaceutical composition comprising an inert carrier and an effective
5 amount of a compound according to Claim 1.

12. The composition according to claim 11 further comprising one or more
therapeutically active compounds selected from the group consisting of opiate agonists or
antagonists, calcium channel antagonists, 5HT, 5-HT_{1A} complete or partial receptor agonists or
10 antagonists, sodium channel antagonists, N-methyl-D-aspartate (NMDA) receptor agonists or
antagonists, COX-2 selective inhibitors, neurokinin receptor 1 (NK1) antagonists, non-steroidal
anti-inflammatory drugs (NSAID), selective serotonin reuptake inhibitors (SSRI) and/or selective
serotonin and norepinephrine reuptake inhibitors (SSNRI), tricyclic antidepressant drugs,
norepinephrine modulators, lithium, valproate, norepinephrine reuptake inhibitors, monoamine
15 oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), alpha-
adrenoreceptor antagonists, atypical anti-depressants, benzodiazepines, corticotropin releasing
factor (CRF) antagonists, neurontin (gabapentin) and pregabalin.

13. A method for treating and preventing disorders which are caused by
20 activation or by activated TASK-1 and/or TASK-3 comprising administering to a patient a
therapeutically effective amount of a compound of formula I in claim 1 or pharmaceutically
acceptable salts, individual enantiomers or diastereomers thereof.

14. A method for treating and preventing disorders which have TASK-1 and/or
25 TASK-3-related damage as a secondary cause comprising administering to a patient a
therapeutically effective amount of a compound of formula I in claim 1 or pharmaceutically
acceptable salts, individual enantiomers or diastereomers thereof.

15. The method according to claim 13 wherein the disorder is selected from
30 the group consisting of epilepsy, respiratory disorders, neuropsychiatric disorders, mood disorders,
depressive disorders, atypical depression, bipolar disorders, panic disorders and sleep disorders.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2010/070751

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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)

IPC: C07D471/04, C07D471/18, A61K31/-, A61P11/-, A61P25/-

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 practicable, search terms used)

CNPAT, CNKI, WPI, EPODOC, REG, CAPLUS, pyrimidin?, pyrido, piperidin+, piperazin+, TASK, potassium, structure search according to the formula I**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstract No:149:44292 & Gozalbes, Rafael et al., Development and Experimental Validation of a Docking Strategy for the Generation of Kinase-Targeted Libraries, Journal of Medicinal Chemistry (2008), Vol.51, No.11, pages 3124-3132 See the compounds of CAS RNs 1032184-45-4, 1032182-40-3, 1032183-23-5 and 1032184-62-5	1-3, 5
A		4, 6-15
A	WO2006040966A1 (ASTELLAS PHARMA INC) 20 Apr. 2006 (20.04.2006), see 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 application or patent 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
06 Nov. 2010(06.11.2010)Date of mailing of the international search report
09 Dec. 2010 (09.12.2010)Name and mailing address of the ISA/CN
The State Intellectual Property Office, the P.R.China
6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China
100088
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2010/070751

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO2007146122A2 (NEUROGEN CORP) 21 Dec. 2007 (21.12.2007), see the whole document	1-15
A	CN101636154A (SANOFI-AVENTIS DEUT GMBH) 27 Jan. 2010 (27.01.2010), see the whole document	1-15

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2010/070751

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.: 13-15

because they relate to subject matter not required to be searched by this Authority, namely:

Although the subject matter of claims 13-15 is directed to a method of treatment of the human/animal body (see PCT Article 17 (2)(a)(i) and Rule 39.1(iv)), the search has been carried out and based on the alleged effect of the compounds.

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 extra 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 fee.
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.: 1-3 (part), 4-5, 6 (part), 7-8, 9-15 (part).

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.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2010/070751

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO2006040966A1	20.04.2006	CA2583259A	20.04.2006
		EP1806347A	11.07.2007
		US2007249587A	25.10.2007
WO2007146122A2	21.12.2007	US2008051387A	28.02.2008
		EP2029588A	04.03.2009
CN101636154A	27.01.2010	DE102006019589A	31.10.2007
		CA2650391A	08.11.2007
		AU2007245891A	08.11.2007
		WO2007124849A	08.11.2007
		DOP20070083A	15.11.2007
		UY30313A	30.11.2007
		AR060822A	16.07.2008
		MX2008012920A	15.10.2008
		NO20084513A	24.11.2008
		ECSP088847A	27.11.2008
		KR20080111509A	23.12.2008
		CR10342A	09.01.2009
		EP2012758A	14.01.2009
		US2009149496A	11.06.2009
		JP2009534434T	24.09.2009
		ZA200808171A	28.10.2009
		RU2008146755A	10.06.2010

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2010/070751

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

Although the subject matter of claims 13-15 is directed to a method of treatment of the human/animal body, the examination has been carried out and based on the alleged effect of the compounds.

This international application contains the following 12 groups of inventions:

1) the invention of compounds of formula I in which R^1 represents C1-6 alkyl C(O)OC1-6 alkyl, a pharmaceutical composition and alleged effect thereof;

2) the invention of compounds of formula I in which R^1 represents $(CH_2)_n$ C6-10 aryl, a pharmaceutical composition and alleged effect thereof;;

3) the invention of compounds of formula I in which R^1 represents $(CH_2)_n$ C3-10 cycloalkyl, a pharmaceutical composition and alleged effect thereof;;

4) the invention of compounds of formula I in which R^1 represents $N(CH_3)(CH_2)_n$ C(O)NHC6-10 aryl, a pharmaceutical composition and alleged effect thereof;

5) the invention of compounds of formula I in which R^1 represents $N(CH_3)(CH_2)_n$ C5-10 heterocycle or $(CH_2)_n$ C5-10 heterocycle, a pharmaceutical composition and alleged effect thereof, said heterocycle is the first or second heterocycle in claim 3;

6) the invention of compounds of formula I in which R^1 represents $N(CH_3)(CH_2)_n$ C5-10 heterocycle or $(CH_2)_n$ C5-10 heterocycle, a pharmaceutical composition and alleged effect thereof, said heterocycle is the third heterocycle in claim 3;

7) the invention of compounds of formula I in which R^1 represents $N(CH_3)(CH_2)_n$ C5-10 heterocycle or $(CH_2)_n$ C5-10 heterocycle, a pharmaceutical composition and alleged effect thereof, said heterocycle is the fourth heterocycle in claim 3;

8) the invention of compounds of formula I in which R^1 represents $N(CH_3)(CH_2)_n$ C5-10 heterocycle or $(CH_2)_n$ C5-10 heterocycle, a pharmaceutical composition and alleged effect thereof, said heterocycle is the fifth heterocycle in claim 3;

9) the invention of compounds of formula I in which R^1 represents $N(CH_3)(CH_2)_n$ C5-10 heterocycle or $(CH_2)_n$ C5-10 heterocycle, a pharmaceutical composition and alleged effect thereof, said heterocycle is the sixth heterocycle in claim 3;

10) the invention of compounds of formula I in which R^1 represents $N(CH_3)(CH_2)_n$ C5-10 heterocycle or $(CH_2)_n$ C5-10 heterocycle, a pharmaceutical composition and alleged effect thereof, said heterocycle is the seventh heterocycle in claim 3;

11) the invention of compounds of formula I in which R^1 represents $N(CH_3)(CH_2)_n$ C5-10 heterocycle or $(CH_2)_n$ C5-10 heterocycle, a pharmaceutical composition and alleged effect thereof, said heterocycle is the eighth heterocycle in claim 3;

12) the invention of compounds of formula Ia, a pharmaceutical composition and alleged effect thereof.

In above items, the heterocycle in claim 3 is numbered consecutively from left to right.

When the Markush grouping is for alternatives of chemical compounds, they are regarded as being of a similar nature where the following criteria are fulfilled:

(A) all alternatives have a common property or activity, and

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(B)(1) a common structure is present, that is, a significant structural element is shared by all of the alternatives, or

(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

Formula I and formula Ia do not have a common chemical structure and do not belong to a recognized class of chemical compounds. Although group 1)- group 12) possess a common chemical structure, i.e. tetrahydropyrido[4,3-d]pyrimidine, this common chemical structure does not occupy a large portion of their structures that we can see from definitions of each R group and structures of example compounds. Moreover, in view of existing prior art, the commonly shared structure does not constitute a structurally distinctive portion, and the common structure is not essential to the common property or activity, because the prior art has disclosed various compounds having different property or activity which possess the common structure, i.e. said tetrahydropyrido[4,3-d]pyrimidine moiety. Thus, the compounds related to above said twelve groups of inventions do not have a common chemical structure which occupies a large portion of their structures, or in case the compounds do not belong to a recognized class of chemical compounds. Therefore, the compounds related to above said twelve groups of inventions do not meet above criteria, and these inventions lack unity within the meaning of PCT Rule 13.

Consequently, this international search report is restricted to the major invention first mentioned in the claims because no required additional search fees were timely paid by the applicant; it is covered by claims Nos.:1-3 (part), 4-5, 6 (part), 7-8, 9-15 (part) related the above-said group 5) invention.

A. CLASSIFICATION OF SUBJECT MATTER

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

C07D471/04 (2006.01)i

C07D471/18 (2006.01)i

A61K31/519 (2006.01)i

A61K31/529 (2006.01)i

A61P11/00 (2006.01)i

A61P25/08 (2006.01)i

A61P25/20 (2006.01)i

A61P25/24 (2006.01)i