

(19) (KR)
(12) (A)

(51) 。 Int. Cl.⁷
C07D 403/14

(11)
(43)

2003-0061463
2003 07 18

(21) 10-2003-7008364

(22) 2003 06 20

2003 06 20

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(87)

WO 2002/50066

(86) 2001 12 20

(87)

2002 06 27

(30) 60/257,887

2000 12 21

(US)

60/286,949

2001 04 27

(US)

(71)

02139-4242

130

(72)

68

8

144

3

-

472

6141

6

(74)

:

(54)

가 2000 12 21
60/286,949

가 60/257,887 2001 4 27

가 .

(Aurora)-2
-2

가

(: (TNF-) , [: - , H₂O₂) , [: -1(IL-1) (GM-CSF) (FGF)]가

가 -2 / -2

-2 [: Bischoff et al., EMBO J., 1998, 17, 3052-3065; Schumacher et al., J. Cell Biol., 1998, 143, 1635-1646; Kimura et al., J. Biol. Chem., 1997, 272, 13766-13771].

-3(GSK-3) / [: Coghlan et al., Chemistry amp; Biology, 7, 793-803 (2000); Kim and Kimmel, Curr. Opinion Genetics Dev., 10, 508-514 (2000)]. GSK-3 CNS (:) (cardiomyocyte hypertrophy) [: WO 99/65897 , WO 00/38675 Haq et al., J. Cell Biol. (2000) 151, 117]. GS

K-3 . GSK-3 Tau, e1F2B, ATP , -1, c-Jun, c-Myc, c-Myb, CREB CEPB GSK-3

II GSK-3 , GSK-3 . GSK-3 가 [: Klein et al., PNAS, 93, 8455-9 (1996); Cross et al., Biochem. J., 303, 21-26 (1994); Cohen, Biochem. Soc. Trans., 21, 555-567 (1993); Massillon et al., Biochem J. 299, 123-128 (1994)].

가 , GSK-3 [: WO 00/38675] . II , GSK-3

GSK-3 Tau (, Tau) . GSK-3 Tau [: Lovestone et al., Current Biology 4, 1077-86 (1994); Brownlees et al., Neuroreport 8, 3251-55 (1997)]. , GSK-3

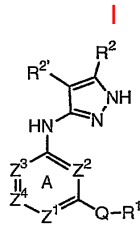
GSK-3 GSK-3 가 [: Zhong et al., Nature, 395, 698-702 (1998); Takashima et al., PNAS, 90, 7789-93 (1993); Pei et al., J. Neuropathol. Exp, 56, 70-78 (1997)].

GSK-3 가 ,
 GSK-3 가 [:
 38675 (SmithKline Beecham)].

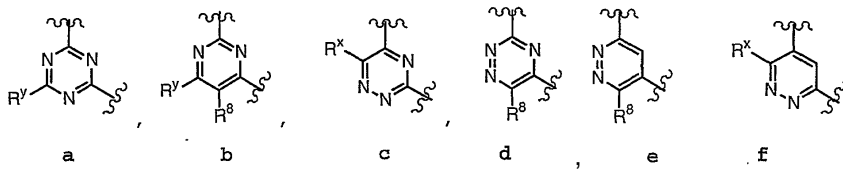
GSK-3 가
 WO 99/65897 (Chiron) WO 00/

GSK-3 가 , 가
 가 p38 , 가
 p38- / TGF- [: WO 00/12497 (Scios
 p38 , p38 , GSK
 -3 , p38 /
 가 가 . -2 GSK-3

(prodrug) . | , -2



| ,
 Z 1 Z 4 ,



R x T-R 3 L-Z-R 3 ,
 R y Z-R 3 , C 1-6 , C 6-10 , 5 10 5 10
 R y R 8 , 0 3 5 7

Q -N(R 4)-, -O-, -S- -CH(R 6)- ,
 R 1 T-(D) ,
 D , 5 7 8
 10 가 , D 가 , T-R 5 V-Z-R 5 1 4

, D 가 -R 4 ,

T 가 C 1-4 , Q가 -CH(R 6)- , C 1-4
-O-, -S-, -N(R 4)-, -CO-, -CONH-, -NHCO-, -SO 2 -, -SO 2 NH-, -NHCO 2 -, -CO 2 -, -OC(O)-, -OC(O)NH- -NHCO 2 -

Z C 1-4 ,

L -O-, -S-, -SO-, -SO 2 -, -N(R 6)SO 2 -, -SO 2 N(R 6)-, -N(R 6)-, -CO-, -CO 2 -, -N(R 6)CO-, -N(R 6)C(O)O-, -N(R 6)CON(R 6)-, -N(R 6)SO 2 N(R 6)-, -N(R 6)N(R 6)-, -C(O)N(R 6)-, -OC(O)N(R 6)-, -C(R 6) 2 O-, -C(R 6) 2 S-, -C(R 6) 2 SO-, -C(R 6) 2 SO 2 -, -C(R 6) 2 SO 2 N(R 6)-, -C(R 6) 2 N(R 6)-, -C(R 6) 2 N(R 6)C(O)-, -C(R 6) 2 N(R 6)C(O)O-, -C(R 6)=NN(R 6)-, -C(R 6)=N-O-, -C(R 6) 2 N(R 6)N(R 6)-, -C(R 6) 2 N(R 6)SO 2 N(R 6)- -C(R 6) 2 N(R 6)CON(R 6)- ,

R 2 R 2' -R -T-W-R 6 , R 2 R 2' ,
0 3 5 8
, R 2 R 2' 가 , -CN, -
NO 2, -R 7 -V-R 6 , R 2 R 2' 가

R 3 -R, - , -OR, -C(=O)R, -CO 2 R, -COCOR, -COCH 2 COR, -NO 2, -CN, -S(O)R, -S(O) 2 R, -SR, -N(R 4) 2, -CON(R 7) 2, -SO 2 N(R 7) 2, -OC(=O)R, -N(R 7)COR, -N(R 7)CO 2 (C 1-6), -N(R 4)N(R 4) 2, -C=NN(R 4) 2, -C=N-OR, -N(R 7)CON(R 7) 2, -N(R 7)SO 2 N(R 7) 2, -N(R 4)SO 2 R -OC(=O)N(R 7) 2

R 3' - , -OR, -C(=O)R, -CO 2 R, -COCOR, -COCH 2 COR, -NO 2, -CN, -S(O)R, -S(O) 2 R, -SR, -N(R 4) 2, -CON(R 7) 2, -SO 2 N(R 7) 2, -OC(=O)R, -N(R 7)COR, -N(R 7)CO 2 (C 1-6), -N(R 4)N(R 4) 2, -C=NN(R 4) 2, -C=N-OR, -N(R 7)CON(R 7) 2, -N(R 7)SO 2 N(R 7) 2, -N(R 4)SO 2 R, -OC(=O)N(R 7) 2, C 1-6, C 6-10, 5 10 5 10

10 R , C 1-6 , C 6-10 , 5 10 5

R 4 -R 7, -COR 7, -CO 2 (C 1-6), -CON(R 7) 2 -SO 2 R 7

R 5 -R, - , -OR, -C(=O)R, -CO 2 R, -COCOR, -NO 2, -CN, -S(O)R, -SO 2 R, -SR, -N(R 4) 2, -CON(R 4) 2, -SO 2 N(R 4) 2, -OC(=O)R, -N(R 4)COR, -N(R 4)CO 2 (C 1-6), -N(R 4)N(R 4) 2, -C=NN(R 4) 2, -C=N-OR, -N(R 4)CON(R 4) 2, -N(R 4)SO 2 N(R 4) 2, -N(R 4)SO 2 R -OC(=O)N(R 4) 2

V -O-, -S-, -SO-, -SO 2 -, -N(R 6)SO 2 -, -SO 2 N(R 6)-, -N(R 6)-, -CO-, -CO 2 -, -N(R 6)CO-, -N(R 6)C(O)O-, -N(R 6)CON(R 6)-, -N(R 6)SO 2 N(R 6)-, -N(R 6)N(R 6)-, -C(O)N(R 6)-, -OC(O)N(R 6)-, -C(R 6) 2 O-, -C(R 6) 2 S-, -C(R 6) 2 SO-, -C(R 6) 2 SO 2 -, -C(R 6) 2 SO 2 N(R 6)-, -C(R 6) 2 N(R 6)-, -C(R 6) 2 N(R 6)C(O)-, -C(R 6) 2 N(R 6)C(O)O-, -C(R 6)=NN(R 6)-, -C(R 6)=N-O-, -C(R 6) 2 N(R 6)N(R 6)-, -C(R 6) 2 N(R 6)SO 2 N(R 6)- -C(R 6) 2 N(R 6)CON(R 6)- ,

W -C(R 6) 2 O-, -C(R 6) 2 S-, -C(R 6) 2 SO-, -C(R 6) 2 SO 2 -, -C(R 6) 2 SO 2 N(R 6)-, -C(R 6) 2 N(R 6)-, -CO-, -CO 2 -, -C(R 6)OC(O)-, -C(R 6)OC(O)N(R 6)-, -C(R 6) 2 N(R 6)CO-, -C(R 6) 2 N(R 6)C(O)O-, -C(R 6)=NN(R 6)-, -C(R 6)=N-O-, -C(R 6) 2 N(R 6)N(R 6)-, -C(R 6) 2 N(R 6)SO 2 N(R 6)-, -C(R 6) 2 N(R 6)CON(R 6)- -CON(R 6)- ,

R 6 R 6 5 6 C 1-4 , 2

7 R 7 5 8 C 1-6 , 2 R

R⁸ -R, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CO
 N(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(C₁₋₆), -N(R⁴)
 N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R
 -OC(=O)N(R⁴)₂.

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 가
 C₁-C₁₂
 [:() , ()]
 1 12 2 12
 C₃-C₁₂
 F, Cl, Br I
 4
 0 3
), NH() NR + (N-
 N(3,4-) -2H-
 3 14
 가
 가
 5 14
 가
 1- , 2- , 1- 2- 가
 1- , 2- , 1- 2- 가
 4 가 N, O S
 5 14 , 5 10
 3-1H- -2- , (1-)-2- -
 , 4- , 3- , [1,3]- , 3- , [1,3]- , 2- , 3-
 , 4- , 3- , 2- , 3- , [1,3]- , 2- , 3-
 , 4- , 3- , 1- , 2- , 3- , 4- , 1- , 2- , 3- , 1- , 2-
 , 3- , 4- , 4- , N- , 1- ,
 가
 가
 5 14
 , 2- , 4- , 5- , 3- , 4- , 2- , 3- , N-
 , 2- , 4- , 5- , 1- , 2- , 3- , 2- , 3- , 4-

가 | , , -2

-2-

-2- 가 -2

-2 | -2

-2

GSK-3- GSK-3

GSK-3- GKS-3

/ , AIDS- (AML), (MS), ,
가 /

/ | Tau

SK-3 | GSK-3 , G

GSK-3

가 .

-2 GSK-3
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(:), (:),
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C₁₋₄) 4

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N⁺ (

4

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0.01 100mg/ kg/

가 가
- 가

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가

가

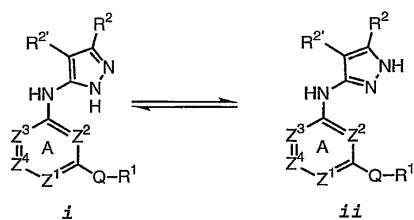
, TNF , IL-1 RA,

, MAO
, ACE

가

가

(i ii)

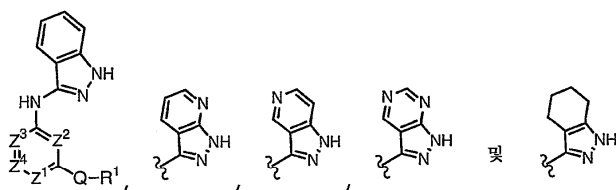


R^x, C₁₋₄ (:
 R^y, Z-R^{3'}, C₁₋₆, 5, 6, Z⁶, R^{3'}, -N(R⁴)₂, -OR,
 C₁₋₆, C₆₋₁₀, 5, 10, R^y, 5, 6, 10
 (: 2-, 4-, 3-), (:), C₁₋₆ (:
), (:), (:), (:)

R² R^{2'}

6

I



R² / R^{2'}

: - , -N(R⁴)₂ -, -C₁₋₃ -, -C₁₋₃
 H₂, -NH₂, SO₂(C₁₋₃), -NHC(O)(C₁₋₃), -C(O)NH₂, -CO(C₁₋₃),
 -NO₂, -O(C₁₋₃), -CO₂(C₁₋₃), -CN, -SO₂(C₁₋₃), -SO₂NH₂, -OC(O)N
 가]

R²

C₁₋₄

(

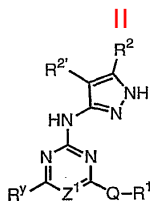
(N-

R²

CH₂OH, CH₂OCH₃, CH₂CH₂CH₂OH, CH₂CH₂CH₂OCH₃, CH₂CH₂CH₂OCH₂Ph, CH₂
 CH₂CH₂NH₂, CH₂CH₂CH₂NHCOOC(CH₃)₃, CONHCH(CH₃)₂, CONHCH₂CH=CH₂, CONH
 CH₂CH₂OCH₃, CONHCH₂Ph, CONH(), CON(Et)₂, CON(CH₃)CH₂Ph, CONH(n-C₃H
 7), CON(Et)CH₂CH₂CH₃, CONHCH₂CH(CH₃)₂, CON(n-C₃H₇)₂, CO(3-
 -1-), CONH(3-), CONH(4-), CONHCH₃, CO(-1-), CO(4- -1-), CONHCH₂
 CH₂OH, CONH₂ CO(-1-) R^{2'}

I Q -S-, -NH- -CH₂- I Q -S-
 -NH-

II



II

Z¹ CR⁸ ,

R^y Z-R^{3'}, C₁₋₆ , C₆₋₁₀ , 5 10 5 10

R^y R⁸ , 0 3 5 7

Q -N(R⁴)-, -O-, -S- -CH(R⁶)- ,

R¹ T-(D) ,

D , 5 7 8

10 가 , D 가 , T-R⁵ V-Z-R⁵ 1 4

, D 가 -R⁴ ,

T 가 C₁₋₄ , Q가 -CH(R⁶)- , C₁₋₄

-O-, -S-, -N(R⁴)-, -CO-, -CONH-, -NHCO-, -SO₂-, -SO₂NH-, -NHSO₂-, -CO₂-, -OC(O)-, -OC(O)NH- -NHCO₂- ,

Z C₁₋₄ ,

L -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)- -C(R⁶)₂N(R⁶)CON(R⁶)- ,

R² R^{2'} -R -T-W-R⁶ , R² R^{2'} ,

0 3 5 8

, R² R^{2'} 가 , -CN, -

NO₂, -R⁷ -V-R⁶ , R² R^{2'} 가

R⁴ ,

R^{3'} - , -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁷)₂, -SO₂N(R⁷)₂, -OC(=O)R, -N(R⁷)COR, -N(R⁷)C(O)₂(C₁₋₆), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁷)CON(R⁷)₂, -N(R⁷)SO₂N(R⁷)₂, -N(R⁴)SO₂R, -OC(=O)N(R⁷)₂, C₁₋₆ , C₆₋₁₀ , 5 10 5 10

R , C₁₋₆ , C₆₋₁₀ , 5 10 5

10 ,

R⁴ -R⁷, -COR⁷, -CO₂(C₁₋₆), -CON(R⁷)₂ -SO₂R⁷

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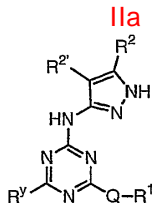
R⁵ -R, - , -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)C(O)₂(C₁₋₆), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R -OC(=O)N(R⁴)₂ ,

V -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)- -C(R⁶)₂N(R⁶)CON(R⁶)- ,

W -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-, -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)CON(R⁶)-, -CON(R⁶)-,

R⁶ C₁₋₄, R⁷ C₁₋₆, R⁸ -R, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(C₁₋₆), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R-OC(=O)N(R⁴)₂, Q가 -NH-, R^y R⁸, R¹ -3- -3-

Ila



Ila

R^y Z-R^{3'}, C₁₋₆, C₆₋₁₀, 5 10, 5 10

Q -N(R⁴)-, -O-, -S- -CH(R⁶)-, R¹ T-(D)

D, 5 7, 8 10, 가, D 가, -R⁴, T-R⁵ V-Z-R⁵ 1 4

T 가 C₁₋₄, Q가 -CH(R⁶)-, C₁₋₄, -O-, -S-, -N(R⁴)-, -CO-, -CONH-, -NHCO-, -SO₂-, -SO₂NH-, -NHCO₂-, -CO₂-, -OC(O)-, -OC(O)NH-, -NHCO₂-

Z C₁₋₄

L -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)CON(R⁶)-

R² R^{2'} -R₀ -T-W-R⁶₃, R² R^{2'}_{5 8},
 NO₂, -R⁷_{R⁴}, -V-R⁶_{R⁴}, R² R^{2'}_가, -CN, -

R^{3'} -, -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁷)₂, -SO₂N(R⁷)₂, -OC(=O)R, -N(R⁷)COR, -N(R⁷)CO₂(C₁₋₆), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁷)CON(R⁷)₂, -N(R⁷)SO₂N(R⁷)₂, -N(R⁴)SO₂R, -OC(=O)N(R⁷)₂, C₁₋₆, C₆₋₁₀, 5 10 5 10

R, C₁₋₆, C₆₋₁₀, 5 10 5

R⁴ -R⁷, -COR⁷, -CO₂(C₁₋₆), -CON(R⁷)₂ -SO₂R⁷

R⁵ -R, -, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(C₁₋₆), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -OC(=O)N(R⁴)₂

V -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)₂N(R⁶)=NN(R⁶)-, -C(R⁶)₂N(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)CON(R⁶)-

W -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-, -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)CON(R⁶)- -CON(R⁶)-

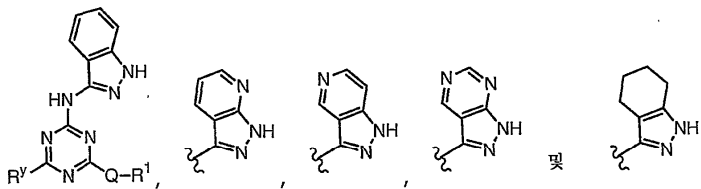
R⁶ C₁₋₄, 2

R⁷ C₁₋₆, 2 R

Ila R^y Z-R^{3'}, C₁₋₆, 5 6, Z, R^{3'}, -N(R⁴)₂, -OR, C₁₋₆, C₆₋₁₀, 5 10 5 10

R^y 2-, 4-, 3-, (:), (:), (:), (:)

Ila R² R^{2'} 6 : Ila :



IIa R²/R^{2'} : -, -N(R⁴)₂-, -C₁₋₄, -C₁₋₄, -NO₂, -O(C₁₋₄), -CO₂(C₁₋₄), -CN, -SO₂(C₁₋₄), -SO₂NH₂, -OC(O)NH₂, -NH₂SO₂(C₁₋₄), -NHC(O)(C₁₋₄), -C(O)NH₂, -CO(C₁₋₄)[(C₁₋₄)]·(C₁₋₄) 가

IIa R², R^{2'}, C₁₋₆, H, R², R^{2'}, i-

IIa D가, D

IIa D가, D, [b], [b], 1,8-

IIa D, T-R⁵, V-Z-R⁵, -CN, -NO₂, -N(R⁴)₂, C₁₋₆, -OR, -C(O)R, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -N(R⁴)CO₂R, -SO₂N(R⁴)₂, -N(R⁴)SO₂R, -N(R⁶)COCH₂N(R⁴)₂, -N(R⁶)COCH₂CH₂N(R⁴)₂, -N(R⁶)COCH₂CH₂CH₂N(R⁴)₂, R, C₁₋₆, R⁵, -Cl, -Br, -F, -CN, -CF₃, -COOH, -CONHMe, -CONHEt, -NH₂, -NHAc, -NHSO₂Me, -NHSO₂Et, -NHSO₂(n-), -NHSO₂(), -NHC(O)Et, -NHCOCH₂NHCH₃, -NHCOCH₂N(CO₂t-Bu)CH₃, -NHCOCH₂N(CH₃)₂, -NHCOCH₂CH₂N(CH₃)₂, -NHCOCH₂CH₂CH₂N(CH₃)₂, -NHCO(), -NHCO(), -NHCOCH₂(-4-), -NHCOCH₂CH₂(-4-), -NHCOCH₂CH₂CH₂(-4-), -NHCO₂(3-), -NH(C₁₋₄)(: -NHMe), -N(C₁₋₄)(: -NMe₂), OH, -O(C₁₋₄)(: -OMe), C₁₋₄(: , , 3 -) -CO₂(C₁₋₄)

IIa

R^y가 Z-R^{3'}[, Z, R^{3'}, -N(R⁴)₂, -OR, C₁₋₆, C₆₋₁₀, 5, 6], C₁₋₆, 5, 6 (a), 5, 6

R¹ T-(D)(, T 가) (b),

D가 5, 7, 8, 10 (c)

R²가 -R, -T-W-R⁶, R^{2'}가, R², R^{2'}가 (d), (a) (d)

IIa

R^y가 C₁₋₆ (a), 5, 6, 5, 6

R¹ T-(D)(, T 가) , Q가 -S-, -NH- -CH₂- (b),

D가 5, 7, 8, 10 (c)
 R²가 -R(, R, C₁₋₆, 5, 6 (d)
 (a) (d)

IIa

R^y가 2-, 3-, 4- (a),

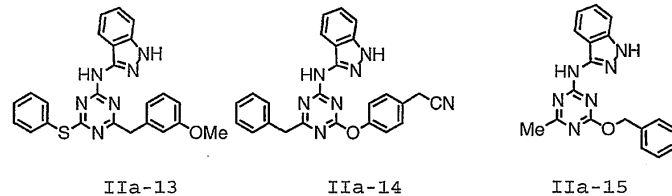
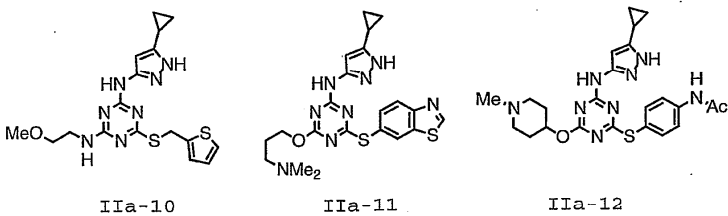
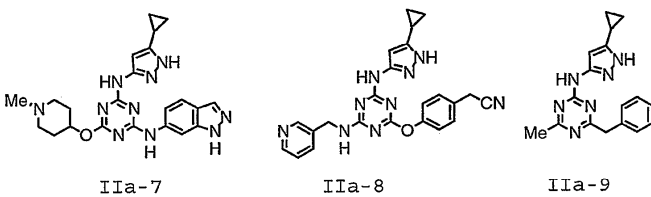
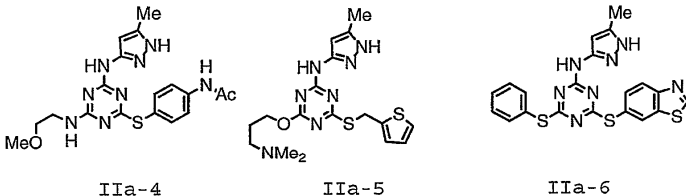
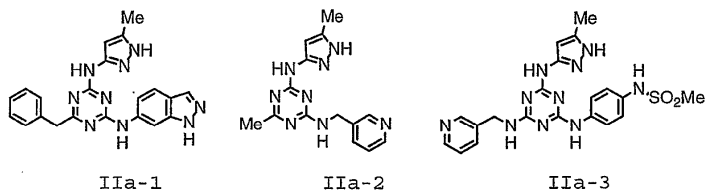
R¹ T-(D)[, T, D_{5, 6}, -CN, -NO₂, -N(R⁴)₂, C₁₋₆, -OR, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -N(R⁴)SO₂R, -N(R⁶)COCH₂CH₂N(R⁴)₂, -N(R⁶)COCH₂CH₂CH₂N(R⁴)₂], Q가 -S-, -NH- (b)

R²가 C₁₋₆, L -O-, -S-, -NH- (c)
 (a) (c)

IIa

1

[1]



IIa

-2-

la

-2

IIa

-2

GSK-3-

GSK-3

IIa

IIa

Tau

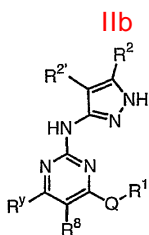
IIa

GSK-3

GSK-3 Ila -2 GSK-3 -2 GSK-3 -2

-2 GSK-3 Ila

Ilb ,



Ilb ,

R^y Z-R^{3'}, C₁₋₆, C₆₋₁₀, 5 10 5 10

R^y R⁸, 0 3 5 7

Q -N(R⁴)-, -O-, -S- -CH(R⁶)- ,

R¹ T-(D) ,

D , 5 7 8
10 가 , D 가 , T-R⁵ V-Z-R⁵
D 가 -R⁴ , 1 4

T 가 C₁₋₄ , Q가 -CH(R⁶)- , C₁₋₄
-O-, -S-, -N(R⁴)-, -CO-, -CONH-, -NHCO-, -SO₂-, -SO₂NH-, -NHSO₂-, -CO₂-, -OC(O)-, -OC(O)NH-, -NHCO₂- ,

Z C₁₋₄ ,

L -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)- -C(R⁶)₂N(R⁶)CON(R⁶)- ,

R² R^{2'} -R -T-W-R⁶ , R² R^{2'} ,
0 3 5 8
가 , -CN, -

NO₂, -R⁷ -V-R⁶ , R² R^{2'} 가 , R⁴ ,

R^{3'} -, -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁷)₂, -SO₂N(R⁷)₂, -OC(=O)R, -N(R⁷)COR, -N(R⁷)CO₂(C₁₋₆), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁷)CON(R⁷)₂, -N(R⁷)SO₂N(R⁷)₂, -N(R⁴)SO₂R, -OC(=O)N(R⁷)₂, C₁₋₆, C₆₋₁₀, 5, 10

R, C₁₋₆, C₆₋₁₀, 5, 10, 5

R⁴ -R⁷, -COR⁷, -CO₂(C₁₋₆), -CON(R⁷)₂ -SO₂R⁷

R⁵ -R, -, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(C₁₋₆), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R -OC(=O)N(R⁴)₂

V -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)CON(R⁶)-

W -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-, -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)CON(R⁶)- -CON(R⁶)-

R⁶ C₁₋₄, 2

R⁷ C₁₋₆, 2 R

R⁸ -R, -, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(C₁₋₆), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R -OC(=O)N(R⁴)₂

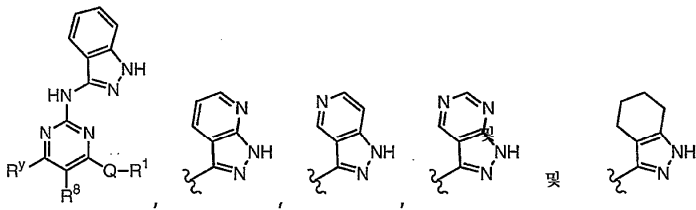
, Q가 -NH-, R^y R⁸, R¹ -3- -3-

IIb R^y Z-R^{3'}, C₁₋₆, 5, 6, Z, R^{3'} -N(R⁴)₂, -OR, C₁₋₆, C₆₋₁₀, 5, 10, 5, 10

R^y 2-, 4-, 3- (:), (:), (:)

IIa R² R^{2'}

IIb 6 :



IIb R²/R^{2'} : -, -N(R⁴)₂-, -C₁₋₄, -C₁₋₄, -NO₂, -O(C₁₋₄), -CO₂(C₁₋₄), -CN, -SO₂(C₁₋₄), -SO₂NH₂, -OC(O)NH₂, -NH₂SO₂(C₁₋₄), -NHC(O)(C₁₋₄), -C(O)NH₂-CO(C₁₋₄)[, (C₁₋₄)], (C₁₋₄)]. (C₁₋₄)

IIb R², R^{2'}, C₁H, R², R^{2'}, R^{2'}, i-, R^{2'}

IIb D가

D

IIb D가

D

[b]

[b]

, 1,8-

IIb D, T-R⁵, V-Z-R⁵, -CN, -NO₂, -N(R⁴)₂, C₁₋₆, -OR, -C(O)R, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -N(R⁴)CO₂R, -SO₂N(R⁴)₂, -N(R⁴)SO₂R, -N(R⁶)COCH₂N(R⁴)₂, -N(R⁶)COCH₂CH₂N(R⁴)₂, -N(R⁶)COCH₂CH₂CH₂N(R⁴)₂, R, C₁₋₆, R⁵, -Cl, -Br, -F, -CN, -CF₃, -COOH, -CONHMe, -CONHEt, -NH₂, -NHAc, -NHSO₂Me, -NHSO₂Et, -NHSO₂(n-), -NHSO₂(), -NHCOEt, -NHCOCH₂NHCH₃, -NHCOCH₂N(CO₂t-Bu)CH₃, -NHCOCH₂N(CH₃)₂, -NHCOCH₂CH₂N(CH₃)₂, -NHCO(CH₂), -NHCO(CH₂), -NHCO(CH₂), -NHCOCH₂CH₂(-4-), -NHCOCH₂CH₂CH₂(-4-), -NHCOCH₂CH₂CH₂(-4-), -NHC(O)₂(3-), -NH(C₁₋₄)(: -NHMe), -N(C₁₋₄)(: -NMe₂), OH, -O(C₁₋₄)(: -OMe), C₁₋₄(: , , 3-) -CO₂(C₁₋₄)

R^y, R⁸, R^y, R⁸, R^y, R⁸, 0, 2, 5, 6, R^y, R⁸

IIb R⁸, R⁸, R⁸, NH₂, NH₂CH₂CH₂NH, N(CH₃)₂CH₂CH₂NH, N(CH₃)₂CH₂CH₂O, (-1-)CH₂CH₂O, NH₂CH₂CH₂O가

IIb

R^y가 Z-R^{3'} [, Z, R^{3'}, -N(R⁴)₂, -OR, C₁₋₆, C₆₋₁₀, 5, 6] C₁₋₆, 5, 6, 5, 6 (a),

R¹, T-(D)(, T가) (b),

D가 5, 7, 8, 10 (c)

R²가 -R, -T-W-R⁶, R^{2'}가, R², R^{2'}가

(d) , (a) (d)

IIb

R^y가 C₁₋₆, 5 6 (a),

R¹ T-(D)(, T 가) , Q가 -S-, -NH- -CH₂- (b),

D가 5 7 8 10 (c),

R²가 -R(, R, C₁₋₆, 5 6 5 6 (a) (d) (d) .

IIb

R^y가 2-, 4-, 3-, , R^y R⁸, (a),
0 2 5 6

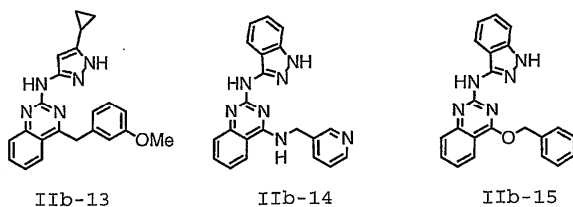
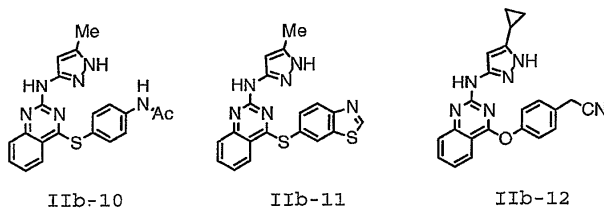
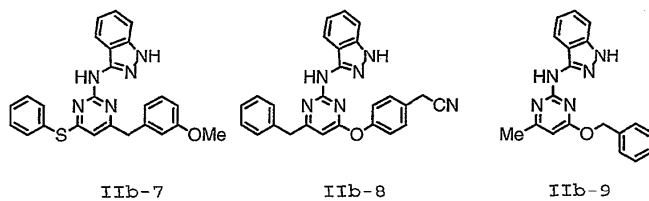
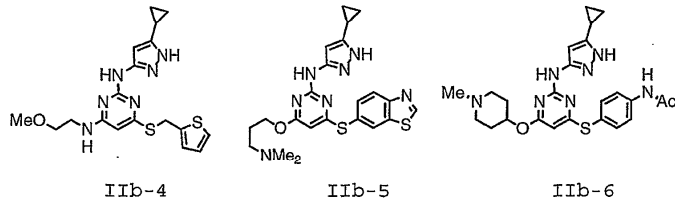
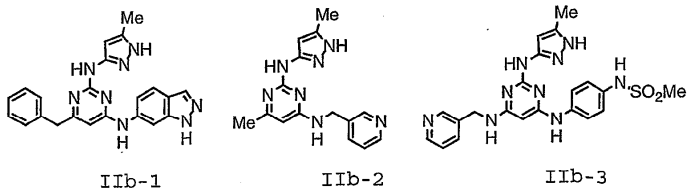
R¹ T-(D)[, T 가 , D 5 6 - , -CN, -NO
2, -N(R⁴)₂, C₁₋₆, -OR, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -N(R⁴)SO₂R
, -N(R⁶)COCH₂CH₂N(R⁴)₂ -N(R⁶)COCH₂CH₂CH₂N(R⁴)₂] , Q가 -S- -NH- (b)

R²가 C₁₋₆, L -O-, -S- -NH- (c)
(a) (c)

IIb

2

[2]



IIb

-2-

Ib

-2

IIb

-2

GSK-3-

GSK-3

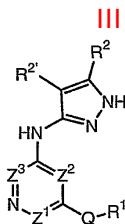
IIb

IIb

Tau

GSK-3 IIb ,
 GSK-3 IIb -2 GSK-3 -2 GSK-3 -2
 -2 GSK-3 IIb

III ,



III ,

Z¹ CR⁸ , Z² CH , Z³ CR^x , Z¹ Z³

R^x T-R³ L-Z-R³ ,

Q -N(R⁴)-, -O-, -S- -CH(R⁶)- ,

R¹ T-(D) ,

D , , 5 7 8
 10 가 , D 가 , T-R⁵ V-Z-R⁵_{1 4}
 , D 가 -R⁴ ,

T 가 C₁₋₄ , Q가 -CH(R⁶)- , C₁₋₄
 -O-, -S-, -N(R⁴)-, -CO-, -CONH-, -NHCO-, -SO₂-, -SO₂NH-, -NHSO₂-, -CO₂-, -OC(O)-, -OC(O)NH-, -NHCO₂- ,

Z C₁₋₄ ,

L -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)- -C(R⁶)₂N(R⁶)CON(R⁶)- ,

R² R^{2'} -R⁰ -T-W-R⁶ , R² R^{2'}
 3 5 8

NO₂, -R⁷ -V-R⁶ , R² R^{2'} 가 , -CN, -
 R⁴ ,

R^{3'} -R, -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁷)₂, -SO₂N(R⁷)₂, -OC(=O)R, -N(R⁷)COR, -N(R⁷)CO₂(C₁₋₆), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁷)CON(R⁷)₂, -N(R⁷)SO₂N(R⁷)₂, -N(R⁴)SO₂R -OC(=O)N(R⁷)₂

R, C₁₋₆, C₆₋₁₀, 5, 10, 5

R⁴ -R⁷, -COR⁷, -CO₂(C₁₋₆), -CON(R⁷)₂ -SO₂R⁷

R⁵ -R, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(C₁₋₆), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R -OC(=O)N(R⁴)₂

V -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)CON(R⁶)-

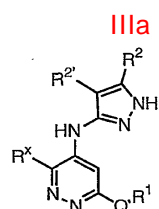
W -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-, -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)CON(R⁶)- -CON(R⁶)-

R⁶ C₁₋₄, 2

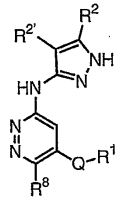
R⁷ C₁₋₆, 2 R

R⁸ -R, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(C₁₋₆), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R -OC(=O)N(R⁴)₂

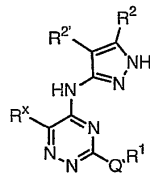
IIIa, IIIb, IIIc IIId



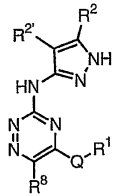
IIIb



IIIc



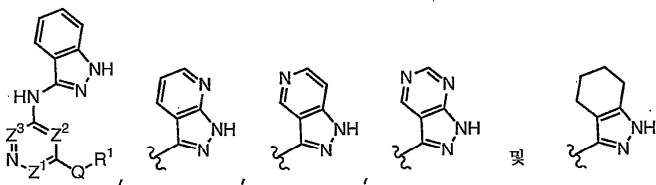
III d



III R^x T-R³, T 가 R³ CN, -R
 -OR R³ -R R³ C¹⁻⁶ R³ -OR 5 6 R
 C¹⁻⁶ (: -) R^x
 , CN, , , -1- , -2- ,
 , , , , 3 - , NH₂CH₂CH₂NH NH₂CH₂CH₂O가 .
 III R⁸ , R, OR N(R⁴)₂ R⁸
 , NH₂, NH₂CH₂CH₂NH, N(CH₃)₂CH₂CH₂NH, N(CH₃)₂CH₂CH₂O, (-1-)CH
 2 CH₂O NH₂CH₂CH₂O가 .

III R² R^{2'}

III 6



III R²/R^{2'} : - , -N(R⁴)₂ -, -C¹⁻
 4 , -C¹⁻⁴ , -NO₂ , -O(C¹⁻⁴) , -CO₂(C¹⁻⁴) , -CN, -SO₂(C¹⁻⁴) , -SO₂NH₂ ,
 -OC(O)NH₂ , -NH₂SO₂(C¹⁻⁴) , -NHC(O)(C¹⁻⁴) , -C(O)NH₂ -CO(C¹⁻⁴) [, (C¹⁻
 4)] . (C¹⁻⁴) .

III, R², C₁H,
 -6, R^{2'}, i-

III D가 D

III D가 D [b] [b], 1,8-

III D, T-R⁵ V-Z-R⁵, -CN, -NO₂, -N(R⁴)₂,
 C₁₋₆, -OR, -C(O)R, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -N(R⁴)CO₂R, -SO₂N(R⁴)₂, -
 N(R⁴)SO₂R, -N(R⁶)COCH₂N(R⁴)₂, -N(R⁶)COCH₂CH₂N(R⁴)₂, -N(R⁶)COCH₂CH₂CH₂
 N(R⁴)₂, R⁵, C₁₋₆, 5, 6, -Cl, -Br, -F, -CN, -CF₃, -COOH, -CONHMe,
 -CONHEt, -NH₂, -NHAc, -NHSO₂Me, -NHSO₂Et, -NHSO₂(n-), -NHSO₂(), -NHC
 OEt, -NHCOCH₂NHCH₃, -NHCOCH₂N(CO₂t-Bu)CH₃, -NHCOCH₂N(CH₃)₂, -NHCOCH₂CH₂
 N(CH₃)₂, -NHCOCH₂CH₂CH₂N(CH₃)₂, -NHCO(), -NHCO(), -NHCOCH₂
 (-4-), -NHCOCH₂CH₂(-4-), -NHCOCH₂CH₂CH₂(-4-), -NHCO₂(3
 -), -NH(C₁₋₄)(: -NHMe), -N(C₁₋₄)(: -NMe₂), OH, -O(C₁₋₄)(: -OMe),
 C₁₋₄ (: , , 3 -) -CO₂(C₁₋₄)

IIIa, IIIb, IIIc IIId

R^x가 , - C₁₋₄ (a),

R¹ T-(D)(, T 가) (b),

D가 5 7 8 10 (c)

R²가 -R -T-W-R⁶ , R^{2'}가 , R² R^{2'}가 (a) (d)

IIIa, IIIb, IIIc IIId

R¹ T-(D)(, T 가) , Q가 -S-, -NH- -CH₂- (a) ,

D가 5 7 8 10 (b)

R²가 -R(, R , C₁₋₆ , 5 6 5 6) , R^{2'}가 (c) , (a) (c)

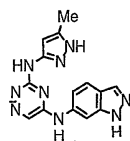
IIIa, IIIb, IIIc IIId

R^x가 , , , , (a),

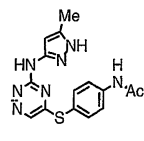
R¹ T-(D)[, T 가 , D 5 6 - , -CN, -NO₂, -N(R⁴)₂, C₁₋₆, -OR, -CO₂R, -CON(R⁴)₂, -OCO(R⁴)₂-, -N(R⁴)CO
 R, -N(R⁴)SO₂R, -N(R⁶)COCH₂CH₂N(R⁴)₂, -N(R⁶)COCH₂CH₂CH₂N(R⁴)₂] , Q가 -S- -NH- (b)

R²가 (a) C₁₋₆ (c)

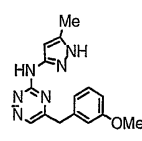
[3A]



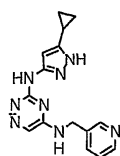
III-1



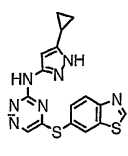
III-2



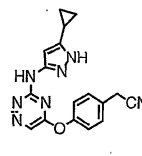
III-3



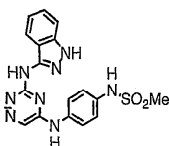
III-4



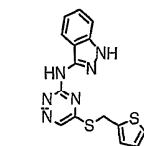
III-5



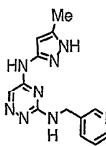
III-6



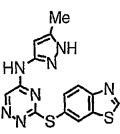
III-7



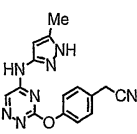
III-8



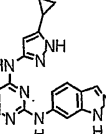
III-9



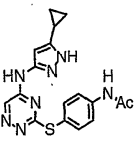
III-10



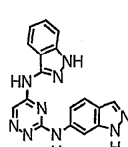
III-11



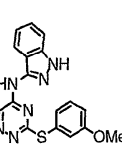
III-12



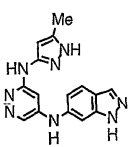
III-13



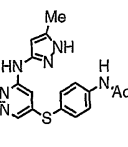
III-14



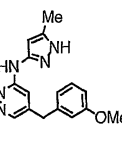
III-15



III-16

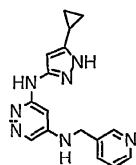


III-17

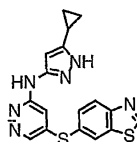


III-18

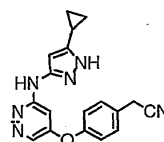
[3B]



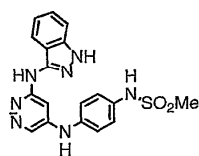
III-19



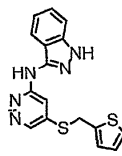
III-20



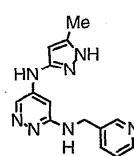
III-21



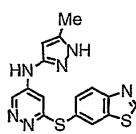
III-22



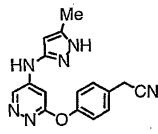
III-23



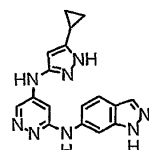
III-24



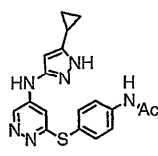
III-25



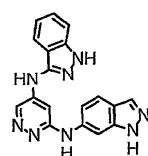
III-26



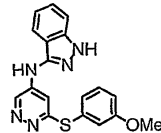
III-27



III-28



III-29



III-30

III

-2-

II

-2

III

-2

GSK-3-

GSK-3

III

III

/

/

Tau

III

GSK-3

III

-2

GSK-3

-2

GSK-3

-2

GSK-3

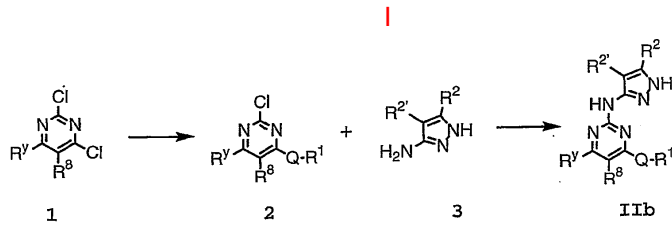
-2

GSK-3

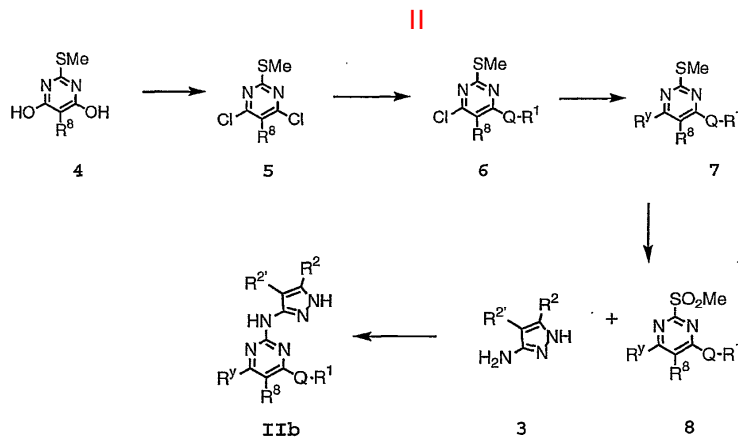
III

I VII

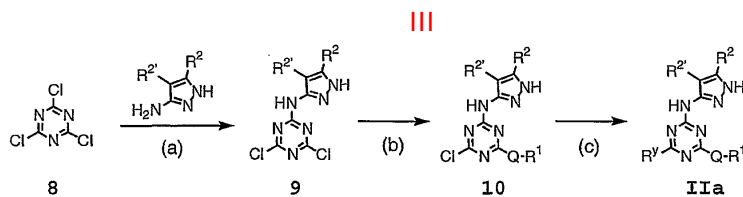
가



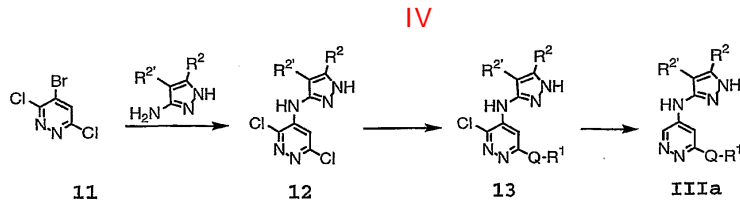
I IIb (1) { [: J. Indian. Chem. Soc., 61, 690-693 (1984) J. Med. Chem., 37, 3828-3833 (1994)]
 } 2 : R¹ -QH 4 (2)
 , [: J. Med. Chem, 38, 14, 2763-2773, (1995)]
 (2) () 2 IIb



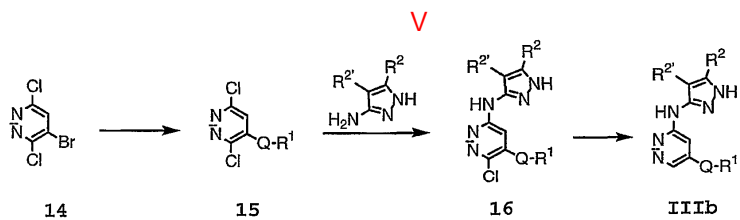
II Q가 N, O S , R γ가 4,6- -2- (4) IIb [: J. Med. Chem., 27, 12, 1621-1629 (1984)] (4) PO
 Cl₃ (5) (5) 2 (6) 2,585,906
) (7) , R¹ -QH (7) R γ -H (8) R¹ -OH
) (7) I (b) IIb ()



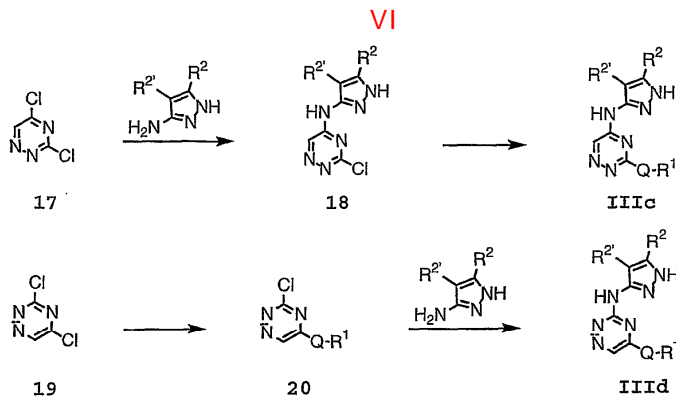
III (a) (10) R^y-H (11) (12) (13) (14) (15) (16) (17) (18) (19) (20) (21) (22) (23) (24) (25) (26) (27) (28) (29) (30) (31) (32) (33) (34) (35) (36) (37) (38) (39) (40) (41) (42) (43) (44) (45) (46) (47) (48) (49) (50) (51) (52) (53) (54) (55) (56) (57) (58) (59) (60) (61) (62) (63) (64) (65) (66) (67) (68) (69) (70) (71) (72) (73) (74) (75) (76) (77) (78) (79) (80) (81) (82) (83) (84) (85) (86) (87) (88) (89) (90) (91) (92) (93) (94) (95) (96) (97) (98) (99) (100)



IV (11) (12) (13) (14) (15) (16) (17) (18) (19) (20) (21) (22) (23) (24) (25) (26) (27) (28) (29) (30) (31) (32) (33) (34) (35) (36) (37) (38) (39) (40) (41) (42) (43) (44) (45) (46) (47) (48) (49) (50) (51) (52) (53) (54) (55) (56) (57) (58) (59) (60) (61) (62) (63) (64) (65) (66) (67) (68) (69) (70) (71) (72) (73) (74) (75) (76) (77) (78) (79) (80) (81) (82) (83) (84) (85) (86) (87) (88) (89) (90) (91) (92) (93) (94) (95) (96) (97) (98) (99) (100)



V (15) (16) (17) (18) (19) (20) (21) (22) (23) (24) (25) (26) (27) (28) (29) (30) (31) (32) (33) (34) (35) (36) (37) (38) (39) (40) (41) (42) (43) (44) (45) (46) (47) (48) (49) (50) (51) (52) (53) (54) (55) (56) (57) (58) (59) (60) (61) (62) (63) (64) (65) (66) (67) (68) (69) (70) (71) (72) (73) (74) (75) (76) (77) (78) (79) (80) (81) (82) (83) (84) (85) (86) (87) (88) (89) (90) (91) (92) (93) (94) (95) (96) (97) (98) (99) (100)



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ATPase

가 /

1

GSK-3 Ki

[: Fox et al. (1998) Protein Sci. 7, 2249] GSK-3 (AA 1-420)

100mM HEPES(pH 7.5), 10mM MgCl₂, 25mM NaCl, 300 μ M NADH, 1mM DTT, 1.5% DMSO가 20 μ M ATP(Sigma Chemicals, St Louis, MO) 300 μ M (HSSPHQS(PO₃H₂)EDEEE, American Peptide, Sunnyvale, CA) 2.5mM, 30 20nM GSK-3, 300 μ M NADH, 30μg/ml 10μg/ml

ATP (175μℓ) 96 5μℓ 0.002 μ M 30 μ M 30 10
 DMSO (10mM) 20 μ M 30 10
 Molecular Devices Spectramax Ki (Sunnyvale, CA)

2

-2 Ki

[: Fox et al. (1998) Protein Sci. 7, 2249] -2

0.1M HEPES 7.5, 10mM MgCl₂, 1mM DTT, 25mM NaCl, 2.5mM 300mM NADH, 30m g/ml, 10mg/ml, 40mM ATP 800 μ M (LRRASLG, American Peptide, Sunnyvale, CA)가 30 10 70nM DMSO 30 μ M 가 10μℓ 가 -2 가 BioRad Ultramark (Hercules, CA) 30 5 340nm Ki

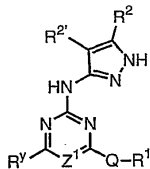
가

(57)

1.

II (prodrug).

II



II ,

Z¹ CR⁸ ,

R^y Z-R^{3'} , C₁₋₆ , C₆₋₁₀ , 5 10 5 10

R^y R⁸ , 0 3 5 7

Q -N(R⁴)-, -O-, -S- -CH(R⁶)- ,

R¹ T-(D) ,

D , 5 7 8
 10 가 , D 가 , T-R⁵ V-Z-R⁵_{1 4}
 , D 가 -R⁴ ,

T 가 C₁₋₄ , Q가 -CH(R⁶)- , C₁₋₄
 -O-, -S-, -N(R⁴)-, -CO-, -CONH-, -NHCO-, -SO₂-, -SO₂NH-, -NHSO₂-, -CO₂-, -OC(O)-, -OC(O)NH-, -NHCO₂- ,

Z C₁₋₄ ,

L -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)- -C(R⁶)₂N(R⁶)CON(R⁶)- ,

R² R^{2'} -R -T-W-R⁶ , R² R^{2'}
 0 3 5 8
 , R² R^{2'} 가 , -CN, -
 NO₂, -R⁷ -V-R⁶ , R² R^{2'} 가

R^{3'} - , -OR, -C(=O)R, -CO₂R, -COCOR, -COCH₂COR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁷)₂, -SO₂N(R⁷)₂, -OC(=O)R, -N(R⁷)COR, -N(R⁷)CO₂(C₁₋₆), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁷)CON(R⁷)₂, -N(R⁷)SO₂N(R⁷)₂, -N(R⁴)SO₂R, -OC(=O)N(R⁷)₂, C₁₋₆, C₆₋₁₀, 5 10 5 10

R , C₁₋₆, C₆₋₁₀, 5 10 5

R⁴ -R⁷, -COR⁷, -CO₂(C₁₋₆), -CON(R⁷)₂ -SO₂R⁷

R⁵ -R, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(C₁₋₆), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -CN-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N

R⁴)SO₂R -OC(=O)N(R⁴)₂ ,

V -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)- -C(R⁶)₂N(R⁶)CON(R⁶)- ,

W -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -CO-, -CO₂-, -C(R⁶)OC(O)-, -C(R⁶)OC(O)N(R⁶)-, -C(R⁶)₂N(R⁶)CO-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)CON(R⁶)- -CON(R⁶)- ,

R⁶ R⁶ C₁₋₄ , 2

R⁷ C₁₋₆ , 2 R

R⁸ -R, -OR, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN, -S(O)R, -S(O)₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(C₁₋₆), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR, -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R -OC(=O)N(R⁴)₂ ,

, Q가 -NH- , R y R⁸ , R¹ -3- -3-

2.

1 , Z¹ ,

R y 가 Z-R³ [, Z , R^{3'} -N(R⁴)₂, -OR, C₁₋₆ , C₆₋₁₀ , 5 10], C₁₋₆ (a), 5 6

R¹ T-(D)(, T 가) (b),

D가 5 7 8 10 (c)

R² 가 -R -T-W-R⁶ , R^{2'} 가 , R² R^{2'} 가 (d)

3.

2 ,

R y 가 Z-R³ [, Z , R^{3'} -N(R⁴)₂, -OR, C₁₋₆ , C₆₋₁₀ , 5 10], C₁₋₆ (a), 5 6

R¹ T-(D)(, T 가) (b),

D가 5 7 8 10 (c)

R² 가 -R -T-W-R⁶ , R^{2'} 가 , R² R^{2'} 가 (d)

4.

2 ,

R^y가 C₁₋₆ (a), 5 6 , 5 6

R¹ T-(D)(, T 가) , Q가 -S-, -NH- -CH₂- (b),

D가 5 7 8 10 (c)

R²가 -R(, R , C₁₋₆ , 5 6 5 6) , R^{2'}가 (d)

5.

4 ,

R^y가 C₁₋₆ (a), 5 6 , 5 6

R¹ T-(D)(, T 가) , Q가 -S-, -NH- -CH₂- (b),

D가 5 7 8 10 (c)

R²가 -R(, R , C₁₋₆ , 5 6 5 6) , R^{2'}가 (d)

6.

4 ,

R^y가 2- , 4- , 3- , (a),

R¹ T-(D)[, T 가 , D 5 6 - , -CN, -NO , -N(R⁴)₂, C₁₋₆ , -OR, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -N(R⁴)SO₂R , -N(R⁶)COCH₂CH₂N(R⁴)₂ -N(R⁶)COCH₂CH₂CH₂N(R⁴)₂] , Q가 -S- -NH- (b)

R²가 C₁₋₆ , L -O-, -S- -NH- (c)

7.

6 ,

R^y가 2- , 4- , 3- , (a),

R¹ T-(D)[, T 가 , D 5 6 - , -CN, -NO , -N(R⁴)₂, C₁₋₆ , -OR, -CO₂R, -CONH(R⁴), -N(R⁴)COR, -N(R⁴)SO₂R , -N(R⁶)COCH₂CH₂N(R⁴)₂ -N(R⁶)COCH₂CH₂CH₂N(R⁴)₂] , Q가 -S- -NH- (b)

R²가 C₁₋₆ , L -O-, -S- -NH- (c)

8.

1 , Z¹ CR⁸ ,

R^y가 Z-R^{3'} [, Z , R^{3'} -N(R⁴)₂, -OR, C₁₋₆, C₆₋₁₀, 5 10], C₁₋₆, 5 6 (a),

R¹ T-(D)(, T 가) (b),

D가 5 7 8 10 (c)

R²가 -R -T-W-R⁶ , R^{2'}가 , R² R^{2'}가 (d)

9.

8 ,

R^y가 Z-R^{3'} [, Z , R^{3'} -N(R⁴)₂, -OR, C₁₋₆, C₆₋₁₀, 5 10], C₁₋₆, 5 6 (a),

R¹ T-(D)(, T 가) (b),

D가 5 7 8 10 (c)

R²가 -R -T-W-R⁶ , R^{2'}가 , R² R^{2'}가 (d)

10.

8 ,

R^y가 C₁₋₆, 5 6 (a),

R¹가 T-(D)(, T 가) , Q가 -S-, -NH- -CH₂- (b),

D가 5 7 8 10 (c)

R²가 -R(, R , C₁₋₆ , 5 6 , R^{2'}가 (d) 5 6 .

11.

10 ,

R^y가 C₁₋₆, 5 6 (a),

R¹ T-(D)(, T 가) , Q가 -S-, -NH- -CH₂- (b),

D가 5 7 8 10 (c)

R²가 -R(, R , C₁₋₆ , 5 6 , R^{2'}가 (d) 5 6 .

12.

10 ,

R^y가 2- , 4- , , , , , , ,

, 3 - , , , - , R y R 8 ' - , ,
 0 2 5 6 (a),

R 1 T-(D)[, T 가 , D 5 6 - , -CN, -NO
 2, -N(R 4) 2, C 1-6 , -OR, -CO 2 R, -CONH(R 4), -N(R 4)COR, -N(R 4)SO 2 R
 , -N(R 6)COCH 2 CH 2 N(R 4) 2 -N(R 6)COCH 2 CH 2 CH 2 N(R 4) 2 (b)
], Q가 -S- -NH-

R 2 가 C 1-6 , L -O-, -S- -NH- (c)

13.

12 ,

R y 가 2- , 4- , , , , , , , , , ,
 , 3 - , , , - , R y R 8 ' - , ,
 0 2 5 6 (a),

R 1 T-(D)[, T 가 , D 5 6 - , -CN, -NO
 2, -N(R 4) 2, C 1-6 , -OR, -CO 2 R, -CONH(R 4), -N(R 4)COR, -N(R 4)SO 2 R
 , -N(R 6)COCH 2 CH 2 N(R 4) 2 -N(R 6)COCH 2 CH 2 CH 2 N(R 4) 2 (b)
], Q가 -S- -NH-

R 2 가 C 1-6 , L -O-, -S- -NH- (c)

14.

6- -N-(1H- -6-)-N'-(5- -1H- -3-)-[1,3,5]- -2,4- ,
 6- -N-(5- -1H- -3-)-N'- -3- -[1,3,5]- -2,4- ,
 N-(4-{4-(5- -1H- -3-)-6-[(-3-)-]-[1,3,5]- -2- }-
)- ,
 N-{4-[4-(2- -)-6-(5- -1H- -3-)-[1,3,5]- -2-]- }-
 ,
 [4-(3- -)-6-(-2-)-[1,3,5]- -2-]-(5- -1H- -3-
)- ,
 [4-(-6-)-6- -[1,3,5]- -2-]-(5- -1H- -3-)- ,
 N-(5- -1H- -3-)-N'-(1H- -6-)-6-(1- - -4-)-[1,3,5]-
 -2,4- ,
 (4-{4-(5- -1H- -3-)-6-[(-3-)-]-[1,3,5]- -2-
 }-)- ,
 (4- -6- -[1,3,5]- -2-)-(5- -1H- -3-)- ,
 N-(5- -1H- -3-)-N'-(2-)-6-(-2-)-[1,3,5]- -2,
 4- ,
 [4-(-6-)-6-(3-)-[1,3,5]- -2-]-(5- -1H-
 -3-)- ,

N-{4-[4-(5-
-]- }-
{4-[4-
(4-
6-
6-
N-(4-{2-(5-
N²-(5-
[4-(
N-(4-[2-(5-
N-{4-[2-(5-
[4-(
{4-[2-(5-
(5-
N²-(1H-
(4-(

15.

1 14

16.

15 , 가 가

17.

1 14
(Aurora)-2 GSK-3

18.

15 , -2

19.

16 , -2

20.

-2- 15
, -2-

21.

20 , , ,

21 22. , 가 가 .

22 23. , 가 가 .

24. 15 , GSK-3 .

25. 16 , GSK-3 .

26. GSK-3- 15 , GSK-3- .

26 27. , GSK-3- , , , , AIDS- , (AML), (MS), / .

27 28. , GSK-3- .

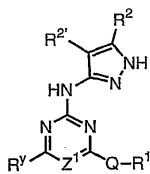
29. 15 .

30. Tau 15 , Tau .

31. 15 , - .

II .

II



II ,

Z 1 CR 8 ,

Q -S-, -O-, -N(R 4)- -CH(R 6) ,

R 1 T- D ,

D
10 , ,

5 7

8

R y , R 2 R 2'

, -2 GSK-3 ,

, -2, GSK-2, , .