

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

(51) Int. Cl.⁷
C07D 417/14
C07D 417/12

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10-2005-0006237
2005 01 15

(21) 10-2004-7017933

(22) 2004 11 06

2004 11 06

(86) PCT/US2003/014223

(87)

WO 2004/058753

(86) 2003 05 06

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(30) 60/378,185 2002 05 06 (US)

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(72) 02476 256

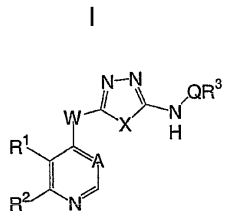
02140 203 5

01720 36

(74)
:

(54) J A K

I JAK 가 ,



I ,

W X ,

A , CH, C-CN C-(C₁₋₃) ,

R¹ R² .

가 , , JAK , , .

35 U.S.C. § 119(e) , 2002 5 6
JAK ('Inhibitors of Jak Protein Kinase') 가 60/378,185

가

[: Hardie, G. and Hanks, S. The Protein Kinase Facts Book, I and II, Academic Press, San Diego, CA: 1995]

250 300

(: Hanks, S. K., Hunter, T., FASEB J. 1995,9, 576-596; Knighton et al., Science 1991, 253, 407-414; Hiles et al., Cell 1992,70, 419-429; Kunz et al., Cell 1993,73, 585-596; Garcia-Bustos et al., EMBO J. 1994,13, 2352-2361].

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2), [: -1(IL-1) (GM-CSF) (TNF-)], [: , H₂O (FGF)]가 (migration), 가

가

(Janus) (JAK) JAK1, JAK2, JAK3 TYK2 . JAK
JAK

(STAT) . JAK/STAT , , 가 (:), ,

. JAK/STAT [: Frank Mol. Med. 1999,5, 4
32-456 and Seidel et al., Oncogene 2000,19, 2645-2656]

JAK1, JAK2 TYK2 , JAK3 . JAK3
(c) , IL-2, IL-4, IL-7, IL-9 IL-15 . IL-4 IL-9
JAK-3 c - [: Suzuki et
al., Blood 2000,96, 2172- 2180].

(Ig) E , (1)
 [: Gordon et al., N
 ature 1990, 346, 274-276 and Galli, N. Engl. J. Med. 1993,328, 257-265].
 IgE

JAK3 [: Malaviya et al., Biochem. Biophys. Res. Co
 mmun. 1999,257, 807-813] , JAK3
 [: Malaviya et al., J. Biol. Chem. 1999 274, 27028-27
 038] JAK3
 IgE /

JAK3 , JAK3
 (Wistar Furth) [: Kirken, Transpl. Proc.
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IL-4 STAT (RA) IL-4/STAT IL-4
 . RA (JAK 1 amp; 3) , IL-4 JAK RA
 [: Muller-Ladner et al., J. Immunol. 2000, 164, 3894-3901].

가 (FALS) ALS 10% . FALS
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 [: Trieu et al., Biochem. Biophys. Res. Commun. 2000,267,22-25].

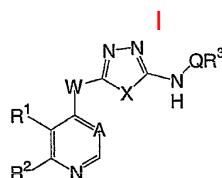
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, TEL/JAK2 TEL/JAK2 ST
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JAK3 TYK2 STAT3 , T JAK/STAT JAK
 [: Nielsen et al., Proc. Nat. Acad. Sci. U. S. A. 1997, 94, 6764-6769]. , STA
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 159, 5206-5210]. , IL6 STAT3 JAK
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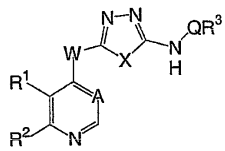
, JAK-3

JAK-3



I, A, Q, W, X, R¹, R², R³ (:), (: SLE) , (:) , (:) .

I. :

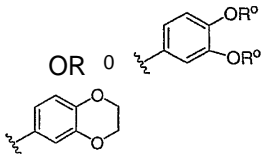


I, W, X, A, CH, C-CN, C-(C₁₋₃), R¹, R², R³, Q, C₁₋₆, NR-, -C(O)-, -C(O)NR-, -C(O)C(O)-, -C(O)C(O)₂-, -C(O)C(O)₂-, -SO₂-, -O-, -S-, -NR-, -C(O)-, -C(O)₂-, -C(O)NR-, -OC(O)NR-, -NRC(O)-, NRCO₂-, -NRC(O)NR-, -S(O)-, -SO₂-, -NRSO₂-, -SO₂NR-, -NRSO₂NR-, R, C₁₋₆, R³, R, Ar, Ar (a) 3, 8, 10, 1, 3, 10, 3, 7, 8, 10, 1, 4, 5, 6, 8, 10, (b), (c).

2. : (CAS version, Handbook of Chemistry and Physics, 75th Ed.) 가

[: 'Organic Chemistry', Thomas Sorrell, University Science Books, Sausalito: 1999, and 'March's Advanced Organic Chemistry', 5th Ed. , Ed.: Smith, M. B. and March, J. , John Wiley amp; Sons, New York: 2001]

가
 가
 가
 가
 1 40
 (가)
 1 20
 1 6
 1 8
 1 4
 $C_8 - C_{12}$
 $C_7 - C_8$
 ()
 1 2 가
 3 14
 3 7
 ; 4
 -2H-) , NH() NR + (N- , N(3,4-)
 가
 (') (')
 F, Cl, Br I
 5 14
 3 7



가 6 가 .2 R⁰ (R +

(Z) (E) (,) , R (S , (Z) (E) , (,) , 가 , , 가 13 C- 14 C-

3.

I R¹ R² , 0 2
 . R¹ R² 5 7
 , R⁰, OR⁰, N(R⁰)₂ SR⁰ . R¹ R² , R⁰
 . R¹ R² , Me, Et, CF₃,
 OH OCH₃

I Q 1가 , -C(O)-, -C(O)NR-, -CO₂-, -C(O)CO₂-, -SO₂- C₁₋₄
 , Q 2 -O-, -S-, -NR-, -C(O)-, -CO₂-, -SO₂-, -C(O)CH₂O-, -C(O)CH₂S- Q 1가 , -C(O)-, -C(O)NH-, -CO
 C(O)NHCH₂-

I R³ C₁₋₆

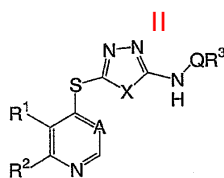
(a) 3 6 ;

(b) , 1 2 5 6

(c) , 1 3 5 6
 9 10

I R³ , , , , 3 - , ,
 , , , , R³ , R⁰, [1,3]
 0 SR⁰ , R⁰ , N(R⁰)₂, OR

II

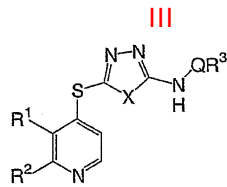


A, Q, X, R¹, R², R³

II Q, R¹, R², R³

I

III

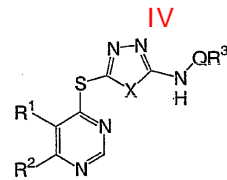


Q, X, R¹, R², R³

III Q, R¹, R², R³

I

IV



Q, X, R¹, R², R³

IV Q, X, R¹, R², R³

I

X가

II, III IV

R¹, R²가

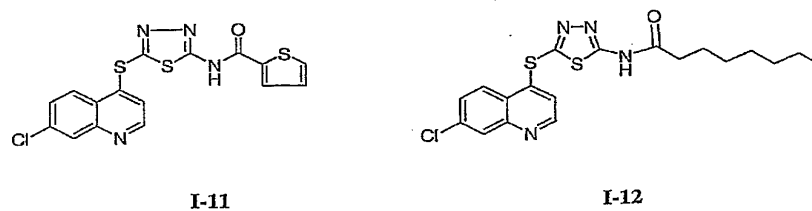
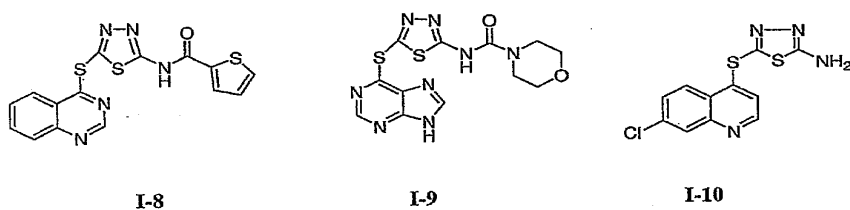
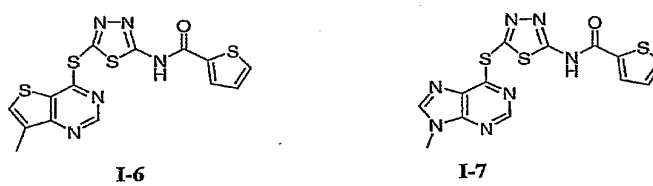
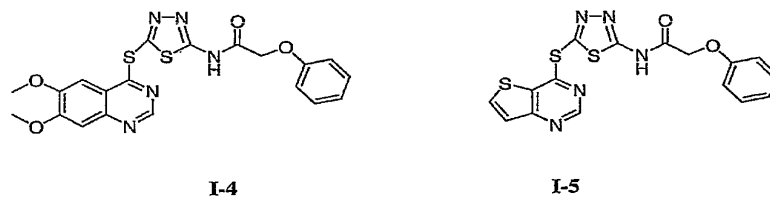
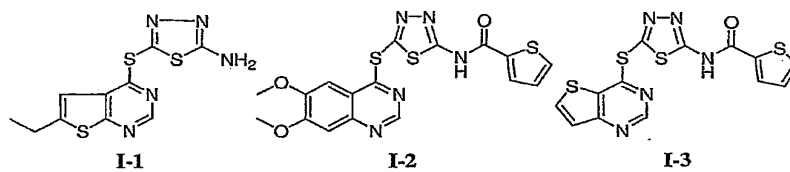
II, III IV

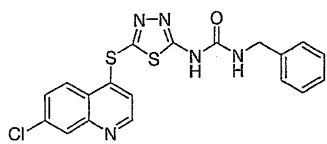
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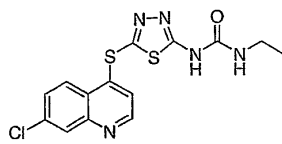
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화학식 I의 화합물의 예

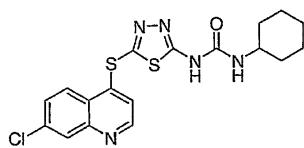




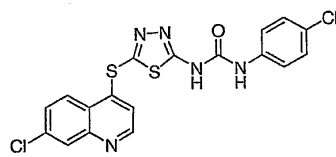
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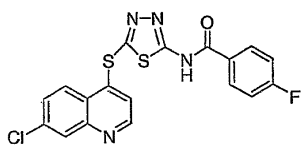
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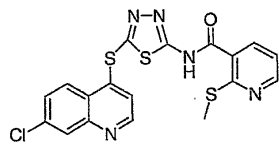
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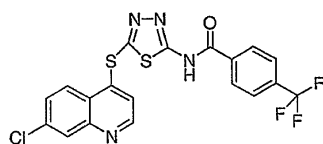
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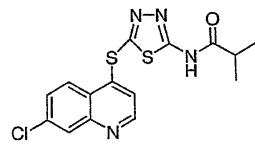
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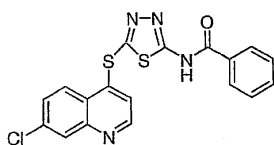
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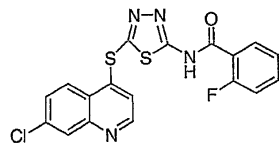
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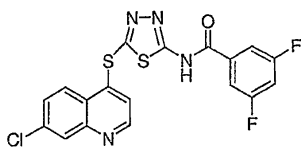
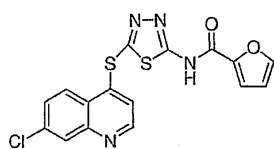
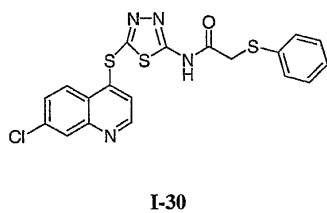
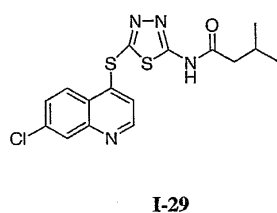
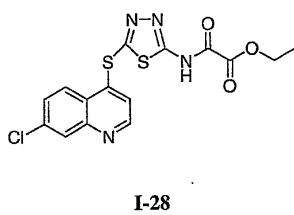
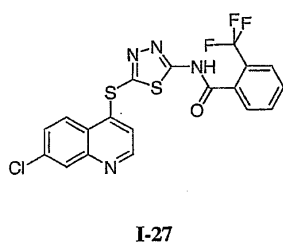
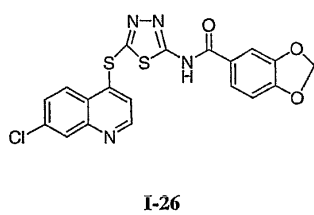
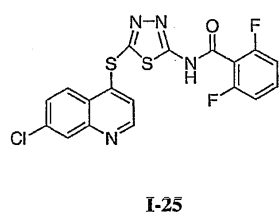
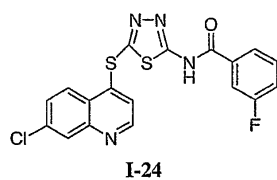
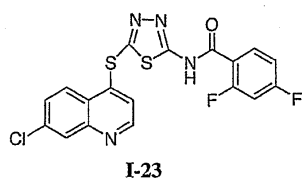
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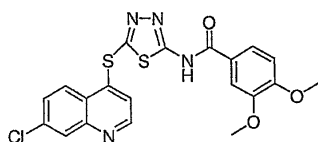
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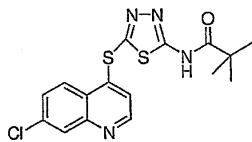
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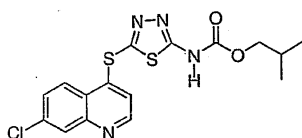
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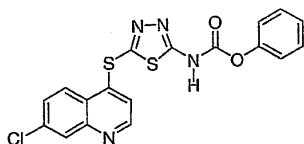
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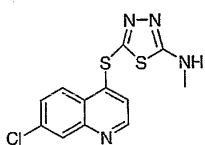
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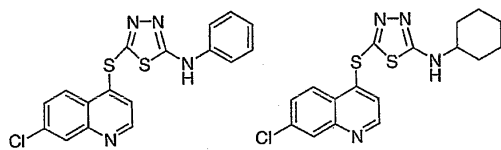
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I-35



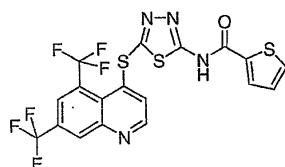
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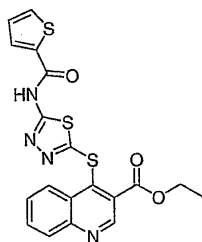
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I-38

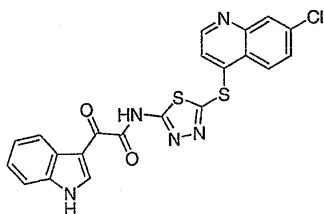
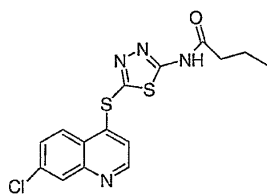
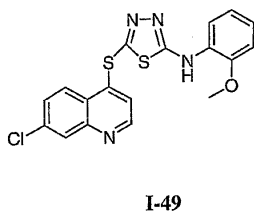
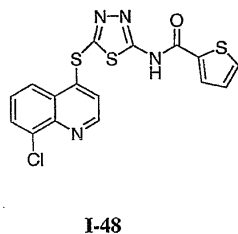
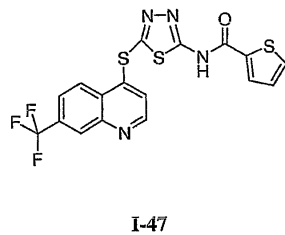
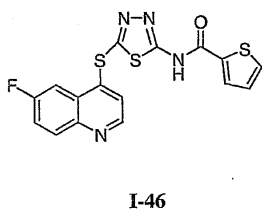
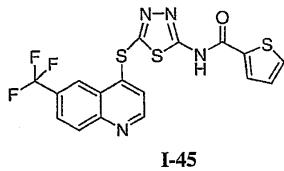
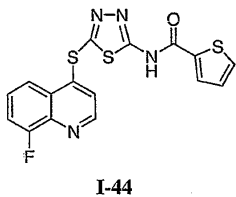
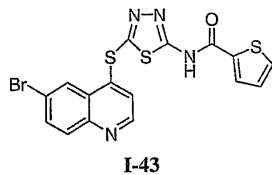
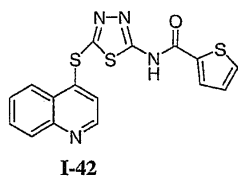
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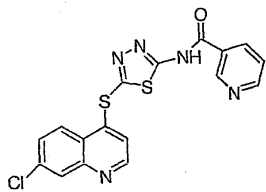
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I-41

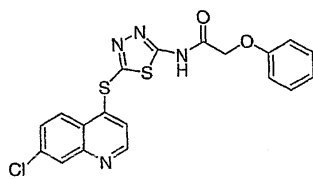


I-50

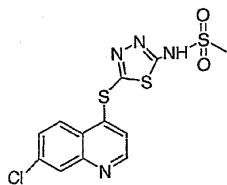


I-52

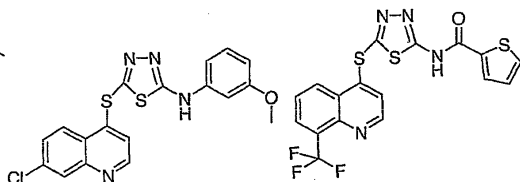
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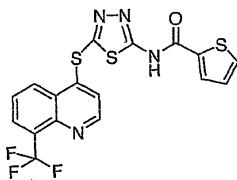
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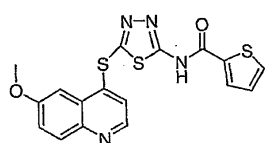
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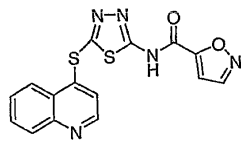
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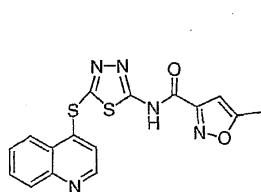
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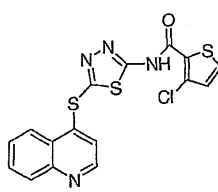
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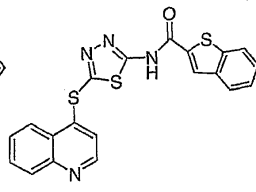
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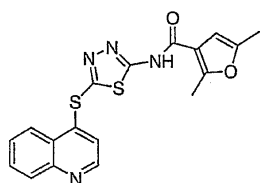
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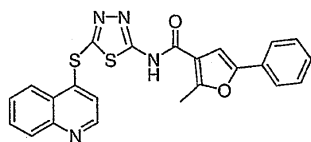
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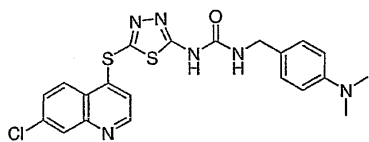
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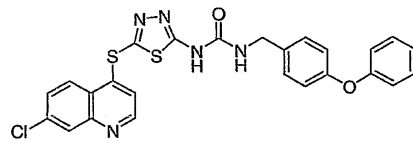
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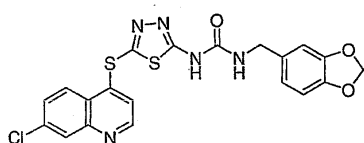
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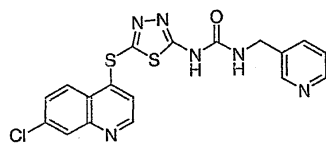
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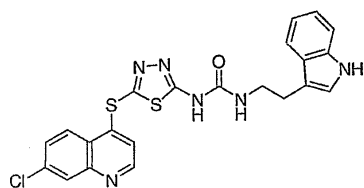
I-65



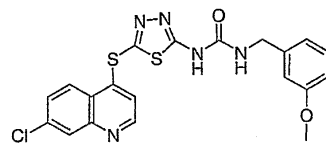
I-66



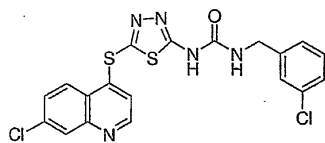
I-67



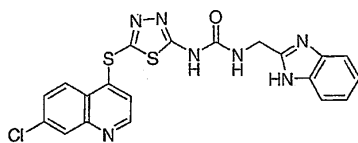
I-68



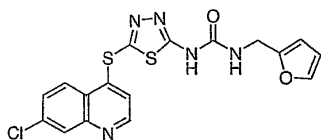
I-69



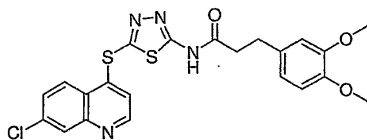
I-70



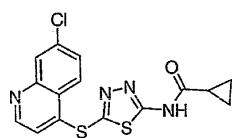
I-71



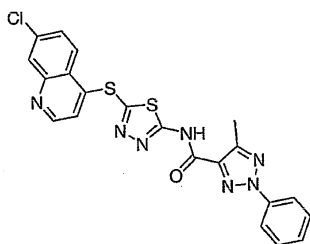
I-72



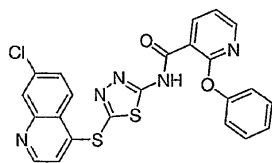
I-73



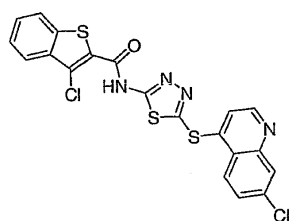
I-74



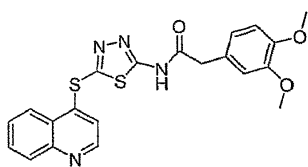
I-75



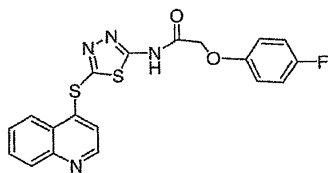
I-76



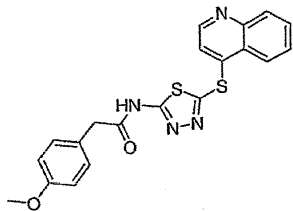
I-77



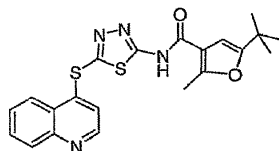
I-78



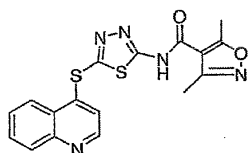
I-79



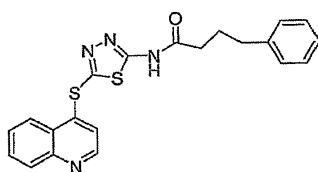
I-80



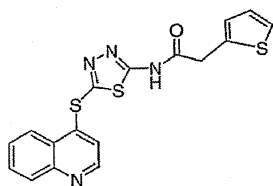
I-81



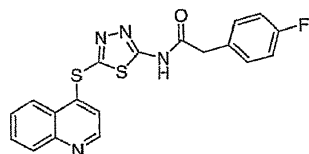
I-82



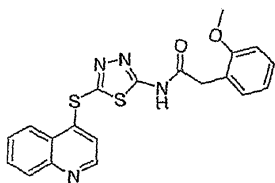
I-83



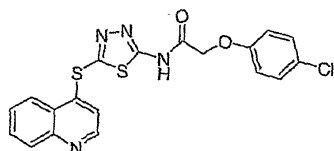
I-84



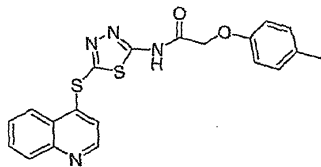
I-85



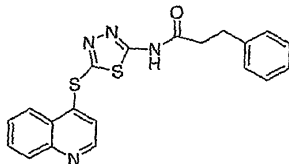
I-86



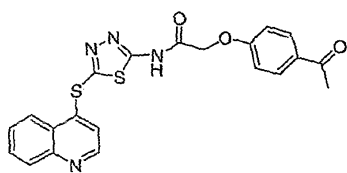
I-87



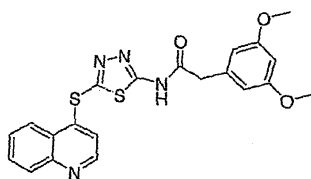
I-88



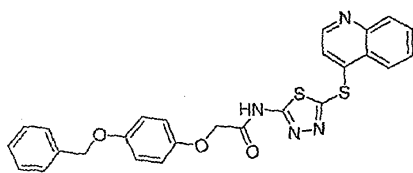
I-89



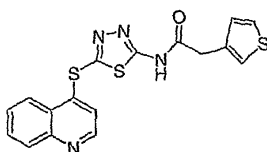
I-90



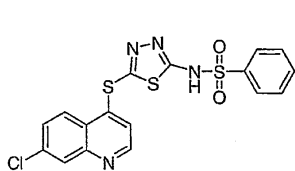
I-91



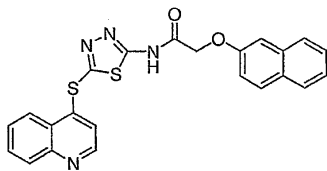
I-92



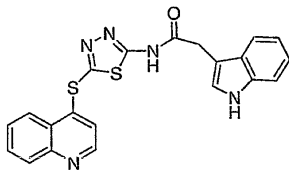
I-93



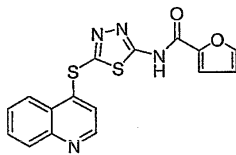
I-94



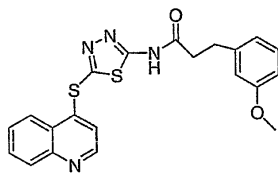
I-95



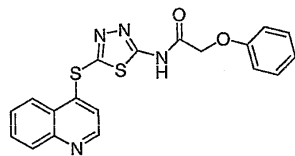
I-96



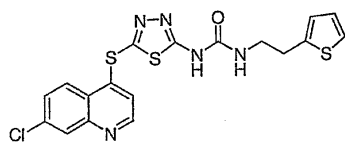
I-97



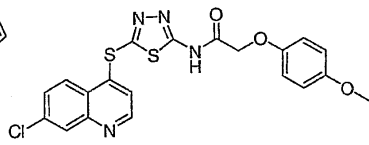
I-98



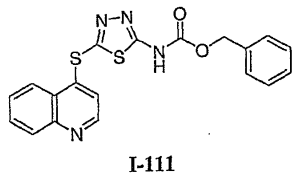
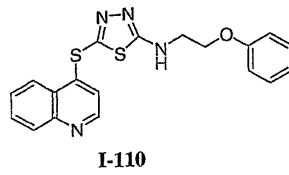
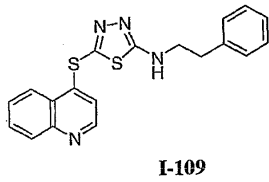
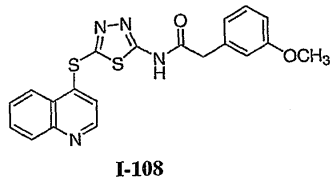
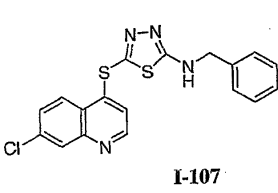
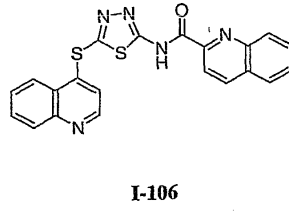
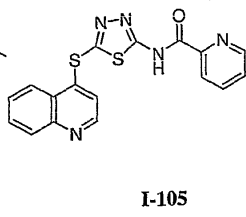
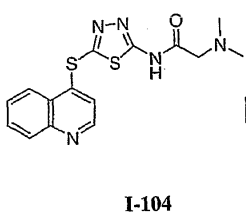
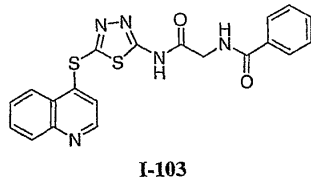
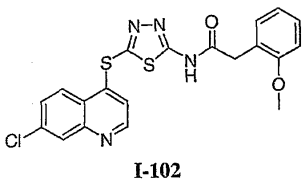
I-99



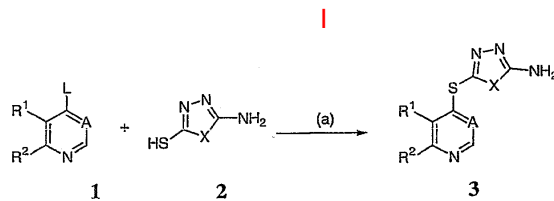
I-100



I-101

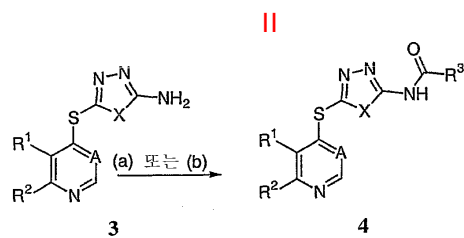


4. 가



: (a) NaH, DMF

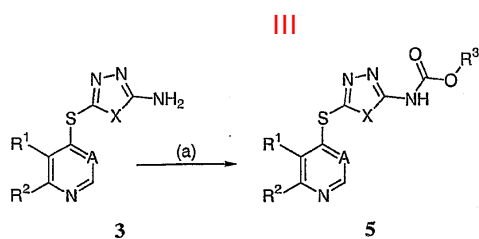
가 , Q가 가 , R³ (3) | (3)
 | (L) (2) | (3)
 가 , (L) | (3)



: (a) $R^3 C(O)Cl$, $Et_3 N$, $CH_3 CN$, ;

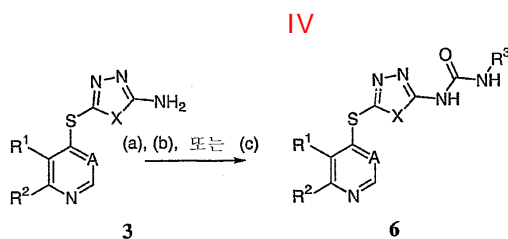
(b) $R^3 CO_2 H$, $EtOC(O)Cl$

II Q가 $R^3 C(O)Cl$ (4) (3) (b)
 , R^3 (4) (3)



: (a) $R^3 OC(O)Cl$,

III Q가 $-CO_2-$ $R^3 OC(O)Cl$ (5) (3)
 , R^3 (5)



: (a) $R^3 NCO$, $CH_3 CN$, ; (b) $PhOCOCl$, ;

(c) $R^3 NH_2$, DME ,

IV Q가 $-C(O)NH-$ $R^3 NCO$ (6) (3)

가 ; 가

가 , 가 50% 100%

(-)

6,099,562 , 5,886,026 5,304,121

가

JAK-3 ;

JAK-3 가

A)

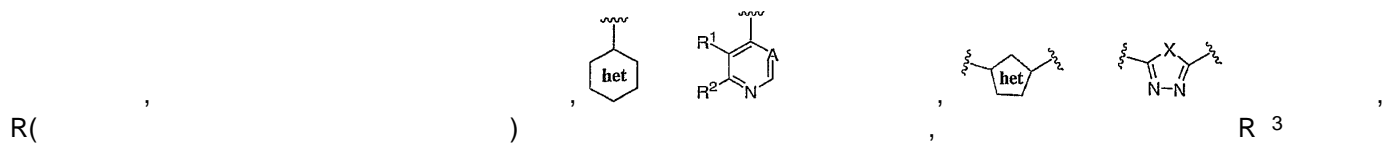
¹H NMR Bruker DPX 400 400MHz ¹³C NMR
 mass) ZQ 가 LC/MS HPLC Phenomenex C₁₈(2) Luna (Micro
 40 100MHz 1mg/ml 2ml/ (30 ×4.6mm) 1-5ml

0 , 80% H₂O-20%MeCN,
 2.5 , 0% H₂O-100%MeCN,
 3.5 , 0% H₂O-100%MeCN.

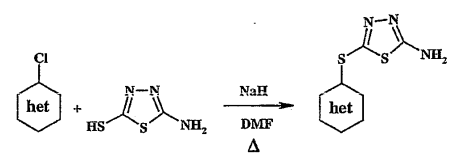
214 254 1 2

DMF 4 (Fisher Scientific)
 60(Fluka) TLC - Polygram SIL G/U
 V₂₅₄ (Macherey - Nagel)

B) :

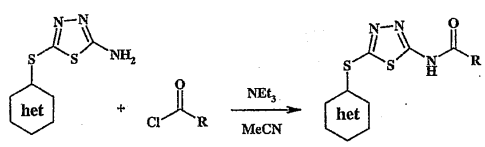


5- -[1,3,5] -2-



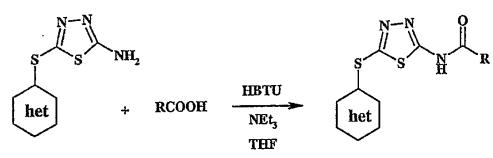
NaH(1.2mmol) DMF(8Mℓ) 5- -2- (1.1mmol) 가 (1.1m
 mol) 가 , 20 가 ,
 (20-40Mℓ) 가 80 90 () 18 가 ,
 O (25-96%). , Et₂O

A:



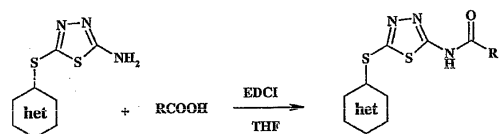
NEt₃ (0.45mmol) MeCN(9Mℓ) (0.3mmol) 가 , 0 가 80 ()
 (0.36mmol) 가 . 0 20 , 가
) 18 가 , 가
 Et₂O (~5Mℓ) ,
 (40-96%). Et₂O

B:

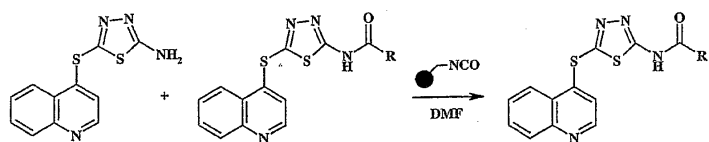


THF(15Mℓ) (0.34mmol) (0.37mmol) 가 NEt₃ (0.41mmol) 가 ,
 0 HBTU(0.37mmol) 가 . 0 40 ,
 가 50 60 () 18 가 ,
 (~40Mℓ) 가 , Et₂O
 (43-56%).

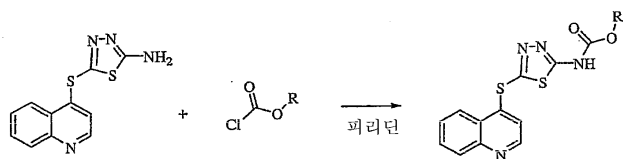
C



THF(15Mℓ) (0.39mmol) 18 (0.43mmol) 가 EDCI(0.78mmol) 가 (~40Mℓ) 가 (58-69%)
 60 가 , Et₂O)

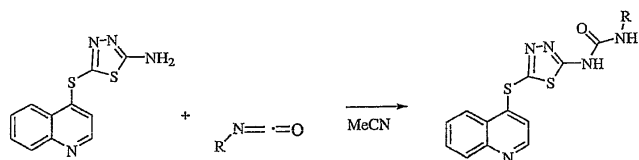


(0.15mmol), (¹H NMR (3) 가 , ~15%) DMF(2Mℓ) 50 60 18
 , Et₂O 가 DMF(3 x ~2Mℓ))



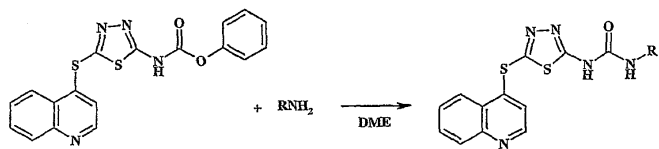
(0.33mmol) 0 (0.26mmol) 가
 가 가 48 (5Mℓ) 가 ,
 , Et₂O (41 72%)

A



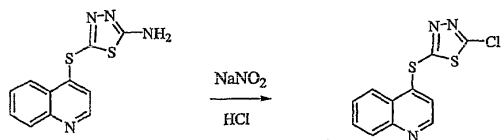
(0.29mmol) MeCN(10Mℓ) (0.22mmol) 가 가 70 75
 () 18 가
 , Et₂O (35-67%)

B



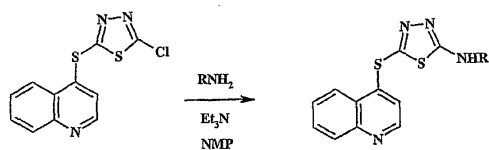
(0.19mmol) DME(10Mℓ) (0.15mmol) 가 ~80 ()
 18 가 . Et₂O 가 (14)
 63%).

4-(5- -[1,3,4] -2-)

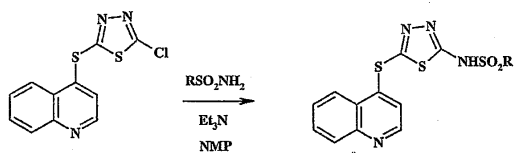


(4.93mmol) -10 HCl(20Mℓ), H₂O(4Mℓ) NaNO₂ (14.8mmol)
 가 0 가 H₂O(20Mℓ) 가 , K₂CO₃ 가 3 (EtOAc).
 가 (MgSO₄), (SiO₂, /
 , 1:1 v/v) (53-95%).

4-(5- -[1,3,4] -2-)

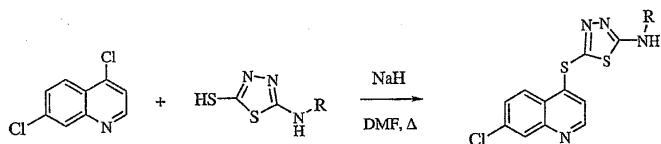


NMP(5Mℓ) (0.72mmol) , NEt₃ (0.8mmol) 가 (0.72mmol) 가 .
 72 70 { (stem block) } 가 .
 EtOAc/H₂O(20Mℓ, 1:1v/v) . (EtOA
 c). (MgSO₄), (SiO₂, /
 , 1:1 v/v) .



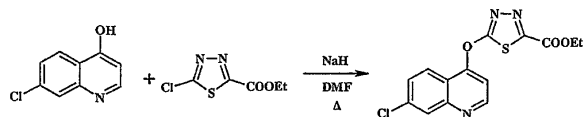
DMF(2Mℓ) (0.12mmol) , (0.14mmol) 가 K₂CO₃ (0.24mmol) 가
 72 70 () 가 EtOAc/H₂
 O(20Mℓ, 1:1 v/v) , pH2 (2M HCl) (EtOAc).
 (MgSO₄) (8-56%).

N- 5- -2- 4,7- -



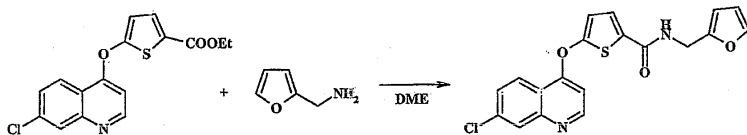
NaH(1.2mmol) 가 (20 40Mℓ) 가 70 () 가 DMF(8Mℓ) 20 N- 3 5- 18 가 (0.1mmol) (0.1mmol) Et₂O

5-(7- - 4-)-[1,3,4] -2-

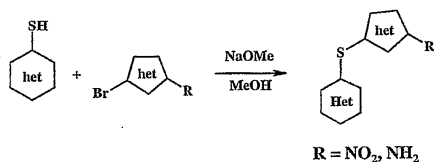


NaH(0.022mg, 0.5mmol) 가 (0.097mg, 0.5mmol) Et₂O DMF(6Mℓ) 20 7- 15 30Mℓ) 가 70 80 () 가 (0.093mg, 0.5mmol) 2- -[1,3,4] 18 가 (0.081mg, 47%)

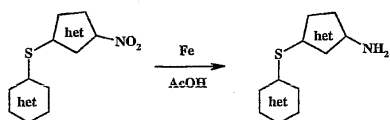
(7- - 4-)-[1,3,4] -2- (-2-)-



(0.042mg, 12.0mmol) 18 가 DME(4Mℓ) (0.035mg, 0.36mmol) Et₂O 가 (0.035mg, 75%) 80

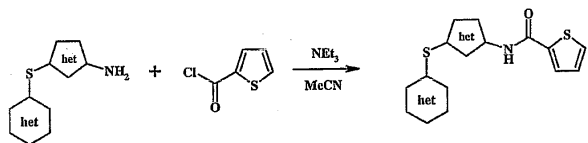


NaOMe(19.2mmol) 0 가 18 가 (SiO₂, Et₂O) MeOH(15Mℓ) 0 10 (16mmol) (16mmol) 가 45 50 4



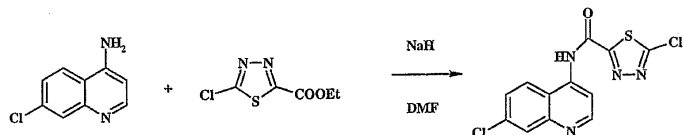
Fe(0.22g, 3.9mmol) 80 () H₂O NaOH (2M) (SiO₂, Et₂O) AcOH(3Mℓ) 10 가 2- (EtOAc), (MgSO₄) (0.1g, 0.3mmol) 가 (Na₂CO₃) (EtOAc)

-2-



(SiO₂, Et₂O) (A) (18 62%)

5- [1,3,4] -2- (7- -4-)-

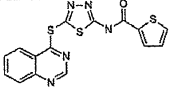
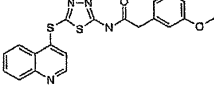
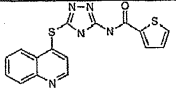
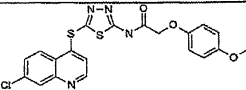
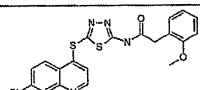
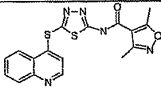
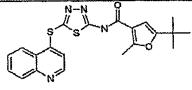
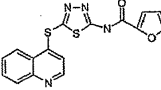
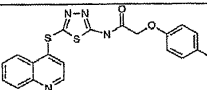
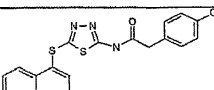


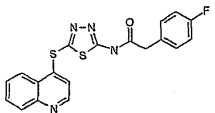
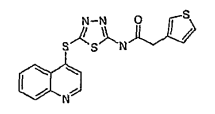
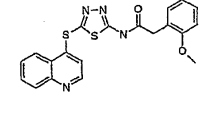
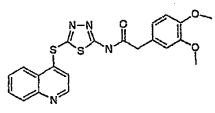
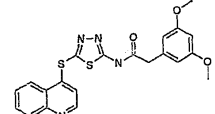
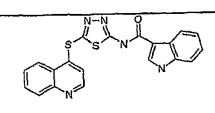
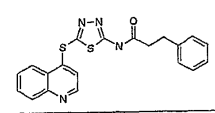
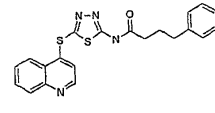
NaH(0.023g, 0.58mmol) DMF(6Mℓ) 4- -7- (0.1g, 0.56mmol)
 가 20 5- -[1,3,4] (0.108g, 0.56m
 mol) 가 80 () 18 가
 (15Mℓ) 가 , Et₂O
 (0.08g, 60%)

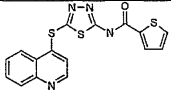
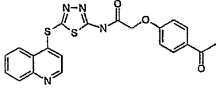
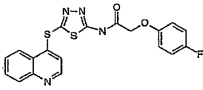
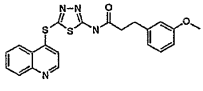
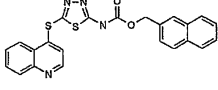
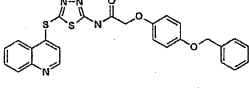
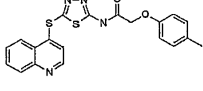
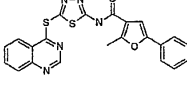
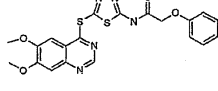
LCMS 가 2

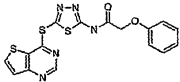
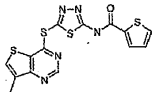
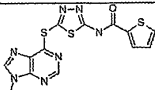
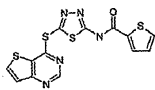
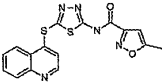
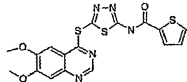
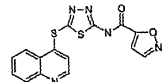
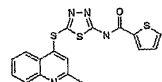
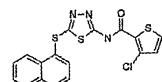
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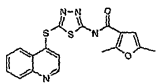
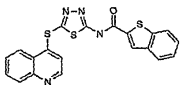
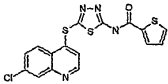
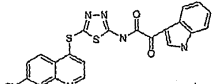
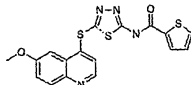
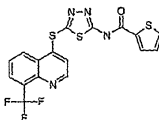
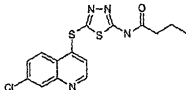
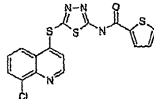
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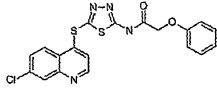
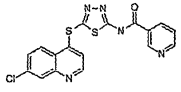
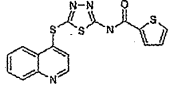
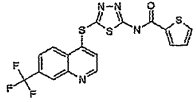
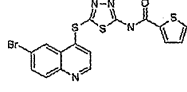
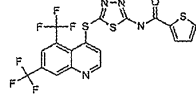
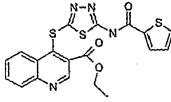
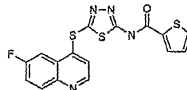
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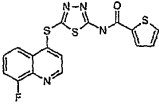
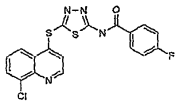
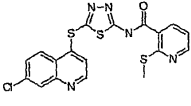
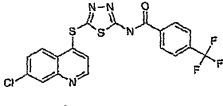
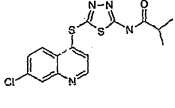
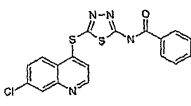
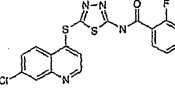
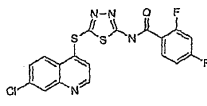
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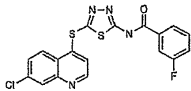
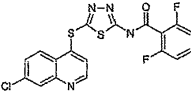
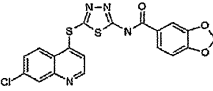
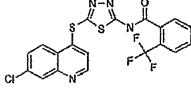
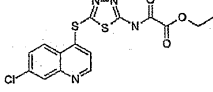
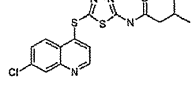
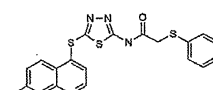
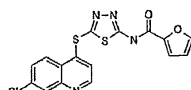
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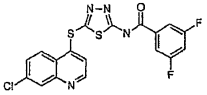
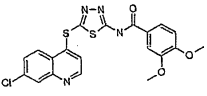
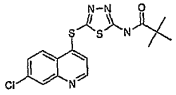
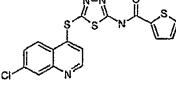
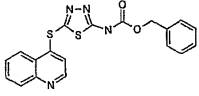
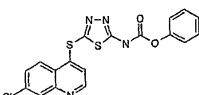
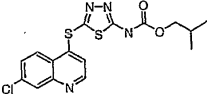
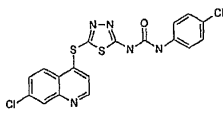
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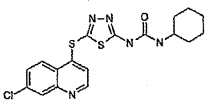
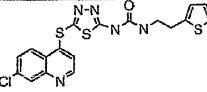
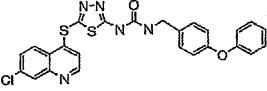
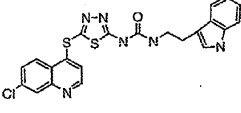
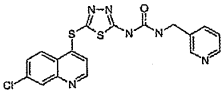
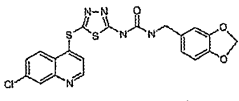
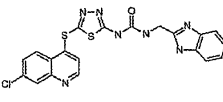
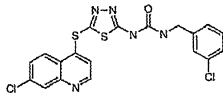
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|  | 365 |
|  | 405 |

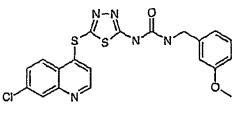
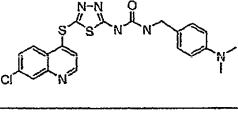
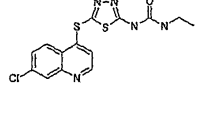
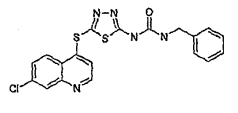
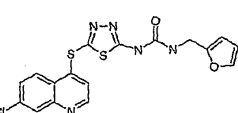
| | |
|---|-----|
|  | 429 |
|  | 400 |
|  | 371 |
|  | 439 |
|  | 550 |
|  | 507 |
|  | 443 |
|  | 389 |

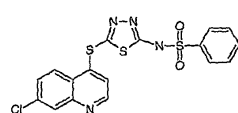
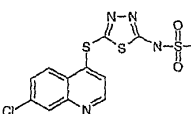
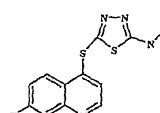
| | |
|---|-----|
|  | 389 |
|  | 417 |
|  | 446 |
|  | 467 |
|  | 365 |
|  | 399 |
|  | 417 |
|  | 435 |

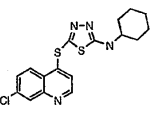
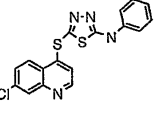
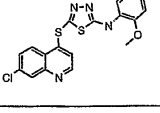
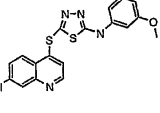
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|---|-----|
|  | 417 |
|  | 435 |
|  | 443 |
|  | 467 |
|  | 395 |
|  | 379 |
|  | 445 |
|  | 389 |

| | |
|---|-----|
|  | 435 |
|  | 459 |
|  | 379 |
|  | 405 |
|  | 395 |
|  | 415 |
|  | 395 |
|  | 448 |

| | |
|---|-----|
|  | 420 |
|  | 448 |
|  | 520 |
|  | 481 |
|  | 429 |
|  | 472 |
|  | 468 |
|  | 462 |

| | |
|---|-----|
|  | 458 |
|  | 471 |
|  | 366 |
|  | 428 |
|  | 418 |

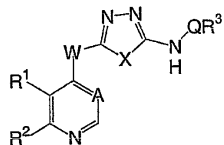
| | |
|---|-----|
|  | 435 |
|  | 373 |
|  | 309 |

| | |
|---|------|
| | |
|  | 381 |
|  | 3.71 |
|  | 401 |
|  | 401 |

JAK
 JAK [: G.R. Brown, et al. Med. Bioorg. Chem. Lett. 2000, vol.10, pp 575-579]
 (Glu, Ala, Tyr) 6:3:1 4
 0.05% Tween(PBST) Maxisorb 2 μ M ATP, 5mM MgCl₂ DMSO
 가 , JAK 30 60
 PBST , 100μℓ HRP- 4G10 가 , 30 90
 PBST , 100μℓ TMB 가 , 30
 30 (1M 100μℓ) 가 450nm
 , IC₅₀
 (1) JAK 2 μ M IC
 50
 (1) JAK 2 5
 μ M IC₅₀

(57)

1.



W X ,
 A , CH, C-CN C-(C₁₋₃) ,
 R¹ R² , 0 3 ,
 3 7 ,
 Q , -C(O)-, -C(O)NR-, -C(O)C(O)-, -CO₂-, -C(O)CO₂-, -SO₂- C₁₋₆
 , Q₁ Q₂ -O-, -S-, -NR-, -C(O)-, -
 CO₂-, -C(O)NR-, -OC(O)NR-, -NRC(O)-, -NRCO₂-, -NRC(O)NR-, -S(O)-, -SO₂-, NRSO₂-, -SO₂N
 R- NRSO₂ NR- ,
 R C₁₋₆ , 2 R
 , 0 2
 , 3 7 ,
 R³ R Ar ,
 Ar 3 8 8 10 1 3 3 7
 (a), 1 3 5 6
 (b) 8 10 (c) 1 4 ,
 , 3- - [b] -2- [5-(7- - -4-)-[1,3,4] -2-] ,

N-[5-(7- -4-)-[1,3,4] -2-]-2- ,
 5- -2- -2H-[1,2,3] -4- [5-(7- -4-)-[1,3,4] -2-]
 ,
 [5-(7- -4-)-[1,3,4] -2-]- ,
 N- [5-(7- -4-)-[1,3,4] -2-] ,
 -2- [5-(7- -4-)-[1,3,4] -2-] ,
 5-(6- - [2,3-d] -4-)-[1,3,4] -2- ,
 5-(2- - [2,3-d] -4-)-[1,3,4] -2- ,
 2- -N-[5-(7- -4-)-[1,3,4] -2-]-2- - ,
 4- -2- -2,3- - -3- [5-(7- -4-)-[1,3,4]
 -2-] ,
 5-[(7- [3,2-d] -4-)]-1,3,4- -2-
 N[5-(1H- -6-)-1,3,4- -2-]
 .

2.

1 , R¹ R²가 , 0 2
 , 5 7 .

3.

2 , R¹ R²가 , , , , , .

4.

1 , Q가 , -C(O)-, -C(O)NR-, -CO₂, -C(O)CO₂-, -SO₂-
 CO₂- -SO₂- , Q₁ 1 2 가 C₁₋₄ -O-, -S-, -NR-, -C(O)-, -

5.

1 , R³ C₁₋₆ , 3 6 (a),
) 9 10 , (c) 1 2 3 5 6 (b)
 5 6

6.

5 , R³ , , , , , 3 , [1,3] , ,

7.

1 6 , W가 .

8.

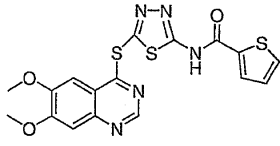
7 , X가 .

9.

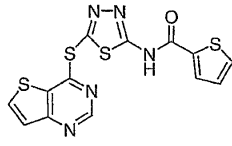
8 , A가 .

8 10. , A가 CH

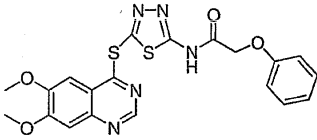
11.



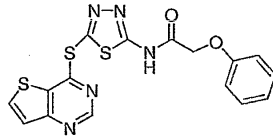
I-2



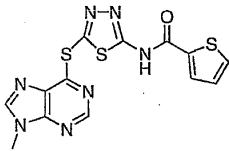
I-3



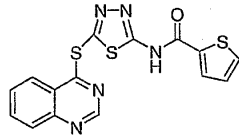
I-4



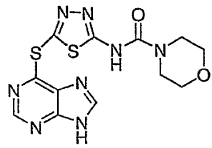
I-5



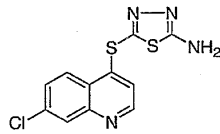
I-7



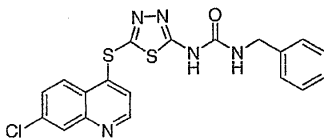
I-8



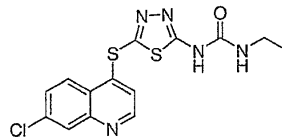
I-9



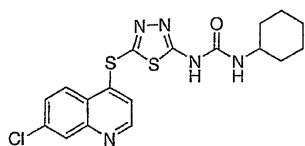
I-10



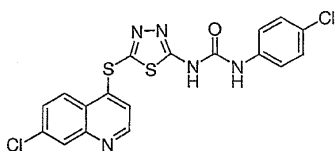
I-13



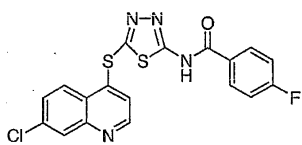
I-14



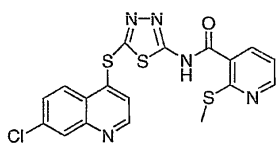
I-15



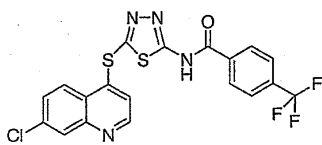
I-16



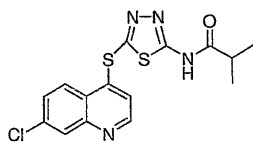
I-17



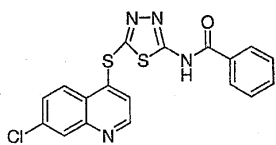
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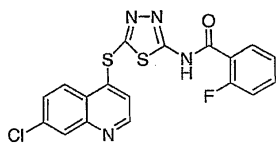
I-19



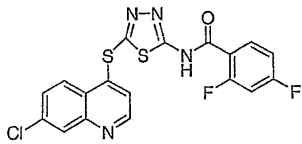
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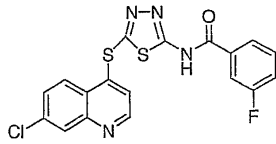
I-21



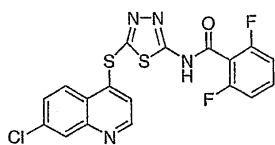
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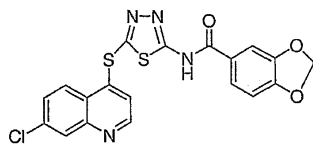
I-23



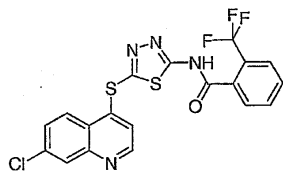
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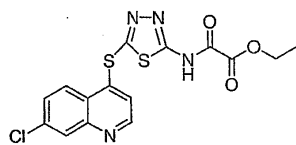
I-25



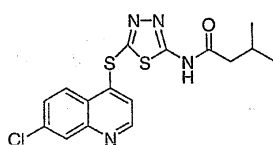
I-26



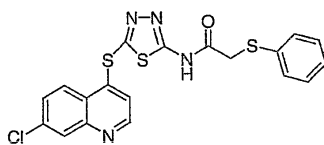
I-27



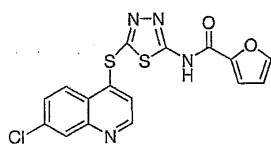
I-28



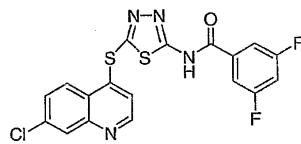
I-29



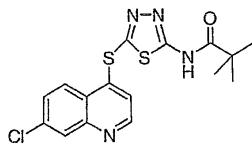
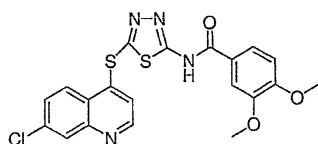
I-30



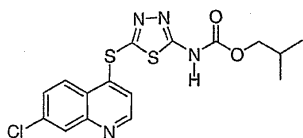
I-31



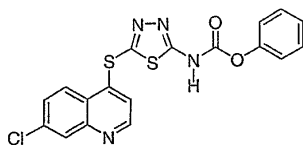
I-32



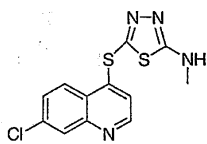
I-33



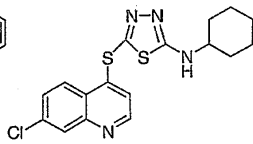
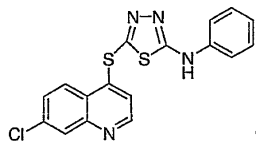
I-34



I-35



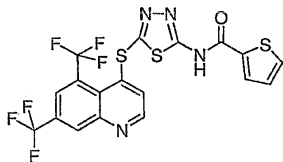
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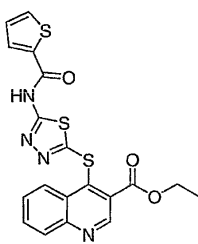
I-37

I-38

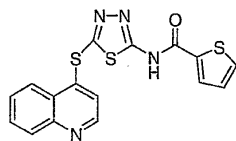
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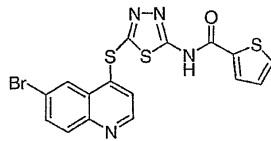
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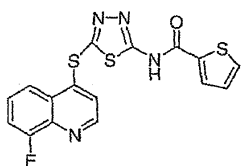
I-41



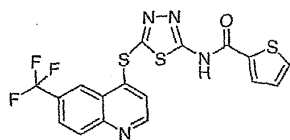
I-42



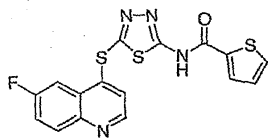
I-43



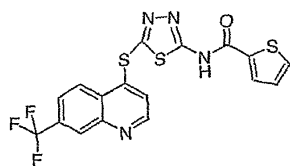
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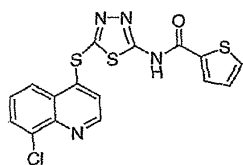
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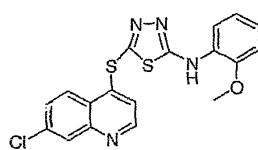
I-46



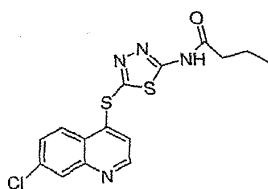
I-47



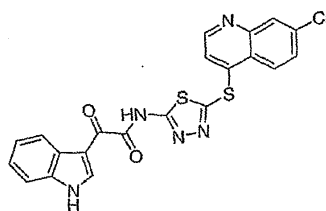
I-48



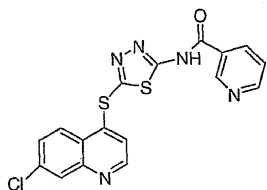
I-49



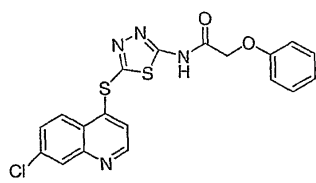
I-50



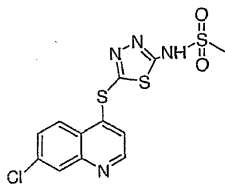
I-51



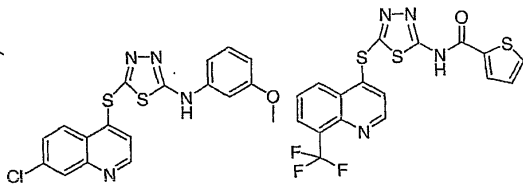
I-52



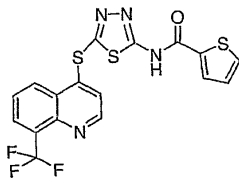
I-53



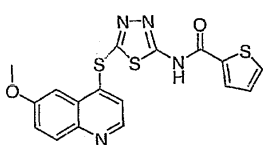
I-54



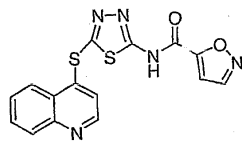
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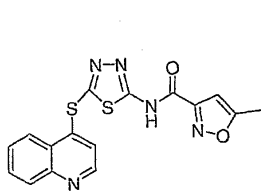
I-56



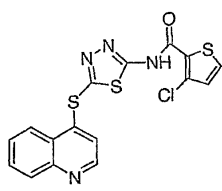
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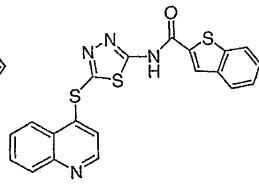
I-58



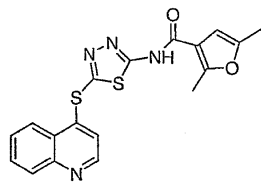
I-59



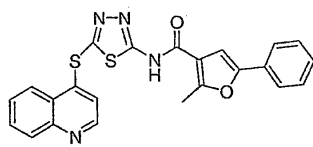
I-60



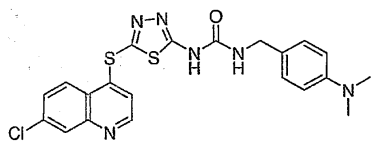
I-61



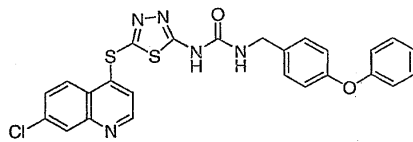
I-62



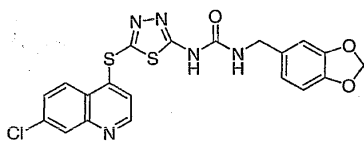
I-63



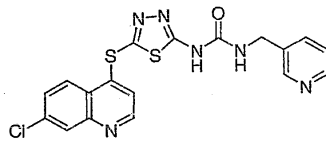
I-64



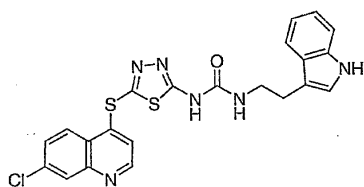
I-65



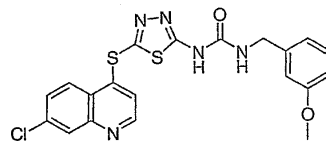
I-66



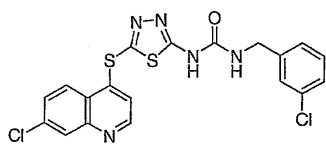
I-67



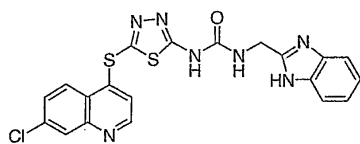
I-68



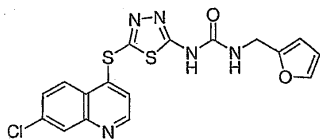
I-69



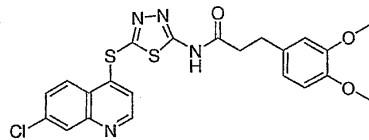
I-70



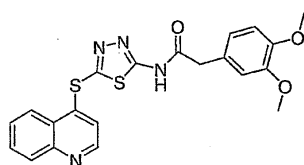
I-71



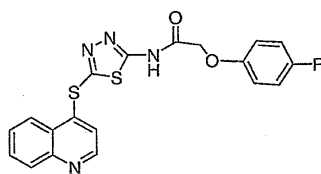
I-72



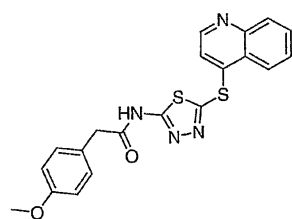
I-73



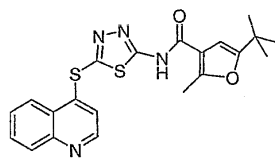
I-78



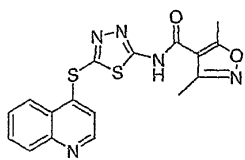
I-79



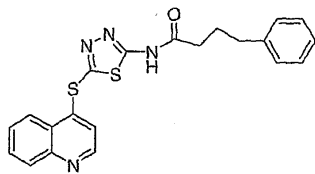
I-80



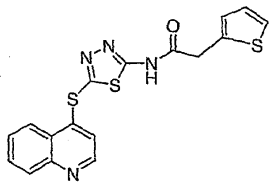
I-81



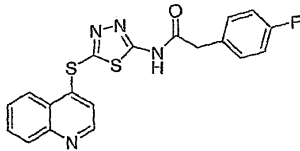
I-82



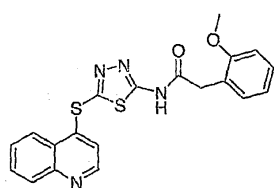
I-83



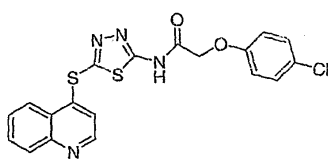
I-84



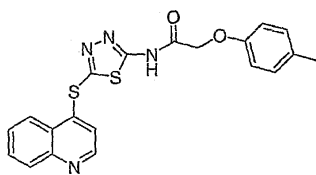
I-85



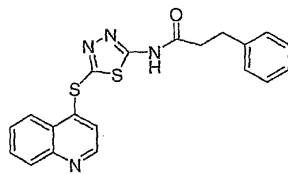
I-86



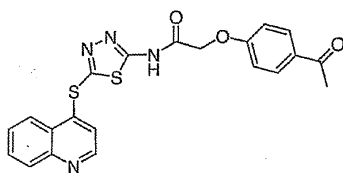
I-87



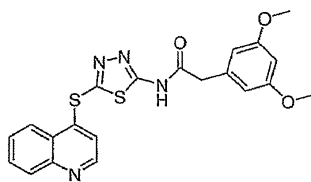
I-88



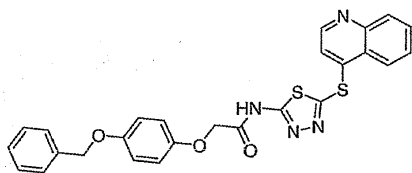
I-89



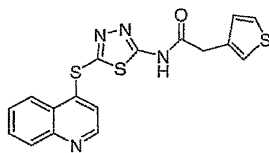
I-90



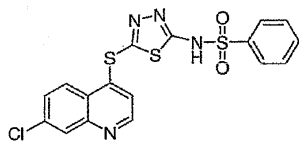
I-91



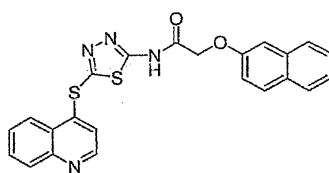
I-92



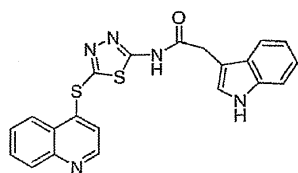
I-93



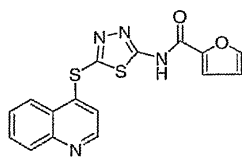
I-94



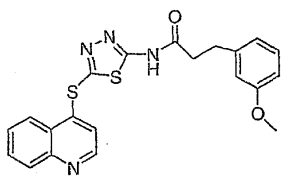
I-95



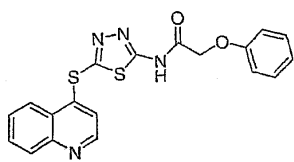
I-96



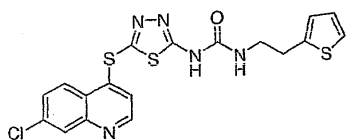
I-97



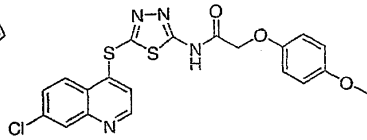
I-98



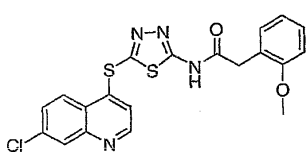
I-99



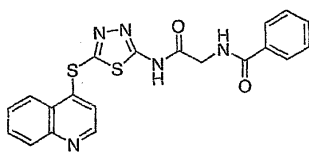
I-100



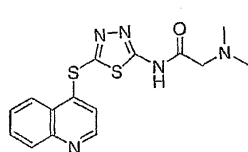
I-101



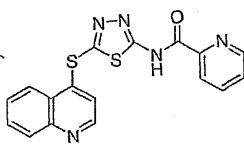
I-102



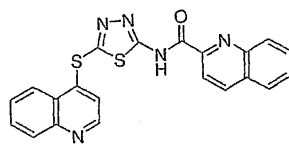
I-103



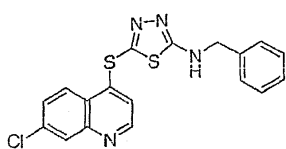
I-104



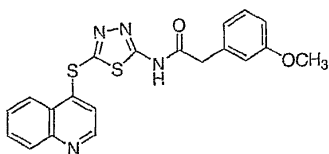
I-105



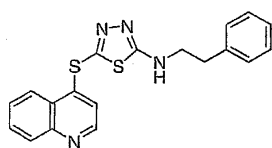
I-106



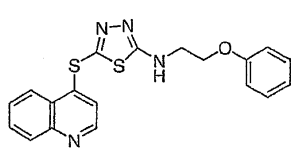
I-107



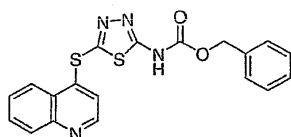
I-108



I-109

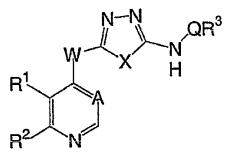


I-110



I-111

12.



I ,

W X ,

A , CH, C-CN C-(C₁₋₃) ,

R¹ R² , 0 3 ,
3 7 ,

Q , -C(O)-, -C(O)NR-, -C(O)C(O)-, -CO₂-, -C(O)CO₂-, -SO₂- C₁₋₆
Q₁ Q₂ -O-, -S-, -NR-, -C(O)-, -
CO₂-, -C(O)NR-, -OC(O)NR-, -NRC(O)-, -NRCO₂-, -NRC(O)NR-, -S(O)-, -SO₂-, NRSO₂-, -SO₂N
R- NRSO₂NR- ,

R C₁₋₆ , 0 2 R
3 7 ,

R³ R Ar ,

Ar₃ 8 8 10 1 3 3 7
(a), , 1 4 5 6
(b) 8 10 (c) ,

13.

12 , R¹ R²가 , 0 2
5 7 .

14.

12 , Q가 , -C(O)-, -C(O)NR-, -CO₂-, -C(O)CO₂-, -SO₂- C₁₋₄
Q₁ Q₂ 가 -O-, -S-, -NR-, -C(O)-,
-CO₂- -SO₂- .

15.

12 , R³ C₁₋₆ , 3 6 (a),
(b)
) 9 10 (c) 1 2 3 5 6 6

16.

12 15 , W가 .

17.

16 , X가 .

18.

16 , A가 .

19.

16 , A가 CH .

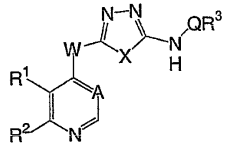
20.

12 가 , , , 가

21.

12 , (a) (b) JAK-3 .

I



I ,

W X ,

A , CH, C-CN C-(C₁₋₃) ,

R¹ R² , 0 3 ,
3 7 ,

Q , -C(O)-, -C(O)NR-, -C(O)C(O)-, -CO₂-, -C(O)CO₂-, -SO₂- C₁₋₆
Q₁ Q₂ -O-, -S-, -NR-, -C(O)-, -
CO₂-, -C(O)NR-, -OC(O)NR-, -NRC(O)-, -NRCO₂-, -NRC(O)NR-, -S(O)-, -SO₂-, NRSO₂-, -SO₂N
R- NRSO₂NR-

R , C₁₋₆ , 0 2 R
3 7 , 2

R³ R Ar ,

Ar 3 8 8 10 1 3 3 7
(a), , 1 4 5 6
(b) 8 10 (c) , .

22.

12 , 가 ,

23.

22 , 가 , 가 I , , (FALS), .

24.

22 , , 가 , 가 가 , 12