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(10) CN 108358838 B
(45) 2021.05.18

(21) 201810385395.X
(22) 2018.04.26
(65)
CN 108358838 A
(43) 2018.08.03
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(51) Int.Cl.
C07D 215/12(2006.01)
C07D 215/14(2006.01)
C07D 405/12(2006.01)
C07D 409/12(2006.01)
A61P 35/00(2006.01)
A61P 3/10(2006.01)
A61P 3/04(2006.01)
(56)
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权利要求书1页 说明书11页

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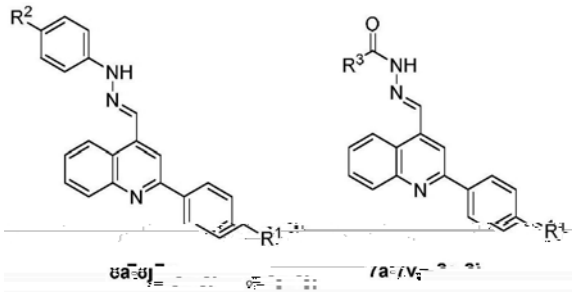

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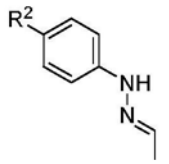
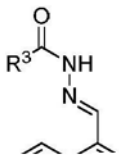
1. 25B





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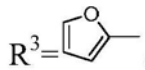
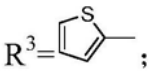
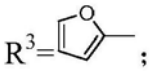
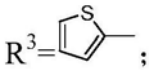
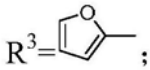
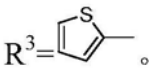
8a R^1 F  ; 8b R^1 F  ; 8c R^1 F R^3 Ph 8d R^1 F R^3 o-OHPh- 8e R^1 H  ; 8f R^1 H  ; 8g R^1 F R^3 o-OHPh- 8h R^1 F R^3 Ph 8i R^1 CF_3  ; 8j R^1 CF_3  。

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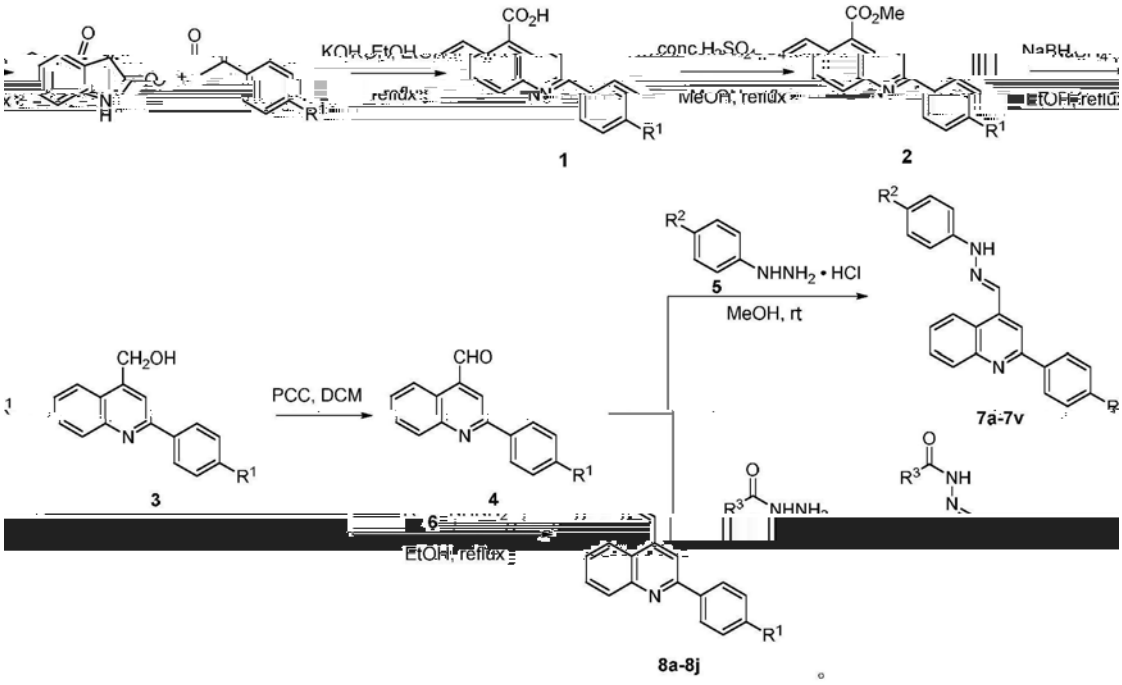

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[0017]

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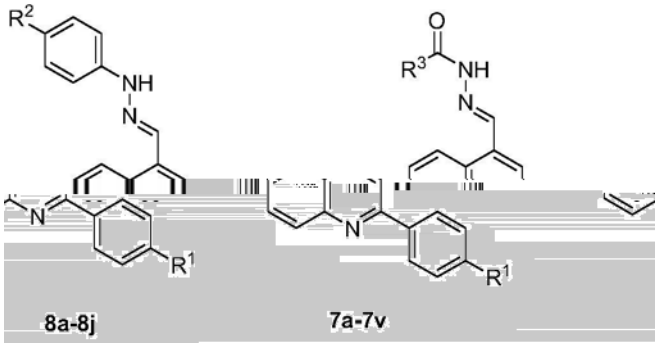
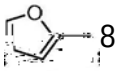
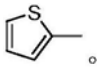
[0018]

[0019] 

[0020] 7a R^1 F R^2 H 7b R^1 F R^2 OCH_3 7c R^1 F R^2 CH_3 7d R^1 F R^2 F 7e R^1 F R^2 Cl 7f R^1 F R^2 CN 7g R^1 F R^2 CF_3 7h R^1 F R^2 NO_2 7i R^1 H R^2 H 7j R^1 H R^2 NO_2 7k R^1 H R^2 OCH_3 7l R^1 H R^2 CH_3 7m R^1 H R^2 F 7n R^1 H R^2 Cl 7o R^1 H R^2 CF_3 7p R^1 CF_3 R^2 OCH_3 7q R^1 CF_3 R^2 NO_2 7r R^1 CF_3 R^2 CH_3 7s R^1 CF_3 R^2 F 7t R^1 CF_3 R^2 Cl 7u R^1 CF_3 R^2 CF_3 7v R^1 CF_3 R^2 H

[0021] 8a R^1 F R^3  ; 8b R^1 F R^3  ; 8c R^1 F R^3 Ph 8d R^1 F R^3 o-OHPh- 8e R^1 H R^3  ; 8f R^1 H R^3  ; 8g R^1 F R^3 o-OHPh- 8h R^1 F R^3 Ph 8i R^1 CF_3 R^3  8j R^1 CF_3 R^3  。

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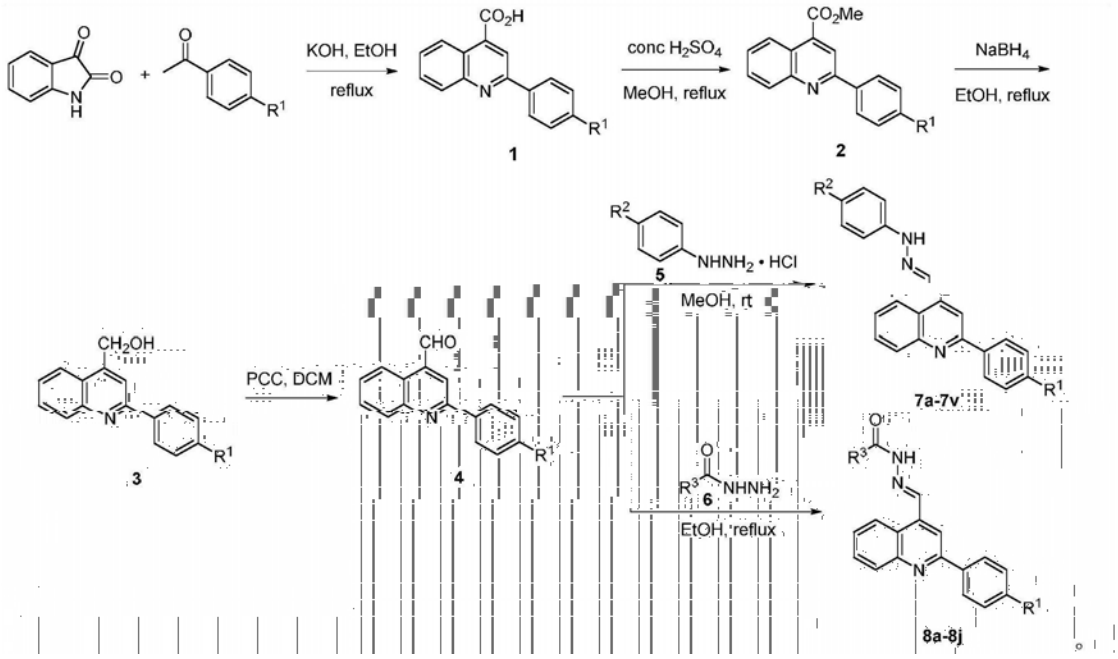
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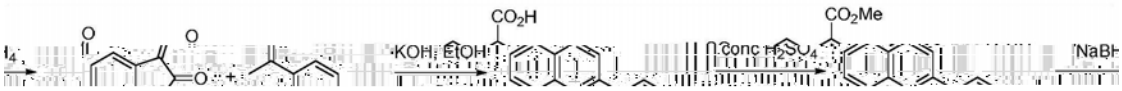

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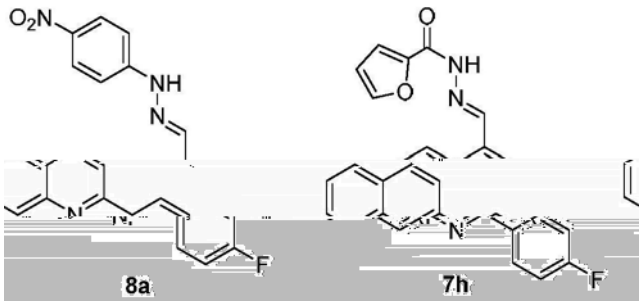
[0032] 

[0033] 1.1 2-(4-) -4- 1a

[0034] 250mL 50mmol 2,3- 60mmol 4- 20mL 35mL 34wt KOH 80 TLC 2M 1a 85

[0035] 1.2 2-(4-) -4- 2a

[0036] 100mL 20mmol 2-(4-) -4- 20mL 5mL 75 TLC 20mL PH (5×30mL) (/ 150/1) 2a 87

[0037] 1.3 (2-(4-) -4-) 3a

[0038] 100mL 15mmol 2-(4-) -4- 45mmol 50mL 80 TLC 50mL 3a 92

[0039] 1.4 (2-(4-) -4-) 4a

[0040] 250mL 13mmol (2-(4-) -4-) 26mmol

100mL TLC
(/ 25/1) 4a
30

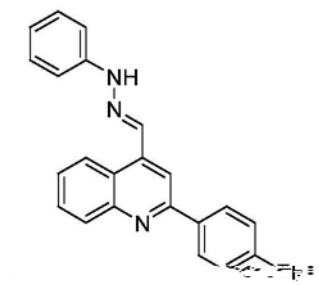
[0041] 1.5 (E)-2-(4-)-4-((2-(4-))) 7h

[0042] 25mL 0.15mmol(2-(4-) -4-) 4a 4-
5mL TLC
10mL, 7h

[0043] 1.6 (E)-N'-((2-(4-) -4-)) -2- 8a

[0044] 25mL 0.15mmol(2-(4-) -4-) 4a 2-
5mL 80 TLC
10mL 8a

[0045]



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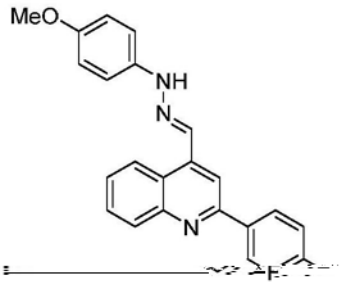

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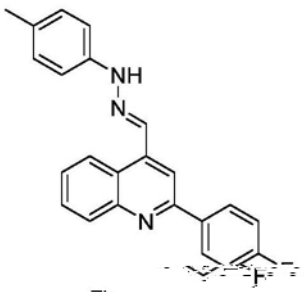
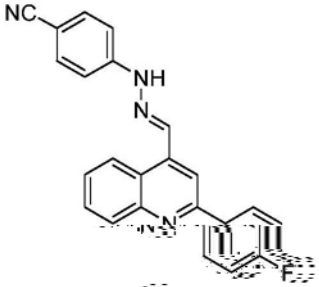
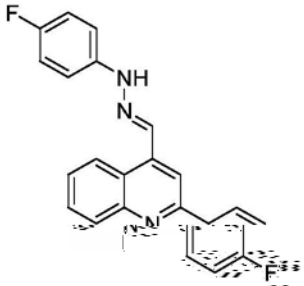


7b

[0046]



7f



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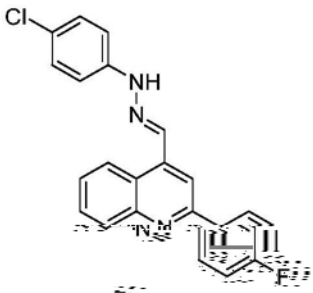

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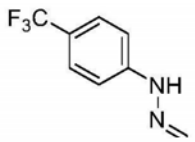
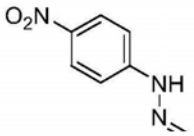
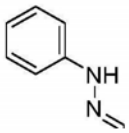

[0047]

[0048]

[0049] (E)-2-(4-)-4-((2-)) (7a): 88 .m.p.116-118 ^{1}H NMR(600MHz,DMSO-d_6)δ11.00(s,1H),8.75(d,J 8.3Hz,1H),8.54(s,1H),8.38(dd,J 8.7,5.6Hz,2H),8.32(s,1H),8.10(d,J 8.2Hz,1H),7.81(t,J 7.1Hz,

1H) ,7 .70(dd ,J 11 .2 ,3 .9Hz ,1H) ,7 .40(t ,J 8 .8Hz ,2H) ,7 .32(t ,J 7 .8Hz ,2H) ,7 .24(d , J 7 .7Hz ,2H) ,6 .87(t ,J 7 .2Hz ,1H) .HRMS(ESI)m/z calcd .for $C_{26}H_{16}FN_3$([M+H]$^+$) 342 .1401 ,found:342 .1401

[0050] (E)-2-(4-)-4-((2-(4-))) (7b):

85 .m .p .220-222 ^{1}H NMR(400MHz ,DMSO-d_6)δ11 .70(s ,1H) ,8 .73(d ,J 8 .4Hz ,1H) , 8 .54(s ,1H) ,8 .34(s ,1H) ,8 .25(dd ,J 15 .9 ,7 .3Hz ,3H) ,7 .99(t ,J 7 .7Hz ,1H) ,7 .82(t ,J 7 .7Hz ,1H) ,7 .51(t ,J 8 .8Hz ,2H) ,7 .29(d ,J 8 .9Hz ,2H) ,6 .96(d ,J 8 .9Hz ,2H) ,3 .74 (s ,3H) .HRMS(ESI)m/z calcd .for $C_{23}H_{18}FN_3O$([M+H]$^+$)372 .1507 ,found:372 .1508

[0051] (E)-2-(4-)-4-((2-(4-))) (7c):

71 .m .p .216-218 ^{1}H NMR(400MHz ,DMSO-d_6)δ11 .69(s ,1H) ,8 .73(d ,J 8 .5Hz ,1H) , 8 .61(s ,1H) ,8 .33(dd ,J 19 .2 ,10 .5Hz ,4H) ,7 .98(t ,J 7 .4Hz ,1H) ,7 .83(t ,J 7 .4Hz , 1H) ,7 .52(t ,J 8 .6Hz ,2H) ,7 .24(d ,J 8 .1Hz ,2H) ,7 .16(d ,J 8 .2Hz ,2H) ,2 .27(s ,3H) .HRMS(ESI)m/z calcd .for $C_{23}H_{18}FN_3$([M+H]$^+$)356 .1558 ,found:356 .1556

[0052] (E)-2-(4-)-4-((2-(4-))) (7d):

63 .m .p .127-129 ^{1}H NMR(400MHz ,DMSO-d_6)δ11 .36(s ,1H) ,8 .73(d ,J 8 .5Hz ,1H) ,8 .62 (s ,1H) ,8 .41-8 .35(m ,3H) ,8 .11(d ,J 7 .9Hz ,1H) ,7 .85-7 .80(m ,1H) ,7 .72-7 .68(m ,1H) , 7 .64(d ,J 8 .5Hz ,2H) ,7 .44-7 .35(m ,5H) .HRMS(ESI)m/z calcd .for $C_{22}H_{15}F_2N_3$([M+H]$^+$) 360 .1307 ,found:360 .1316

[0053] (E)-2-(4-)-4-((2-(4-))) (7e):

79 .m .p .248-250 ^{1}H NMR(400MHz ,DMSO-d_6)δ11 .63(s ,1H) ,8 .79-8 .58(m ,2H) ,8 .49-8 .19(m ,4H) ,7 .95(s ,1H) ,7 .81(s ,1H) ,7 .49(s ,2H) ,7 .35(d ,J 18 .2Hz ,4H) .HRMS(ESI)m/z calcd .for $C_{22}H_{15}FClN_3$([M+H]$^+$)376 .1011 , ,found:376 .1011

[0054] (E)-4-(2-((2-(4-) -4-))) (7f):

64 .m .p .250-252 ^{1}H NMR(400MHz ,DMSO-d_6)δ11 .63(s ,1H) ,8 .72(d ,J 8 .1Hz ,1H) ,8 .63 (s ,1H) ,8 .38(d ,J 27 .8Hz ,3H) ,8 .25(s ,1H) ,7 .95(s ,1H) ,7 .81(s ,1H) ,7 .49(s ,2H) ,7 .35 (d ,J 18 .2Hz ,4H) .HRMS(ESI)m/z calcd .for $C_{23}H_{15}FN_4$([M+H]$^+$)367 .1354 ,found: 367 .1359

[0055] (E)-2-(4-)-4-((2-(4-))) (7g):

78 .m .p .238-240 ^{1}H NMR(400MHz ,DMSO-d_6)δ11 .76(s ,1H) ,8 .80-8 .65(m ,2H) ,8 .43 (s ,1H) ,8 .41-8 .30(m ,2H) ,8 .23(s ,1H) ,7 .93(s ,1H) ,7 .80(s ,1H) ,7 .66(d ,J 8 .4Hz ,2H) , 7 .45(dd ,J 23 .5 ,8 .2Hz ,4H) .HRMS(ESI)m/z calcd .for $C_{23}H_{15}F_4N_3$([M+H]+)410 .1275 , found:410 .1275

[0056] (E)-2-(4-)-4-((2-(4-))) (7h):

69 .m .p .234-236 ^{1}H NMR(400MHz ,DMSO-d_6)δ11 .76(s ,1H) ,8 .72(d ,J 6 .8Hz ,2H) ,8 .39 (dd ,J 8 .0 ,4 .9Hz ,3H) ,8 .22(d ,J 9 .2Hz ,2H) ,8 .13(d ,J 8 .3Hz ,1H) ,7 .84(t ,J 7 .4Hz , 1H) ,7 .73(t ,J 7 .4Hz ,1H) ,7 .47-7 .29(m ,4H) .^{13}C NMR(101MHz ,DMSO)δ154 .8 ,150 .0 , 148 .5 ,139 .4 ,139 .0 ,138 .8 ,130 .1 ,130 .0 ,129 .6 ,129 .5 ,127 .4 ,126 .2 ,124 .2 ,123 .5 , 116 .3 ,115 .9 ,115 .7 ,112 .2 .HRMS(ESI)m/z calcd .for $C_{22}H_{15}FN_4O_2$([M+H]$^+$)387 .1252 , found:387 .1262

[0057] (E)-2- -4-((2-)) (7i): 91 .m.p.82-84 ^{1}H NMR(600MHz,DMSO-d_6)δ11.06(s,1H),8.76(d,J 8.3Hz,1H),8.55(s,1H),8.34(s,1H),8.30(d,J 7.3Hz,2H),8.12(d,J 8.3Hz,1H),7.83(t,J 7.5Hz,1H),7.71(t,J 7.6Hz,1H),7.59(t,J 7.5Hz,2H),7.54(t,J 7.2Hz,1H),7.33(t,J 7.8Hz,2H),7.25(d,J 7.7Hz,2H),6.88(t,J 7.2Hz,1H).HRMS(ESI)m/z calcd.for $C_{22}H_{17}N_3$([M+H]$^+$)324.1495,found:324.1494

[0058] (E)-4-((2-(4-)))-2- (7j): 80 .m.p.216-218 ^{1}H NMR(600MHz,DMSO-d_6)δ11.76(s,1H),8.72(s,2H),8.41(s,1H),8.32(d,J 7.1Hz,2H),8.22(d,J 8.1Hz,2H),8.14(d,J 8.1Hz,1H),7.89-7.81(m,1H),7.76-7.69(m,1H),7.63-7.57(m,2H),7.54(d,J 6.2Hz,1H),7.35(d,J 6.6Hz,2H).HRMS(ESI)m/z calcd.for $C_{22}H_{16}N_4O_2$([M+H]$^+$)369.1346,found:3 4. ,

138 .3 ,130 .0 ,129 .8 ,128 .9 ,127 .5 ,127 .2 ,124 .3 ,123 .8 ,117 .4 ,112 .3 .HRMS(ESI) ,m/z calcd .for $C_{21}H_{15}N_3O_2$([M+Na]$^+$)342 .1237 ,found:342 .1247

[0064] (E)-N'-((2- -4) -2- (8f): 88 .m .p .238-240 ^{1}H NMR(400MHz ,DMSO-d_6)δ1 26(s ,1H) ,8 .16(s ,1H) ,8 .78(d ,J 6 .1Hz ,1H) ,8 .35(s ,1H) ,8 .28(d ,J 7 .1H 2H) ,8 (d ,J 8 .3Hz H) ,8 .02(d ,J 0 .8Hz ,1H) ,7 .90-7 .80(m ,1H) ,7 .72(t ,J 7 z ,1H) ,7 (ddd 9 .6 ,5 .7Hz ,3H) ,7 .42(s ,1H) ,6 .76(dd ,J 3 .5 ,1 .7Hz ,1H) C NMR(101 z ,DMSO-d_6) 55 .9 ,148 .4 ,146 .3 ,138 .5 ,

a• 5ÏpRv* òt

CDC 25B

[0071] CDC 25B OMFP CDC 25B OMF 485nm 535nm CDC 25B Na_3VO_4

[0072] PTP1B (protein tyrosine phosphatase) PTP1B PTP1B PTP1B

[0073] PTP1B 96 384 pNPP PTP1B 405nm 405nm

[0074]

[0075] 1 7a 7v 8a 8j CDC 25B (/)

Compds	Inhibition rate(%)	Compds	Inhibition rate(%)
7a	15.14 ±11.62	**7r**	86.74 ± 1.95
7b	17.19 ± 2.83	**7s**	18.50 ± 5.20
7c	29.17 ± 3.16	**7t**	83.89 ± 2.73
7d	22.64 ± 6.27	**7u**	80.52 ± 1.00
7e	16.57 ± 5.89	**7v**	74.17 ± 2.72
7f	43.37 ± 0.90	**8a**	2.46 ± 3.13
7g	18.42 ± 9.26	**8b**	12.10 ± 3.43
7h	25.54 ± 10.15	**8c**	15.07 ± 2.42
7i	16.20 ± 4.91	**8d**	53.85 ± 4.75
7j	80.90 ± 3.69	**8e**	4.10 ± 3.52
7k	60.99 ± 2.56	**8f**	68.55 ± 0.68
7l	53.11 ± 7.49	**8g**	42.85 ± 4.09
7m	7.36 ± 0.08	**8h**	42.62 ± 5.32
	55.00 ± 15.00	**7n**	25.60 ± 0.84

[0076]

[0077] 2 7a 7v 8a 8j PTP1B (/)

[0078]

Compds	Inhibition rate(%)	Compds	Inhibition rate(%)
7a	80.64 ± 1.57	**7r**	78.04 ± 7.94
7b	90.50 ± 11.51	**7s**	83.48 ± 0.38
7c	95.45 ± 12.97	**7t**	73.58 ± 16.29
7d	92.07 ± 1.47	**7u**	97.98 ± 2.36
7e	96.34 ± 1.48	**7v**	94.85 ± 2.95
7f	96.40 ± 2.88	**8a**	83.47 ± 1.38
7g	90.68 ± 1.00	**8b**	76.70 ± 4.74
7h	73.33 ± 16.92	**8c**	86.58 ± 6.02

[0079] CDC 25B PTP1B 7t 7f 7e 7j PTP1B
97 .98 96 .40 96 .34 96 .13

[0080] 3 .

[0081] 32 4-(2-) PTP1B
CDC 25B PTP1B
7p 6 PTP1B 70
PTP1B

[0082]