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(12)

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CN 108358838 B

(45)

2021.05.18

(21)	201810385395.X	A61P 3/04(2006.01)
(22)	2018.04.26	(56)
(65)		W0 2009148004 A1, 2009.12.10
	CN 108358838 A	W0 2009148004 A1, 2009.12.10
(43)	2018.08.03	CN 104059060 A, 2014.09.24
(73)		Raed A. Al -Qawasneh et al . . Design, Synthesis and Qual i tative Structure Acti vi ty Rel ati onshi p Eval uati ons of Qui nol i ne-Based Bi saryl i mi dazol es as Anti bacteri al Moti fs. Medi cal Chemi stry (Sharjah, Uni ted Arab Emi rates) . 2016, 12 (6) , 563-573 .
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(74)	() 41139	3,4 - -2(1H) - 1 B
		. 2012, 32
(51) Int. Cl .		2108-2114 .
	C07D 215/12(2006.01)	
	C07D 215/14(2006.01)	CDC25B
	C07D 405/12(2006.01)	. 2014, 23 (
	C07D 409/12(2006.01)	24) , 2881-2885 .
	A61P 35/00(2006.01)	
	A61P 3/10(2006.01)	权利要求书1页 说明书11页

(54)

[h]

25B

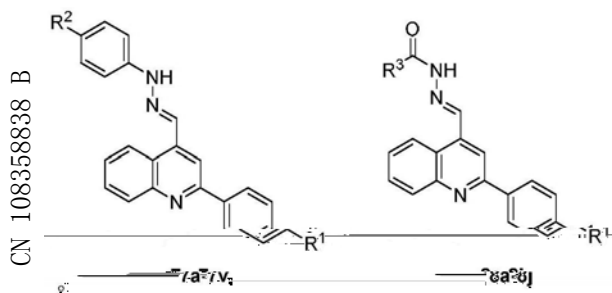
(57)

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25B

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1.

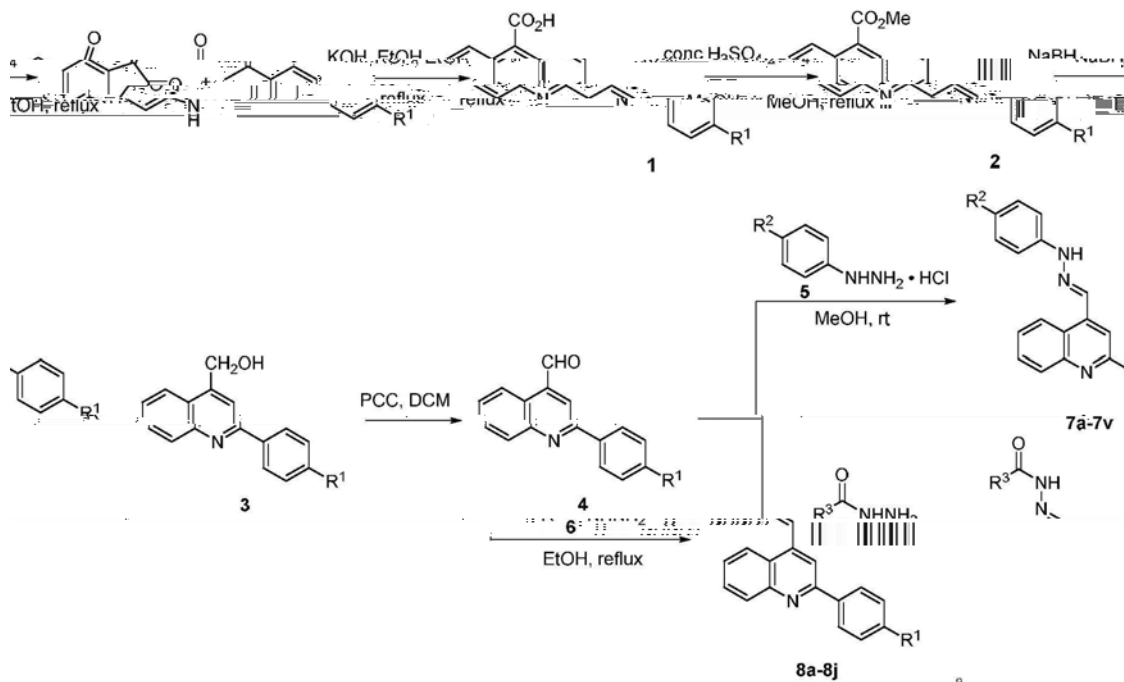
25B



7a R¹ F R² H 7b R¹ F R² OCH₃ 7c R¹ F R² CH₃ 7d R¹ F R² F 7e R¹ F R² Cl 7f R¹ F R² CN 7g R¹ F R² CF₃ 7h R¹ F R² NO₂ 7i R¹ H R² H 7j R¹ H R² NO₂ 7k R¹ H R² OCH₃ 7l R¹ H R² CH₃ 7m R¹ H R² F 7n R¹ H R² Cl 7o R¹ H R² CF₃ 7p R¹ CF₃ R² OCH₃ 7q R¹ CF₃ R² NO₂ 7r R¹ CF₃ R² CH₃ 7s R¹ CF₃ R² F 7t R¹ CF₃ R² Cl 7u R¹ CF₃ R² CF₃ 7v R¹ CF₃ R² H

8a R¹ F R³ = ; 8b R¹ F R³ = ; 8c R¹ F R³ Ph 8d R¹ F R³ o-ClPh-
 8e R¹ H R³ = ; 8f R¹ H R³ = ; 8g R¹ F R³ o-ClPh- 8h R¹ F R³ Ph 8i R¹ CF₃ R³ = ; 8j R¹ CF₃ R³ = .

2. 1



[0001]

[0002]

CA A Cancer Journal for Clinicians			2017
1688780	600920		2016 1 25
CA A Cancer Journal for Clinicians			2015
[1]	2015	429.2	281.4

[0003]

[2]

[3-5]

[6-9]

[0004]

[10]

[11]

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32

4-(2-

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25B(CDC 25B)

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[0005]

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[0017]

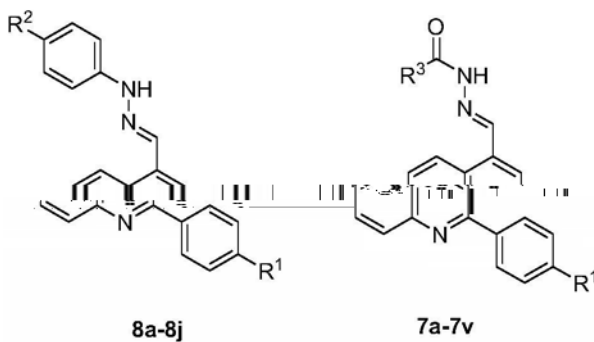
PTP1B

25B

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[0018]

[0019]

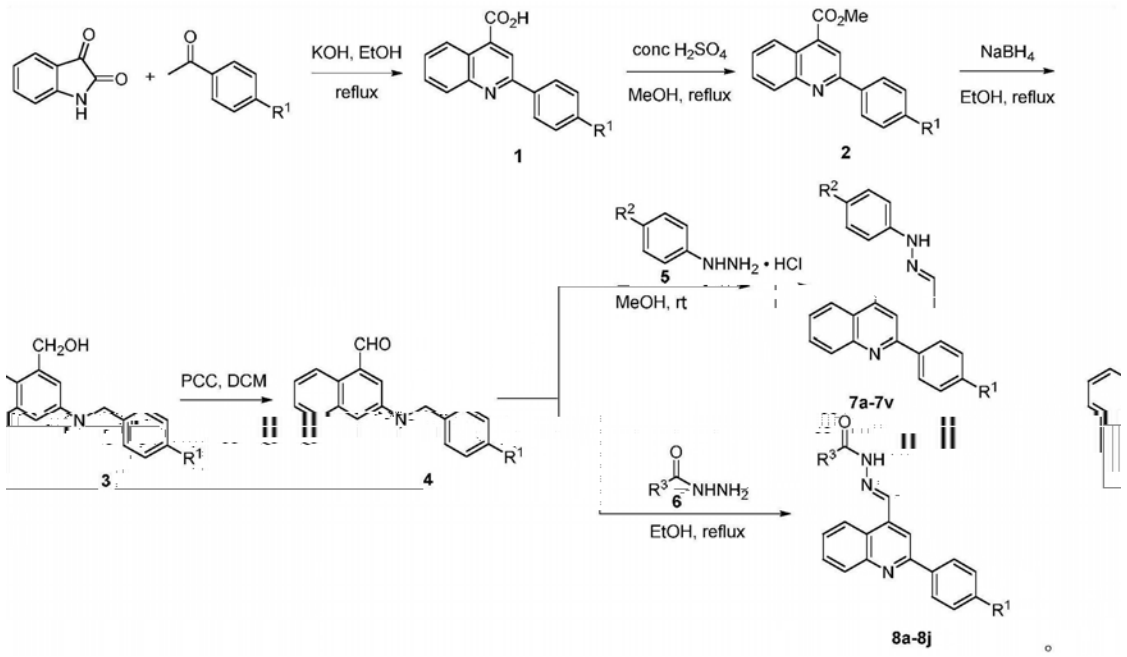


[0020] 7a R¹ F R² H 7b R¹ F R² OCH₃ 7c R¹ F R² CH₃ 7d R¹ F R² F 7e R¹ F R² Cl 7f R¹ F R² CN 7g R¹ F R² CF₃ 7h R¹ F R² NO₂ 7i R¹ H R² H 7j R¹ H R² NO₂ 7k R¹ H R² OCH₃ 7l R¹ H R² CH₃ 7m R¹ H R² F 7n R¹ H R² Cl 7o R¹ H R² CF₃ 7p R¹ CF₃ R² OCH₃ 7q R¹ CF₃ R² NO₂ 7r R¹ CF₃ R² CH₃ 7s R¹ CF₃ R² F 7t R¹ CF₃ R² Cl 7u R¹ CF₃ R² CF₃ 7v R¹ CF₃ R² H

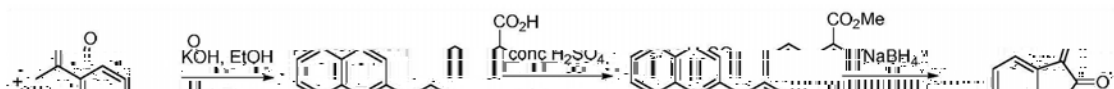
[0021] 8a R¹ F R³ ; 8b R¹ F R³ ; 8c R¹ F R³ Ph 8d R¹ F R³ o-CHPh- 8e R¹ H R³ ; 8f R¹ H R³ ; 8g R¹ F R³ o-CHPh- 8h R¹ F R³ Ph 8i R¹ CF₃ R³ ; 8j R¹ CF₃ R³ .

[0022]

[0023]

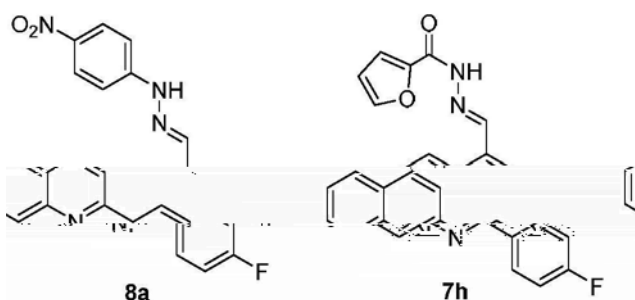


[0024]



[0030]

[0031]



[0032]

[0033]

[0034]

[0035]

[0036]

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[0037]

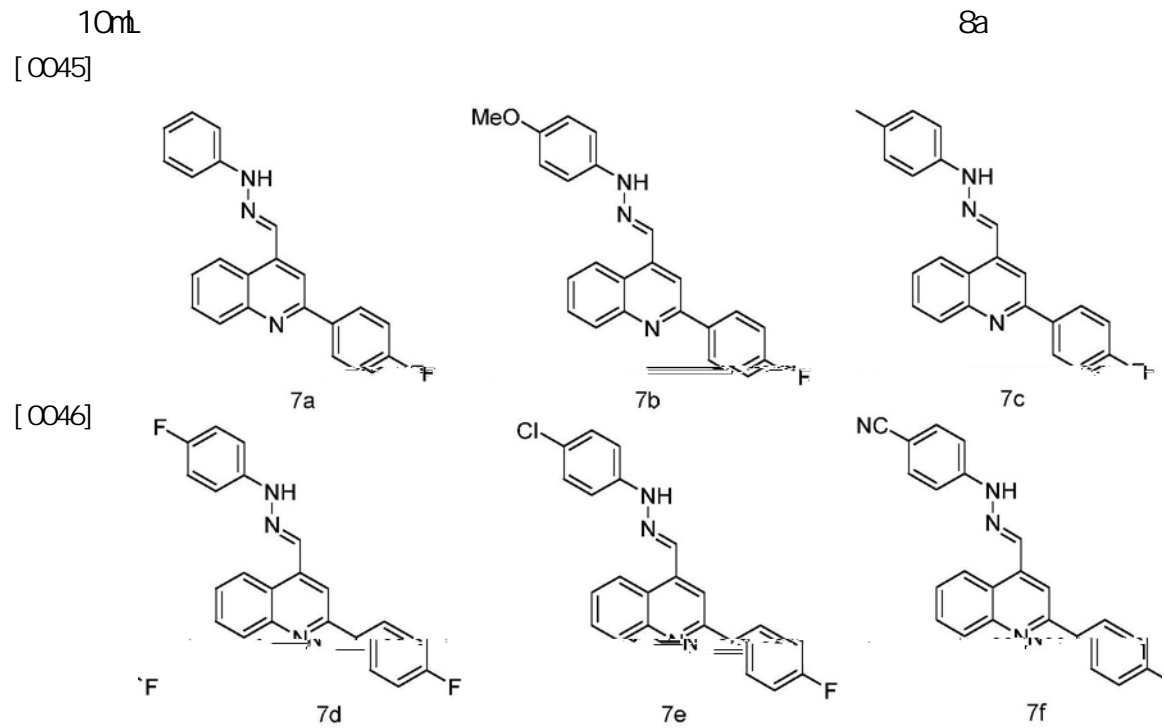
[0038]

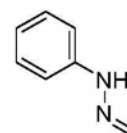
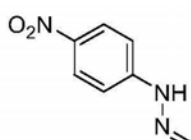
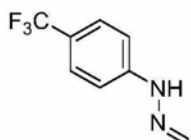
[0039]

[0040]

1.1	2-(4-)	-4-	1a				
	250mL		50mmol	2,3-	60mmol	4-		20mL
	35mL	34wt	KOH	80		TLC		
		2M						
							1a	85
1.2	2-(4-)	-4-	2a				
	100mL		20mmol	2-(4-)	-4-	20mL	
	5mL	75			TLC			20mL
				PH		(5×30mL)		
						(/
		2a	87					
1.3	(2-(4-)	-4-	3a				
	100mL		15mmol	2-(4-)	-4-	45mmol	
	50mL	80			TLC			
	50mL						3a	92
1.4	(2-(4-)	-4-	4a				
	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





[0047]

[0048]

[0049] (E)-2-(4-)-4-((2-)) (7a): 88
.mp. 116-118 1H NMR (600 MHz, $DNMSO-d_6$) 11.00 (s, 1H), 8.75 (d, J 8.3 Hz, 1H), 8.54 (s, 1H), 8.38 (dd, J 8.7, 5.6 Hz, 2H), 8.32 (s, 1H), 8.10 (d, J 8.2 Hz, 1H), 7.81 (t, J 7.1 Hz,

1H), 7.70(dd, J 11.2, 3.9 Hz, 1H), 7.40(t, J 8.8 Hz, 2H), 7.32(t, J 7.8 Hz, 2H), 7.24(d, J 7.7 Hz, 2H), 6.87(t, J 7.2 Hz, 1H). HRMS(ESI) m/z cal cd. for C₂₆H₁₆FN₃([M+H]⁺) 342.1401, found: 342.1401

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

85 .mp. 220-222 ¹H NMR(400MHz, DMSO-d₆) 11.70(s, 1H), 8.73(d, J 8.4 Hz, 1H), 8.54(s, 1H), 8.34(s, 1H), 8.25(dd, J 15.9, 7.3 Hz, 3H), 7.99(t, J 7.7 Hz, 1H), 7.82(t, J 7.7 Hz, 1H), 7.51(t, J 8.8 Hz, 2H), 7.29(d, J 8.9 Hz, 2H), 6.96(d, J 8.9 Hz, 2H), 3.74(s, 3H). HRMS(ESI) m/z cal cd. for C₂₃H₁₈FN₃O([M+H]⁺) 372.1507, found: 372.1508

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

71 .mp. 216-218 ¹H NMR(400MHz, DMSO-d₆) 11.69(s, 1H), 8.73(d, J 8.5 Hz, 1H), 8.61(s, 1H), 8.33(dd, J 19.2, 10.5 Hz, 4H), 7.98(t, J 7.4 Hz, 1H), 7.83(t, J 7.4 Hz, 1H), 7.52(t, J 8.6 Hz, 2H), 7.24(d, J 8.1 Hz, 2H), 7.16(d, J 8.2 Hz, 2H), 2.27(s, 3H). HRMS(ESI) m/z cal cd. for C₂₃H₁₈FN₃([M+H]⁺) 356.1558, found: 356.1556

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

63 .mp. 127-129 ¹H NMR(400MHz, DMSO-d₆) 11.36(s, 1H), 8.73(d, J 8.5 Hz, 1H), 8.62(s, 1H), 8.41-8.35(m 3H), 8.11(d, J 7.9 Hz, 1H), 7.85-7.80(m 1H), 7.72-7.68(m 1H), 7.64(d, J 8.5 Hz, 2H), 7.44-7.35(m 5H). HRMS(ESI) m/z cal cd. for C₂₂H₁₅F₂N₃([M+H]⁺) 360.1307, found: 360.1316

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

79 .mp. 248-250 ¹H NMR(400MHz, DMSO-d₆) 11.63(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 18.2 Hz, 4H). HRMS(ESI) m/z cal cd. for C₂₂H₁₅FN₃([M+H]⁺) 376.1011, found: 376.1011

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

64 .mp. 250-252 ¹H NMR(400MHz, DMSO-d₆) 11.63(s, 1H), 8.72(d, J 8.1 Hz, 1H), 8.63(s, 1H), 8.38(d, J 27.8 Hz, 3H), 8.25(s, 1H), 7.95(s, 1H), 7.81(s, 1H), 7.49(s, 2H), 7.35(d, J 18.2 Hz, 4H). HRMS(ESI) m/z cal cd. for C₂₃H₁₅FN₄([M+H]⁺) 367.1354, found: 367.1359

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

78 .mp. 238-240 ¹H NMR(400MHz, DMSO-d₆) 11.76(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 8.4 Hz, 2H), 7.45(dd, J 23.5, 8.2 Hz, 4H). HRMS(ESI) m/z cal cd. for C₂₃H₁₅F₄N₃([M+H]⁺) 410.1275, found: 410.1275

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

69 .mp. 234-236 ¹H NMR(400MHz, DMSO-d₆) 11.76(s, 1H), 8.72(d, J 6.8 Hz, 2H), 8.39(dd, J 8.0, 4.9 Hz, 3H), 8.22(d, J 9.2 Hz, 2H), 8.13(d, J 8.3 Hz, 1H), 7.84(t, J 7.4 Hz, 1H), 7.73(t, J 7.4 Hz, 1H), 7.47-7.29(m 4H). ¹³C NMR(101MHz, DMSO) 154.8, 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 cal cd. for C₂₂H₁₅FN₄O₂([M+H]⁺) 387.1252, found: 387.1262

[0057] (E)-2-(4-((2-)) (7i): 91 .mp. 82-84
¹H NMR(600MHz, DMSO-d₆) 11.06(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 cal cd. for C₂₂H₁₇N₃([M+H]⁺) 324.1495, found: 324.1494

[0058] (E)-4-((2-(4-)))-2- (7j): 80
 .mp. 216-218 ¹H NMR(600MHz, DMSO-d₆) 11.76(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 cal cd. for C₂₂H₁₆N₄O₂([M+H]⁺) 369.1346, found: 369.1390u p⁻ 8

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-
-2- (8f): 88
. mp. 238-240 1H NMR(400MHz, $SO-d_6$) 1.26(s, 1H), 0.16(s, 1H), 8.78(d, J 6.1Hz, 1H), 8.35(s, 1H), 8.28(d, J 7.1Hz, 1H), 8.02(d, J 8.3Hz, 1H), 7.90-7.80(m, 1H), 7.72(t, J 7.1Hz, 1H), 7.55(ddd, J 9.6, 5.7Hz, 3H), 7.42(s, 1H), 6.76(dd, J 3.5, 1.7Hz, 1H). ^{13}C NMR(100MHz, $SO-d_6$) 55.9, 148.4, 146.3, 138.5,
a• 5iu .vò0

CDC 25B
 [0071] CDC 25B CNMP CDC 25B CNF
 485nm 535nm
 CDC 25B Na₃VO₄
 [0072] PTP1B (protein tyrosine
 phosphatase) PTP1B PTP1B

PTP1B
 [0073] PTP1B 96 384
 pN PP 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	25.34 ± 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

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

Comps	Inhibition rate(%)	Comps	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

[0078]

[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]