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(43) 1996 03 22

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- 4070 124

(72) 80301 821

(74)

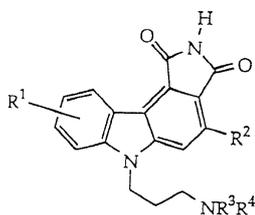
:

(54)

(I)

가

:



I

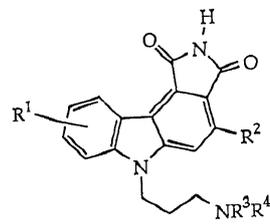
R¹

;

R² ;

R³ R⁴ .

, , ,
 ,
 : (I) 가



R¹ ;

R² ,

R³ R⁴ .

, R¹ , R² 가 (I)
 , 가 (I)

, 가 (I) 가

" " , , n- , , n- , 3 - , n- , n-
 1 6 .

- 1. 1,3- - 6 - (3-) - 1,2,3,6- - 4 - (- 3 -) - [3,4, - c] .
- 2. 1,3- - 8- - 6 - (3-) - 1,2,3,6- - 4 - (- 2 -) - [3,4, - c] .
- 3. 1,3- - 6 - (3-) - 1,2,3,6- - 4 - (- 3 -) - [3,4, - c] .
- 4. 1,3- - 6 - (3- ()) - 1,2,3,6- - 4 - (- 3 -) - [3,4, - c] .

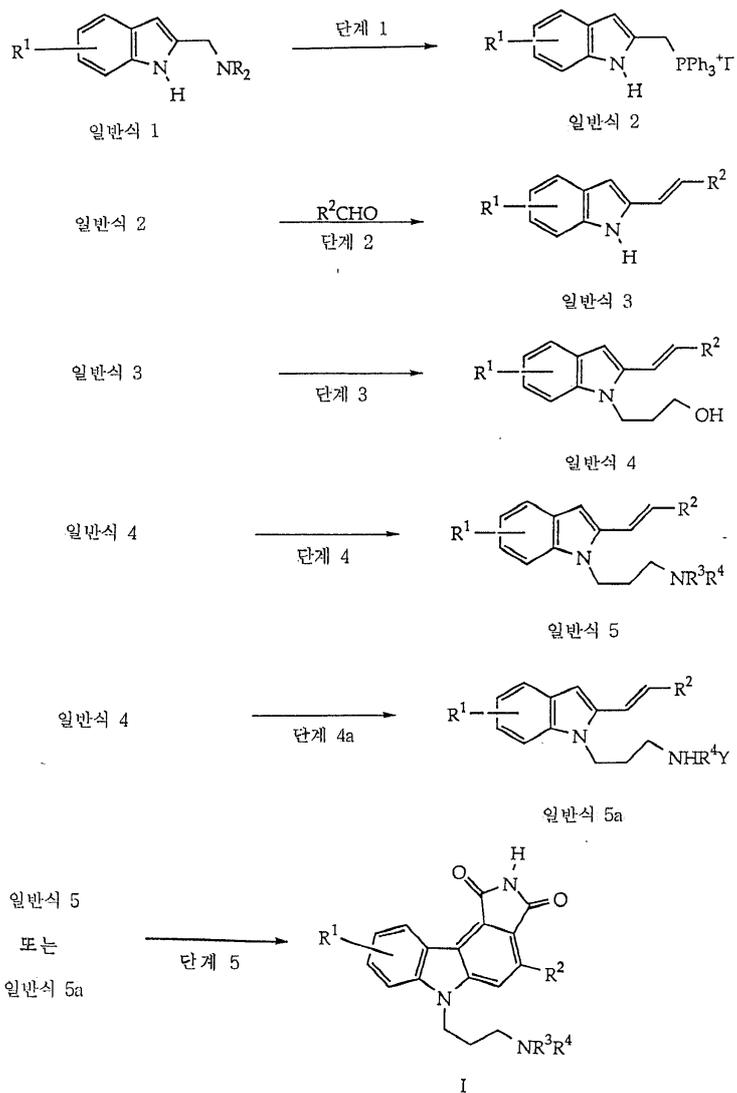
" " , " " " " " (" THF") , (" DMF") , () ,] .

" (q.s.)" , (, 100%) 가 .

" " " , " , 20) 5 100 (10 50 ; 가 1 10 (5) 5 100 (10 50 ; 가 20) .

(I) R¹, R², R³ R⁴ 1 .

(I) N,N- () 가 , N,N- (Aldrich Chemical Company) 가 .



, R, Y .

(1) [Canadian J. Chem., Vol. 51, p.792 (1973)]

N,N- () (2)

(1) , 10 50 (25) 1 10 , , 100 150

(2) 6 24 , 16 ,

R²CHO 1 2 , (2) (3)

(2) ((, 1,5 - [4.3.0] - 5 - 1,8 - DMSO [5.4.0] - 7 -) , 20 6 48 (2 20 100 (80)) (3)

1 3 , (3) 1 - - 3 - (t -) (4) N -

(3) (DMF DMSO) 0 50 (25) , 5 3 (15) , 1 - - 3 - (t -) 가 , 1 24 (16) , 1 12 (, 2) 20 30 (4) N -

1 4 , (4) - () , R³ R⁴ 가 (5)

(4) () , - 10 20 (0) 15 1 (30) (, 2,6 - 2,4,6 - 3 0 40 (25) , 6 24 (12) 0 R (, R³ R⁴) (5) , 5

1 4a , R³ R⁴ (4) (5a)

(4) () , 15 1 (30) - 10 20 (0) (, 2,6 - 2,4,6 - 3 0 40 (25) , 6 24 (12) 0 R³R⁴ NH (, R³ R⁴) (5)

1 2 (, R³ R⁴) , 3 ()
 , 25 5 4 (30)
 (5a)
 , R³ R⁴ , 3 ()
 , t- , t-
 1 5 , (5) (5a)
 (1)
 (5) (5a) ()
 , 6 24 (16) 2 3 (2)
 (Diels - Alder) 가
 , 20 50 (25) 15 3 (30) 2 3)
 (2) (5a) , Y , 25
 15 (, ,)
 (I) , t - BOC ,
 (I) 가 (,)
 3) , , 가 0 5
 (I) 가 0 50
 , R⁴가 R¹ , R²가 3 - (I) R³
 . 가 1,3 - - 6 - (3 -) - 1,2,3,6 - - 4 - (
 - 3 -) - [3,4 - c] .
 CHO/PKC - C : , MCS7, MDA - MB - 435 MDA - N
 PKC ,
 C - ³² P ATP ³² P

Natl, Acad, Sci. USA, Vol 89, 1169 - 1173 (Feb. 1992)]
HT - 29 , SCLC H82

(Maneckjee)

[Proc.

, CHO/PKC -

CHO/PKC -

(I)

가

가

kg,
0 kg

0.5

10.0 mg/

kg 가

7.0

1,400 mg,

1.0

5.0 mg/

35.0

0.1 20.0 mg/

kg

, 7

700 mg 가

70

350 mg

가

(I)

가

(I)

() (Patch)

(I)

가

가

(multidrug resistance reversing agent)

5 50 %

(I)

가

0.1

90 %,

0.

가

가

, pH

[Remington's Ph

armaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 15th Edition, 1975]

0.005% 95%

가

0.01% 95%,

0.1 50%

245 , 4,409,239 ; 4,410,545

4,328,

(shell)

Re. 28,819

4,358,603

가

pH

가

3,710,795

0.01% 10%

가

0.2 2%

가

(鼻側)

50

10

가

1

(2)

1A R¹

40 Mℓ 2-N,N- (5.4 g) [Acta. Chim. Acad. Sci. Hung. Vol 34, P 439 (1962)]
 (DMF) (100 Mℓ) 가 , 3 (11.6 g)
 (75 Mℓ) , DMF ,
 (10.4 g) , -2-

1B. R¹

2- R¹ (R¹ , n- , n- , 3 - , n- ,
 n-) 2- 1A , 4-
 -2- , 5- -2- , 6-n- -
 2- 7-n- -2- (2)

2

(3)

2A. R¹ , R²가 -3-

60 Mℓ 1.04 g -2- - 175 μℓ -3-
 250 μℓ 1,8- [5.4.0] -7- 가 1 4
 0 N₂ , 2 80 , 20
 2-[2-(-3-)] 200 mg (44%)

2B. R¹ R²가

-2- 1 (2)
 , -3- R²CHO 2A
 (3) :

2-[2-(-2-)] ;

2-[2-(-3-)] ;

2-[2-(-3-)] ;

2-[2-(-3-)] ;

4- -2-[2-(-3-)] ;

5- -2-[2-(-3-)] ;

6-n- -2-[2-(-3-)] ;

7-n- -2-[2-(-3-)] .

3

(4)

3A. R¹ , R²가 -3-

2-[2-(-3-)] (200 mg) 3 Mℓ , 15 25
 40 mg , 1- -3-(t- (500mg) 가 ,
 25 .
 (t-)]-2-[2-(-3-)] TLC(5:1 /EtOAc) . 1-[3-
 330 mg (71%) .

2 Mℓ , 2 Mℓ 1M 2
 25 .
)-2-[2-(-3-)] TLC(2:1 /EtOAc) , 121 mg 1-(3-
 (68%) .

3B. R¹ R²

2-[2-(-3-)] (2) (3) 3A
 (4) .

4

(5a)

A. R¹ , R²가 -3- , R³ , R⁴가

3 Mℓ 1-(3-)-2-[2-(-3-)] (121 mg) 120 μℓ
 2,6- , 0 . (100 μℓ) 가 , 30
 , 5 Mℓ 40% , 25 3 . 가 0 12
 .
 -[2-(-3-)] TLC(10% /) 83 mg 1-[3-())-2
 (67%) . 150 μℓ 3 Mℓ
 (40 μℓ) 가 . 30 .
 /EtOAc) 80 mg 1-[3-(N-))-2-[2-(-3-)] TLC(3:1
] (73%) .

4B. R¹, R², R³ R⁴

1-(3-)-2-[2-(-3-)] 3 (4)
 4A , (5) (5a) .

5

(I)

5A. R¹ , R²가 - 3 - , R³가 , R⁴가
 2 Mℓ 1 - [3 - (N -) -] - 2 - [2 - (- 3 -)] (8
 0 mg) 40 mg
 TLC , 20 mg 가 (20%)
¹H NMR (CDCl₃): 7.96 (m, 1H), 7.35-7.15 (m, 4H), 7.13 (m,
 1H), 7.02 (m, 1H), 4.40 (d, 1H), 4.13 (t, 2H), 3.73 (m, 2H), 3.45 (t,
 2H), 3.12 (m, 2H), 3.06 (s, 3H), 2.02 (5.2H)

3 Mℓ , 20 mg (DDQ) . 20 ,
 10 mg DDQ 가 . 10 TLC , 2:1 /EtOAc .
 , 18 mg 1,3 - - 6 - (N -) - 1,2,3,6 - - 4 - (
 - 3 -) - [3,4 - c] (foam)
 4 Mℓ 1:1 MeOH/THF , 1 Mℓ 1M NaOH 가 . 15 ,
 10%) 15 mg 1,3 - - 6 - (3 -) - 1,2,3,6 - TLC(
 4 - (- 3 -) - [3,4 - c] .
¹H NMR (d₆-DMSO): 8.96 (d, H), 8.00 (s, 1H), 7.95 (m,
 1H), 7.74 (d, 1H), 7.62 (m, 3H), 7.35 (t, 1H), 4.59 (t, 2H), 2.55 (t, 2H),
 2.29 (s, 3H), 1.97 (t, 2H).

C₂₂ H₁₉ N₃ O₂ S HRMS : 389,1197; : 389,1198.

5B. R¹ , R² R³
 1 - [3 - (N -)) - 2 - [2 - (- 3 -)] (4B)
 (5) (5a) 5A
 (I)

6

(I) , 1,3 - - 6 - (3 -) - 1,2,3,6 -
 - 4 - (- 3 -) - [3,4 - c]

성분	정제당 정량 (mgs)
활성 화합물	200
스프레이-건조된 락토즈	148
마그네슘 스테아레이트	2

1 5 (I)

7

- 4 - ((I) , 1,3 - - 6 - (3 -) - 1,2,3,6 -
 - 3 -) - [3,4 - c]

성 분 정제당 정량 (mgs)

활성 화합물	400
옥수수 전분	50
락토즈	145
마그네슘 스테아레이트	5

1 5 (I)

8

- 4 - ((I) , 1,3 - - 6 - (3 -) - 1,2,3,6 -
 - 3 -) - [3,4 - c]

성 분 양

활성 화합물	1.0 g
푸마르산	0.5 g
염화 나트륨	2.0 g
메틸 파라벤	0.1 g
과립 당분	25.5 g
소르비톨 (70% 용액)	12.85 g
비균 (Veegum) K (판데르빌트 캄파니 (Vanderbilt Co.))	1.0 g
향료	0.035 ml
착색제	0.5 mg
증류수	총 100 ml가 되게 하는 적정량

1 5 (I)

9

- 4 - (- 3 -) - (I) , 1,3 - - 6 - (3 -) - 1,2,3,6 -
[3,4 - c]

pH 7.4 가 :

성 분	정제당 정량 (mgs)
활성 화합물	0.2 g
나트륨 아세테이트 완충액 (0.4 M)	2.0 ml
HCl(1N)	pH 7.4가 되게 하는 적정량
물 (중류, 멸균)	총 20 ml가 되게 하는 적정량

1 5 (I)

10

- 4 - (- 3 -) - (I) , 1,3 - - 6 - (3 -) - 1,2,3,6 -
[3,4 - c]

2.5 g :

500 mg

(witepsol) H - 15 *

(* nc.) ; - (Riches - Nelson, I)

1 5 (I)

11

K

C (PKC)

ser - leu - arg - ala PKC 1 - ³²P ATP ³²P ala - lys - arg - arg - leu - ser -

25 mM HCl, pH 7.5, 2.5 mM Mg (NO₃), 1.0 mM EGTA, 20 μM PKC, 1 μg/mL (PS), 5 × 10⁻⁶ M (di-C8) 50 μM ATP, 32-P ATP (> 5,000 Ci/μmol), 10⁶ CPM (well) 50 μl, 0.08 μg/mL PKC, 5, 0.2 V, 50% TCA, 32-P, 30 μl P-81, 5 × 10⁻⁶ H diC8 1 μg/mL (Beckman) LS 5000 TA (scintillation), 50% PKC

(%) =

$$1.0 - [(CPM - CPM)/(CPM - CPM)] \times 100$$

C ;

, 1,3-3OnM -6-(3-IC₅₀) -1,2,3,6-4-(3-)-[3,4-c]

12

[Proc. Natl. Acad. Sci. USA, Vol 89, 1169 - 1173 (Feb. 1992)]

H82 (SCLC), RPMI, PBS: (Matrigel) (1:2) 5 × 10⁵ 1.5 × 10⁶ /ml, 4, 5 (Harlan Sprague Dawley) 200R/0.2 mL SCLC/ (1 × 10⁵) 3 × 10⁵ SCLC / .30 10 mg/kg (DMSO, PBS, 20% DMSO) 2, 45

: (Fisher) (Exact) [kendall M., Stuart A., The Advanced Theory of Statistics, Vol., 2 (MacMillan Pub Co. NY, 1979)] (Mann Whitney) U [Hollander N., Wolfe D.A., Non-parametric Statistical Methods (John Wiley and Sons, Inc., NY, 1973)] (log rank) [Kalbfleisch J.D., Prentice R.L., The Statistical Analysis of Failure Time Data (John Wiley and Sons, Inc., NY 1980)] 20 00 mm³

13

H82 HT-29, 5 × 10⁶ /ml, 1 × 10⁶ /

5.

1 가 , .