

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

(51) 。 Int. Cl.⁷ (11) 10-2004-0018341
A61K 31/704 (43) 2004 03 03

(21) 10-2003-7012324
(22) 2003 09 22
2003 09 22
(86) PCT/CA2002/000426 (87) WO 2002/76472
(86) 2002 03 25 (87) 2002 10 03

(30) 60/277,975 2001 03 23 (US)
60/330,601 2001 10 25 (US)

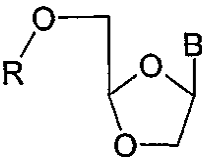
(71) 7 4 7 - 275

(72) , , 77030, 1515, 61,
, , 77030, 1515, 61,
, , 7 4 9, , 2235

(74) :

(54)

, () 1 : / ;
() 1 , / 1



(I)

, , , -L-OddC

2001. 03. 23.
60/330,601 .

60/277,975

2001. 10. 25.

, 1 /

(cancer) 2 30 %가 가 , , ,
4 가 .

가 Clinical Cancer
Research (2000), 6(4), pp 1574~1578 Journal of Clinical Oncology (2001), 19(3), pp 762~771
Cancer Chemother. Pharmacol. (2001), 47(3), pp 236~240 (-L -
, -L-OddC, Troxatyl) (,)

(gemcitabine) (cladribine) (Ara-C), (fludarabine)

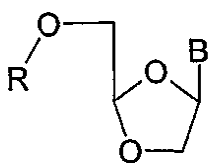
(cytarabine) 가 가 . 가

(troxacitabine) /
가 .

[]

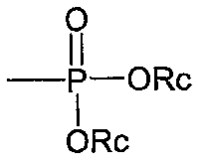
, () 1

1 가 ; /



(I)

(C₁₋₆ B, C₂₋₆ 5-, C₂₋₆ , R) , , , ,


$$\left(\begin{array}{cccc} & & \text{Rc} & \\ & & & \\ & & & \end{array} \right), \text{C}_{1-6}, \text{C}_{2-6}, \text{C}_{2-6}$$

() 1

() 1 : 250 250 : 1 (doxorubicin) 1 : 50 50 : 1 ,

1 : 20 20 : 1 .

() 1 가

1 : 50 50 : 1 , () 1 : 250 250 : 1 ,

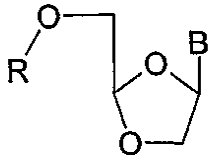
1 : 20 20 : 1 .

()

1 1 : 250 250 : 1

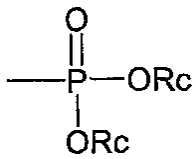
1 : 50 50 : 1 , 1 : 20 20 : 1 .

() 1 / 가 ;



(I)

, B 5- , R , ,
(C₁₋₆ , C₂₋₆ , C₂₋₆ , C₆₋₁₀)



(, Rc , C₁₋₆ , C₂₋₆ , C₂₋₆)

, R .
, B .
, R B .
, B 5- .

, () (-)- -L- - (-L-OddC) .
() (-)- -L- -5- - (5-FddC) .

, () (Substantially) (-) .

95 % , (-) () (+) 가

97 % , (-) () (+) 가

99 % , (-) () (+) 가

() 2 가

, () (, (+) (-) -L -D)가 .

tic resolution) (chiral auxiliary) , HPLC, (enzyma
()

[illegible]

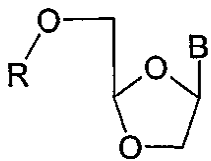
(myelogenous leukemia)
 , 가 () 가 1
 : 250 , 250 : 1 , 1 : 50 , 50 : 1 , 1 : 20 20 : 1
 1 .

(acute myelogenous leukemia)
 , 가 () 가
 1 : 250 , 250 : 1 , 1 : 50 , 50 : 1 ,
 1 : 20 20 : 1 .

(chronic myelogenous leukemia)
 , 가 ()
 가 1 : 250 , 250 : 1 , 1 : 50 , 50 : 1 ,
 1 : 20 20 : 1 .

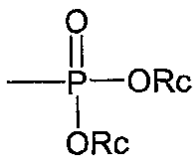
(refractory/relapsed leukemia)
 , / 가 ()
 가 1 : 250 , 250 : 1 , 1 : 50 , 50 : 1 ,
 1 : 20 20 : 1 .

, .
 , / () 1 가 ;
 , /



(I)

, B 5- , R ,
 , (C₁₋₆ , C₂₋₆ , C₂₋₆ , C₆₋₁₀) ,



(R_c) , C₁₋₆ , C₂₋₆ , C₂₋₆ .

, , , , , , , , , ,
 , () 가 1 : 250 250 : 1 ,
 1 : 50 50 : 1 , 1 : 20 20 : 1 .

, , , , , , , , , ,
 .

, () /
 가 1 , () 1 : 250 250 : 1 ,

1 : 50 50 : 1 , 1 : 20 20 : 1 .

, () /

가 , 1 () 가 1 : 250 250 : 1 .

, 1 : 50 50 : 1 , 1 : 20 20 : 1 .

, () /

가 , 1 () 가 1 : 250 250 : 1 .

, 1 : 50 50 : 1 , 1 : 20 20 : 1 .

, () /

1 () (blastic phase) 가 () 가

1 : 250 250 : 1 , 1 : 50 50 : 1 , 1 : 20 2

0 : 1 .

, () /

가 , 1 () / 가 1 : 250 250 : 1 .

, 1 : 50 50 : 1 , 1 : 20 20 : 1 .

, () /

1 () / 가 () 가

1 : 250 250 : 1 , 1 : 50 50 : 1 ,

1 : 20 20 : 1 .

, () /

1 () 가 1 : 250 250 : 1 , 1 : 50 ,

50 : 1 , 1 : 20 20 : 1 .

, -L-OddC

/ 0 250 : 1 , 1 : 50 50 : 1 , -L-OddC 1 : 25 20 : 1 .

, -L-OddC , 1

20 1 : 250 250 : 1 , 1 : 50 50 : 1 , -L-OddC 가 1 :

20 20 : 1 .

, -L-OddC , 1

(synergistic combination)

, -L-OddC

50 , -L-OddC 1 : 250 250 : 1 , 1 :

50 50 : 1 , 1 : 20 20 : 1 .

, -L-OddC

50 , -L-OddC 1 : 250 250 : 1 , 1 :

50 50 : 1 , 1 : 20 20 : 1 .

, -L-OddC

[illegible]

(, ,) , 가

/ (refractory/relapsed leukemia) (response)

(patient)

(alkyl)' (, , CONH₂, COOH, O-C₁₋₆, O-C₂₋₆,
O-C₂₋₆) , 가 COOQ , , Q C₁₋₆ ; C₂₋₆ ; C₂₋₆
(, , , n- , , , , ,
, 가 , , (CF₃ - CF₃CH₂-)
, , 1- (alkenyl)' (alkynyl)' (, 1- , 2- , 2- , 1- , 2-) .

(aryl)' (,) .

(hydroxy protecting group)'
(T.Greene) Protective Groups In Organic Synthesis.(John Wiley amp; Sons, 1981) .

-2-

, () 1 mg/m² 8 mg/m² 1 ;
가 0.1 gm/m² 6 gm/m² 1 .

, () 1 mg/m² 8 mg/m² 1 ;
가 0.1 gm/m² 6 gm/m² 1 .

, () 1 mg/m² 8 mg/m² 1 ;
가 1 gm/m² 30 gm/m² .

2 , -L-OddC 1 5 1 30 6 mg/m² 1 5
1 gm/m² .

2 , -L-OddC 1 5 1 30 5 mg/m² 1 3
12 gm/m² .

, , , .

, 1 0.1 750 mg/kg , 0.5 500
mg/kg/day , 가 1 300 mg/kg/day .

, , 1 2 , 3 , 4

, .

3 30 μM 가 1 75 μM, 2 50 μM, 가
30 μM .

1 500 mg 0.1 5 % ,
(bolus) .

0.01 5.0 mg/kg/hour , 0.4 15 mg/kg

(, ,)

,

,

가

,

/

.

,

.

가

가

(transdermal patch) (linalool), (carvacrol), (citral),

(t-anethole) /

가

(mouth)

(lozenges); (pastilles); (mouthwashes)

가

가

가

(forms)

가

, 가

가

(insufflator), (nebulizer) 가 (pressured pack),

가

가 (propellant) . 가










,

(inhalation) (insufflation)










(inhalator) (insufflator) 가

(I) WO 96/07413 AI, WO 97/21706 WO 00/47759
(Shire BioChem Inc.) -L -OddC

1 MiaPaCa

[ : (i.v.; qd x5);  : 10 mg/kg(i.v.; qd x5);  : 25 mg/kg(i.v.; qd x5);  : 40 mg/kg(i.p.; ;  : 80 mg/kg;  : 10 mg/kg(i.v. ; qd x5), 40 mg/kg(i.p.; ;  : 10 mg/kg(i.v.; qd x5), 80 mg/kg(i.p.; ;  : 25 mg/kg(i.v.; qd x5), 40 mg/kg(i.p.; ;  : 25 mg/kg(i.v.; qd x5), 80 mg/kg(i.p.;]

2 Panc-01

[ : (i.v.; qd x5);  : 10 mg/kg(i.v.; qd x5);  : 25 mg/kg(i.v.; qd x5);  : 40 mg/kg(i.p.; q3d x4);  : 80 mg/kg(i.p.; q3d x4);  : 10 mg/kg(i.v.; qd x5), 40 mg/kg(i.p.; q3d x4);  : 10 mg/kg(i.v.; qd x5), 80 mg/kg(i.p.; q3d x4);  : 25 mg/kg(i.v.; qd x5), 40 mg/kg(i.p.; q3d x4);  : 25 mg/kg(i.v.; qd x5), 80 mg/kg(i.p.;q3d x4)]

3 CCRF-CEM analysis

- (Ara-C)

CalcuSyn A

(72 ;

Experimental set up and example of results for a 72 h continuous exposure)

1

	-L OddC		가					
	/			-L OddC	가			
	(AML)	(ALL)	,	(MDS),				(CML
-BP)	가	16	가	AML	2	39	1	(18 %)

2

Ara-C	-L OddC	가						
/			Ara-C	-L OddC				
			Ara-c		-L OddC	Ara-C		
			(AML),		(MDS)			
(CML_BP)								
(0)			-L OddC 5 mg/m ²		()	30	5	
, Ara-C 1 gm/m ²	1	5	2		(IV)			
49	가		0	3				
-1 (4 mg/m ²	-L OddC / 0.75 gm/m ²	Ara-C)						
(prednisone)		가	13	가				
0	3	가	3					(hand-foot)
가	0	Ara-C	-L OddC	가				7
5 mg/m ²	-L OddC / 1.25 gm/m ²	Ara-C	19	6 mg/m ²	-L OddC / 1 gm/m ²	Ara-C		
.5	6 mg/m ²	-L Oddc / 1.25 gm/m ²	Ara-C					
(transaminitis)								-L OddC 6 mg/m
2	5	30	, ara-c 1 gm/m ²	1	5	2		
25 mg								

(response criteria) 가 : (CR)

(CRp) . CR 5 %

가 , - , $1 \times 10^9 / L$

4 $100 \times 10^9 / L$. CRp CR $<100 \times 10^9 /$

L .

7 CR (4 AML, 1 CML-BP 2 MDS) 4 CRp (4 AML) . -L Ara

-C 22 % (11/49) 가 1

, -L OddC Ara-C Ara-C /

3

CRRF-CEM -L OddC Ara-C

CRRF-CEM -L OddC Ara-C MTT

(tetrazolium) 가

(dehydrogenase) (formazen) . 490

nm 가 , (linear curve fitting)(-L OddC Ara-c ;

3) , Chou Talalay, Adv. Enz. Regulation 22, 1984, pp.27-55 Cal

cuSyn (Boissoft, Ferguson, MO) 50 %

(IC₅₀) 72 MTT 72 IC₅₀

IC₅₀'s 가 (CI's) CalcuSyn , 3

, 1 CI , CI 가 1 가 , CI 가 1

1

CCRF-CEM /araC CalcuSyn (CI)

(A)
2h

Troxacitabine		araC		Trox/araC (2:1)		CI*
(nM)	% Toxicity	(nM)	% Toxicity	(nM)	% Toxicity	
31	3 ± 3	15	15 ± 8	31 / 15	31 ± 9	0.71 ± 0.08
62	12 ± 7	31	38 ± 11	62 / 31	47 ± 11	0.72 ± 0.09
125	11 ± 2	62	61 ± 10	125 / 62	70 ± 13	0.59 ± 0.16
250	24 ± 3	125	78 ± 6	250 / 125	85 ± 7	0.52 ± 0.10
500	34 ± 6	250	88 ± 4	500 / 250	92 ± 4	0.55 ± 0.09

n=3 in triplicate

(B)
72h

Troxacitabine		araC		Trox/araC (25:1)		CI
(nM)	% Toxicity	(nM)	% Toxicity	(nM)	% Toxicity	
20	0	0.8	1 ± 2	20 / 0.8	9 ± 7	0.2 ± 0.1
100	28 ± 5	4	13 ± 7	100 / 4	43 ± 6	0.3 ± 0.1
500	65 ± 2	20	50 ± 5	500 / 20	78 ± 2	0.7 ± 0.1
2500	90 ± 2	100	85 ± 2	2500 / 100	92 ± 2	2.1 ± 0.2
12500	98 ± 1	500	97 ± 2	12500 / 500	98 ± 1	6.0 ± 0.8

n=3 in triplicate

*CI : (CI<1 ; CI=1 가 ; CI>1)

4

(idarubicin) -L OddC 가

-L OddC (CML - BP) (AML), (MDS) .
 (0) -L OddC 5 mg/m² 5 30 , 1 3
 (1 ~ 5) 12 mg/m² .
 20 . 4 2 0 3
 mg/m² 3 - (hand-foot) . 16 -1 (4 mg/m² -L OddC / 9

(SAEs) 가 :

GI 가 , 가 .
 AML 10 2 CRs , MDS CR CML - MP CR
 가 -1 .
 5

(gemcitabine) -L OddC 가

-L OddC 가 .

MiaPaCa Panc-01

() (Troxacitabin) ± vs. MiaPaCa

가

20 g (nude) 가 58 mg (12) ,
 . 10 가 , 가
 . 1 qdx5 10 mg/kg 25 mg/kg
 (Eli Lilly, Lot# 4MT16M) q3dx4 40 mg/kg 80 mg/kg .
 , , .
 2 가 2 (calipers)
 가 1 (gram) , (W² × L)/2 mg , ,
 / ×100 (T/ C) 100 %
 (TGI) .

1

() Panc.-01 : () ± v
 s. Panc.-01 가 .

() (MTD)

/ (MTD)
 qdx5 - 10 mg/kg 가 .
 25 mg/kg , 5 1 가 . 23
 qdx5 25 mg/kg .

q3dx4	i.p.	4	10	25 mg/kg	40	80 mg/kg
5	6	12	. 10 mg/kg	40 mg/kg	가	
				. 10 mg/kg	80 mg/kg	
				(5 4.8)	. 25 mg/kg	, 25
40 mg/kg	80 mg/kg	5	5.6			
mg/kg			5	4		

2 MiaPaCa

1

3 Panc-1

2

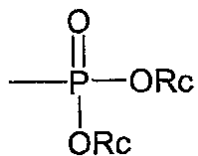
/

2

트록사시타빈 ± 겐시타빈 vs. MiPaCa 인간 췌장 세포노그라프트 모델

Group	n	Dose (mg/kg)	Route & Schedule	Weight Change (Day 6)	Weight Change (Day 12)	Final Tumor Wt. (Mean±SEM)	% Tumor Growth Inhibition	Mice with Partial Shrinkage	Mice with Complete Shrinkage	# of Toxic Deaths
Control	(10)	---	i.v.; qdx5	+2.6%	+2.8%	1133.4 ± 159.1	---	0	0	2
Troxactabine ¹	(10)	10	i.v.; qdx5	+0.2%	+3.0%	872.7 ± 171.1	23.9%	0	0	3
Troxactabine ¹	(10)	25	i.v.; qdx5	-3.9%	+8.0%	813.4 ± 57.9	29.7%	0	0	0
Gencitabine ²	(10)	40	i.p.; qdx4	-1.5%	+3.2%	733.0 ± 98.7	37.3%	0	0	0
Gencitabine ²	(10)	80	i.p.; qdx4	-1.0%	+2.8%	553.8 ± 124.3	53.6%	0	0	1
Troxactabine ¹	(10)	10	i.v.; qdx5	-6.0%	+3.5%	826.5 ± 81.8	28.5%	0	0	0
Gencitabine ²	(10)	40	i.p.; qdx4	-9.3%	-2.9%	483.4 ± 97.5	60.0%	0	0	1
Troxactabine ¹	(10)	25	i.v.; qdx5	-8.4%	+2.4%	492.3 ± 52.3	59.7%	0	0	0
Gencitabine ²	(10)	80	i.p.; qdx4	-9.7%	-16.4%	316.3 ± 58.7	76.3%	0	0	3

Note: The control and vehicle for Troxactabine was saline.
¹BioChem Pharma, Lot# 23g1-AL-2P.
²Eli Lilly, Lot# 4AMT16M.



(, Rc , C₁₋₆ , C₂₋₆ , C₂₋₆) .

2.

1 , R .

3.

1 , B 가 .

4.

1 , R B 가 .

5.

1 , B 가 5- .

6.

1 , (I) (-) - -L- - (-L-OddC) .

7.

1 , (I) (-) - -L- - 5 - - (5-FddC) .

8.

1 , (I) (-) .

9.

1 , (I) (+) 가 97% .

10.

1 , 1 가 .

11.

1 , 1 가 .

12.

11 , 1 가 .

13.

11 , 1 가 .

14.

11 , 1 가 .

15.

1 , 1 가 .

16.

15 , 1 가 .

17.

1 , (I) ,

18.

1 , -L-OddC , 가 가 .

19.

1 , -L-OddC , 가 가 .

20.

1 , -L-OddC , 가 가 .

21.

1 20 , .

22.

1 20 , .

23.

1 20 , .

24.

1 23 , 가

25.

1 23 , 가 1 : 250 250 : 1

26.

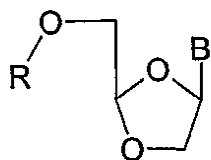
1 23 , 가 1 : 50 50 : 1

27.

1 23 , 가 1 : 20 20 : 1

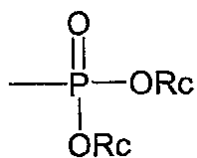
28.

/ (I) 1 가 ;



(I)

, B 5- , R , ,
(C₁₋₆ , C₂₋₆ , C₂₋₆ , C₆₋₁₀)



(, Rc , C₁₋₆ , C₂₋₆ , C₂₋₆)

.

29.

28 , (the step of administering) .

30.

28 , .

31.

28 , .

32.

28 , / .

33.

28 , / .

34.

33 , - L - OddC .

35.

28 , .

36.

28 , - L - OddC .

37.

28 , - L - OddC .

38.

28 , - L - OddC .

39.

28 , r , B .

40.

28 , - L - (+) 가 97 % .

41.

28 , 가 가 .

42.

28 , 가 가 .

43.

28 , 가 가 .

44.

28 43 , () .

45.

28 43 , ()

46.

28 43 , 가

47.

28 43 , 가 1 : 250 250 : 1

48.

28 43 , 가 1 : 50 50 : 1

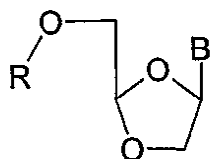
49.

28 43 , 가 1 : 20 20 : 1

50.

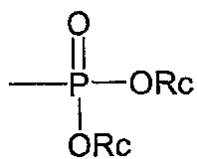
1 27 1 가

51.

() 가 ; , ,
1

(I)

, B 5-
(C₁₋₆ , C₂₋₆ , C₂₋₆ , C₆₋₁₀ , R) , ,



(, Rc , C₁₋₆ , C₂₋₆ , C₂₋₆)

52.

51 , () (+) 가 97 %

53.

51 , 1 가

54.

51 , 1 가 .

55.

51 , 1 가 .

56.

51 55 , .

57.

51 55 , .

58.

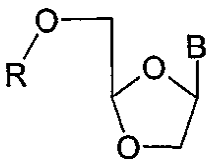
51 55 , 가 .

59.

51 55 , 가 .

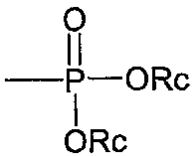
60.

() 1 1 가 ;
/ () 1 1 가
() 1 1 : 250 250 : 1 .



(I)

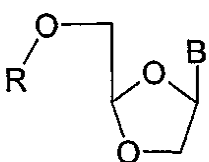
, B 5- , R ,
(C₁₋₆ , C₂₋₆ , C₂₋₆ , C₆₋₁₀)



(, Rc , C₁₋₆ , C₂₋₆ , C₂₋₆)

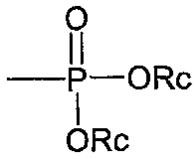
61.

() 1 1 가 ;
/ () 1 1 가 .



(I)

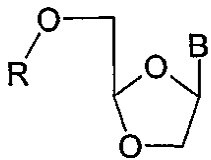
, B, 5-, R, ,
(C₁₋₆, C₂₋₆, C₂₋₆, C₆₋₁₀)



(, Rc, C₁₋₆, C₂₋₆, C₂₋₆)

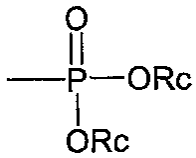
62.

() 1 가 ;
, / 1 가
() 1 1 : 250 250 : 1



(I)

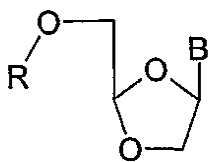
, B, 5-, R, ,
(C₁₋₆, C₂₋₆, C₂₋₆, C₆₋₁₀)



(, Rc, C₁₋₆, C₂₋₆, C₂₋₆)

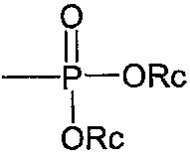
63.

() 1 가 ;
, / 1 가



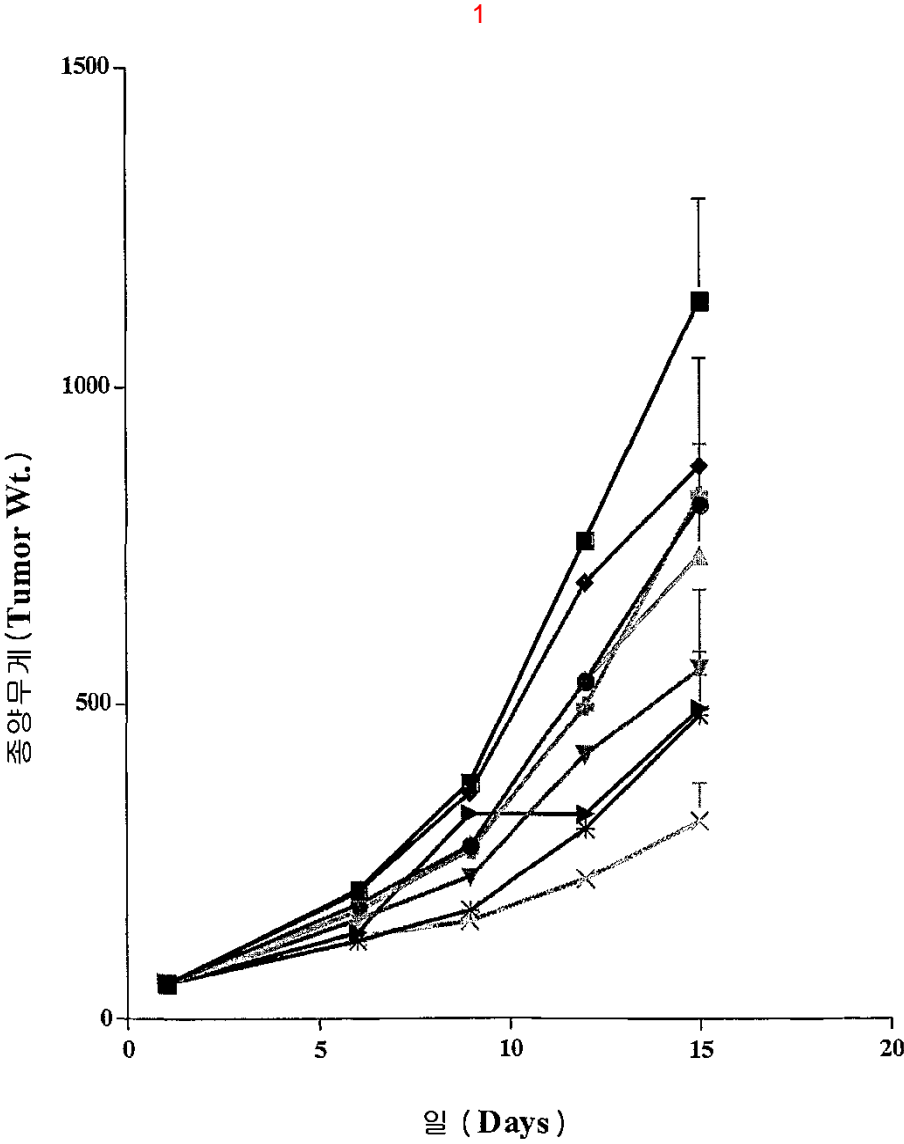
(I)

, B, 5-, R, ,
(C₁₋₆, C₂₋₆, C₂₋₆, C₆₋₁₀)

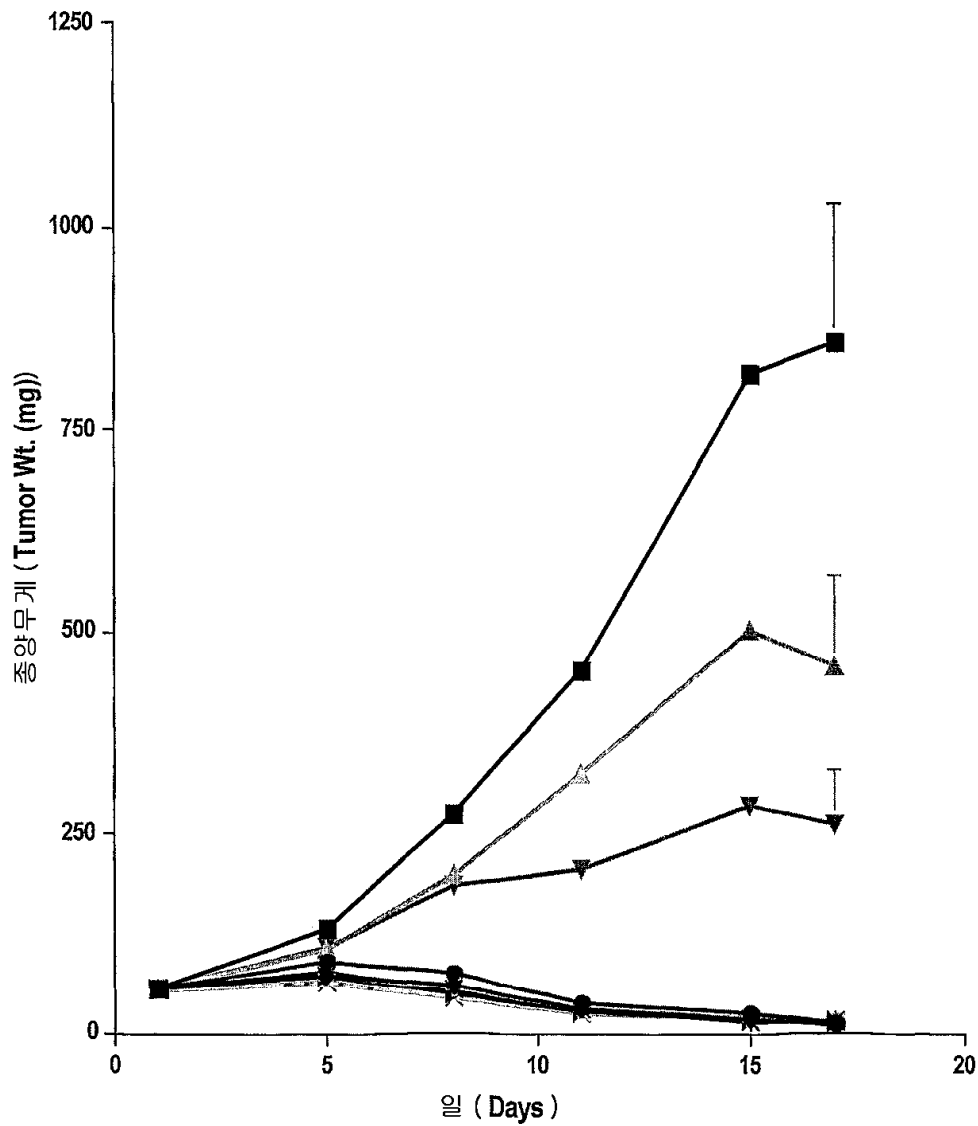


(, Rc , C 1-6 , C 2-6 , C 2-6)

60 64. 1 가



2

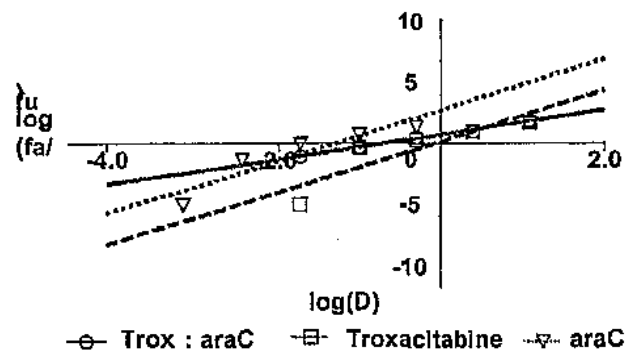


3a

MTT 72h		araC (uM)					
		0	0.00080	0.0040	0.020	0.10	0.50
Tr ox aci tab ine	0						
	0.020						
	0.10						
	0.50						
	2.5						
	12.5						

3b

Media-effe



3c

CI-effe

