

(19)
(12)

(KR)
(A)

(51) . Int. Cl.⁷
A61K 31/704

(11)
(43)

10-2004-0018341
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
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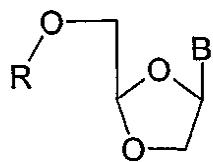
(72)	, , 77030,	1515,	61,
	, , 77030,	1515,	61,
	, , 7 4 9, ,	2235	

(74)

:

(54)

,	1	()	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

Research (2000), 6(4), pp 1574~1578

Clinical Cancer
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

(troxacicabine)

/

가

[]

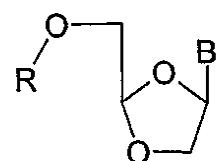
가

;

,

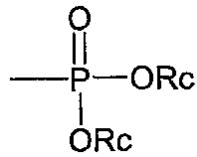
()

1



(I)

(C₁₋₆ B, C₂₋₆, C₂₋₆⁵⁻, C₆₋₁₀, R)



(, Rc , C₁₋₆ , C₂₋₆ , C₂₋₆)

, ()

, , () 1

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

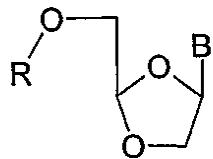
, () 1 가

$$1 : 50 \quad 50 : 1, \quad . \quad () \quad 1 : 20 \quad 20 : 1 \quad . \quad 1 : 250 \quad 250 : 1,$$

, ()

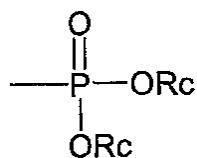
$$1 : 50 \quad 50 : 1 \quad () \quad 1 : 20 \quad 20 : 1 \quad 1 : 250 \quad 250 : 1$$

() 1 / ;



(I)

, B , C ₂₋₆ , C ₂₋₆ ⁵⁻ , C ₆₋₁₀ , R , , ,



(, Rc , C ₁₋₆ , C ₂₋₆ , C ₂₋₆)

, R

, B

, R

B

, B 5-

, () (-)- -L- - (-L-OddC)

() (-)- -L- -5- - (5-FddC)

, () (Substantially) (-)

()

(+)

가

95 %

(-)

, (-)

()

(+)

가

97 %

, (-)

()

(+)

가

99 %

, (-)

()

(+)

가

()

2

가

, () (, (+) (-) - L - D) 가

tic resolution)

(chiral auxiliary)

() HPLC,

(enzyma

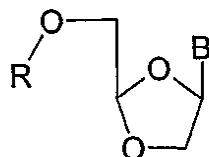
, 가 (myelogenous leukemia) 가 1 : 20 20 : 1
 $250 : 1$, $1 : 50$, $50 : 1$, $1 : 20$ 20 : 1
 $1 : 1$.

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

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

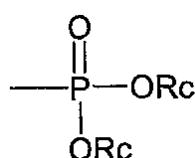
, / (refractory/relapsed leukemia)
 가 1 : 250, 250 : 1, 1 : 50, 50 : 1 (),
 1 : 20, 20 : 1,

, () 1 가 ; / 가



(I)

, B , C 2-6 , C 2-6 , C 6-10) , , , ,



$$(\quad \quad \quad \mathsf{Rc} \quad \quad \quad , \mathbf{C}_{1-6} \quad , \mathbf{C}_{2-6} \quad , \mathbf{C}_{2-6})$$

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

, , , , , , , ,
,

, () /
1
가 () 1 : 250 250 : 1

1 : 50 50 : 1 , 1 : 20 20 : 1 .
 , () /
 1
 가 , 1 : 50 , 50 : 1 , 가 1 : 20 1 : 250 250 : 1
 , () /
 1
 가 , 1 : 50 , 50 : 1 , 가 1 : 20 1 : 250 250 : 1
 , () /
 1
 가 , 1 : 50 , 50 : 1 , (blastic phase) 가 1 : 20 2
 1 : 250 250 : 1 ,
 0 : 1 .
 , () /
 1
 가 , 1 : 50 , 50 : 1 , 가 1 : 20 1 : 250 250 : 1
 , () /
 1
 1 : 250 250 : 1 , 가 1 : 50 , 50 : 1 , 가
 1 : 20 20 : 1 .
 , () /
 1
 / () , 가 1 : 20 1 : 250 250 : 1 , 가 1 : 50 ,
 50 : 1 ,
 , -L-OddC / 1 : 25
 0 250 : 1 , 1 : 50 , 50 : 1 , 1 : 20 20 : 1
 , -L-OddC ,
 1 : 250 250 : 1 , 1 : 50 , 50 : 1 , -L-OddC 가
 20 20 : 1 .
 , -L-OddC ,
 1 : 250 250 : 1 , 1 : 50 , 50 : 1 , -L-OddC 가
 1 :
 1 : 250 250 : 1 , 1 : 20 20 : 1 .
 , -L-OddC ,
 1 : 250 250 : 1 , 1 : 50 , 50 : 1 , -L-OddC
 50 50 : 1 , 1 : 20 .
 , -L-OddC ,
 1 : 250 250 : 1 , 1 : 50 , 50 : 1 , -L-OddC
 50 50 : 1 , 1 : 20 .
 , -L-OddC

, -L-OddC 1 : 250 250 : 1 ,
 1 : 50 50 : 1 , 1 : 20 20 : 1 .
 , -L-OddC , , -L-OddC 가 1
 250 250 : 1 , 1 : 50 50 : 1 , 1 : 20 20 : 1
 1 .
 , -L-OddC , , , , , , , , , , ,
 , , , , , , , , , , , ,
 , -L-OddC , 가 1 : 250 250 : 1 , 1 : 50 ,
 50 : 1 , 1 : 20 20 : 1 .
 , -L-OddC , , , , , , , , , , ,
 , , , , , , , , , , , ,
 1 : 250 250 : 1 , 1 : 50 , 50 : 1 ,
 1 : 20 20 : 1 .
 , -L-OddC , , , , , , , , , , ,
 , , , , , , , , , , , ,
 , -L-OddC , 가 1 : 250 250 : 1 , 1 : 50 , 50 : 1 ,
 : 1 , 1 : 20 20 : 1 .
 , -L-OddC , , 1
 (synergistic combination)

(acute myelogenous leukemia or acute myeloid leukemia : AML) (chronic myelo-
genous leukemia or chronic myeloid leukemia : CML), (chronic lymphocytic leukemia : CL
L), (acute lymphocytic leukemia : ALL), (hairy cell leukemia : HCL),
(myelodysplastic syndromes : MDS) (chronic myelogenous leuke-
mia in blastic : CML - BP) 가 ,

(myelogenous leukemia)'

(AML, CML)

(, ,) , 가

/ (refractory/relapsed leukemia)' (response)

(patieut)'

(aryl)' (,)

(T.Greene) Protective Groups In Organic Synthesis.(John Wiley & Sons, 1981)

		()	0.1 gm/m ²	1 mg/m ²	6 gm/m ²	8 mg/m ²	1	
가	,	()	0.1 gm/m ²	1 mg/m ²	6 gm/m ²	8 mg/m ²	1	
가	,	()	0.1 gm/m ²	1 mg/m ²	6 gm/m ²	8 mg/m ²	1	
가	,	()	1 gm/m ²	1 mg/m ²	30 gm/m ²	8 mg/m ²	1	
2	,	- L - OddC	1 1 gm/m ²	5	1	30	6 mg/m ²	1 5
2	,	- L - OddC	1 12 gm/m ²	5	1	30	5 mg/m ²	1 3

, mg/kg/day , 가 1 0.1 750 mg/kg 1 300 mg/kg/day . , 0.5 500 , 1 2 , 3 , 4

가 1 75 μM. 2 50 μM. 가

0.1 5 %

(, , ,)

가

가 가 (transdermal patch) (linalool), (carvacrol), (citrał), / (t-anethole)

(mouth) , 가
(lozenges); (pastilles); (mouthwashes)
가 .

가 가

가 가

forms)

가

108

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

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 × 5);  : 10 mg/kg(i.v.; qd × 5);  : 25 mg/kg(i.v.; qd × 5);  : 40 mg/kg(i.p.; ;  : 80 mg/kg;  : 10 mg/kg(i.v.; ;  : 10 mg/kg(i.v.; qd × 5), 40 mg/kg(i.p.; ;  : 10 mg/kg(i.v.; qd × 5), 80 mg/kg(i.p.; ;  : 25 mg/kg(i.v.; qd × 5), 40 mg/kg(i.p.; ;  : 25 mg/kg(i.v.; qd × 5), 80 mg/kg(i.p.;]

2 Panc - 01

[ : (i.v.; qd × 5);  : 10 mg/kg(i.v.; qd × 5);  : 25 mg/kg(i.v.; qd × 5);  : 40 mg/kg(i.p; q3d × 4);  : 80 mg/kg(i.p.; q3d × 4);  : 10 mg/kg(i.v.; qd × 5), 40 mg/kg(i.p.; q3d × 4);  : 10 mg/kg(i.v.; qd × 5), 80 mg/kg(i.p.; q3d × 4);  : 25 mg/kg(i.v.; qd × 5), 40 mg/kg(i.p.; q3d × 4);  : 25 mg/kg(i.v.; qd × 5), 80 mg/kg(i.p.; q3d × 4)]

3 CCRF - CEM nalysis

- (Ara-C)

CalcuSyn A

(72)

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

1

- L OddC 가

- BP)	/	(AML)	(ALL)	42	,	-L OddC	(MDS),	가	.	(CML
가	.	16	가	AML	2	.	,	39	1	(18 %)

2

Ara-C -L OddC 가

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

(response criteria) 가 : (CR)
 (CRp) CR 5%
 가 , 1 × 10⁹ /L CRp CR
 4 100 × 10⁹ /L <100 × 10⁹ /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

CCRF-CEM - L OddC Ara-C

CCRF-CEM - L OddC Ara-C MTT
 (tetrazolium) 가
 (dehydrogenase) (formazan) 490
 nm
 가 , - L OddC Ara-c
 3) Chou Talalay, Adv. Enz. Regulation 22, 1984, pp.27-55 (linear curve fitting)(- ;
 cuSyn (Boissoft, Ferguson, MO) 50 %
 (IC₅₀) 72 MTT 72 IC₅₀
 IC₅₀'s (CI's) CalcuSyn , 3
 , 1 CI , CI 가 1 , CI 가 1 , 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 ± 9	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

5
(gemcitabine) - L OddC 가
- I OddC 가

MiaPaCa Panc-01
() (Troxacitabin) ± vs. MiaPaCa

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

() Panc.-01 : () ± v
s. Panc.-01 가 .

() _____ (MTD) _____

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

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

2 MiaPaCa

1

3 Panc - 1

2

/

2

트록사시티빈 ± 겔시티빈 vs. MiaPaCa 인간 죽장 세포그라프트 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
Gemcitabine ²	(10)	40	i.p.; q3dx4	-1.6%	+3.2%	733.0 ± 98.7	37.3%	0	0	0
Gemcitabine ²	(10)	80	i.p.; q3dx4	-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
Gemcitabine ²	(10)	40	i.p.; q3dx4	-9.8%	-2.9%	483.4 ± 97.5	60.0%	0	0	1
Troxactabine ¹	(10)	80	i.p.; q3dx4	-9.8%	-2.9%	483.4 ± 97.5	60.0%	0	0	0
Troxactabine ¹	(10)	25	i.v.; qdx5	-8.4%	+2.4%	492.3 ± 52.3	59.7%	0	0	0
Gemcitabine ²	(10)	40	i.p.; q3dx4	-9.7%	-16.4%	316.3 ± 58.7	75.3%	0	0	3
Troxactabine ¹	(10)	25	i.v.; qdx5	-9.7%	-16.4%	316.3 ± 58.7	75.3%	0	0	3
Gemcitabine ²	80	i.p.; q3dx4								

Note: The control and vehicle for Troxactabine was saline.

¹BioChem Pharma, Lot#23g1-AL-2P.

²Eli Lilly, Lot# 4MT16M.

트로사티빈 ± 켐사티빈 vs. Panc-01 일기 죽장 종양 제노그라프트 모델

Group (n=10) (mg/kg) Schedule	Dose (Day 8)	Route & (Day 17)	Weight Change (Mean±SEM)	Final Tumor Wt	%Tumor Growth Inhibition	Mice with Partial Shrinkage	Mean %tumor shrinkage	Mice with Complete Deaths
Control	Saline	i.v.; qd×5	+0.7%±7.9%	855.9±170.7	—	0	—	0
Troxactabinet ¹	10	i.v.; qd×5	+0.3%	+11.7%	11.1±2.1	—	9	77.5% 1 0
Troxactabinet ¹	25	i.v.; qd×5	-2.1%	+11.1%	12.5±1.9	—	9	72.6% 1 0
Gemcitabine ²	40	i.p.; q3d×4	+1.4%	+13.0%	457.8±113.9	49.8% 0	—	0 0
Gemcitabine ²	80	i.p.; q3d×4	-1.7%	+15.9%	262.2±67.7	74.3% 0	—	0 0
Troxactabinet ¹	10	i.v.; qd×5	-7.1%	+6.8%	13.2±1.1	—	10	73.9% 0 0
Gemcitabine ²	40	i.p.; q3d×4	-5.8%	+9.1%	14.6±0.8	—	10	70.1% 0 0
Troxactabinet ¹	10	i.v.; qd×5	i.p.; q3d×4	-15.4%	+4.1%	14.0±1.4	—	9 73.1% 0 1
Gemcitabine ²	80	i.p.; q3d×4	-15.4%	+4.1%	14.0±1.4	—	9 73.1% 0 1	

Note: The control and vehicle for Troxactabinet was saline.

BioChem Pharma, Lot# 23g1-A1-2P.
ELI Lilly, Lot# 4MT16M.

(57)

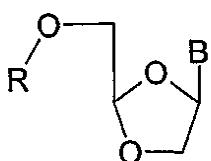
1.

(I)

1

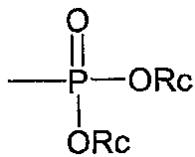
1

가



(II)





(, 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

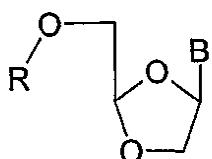
28.

(I)

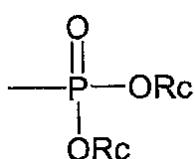
1

가

;



(I)

$$,(C_{1-6}, B, C_{2-6}, C_{2-6}^{5-}, C_{6-10}, R), , , ,$$


(, 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 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.

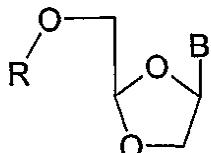
28 43 , 가 1 : 50 50 : 1

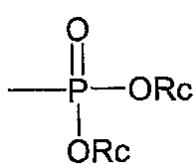
49.

28 43 , 가 1 : 20 20 : 1

50.

1 27 1 가

51.()
1 가 ; , ,

$$,(C_{1-6}, B, C_{2-6}, C_{2-6}^{5-}, C_{6-10}, R), , , ,$$


$$(, Rc, C_{1-6}, C_{2-6}, C_{2-6})$$
52.

51 , () (+) 가 97 %

53.

51 , 1 가

54.

51 , 1 가

55. 51 , 1 가

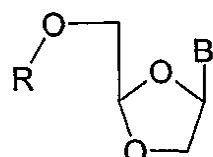
56.

57.

58. 51 55 , 가

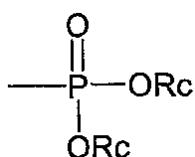
59. 51 55 , 가

$$60. \quad () \quad 1 \quad 1 \quad , \quad 1 : 250 \quad 250 : 1 \quad \text{가} \\ / \quad () \quad 1 \quad \text{가}$$



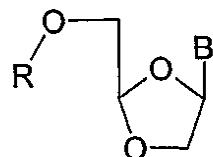
(1)

, B , C 2-6 , C 2-6 , C 6-10 , R) ,



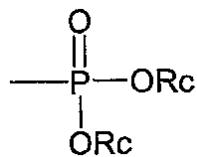
$$(\quad , \quad \text{Rc} \quad , \quad C_{1-6} \quad , \quad C_{2-6} \quad , \quad C_{2-6})$$

61. () 1 1 , 가 가
/ () 1 가



(I)

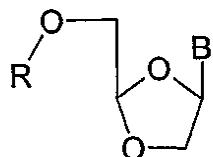
, B , C₂₋₆ , C₂₋₆ , C₆₋₁₀ , R) , , ,



(, Rc , C₁₋₆ , C₂₋₆ , C₂₋₆)

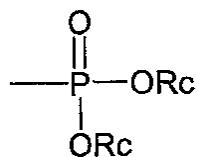
62.

() 1 / () 1 1 : 250 , 250 : 1 가 ;



(I)

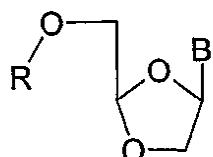
, B , C₂₋₆ , C₂₋₆ , C₆₋₁₀ , R) , , ,



(, Rc , C₁₋₆ , C₂₋₆ , C₂₋₆)

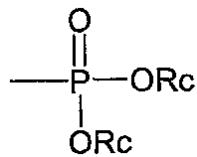
63.

() 1 / 1 , ;



(I)

, B , C₂₋₆ , C₂₋₆ , C₆₋₁₀ , R) , , ,



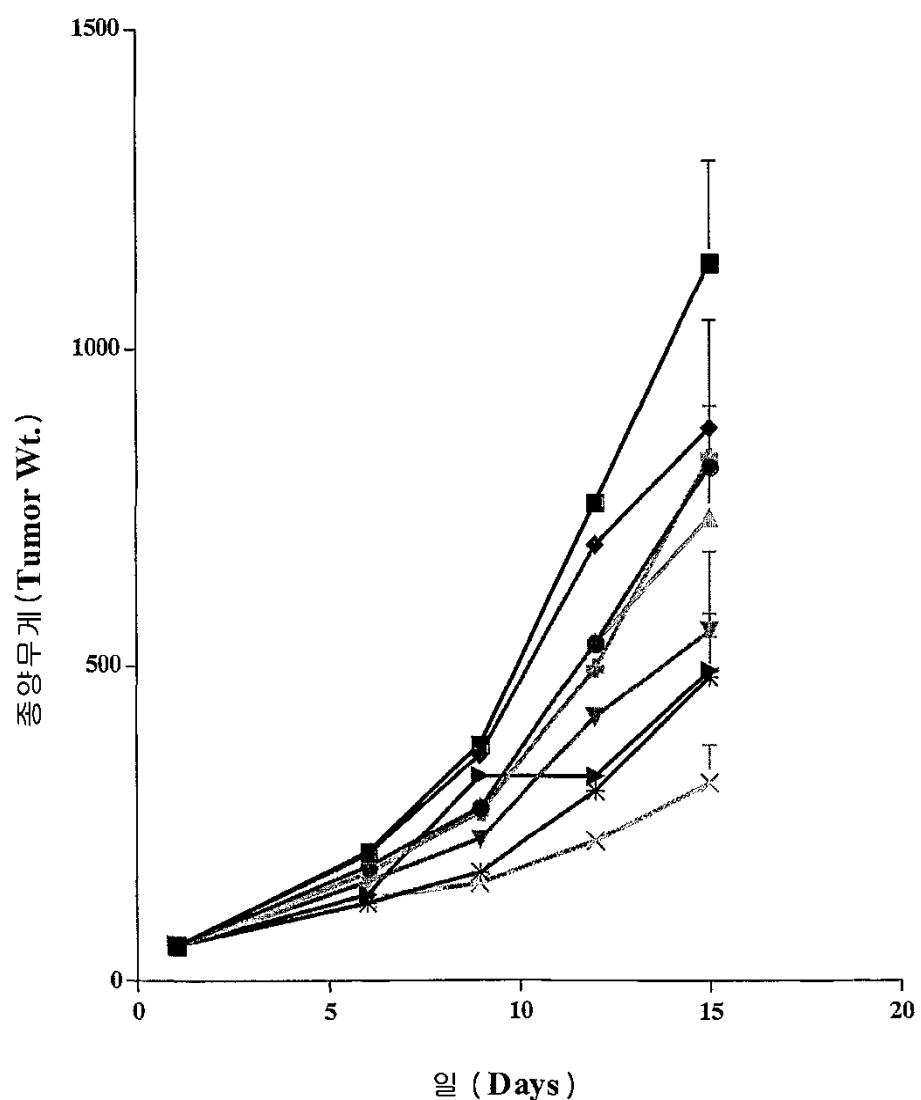
(, Rc , C₁₋₆ , C₂₋₆ , C₂₋₆)

64.

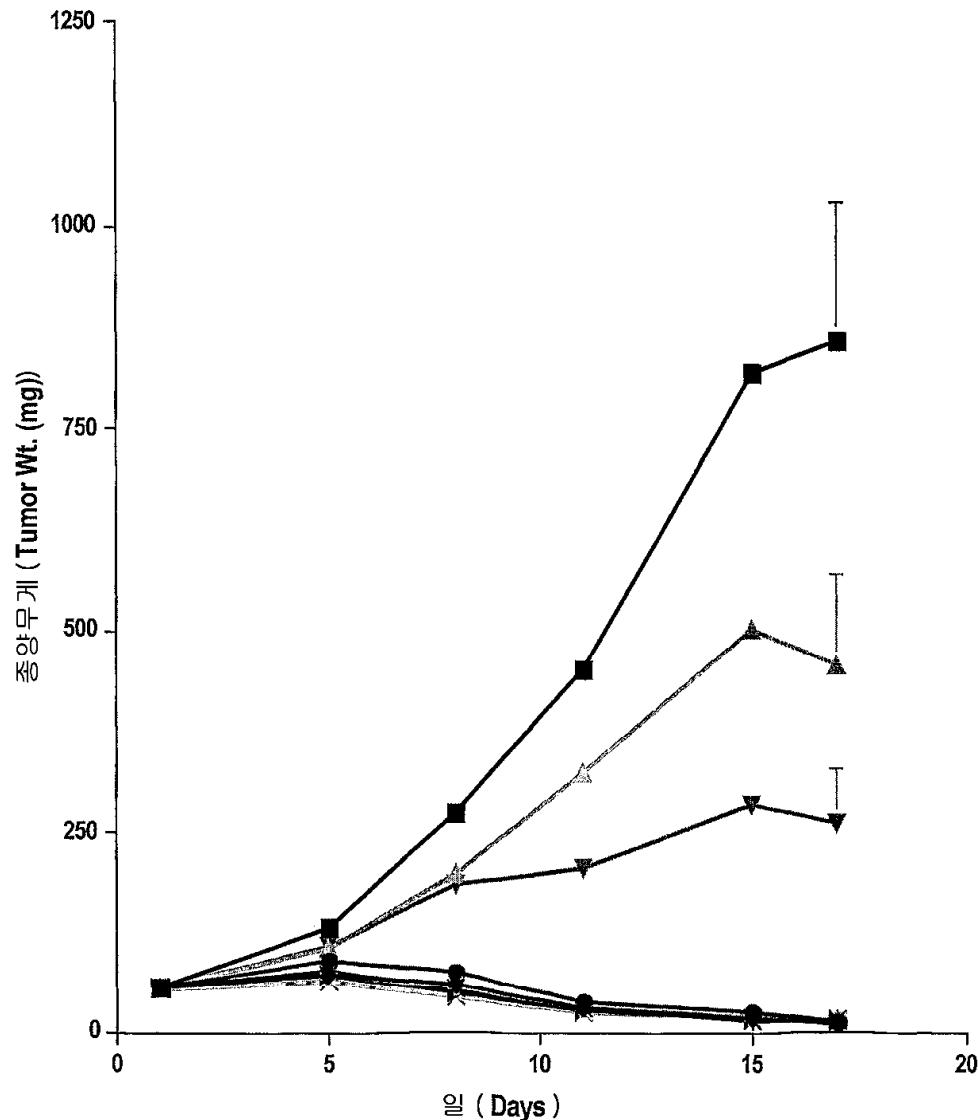
1

가

1



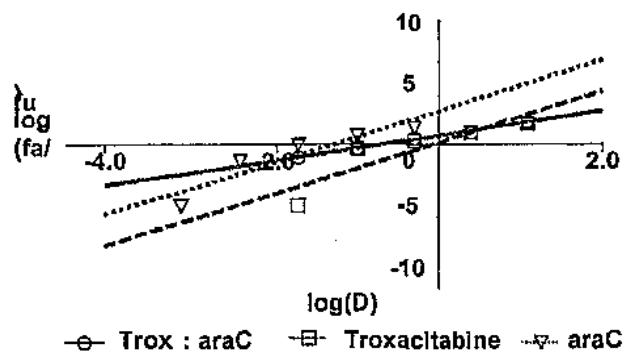
2



3a

MTT 72h	araC (μ M)					
	0	0.00050	0.0040	0.020	0.10	0.50
0						
0.020						
Tr						
ox						
aci						
tab						
ine						
2.5						
12.5						

3b

Media-effe

3c

Cl-effe