

(74)

:

(54) s P L A 2

) - 1H - - 4 -)) sPLA₂ ((3 - (2 - - 1,2 -) - 2 - - 1 - (N - .

sPLA , , 1H - - 3 -

sPLA₂ .

A₂ (" sPLA₂ ") 2 가

(Seilhamer, Jeffrey J.; Pruzanski, Waldemar;

Vadas Peter; Plant, Shelley; Miller, Judy A.; Kloss, Jean; and Johnson, Lorin K.; " Cloning and Recombinant Expression of Phospholipase A₂ Present in Rheumatoid Arthritic Synovial Fluid" The Journal of Biological Chemistry, Vol. 264, No. 10, Issue of April 5, pp. 5335 - 5338, 1989; Kramer, Ruth M.; Hession, Catherine; Johansen, Berit; Hayes, Gretchen; McGray, Paula; Chow, E. Pingchang; Tizard, Richard; and Pepinsky, R. Blake; " Structure and Properties of a Human Non - pancreatic Phospholipase A₂ " The Journal of Biological Chemistry, Vol. 264, No. 10, Issue of April 5, pp. 5768 - 5775, 1989).

sPLA₂ 가 . , sPLA₂

(,) sPLA₂ / (,

, , , , , , ,)

, 가 가 가

5,654,326 sPLA₂ 가 . ,

가 ((3 - (2 - - 1,2 -) - 2 - - 1 - () - 1H - - 4 -))

sPLA₂ , 가 가 .

< >

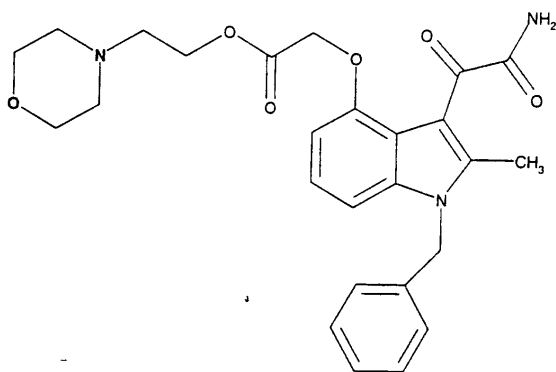
) - 1H - 4 -)) N - ((3 - (2 - 1,2 -) - 2 - 1 - (

((3 - (2 - 1,2 -) - 2 - 1 - () - 1H - 4 -)) N -

1H - 3 - :

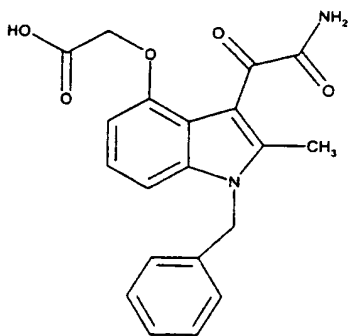
N - ((3 - (2 - 1,2 -) - 2 - 1 - () - 1H - 4 -))

I



- 1,2 - I N - II sPLA₂ ((3 - (2 -) - 2 - 1 - () - 1H - 4 -))

II



II 95302166.4 , 5,654,326 (: 1995 10 4) 1

I sPLA₂

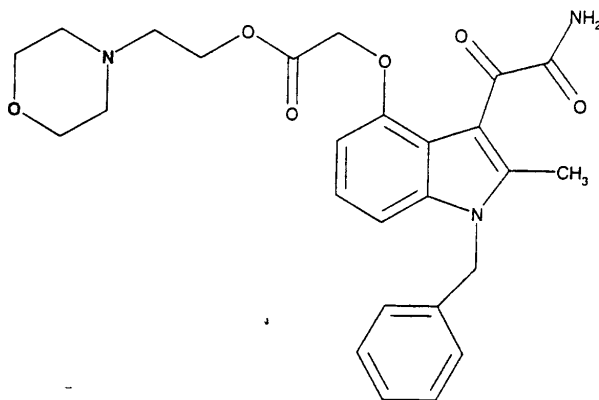
:

((3-(2-(1,2-...))-2-...-1-(...))-1H-...-4-...)) N-
 (I) ((3-(2-(1,2-...))-2-...-1-(...))-1H-...-4-...))
 5,654,326 (II) 1
 95302166.4 , 0 675 110 (: 1995 10 4)

1

I ((3-(2-(1,2-...))-2-...-1-(...))-1H-...-4-...))
 N- :

< I >



A. N-tert-...-3-...-2-

400 mL THF 3-...-2- 44.4 g(344 mmol) -tert- 75 g(344 mmol)
 가 , , 1N

64.5 g(84%) N-tert-...-3-...-2-

:56 - 57

C₁₃ H₁₉ NO₃ :

: C, 65.80; H 8.07; N, 5.90

: C, 63.32; H 7.83; N, 5.56

B. 4-...-2-...-1H-

2-가 (43 g, 0.18 mol) 300 Mℓ THF N-tert-sec- (1.3M) 280 Mℓ
 -60가, THF 18.5 g(0.18 mol) N-N-가
 600 Mℓ 1N 600 Mℓ, 1
 39.5 g 1-(2-(tert-)-6-)-2- 40 Mℓ
 26 20% / CH₂Cl₂/
 13.9 g 4- -2- -1H-
 : 80 - 86

C₁₀ H₁₁ NO

: C, 74.51; H, 6.88; N, 8.69

: C, 74.41; H, 7.08; N, 8.47

C. 4- -2- -1-() -1H-

15 Mℓ DMF 248 mg(6.2 mmol) 60% / (DMF 가) 4-
 -2- -1H- (1 g, 6.2 mmol) 가 0.5 0.74 Mℓ(6.2 mmol)
 가 18

20% / 1.3 g(84%) 4- -2- -1-() -1H-

: 96 - 116

C₁₇ H₁₇ NO

: C, 81.24; H, 6.82; N, 5.57

: C, 81.33; H, 6.74; N, 5.29

D. 4- -2- -1-() -1H-

50 Mℓ 5 4- -2- -1-() -1H- 1.25 g(5 mmol) 1M BBr₃/CH₂Cl₂ 20 Mℓ가
 577 mg(49%) 4- -2- -1-() -1H- /
 20%

: 125 - 127

C₁₆ H₁₅ NO

: C, 80.98; H, 6.37; N, 5.90

: C, 80.76; H, 6.26; N, 5.80

E. ((2- -1-() -1H- -4-))

20 Mℓ DMF 88 mg(2.2 mmol) 60% / 4- -2- -1-() -1H- (5
30 mg, 2.2 mmol) 가 , 0.67 0.21 Mℓ(2.2 mmol)
가 17

20% / 597 mg(88%) ((2- -1-(
) -1H- -4-))

: 140 - 143

C₁₉ H₁₉ NO₃ :

: C, 73.77; H, 6.19; N, 4.53

: C, 74.01; H, 6.23; N, 4.32

F. ((3-(2- -1,2-) -2- -1-() -1H- -4-))

10 Mℓ 582 mg(1.9 mmol) ((2- -1-() -1H- -4-))
(0.16 Mℓ, 1.9 mmol) 가 1.5
10 Mℓ 0.25 가 , 1.5
20 Mℓ 가
((3-(2- -1,2-) -2- -1-() -1H- -4-))
672 mg

: 202 - 215

G. ((3-(2- -1,2-) -2- -1-() -1H- -4-))

30 Mℓ 660 mg(1.7 mmol) ((3-(2- -1,2-) -2- -1-() -1H- -
4-)) 10 Mℓ 1N NaOH 1 가 , 가
0.5 / 1N
pH 2 - 3
431 mg(69%) ((3-(2- -1,2-) -2- -1-() -1H- -4-))

: 218 - 220

C₂₀ H₁₈ N₂ O₅ :

: C, 65.57; H, 4.95; N, 7.65

: C, 63.31; H, 4.79; N, 6.91

H. ((3 - (2 - - 1,2 -) - 2 - - 1 - () - 1H - - 4 -)) N -

3) 4 - (2 -) (Cs₂CO₃); ((3 - (2 - - 1,2 -) - 2 - - 1 - () - 1H - C₄,220 -
- 4 -)) () 가 , 가
60 가 , 가

< 1 >

6 가 가 10 mg/kg (3)

24 . LC/MS
(auc) 8 24

sPLA₂ 가

:

:

:

:

sPLA₂

:

10% sPLA₂

:

:

:

: 10 mg/kg ()

: 5 M \emptyset /kg

[1]

	C (ng/Mℓ)	T	AUC(0-8)ng*h/Mℓ	AUC(0-24)ng*h/Mℓ
1	1604	2.0	5131	5425
2	200	2.0	1356	2038
3	213	2.0	1277	1761
4	245	2.0	1675	3404
5	3296	2.0	11919	13161
6	615	3.3	- - -	8730

1 = "((3 - (2 - 1,2 -) - 2 - 1 - () - 1H - 4 -)) N -

2 = "((3 - (2 - 1,2 -) - 2 - 1 - () - 1H - 4 -))

3 = "((3 - (2 - 1,2 -) - 1 - ((1,1' -) - 2 -) - 2 - 1H - 4 -)) N,N -

4 = "((3 - (2 - 1,2 -) - 2 - 1 - () - 1H - 4 -))

5 = "((3 - (2 - 1,2 -) - 2 - 1 - () - 1H - 4 -)) N -

6 = "((3 - (2 - 1,2 -) - 2 - 1 - () - 1H - 4 -))

< 2 >

N - ((3 - (2 - 1,2 -) - 2 - 1 - () - 1H - 4 -))

sPLA₂

가

:

:

: 344

sPLA₂

:

10% sPLA₂

:

:

:

: 10 mg/kg()

: 5 M ℓ /kg

:

(0.8 M ℓ) : 0.5, 1, 2, 4, 6 8 (2 /)

:

HPLC sPLA₂ ()

C () AUC -

[2]

	C (ng/M ℓ)	AUC(0 - 8)
11	1094	2400
12	79	385
13	258	1229
14	1199	2604
15	612	1504
16	259	1031

11 = "(3 - (2 - - 1,2 -) - 2 - - 1 - () - 1H - - 4 -)
) N - ()

12 = "(3 - (2 - - 1,2 -) - 2 - - 1 - () - 1H - - 4 -)
) N,N -

13 = "(3 - (2 - - 1,2 -) - 2 - - 1 - ((1 -)) - 1H -
 - 4 -)) N,N -

14 = "(3 - (2 - 1,2 -) - 2 - 1 - ((1 -) - 1H -
 - 4 -)) N -

15 = "(3 - (2 - 1,2 -) - 2 - 1 - ((3 -) - 1H -
 - 4 -)) N -

16 = "(3 - (2 - 1,2 -) - 2 - 1 - ((3 -) - 1H -
 - 4 -)) N,N -

(57)

1.

((3 - (2 - 1,2 -) - 2 - 1 - () - 1H - - 4 -)) N -

2.

1