

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

(51) Int. Cl.<sup>7</sup>  
 A61K 31/445  
 A61P 25/22

(11) 10-2004-0029375  
 (43) 2004 04 06

(21)	10-2004-7000901		
(22)	2004 01 19		
	2004 01 19		
(86)	PCT/IB2002/002847	(87)	WO 2003/009848
(86)	2002 07 15	(87)	2003 02 06

(30) 60/306,692 2001 07 20 (US)

(71) 06340

(72) 06340

06340

06340

(74)

:

(54) , NK-1

NK-1 가 ,

NK-1 가 ,

(companion animals) 가 ,

50%가 (J. van der Borg), (W. J. Netto) (D. J. Planta) ['Behavioural Testing of Dogs in Animal Shelters to Predict Problem Behavior', Applied Animal Behaviour Science 32 (1991), pp. 237-251] ).

가 (separation anxiety) (vocalization) (K. Overall) 14% ['Understanding Canine Separation Anxiety'] . , , . , , 가 (lethargy) ( ). ( ).

가 (Soraya Juarbe-Diaz) ['Assessment and Treatment of Excessive Barking in the Domestic Dog', Progress in Companion Animal Behavior 27 (May 1997), pp. 515-532] . : , (buspirone), ( ).

가 , 가 , (Angel) ['Assessment of Pointer Dog Behavior', Pav. J. Biol. Sci. 17 (April-June 1982), pp. 84-88] . (Van der Borg) ['Human Interaction Test'] (matching) (Van der Borget al., at 237).

(tachykinin) , P, A B , P (B.E.B. Sandberg) [J. Med. Chem. 25 (1982) 1009] . , , (Crohn's disease) (gastrointestinal) (D. Regoli) ['Trends in Cluster Headache', edited by F. Sicuteli et al., Elsevier Scientific Publishers, Amsterdam, pp. 85-95 (1987)] .

P	1(NK-1)	NK-1
NK-1	, P W099/07375 6,117,855	NK-1
NK-1	WO 96/10568	WO 98/15277
	,	WO 00/35915
5,773,450	NK-1	1998 6 30
4	['Fluoroalkoxybenzylamino derivatives of nitrogen containing heterocycles']	2001 4 2
	6,222,038	['Quinuclidine derivatives']

NK-1 가 , NK-1

NK-1

g), (circling), 가 ( , , (hypervigilance), (howling); (whining)); ( , , (pacin polydipsia)); ( , , (grooming)( , , ); ( , , ); ( , , ).

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NK - 1

가

가  
NK - 1

가 가 ,

NK - 1

(a)

; (e) 1 ; (d)

; (b)  
가  
2

; (c)

1  
가 48  
)

1

2

NK - 1

가

NK - 1

가

NK - 1

가

가

, NK-1

:

(2S,3S)-3-(5- - -2- ) -2-(3- ) ;  
 (2S,3S)-3-(2- -5- ) -2- - ;  
 (2S,3S)-3-(2- -5- ) -2- - ;  
 (2S,3S)-3-(2- -5- ) -2- - ;  
 (2S,3S)-3-(5- - -2- ) -2- ;  
 2-( )-N-(2- -5- - ) -1- [2.2.2] -3- ;  
 (2S,3S)-3-[5- -2-(2,2,2- )- ] -2- ;  
 (2S,3S)-3-(5- - -2- ) -2- ;  
 (2S,3S)-3-(2- -5- ) -2- ;  
 (2S,3S)-3-(2- -5- ) -2- -2- ;  
 (2S,3S)-2- -3-[2-(2,2,2- )- ] -2- ;  
 (2S,3S)-2- -3-(2- )]- - ;  
 -3-(2- )-2- ;  
 -3-(2- )-2- - ;  
 -3-(2- )-2-(2- )- ;  
 -3-(2- )-2-(2- )- ;  
 -3-(2- )-2-(3- )- ;  
 -3-(2- )-2-(3- )- ;  
 -3-(2- )-2-(3- )- ;  
 -3-(2- )-2- ;  
 -3-(2- )-2-(3- )- ;  
 -3-(2- )-2-(4- )- ;  
 -3-(2- )-2-(3- )- ;  
 -3-(2- )-2- - ;  
 3-(2- )-4- -2- ;  
 3-(2- )-5- -2- ;  
 3-(2- )-6- -2- ;

(2S,3S)-3-(2-) -2- ;  
(2S,3S)-1-(5-) -1- )-3-(2- - )-2- ;  
(2S,3S)-1-(6-) - -1- )-3-(2- - )-2- ;  
(2S,3S)-1-(4-) -4- -1- )-3-(2- - )-2- ;  
(2S,3S)-1-(4-) -4- -1- )-3-(2- - )-2- ;  
(2S,3S)-1-(5,6-) -1- )-3-(2- - )-2- ;  
-3-(5-) -2- )-2- - ;  
(2S,3S)-1-[4-(4-) )-4- -1- ]-3-(2- )-2- ;  
(2S,3S)-1-[4-(4-) )-4- -1- ]-3-(2- )-2- ;  
-3-(2- -5- )-2- - ;  
(2S,3S)-1-(4-) -1- )-3-(2- - )-2- ;  
-3-(2- -1- )-2- - ;  
(2S,3S)-3-(2-) )-1-(5-N- - -1- )-2- ;  
(2S,3S)-1-(4-) -1- )-3-(2- )-2- ;  
(2S,3S)-1-[4-(2-) ) -1- ]-3-(2- - )-2- ;  
(2S,3S)-1-(5-) -1- )-3-(2- - )-2- ;  
(2S,3S)-1-(5-) -1- )-3-(2- )-2- ;  
(2S,3S)-3-(5-) -2- )-2- - ;  
(2S,3S)-3-(2,5-) -2- - ;  
-3-(3,5-) -2- )-2- - ;  
-3-(4,5-) -2- )-2- - ;  
-3-(2,5-) )-1-[4-(4-) )-4- -1- ]-2- ;  
-3-(5- -2- )-1-(5,6- -1- )-2- ;  
-1-(5,6-) -1- )-3-(2,5- - )-2- ;  
-2- -3-[ -2-( -2- ) ] - ;  
-3-(2,5-) ) -2-(3- - ) - ;  
-3-(5- -2- ) -2-(3- - ) - ;  
3-(2- )-2,4- ;

-3-(2- )-2- ;  
 (2S,3S)-3-(5- -2- ) -2- - ;  
 (2S,3S)-3-(5-n- -2- ) -2- - ;  
 (2S,3S)-3-(2- -5-n- ) -2- - ;  
 (2S,3S)-3-(5- -2- ) -2- - ;  
 (2S,3S)-3-(5- -2- ) -2- - ;  
 (2S,3S)-3-(2- -5- ) -2- - ;  
 2,4- -5- [4- -3-((2S,3S)-2- -3- - )] - ;  
 N-(4,5- -2- )-N-[4- -3-((2S,3S)-2- -3- - )] - ;  
 {5-[(4,5- -2- )] -2- }-((2S,3S)-2- -3- ) ;  
 {5-(4,5- -2- )-2- }-((2S,3S)-2- -3- ) ;  
 4,5- -2- -[3-((2S,3S)-2- -3- - )]-4- ] - ;  
 2,4- -5- [4- -3-((2S,3S)-2- -3- - )] - ;  
 2,4- -5- [4- -3-((2S,3S)-2- -3- - )] - ;  
 2,4- -5- [4- -3-((2S,3S)-2- -3- - )] - ;  
 (2S,3S)-N-(5- -2- ) -2- -1- [2.2.2] -3- ;  
 (2S,3S)-N-(5-n- -2- ) -2- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-N,N- -5-(5- -2- - )-6- -1- [2.2.2] -3- ;

(3R,4S,5S,6S)-N,N- -5-(2,5- )-6- -1- [2.2.2] -3- ;

(3R,4S,5S,6S)-5-(5- -2- )-6- -1- [2.2.2] -3- ;

(3R,4S,5S,6S)-5-(2- -2- )-6- -1- [2.2.2] -3- ;

(3R,4S,5S,6S)-5-(2,5- )-6- -1- - [2.2.2] -3- ;

(3R,4S,5S,6S)-5-(2- -5- )-6- -1- [2.2.2] -3- ;

(3R,4S,5S,6S)-5-(5- -2- )-6- -1- [2.2.2] -3- ;

(3R,4S,5S,6S)-5-(2- -5-n- )-6- -1- [2.2.2] -3- ;

(3R,4S,5S,6S)-5-(5- - -2- )-6- -1- [2.2.2] -3- ;

(3R,4S,5S,6S)-5-(5-N- -3- )-6- -1- [2.2.2] ;

(3R,4S,5S,6S)-5-(2- -5- - )-6- -1- [2.2.2] -3- ;

(3R,4S,5S,6S)-5-(2- -5- - )-6- -1- [2.2.2] -3- ;

(3R,4S,5S,6S)-5-(2- -5- - )-6- -1- [2.2.2] -3- ;

(3R,4S,5S,6S)-5-(5- -2- )-6- -1- [2.2.2] -2- ;

(3R,4S,5S,6S)-5-(2- -5- )-6- -1- [2.2.2] -2- ;

(3R,4S,5S,6S)-5-(2,5- )-6- -1- [2.2.2] -2- ;

(3R,4S,5S,6S)-5-(2- -5- )-6- -1- [2.2.2] -2- ;

(3R,4S,5S,6S)-5-(5- -2- )-6- -1- - [2.2.2] ;

(3R,4S,5S,6S)-5-(2- -5- - )-6- -1- [2.2.2] -2- ;

(3R,4S,5S,6S)-5-(2- -5- - )-6- -1- [2.2.2] -2- ;

(3R,4S,5S,6S)-5-(2- - 5- - )-6- - 1- [2.2.2] - 2-  
; ;  
(3R,4S,5S,6S)-5-(5- - 2- - )-6- - 1- [2.2.2] - 2-

가

, NK-1 :  
, , , ,  
5,162,339 (1992 11 11 ); 5,232,929 (1993 8 3 );  
WO 92/20676 (1992 11 26 ); WO 93/00331 (1993 1 7 );  
WO 92/21677 (1992 12 10 ); WO 93/00330 (1993 1 7 );  
WO 93/06099 (1993 4 1 ); WO 93/10073 (1993 5 27 );  
); WO 92/06079 (1992 4 16 ); WO 92/12151 (1992 7  
23 ); WO 92/15585 (1993 9 17 ); WO 93/10073 (199  
3 5 27 ); WO 93/19064 (1993 9 30 ); WO 94/08997  
(1994 4 28 ); WO 94/04496 (1993 3 3 ); WO 94/  
13663 (1994 6 23 ); WO 94/20500 (1994 9 15 );  
PCT/IB94/00221 (1994 7 18 ); PCT/JP94/00781 (1994 13 );  
PCT/JP94/01092 (1994 7 5 ); PCT/JP94/01514 (1994 9 1  
3 ); 988,653 (1992 12 10 ); 026,382 (1993 3 4  
); 123,306 (1993 9 17 ), 072,629 (1993 6 4  
).

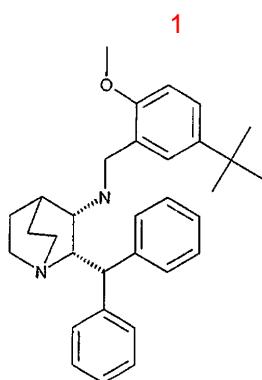
NK-1

가 : EP 499,313 (1992 8 19 );  
EP 520,555 (1992 12 30 ); EP 522,808 (1993 1 13 );  
EP 528,495 (1993 2 24 ); PCT WO 93/14084 (1993 7 22 ); PCT  
WO 93/01169 (1993 1 21 ); PCT WO 93/01165 (1993 1 21  
); PCT WO 93/01159 (1993 1 21 ); PCT WO 92/20661 (1992 11  
26 ); EP 517,589 (1992 12 12 ); EP 428,434 (1991  
5 22 ); EP 360,390 (1990 3 28 ), PCT WO 95/04042  
(1995 2 9 ), PCT WO 95/08549 (1995 3 30 ), PCT WO 95/19  
344 (1995 7 20 ), PCT WO 95/23810 (1995 9 8 ), PCT  
WO 95/20575 (1995 8 3 ).

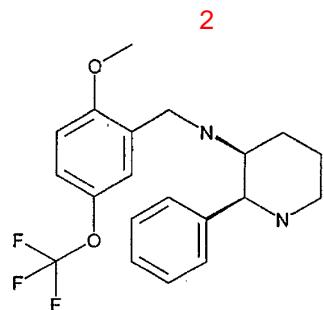
, NK-1

1, 2

가



(2S,3S)(2- - 1- - [2.2.2] - 3- )-(5- - - 2- - )-



$$(2S,3S)(2-\quad -5-\quad \quad \quad -\quad )-(2-\quad -\quad \quad -3-\quad )$$

NK-1 CNS- NK-1 . NK-1 가 CNS  
가 CNS WO 98/15277

NK-1                  100nM                  NK-1                  (IC<sub>50</sub>)                  .                  , NK-1  
           IC<sub>50</sub> #10nM,                  IC<sub>50</sub> # 1 nM                  .

NK-1 , NK-1  
(Cascieri) [J. Pharmacol.Exp. Ther., 1992, 42, 458]

NK-1 . , NK-1  
NK-1 NK-1 가  
가 NK-1 가

NK-1 , , , , NK-1 가

, - NK-1 1kg 0.01 mg 5 mg  
0.1 mg 0.3 mg 1 6 ,  
1 2 . , NK-1 .  
가

] -3- )-(5- - -2- - )- . (2S,3S)(2- -1- - [2.2.2

NK-1

가

NK-1

(venlafaxine)

(sertraline)

(desensitization)

( , 15 ), ( , 15 ); ( , 15 ); ( , (pawing), ) .

(pen)

15

( ) . (fazer gun) 5

6 20

Cmax

11

4

. 3

, 10 . : ( , , , ); ( , , , ); ( , , , ).  
 6 1 . . . . .  
 (screening). 가 . . . . .

15 . , 가

1

0.1 mg/kg SID 7 21 , 1

화학식 1의 화합물		위약
투여 형태	피하 주사	피하 주사
효능(potency)	69%	0%
제제	20%(w/v) SBE에 물 중의 SBE 사이클로덱스트린을 용해시켜 물 중의 5mg/ml의 염기 당량 용액 중의 사이클로덱스트린을 제조	20%(w/v) 물

1

21

1

(double-blind crossover design)

28

1

21

2

1

0.1 mg/kg

1

6 , 2015

가

( 1 )

[ 1 ]

0.1 mg/kg의 화학식 1의 화합물 대 위약(기하 평균 시간(초); 분리기)

		발성	활동 항진
치료	연구 일	평균	평균
위약	6일	36.1	25.8
화학식 1	6일	29.0	24.1
위약	20일	53.1	42.5
화학식 1	20일	25.5	19.1

1 , 1 NK-1 가

2

1

15                  15                  가  
);                  ( , , , ) .                  ( ) . , 15 ( , , ,

, (pen) 15 , , 15 ,  
( ) , , 10 , ,  
(fazer gun) 5 , ,

[ 2 ]

0.1 mg/kg의 화학식 1의 화합물 대 위약(기하 평균 시간(초); "화학식 1"은 화학식

### 1의 화합물을 의미)

분리기		발성	활동항진
치료	연구 일	평균	평균
화학식 1	6일	5.8	23.3
위약	6일	7.9	15.0
화학식 1	20일	6.9	16.8
위약	20일	8.5	17.0
자극기		발성	활동항진
화학식 1	6일	6.5	22.7
위약	6일	8.9	28.8
화학식 1	20일	7.4	36.0
위약	20일	7.3	20.9

## [ 3 ]

0.3 mg/kg의 화학식 1의 화합물 대 -1일(기하 평균 시간(초))

		발성	활동 항진
치료	연구 일	평균	평균
분리	-1일	31.8	71.4
분리	6일	20.9	49.7
분리	20일	18.2	39.1
자극	-1일	33.4	104.9
자극	6일	15.9	43.1
자극	20일	19.2	41.9

## [ 4 ]

0.1 mg/kg의 화학식 1의 화합물 대 -1일(기하 평균 시간(초))

		발성	활동 항진
치료	연구 일	평균	평균
분리	-1일	35.9	47.2
분리	6일	15.5	24.7
분리	20일	9.1	14.8
자극	-1일	48.9	70.9
자극	6일	36.8	48.8
자극	20일	24.7	28.4

## [ 5 ]

0.03 mg/kg의 화학식 1의 화합물 대 -1일(기하 평균 시간(초))

		발성	활동 항진
치료	연구 일	평균	평균
분리	-1일	22.1	46.0
분리	6일	10.6	19.4
분리	20일	12.1	20.1
자극	-1일	38.6	54.9
자극	6일	24.5	38.6
자극	20일	35.6	28.2

## [ 6 ]

0.1 mg/kg의 화학식 1의 화합물 대 위약(기하 평균 시간(초))

분리기		발성	활동 항진
치료	연구 일	평균	평균
화학식 1	6일	29.0	24.1
위약	6일	36.1	25.8
화학식 1	20일	25.5	19.1
위약	20일	53.1	42.5
자극기		발성	활동 항진
화학식 1	6일	35.3	46.7
위약	6일	46.7	47.2
화학식 1	20일	26.4	51.2
위약	20일	56.2	69.6

3      5      '-1       
1      가      0.1 mg/kg SC

           3

5 mg/kg BID      2      10  
1

화합물	화학식 2의 화합물
투여 형태	경구용 캡슐
효능	5 mg/kg 활성의 캡슐

13      , 15

           2

가

,      2      1      5 mg/kg      2      BID      10  
2      5 mg/kg      2      BID      10

)가      18      30      .      가      5      10      BID      15      (      #10

[ 7 ]

효과(\*평가된 지속 시간(초))

	분리 발성 0-15 분		분리 활동항진 0-15분	
개 번호	위약	화합물 2	위약	화합물 2
219662	42	22	50	30
70954	2	0	4	2
234923	6	0	6	2
HIHMFU	0	0	50	12
240893	4	0	6	6
215155	14	12	6	2
227641	6	2	2	2
2943450	90	30	36	18
평균	20.5	8.25	20.0	9.25

가 ( ) 1, 2, 3

1 = 2

$$2 = 10$$

$$3 = 30$$

(57)

1.

NK-1

가

,

2

1

가 , , , , , , ,

3.

1

11

4.

1

NK-1 가

(2S,3S)-3-(5-  
- - - 2 - ) - 2 -(3 - ) ;

$$(2S,3S)-3-(2-\quad -5-\quad ) \quad -2-\quad -\quad ;$$

$$(2S,3S)-3-(2-\quad -5-\quad \quad \quad ) \quad -2-\quad -\quad ;$$

(2S,3S)-3-(2- -5- )- -2- ;  
 (2S,3S)-3-(5- - -2- )- -2- ;  
 2-( )-N-(2- -5- -) )- -1- [2.2.2] -3- ;  
 (2S,3S)-3-[5- -2-(2,2,2- )- ] -2- ;  
 (2S,3S)-3-(5- - -2- )- -2- ;  
 (2S,3S)-3-(2- -5- )- -2- ;  
 (2S,3S)-3-(2- -5- )- -2- ;  
 (2S,3S)-2- -3-[2-(2,2,2- )- ;  
 (2S,3S)-2- -3-(2- )]- - ;  
 -3-(2- )-2- ;  
 -3-(2- )-2- - ;  
 -3-(2- )-2-(2- )- ;  
 -3-(2- )-2-(2- )- ;  
 -3-(2- )-2-(2- )- ;  
 -3-(2- )-2-(3- )- ;  
 -3-(2- )-2-(3- )- ;  
 -3-(2- )-2-(3- )- ;  
 -3-(2- )-2- ;  
 -3-(2- )-2-(3- )- ;  
 -3-(2- )-2-(4- )- ;  
 -3-(2- )-2-(3- )- ;  
 -3-(2- )-2- - ;  
 3-(2- )-4- -2- ;  
 3-(2- )-5- -2- ;  
 3-(2- )-6- -2- ;  
 (2S,3S)-3-(2- )-2- ;  
 (2S,3S)-1-(5- -1- )-3-(2- - )-2- ;  
 (2S,3S)-1-(6- - -1- )-3-(2- - )-2- ;  
 (2S,3S)-1-(4- -4- -1- )-3-(2- - )-2- ;

(2S,3S)-1-(4- -4- -1- )-3-(2- - )-2- ;  
 (2S,3S)-1-(5,6- -1- )-3-(2- - )-2- ;  
 -3-(5- -2- )-2- - ;  
 (2S,3S)-1-[4-(4- )-4- -1- ]-3-(2- )-2- ;  
 (2S,3S)-1-[4-(4- )-4- -1- ]-3-(2- )-2- ;  
 -3-(2- -5- )-2- - ;  
 (2S,3S)-1-(4- -1- )-3-(2- - )-2- ;  
 -3-(2- -1- )-2- - ;  
 (2S,3S)-3-(2- )-1-(5-N- - -1- )-2- ;  
 (2S,3S)-1-(4- -1- )-3-(2- )-2- ;  
 (2S,3S)-1-[4-(2- ) -1- ]-3-(2- - )-2- ;  
 (2S,3S)-1-(5- -1- )-3-(2- - )-2- ;  
 (2S,3S)-1-(5- -1- )-3-(2- )-2- ;  
 (2S,3S)-3-(5- -2- )-2- - ;  
 (2S,3S)-3-(2,5- )-2- - ;  
 -3-(3,5- -2- )-2- - ;  
 -3-(4,5- -2- )-2- - ;  
 -3-(2,5- )-1-[4-(4- )-4- -1- ]-2- ;  
 -3-(5- -2- )-1-(5,6- -1- )-2- ;  
 -1-(5,6- -1- )-3-(2,5- - )-2- ;  
 -2- -3-[ -2-( -2- ) ] - ;  
 -3-(2,5- ) -2-(3- - ) - ;  
 -3-(5- -2- ) -2-(3- - ) - ;  
 -3-(5- -2- ) -2-(3- - ) - ;  
 3-(2- )-2,4- ;  
 -3-(2- )-2- ;  
 (2S,3S)-3-(5- -2- ) -2- - ;  
 (2S,3S)-3-(5-n- -2- ) -2- - ;  
 (2S,3S)-3-(2- -5-n- ) -2- - ;

(2S,3S)-3-(5- -2- ) -2- - ;  
 (2S,3S)-3-(5- -2- ) -2- - ;  
 (2S,3S)-3-(5- -2- ) -2- - ;  
 (2S,3S)-3-(2- -5- ) -2- - ;  
 2,4- -5- [4- -3-((2S,3S)-2- -3- - ) ]- ;  
 N-(4,5- -2- )-N-[4- -3-((2S,3S)-2- -3- - ) ]- ;  
 {5-[(4,5- -2- )] -2- }-((2S,3S)-2- -3- ) ;  
 {5-(4,5- -2- )-2- }-((2S,3S)-2- -3- ) ;  
 4,5- -2- -[3-((2S,3S)-2- -3- - )-4- ]- ;  
 2,4- -5- [4- -3-((2S,3S)-2- -3- - ) ]- ;  
 2,4- -5- [4- -3-((2S,3S)-2- -3- - ) ]- ;  
 2,4- -5- [4- -3-((2S,3S)-2- -3- - ) ]- ;  
 2,4- -5- [4- -3-((2S,3S)-2- -3- - ) ]- ;  
 (2S,3S)-N-(5- -2- ) -2- -1- [2.2.2] -3- ;  
 (2S,3S)-N-(5-n- -2- ) -2- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-N,N- -5-(5- -2- - )-6- -1- [2.2.2]  
 -3- ;  
 (3R,4S,5S,6S)-N,N- -5-(2,5- )-6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(5- -2- )-6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(2- -2- )-6- -1- [2.2.2] -3- ;

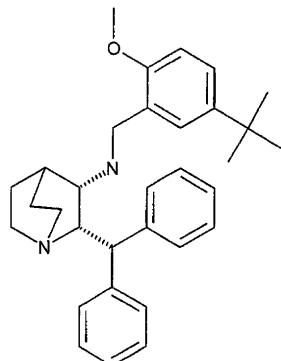
(3R,4S,5S,6S)-5-(2,5-) )-6- - -1- - [2.2.2] -3- ;  
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 (3R,4S,5S,6S)-5-(5- -2- )-6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(2- -5-n- )-6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(5- -2- )-6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(5-N- -3- )-6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(2- -5- - )-6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(2- -5- - )-6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(2- -5- - )-6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(5- -2- )-6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(5- -2- )-6- -1- [2.2.2] -2- ;  
 (3R,4S,5S,6S)-5-(2- -5- )-6- -1- [2.2.2] -2- ;  
 (3R,4S,5S,6S)-5-(2- -5- )-6- -1- [2.2.2] -2- ;  
 (3R,4S,5S,6S)-5-(5- -2- )-6- -1- [2.2.2] -2- ;  
 (3R,4S,5S,6S)-5-(2- -5-n- )-6- -1- [2.2.2] -2- ;  
 (3R,4S,5S,6S)-5-(5- -2- )-6- -1- [2.2.2] -2- ;  
 (3R,4S,5S,6S)-5-(5-N- -2- )-6- -1- [2.2.2] -2- ;  
 (3R,4S,5S,6S)-5-(2- -5- - )-6- -1- [2.2.2] -2- ;  
 (3R,4S,5S,6S)-5-(2- -5- - )-6- -1- [2.2.2] -2- ;  
 (3R,4S,5S,6S)-5-(5- -2- )-6- -1- [2.2.2] -2- ;

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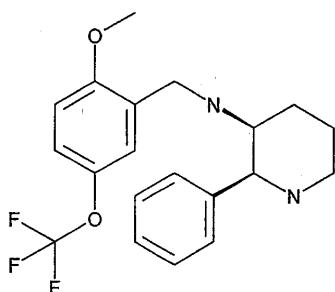
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(2S,3S)-3-(5- - -2- ) -2-(3- ) ;  
 (2S,3S)-3-(2- -5- ) -2- - ;  
 (2S,3S)-3-(2- -5- ) -2- - ;  
 (2S,3S)-3-(2- -5- ) -2- - ;  
 (2S,3S)-3-(5- - -2- ) -2- ;  
 2-( )-N-(2- -5- - ) -1- [2.2.2] -3- ;  
 (2S,3S)-3-[5- -2-(2,2,2- )- ] -2- ;  
 (2S,3S)-3-(5- - -2- ) -2- ;  
 (2S,3S)-3-(2- -5- ) -2- ;  
 (2S,3S)-3-(2- -5- )- -2- ;  
 (2S,3S)-2- -3-[2-(2,2,2- )- ] -2- ;  
 (2S,3S)-2- -3-(2- )- - ;  
 -3-(2- )-2- ;  
 -3-(2- )-2- - ;  
 -3-(2- )-2-(2- )- ;  
 -3-(2- )-2-(2- )- ;  
 -3-(2- )-2-(2- )- ;  
 -3-(2- )-2-(3- )- ;  
 -3-(2- )-2-(3- )- ;  
 -3-(2- )-2- ;  
 -3-(2- )-2-(3- )- ;  
 -3-(2- )-2-(4- )- ;  
 -3-(2- )-2-(3- )- ;

-3-(2- )-2- ;  
 3-(2- )-4- -2- ;  
 3-(2- )-5- -2- ;  
 3-(2- )-6- -2- ;  
 (2S,3S)-3-(2- )-2- ;  
 (2S,3S)-1-(5- -1- )-3-(2- - )-2- ;  
 (2S,3S)-1-(6- - -1- )-3-(2- - )-2- ;  
 (2S,3S)-1-(4- -4- -1- )-3-(2- - )-2- ;  
 (2S,3S)-1-(4- -4- -1- )-3-(2- - )-2- ;  
 (2S,3S)-1-(5,6- -1- )-3-(2- - )-2- ;  
 -3-(5- -2- )-2- - ;  
 (2S,3S)-1-[4-(4- )-4- -1- ]-3-(2- )-2- ;  
 (2S,3S)-1-[4-(4- )-4- -1- ]-3-(2- )-2- ;  
 -3-(2- -5- )-2- - ;  
 (2S,3S)-1-(4- -1- )-3-(2- - )-2- ;  
 -3-(2- -1- )-2- - ;  
 (2S,3S)-3-(2- )-1-(5-N- - -1- )-2- ;  
 (2S,3S)-1-(4- -1- )-3-(2- )-2- ;  
 (2S,3S)-1-[4-(2- ) -1- ]-3-(2- - )-2- ;  
 (2S,3S)-1-(5- -1- )-3-(2- - )-2- ;  
 (2S,3S)-1-(5- -1- )-3-(2- )-2- ;  
 (2S,3S)-3-(5- -2- )-2- - ;  
 (2S,3S)-3-(2,5- )-2- - ;  
 -3-(3,5- -2- )-2- - ;  
 -3-(4,5- -2- )-2- - ;  
 -3-(2,5- )-1-[4-(4- )-4- -1- ]-2- ;  
 -3-(5- -2- )-1-(5,6- -1- )-2- ;  
 -1-(5,6- -1- )-3-(2,5- - )-2- ;  
 -2- -3-[ -2-( -2- ) ] - ;

$-3-(2,5-) ) -2-(3- - ) ;$   
 $-3-(5- -2- ) -2-(3- - ) ;$   
 $-3-(5- -2- ) -2-(3- - ) ;$   
 $3-(2- )-2,4- ;$   
 $-3-(2- )-2- ;$   
 $(2S,3S)-3-(5- -2- ) -2- - ;$   
 $(2S,3S)-3-(5-n- -2- ) -2- - ;$   
 $(2S,3S)-3-(2- -5-n- ) -2- - ;$   
 $(2S,3S)-3-(5- -2- ) -2- - ;$   
 $(2S,3S)-3-(5- -2- ) -2- - ;$   
 $(2S,3S)-3-(5- -2- ) -2- - ;$   
 $(2S,3S)-3-(2- -5- ) -2- - ;$   
 $2,4- -5- [4- -3-((2S,3S)-2- -3- - ) ]- ;$   
 $N-(4,5- -2- )-N-[4- -3-((2S,3S)-2- -3- - ) ]- ;$   
 $\{5-[(4,5- -2- )] -2- }-((2S,3S)-2- -3- ) ;$   
 $\{5-(4,5- -2- )-2- }-((2S,3S)-2- -3- - ;$   
 $4,5- -2- -[3-((2S,3S)-2- -3- - )-4- ]- ;$   
 $2,4- -5- [4- -3-((2S,3S)-2- -3- - ) ]- ;$   
 $2,4- -5- [4- -3-((2S,3S)-2- -3- - ) ]- ;$   
 $2,4- -5- [4- -3-((2S,3S)-2- -3- - ) ]- ;$   
 $(2S,3S)-N-(5- -2- ) -2- -1- [2.2.2] -3- - ;$   
 $(2S,3S)-N-(5- -2- ) -2- -1- [2.2.2] -3- - ;$   
 $(2S,3S)-N-(5- -2- ) -2- -1- [2.2.2] -3- - ;$   
 $(2S,3S)-N-(5- -2- ) -2- -1- [2.2.2] -3- - ;$

(2S,3S)-N-(5- - -2-) ) -2- -1- [2.2.2] -3- ;  
 (2S,3S)-N-(5-n- -2-) ) -2- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-N,N- -5-(5- -2- - -) -6- -1- [2.2.2]  
 -3- ;  
 (3R,4S,5S,6S)-N,N- -5-(2,5- ) -6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(5- -2- ) -6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(2,5- ) -6- -1- - [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(2- -5- ) -6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(5- -2- ) -6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(2- -5-n- ) -6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(5- - -2- ) -6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(5-N- - -) -6- -1- - 1- [2.2.2]  
 ] -3- ;  
 (3R,4S,5S,6S)-5-(2- -5- - -) -6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(2- -5- - -) -6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(5- -2- ) -6- -1- [2.2.2] -3- ;  
 (3R,4S,5S,6S)-5-(5- -2- ) -6- -1- [2.2.2] -2- ;  
 (3R,4S,5S,6S)-5-(2- -5- ) -6- -1- [2.2.2] -2- ;  
 (3R,4S,5S,6S)-5-(2,5- ) -6- -1- [2.2.2] -2- ;  
 (3R,4S,5S,6S)-5-(2- -5- ) -6- -1- [2.2.2] -2- ;  
 (3R,4S,5S,6S)-5-(5- -2- ) -6- -1- [2.2.2] -2- ;  
 (3R,4S,5S,6S)-5-(2- -5-n- ) -6- -1- [2.2.2] -2- ;  
 (3R,4S,5S,6S)-5-(5- - -2- ) -6- -1- [2.2.2] -2- ;  
 (3R,4S,5S,6S)-5-(5-N- - -) -6- -1- [2.2.2]

(3R,4S,5S,6S)-5-(2-  
; - 5- - )-6- - 1- [2.2.2] - 2-  
 (3R,4S,5S,6S)-5-(2-  
2- ; - 5- - )-6- - 1- [2.2.2] -  
 (3R,4S,5S,6S)-5-(2-  
; - 5- - )-6- - 1- [2.2.2] - 2-  
 (3R,4S,5S,6S)-5-(5-  
; - 2- )-6- - 1- [2.2.2] - 2-

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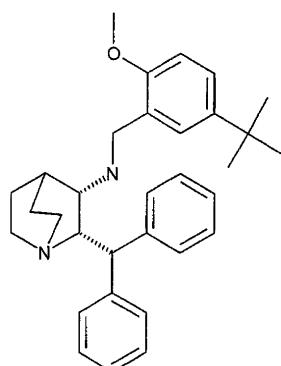
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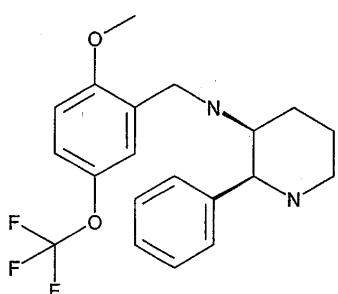
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