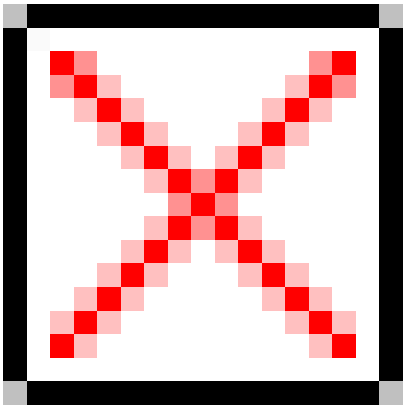
Industria y Comercio
SUPERINTENDENCIA

Radicación	16 46993 0000 0000	2016-02-24 12:35:03	
Trámite	11	PCT-PATENTE DE INVENCION CAPITULOS I Y II	
Evento	378	FASE NACIONAL INCLUIDO CAPITULO I	
Actuación	411	PRESENTACION	Folios: 478
Dependencia	2020	DIRECCION DE NUEVAS CREACIONES	
Pago #1	17264	$ 229000	

DIRECCIÓN DE NUEVAS CREACIONES
SOLICITUD FASE NACIONAL - PCT



1	**Titulo de la Invención**(200 caractares o espacios máximos)
	DERIVADO DE BIFENILO NOVEDOSO Y MÉTODO PARA PREPARAR EL MISMO

2	**Datos del Solicitante**			
	Nombre:	DONG-A ST CO., LTD	**Dirección Electrónica:**	notificaciones@clarkemodet.com.co
	Dirección:	64, Cheonho-daero, Dongdaemun-gu	**Domicilio/País de constitución:**	REPUBLICA DE COREA - SEOUL - SEOUL
	Identificación: ☐ CEDULA DE CIUDADANIA ☐ CEDULA DE EXTRANJERIA ☒ EMPRESA EXTRANJERA ☐ NIT ☐ PASAPORTE **Número:** 1047796-			

3	**Solicitantes**

	Apellidos - Nombres o Razón Social	Tipo	Identificación
1.	DONG-A ST CO., LTD	NN	1047796

4	Datos del Inventor			
Nombre:	Soon-Hoe KIM	**Dirección Electrónica:**	notificaciones@clarkemodet.com.co
Dirección:	Yeongtong-ro, Yeongtong-gu	**Domicilio/País de constitución:**	REPUBLICA DE COREA - GYEONGGI-DO - SUWON-SI

Identificación:

☐ CEDULA DE CIUDADANIA ☐ CEDULA DE EXTRANJERIA
☐ EMPRESA EXTRANJERA ☐ NIT
☐ PASAPORTE ☒ No Aplica

Número: -

5	Inventor(es)	
	Apellidos - Nombres	**Domicilio**
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6	Datos Inventor(es)

	País de Residencia	Departamento/Estado	Ciudad	Dirección
1.	REPUBLICA DE COREA	GYEONGGI-DO	SUWON-SI	Yeongtong-ro, Yeongtong-gu
2.	REPUBLICA DE COREA	GYEONGGI-DO	YONGIN-SI	Jukjeon-ro, Suji-gu
3.	REPUBLICA DE COREA	GYEONGGI-DO	YONGIN-SI	Gugal-ro 28beon-gil, Giheung-gu
4.	REPUBLICA DE COREA	SEOUL	SEOCHO-GU	Seoripul 4-gil
5.	REPUBLICA DE COREA	GYEONGGI-DO	OSAN	Osan-ro 160beon-gil, Osan-si
6.	REPUBLICA DE COREA	GYEONGGI-DO	YONGIN-SI	Hanbora 1-ro, Giheung-gu
7.	REPUBLICA DE COREA	GYEONGGI-DO	SEONGNAM-SI	Naejeong-ro, Bundang-gu
8.	REPUBLICA DE COREA	GYEONGGI-DO	SUWON-SI	Yeongtong-ro 514beon-gil, Yeongtong-gu
9.	REPUBLICA DE COREA	GYEONGGI-DO	YONGIN-SI	Pungdeockcheon-ro, Suji-gu

7	**Datos del Representante Legal / Apoderado**		
Nombre:	CAROLINA MERCEDES DAZA MONTALVO	**Dirección Electrónica:**	notificaciones@clarkemodet.com.co
Dirección:	CARRERA 11 NO. 86-53, PISO 6	**Domicilio/País de constitución:**	COLOMBIA - BOGOTA D.C. - BOGOTA D.C.

Identificación:

☒ CEDULA DE CIUDADANIA ☐ CEDULA DE EXTRANJERIA

☐ EMPRESA EXTRANJERA ☐ NIT

☐ PASAPORTE

Número:	66783790-

Presentación de Poder

Año de Radicación	
Número de Radicación	

8	**Datos Solicitud: PCT / WO**		
Número Solicitud:	PCT/KR2014/006483	**Fecha Solicitud:**	17/07/2014
Número Publicacion:	WO 2015/016511 A1	**Fecha Publicacion:**	05/02/2015

9	**Declaraciones de prioridad**	☒ SI ☐ NO

	(33) País de origen	**Codigo del país**	**(31) No. Solicitud**	**(32) Fecha** _
1.	REPUBLICA DE COREA	KR	10-2013-0090175	30/07/2013

10	**Reivindicaciones**			
Número reivindicaciones:	15	**Pago Reivindicaciones:**	Si	

11 Reducción de tasas.

Declaro que carezco de medios económicos para presentar la solicitud de patente.

☐ SI ☒ NO

Nota: En caso de ser persona natural y carecer de medios económicos, y por lo tanto, aplique la reducción de tasas a que se refiere la resolucón vigente en tarifas, debe firmar la presente solicitud bajo la gravedad de juramento.

☐ Micro, pequeñas y medianas empresas
☐ Universidades públicas o privadas
☐ Entidades sin ánimo de lucro

Debe aportar los documentos que se indican en el numeral 17 de anexos

12 Documentos Anexos

☒ Reivindicaciones
☒ Descripción
☐ Dibujos y/o Figuras
☒ Resumen
☐ Certificado Depósito Material Biológico
☐ Uso de Conocimiento tradicional
☐ Listado de secuencias
☐ Artes finales 12 x 12 cm
☐ Poderes, si fuere el caso
☐ Copia de la primera solicitud si se reivindica prioridad
☐ Traducción simple de la primera solicitud, si se reivindica prioridad

☒ Otros Anexos

DERIVADO DE BIFENILO NOVEDOSO Y MÉTODO PARA PREPARAR EL MISMO

CAMPO DE LA INVENCIÓN

La presente invención se relaciona a antagonistas del receptor muscarínico M3 novedosos, y más particularmente, a derivados de bifenilo novedosos que tienen actividad de antagonistas del receptor muscarínico M3, o isómeros de los mismos, sales farmacéuticamente aceptables de los mismos, o hidratos de los mismos, métodos para preparar los mismos, y una composición farmacéutica que contienen los mismos como un ingrediente activo.

ANTECEDENTES DE LA INVENCIÓN

Los receptores muscarínicos se encuentran en todas partes del cuerpo humano, incluyendo el cerebro y las glándulas salivales. Dichos receptores son miembros de los receptores acoplados a la proteína G, y además se dividen en cinco subtipos (M1 a M5). Entre estos subtipos, los receptores M1, M2 y M3 se encuentran extensivamente en tejidos animales y humanos, y sus propiedades farmacológicas han sido elucidadas. El receptor M1 muscarínico se expresa principalmente en la corteza cerebral, y está involucrado en la regulación de funciones cognitivas mayores. El receptor M2 se encuentra principalmente en los músculos lisos del corazón

y vejiga, y se involucra en la regulación del ritmo cardiaco. Se sabe que el receptor M3 se expresa extensivamente en muchos tejidos periféricos y se involucra en la estimulación del tracto gastrointestinal y el tracto urinario, y la salivación. Los receptores M4 y M5 se encuentran en el cerebro, y el receptor M4 se involucra principalmente en el movimiento, pero el papel de receptor M5 sigue siendo una incógnita.

Generalmente, se encontró que los antagonistas de receptores muscarínicos son útiles para el tratamiento de varias enfermedades, por ejemplo, enfermedad pulmonar obstructiva crónica, asma, síndrome de intestino irritable, incontinencia urinaria, rinitis, colitis espasmódica, cistitis crónica, enfermedad de Alzheimer, demencia senil, glaucoma, esquizofrenia, enfermedad de reflujo gastroesofágico, arritmia cardiaca, y síndromes de hipersalivación (Invest. Drugs, 1997, 6 (10), 1395-1411, Drugs Future, 1997, 22 (2) 135-137, Drugs Future, 1996, 21 (11), 1105-1108, Drugs Future, 1997, 22 (7), 733-737).

Mientras tanto, se sabe que, entre los receptores muscarínicos, los receptores M2 y M3 son predominantes en la vejiga humana y juegan un papel en la regulación de la contracción de la vejiga. El receptor M2 está presente en la vejiga en una cantidad que es al menos tres veces más grande

que el receptor M3, y juega un rol en inhibir la relajación de la vejiga por el beta-receptor en vez de estar involucrado directamente en la contracción de la vejiga. Por tanto, el receptor M3 parece jugar el papel más importante en la contracción de la vejiga. Por lo tanto, los antagonistas selectivos contra el receptor M3 exhiben excelentes efectos inhibidores contra la contracción muscarínica de la vejiga, pero inhiben la secreción salival para causar sequedad en la boca.

En consecuencia, los inventores presentes han preparado derivados novedosos que exhiben actividad funcional por su unión selectiva al receptor muscarínico M3 y han minimizado los efectos secundarios, por tanto completando la presente invención.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Es un objeto de la presente invención proporcionar derivados de bifenilo novedosos o sales farmacéuticamente aceptables de los mismos.

Otro objeto de la presente invención es proporcionar métodos para preparar derivados de bifenilo novedosos o sales farmacéuticamente aceptables de los mismos.

Aún otro objeto de la presente invención es proporcionar un antagonista del receptor muscarínico M3 que contiene

derivados de bifenilo novedosos, sales farmacéuticamente aceptables de los mismos, o hidratos de los mismos como un ingrediente activo.

Solución Técnica

La presente invención proporciona derivados de bifenilo novedosos o sales farmacéuticamente aceptables de los mismos.

La presente invención también proporciona métodos para preparar derivados de bifenilo novedosos o sales farmacéuticamente aceptables de los mismos.

La presente invención también proporciona antagonistas del receptor muscarínico M3s que contienen derivados de bifenilo novedosos, sales farmacéuticamente aceptables de los mismos, o hidratos de los mismos como un ingrediente activo.

Como se usa en la presente, el término "alquilo" significa un radical de hidrocarburo recto o ramificado. Por ejemplo, alquilo C_1-C_6 es un hidrocarburo alifático que tiene 1 a 6 átomos de carbono, y se pretende que incluya metilo, etilo, propilo, n-butilo, n-pentilo, n-hexilo, isopropilo, isobutilo, sec-butilo, tert-butilo, neopentilo, isopentilo y similares.

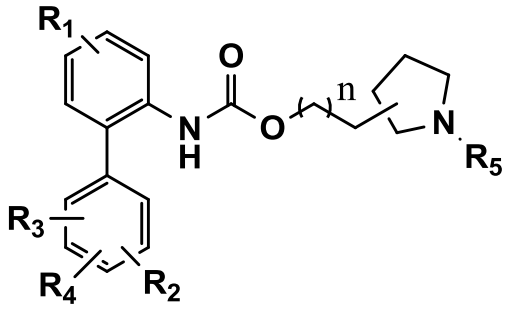
Como se usa en la presente, el término "alcoxi" significa un radical donde el átomo de hidrógeno de un grupo hidroxilo se sustituye con alquilo. Por ejemplo, alcoxi C_1-C_6 se pretende que incluya metoxi, etoxi, propoxi, n-butoxi, n-

pentiloxi, isopropoxi, sec-butoxi, tert-butoxi, neopentiloxi, isopentilooxi y similares.

Derivados de bifenilo novedosos

La presente invención proporciona derivados de bifenilo novedosos representados por la siguiente Fórmula 1, o sales farmacéuticamente aceptables de los mismos:

Fórmula 1



donde

R_1 es hidrógeno, halógeno, hidroxi, alquilo C_1-C_6 sustituido o no sustituido, o alcoxi C_1-C_6;

R_2, R_3 y R_4 son independientemente hidrógeno, halógeno, amino sustituido o no sustituido, nitro, ciano, hidroxi, alquilo C_1-C_6 sustituido o no sustituido, alcoxi C_1-C_6 sustituido o no sustituido, o $-C(O)R_6$;

R_5 es hidrógeno o alquilo C_1-C_6;

n es 0 o 1; y

R_6 es hidrógeno o amino.

En una modalidad preferida de la presente invención, R_1 en la Fórmula 1 puede ser hidrógeno o halógeno; R_2, R_3 y R_4

pueden ser independientemente hidrógeno, halógeno, o alquilo C_1-C_6; y R_5 puede ser alquilo C_1-C_6.

En otra modalidad preferida de la presente invención, R_1 en la Fórmula 1 puede ser hidrógeno; R_2, R_3 y R_4 pueden ser independientemente hidrógeno o halógeno; R_5 puede ser alquilo C_1-C_6; y n puede ser 0 o 1.

En la presente invención, las sales farmacéuticamente aceptables son preferiblemente sales de adición ácida formadas con ácidos libres farmacéuticamente aceptables. Los ácidos libres que pueden usarse en la presente invención incluyen ácidos orgánicos y ácidos inorgánicos. Los ácidos inorgánicos incluyen ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido fosfórico, etc., y los ácidos orgánicos incluyen ácido cítrico, ácido acético, ácido láctico, ácido maleico, ácido cumárico, ácido glucónico, ácido metanosulfónico, ácido glicólico, ácido succínico, ácido 4-toluenosulfónico, ácido trifluoroacético, ácido galacturónico, ácido embónico, ácido glutámico, ácido aspártico, etc.

Además, los compuestos de la Fórmula 1 o sales farmacéuticamente aceptables de los mismos pueden mostrar polimorfismo, y pueden también existir como solvatos (por ejemplo, hidratos, etc.). Más aún, los compuestos de la presente invención pueden también existir como

estereoisómeros individuales o mezclas de estereoisómeros.

La presente invención también se dirige a derivados de bifenilo novedosos seleccionados del grupo que consiste de los siguientes compuestos:

1) (4'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

2) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

3) (3',4',5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

4) (3'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

5) (4'-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

6) [1,1'-bifenil]-2-ilcarbamato de 2-(1-metilpirrolidin-2-il)etilo;

7) (4'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

8) (3'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

9) (3',5'-dicloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

10) (4'-trifluorometoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

11) (4'-nitro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

12) (3'-trifluorometil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

13) (4'-trifluorometil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

14) ((3'-fluoro-4'-metil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

15) (3'-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

16) (3'-etoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

17) (3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

18) (3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

19) (4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

20) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

21) (5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

22) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

23) (4-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

24) (3',4-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

25) (4-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

26) (5-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

27) (3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

28) (4'-ciano-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

29) (3'-(3-hidroxipropil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

30) (4'-(dimetilamino)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

31) (4'-(tert-butil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

32) (2'-amino-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

33) (3'-amino-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

34) (2'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

35) (2'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

36) (2'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

37) (3'-tert-butil-5'-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

38) (4'-fluoro-3'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

39) (4'-amino-3'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

40) (3'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

41) (3'-cloro-4’-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

42) (3',4',5-trifluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

43) (3',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

44) (3'-etil-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

45) (5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

46) (3'-amino-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

47) (5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

48) (4'-fluoro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

49) (3'-fluoro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

50) (3',5'-difluoro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

51) (3'-cloro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

52) (3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

53) (3'-cloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

54) (4'-cloro-3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

55) (3',5'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

56) (3',5'-dicloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

57) (3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

58) (3'-cloro-5-fluoro-4'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

59) (5-fluoro-3',4'-dimetil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

60) (5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

61) (3'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

62) (3',5'-difluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

63) (3'-cloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

64) (3',5'-dicloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

65) (3'-cloro-4'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

66) (5-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

67) (5-cloro-3'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

68) (5-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

69) (5-cloro-3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

70) (3',5-dicloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

71) (3',5,5'-tricloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

72) (3',5-dicloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

73) (3',5-dicloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

74) (3'-fluoro-4'-formil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

75) (3',5'-difluoro-5-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

76) (3',5'-dicloro-5-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

77) (3'-cloro-4'-fluoro-5-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

78) [1,1'-bifenil]-2-ilcarbamato de (R)-pirrolidin-3-ilmetilo;

79) [1,1'-bifenil]-2-ilcarbamato de (S)-pirrolidin-3-ilmetilo;

80) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo;

81) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo;

82) (5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo;

83) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo;

84) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo;

85) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo;

86) (5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo;

87) (3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo;

88) (4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-2-ilmetilo;

89) [1,1'-bifenil]-2-ilcarbamato de (R)-(1-metilpirrolidin-3-il)metilo;

90) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-metilpirrolidin-3-il)metilo;

91) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

92) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

93) (5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

94) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

95) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

96) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

97) (5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

98) (3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

99) (4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

100) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

101) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

102) [1,1'-bifenil]-2-ilcarbamato de (R)-(1-etilpirrolidin-3-il)metilo;

103) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-etilpirrolidin-3-il)metilo;

104) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-etilpirrolidin-3-il)metilo;

105) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-etilpirrolidin-3-il)metilo;

106) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-etilpirrolidin-2-il)metilo;

107) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-isobutilpirrolidin-2-il)metilo;

108) (3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

109) [1,1'-bifenil]-2-ilcarbamato de (R)-(1-metilpirrolidin-2-il)metilo;

110) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-2-il)metilo;

111) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-2-il)metilo;

112) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-isopropilpirrolidin-2-il)metilo;

113) (3'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

114) (4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

115) (3',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

116) (3'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

117) (3'-cloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

118) (3'-cloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

119) (3',5'-dicloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

120) (3'-cloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

121) (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

122) (5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

123) (3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

124) (4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

125) (3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

126) (3',5'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

127) (4'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

128) (3',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

129) (3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

130) (3',4'-dicloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

131) (3',5'-dicloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

132) (3'-cloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

133) (5-fluoro-3'-amino-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

134) (3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

135) (3',5'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

136) (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

137) (3'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

138) (3'-cloro-5'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

139) (3'-cloro-5-fluoro-5'-metoxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

140) (3'-cloro-5-fluoro-5'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

141) (4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

142) (3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-

il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

143) (3'-cloro-4',5-dlfluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

144) (2',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

145) (3',5-dicloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

146) (3',5-dicloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

147) (3'-cloro-4'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

148) (3'-cloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

149) (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

150) (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-etilpirrolidin-3-il)metilo;

151) (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-isopropilpirrolidin-3-il)metilo;

152) (3'-(hidroximetil)-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

153) (3'-carbamoil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

154) (3'-amino-[1,1'-bifenil]-2-il)carbamato de (R)-(1-

metilpirrolidin-3-il)metilo;

155) (3'-ciano-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

156) (2'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

157) (2',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

158) (2',3'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

159) (3'-cloro-6'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

160) (3'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

161) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

162) (3',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

163) (2',4',5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

164) (4'-cloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

165) (3'-cloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

166) (3',4'-dicloro-[1,1'-bifenil]-2-il)carbamato de

(S)-(1-metilpirrolidin-2-il)metilo;

167) (2',4'-dicloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

168) (3'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

169) (3'-ciano-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

170) (3'-amino-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

171) (3',4',5-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

172) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

173) (2',4',5,5'-tetrafluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

174) (3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

175) (4'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

176) (2',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

177) (3',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

178) (3'-ciano-5-fluoro-[1,1'-bifenil]-2-il)carbamato de

(S)-(1-metilpirrolidin-2-il)metilo;

179) (3'-hidroxi-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

180) (5-fluoro-3'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

181) (3'-cloro-4,4',5-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

182) (3'-cloro-4,5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

183) (2',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

184) (2',3'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

185) (2',6'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

186) (5'-cloro-2'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

187) (2'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

188) (2',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

189) (2',3'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

190) (3'-cloro-6'-fluoro-[1,1'-bifenil]-2-il)carbamato

de (S)-(1-metilpirrolidin-2-il)metilo;

191) (3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

192) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

193) (5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

194) (3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

195) (3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

196) (3'-cloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-etilpirrolidin-3-il)metilo;

197) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-metilpirrolidin-2-il)metilo;

198) (4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

199) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

200) (5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

201) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

202) (3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de

(S)-(1-metilpirrolidin-2-il)metilo;

203) (4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

204) (4-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

205) (3',4-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

206) (5-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

207) (3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

208) (5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

209) (4'-(tert-butil)-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

210) (3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

211) (3'-cloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

212) (4'-cloro-3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

213) (3'-amino-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

214) (2',5-difluoro-3'-(trifluorometil)-[1,1'-bifenil]-

2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

215) (3'-cloro-5-fluoro-5'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

216) (3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

217) (3'-cloro-5-fluoro-5'-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

218) (5-fluoro-2',4'-bis(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

219) (3'-etoxi-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

220) (5-fluoro-3',4'-dimetoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

221) (5-fluoro-3',5'-dimetoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

222) (5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

223) (3'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

224) (3'-cloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

225) (3',4'-dicloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo; y

226) (3',5'-dicloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo.

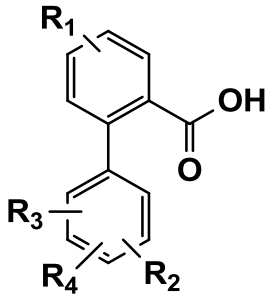
Métodos para la Preparación de Derivados de bifenilo novedosos

La presente invención proporciona métodos para preparar los compuestos de Fórmula 1 o sales farmacéuticamente aceptables de los mismos (Métodos de Preparación 1 a 4).

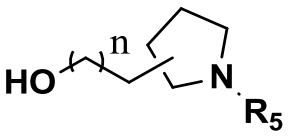
Método de Preparación 1

El método para preparar los compuestos de Fórmula 1 o sales farmacéuticamente aceptables de los mismos de acuerdo a la presente invención puede comprender una etapa para hacer reaccionar un compuesto de la siguiente Fórmula 2 con un compuesto de la siguiente Fórmula 3 en presencia de un reactivo de síntesis de carbamato:

Fórmula 2



Fórmula 3



donde R_1 a R_5 y n son las mismas como se definen en la

Fórmula 1.

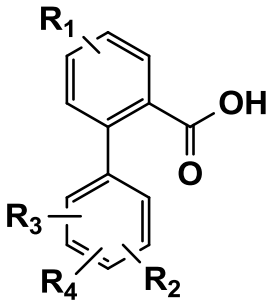
El reactivo de la síntesis de carbamato preferiblemente comprende un compuesto de azida. Específicamente, el reactivo de la síntesis de carbamato que se usa en la presente invención puede ser una mezcla de azida de difenilfosforilo (DPPA) y trietilamina, una mezcla de anhídrido propilfosfónico (T3P), azida de trimetilsililo ($TMSN_3$) y trietilamina, una mezcla de azida de sodio (NaN_3), bromuro de tetrabutilamonio y triflato de zinc(II), o similares.

Además, la reacción de síntesis de carbamato puede realizarse a una temperatura entre 100°C y 120°C por 4 a 12 horas.

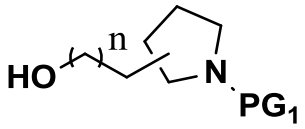
Método de Preparación 2

Además, el método para preparar los compuestos de la Fórmula 1 o sales farmacéuticamente aceptables de la misma de acuerdo con la presente invención puede comprender las etapas de: hacer reaccionar un compuesto de la siguiente Fórmula 2 con un compuesto de la siguiente Fórmula 3a en presencia de un reactivo de síntesis de carbamato para preparar un compuesto de la siguiente Fórmula 4; removiendo un grupo protector amina del compuesto de la Fórmula 4 para preparar un compuesto de la siguiente Fórmula 1a; e introduciendo un sustituyente de R_5 al compuesto de la Fórmula 1a:

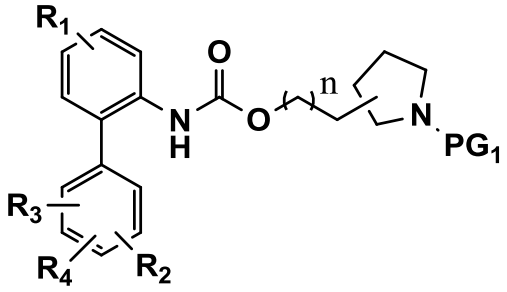
Fórmula 2



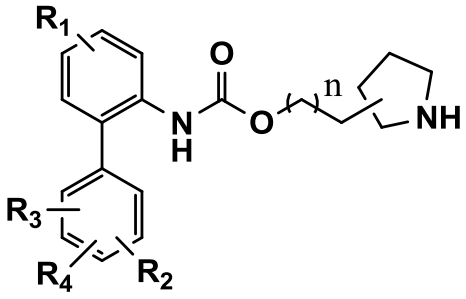
Fórmula 3a



Fórmula 4



Fórmula 1a



donde R_1 a R_4 y n son las mismas como se define en la Fórmula 1, y PG_1 es un grupo protector amina que puede seleccionarse del grupo que consiste de Boc (tert-

butiloxicarbonilo), bencilo, tert-butilo, PMB (4-metoxibencilo), Fmoc (fluorenilmetiloxicarbonilo), Ts (tosilato), MOM (metoximetilo), THP (tetrahidropiranilo), TBDMS (tert-butildimetilsililo), y TBDPS (tert-butildimetilsililo).

El reactivo de síntesis de carbamato y las condiciones de la reacción son las mismas como se describen para el método de preparación 1.

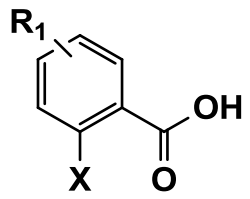
Además, paladio-carbono (Pd-C), un ácido fuerte tal como ácido trifluoroacético, ácido sulfúrico, ácido bromhídrico o similares; o una base tal como piperidina; nitrato de cerio (IV) amonio; fluoruro de amonio de tetra-n-butilo o similares puede usarse en la reacción de eliminación del grupo protector amina. La reacción puede realizarse a temperatura ambiente por 3 a 12 horas.

Además, la reacción de introducir el sustituyente de R_5 puede realizarse usando una solución de formaldehido, ácido acético y zinc, o puede realizarse usando haluro de alquilo, carbonato de potasio, yoduro de potasio o trietilamina. Agua o dimetilformamida pueden usarse como un solvente. La reacción puede realizarse a temperatura ambiente a 120°C por 5-12 horas.

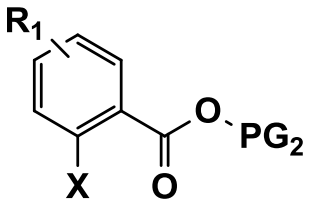
Mientras tanto, el compuesto de la Fórmula 2 puede prepararse por un método que comprende las etapas de; hacer

reaccionar un compuesto de la siguiente Fórmula 5 en presencia de un ácido para preparar un compuesto de la siguiente Fórmula 6, que tiene un grupo protector de ácido carboxílico introducido en la misma; acoplar el compuesto de la Fórmula 6 con un compuesto de la siguiente Fórmula 7 para preparar un compuesto de la siguiente Fórmula 8; y de-esterificar el compuesto de la Fórmula 8 en presencia de una base:

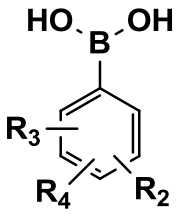
Fórmula 5



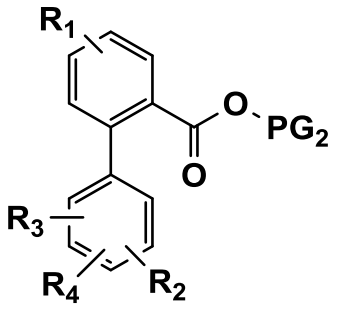
Fórmula 6



Fórmula 7



Fórmula 8



donde R_1 a R_5 y n son las mismas como se define en la Fórmula 1; X es halógeno; y PG_2 es un grupo protector que puede seleccionarse del grupo que consiste de un grupo alquilo C_1-C_4, bencilo, PMB (4-metoxibencilo), THP (tetrahidropiranilo), TBDMS (tert-butildimetilsililo), y TBDPS (tert-butildimetilsililo).

En la reacción para introducir el grupo protector de ácido carboxílico, cloruro de tionilo o ácido sulfúrico se usa preferiblemente como el ácido, y etanol o metanol pueden usarse como un solvente. La reacción puede realizarse a una temperatura entre 80°C y 100°C por 4 a 24 horas.

Además, la base que se usa en la reacción de acoplamiento se selecciona preferiblemente entre carbonato de potasio y carbonato de sodio. Un catalizador que se usa en la reacción de acoplamiento puede ser paladio de tetraquistrifenilfosfina o palado diclorobistrifenilfosfina, y un solvente que se usa en la reacción de acoplamiento puede ser tolueno, una mezcla de tolueno y etanol, una mezcla de

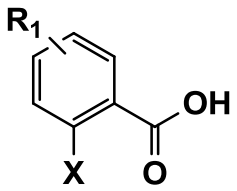
etanol y agua, una mezcla de acetonitrilo y agua, o similares. Más aún, la reacción de acoplamiento puede realizarse a una temperatura de entre 100°C y 120°C por 10 minutos a 12 horas.

Más aún, la base que se usa en la reacción de des-esterificación se selecciona preferiblemente entre hidróxido de sodio e hidróxido de potasio, y un solvente que se usa en la reacción de des-esterificación puede ser etanol o una mezcla de etanol y agua. La reacción de des-esterificación puede realizarse a una temperatura entre 100°C y 120°C por 2 a 12 horas.

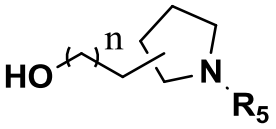
Método de Preparación 3

Además, el método para preparar los compuestos de Fórmula 1 o sales farmacéuticamente aceptables de los mismos de acuerdo con la presente invención puede comprender las etapas de: hacer reaccionar un compuesto de la siguiente Fórmula 5 con un compuesto de la siguiente Fórmula 3 en presencia de un reactivo de síntesis de carbamato para preparar un compuesto de la siguiente Fórmula 9; y acoplar un compuesto de la siguiente Fórmula 7 al compuesto de la Fórmula 9:

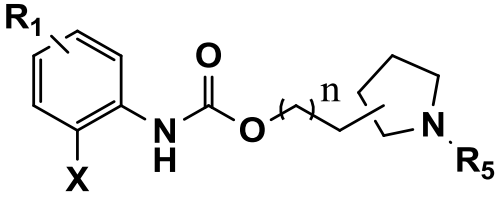
Fórmula 5



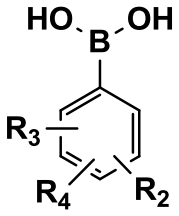
Fórmula 3



Fórmula 9



Fórmula 7



donde R_1 a R_5 y n son las mismas como se define en la Fórmula 1, y X es halógeno.

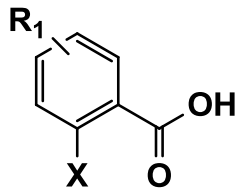
El reactivo de síntesis de carbamato y las condiciones de reacción son las mismas como se describe en lo anterior para el método de preparación 1.

Además, los reactivos de reacción de acoplamiento y las condiciones de reacción son las mismas como se describen en lo anterior para el método de preparación 2.

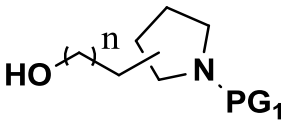
Método de preparación 4

Además, el método para preparar los compuestos de Fórmula 1 o sales farmacéuticamente aceptables de los mismos de acuerdo con la presente invención puede comprender las etapas de: hacer reaccionar un compuesto de la siguiente Fórmula 5 con un compuesto de la siguiente Fórmula 3a en presencia de un reactivo de síntesis de carbamato para preparar un compuesto de la siguiente Fórmula 9a; desproteger el compuesto de la Fórmula 9a para obtener un compuesto de la siguiente Fórmula 9b; introducir un sustituyente de R_5 al compuesto de la Fórmula 9b para preparar un compuesto de la siguiente Fórmula 9; y acoplar un compuesto de la siguiente Fórmula 7 al compuesto de la Fórmula 9:

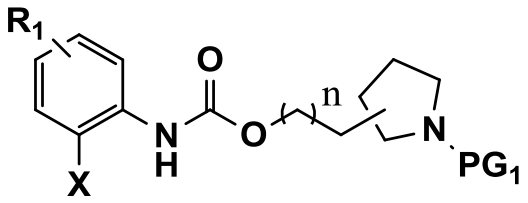
Fórmula 5



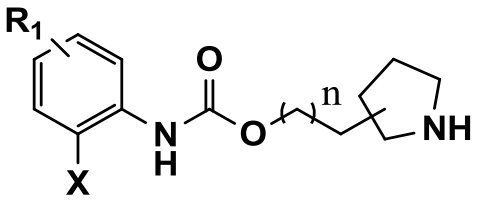
Fórmula 3a



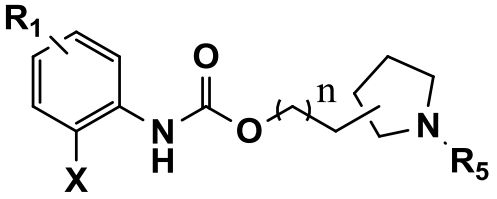
Fórmula 9a



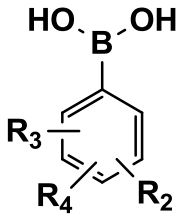
Fórmula 9b



Fórmula 9



Fórmula 7



donde R_1 a R_5 y n son las mismas como se define en la Fórmula 1; X es halógeno; y PG_1 es el mismo como se define en el método de preparación 2.

El reactivo de síntesis de carbamato y las condiciones de reacción son como se describen en lo anterior para el método de preparación 1.

Además, la reacción de desprotección, la reacción para introducir el sustituyente de R_5 y la reacción de acoplamiento son como se describen en lo anterior para el método de preparación 2.

Composición Farmacéutica que contiene Derivados de bifenilo novedosos

La presente invención proporciona un antagonista del receptor muscarínico M3 que contiene el compuesto de la Fórmula 1, un isómero del mismo, una sal farmacéuticamente aceptable del mismo, o un hidrato del mismo como un ingrediente activo.

En la presente invención, el antagonista del receptor muscarínico M3 puede ser una composición para la prevención o tratamiento de una enfermedad seleccionada del grupo que consiste de enfermedad pulmonar obstructiva crónica, asma, síndrome de intestino irritable, incontinencia urinaria, rinitis, colitis espasmódica, cistitis crónica, enfermedad de Alzheimer, demencia senil, glaucoma, esquizofrenia, enfermedad de reflujo gastroesofágico, arritmia cardiaca, y síndromes de hipersalivación.

En la presente invención, el antagonista del receptor muscarínico M3 puede contener, además al compuesto de la Fórmula 1 o una sal farmacéuticamente aceptable del mismo, uno o más ingredientes activos que muestran una función igual

o similar al compuesto de la Fórmula 1 o una sal farmacéuticamente aceptable del mismo.

Para la administración, la composición de la presente invención puede además comprender al menos un portador farmacéuticamente aceptable. El portador farmacéuticamente aceptable que se usa en la composición de la presente invención puede ser solución salina fisiológica, agua destilada, solución de Ringer, solución salina amortiguada, solución de dextrosa, solución de maltodextrin, glicerol, etanol, o una mezcla de uno o más de los mismos. Si es necesario, otros aditivos convencionales tal como agentes antioxidantes, amortiguadores o bacteriostáticos pueden agregarse a la composición de la presente invención. Además, diluyentes, dispersantes, tensoactivos, aglutinantes y lubricantes pueden además agregarse a la composición para formular soluciones inyectables tal como soluciones acuosas, suspensiones o emulsiones, píldoras, cápsulas, gránulos o tabletas. Más aún, la composición de la presente invención puede formularse preferiblemente dependiendo en enfermedades en particular o en sus componentes, usando un método adecuado conocido en la técnica o el método descrito en Remington's Pharmaceutical Science, Merck Publishing Company, Easton PA.

Además, cuando el antagonista del receptor muscarínico M3 de la presente invención es para la administración oral,

el compuesto de la Fórmula 1 o una sal farmacéuticamente aceptable del mismo puede contenerse en una cantidad de 1-95% en peso, preferiblemente 1-70% en peso, en base al peso total del Antagonista del receptor M3.

La composición farmacéutica de la presente invención puede administrarse oralmente o puede administrarse parenteralmente en forma de soluciones inyectables, supositorios, agentes transdérmicos, agentes de inhalación o agentes intravesicales.

La presente invención también proporciona un método para tratar o aliviar una enfermedad causada por la disminución de la actividad en el receptor muscarínico M3, el método que comprende administrar un antagonista del receptor muscarínico M3 que contiene el compuesto de la Fórmula 1 o una sal farmacéuticamente aceptable como un ingrediente activo a mamíferos incluyendo humanos en necesidad de la actividad del antagonista del receptor muscarínico M3.

El antagonista del receptor muscarínico M3 de la presente invención puede usarse solo o en combinación con cirugía, terapia hormonal, terapia de fármacos y un modificador de la respuesta biológica a fin de prevenir o tratar una enfermedad causada por la disminución de la actividad en el receptor muscarínico M3.

Método para la Prevención o tratamiento de Enfermedades relacionadas con el Receptor muscarínico M3

La presente invención también proporciona un método para prevenir o tratar una enfermedad relacionada con el receptor muscarínico M3, por ejemplo, una enfermedad seleccionada entre enfermedad pulmonar obstructiva crónica, asma, síndrome de intestino irritable, incontinencia urinaria, rinitis, colitis espasmódica, cistitis crónica, enfermedad de Alzheimer, demencia senil, glaucoma, esquizofrenia, enfermedad de reflujo gastroesofágico, arritmia cardiaca, y síndromes de hipersalivación, el método que comprende administrar a sujetos en necesidad de la misma una composición que contiene, como un ingrediente activo, el compuesto de la Fórmula 1, o un isómero de mismo, una sal farmacéuticamente aceptable del mismo, o un hidrato del mismo.

La composición que se usa en el método de prevención o tratamiento de la presente invención incluye la composición farmacéutica como se describe en la presente.

Además, los sujetos en necesidad del método de prevención o tratamiento de la presente invención incluyen mamíferos, particularmente humanos.

Efectos Benéficos

Los derivados de bifenilo de acuerdo con la presente

invención tienen afinidad y selectividad para el receptor muscrínico M3 y son menos tóxicos. Por lo tanto, estos derivados de bifenilo pueden usarse como agentes para prevenir o tratar varias enfermedades, particularmente, enfermedades del sistema urinario tal como enuresis, polaquiuria nerviosa, vejiga neurogénica, vejiga inestable, cistitis crónica, cistoespasmos, incontinencia urinaria, o micción frecuente, enfermedades del sistema respiratorio tales como enfermedad pulmonar obstructiva crónica, bronquitis crónica, asma, o rinitis, enfermedades digestivas y tal como síndrome del intestino irritable, colitis espástica o diverticulitis, en las que el receptor muscarínico M3 se involucra.

Particularmente, ya que los derivados de bifenilo de la presente invención tienen una alta selectividad para el receptor muscarínico M2 y el receptor muscarínico M3 que está presente en músculos lisos, tejidos glandulares y similares, estos derivados de bifenilo son antagonistas del receptor M3 que tienen menos efectos secundarios, y por lo tanto son de gran utilidad como agentes para prevenir o tratar incontinencia urinaria, micción frecuente, bronquitis crónica, enfermedad pulmonar obstructiva crónica, asma, rinitis, y similares.

EJEMPLOS

La presente descripción se describirá a mayor detalle a partir de aquí con referencia a los ejemplos de Síntesis, ejemplos y ejemplos experimentales adjuntos. Sin embargo, los Ejemplos de acuerdo con la presente invención pueden modificarse en varias maneras, y el alcance de la presente invención no debe interpretarse como limitante a los siguientes Ejemplos. Los Ejemplos de la presente invención se proporcionan de modo que aquellos expertos en la técnica puedan entender suficientemente la presente invención.

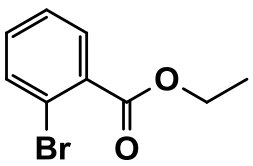
Más aún, los agentes establecidos en la presente se compraron de Aldrich Korea, Acros, Lancaster, TCI a menos que se especifique lo contrario. ^{1}H NMR como se usa en la presente fue Varian 400 MHz, y el horno de microondas usado en la presente fue el Microondas 300 de Anton Paar company.

Ejemplo de Síntesis 1

Síntesis de ácido 4'-fluoro-[1,1'-bifenil]-2- carboxílico

Etapa 1

Síntesis de etil-2-bromobenzoato

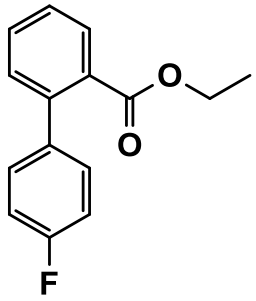


Ácido 2-borobenzoico (5g, 24.87mmol) se disolvió en etanol (100mL). Ácido sulfúrico (5mL) se agregó al mismo y

se agitó bajo reflujo por 24 horas. Después de que la reacción se terminó, el reactivo se enfrió a temperatura ambiente. El solvente se removió al concentrar el reactivo bajo presión reducida, y se extrajo con agua y acetato de etilo. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (4.9g, 86%).

Etapa 2

Síntesis de 4'-fluoro-[1,1'-bifenil]-2-carboxilato etilo

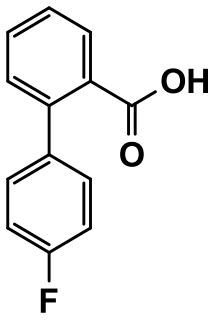


Etil-2-bromobenzoato (1g, 4.37mmol) preparado en la Etapa 1 se disolvió en una solución mezclada de tolueno (20mL) y etanol (4mL), y luego ácido 4-fluorofenil borónico (672mg, 4.80mmol), carbonato de potasio (1.21g, 8.73mmol) y paladio de tetraquis trifenilfosfina (504mg, 0.44mmol) se agregaron al mismo. El reactivo se agitó a 100°C por 6 horas, se enfrió a temperatura ambiente y se filtró a través de Celite. El solvente se removió al concentrar el reactivo bajo presión reducida. El mismo se extrajo con agua y

acetato de etilo. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (948mg, 89%).

Etapa 3

Síntesis de ácido 4'-Fluoro-[1,1'-bifenil]-2-carboxílico



4'-fluoro-[1,1'-bifenil]-2-carboxilato de etilo (948mg, 3.33mmol) preparado en la Etapa 2 se disolvió en etanol (20mL). La solución de hidróxido de sodio 2N (5.82mL, 11.64mmol) se agregó al mismo y se agitó bajo reflujo por 12 horas. El reactivo se enfrió a temperatura ambiente. El solvente se removió al concentrar el reactivo bajo presión reducida. El mismo se extrajo con 1N-ácido clorhídrico y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró para preparar el compuesto del título (747mg, 89%).

Ejemplos de síntesis 2-15

El ácido 2-borobenzoico como un material de partida y los materiales de reacción en la Tabla 1 se usaron para

preparar los compuestos de los Ejemplos de síntesis 2-15 de la misma manera que el Ejemplo de Síntesis 1.

Tabla 1 Ejemplos de síntesis 1-15

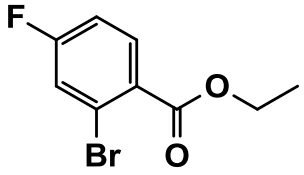
Síntesis Ejemplo	Nombre Químico	Material de Reacción
1	ácido 4'-Fluoro-[1,1'-bifenil]-2-carboxílico	ácido 4-Fluorofenil borónico
2	ácido 3',5'-Difluoro-[1,1'-bifenil]-2-carboxílico	ácido 3,5-Difluorofenil borónico
3	ácido 3',4',5'-trifluoro-[1,1'-bifenil]-2-carboxílico	ácido 3,4,5-Trifluorofenil borónico
4	ácido 3'-fluoro-[1,1'-bifenil]-2-carboxílico	ácido 3-Fluorofenil borónico
5	ácido 4'-metoxi-[1,1'-bifenil]-2-carboxílico	ácido 4-Metoxifenil borónico
6	ácido 4'-Cloro-[1,1'-bifenil]-2-carboxílico	ácido 4-Clorofenil borónico
7	ácido 3'-Cloro-[1,1'-bifenil]-2-carboxílico	ácido 3-Clorofenil borónico
8	ácido 3',5'-Dicloro-[1,1'-bifenil]-2-carboxílico	ácido 3,5-Diclorofenil borónico
9	ácido 4'-Trifluorometoxi-[1,1'-bifenil]-2-carboxílico	ácido 4-Trifluorometoxifenil borónico
10	ácido 4'-Nitro-[1,1'-bifenil]-2-carboxílico	ácido 4-Nitrofenil borónico

11	ácido 3'-trifluorometil-[1,1'-bifenil]-2-carboxílico	ácido 3-Trifluorometilfenil borónico
12	ácido 4'-trifluorometil-[1,1'-bifenil]-2-carboxílico	ácido 4-Trifluorometilfenil borónico
13	ácido 3'-Fluoro-4'-metil-[1,1'-bifenil]-2-carboxílico	ácido 3-Fluoro-4-metilfenil borónico
14	ácido 3'-Metil-[1,1'-bifenil]-2-carboxílico	ácido 3-Metilfenil borónico
15	ácido 3'-Etoxi-[1,1'-bifenil]-2-carboxílico	ácido 3-Etoxifenil borónico

Ejemplo de Síntesis 16

Síntesis de ácido 3'-cloro-5-fluoro-[1,1'-bifenil]-2-carboxílico

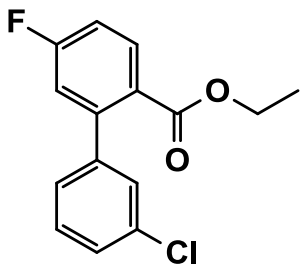
Etapa 1 2-bromo-4-fluorobenzoato de etilo



El ácido 2-bromo-4-fluorobenzoico (2.37g, 10.82mmol) se disolvió en etanol (100mL). Cloruro de tionilo (1.57mL, 21.64mmol) se agregó al mismo y se agitó bajo reflujo por 24 horas. El reactivo se enfrió a temperatura ambiente después de que la reacción se terminó. El solvente se removió al concentrar el reactivo bajo presión reducida. El mismo se

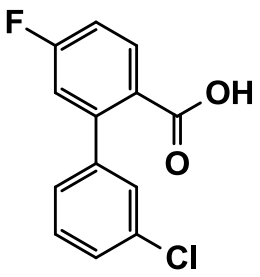
extrajo con agua y acetato de etilo. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (2.29g, 87%).

Etapa 2 3'-cloro-5-fluoro-[1,1'-bifenil]-2-carboxilato de etilo



2-bromo-4-fluorobenzoato de etilo (1.1g, 4.47mmol) preparado en la Etapa 1 se disolvió en tolueno (20mL). Ácido 3-Clorofenil borónico (766mg, 4.90mmol), carbonato de potasio (1.23g, 8.90mmol) y paladio de tetraquis trifenilfosfina (520mg, 0.44mmol) se agregaron al mismo. El reactivo se agitó a 100°C por 6 horas y se enfrió a temperatura ambiente. El mismo se filtró a través de Celite y el solvente se removió al concentrar el reactivo bajo presión reducida. El mismo se extrajo con agua y acetato de etilo. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (850mg, 69%).

Etapa 3 ácido 3'-cloro-5-fluoro-[1,1'-bifenil]-2-carboxílico



3'-cloro-5-fluoro-[1,1'-bifenil]-2-carboxilato de etilo (850mg, 3.05mmol) preparado en la Etapa 2 se disolvió en etanol (20mL). Solución de hidróxido de sodio 2N (4.57mL, 9.15mmol) se agregó al mismo y se agitó bajo reflujo por 12 horas. El reactivo se enfrió a temperatura ambiente. El solvente se removió al concentrar el reactivo bajo presión reducida y se extrajo con ácido clorhídrico 1N y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró para preparar el compuesto del título (650mg, 85%).

Ejemplos de síntesis 17-26

Los materiales de partida y los materiales de reacción en la Tabla 2 se usaron para preparar los compuestos de los Ejemplos de síntesis 17-26 de la misma manera que el Ejemplo de Síntesis 16.

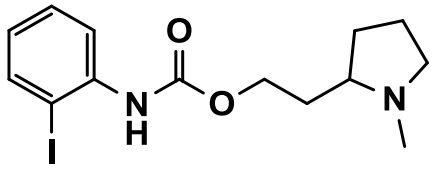
Tabla 2 Ejemplos de síntesis 16-26

Síntesis Ejemplo	Nombre Químico	Material de Partida	Material de Reacción
16	ácido 3'-cloro-5-fluoro-[1,1'-bifenil]-2-carboxílico	ácido 2-bromo-4-fluorobenzoico	ácido 3-Clorofenil borónico
17	ácido 3',5-Difluoro-[1,1'-bifenil]-2-carboxílico	ácido 2-bromo-4-fluorobenzoico	ácido 3-Fluorofenil borónico
18	ácido 4',5-Difluoro-[1,1'-bifenil]-2-carboxílico	ácido 2-bromo-4-fluorobenzoico	ácido 4-Fluorofenil borónico
19	ácido 3',5,5'-Trifluoro-[1,1'-bifenil]-2-carboxílico	ácido 2-bromo-4-fluorobenzoico	ácido 3,5-Difluorofenil borónico
20	ácido 5-Fluoro-[1,1'-bifenil]-2-carboxílico	ácido 2-bromo-4-fluorobenzoico	ácido Fenil borónico
21	ácido 5-Fluoro-3'-metil-[1,1'-bifenil]-2-carboxílico	ácido 2-bromo-4-fluorobenzoico	ácido 3-Metilfenil borónico
22	ácido 4-Fluoro-[1,1'-bifenil]-2-carboxílico	ácido 2-Bromo-5-fluorobenzoico	ácido Fenil borónico
23	ácido 3',4-Difluoro-[1,1'-bifenil]-2-carboxílico	ácido 2-Bromo-5-fluorobenzoico	ácido 3-Fluorofenil borónico

24	ácido 4-Metoxi-[1,1'-bifenil]-2-carboxílico	ácido 2-Bromo-5-metoxibenzoico	ácido Fenil borónico
25	ácido 5-Metil-[1,1'-bifenil]-2-carboxílico	ácido 2-Bromo-4-metilbenzoico	ácido Fenil borónico
26	ácido 3'-Fluoro-5-metil-[1,1'-bifenil]-2-carboxílico	ácido 2-Bromo-4-metilbenzoico	ácido 3-Fluorofenil borónico

Ejemplo de Síntesis A

Síntesis de (2-yodofenil)carbamato de 2-(1-metilpirrolidin-2-il)etilo



Ácido 2-Yodobenzoico (1g, 4.03mmol) se disolvió en tolueno (50mL). Azida de bifenilfosforilo (1.04mL, 4.84mmol) y trietilamina (566uL, 4.03mmol) se agregaron al mismo. El mismo se agitó a temperatura ambiente por 30 minutos, y luego se agitó bajo reflujo por 1 hora. El reactivo se enfrió a temperatura ambiente. 2-(2-Hidroxietil)-1-metilpirrolidina (651uL, 4.84mmol) se agregó al mismo y se agitó bajo reflujo por 12 horas. El reactivo se enfrió a temperatura ambiente. El solvente se removió al concentrar el reactivo bajo presión reducida y el mismo se extrajo con agua y acetato de etilo.

La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (1.16g, 77%).

Ejemplos de síntesis B-E

Los materiales de partida en la Tabla 3 se usaron en vez de ácido 2-yodobenzoico para preparar los compuestos de los Ejemplos de síntesis B-E de la misma manera que el Ejemplo de Síntesis A.

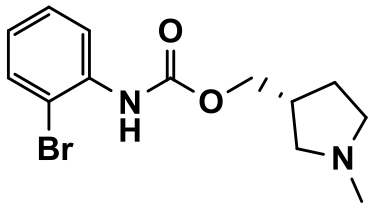
Tabla 3 Ejemplos de síntesis A-E

Ejemplo de Síntesis	Nombre Químico	Material de Partida
A	(2-yodofenil)carbamato de 2-(1-metilpirrolidin-2-il)etilo (1.16g, 77%)	ácido 2-Yodobenzoico (1g, 4.03mmol)
B	(2-bromo-4-fluorofenil)carbamato de 2-(1-Metilpirrolidin-2-il)etilo (3.7g, 94%)	ácido 2-bromo-4-fluorobenzoico (2.5g, 11.42mmol)
C	(2-bromo-4-(trifluorometil)fenil)carbamato de 2-(1-Metilpirrolidin-2-il)etilo (1.72g, 94%)	ácido 2-Bromo-4-(trifluorometil)benzoico (2g, 7.43mmol)

D	(2-bromo-4-metoxifenil)carbamato de 2-(1-Metilpirrolidin-2-il)etilo (2.5g, 81%)	ácido 2-bromo-4-metoxibenzoico (2g, 7.43mmol)
E	(2-bromo-4-clorofenil)carbamato de 2-(1-Metilpirrolidin-2-il)etilo (38g, 99%)	ácido 2-bromo-4-clorobenzoico (2.5g, 10.62mmol)

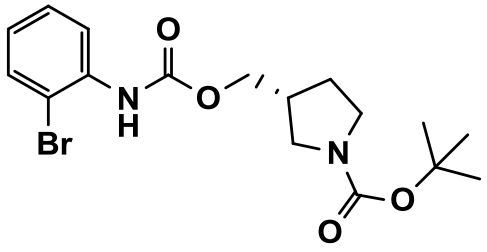
Ejemplo de Síntesis F

Síntesis de (2-bromofenil)carbamato de (R)-(1-metilpirrolidin-3-il)metilo



Etapa 1

Síntesis de 3-((((2-bromofenil)carbamoil)oxi)metil)pirrolidin-1-carboxilato de (R)-tert-butilo

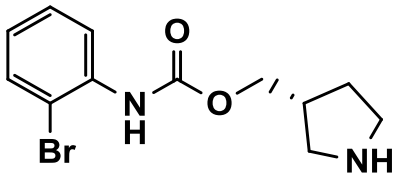


Ácido 2-borobenzoico (4.5g, 22.4mmol) se disolvió en tolueno (100mL) y azida de bifenilfosforilo (5.8mL, 26.9mmol)

y trietilamina (3.15mL, 22.4mmol) se agregaron al mismo. El mismo se agitó a temperatura ambiente por 30 minutos, y luego se agitó bajo reflujo por 1 hora. El reactivo se enfrió a temperatura ambiente, 3-(hidroximetil)pirrolidin-1-carboxilato de (R)-tert-butilo (5.41g, 26.9mmol) se agregó al mismo, y se agitó bajo reflujo por 12 horas. El reactivo se enfrió a temperatura ambiente. El solvente se removió al concentrar el reactivo bajo presión reducida. El mismo se extrajo con agua y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (8.1g, 91%).

Etapa 2

Síntesis de (2-bromofenil)carbamato de ((R)-pirrolidin-3-ilmetilo

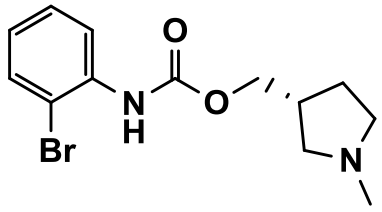


3-((((2-bromofenil)carbamoil)oxi)metil)pirrolidin-1-carboxilato de (R)-tert-butilo (8.1g, 20.29mmol) preparado en la Etapa 1 se disolvió en diclorometano (100mL). Ácido trifluoroacético (50mL) se agregó al mismo y se agitó a temperatura ambiente por 2 horas. El solvente se removió al concentrar el reactivo bajo presión reducida, y el mismo se

extrajo con solución de hidróxido de sodio 2N y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (3.94g, 65%).

Etapa 3

Síntesis de (2-bromofenil)carbamato de (R)-(1-metilpirrolidin-3-il)metilo



(2-bromofenil)carbamato de (R)-pirrolidin-3-ilmetilo (3.94g, 13.13mmol) preparado en la Etapa 2 se disolvió en agua (100mL). Ácido acético (5mL), solución de formaldehido (15mL) y polvo de zinc (1.5g) se agregaron secuencialmente al mismo y se agitó a temperatura ambiente por 12 horas. El reactivo se filtró, se neutralizó con solución de hidróxido de sodio 2N y se extrajo con agua y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (3.06g, 75%).

Ejemplos de las síntesis G-L

Los materiales de partida y los materiales de reacción en la Tabla 4 se usaron para preparar los compuestos de los Ejemplos de las síntesis G-L de la misma manera que el Ejemplo de la Síntesis F.

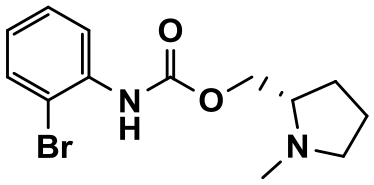
Tabla 4 Ejemplos de las síntesis F-L

Ejemplo de Síntesis	Nombre Químico	Material de Partida	Material de Reacción
F	(2-bromofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (3.06g, 75%)	ácido 2-borobenzoico (4.5g, 22.4mmol)	3-(hidroximetil) pirrolidin-1-carboxilato de (R)-tert-butilo (5.41g, 26.9mmol)
G	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-3-il)metilo	ácido 2-borobenzoico	3-(hidroximetil) pirrolidin-1-carboxilato de (S)-tert-butilo
H	(2-bromo-4-fluorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (2.29g, 30%)	ácido 2-bromo-4-fluorobenzoico (5g, 22.83mmol)	3-(hidroximetil) pirrolidin-1-carboxilato de (R)-tert-butilo (5.51g, 27.4mmol)

I	Síntesis de (2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-3-il)metilo	ácido 2-bromo-4-fluorobenzoico	3-(hidroximetil) pirrolidin-1-carboxilato de (S)-tert-butilo
J	(2-bromo-4-clorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (2.5g, 34%)	ácido 2-bromo-4-clorobenzoico (5g, 21.23mmol)	3-(hidroximetil) pirrolidin-1-carboxilato de (R)-tert-butilo (5.1g, 25.48mmol)
K	(2-bromo-4-metoxifenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (2.3g, 52%)	ácido 2-bromo-4-metoxibenzoico (3g, 12.98mmol)	3-(hidroximetil) pirrolidin-1-carboxilato de (R)-tert-butilo (3.9g, 19.47mmol)
L	(2-bromo-4,5-difluoro fenil)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (884mg, 40%)	ácido 2-bromo-4,5-difluorobenzoico (1.5g, 6.33mmol)	3-(hidroximetil) pirrolidin-1-carboxilato de (R)-tert-butilo (2.55g, 12.65mmol)

Ejemplo de la Síntesis M

Síntesis de (2-bromofenil)carbamato de (S)-(1-metilpirrolidin-2-il)metilo



Ácido 2-borobenzoico (2g, 9.95mmol) se disolvió en tolueno (75 mL), y luego azida de bifenilfosforilo (2.57mL, 11.94mmol) y trietilamina (1.4mL, 9.95mmol) se agregaron al mismo. El mismo se agitó a temperatura ambiente por 30 minutos, y luego se agitó bajo reflujo por 1 hora. El reactivo se enfrió a temperatura ambiente. (S)-(1-metilpirrolidin-2-il)metanol (1.42mL, 11.94mmol) se agregó al mismo y se agitó bajo reflujo por 4 horas. El reactivo se enfrió a temperatura ambiente. El solvente se removió al concentrar el reactivo bajo presión reducida. El mismo se extrajo con agua y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (1.4g, 45%).

Ejemplos de las síntesis N-P

Los materiales de partida y los materiales de reacción en la Tabla 5 se usaron para preparar los compuestos de los ejemplos de las síntesis N-P de la misma manera que el

Ejemplo de la Síntesis M.

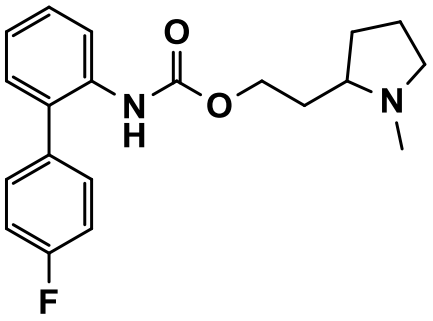
Tabla 5 Ejemplos de las Síntesis M-P

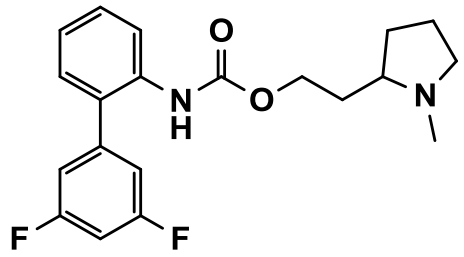
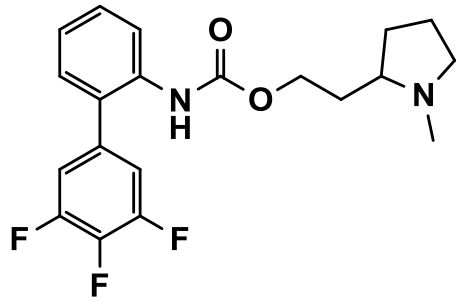
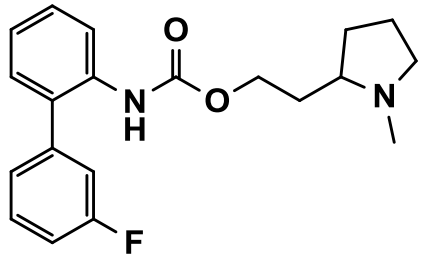
Ejemplo de Síntesis	Nombre Químico	Material de Partida	Material de Reacción
M	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (1.4g, 45%)	ácido 2-borobenzoico (2g, 9.95mmol)	(S)-(1-metilpirrolidin-2-il)metanol (1.42mL, 11.94mmol)
N	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (2.86g, 47%)	ácido 2-bromo-4-fluorobenzoico (4g, 18.26mmol)	(S)-(1-metilpirrolidin-2-il)metanol (2.6mL, 21.91mmol)
O	(2-bromo-4-metoxifenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (600mg, 67%)	ácido 2-bromo-4-metoxibenzoico (600mg, 2.60mmol)	(S)-(1-metilpirrolidin-2-il)metanol (463uL, 3.90mmol)

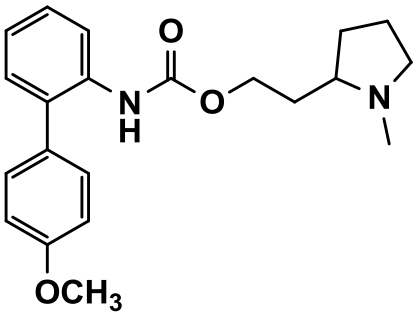
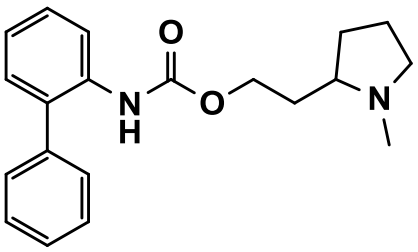
P	(2-bromo-4,5-difluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (737mg, 50%)	ácido 2-bromo-4,5-difluorobenzoico (1g, 4.22mmol)	(S)-(1-metilpirrolidin-2-il)metanol (730mg, 6.33mmol)

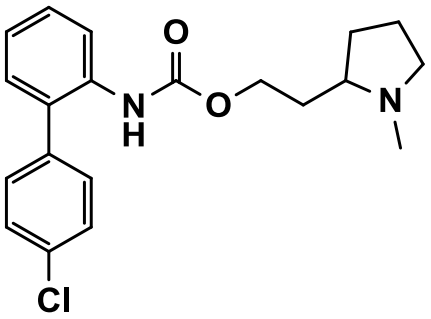
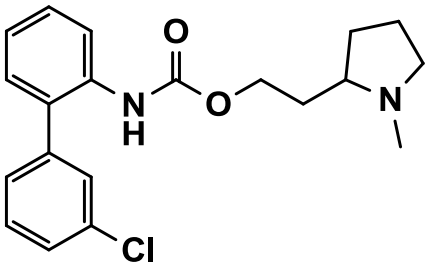
Ejemplo

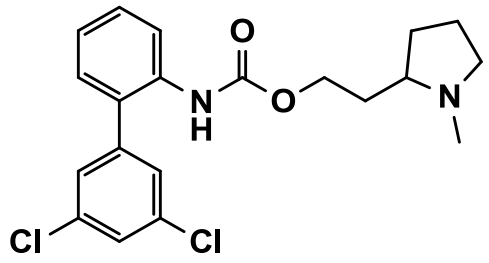
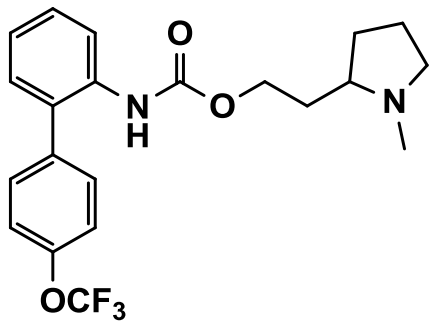
Tabla 6 Compuestos de Ejemplos

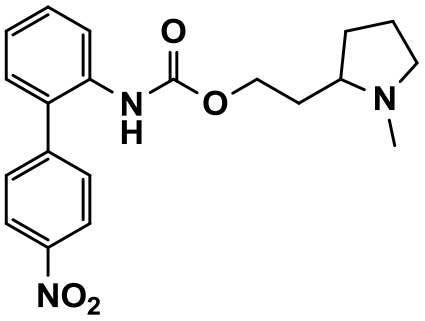
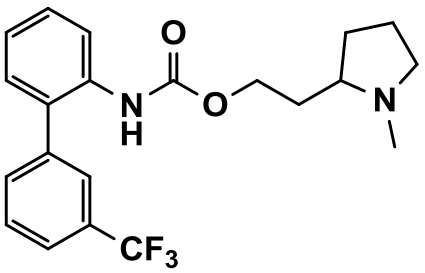
Ejemplo	Compuesto	Valor NMR
1	(4'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-Metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.10-7.99(m, 1H), 7.38-7.26(m, 3H), 7.20-7.06(m, 4H), 6.52-6.41(bs, 1H), 4.21-4.08(m, 2H), 3.12-2.99(m, 1H), 2.29(m, 3H), 2.20-1.87(m, 4H), 1.83-1.61(m, 2H), 1.61-1.40(m, 2H)

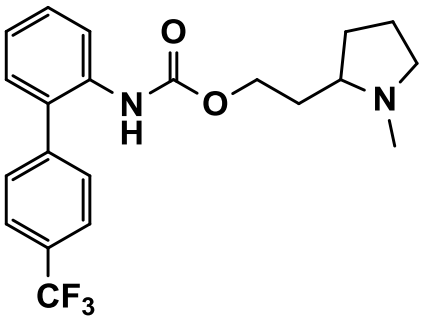
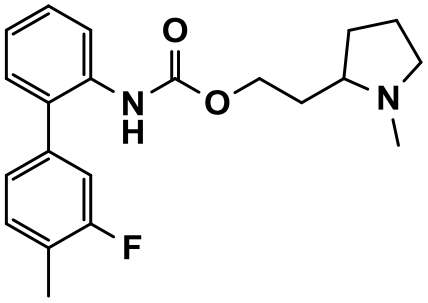
2	(3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-Metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.11-7.96(m, 1H), 7.45-7.32(m, 1H), 7.21-7.07(m, 2H), 6.98-6.79(m, 3H), 6.55-6.39(bs, 1H), 4.27-4.10(m, 2H), 3.14-2.99(m, 1H) 2.30(s, 3H), 2.21-1.85(m, 4H), 1.85-1.41(m, 4H)
3	(3',4',5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.00-7.88(m, 1H), 7.43-7.30(m, 1H), 7.29-7.08(m, 2H), 7.05-6.91(m, 2H), 6.69-6.52(bs, 1H), 4.25-4.06(m, 2H), 3.25-3.08(m, 1H), 2.47-2.17(m, 5H) 2.14-1.91(m, 2H), 1.90-1.45(m, 4H)
4	(3'-fluoro[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.13-7.96(m, 1H), 7.50-7.28(m, 2H), 7.22-7.00(m, 5H), 6.60-6.45(bs, 1H), 4.25-4.07(m, 2H), 3.13-2.99(m, 1H), 2.31(s, 3H), 2.22-1.41(m, 8H)

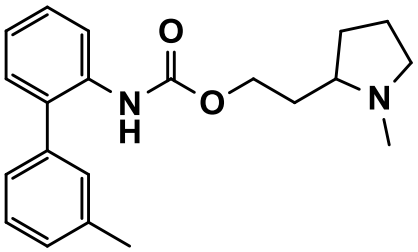
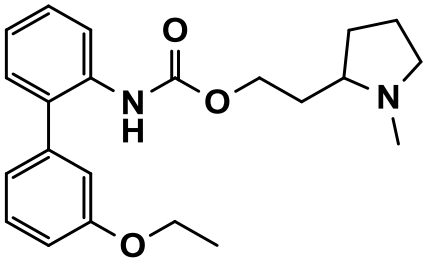
5	(4'-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.13-7.99(m, 1H), 7.35-7.22(m, 4H), 7.20-7.14(m, 1H), 7.12-7.06(m, 1H), 7.03-6.95(m, 2H), 6.63-6.56(bs, 1H), 4.23-4.10(m, 2H), 3.85(s, 3H), 3.10-3.01(m, 1H), 2.28(s, 3H) 2.17-1.88(m, 4H), 1.84-1.62(m, 2H), 1.62-1.41(m, 2H)
6	[1,1'-bifenil]-2-ilcarbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.11(s, 1H), 7.45(t, 1H), 7.38(d, 1H), 7.34(dd, 2H), 7.21(dd, 2H), 7.12(t, 1H), 6.99(t, 1H), 6.64(s, 1H), 4.18-4.14(m, 2H), 3.09-3.01(m, 1H), 2.40(s, 3H), 2.34(m, 3H), 2.12-2.06 (m, 2H), 1.91-1.82(m, 1H), 1.78-1.66(m, 2H), 1.60-1.56(m, 1H)

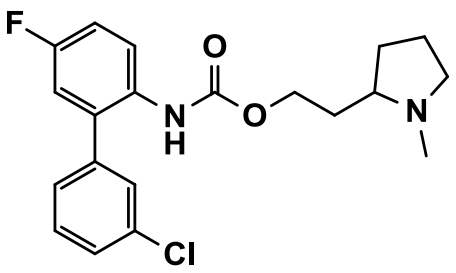
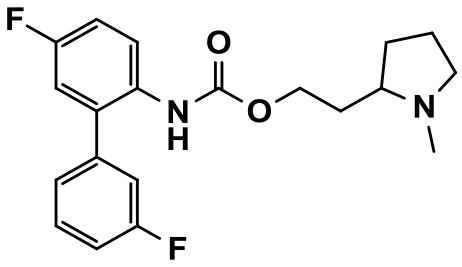
7	(4'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.11-7.94(m, 1H), 7.55-6.97(m, 7H), 6.55-6.35(bs, 1H), 4.25-3.98(m, 2H), 3.14-2.94(m, 1H) 2.29(s, 3H), 2.20-1.84(m, 4H), 1.81-1.37(m, 4H)
8	(3'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.06(s, 1H), 7.41-7.35(m, 4H), 7.26-7.22(m, 1H), 7.19-7.16(m, 1H), 7.14-7.10(m, 1H), 6.47(s, 1H), 4.22-4.15(m, 2H), 3.07-3.02(m, 1H), 2.29(s, 3H), 2.16-2.06(m, 2H), 2.03-1.91(m, 2H), 1.78-1.62(m, 2H), 1.60-1.47(m, 2H)

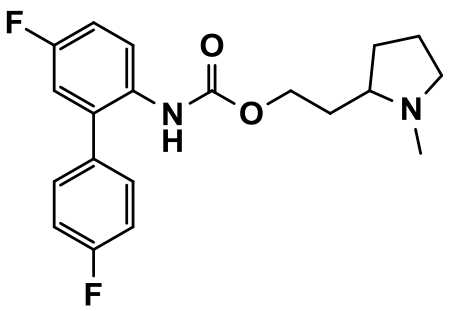
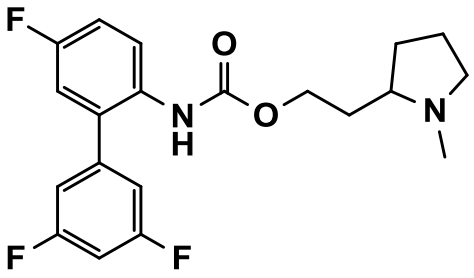
9	(3',5'-dicloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.01(s, 1H), 7.39-7.35(m, 2H), 7.22-7.20(m, 2H), 7.17-7.11(m, 2H), 6.42(s, 1H), 4.22-4.13(m, 2H), 3.10-3.01(s, 1H), 2.30(s, 3H), 2.08-2.04(m, 2H), 2.03-1.90(m, 2H), 1.78-1.60(m, 2H), 1.58-1.42(m, 2H)
10	(4'-trifluorometoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.03(s, 1H), 7.39-7.34(m, 3H), 7.31-7.291(m, 2H), 7.19-7.11(m, 2H), 6.44(s, 1H), 4.24-4.15(m, 2H), 3.04-3.00(m, 1H), 2.27(s, 3H), 2.04-2.01(m, 2H), 2.00-1.88(m, 2H), 1.80-1.63(m, 2H), 1.59-1.44(m, 2H)

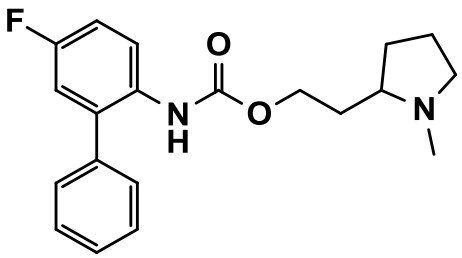
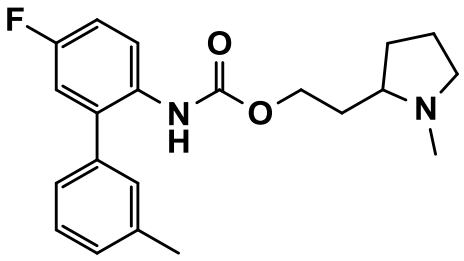
11	(4'-nitro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.27-8.24(m, 1H), 7.55-7.52(m, 1H), 7.41-7.37(m, 1H), 7.22-7.00(m, 3H), 7.01-6.97(m, 1H), 4.14-4.05(m, 2H), 3.37-3.35(m, 1H), 2.50(s, 3H), 2.10-2.04(m, 2H), 1.93-1.88(m, 2H), 1.81-1.77(m, 2H), 1.66-1.62(m, 2H)
12	(3'-trifluorometil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.10-7.92(m, 1H), 7.73-7.46(m, 3H), 7.44-7.31(m, 1H), 7.31-7.05(m, 2H), 6.55-6.34(bs, 1H), 4.26-4.02(m, 2H), 3.20-3.00(m, 1H), 2.31(s, 3H), 2.25-1.88(m, 4H) 1.86-1.40(m, 4H)

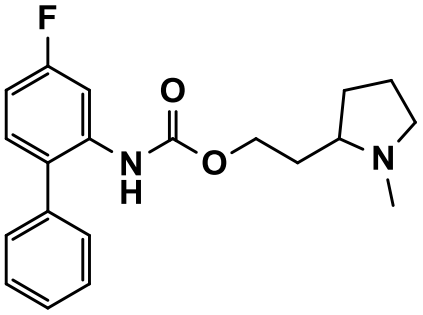
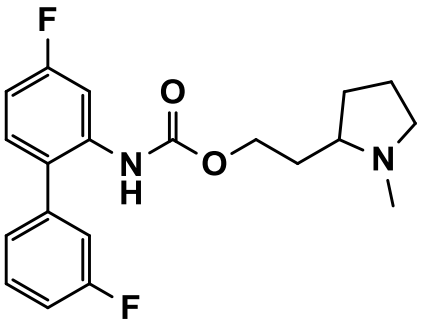
13	(4'-trifluorometil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.04(s, 1H), 7.72(d, 2H, J=8.0), 7.48(d, 2H, J=8.4), 7.41-7.36(m, 1H), 7.20-7.13(m, 2H), 6.41(s, 1H), 4.18-4.14(m, 2H), 3.06-3.01(s, 1H), 2.27(s, 3H), 2.18-2.04(m, 2H), 2.02-1.87(m, 2H), 1.77-1.68(m, 2H), 1.57-1.43(m, 2H)
14	((3'-fluoro-4'-metil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.11-7.99(m, 1H), 7.39-7.30(m, 1H), 7.30-7.14(m, 2H), 7.14-7.07(m, 1H), 7.06-6.95(m, 2H), 6.64-6.54(bs, 1H), 4.26-4.08(m, 2H), 3.30-3.09(m, 1H), 2.36(s, 3H), 2.32(s, 3H), 2.30-2.14(m, 2H) 2.13-1.92(m, 2H), 1.92-1.46(m, 4H)

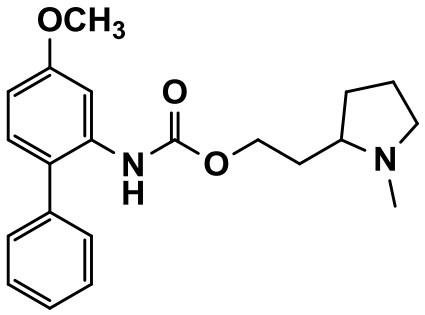
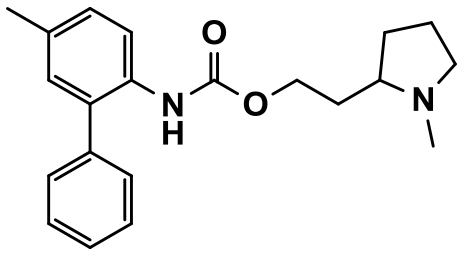
15	(3'-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.10(s, 1H), 7.38-7.33(m, 2H), 7.26-7.17(m, 3H), 7.15-7.09(m, 1H), 6.66(s, 1H), 4.19-4.16(m, 2H), 3.21-3.01 (s, 1H), 2.41(s, 3H), 2.28(s, 3H), 2.23-2.12(m, 2H), 2.10-1.91(m, 2H), 1.83-1.63(m, 2H), 1.60-1.43(m, 2H)
16	(3'-etoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.10(s, 1H), 7.37-7.31(m, 2H), 7.23-7.18(m, 2H), 7.11-7.08(m, 1H), 7.00-6.86(m, 2H), 6.70(s, 1H), 4.17-4.01(m, 4H), 3.18-3.15(m, 1H), 2.36(s, 3H), 2.23-2.16(m, 2H), 2.08-1.91(m, 2H), 1.81-1.71(m, 2H), 1.63-1.41(m, 2H), 1.40-1.38(m, 3H)

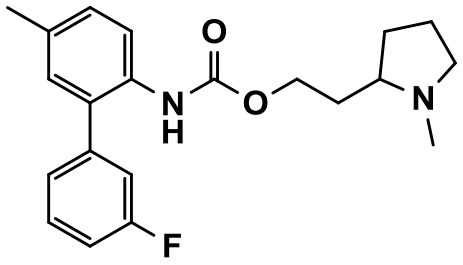
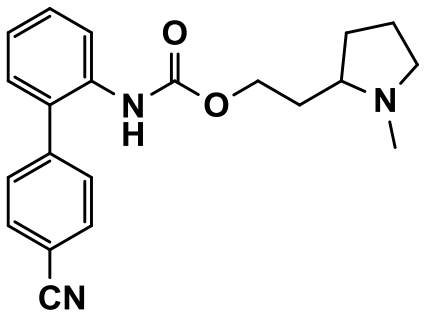
17	(3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.94(s, 1H), 7.41-7.36(m, 2H), 7.32(s, 1H), 7.22-7.20(m, 1H), 7.07-7.02(m, 1H), 6.92-6.89(m, 1H), 6.38(s, 1H), 4.17-4.13(m, 2H), 3.04-3.00(m, 1H), 2.27(s, 3H), 2.15-2.03(m, 2H), 2.00-1.87(m, 2H), 1.80-1.64(m, 2H), 1.56-1.40(m, 2H)
18	(3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.86(s, 1H), 7.44-7.39(m, 1H), 7.26-7.22(m, 1H), 7.17-7.08(m, 1H), 7.06-7.02(m, 1H), 7.01-6.91(m, 2H), 6.75(s, 1H), 4.15-4.06(m, 2H), 3.30-3.27(m, 1H), 2.47(s, 3H), 2.10-1.93(m, 2H), 1.87-1.73(m, 2H), 1.70-1.54(m, 2H)

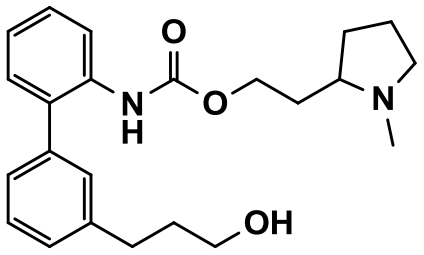
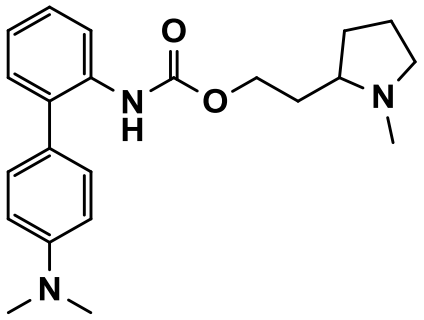
19	(4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.97(s, 1H), 7.32-7.26(m, 1H), 7.24-7.21(m, 1H), 7.19-7.13(m, 2H), 7.07-7.00(m, 1H), 6.92-6.90(m, 1H), 6.48(s, 1H), 4.16-4.10(m, 2H), 3.20-3.17(m, 1H), 2.26(s, 3H), 2.17-2.15(m, 2H), 2.07-1.96(m, 2H), 1.83-1.72(m, 2H), 1.69-1.65(m, 2H)
20	(3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.82-7.66(bs, 1H), 7.12-6.75(m, 5H), 4.27-3.99(m, 2H), 3.51-3.30(bs, 1H) 2.75-2.34(m, 5H), 2.20-1.55(m, 6H)

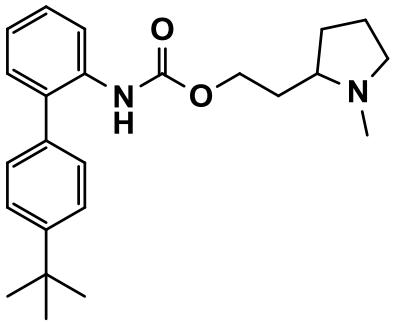
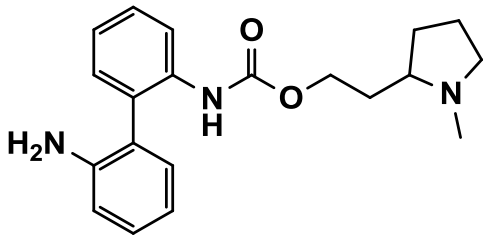
21	(5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.98(s, 1H), 7.50-7.39(m, 3H), 7.34-7.27(m, 2H), 7.06-7.01(m, 1H), 6.98-6.92(m, 1H), 6.45(s, 1H), 4.17-4.07(m, 2H), 3.05-3.01(m, 1H), 2.27(s, 3H), 2.22-2.02(m, 2H), 2.01-1.80(m, 2H), 1.78-1.61(m, 2H), 1.58-1.40(m, 2H)
22	(5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.01(s, 1H), 7.36-7.32(m, 1H), 7.27-7.21(m, 2H), 7.13-7.11(m, 1H), 7.05-7.00(m, 1H), 6.96-6.90(m, 1H), 6.51(s, 1H), 4.16-4.09(m, 2H), 3.06-3.02(m, 1H), 2.39(s, 3H), 2.28(s, 3H), 2.18-2.07(m, 2H), 2.05-1.88(m, 2H), 1.81-1.62(m, 2H), 1.58-1.44(m, 2H)

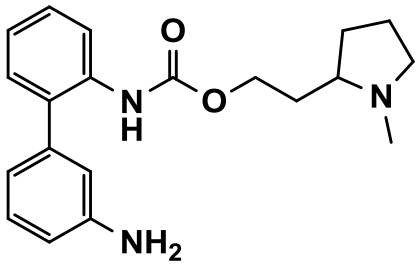
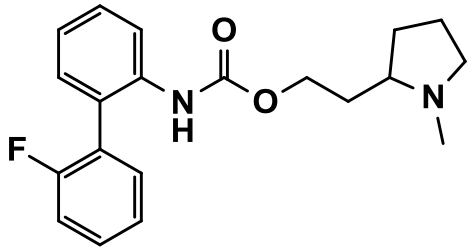
23	(4-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.97(s, 1H), 7.48-7.45(m, 2H), 7.42-7.40(m, 1H), 7.32-7.30(m, 2H), 7.15-7.11(m, 1H), 6.82-6.79(m, 1H), 6.66(s, 1H), 4.18-4.14(m, 2H), 3.06-3.04(m, 1H), 2.30(s, 3H), 2.15-2.00(m, 2H), 1.99-1.91(m, 2H), 1.69-1.58(m, 2H), 1.56-1.48(m, 2H)
24	(3',4-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.97(s, 1H), 7.48-7.44(m, 1H), 7.28-7.17(m, 2H), 7.15-7.11(m, 1H), 7.05-6.97(m, 1H), 6.86-6.80(m, 1H), 6.68(s, 1H), 4.19-4.13(m, 2H), 3.31-3.28(m, 1H), 2.48(s, 3H), 2.19-2.07(m, 2H), 1.95-1.88(m, 2H), 1.85-1.70(m, 2H), 1.67-1.54(m, 2H)

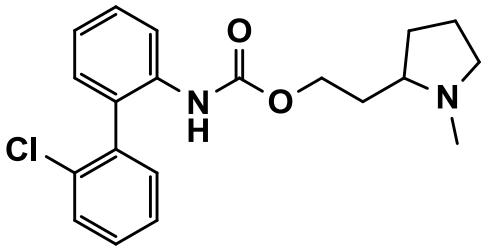
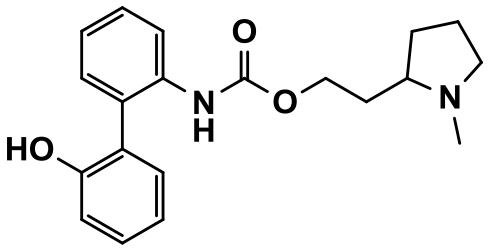
25	(4-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.80(s, 1H), 7.44-7.36(m, 1H), 7.34-7.29(m, 3H), 7.09-7.07(m, 1H), 6.68-6.64(m, 2H), 4.20-4.14(m, 2H), 3.82(s, 3H), 3.04-3.00(m, 1H), 2.26(s, 3H), 2.14-2.00(m, 2H), 2.13-1.87(m, 2H), 1.79-1.59(m, 2H), 1.56-1.40 (m, 2H)
26	(5-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.91 (s, 1H), 7.46-7.42(m, 2H), 7.38-7.29(m, 2H), 7.22-7.18(m, 1H), 7.02(s, 1H), 6.54(s, 1H), 4.18-4.10(m, 2H), 3.21-3.10(m, 1H), 2.32(s, 3H), 2.31(s, 3H), 2.22-2.16(m, 2H), 2.12-1.91(m, 2H), 1.81-1.68(m, 2H), 1.65-1.48(m, 2H)

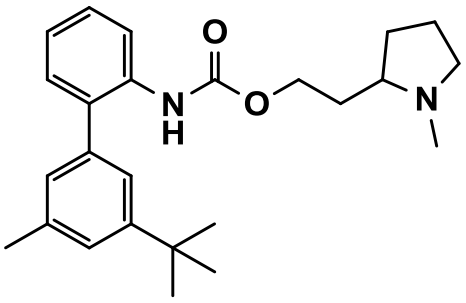
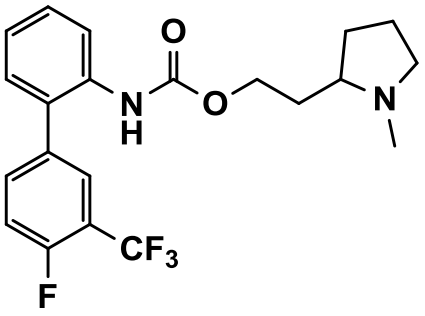
27	(3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.92 (s, 1H), 7.44-7.38(m, 2H), 7.20-7.15(m, 1H), 7.13-7.09(m, 1H), 7.07-6.97(m, 2H), 6.55(s, 1H), 4.17-4.07(m, 2H), 3.30-3.23(m, 1H), 2.49(s, 3H), 2.37(s, 3H), 2.15-2.05(m, 2H), 1.93-1.90(m, 2H), 1.79-1.76(m, 2H), 1.63-1.61(m, 2H)
28	(4'-ciano-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.06-7.93(m, 1H), 7.75(d, 8.4Hz, 2H), 7.49(d, J=8.0, 2H), 7.44-7.33(m, 1H), 7.21-7.09(m, 2H), 6.42-6.38(bs, 1H), 4.22-4.07(m, 2H), 3.11-2.98(m, 1H), 2.29(s, 3H), 2.19-1.85(m, 3H) 1.85-1.39(m, 5H)

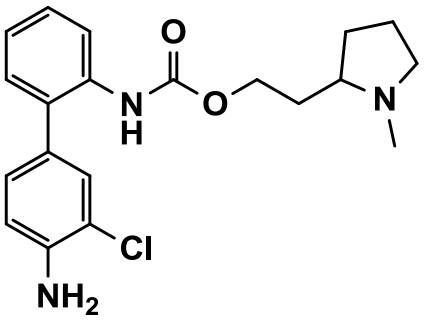
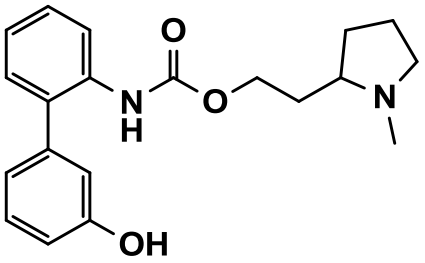
29	(3'-(3-hidroxipropil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.03(s, 1H), 7.39-7.28(m, 3H), 7.23-7.11(m, 3H), 7.05-7.01(m, 1H), 6.67(s, 1H), 4.23-4.14(m, 2H), 3.66-3.60(m, 2H), 3.17-3.03(m, 1H), 2.75-2.71(m, 2H), 2.32(s, 3H), 2.24-2.10(m, 2H), 2.05-1.96 (m, 2H), 1.94-1.83 (m, 2H), 1.81-1.69(m, 2H), 1.61-1.46(m, 2H)
30	(4'-(dimetilamino)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.11(s, 1H), 7.28(t, 1H, J=7.2), 7.23-7.19(m, 2H), 7.19-7.17(m, 1H), 7.07(t, 1H, J=7.6), 6.81(t, 2H, J=2.8), 6.74(s, 1H), 4.18-4.14(m, 2H), 3.09-3.01(m, 1H), 3.00(s, 9H), 2.14(s, 3H), 2.12-2.06(m, 2H), 2.01-1.92(m, 2H), 1.79-1.66(m, 2H), 1.58-1.46(m, 2H)

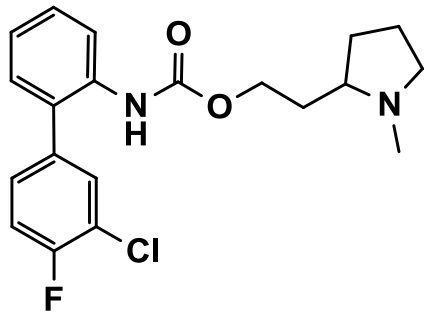
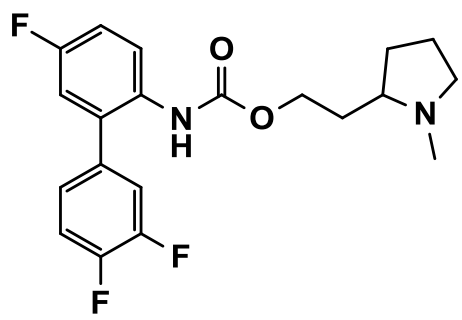
31	(4'-(tert-butil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.04(s, 1H), 7.48-7.46(m, 2H), 7.35-7.27(m, 3H), 7.24-7.19(m, 1H), 7.12-7.08(m, 1H), 6.67(s, 1H), 4.17-4.13(m, 2H), 3.10-3.07(m, 1H), 2.30(s, 3H), 2.18-1.99(m, 2H), 1.98-1.90(m, 2H), 1.80-1.62(m, 2H), 1.44-1.36(m, 2H), 1.36(s, 9H)
32	(2'-amino-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.11(s, 1H), 7.37(t, 1H, J=8.0), 7.22-7.20(m, 2H), 7.13(t, 1H, J=7.6), 7.06(d, 1H, J=7.6), 6.86-6.78(m, 2H), 4.15-4.11(m, 2H), 3.08-3.04(s, 1H), 2.25(s, 3H), 2.17-2.10(m, 2H), 2.02-1.90(m, 2H), 1.78-1.66(m, 2H), 1.58-1.46(m, 2H)

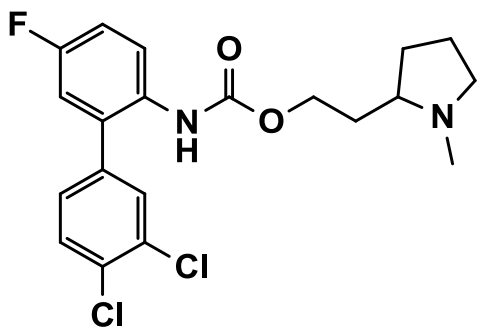
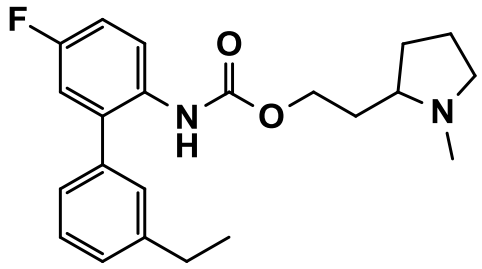
33	(3'-amino-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR(CD_3OD): δ 7.83(s, 1H), 7.29-7.15(m, 3H), 7.06-7.00(m, 2H), 6.80-6.77(m, 2H), 4.14-4.10(m, 2H), 3.30(s, 3H), 3.20-3.15(m, 1H), 2.45-2.43(m, 2H), 2.10-2.00 (m, 2H), 1.84-1.81(m, 2H), 1.62-1.47(m, 2H)
34	(2'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.96(s, 1H), 7.42-7.36(m, 3H), 7.31-7.14(m, 3H), 6.99-6.97(m, 1H), 6.45(s, 1H), 4.15-4.08(m, 2H), 3.26-3.22(s, 1H), 2.39(s, 3H), 2.35-2.25(m, 2H), 2.09-1.96(m, 2H), 1.88-1.64(m, 2H), 1.60-1.53(m, 2H)

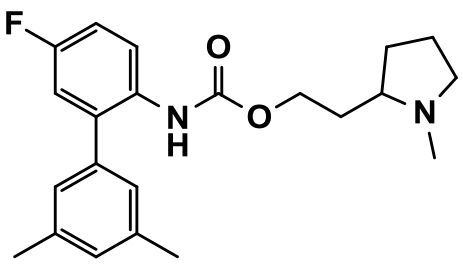
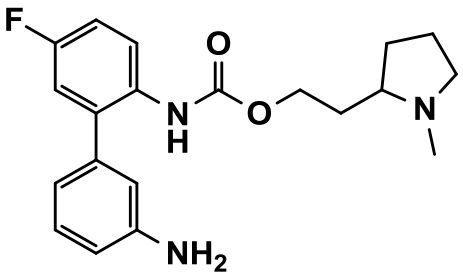
35	(2'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.01(s, 1H), 7.51-7.48(m, 1H), 7.41-7.34(m, 2H), 7.28-7.13(m, 3H), 6.96-6.93(m, 1H), 6.26(s, 1H), 4.18-4.05(m, 2H), 3.22-3.20(s, 1H), 2.37(s, 3H), 2.35-2.28(m, 2H), 2.07-1.93(m, 2H), 1.84-1.63(m, 2H), 1.57-1.52(m, 2H)
36	(2'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.84(s, 1H), 7.39-7.33(m, 1H), 7.31-7.12(m, 4H), 7.05-7.01(m, 1H), 6.96-6.90(m, 1H), 4.21-4.09(m, 2H), 3.21-3.14(s, 1H), 2.40(s, 3H), 2.36-2.26(m, 2H), 2.13-1.96(m, 2H), 1.84-1.66(m, 2H), 1.64-1.53(m, 2H)

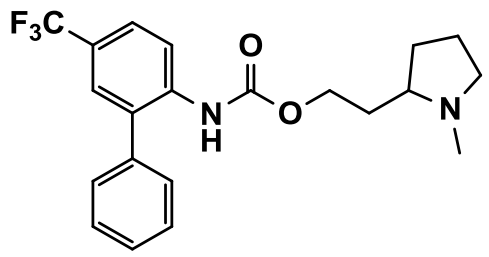
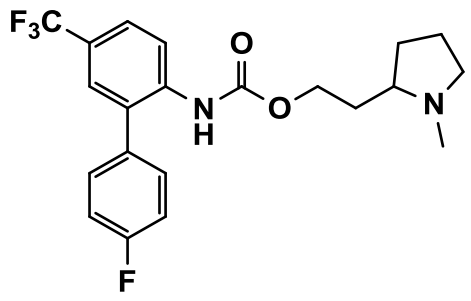
37	(3'-tert-butil-5'-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.11(s, 1H), 7.35-7.27(m, 1H), 7.23-7.21(m, 2H), 7.18(s, 1H), 7.13-7.09(m, 1H), 6.99(s, 1H), 6.74(s, 1H), 4.17-4.12(m, 2H), 3.12-3.09(m, 1H), 2.39(s, 3H), 2.30(s, 3H), 2.23-2.11(m, 2H), 2.01-1.98(m, 2H), 1.79-1.66(m, 2H), 1.58-1.46(m, 2H), 1.32(m, 9H)
38	(4'-fluoro-3'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.99(s, 1H), 7.60-7.58(m, 1H), 7.56-7.53(m, 1H), 7.41-7.36(m, 1H), 7.32-7.27(m, 1H), 7.20-7.14(m, 2H), 6.37(s, 1H), 4.18-4.13(m, 2H), 3.14-3.12(m, 1H), 2.34(s, 3H), 2.34-2.21(m, 2H), 2.06-1.93(m, 2H), 1.76-1.68(m, 2H), 1.64-1.46(m, 2H)

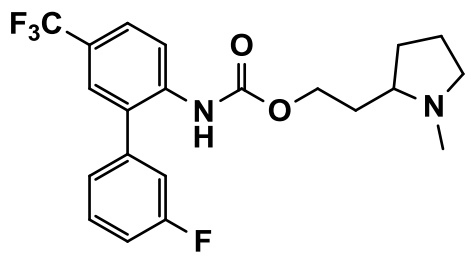
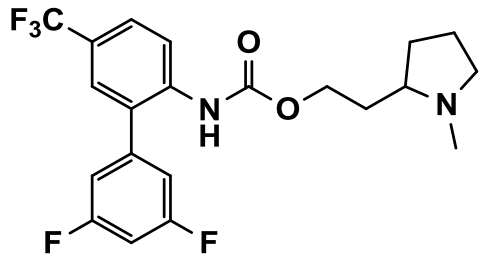
39	(4'-amino-3'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.04(s, 1H), 7.30(t, 1H, J=8.0), 7.15-7.12(m, 2H), 7.07-7.03(m, 2H), 6.82(d, 1H, J=8.4), 6.59(s, 1H), 4.18-4.09(m, 2H), 3.08-3.04(m, 1H), 2.30(s, 3H), 2.25-2.10 (m, 2H), 2.08-1.91(m, 2H), 1.81-1.57(m, 2H), 1.56-1.43(m, 2H)
40	(3'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR(CD_3OD): δ 7.84(s, 1H), 7.31-7.18(m, 3H), 7.06-7.02(m, 2H), 6.82-6.79(m, 2H), 4.11-4.08(m, 2H), 3.30(s, 3H), 3.21-3.18(m, 1H), 2.45-2.43(m, 2H), 2.08-2.01(m, 2H), 1.84-1.82(m, 2H), 1.61-1.45(m, 2H)

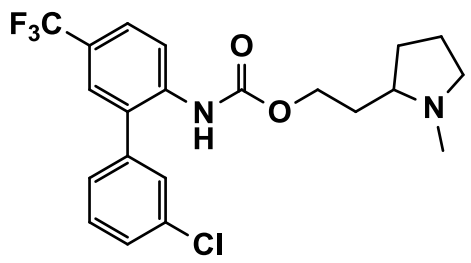
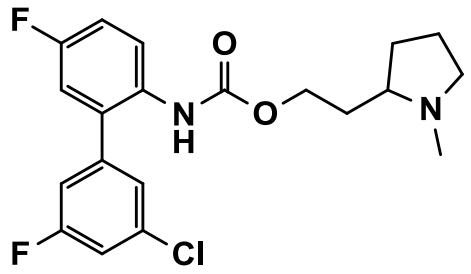
41	2-(1-Metilpirrolidin-2-il)etilo (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato 	^{1}H NMR($CDCl_3$): δ 8.06-7.93(bs, 1H), 7.41-7.38(m, 1H), 7.38-7.34(m, 1H), 7.23-7.19(m, 3H), 7.17-7.10(m, 2H), 6.51-6.44(bs, 1H), 4.20-4.12(m, 2H), 3.16-3.07(bs, 1H) 2.33(s, 3H), 2.25-2.13(m, 2H), 2.07-1.92(m, 2H), 1.84-1.65(m, 2H), 1.65-1.46(m, 2H)
42	(3',4',5-trifluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.98(s, 1H), 7.29-7.28(m, 1H), 7.17-7.14(m, 1H), 7.08-7.03(m, 2H), 6.90(dd, 1H, J=8.8, J=2.8), 6.33(s, 1H), 4.17-4.13(m, 2H), 3.05-3.03(m, 1H), 2.28(s, 3H), 2.08-2.03(m, 2H), 2.02-1.89(m, 2H), 1.79-1.63(m, 2H), 1.60-1.42(m, 2H)

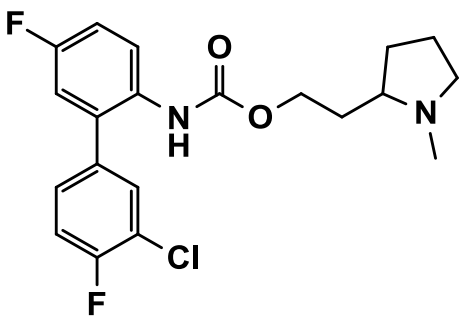
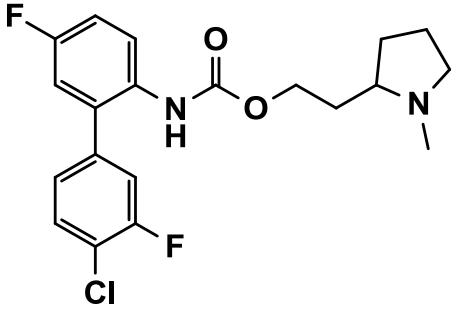
43	(3',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.94(s, 1H), 7.54(d, 1H, J=8.4), 7.44(d, 1H, J=2.0), 7.19(dd, 1H, J=8.4, J=2.0), 7.09-7.05(m, 1H), 6.91(dd, 1H, J=8.4, J=2.8), 6.38(s, 1H), 4.20-4.14(m, 2H), 3.17-3.16(m, 1H), 2.36(s, 3H), 2.07-1.96(m, 2H), 1.83-1.80(m, 2H), 1.77-1.71(m, 2H), 1.58-1.54(m, 2H)
44	(3'-etil-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.01(s, 1H), 7.38(t, 1H, J=8.0), 7.25-7.23(m, 1H), 7.16-7.13(m, 2H), 7.05-7.00(m, 1H), 6.95-6.92(m, 1H), 6.53(s, 1H), 4.17-4.12(m, 2H), 3.05-3.03(m, 1H), 2.68(q, 2H, J=7.6), 2.28(s, 3H), 2.16-2.02(m, 2H), 2.00-1.88(m, 2H), 1.78-1.62(m, 2H), 1.59-1.41(m, 2H), 1.25(t, 3H, J=7.6)

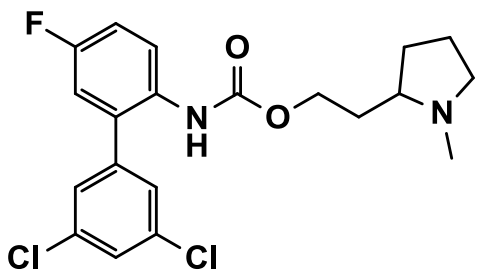
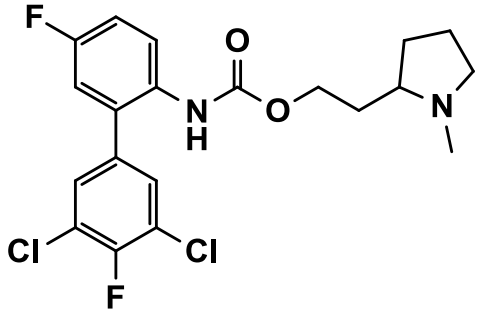
45	(5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.01(s, 1H), 7.03-6.98(m, 2H), 6.93-6.89(m, 2H), 6.55(s, 1H), 4.20-4.14(m, 2H), 3.03-3.01(m, 1H), 2.38(s, 6H), 2.35(s, 3H), 2.09-2.04(m, 2H), 2.03-1.90(m, 2H), 1.79-1.63(m, 2H), 1.59-1.44(m, 2H)
46	(3'-amino-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.02(s, 1H), 7.25-7.21(m, 2H), 7.03-6.99(m, 1H), 6.92-6.89(m, 1H), 6.71-6.67(m, 2H), 6.60(s, 2H), 4.16-4.12(m, 2H), 3.04-3.01(m, 1H), 2.28(s, 3H), 2.02-1.97(m, 2H), 1.96-1.89(m, 2H), 1.78-1.63(m, 2H), 1.57-1.41(m, 2H)

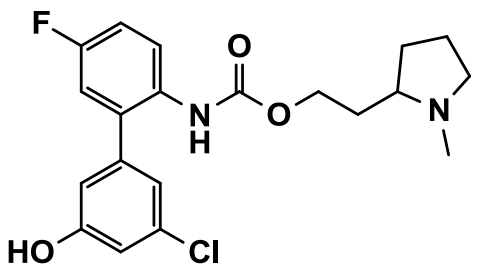
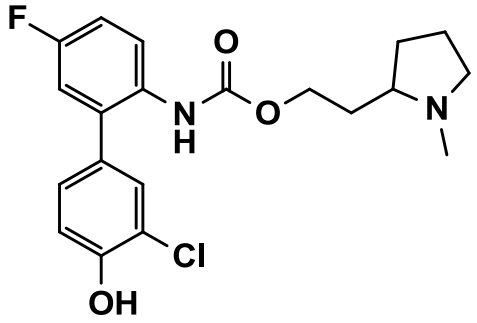
47	(5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.29(d, 1H, J=8.8), 7.59(d, 1H, J=8.8), 7.52-7.49(m, 2H), 7.46-7.44(m, 2H), 7.36-7.34(m, 2H), 6.78(s, 1H), 4.19-4.16(m, 2H), 3.12-3.10(m, 1H), 2.33(s, 3H), 2.17-2.05(m, 2H), 2.03-1.93(m, 2H), 1.78-1.64(m, 2H), 1.53-1.51(m, 2H)
48	(4'-fluoro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.27(d, 1H, J=8.4), 7.59(d, 1H, J=8.8), 7.41(d, 1H, J=1.2), 7.34-7.31 (m, 2H), 7.22-7.18(m, 2H), 6.70(s, 1H), 4.22-4.16(m, 2H), 3.26-3.24(m, 1H), 2.41(s, 3H), 2.35-2.29(m, 2H), 2.13-1.98(m, 2H), 1.88-1.77(m, 2H), 1.62-1.59(m, 2H)

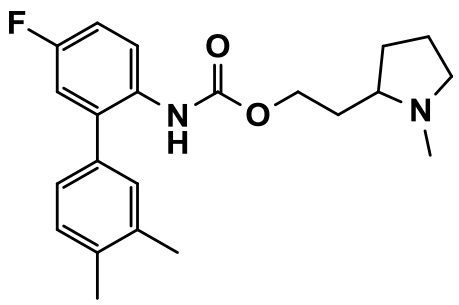
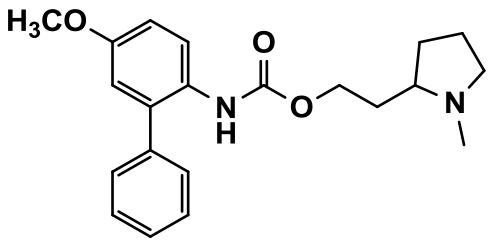
49	(3'-fluoro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.29(d, 1H, J=8.8), 7.61(d, 1H, J=8.8), 7.51-7.45(m, 1H), 7.43(s, 1H), 7.18-7.13(m, 2H), 7.08-7.06(m, 1H), 6.71(s, 1H), 4.21-4.17(m, 2H), 3.12-3.10(m, 1H), 2.33(s, 3H), 2.19-2.15(m, 2H), 2.07-1.92(m, 2H), 1.74-1.71(m, 2H), 1.53-1.50(m, 2H)
50	(3',5'-difluoro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.26(d, 1H, J=8.8), 7.62(d, 1H, J=8.8), 7.43(s, 1H), 6.93-6.89(m, 3H), 6.78(s, 1H), 4.24-4.19(m, 2H), 3.28-3.21(m, 1H), 2.45(s, 3H), 2.15-2.04(m, 2H), 1.89-1.87(m, 2H), 1.82-1.80(m, 2H), 1.67-1.63(m, 2H)

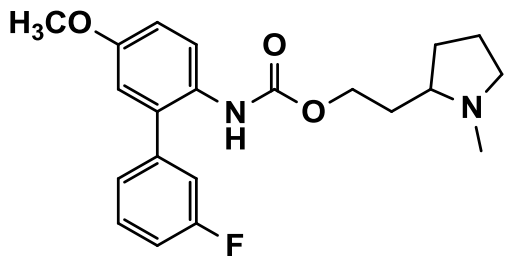
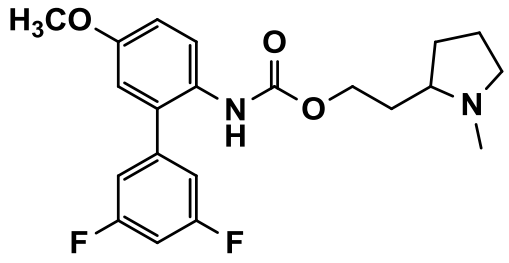
51	(3'-cloro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.27(d, 1H, J=8.4), 7.61(d, 1H, J=8.8), 7.47-7.43(m, 3H), 7.35(s, 1H), 7.25-7.23(m, 1H), 6.75(s, 1H), 4.23-4.17(m, 2H), 3.34-3.32(m, 1H), 2.42(s, 3H), 2.11-2.05(m, 2H), 2.02-1.91(m, 2H), 1.90-1.83(m, 2H), 1.83-1.80(m, 2H)
52	(3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.91(s, 1H), 7.22-7.20(m, 1H), 7.15-7.13(m, 1H), 7.10-7.05(m, 1H), 6.99-6.97(m, 1H), 6.92(dd, 1H, J=8.8, J=2.8), 6.44(s, 1H), 4.21-4.14(m, 2H), 3.22-3.19(m, 1H), 2.40(s, 3H), 2.32-2.28(m, 2H), 2.10-2.02(m, 2H), 1.86-1.59(m, 2H), 1.26-1.22(m, 2H)

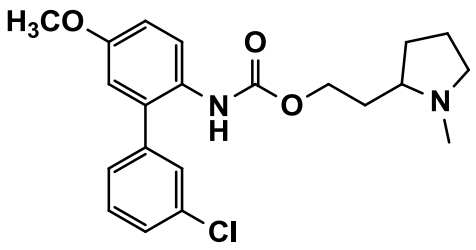
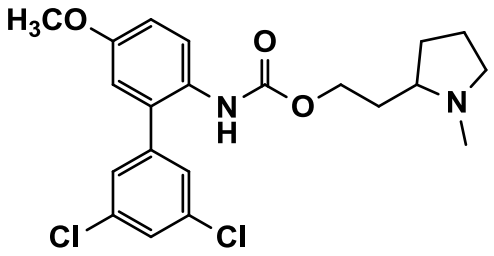
53	(3'-cloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.91(s, 1H), 7.39(dd, 1H, J=7.2, J=2.0), 7.23-7.19(m, 2H), 7.08-7.04(m, 1H), 6.90(dd, 1H, J=8.4, J=2.8), 6.37(s, 1H), 4.18-4.13(m, 2H), 3.14-3.10(m, 1H), 2.33(s, 3H), 2.23-2.16(m, 2H), 2.06-1.91(m, 2H), 1.82-1.65(m, 2H), 1.60-1.51(m, 2H)
54	(4'-cloro-3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.81(s, 1H), 7.47-7.43(m, 1H), 7.19-7.11(m, 2H), 7.11-6.95(m, 1H), 6.90(dd, 1H, J=8.8, J=3.2) 6.62(s, 1H), 4.14-4.04(m, 2H), 3.21-3.16(m, 1H), 2.37(s, 3H), 2.04-1.95(m, 2H), 1.84-1.69(m, 2H), 1.67-1.61(m, 1H), 1.57-1.48(m, 2H)

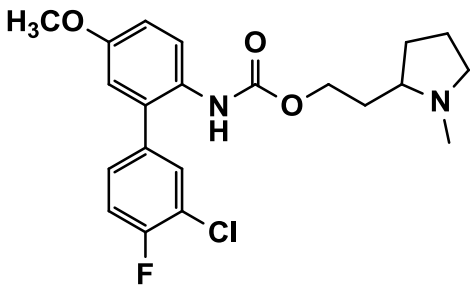
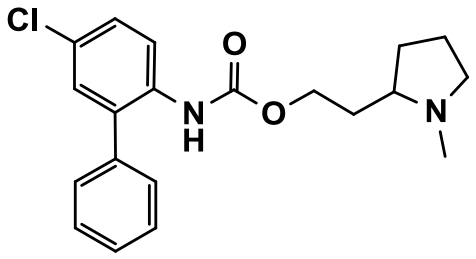
55	(3',5'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.90(s, 1H), 7.41-7.40(m, 1H), 7.25-7.22(m, 2H), 7.10-7.05(m, 1H), 6.91(dd, 1H, J=8.8, J=2.8), 6.38(s, 1H), 4.20-4.16(m, 2H), 3.16-3.12(m, 1H), 2.36(s, 3H), 2.23-2.21(m, 2H), 2.09-1.94(m, 2H), 1.80-1.64(m, 2H), 1.56-1.52(m, 2H)
56	(3',5'-dicloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.81(s, 1H), 7.31-7.30(m, 1H), 7.19-7.18(m, 1H), 7.09-7.04(m, 1H), 6.91-6.62(m, 1H), 6.61(s, 1H), 4.20-4.11(m, 2H), 3.26-3.22(m, 1H), 2.42-2.30(m, 4H), 2.11-1.93(m, 2H), 1.88-1.63(m, 2H), 1.61-1.54(m, 2H)

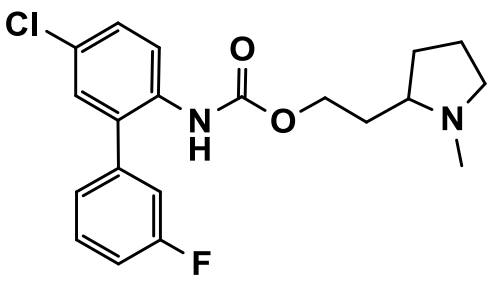
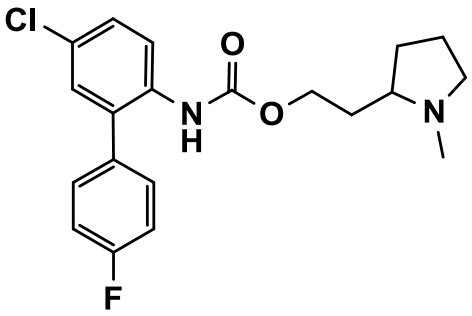
57	(3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.83(s, 1H), 7.03-6.95(m, 1H), 6.91-6.88(m, 1H), 6.80(s, 1H), 6.73-6.66(m, 2H), 4.12-4.07(m, 2H), 3.21-3.17(m, 1H), 2.35(s, 3H), 2.28-2.24(m, 2H), 1.82-1.65(m, 2H), 1.62-1.55(m, 2H), 1.25-1.21(m, 2H)
58	(3'-cloro-5-fluoro-4'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.83(s, 1H), 7.25-7.20(m, 1H), 7.05-6.92(m, 3H), 6.88(dd, 1H, J=8.8, J=2.8), 6.57(s, 1H), 4.14-4.06(m, 2H), 3.22-3.17(m, 1H), 2.40(s, 3H), 2.39-2.29(m, 2H), 2.10-1.97(m, 2H), 1.86-1.66(m, 2H), 1.65-1.54(m, 2H)

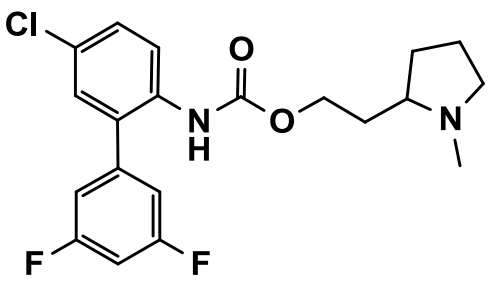
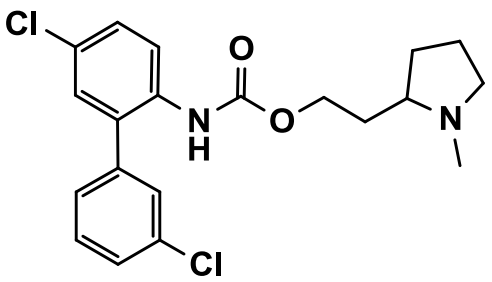
59	(5-fluoro-3',4'-dimetil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.99(s, 1H), 7.22-7.20(m, 1H), 7.08-6.97(m, 3H), 6.90(dd, 1H, J=9.2, J=2.8), 6.57(s, 1H), 4.15-4.13(m, 2H), 3.16-3.12(m, 1H), 2.31(s, 3H), 2.29(s, 6H), 2.02-2.17(m, 2H), 2.00-1.89(m, 2H), 1.76-1.55(m, 2H), 1.53-1.42(m, 2H)
60	(5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.93(s, 1H), 7.46-7.40(m, 2H), 7.39-7.36(m, 1H), 7.35-7.33(m, 2H), 6.89(dd, 1H, J=8.8, J=2.8), 6.77(d, 1H, J=2.8), 6.38(s, 1H), 4.15-4.10(m, 2H), 3.86(s, 3H), 3.14-3.11(m, 1H), 2.35(m, 3H), 2.26-2.16(m, 2H), 2.06-1.91(m, 2H), 1.82-1.62(m, 2H), 1.60-1.45(m, 2H)

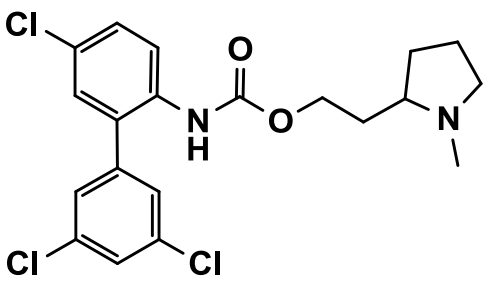
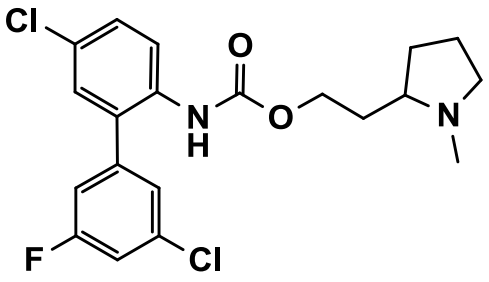
61	(3'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.82(s, 1H), 7.42-7.39(m, 1H), 7.14-7.10(m, 1H), 7.07-7.05(m, 2H), 6.90(dd, 1H, J=8.8, J=3.2), 6.75(d, 1H, J=3.2), 6.37(s, 1H), 4.17-4.13(m, 2H), 3.79(s, 3H), 3.21-3.18(m, 1H), 2.38(s, 3H), 2.30-2.26(m, 2H), 2.09-1.99(m, 2H), 1.74-1.70(m, 2H), 1.56-1.53(m, 2H)
62	(3',5'-difluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.72(s, 1H), 7.28-7.26(m, 1H), 6.92-6.79(m, 3H), 6.74-6.73(m, 1H), 6.29(s, 1H), 4.15-4.10(m, 2H), 3.75(s, 3H), 3.15-3.10(m, 1H), 2.34(s, 3H), 2.27-2.25(m, 2H), 2.06-1.96(m, 2H), 1.78-1.69(m, 2H), 1.63-1.50(m, 2H)

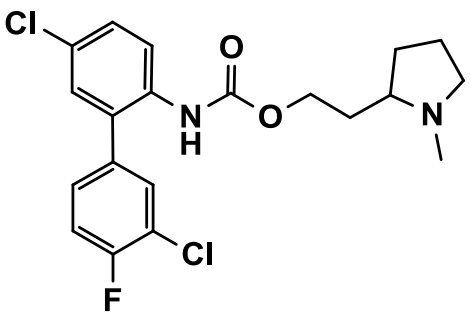
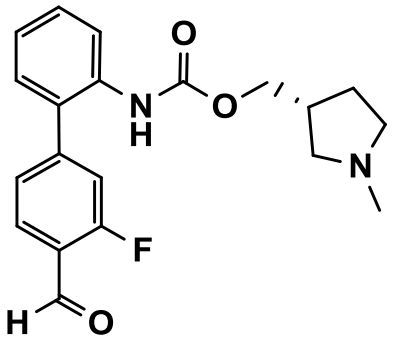
63	(3'-cloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.82(s, 1H), 7.38-7.34(m, 2H), 7.23-7.21(m, 2H), 6.90(dd, 1H, J=9.2, J=2.8), 6.74(d, 1H, J=2.8), 6.28(s, 1H), 4.17-4.12(m, 2H), 3.78(s, 3H), 3.16-3.14(m, 1H), 2.35(s, 3H), 2.23-2.18(m, 2H), 2.21-1.93(m, 2H), 1.79-1.64(m, 2H), 1.60-1.50(m, 2H)
64	(3',5'-dicloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.70(s, 1H), 7.36-7.35(m, 1H), 7.23-7.20(m, 2H), 6.90(dd, 1H, J=8.8, J=2.8), 6.73-6.72(m, 1H), 6.58(s, 1H), 4.16-4.08(m, 2H), 3.75(s, 3H), 3.28-3.26(m, 1H), 2.43(s, 3H), 2.40-2.38(m, 2H), 2.08-2.02(m, 2H), 1.85-1.72(m, 2H), 1.60-1.57(m, 2H)

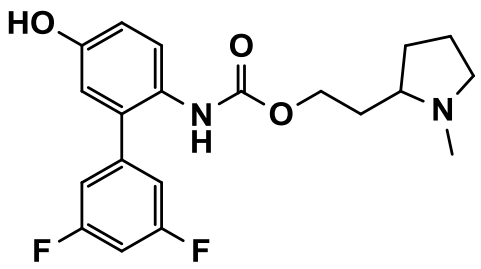
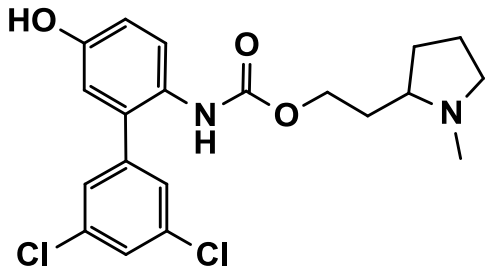
65	(3'-cloro-4'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.70(s, 1H), 7.39-7.38(m, 1H), 7.21-7.19(m, 2H), 6.90(dd, 1H, J=8.8, J=2.8), 6.72-6.71(m, 1H), 6.21(s, 1H), 4.15-4.09(m, 2H), 3.76(s, 3H), 3.13-3.11(m, 1H), 2.37(s, 3H), 2.30-2.23(m, 2H), 2.02-1.97(m, 2H), 1.79-1.71(m, 2H), 1.62-1.56(m, 2H)
66	(5-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.04(s, 1H), 7.48-7.45(m, 2H), 7.43-7.39(m, 1H), 7.32-7.28(m, 3H), 7.23-7.18(m, 1H), 6.56(s, 1H), 4.16-4.12(m, 2H), 3.06-3.02(m, 1H), 2.28(s, 3H), 2.12-1.96(m, 2H), 1.94-1.87(m, 2H), 1.76-1.64(m, 2H), 1.57-1.44(m, 2H)

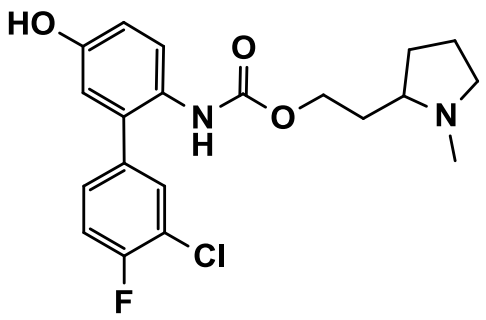
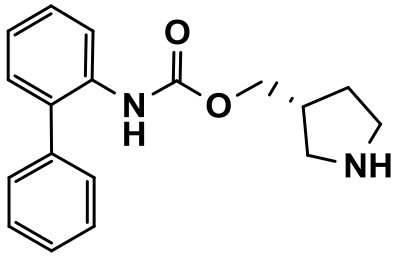
67	(5-cloro-3'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.03(s, 1H), 7.44(q, 1H, J=8.0), 7.31(dd, 1H, J=8.8, J=2.4), 7.14-7.10(m, 2H), 7.05-7.03(m, 1H), 6.49(s, 1H), 4.17-4.13(m, 2H), 3.03-3.01(m, 2H), 2.29(s, 3H), 2.13-1.98(m, 2H), 1.97-1.88(m, 2H), 1.77-1.64(m, 2H), 1.59-1.42(m, 2H)
68	(5-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.02(s, 1H), 7.31-7.28(m, 3H), 7.18-7.14(m, 3H), 6.44(s, 1H), 4.17-4.13(m, 2H), 3.04-3.01(m, 1H), 2.28(s, 3H), 2.10-2.00(m, 2H), 1.98-1.87(m, 2H), 1.78-1.65(m, 2H), 1.57-1.44(m, 2H)

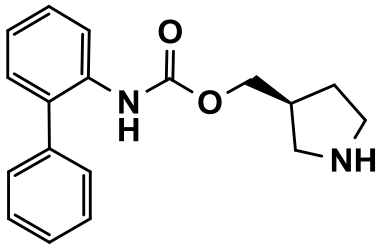
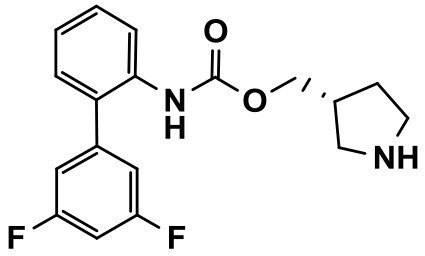
69	(5-cloro-3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.99(s, 1H), 7.34-7.31(m, 2H), 7.17-7.16(m, 1H), 6.88-6.84(m, 2H), 6.51(s, 1H), 4.18-4.10(m, 2H), 3.16-3.13(m, 1H), 2.36(s, 3H), 2.32-2.29(m, 2H), 2.08-1.96(m, 2H), 1.82-1.61(m, 2H), 1.57-1.49(m, 2H)
70	(3',5-dicloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 8.01(s, 1H), 7.43-7.38(m, 2H), 7.32-7.30(m, 2H), 7.23-7.21(m, 1H), 7.17(d, 1H, J=2.4), 6.47(s, 1H), 4.18-4.13(m, 2H), 3.06-3.04(m, 1H), 2.25(s, 3H), 2.19-2.06(m, 2H), 2.05-1.90(m, 2H), 1.80-1.59(m, 2H), 1.58-1.44(m, 2H)

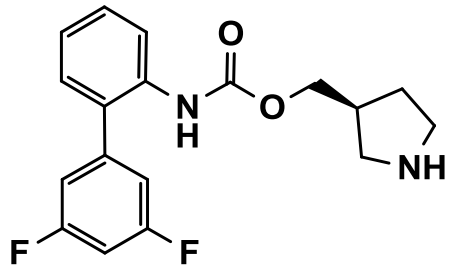
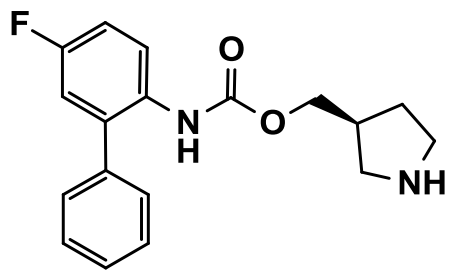
71	(3',5,5'-tricloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.98(s, 1H), 7.41(s, 1H), 7.33(dd, 1H, J=8.8, J=2.4), 7.23-7.22(m, 2H), 7.15(d, 1H, J=2.4), 6.39(s, 1H), 4.19-4.14(m, 2H), 3.09-3.05(m, 1H), 2.30(s, 3H), 2.19-2.07(m, 2H), 2.04-1.91(m, 2H), 1.77-1.61(m, 2H), 1.59-1.43(m, 2H)
72	(3',5-dicloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.99(s, 1H), 7.33(dd, 1H, J=8.8, J=2.4), 7.21-7.13(m, 3H), 6.96(dd, 1H, J=8.8, J=2.4), 6.46(s, 1H), 4.20-4.12(m, 2H), 3.11-3.07(m, 1H), 2.32(s, 3H), 2.20-2.14(m, 2H), 2.06-1.91(m, 2H), 1.79-1.62(m, 2H), 1.60-1.45(m, 2H)

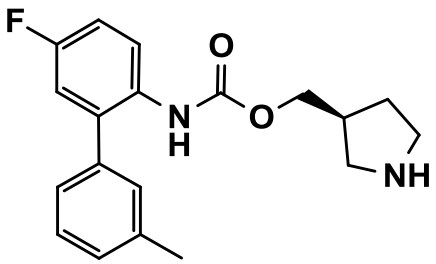
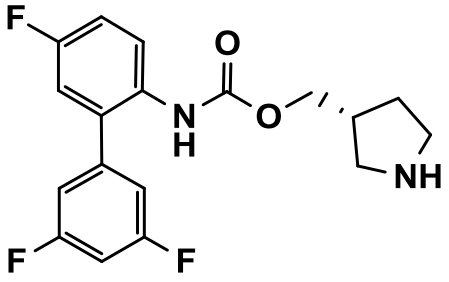
73	(3',5-dicloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.98(s, 1H), 7.39-7.37(m, 1H), 7.32-7.26(m, 1H), 7.23-7.21(m, 2H), 7.19(d, 1H, J=2.8), 6.41(s, 1H), 4.17-4.13(m, 2H), 3.06-3.03(m, 1H), 2.26(s, 3H), 2.39-2.10(m, 2H), 2.03-1.89(m, 2H), 1.80-1.59(m, 2H), 1.57-1.43(m, 2H)
74	(3'-fluoro-4'-formil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.00-7.93(m, 2H), 7.41-7.37(t, 1H, J=15.2), 7.29-7.27(d, 1H, J=8.0), 7.23-7.15(m, 3H), 6.51(s, 1H), 4.08-3.97(m, 2H), 2.60-2.56(t, 1H, J=17.2), 2.49-2.45(m, 3H), 2.29-2.24(m, 4H), 1.96-1.91(m, 1H), 1.48-1.43(m, 1H)

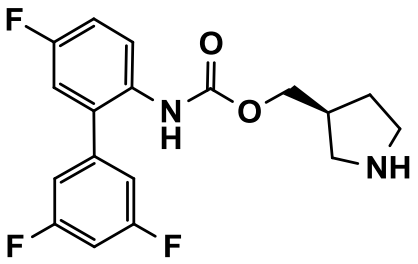
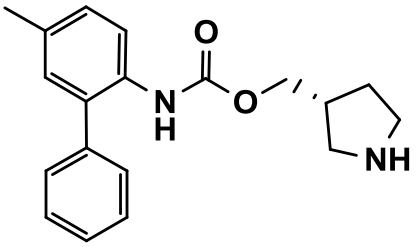
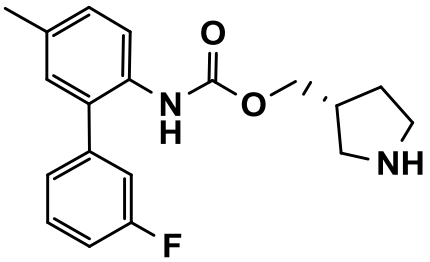
75	(3',5'-difluoro-5-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR(CD_3OD): δ 7.19-7.17(m, 1H), 6.92-6.90(m, 2H), 6.85-6.76(m, 2H), 6.72-6.71(m, 1H), 4.10-4.02(m, 2H), 3.70-3.61(m, 1H), 3.16-3.10(m, 2H), 2.83(s, 3H), 2.27-2.13(m, 2H), 2.13-2.02(m, 2H), 1.77-1.72(m, 2H)
76	(3',5'-dicloro-5-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR(CD_3OD): δ 7.33-7.32(m, 1H), 7.27-7.23(m, 1H), 7.17-7.15(m, 1H), 7.05-7.01(m, 1H), 6.82-6.79(m, 1H), 6.72-6.71(m, 1H), 4.11-4.07(m, 2H), 3.50-3.47(m, 1H), 3.04-3.01(m, 2H), 2.70(s, 3H), 2.20-2.16(m, 2H), 1.95-1.90(m, 2H), 1.75-1.70(m, 2H)

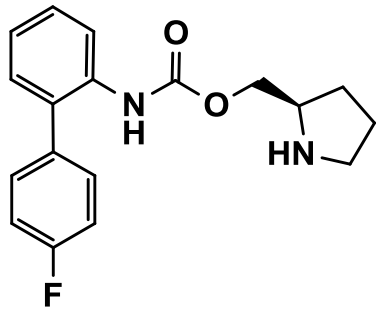
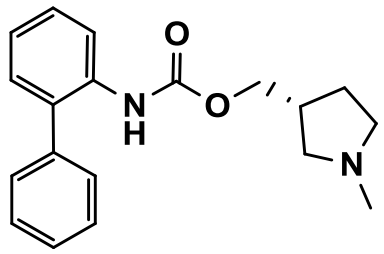
77	(3'-cloro-4'-fluoro-5-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR(CD_3OD): δ 7.44-7.42(m, 1H), 7.27-7.22(m, 2H), 7.16-7.14(m, 1H), 6.77-6.75(m, 1H), 6.70-6.69(m, 1H), 4.08-4.02(m, 2H), 3.64-3.57(m, 1H), 3.13-3.09(m, 2H), 2.86(s, 3H), 2.27-2.22(m, 2H), 1.97-1.93(m, 2H), 1.75-1.70(m, 2H)
78	[1,1'-bifenil]-2-ilcarbamato de (R)-pirrolidin-3-ilmetilo 	^{1}H NMR($CDCl_3$): δ 8.17-7.98(bs, 1H), 7.60-7.29(m, 6H), 7.26-7.06(m, 2H), 6.78-6.61(bs, 1H), 4.17-3.94(m, 2H), 3.09-2.81(m, 3H) 2.75-2.59(m, 1H), 2.56-2.33(m, 2H), 1.98-1.80(m, 1H), 1.54-1.35(m, 1H)

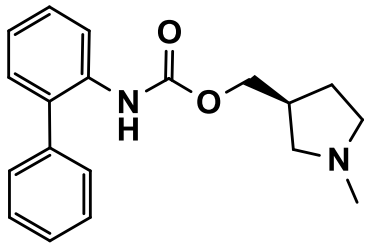
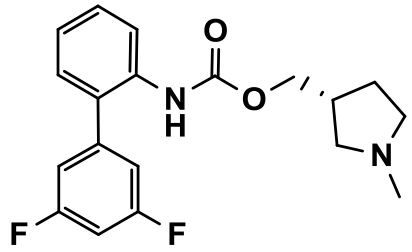
79	[1,1'-bifenil]-2-ilcarbamato de (S)-pirrolidin-3-ilmetilo 	^{1}H NMR($CDCl_3$): δ 8.07-7.89(bs, 1H), 7.58-7.32(m, 6H), 7.32-7.13(m, 2H), 7.01-6.85(bs, 1H), 4.28-3.98(m, 3H), 3.47-3.17(m, 3H), 3.13-2.95(m, 1H), 2.80-2.62(m, 1H), 2.25-2.08(m, 1H), 1.89-1.70(m, 1H)
80	(3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo 	^{1}H NMR($CDCl_3$): δ 8.10-7.93(bs, 1H), 7.45-7.30(m, 1H), 7,21-7.08(m, 2H), 6.98-6.79(m, 3H), 6.67-6.51(bs, 1H), 4.15-3.90(m, 2H), 3.11-2.76(m, 3H), 2.71-2.53(m, 8H), 2.48-2.29(m, 1H), 2.02-2.72(m, 2H), 1.49-1.29(m, 1H)

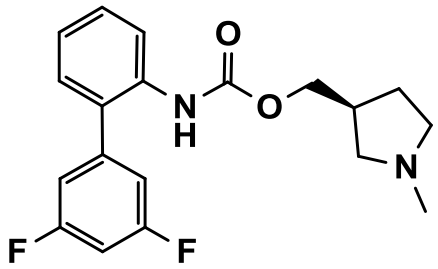
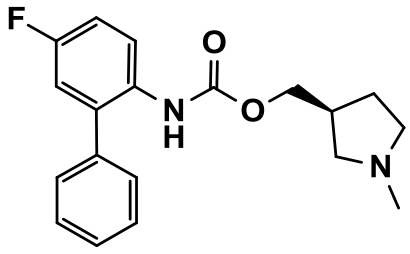
81	(3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo 	^{1}H NMR($CDCl_3$): δ 8.10-7.89(m, 1H), 7.49-7.30(m, 1H), 7.22-7.04(m, 2H), 6.98-6.75(m, 3H), 6.68-6.50(bs, 1H), 4.19-3.85(m, 2H), 3.12-2.75(m, 3H) 2.72-2.52(bs, 1H), 2.52-2.27(m, 1H), 2.07-1.72(m, 2H), 1.50-1.31(m, 1H)
82	(5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo 	^{1}H NMR($CDCl_3$): δ 7.81(s, 1H), 7.45-7.36(m, 3H), 7.33-7.26(m, 2H), 7.06-7.01(m, 1H), 6.97-6.94(m, 1H), 4.12-4.06(m, 2H), 3.35-3.27(m, 1H), 3.23-3.16(m, 1H), 3.05-3.02(m, 1H), 2.69-2.65(m, 1H), 2.17-2.12(m, 1H), 1.82-1.78(m, 2H)

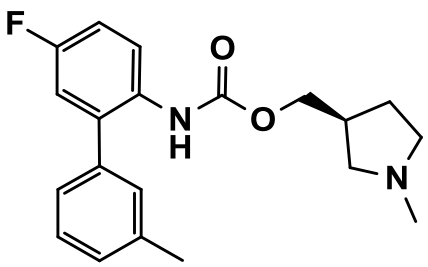
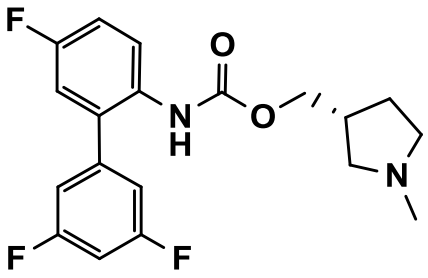
83	(5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo 	^{1}H NMR($CDCl_3$): δ 7.82(s, 1H), 7.35-7.31(m, 1H), 7.20-7.18(m, 1H), 7.18-7.14(m, 1H), 7.13-7.11(m, 1H), 7.07-6.98(m, 1H), 6.95-6.92(m, 1H), 4.13-4.07(m, 2H), 3.38-3.33(m, 2H), 3.25-3.22(m, 1H), 3.09-3.05(m, 1H), 2.69-2.65(m, 1H), 2.38(s, 3H), 2.15-2.13(m, 1H), 1.80-1.76(m, 1H)
84	(3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo 	^{1}H NMR($CDCl_3$): δ 7.98-7.79(bs, 1H), 7.14-7.00(m, 1H), 7,00-6.78(m, 4H), 6.61-6.45(bs, 1H), 4.18-3.90(m, 2H), 3.13-2.80(m, 3H), 2.70-2.57(m, 1H), 2.51-2.21(m, 2H), 1.94-1.80(m, 1H), 1.49-1.35(m, 1H)

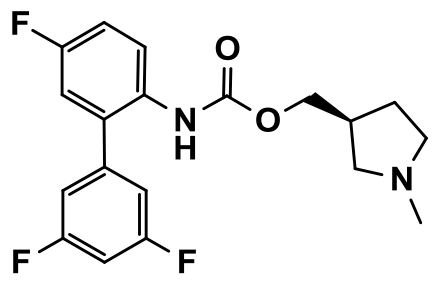
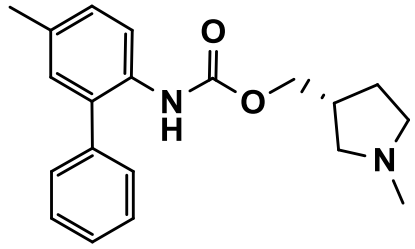
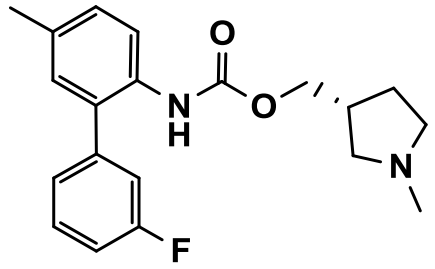
85	(3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo 	^{1}H NMR($CDCl_3$): δ 7.96-7.77(bs, 1H), 7.13-6.99(m, 1H), 6.99-6.76(m, 4H), 6.68-6.50(bs, 1H), 4.15-3.92(m, 2H), 3.16-2.90(bs, 3H), 2.90-2.30(m, 3H), 1.99-1.81(m, 1H), 1.53-1.35(m, 1H)
86	(5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo 	^{1}H NMR($CDCl_3$): δ 7.77 (s, 1H), 7.44-7.40(m, 2H), 7.37-7.31(m, 2H), 7.20-7.13(m, 2H), 7.04(s, 1H), 6.85(s, 1H), 4.13-4.04(m, 2H), 2.78-2.62(m, 3H), 2.32(s, 3H), 2.16-2.09(m, 2H), 2.03(s, 1H), 1.79-1.70(m, 2H)
87	(3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo 	^{1}H NMR($CDCl_3$): δ 7.84 (s, 1H), 7.43-7.38(m, 1H), 7.17-7.08(m, 2H), 7.04-7.02(m, 2H), 7.01(s, 1H), 6.55(s, 1H), 4.08-3.97(m, 2H), 2.47-2.33(m, 3H), 2.32(s, 3H), 1.94-1.80(m, 2H), 1.51-1.40(m, 2H)

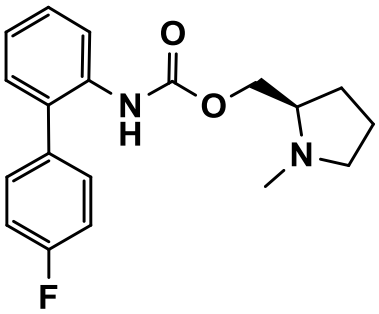
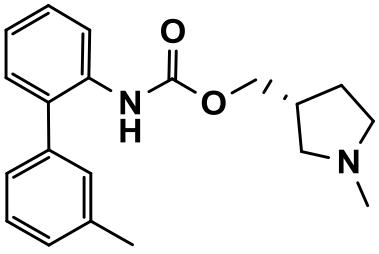
88	(4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-2-ilmetilo 	^{1}H NMR($CDCl_3$): δ 8.13-7.94(m, 1H), 7.41-7.23(m, 3H), 7.20-7.02(m, 4H), 6.75-6.57(bs, 1H), 4.23-4.04(m, 1H), 4.02-3.85(m, 1H), 3.47-3.30(m, 1H), 3.02-2.81(m, 2H), 2.57-2.25(bs, 1H), 1.95-1.59(m, 3H), 1.50-1.32(m, 1H)
89	[1,1'-bifenil]-2-ilcarbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.13-7.94(bs, 1H), 7.55-7.27(m, 6H), 7,26-7.03(m, 2H), 6.77-6.59(bs, 1H), 4.18-3.94(m, 2H), 3.00-2.57(m, 4H), 2.54-2.49(m, 1H), 2.47(s, 3H), 2.10-1.98(m, 1H) 1.67-1.55(m, 1H)

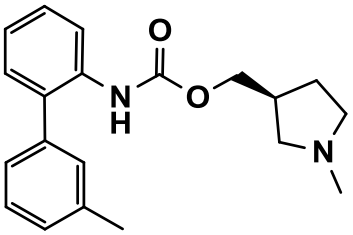
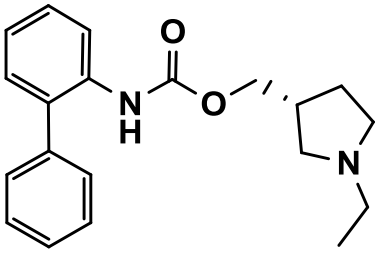
90	[1,1'-bifenil]-2-ilcarbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.09-7.94(bs, 1H), 7.56-7.31(m, 6H), 7.30-7.12(m, 2H), 6.86-6.72(bs, 1H), 4.19-4.02(m, 1H), 3.41-3.05(m, 3H), 2.97-2.77(m, 2H) 2.74(s, 3H), 2.29-2.15(m, 1H), 1.89-1.74(m, 1H)
91	(3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.08-7.95(bs, 1H), 7.42-7.33(m, 1H), 7.21-7.08(m, 2H), 6.98-6.79(m, 3H), 6.59-6.48(bs, 1H), 4.13-3.95(m, 2H), 2.69-2.43(m, 3H), 2.40-2.14(m, 5H), 2.05-1.90(m, 1H), 1.57-1.42(m, 1H)

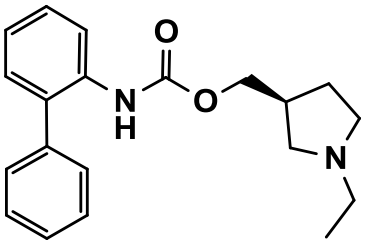
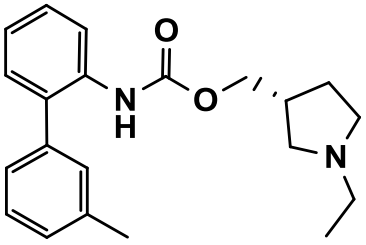
92	(3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.08-7.95(bs, 1H), 7.42-7.33(m, 1H), 7.21-7.08(m, 2H), 6.98-6.79(m, 3H), 6.59-6.48(bs, 1H), 4.13-3.95(m, 2H), 2.69-2.43(m, 3H), 2.40-2.14(m, 5H), 2.05-1.90(m, 1H), 1.57-1.42(m, 1H)
93	(5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.98(s, 1H), 7.49-7.39(m, 3H), 7.34-7.32(m, 2H), 7.06-7.01(m, 1H), 6.94-6.91(m, 1H), 6.49(s, 1H), 4.08-3.96(m, 2H), 2.61-2.57(m, 1H), 2.53-2.44(m, 3H), 2.30(s, 3H), 2.27-2.22(m, 1H), 1.98-1.89(m, 1H), 1.49-1.41(m, 1H)

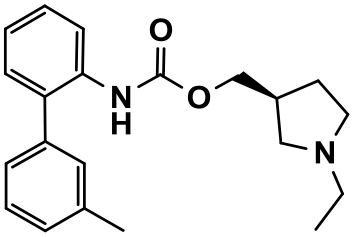
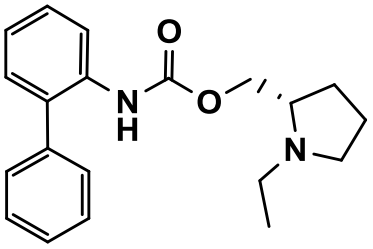
94	(5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.97(s, 1H), 7.37-7.33(m, 1H), 7.30-7.21(m, 2H), 7.13-7.11(m, 1H), 7.04-7.00(m, 1H), 6.95-6.91(m, 1H), 6.58(s, 1H), 4.08-3.98(m, 2H), 2.71-2.66(m, 1H), 2.59-2.46(m, 3H), 2.46-2.33(m, 7H), 2.01-1.97(m, 1H), 1.55-1.48(m, 1H)
95	(3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.97-7.81(bs, 1H), 7.13-7.01(m, 1H), 6.99-6.78(m, 4H), 6.57-6.41(bs, 1H), 4.13-3.94(m, 2H), 2.70-2.42(m, 4H), 2.05-2.88(m, 1H), 1.58-1.41(m, 4H)

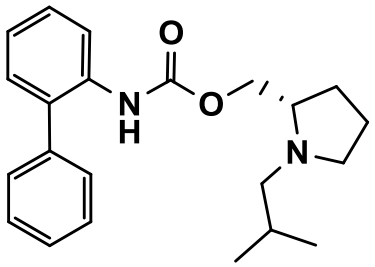
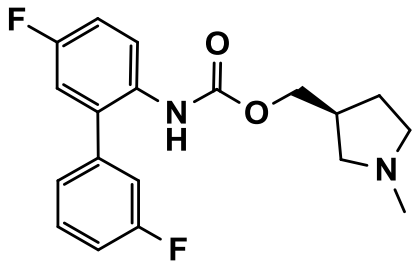
96	(3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.97-7.78(bs, 1H), 7.14-7.00(m, 1H), 6.99-6.78(m, 4H), 6.63-6.45(bs, 1H), 4.14-3.93(m, 2H), 2.71-2.42(m, 4H), 2.40-2.23(bs, 4H), 2.05-1.88(m, 1H), 1.59-1.41(m, 1H)
97	(5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.89 (s, 1H), 7.47-7.43(m, 2H), 7.39-7.31(m, 2H), 7.22-7.13(m, 2H), 7.02(s, 1H), 6.63(s, 1H), 4.09-4.01(m, 2H), 2.67-2.58(m, 3H), 2.52(s, 3H), 2.32(s, 3H), 2.11-2.01(m, 2H), 1.65-1.58(m, 2H)
98	(3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.88 (s, 1H), 7.44-7.38(m, 1H), 7.17-7.10(m, 2H), 7.09-7.05(m, 2H), 7.01(s, 1H), 6.55(s, 1H), 4.09-3.98(m, 2H), 2.38(s, 3H), 2.32(s, 3H), 2.61-2.40(m, 3H), 2.15-1.97(m, 2H), 1.56-1.51(m, 2H)

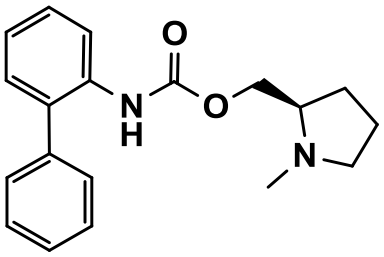
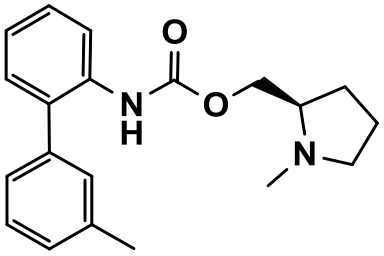
99	(4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.13-7.96(m, 1H), 7.41-7.23(m, 3H), 7.20-7.02(m, 4H), 6.62-6.45(bs, 1H), 4.24-3.97(m, 2H), 3.10-2.96(m, 1H), 2.50-2.27(m, 4H), 2.27-2.13(m, 1H) 1.96-1.80(m, 1H), 1.80-1.51(m, 3H)
100	(3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.13-7.96(bs, 1H), 7.41-7.30(m, 2H), 7.30-7.03(m, 5H), 6.71-6.59(bs, 1H), 4.13-3.95(m, 2H), 2.72-2.59(m, 1H), 2.59-2.43(m, 3H), 2.40(s, 3H), 2.14-2.22(m, 4H) 2.06-1.87(m, 1H), 1.55-1.42(m, 1H)

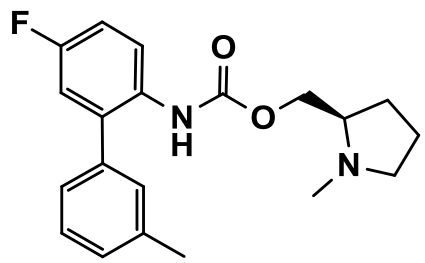
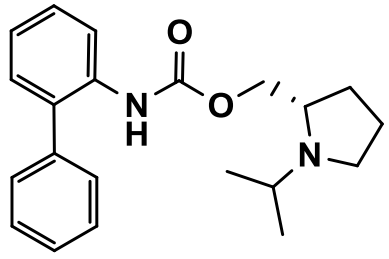
101	(3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.15-7.99(bs, 1H), 7.46-7.29(m, 2H), 7,28-7.02(m, 5H), 6.74-6.58(bs, 1H), 4.15-3.93(m, 2H), 2.70-2.43(m, 4H), 2.40(s, 3H), 2.31(s, 3H), 2.15-2.17(m, 1H) 2.03-1.86(m, 1H), 1.57-1.40(m, 1H)
102	[1,1'-bifenil]-2-ilcarbamato de (R)-(1-etilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.13-7.96(bs, 1H), 7.54-7.26(m, 6H), 7,25-7.02(m, 2H), 6.72-6.55(bs, 1H), 4.15-3.92(m, 2H), 2.91-2.69(m, 1H), 2.69-2.35(m, 5H), 2.33-2.17(m, 1H), 2.04-1.87(m, 1H) 1.60-1.42(m, 1H), 1.00(t, 3H, J=7.2)

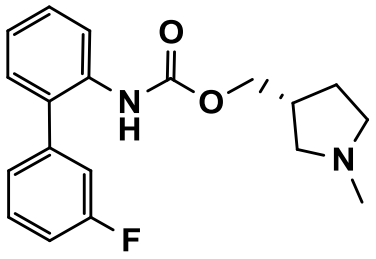
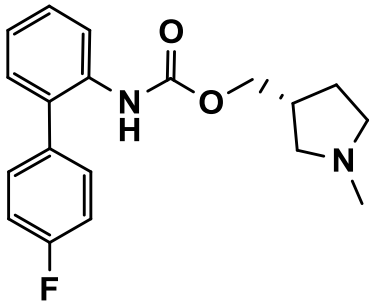
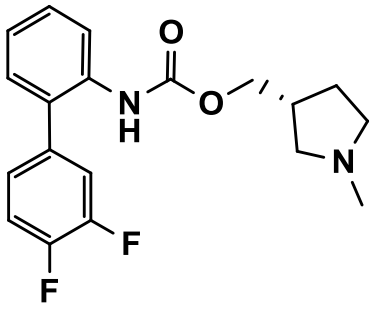
103	[1,1'-bifenil]-2-ilcarbamato de (S)-(1-etilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.15-7.97(bs, 1H), 7.55-7.27(m, 6H), 7,24-7.05(m, 2H), 6.72-6.59(bs, 1H), 4.14-3.94(m, 2H), 2.92-2.71(bs, 1H), 2.71-2.39(m, 5H), 2.38-2.22(m, 1H), 2.04-1.86(m, 1H), 1.59-1.44(m, 1H), 1.11(t, 3H, J=7.2)
104	(3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-etilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.13-8.00(bs, 1H), 7.42-7.27(m, 2H), 7.25-7.03(m, 5H), 6.69-6.59(bs, 1H), 4.13-3.95(m, 2H), 2.80-2.68(m, 1H), 2.68-2.32(m, 9H) 2.30-2.17(m, 1H), 2.03-1.89(m, 1H), 1.58-1.41(m, 1H), 1.18-1.04(t, 3H, J=7.6)

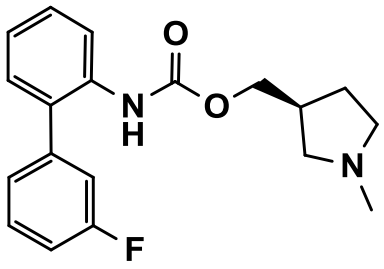
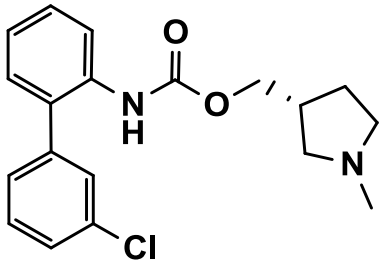
105	(3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-etilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.13-7.99(m, 1H), 7.43-7.27(m, 2H), 7.27-7.02(m, 5H), 6.72-6.58(bs, 1H), 4.13-3.94(m, 2H), 2.89-2.66(m, 1H), 2.66-2.15(m, 9H), 2.06-1.87(m, 1H), 1.57-1.40(m, 1H), 1.09(t, 3H, J=7.6)
106	[1,1'-bifenil]-2-ilcarbamato de (S)-(1-etilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.15-8.01(m, 1H), 7.54-7.26(m, 6H), 7,22-7.05(m, 2H), 6.72-6.58(bs, 1H), 4.22-4.07(m, 1H), 4.07-3.93(m, 1H), 3.21-3.02(m, 1H), 2.92-2.59(m, 2H), 2.41-2.12(m, 2H) 1.95-1.50(m, 5H), 1.08(t, 3H, J=7.2)

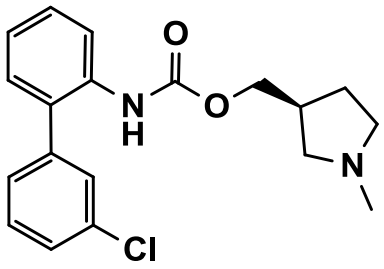
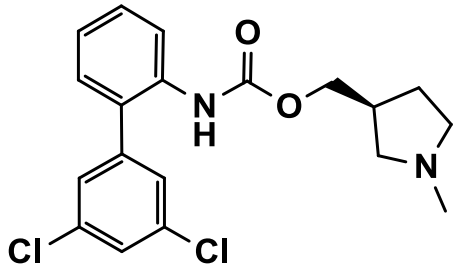
107	[1,1'-bifenil]-2-ilcarbamato de (S)-(1-isobutilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.18-8.02(m, 1H), 7.53-7.27(m, 6H), 7,22-7.03(m, 2H), 6.69-6.54(bs, 1H), 4.18-3.83(m, 2H), 3.15-2.95(bs, 1H), 2.71-2.53(bs, 1H), 2.48-2.30(m, 1H), 2.23-2.02(m, 2H), 1.92-1.45(m, 5H), 0.84(t, 6H, J=6.8)
108	(3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.85(s, 1H), 7.46-7.41(m, 1H), 7.15-7.03(m, 4H), 6.96-6.93(m, 1H), 4.11-4.03(m, 2H), 2.92-2.90(m, 1H), 2.82-2.68(m, 2H), 2.42(s, 3H), 2.12-2.10(m, 2H), 1.71-1.69(m, 2H)

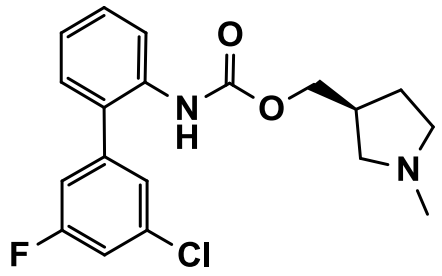
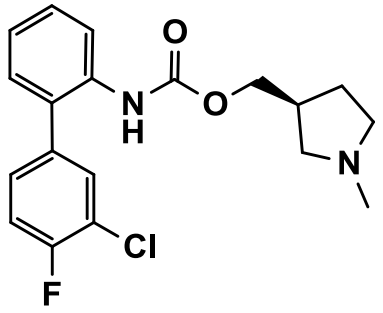
109	[1,1'-bifenil]-2-ilcarbamato de (R)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.18-7.99(m, 1H), 7.49-7.27(m, 6H), 7.22-7.15(m, 1H), 7.15-7.06(m, 1H), 6.72-6.60(bs, 1H), 4.24-3.98(m, 2H), 3.10-2.95(m, 1H), 2.52-2.40(m, 1H), 2.35(s, 3H) 2.26-2.12(m, 1H), 1.97-1.50(m, 4H)
110	(3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.18-7.97(bs, 1H), 7.41-7.28(m, 2H), 7,23-7.01(m, 5H), 6.78-6.62(bs, 1H), 4.12-3.97(m, 2H), 3.05-2.90(m, 1H), 2.52-2.11(m, 8H), 1.95-1.47(m, 4H)

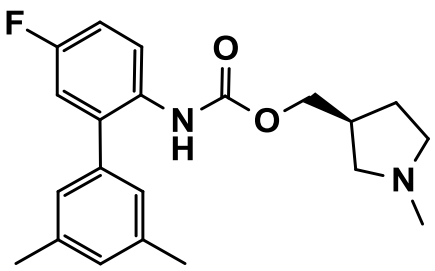
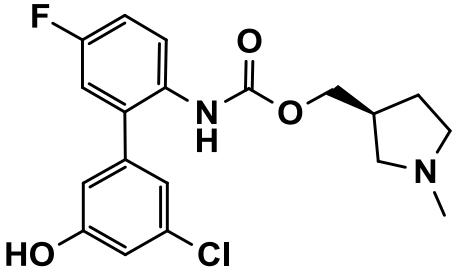
111	(5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.00(s, 1H), 7.34-7.31(m, 1H), 7.21-7.19(m, 1H), 7.12-7.06(m, 2H), 7.04-6.99(m, 1H), 6.92-6.89(m, 1H), 6.59(s, 1H), 4.18-4.04(m, 2H), 3.06-3.02(m, 1H), 2.38(s, 3H), 2.35(s, 3H), 2.22-2.15(m, 2H), 1.92-1.76(m, 2H), 1.68-1.54(m, 2H)
112	[1,1'-bifenil]-2-ilcarbamato de (S)-(1-isopropilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.15-8.01(m, 1H), 7.51-7.27(m, 6H), 7.21-7.06(m, 2H), 6.69-6.56(bs, 1H), 4.12-4.00(m, 1H), 3.87-3.76(m, 1H), 3.04-2.78(m, 3H) 2.53-2.40(m, 1H), 1.80-1.62(m, 4H), 1.08(d, 3H, J=6.4), 0.99(d, 3H, J=6.4)

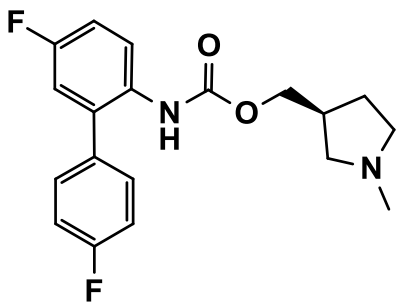
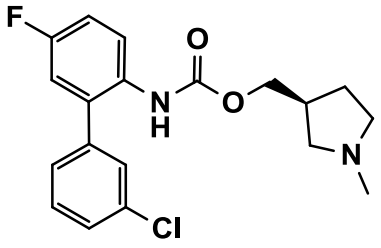
113	(3'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.13-7.98(m, 1H), 7.50-7.31(m, 2H), 7.21-7.00(m, 5H), 6.62-6.49(bs, 1H), 4.14-3.95(m, 2H), 2.75-2.42(m, 4H) 2.42-2.22(m, 4H), 2.03-1.87(m, 1H), 1.58-1.42(m, 1H)
114	(4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.11-7.97(bs, 1H), 7.42-7.27(m, 3H), 7.01-7.03(m, 4H), 6.57-6.42(bs, 1H), 4.13-3.92(m, 2H), 2.70-2.41(m, 4H), 2.41-2.20(m, 4H), 2.06-1.94(m, 1H), 1.56-1.41(m, 1H)
115	(3',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$) δ 8.02-8.01(m, 1H), 7.38-7.06(m, 5H), 6.47(s, 1H), 4.09-3.98(m, 2H), 2.62-2.58(t, 1H, J=17.2), 2.55-2.46(m, 3H), 2.37-2.25(m, 4H), 2.04-1.91(m, 2H), 1.51-1.43(m, 1H)

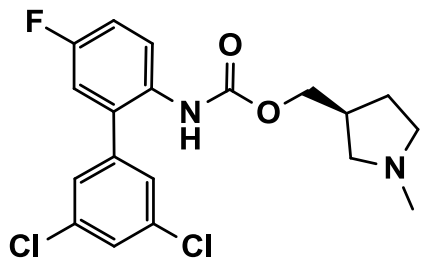
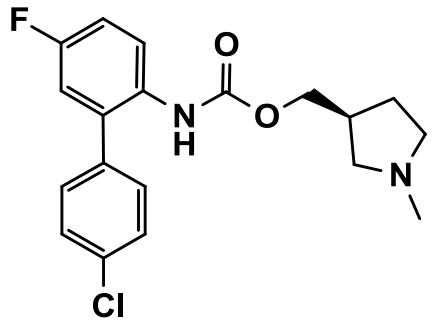
116	(3'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.12-7.98(bs, 1H), 7.50-7.31(m, 2H), 7.24-7.02(m, 5H), 6.70-6.54(bs, 1H), 4.16-3.97(m, 2H), 2.77-2.65(m, 1H) 2.64-2.47(m, 3H), 2.45-2.28(m, 4H), 2.06-1.93(m, 1H), 1.61-1.47(m, 1H)
117	(3'-cloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.08-7.93(bs, 1H), 7.47-7.27(m, 4H), 7.21-7.05(m, 3H), 6.67-6.53(bs, 1H), 4.15-3.93(m, 2H), 2.80-2.50(m, 4H), 2.50-2.24(bs, 4H), 2.09-1.92(m, 1H), 1.62-1.46(m, 1H)

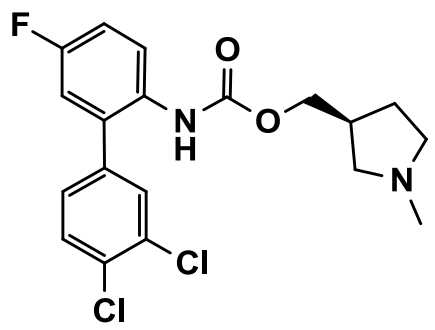
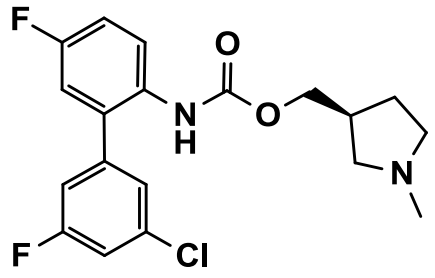
118	(3'-cloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.07-7.92(bs, 1H), 7.42-7.31(m, 4H), 7.27-7.21(m, 1H), 7.20-7.09(m, 2H), 6.66-6.56(bs, 1H), 4.13-3.97(m, 2H), 2.85-2.53(m, 4H), 2.52-2.35(m, 4H), 2.08-1.97(m, 1H), 1.63-1.52(m, 1H)
119	(3',5'-dicloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.02-7.83(bs, 1H), 7.48-7.32(m, 2H), 7.33-7.21(m, 2H), 7.20-7.08(m, 2H), 6.77-6.56(bs, 1H), 4.15-3.95(m, 2H), 2.80-2.54(m, 4H) 2.54-2.30(m, 4H), 2.12-1.92(m, 1H), 1.67-1.49(m, 1H)

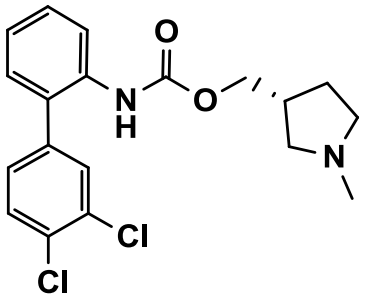
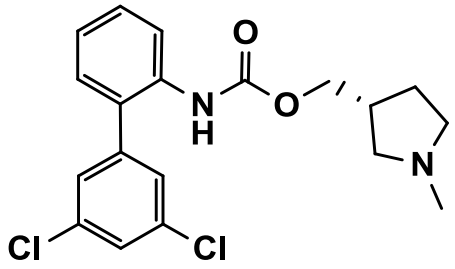
120	(3'-cloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.03-7.89(bs, 1H), 7.45-7.33(m, 1H), 7.23-7.07(m, 4H), 7.05-6.95(m, 1H), 6.72-6.56(bs, 1H), 4.16-3.96(m, 2H), 2.78-2.50(m, 4H) 2.50-2.29(m, 4H), 2.10-1.92(m, 1H), 1.65-1.47(m, 1H)
121	(3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.06-7.96(bs, 1H), 7.49-7.32(m, 2H), 7.25-7.19(m, 2H), 7.18-7.10(m, 2H), 6.65-6.47(bs, 1H), 4.17-3.95(m, 2H), 2.78-2.50(m, 4H) 2.50-2.25(m, 4H), 2.08-1.91(m, 1H), 1.62-1.47(m, 1H)

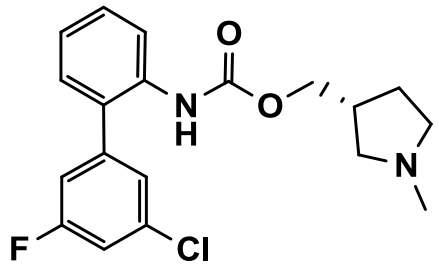
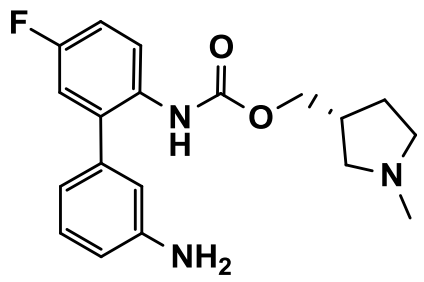
122	(5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.03-7.88(bs, 1H), 7.05-6.96(m, 2H), 6.95-6.87(m, 3H), 6.64-6.58(bs, 1H), 4.12-3.92(m, 2H), 2.68-2.57(m, 1H) 2.57-2.43(m, 3H), 2.34(s, 6H), 2.33-2.15(m, 4H), 2.00-1.77(m, 1H), 1.55-1.45(m, 1H)
123	(3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.77-7.60(bs, 1H), 7.13-6.86(m, 3H), 6.79(s, 1H), 6.70(s, 1H), 6.53(s, 1H), 5.03-4.50(bs, 1H), 4.33-4.18(m, 1H), 4.18-3.98(m, 1H), 3.08-2.95(bs, 1H), 2.95-2.78(bs, 1H) 2.70-2.31(m, 5H), 2.08-1.90(bs, 1H), 1.90-1.70(bs, 1H)

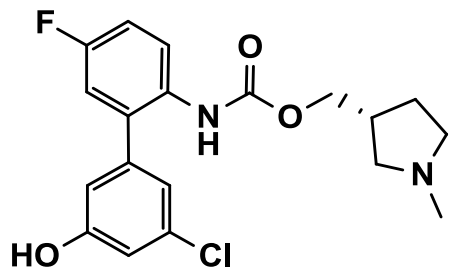
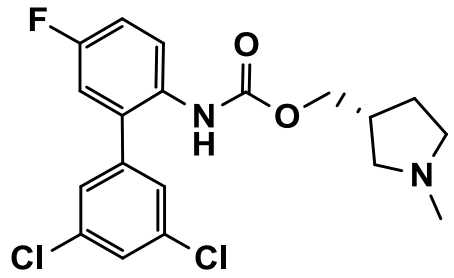
124	(4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.00-7.85(bs, 1H), 7.38-7.25(m, 2H), 7.20-7.19(m, 2H), 7.03(td, 1H, J=8.4, 2.8), 6.90(dd, 1H, J=8.8, 2.8), 6.51-6.39(bs, 1H), 4.12-3.90(m, 2H), 2.63-2.55(m, 1H) 2.55-2.39(m, 3H), 2.37-2.18(m, 4H), 1.99-1.85(m, 1H), 1.54-1.38(m, 1H)
125	(3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.02-7.81(bs, 1H), 7.53-7.30(m, 3H), 7.26-7.19(m, 1H), 7.05(td, 1H, J=8.0, 2.8), 6.91(dd, 1H, J=8.8, 2.8), 6.54-6.45(bs, 1H), 4.13-3.86(m, 2H), 2.65-2.54(m, 1H) 2.54-2.42(m, 3H), 2.37-2.19(m, 4H), 2.00-1.86(m, 1H), 1.55-1.37(m, 1H)

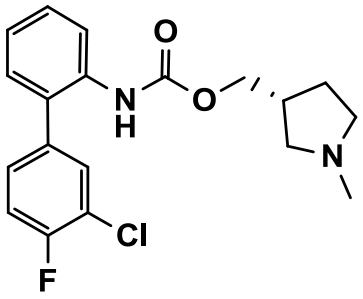
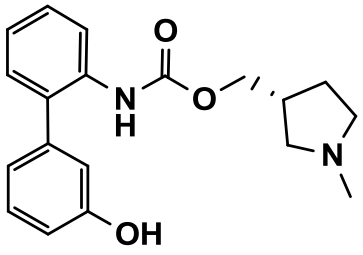
126	(3',5'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.92-7.76(bs, 1H), 7.42-7.36(m, 1H), 7.28-7.17(m, 2H), 7.06(td, 1h, J=8.8, 2.8), 6.90(dd, 1H, J=8.8, 2.8), 6.51-6.39(bs, 1H), 4.12-3.90(m, 2H), 2.63-2.55(m, 1H) 2.55-2.39(m, 3H), 2.37-2.18(m, 4H), 2.00-1.85(m, 1H), 1.54-1.38(m, 1H)
127	(4'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.98-7.82(bs, 1H), 7.49-7.38(m, 2H), 7.34-7.20(m, 2H), 7.03(td, 1H, J=8.4, 2.8), 6.90(dd, 1H, J=8.8, 2.8), 6.60-6.49(bs, 1H), 4.14-3.87(m, 2H), 2.66-2.59(m, 1H) 2.59-2.45(m, 3H), 2.42-2.15(m, 4H), 2.04-1.89(m, 1H), 1.57-1.42(m, 1H)

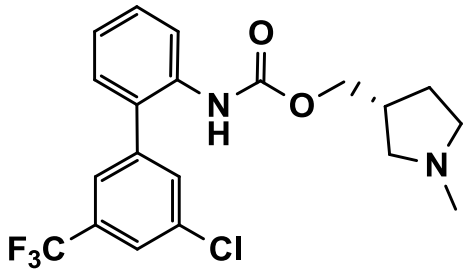
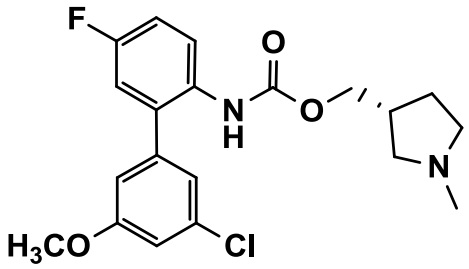
128	(3',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.86-7.65(bs, 1H), 7.58-7.39(m, 2H), 7.26-7.16(m, 1H), 7.04(td, 1H, J=8.4, 3.2), 6.89(dd, 1H, J=8.8, 3.2), 6.89-6.79(bs, 1H), 4.15-3.94(m, 2H), 2.90-2.73(m, 2H) 2.73-2.54(m, 3H), 2.52-2.19(m, 3H), 2.14-1.96(m, 1H), 1.70-1.54(m, 1H)
129	(3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.97-7.76(bs, 1H), 7.18-7.02(m, 3H), 7.03-6.86(m, 2H), 6.54-6.42(bs, 1H), 4.03-3.85(m, 2H), 2.65-2.57(m, 1H) 2.57-2.41(m, 3H), 2.37-2.18(m, 4H), 2.02-1.87(m, 1H), 1.55-1.41(m, 1H)

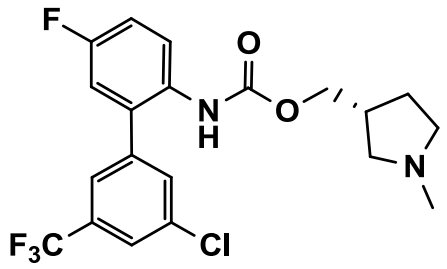
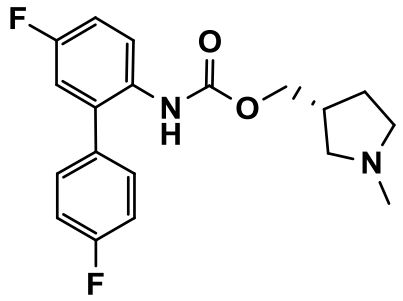
130	(3',4'-dicloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$) δ 8.01-7.99(m, 1H), 7.54-7.51(d, 1H, J=8Hz), 7.46(m, 1H), 7.38-7.34(m, 1H), 7.21-7.11(m, 2H), 6.46(s, 1H), 4.09-3.98(m, 2H), 2.63-2.59(t, 1H, J=17.2), 2.54-2.47(m, 3H), 2.36-2.26(m, 4H), 2.00-1.93(m, 1H), 1.50-1.45(m, 1H)
131	(3',5'-dicloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$) δ 8.01-7.97(m, 1H), 7.43-7.35(m, 2H), 7.26-7.25(m, 2H), 7.18-7.11(m, 2H), 6.46(s, 1H), 4.10-3.99(m, 2H), 2.67-2.61(t, 1H, J=17.2), 2.57-2.50(m, 3H), 2.38-2.28(m, 4H), 2.01-1.93(m, 1H), 1.52-1.48(m, 1H)

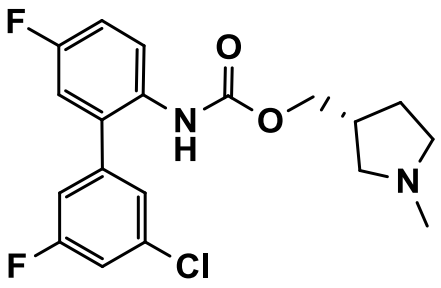
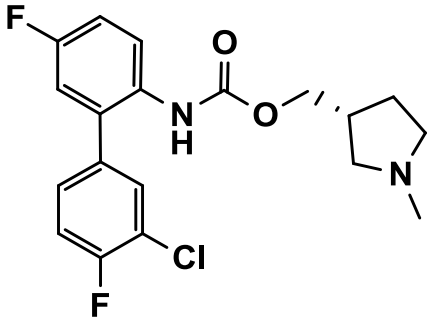
132	(3'-cloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$) δ 8.01-7.99(m, 1H), 7.39-7.35(m, 1H), 7.18-7.11(m, 3H), 6.99-6.97(m, 1H), 6.48(s, 1H), 4.10-3.99(m, 2H), 2.63-2.59(t, 1H, J=17.2), 2.53-2.48(m, 3H), 2.36-2.27(m, 4H), 2.00-1.92(m, 1H), 1.51-1.46(m, 1H)
133	(5-fluoro-3'-amino-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$) δ 8.03(m, 1H), 7.25-7.21(m, 1H), 7.03-6.98(m, 1H), 6.92-6.90(m, 1H), 6.72-6.61(m, 3H), 4.08-3.97(m, 2H),3.80(s, 1H), 2.66-2.62(t, 1H, J=17.2), 2.53-2.46(m, 3H), 2.33-2.28(m, 4H), 2.01-1.93(m, 1H), 1.51-1.48(m, 1H)

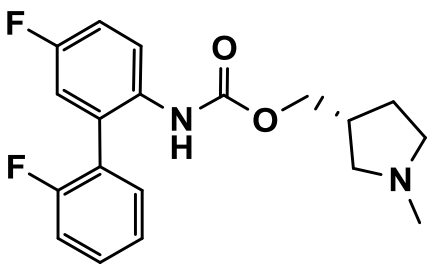
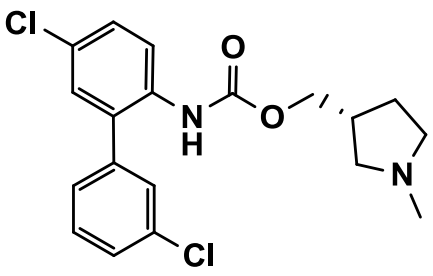
134	(3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$) δ 7.67(m, 1H), 7.06-7.01(m, 1H), 6.97-6.94(m, 3H), 6.73-6.72(m, 1H), 6.54(s, 1H), 4.35-4.05(m, 2H), 3.01-3.00(m, 1H), 2.89-2.88(m, 1H), 2.59-2.57(m, 2H), 2.47-2.41(m, 4H), 1.97-1.96(m, 1H), 1.80(m, 1H)
135	(3',5'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$) δ 7.85(s, 1H), 7.41-7.40(t, 1H, J=4.0), 7.23(s, 2H), 7.10-7.05(m, 2H), 6.93-6.90(m, 2H), 6.36(s, 1H), 4.09-3.99(m, 2H), 2.63-2.59(t, 1H, J=17.2), 2.56-2.45(m, 3H), 2.32-2.28(m, 4H), 2.01-1.93(m, 1H), 1.50-1.46(m, 1H)

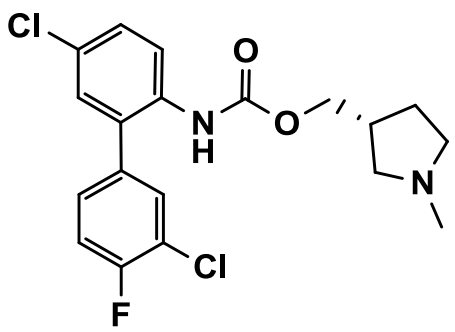
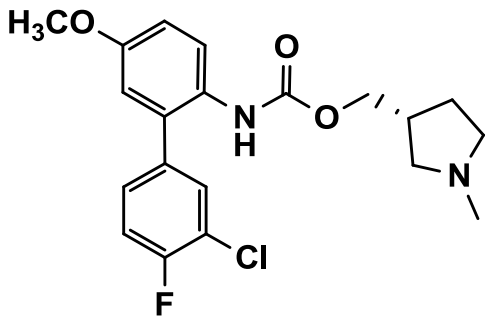
136	(3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$) δ 8.03-7.98(m, 1H), 7.41-7.34(m, 2H), 7.26-7.21(m, 2H), 7.17-7.10(m, 2H), 6.49(s, 1H), 4.09-3.98(m, 2H), 2.63-2.59(t, 1H, J=17.2), 2.51-2.46(m, 3H), 2.36-2.26(m, 4H), 2.00-1.91(m, 1H), 1.51-1.46(m, 1H)
137	(3'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.95-7.81(m, 1H), 7.40-7.19(m, 3H), 7.18-7.06(m, 1H), 6.89-6.65(m, 4H), 4.34-4.18(m, 1H), 4.09-3.94(m, 1H), 2.89-2.51(m, 5H), 2.42(s, 3H), 2.07-1.95(m, 1H), 1.78-1.60(m, 1H)

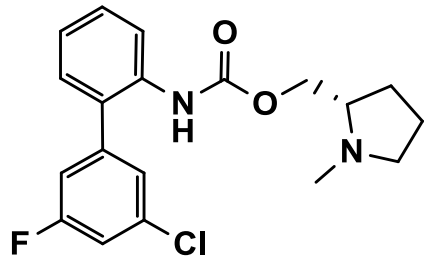
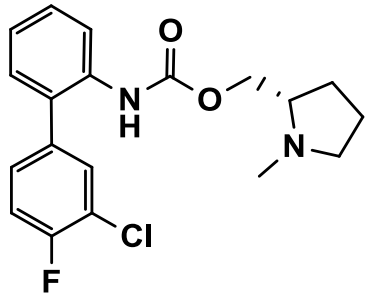
138	(3'-cloro-5'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$) δ 7.96-7.94(m, 1H), 7.63(s, 1H), 7.55-7.52(m, 2H), 7.42-7.37(m, 2H), 7.21-7.17(m, 2H), 6.40(s, 1H), 4.09-3.99(m, 2H), 2.64-2.60(t, 1H, J=17.2), 2.55-2.47(m, 3H), 2.36-2.31(m, 4H), 2.00-1.91(m, 1H), 1.51-1.46(m, 1H)
139	(3'-cloro-5-fluoro-5'-metoxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$) δ 7.97(m, 1H), 7.07-7.03(m, 1H), 6.94-6.89(m, 2H), 6.74-6.73(m, 1H), 6.45(s, 1H), 4.08-3.99(m, 2H), 3.83-3.79(m, 3H), 2.63-2.59(t, 1H, J=17.2), 2.54-2.47(m, 3H), 2.36-2.27(m, 4H), 2.00-1.91(m, 1H), 1.49-1.45(m, 1H)

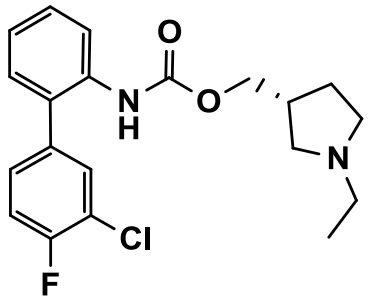
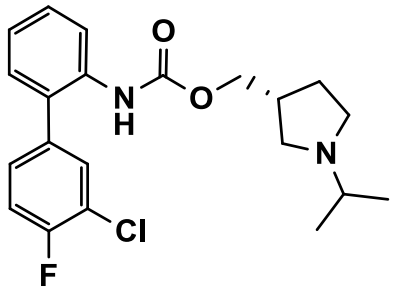
140	(3'-cloro-5-fluoro-5'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$) δ 7.82(m, 1H), 7.65(s, 1H), 7.54-7.51(m, 2H), 7.13-7.08(m, 1H), 6.96-6.93(m, 2H), 6.34(s, 1H), 4.07-3.97(m, 2H), 2.60-2.56(t, 1H, J=17.2), 2.53-2.43(m, 3H), 2.34-2.35(m, 4H), 1.98-1.90(m, 1H), 1.49-1.44(m, 1H)
141	(4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$) δ 7.93(m, 1H), 7.31-7.29(m, 2H), 7.23-7.13(m, 2H), 7.06-7.01(m, 1H), 6.91-6.89(m, 1H), 6.42(s, 1H), 4.07-3.96(m, 2H), 2.61-2.56(t, 1H, J=17.2), 2.53-2.43(m, 3H), 2.35-2.25(m, 4H), 2.00-1.89(m, 1H), 1.51-1.41(m, 1H)

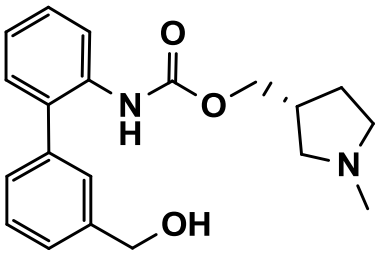
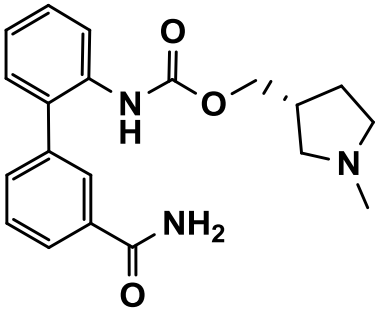
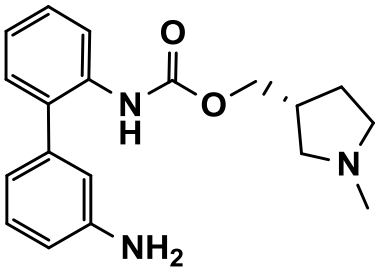
142	(3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$) δ 7.85(m, 1H), 7.14-7.13(m, 2H), 7.10-7.05(m, 1H), 6.98-6.96(m, 1H), 6.93-6.90(m, 1H), 6.43(s, 1H), 4.09-3.99(m, 2H), 2.65-2.60(t, 1H, J=17.2), 2.55-2.47(m, 3H), 2.36-2.31(m, 4H), 2.02-1.95(m, 1H), 1.52-1.47(m, 1H)
143	(R)-(1-metilpirrolidin-3-il)metilo (3'-cloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato 	^{1}H NMR($CDCl_3$) δ 7.85(m, 1H), 7.40-7.38(m, 1H), 7.26-7.19(m, 2H), 7.08-7.03(m, 1H), 6.91-6.88(m, 1H), 6.34(s, 1H), 4.08-3.97(m, 2H), 2.61-2.57(t, 1H, J=17.2), 2.55-2.47(m, 3H), 2.36-2.25(m, 4H), 2.00-1.90(m, 1H), 1.51-1.44(m, 1H)

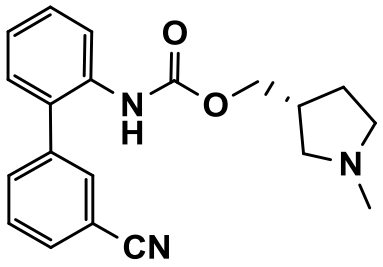
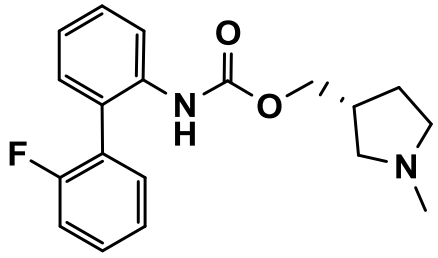
144	(2',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$) δ 8.05(m, 1H), 7.44-7.40(m, 1H), 7.31-7.23(m, 2H), 7.21-7.17(m, 2H), 6.98-6.96(m, 1H), 4.13-4.07(m, 2H), 3.10-3.08(m, 1H), 2.49-2.45(m, 1H), 2.39(s, 3H), 2.29-2.21(m, 1H), 1.95-1.59(m, 4H)
145	(3',5-dicloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$) δ 7.87-7.85(m, 1H), 7.55-7.17(m, 5H), 6.99(m, 1H), 6.55(s, 1H), 4.11-4.02(m, 2H), 3.06-3.02(m, 2H), 2.95-2.89(m, 1H), 2.85-2.81(m, 1H), 2.76-2.66(m, 1H), 2.62(s, 3H), 2.18-2.09(m, 1H), 1.78-1.69(m, 1H)

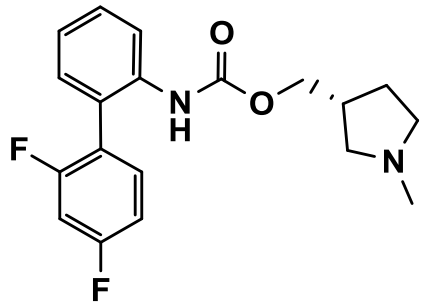
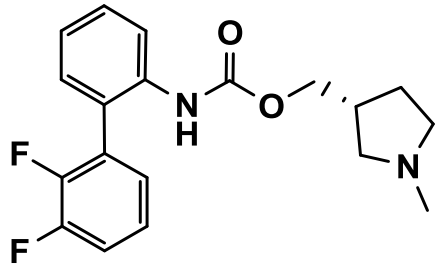
146	(3',5-dicloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$) δ 7.86-7.83(m, 1H), 7.53-7.15(m, 4H), 6.99(m, 1H), 6.50(s, 1H), 4.10-4.02(m, 2H), 3.05-3.02(m, 2H), 2.97-2.90(m, 1H), 2.84-2.82(m, 1H), 2.77-2.67(m, 1H), 2.60(s, 3H), 2.18-2.10(m, 1H), 1.79-1.69(m, 1H)
147	(3'-cloro-4'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$) δ 7.70(s, 1H), 7.44-7.42(d, 1H, J=7.2), 7.26-7.20(m, 2H), 6.93-6.90(m, 1H), 6.75(m, 1H), 6.66(s, 1H), 4.15-4.00(m, 2H), 3.81(s, 3H), 3.42-3.40(m, 1H), 2.81-2.47(m, 2H), 2.34(s, 3H), 2.06-1.60(m, 4H)

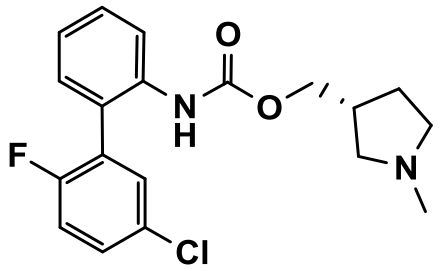
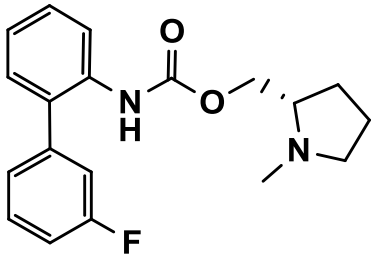
148	(3'-cloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$) δ 7.92(s, 1H), 7.43-7.27(m, 2H), 7.23-7.08(m, 3H), 7.03-6.95(m, 1H), 6.79(s, 1H), 4.33-4.19(m, 2H), 3.28-3.26(m, 1H), 2.75(m, 1H), 2.49-2.28(m, 4H), 1.98-1.59(m, 4H)
149	(3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$) δ 7.90(s, 1H), 7.39-7.31(m, 2H), 7.22-7.05(m, 3H), 7.03-6.97(m, 1H), 6.72(s, 1H), 4.26-4.11(m, 2H), 3.19-3.14(m, 1H), 2.70-2.64(m, 1H), 2.42-2.30(m, 4H), 1.99-1.58(m, 4H)

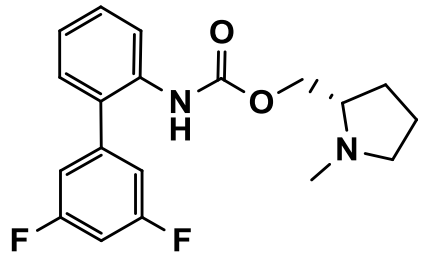
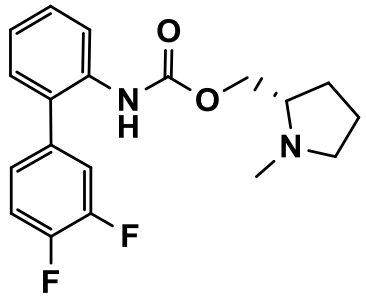
150	(3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-etilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.97(s, 1H), 7.41-7.33(m, 2H), 7.23-7.21(m, 2H), 7.16-7.10(m, 2H), 6.60(s, 1H), 4.10-4.01(m, 2H), 2.74-2.72(m, 1H), 2.65-2.45 (m, 5H), 2.37-2.34(m, 1H), 2.02-1.93(m, 1H), 1.57-1.49(m, 1H), 1.11(t, 3H, J=7.2)
151	(3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-isopropilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.95(s, 1H), 7.41-7.34(m, 2H), 7.23-7.21(m, 2H), 7.18-7.12(m, 2H), 6.68(s, 1H), 4.14-4.04(m, 2H), 3.07-3.05(m, 1H), 2.93-2.90(m, 1H), 2.76-2.74(m, 1H), 2.67-2.64(m, 2H), 2.09-2.02(m, 1H), 1.70-1.65(m, 2H), 1.23(s, 6H)

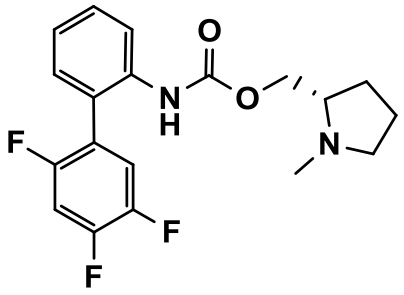
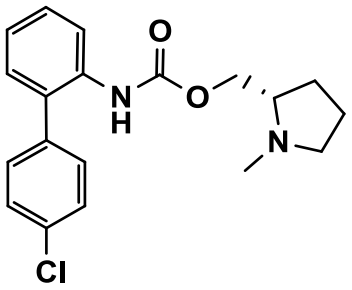
152	(3'-(hidroximetil)-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.10-7.92(bs, 1H), 7.57-6.90(m, 7H), 4.71(s, 1H), 4.21-3.91(m, 3H), 2.73-2.16(m, 9H) 2.08-1.84(m, 1H), 1.64-1.39(m, 1H)
153	(3'-carbamoil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR(DMSO): δ 8.78(s, 1H), 8.20-7.78(m, 3H), 7.78-7.20(m, 7H), 3.99-3.65(bs, 2H), 3.55-3.26(bs, 1H), 2.60-1.97(m, 7H), 1.88-1.63(bs, 1H), 1.41-1.14(bs, 1H)
154	(3'-amino-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.15-8.00(bs, 1H), 7.43-7.13(m, 3H), 7.12-6.99(m, 1H), 6.82-6.55(m, 4H), 4.18-3.93(m, 2H), 3.87-3.67(bs, 2H), 2.72-2.41(m, 4H) 2.41-2.19(m, 4H), 2.03-1.83(m, 1H), 1.55-1.40(m, 1H)

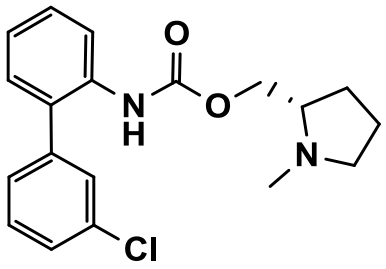
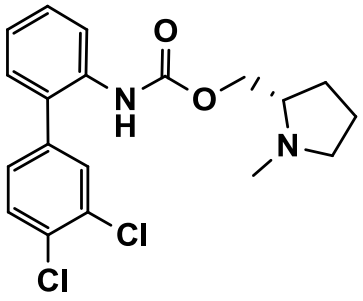
155	(3'-ciano-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.03-7.85(m, 1H), 7.74-7.50(m, 4H), 7,47-7.32(m, 1H), 7.26-7.08(m, 2H), 6.71-6.47(bs, 1H), 4.15-3.90(m, 2H), 2.77-2.48(m, 4H), 2.48-2.25(bs, 4H), 2.09-1.88(m, 1H), 1.63-1.44(m, 1H)
156	(2'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.98(m, 1H), 7.43-7.38(m, 3H), 7.31-7.29(m, 1H), 7,26-7.25(m, 1H), 7.23-7.16(m, 2H), 6.48(s, 1H), 4.11-4.02(m, 2H), 2.94-2.80(m, 1H), 2.51-2.48(m, 1H), 2.44(s, 3H), 2.14-2.01(m, 1H), 1.89-1.55(m, 4H)

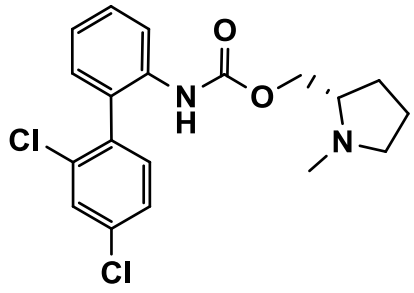
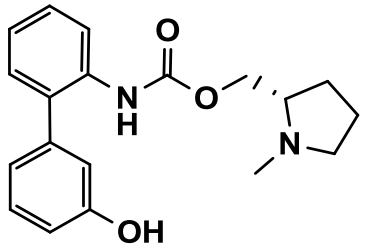
157	(2',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.91(m, 1H), 7.39-7.36(m, 1H), 7.30-7.26(m, 1H), 7,19-7.17(m, 2H), 7.00-6.97(m, 2H), 6.95-6.92(m, 1H), 6.70(s, 1H), 4.12-4.06(m, 2H), 3.00-2.97(m, 1H), 2.75-2.70(m, 1H), 2.60(s, 3H), 2.18-2.14(m, 1H), 1.90-1.52(m, 4H)
158	(2',3'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.84(m, 1H), 7.41-7.39(m, 1H), 7.23-7.17(m, 4H), 7,09-7.07(m, 1H), 4.18-4.11(m, 2H), 3.27-3.14(m, 1H), 2.89-2.85(m, 1H), 2.74(s, 3H), 2.28-2.23(m, 1H), 1.93-1.48(m, 4H)

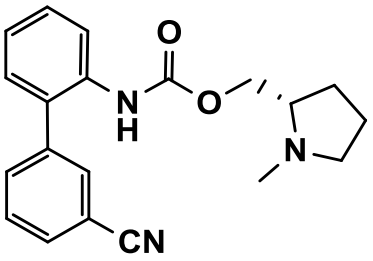
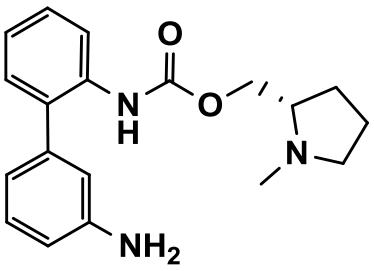
159	(3'-cloro-6'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.94(m, 1H), 7.55-7.42(m, 1H), 7.30-7.22(m, 2H), 7,19-7.15(m, 2H), 7.04-7.00(m, 1H), 4.20-4.08(m, 2H), 3.29-3.17(m, 1H), 2.88-2.85(m, 1H), 2.54(s, 3H), 2.33-2.28(m, 1H), 2.01-1.66(m, 4H)
160	(3'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.10-8.03(m, 1H), 7.36-7.02(m, 6H), 6.89-6.85(m, 1H), 6.63(s, 1H), 4.22-4.02(m, 2H), 3.07-2.98(m, 1H), 2.51-2.41(m, 1H), 2.39(s, 3H), 2.49-2.14(m, 1H), 1.96-1.52(m, 4H)

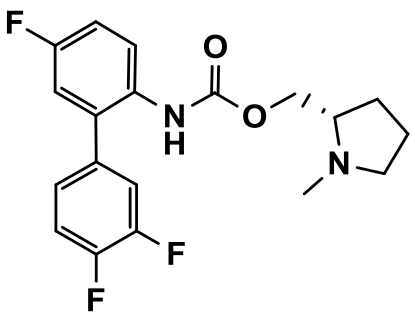
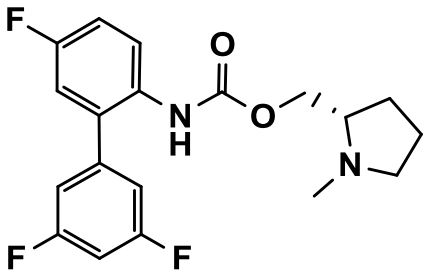
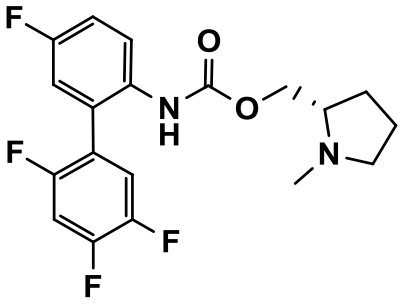
161	(3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.02-8.00(m, 1H), 7.37-7.25(m, 2H), 7.17-7.08(m, 2H), 6.90-6.78(m, 2H), 6.60(s, 1H), 4.23-4.03(m, 2H), 3.08-2.99(m, 1H), 2.51-2.36(m, 1H), 2.34(s, 3H), 2.29-2.15(m, 1H), 1.99-1.54(m, 4H)
162	(3',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.10-8.08(d, 1H, J=8.0), 7.39-7.10(m, 3H), 6.92-6.83(m, 1H), 6.66-6.61(m, 1H), 6.59(s, 1H), 6.52-6.48(m, 1H), 4.28-4.08(m, 2H), 3.14-3.07(m, 1H), 2.59-2.47(m, 1H), 2.38(s, 3H), 2.33-2.21(m, 1H), 2.02-1.58(m, 4H)

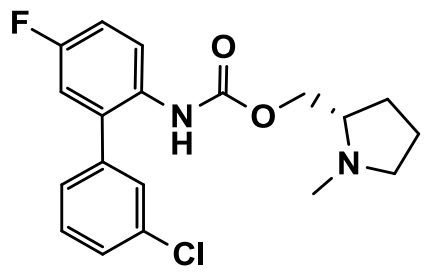
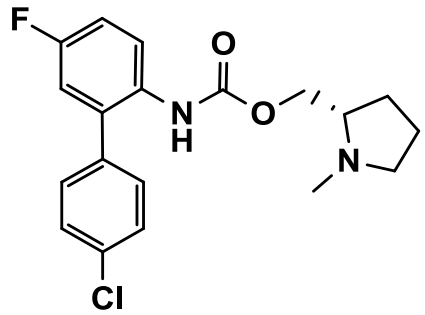
163	(2',4',5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.11-8.09(d, 1H, J=8.0), 7.33-7.23(m, 2H), 7.18-7.14(m, 1H), 7.13-7.10(m, 1H), 6.91-6.87(m, 1H), 6.48(s, 1H), 4.26-4.06(m, 2H), 3.12-3.08(m, 1H), 2.53-2.43(m, 1H), 2.37(s, 3H), 2.30-2.20(m, 1H), 1.98-1.63(m, 4H)
164	(4'-cloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.02-8.00(d, 1H, J=7.6), 7.30-7.23(m, 2H), 7.21-7.09(m, 1H), 7.06-7.04(d, 2H, J=8.8), 6.77-6.75(d, 2H, J=8.8), 6.60(s, 1H), 4.28-4.08(m, 2H), 3.13-3.06(m, 1H), 2.57-2.45(m, 1H), 2.38(s, 3H), 2.33-2.22(m, 1H), 1.99-1.59(m, 4H)

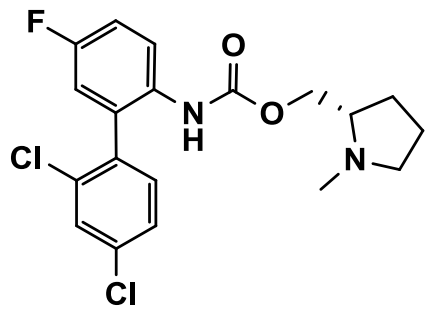
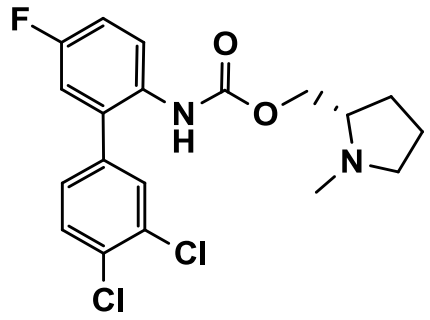
165	(3'-cloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.12-7.99(m, 1H), 7.49-7.28(m, 4H), 7.28-7.02(m, 3H), 6.62-6.49(bs, 1H), 4.26-3.99(m, 2H), 3.12-2.98(m, 1H), 2.53-2.40(m, 1H), 2.36(s, 3H), 2.27-2.14(m, 1H), 1.98-1.81(m, 1H) 1.80-1.55(m, 2H)
166	(3',4'-dicloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.10-8.08(d, 1H, J=8.0), 7.65–7.61(dd, 2H, J=12.0), 7.55-7.42(m, 3H), 7.19-7.10(m, 1H), 6.57(s, 1H), 4.27-4.07(m, 2H), 3.13-3.05(m, 1H), 2.57-2.47(m, 1H), 2.38(s, 3H), 2.33-2.21(m, 1H), 2.01-1.60(m, 4H)

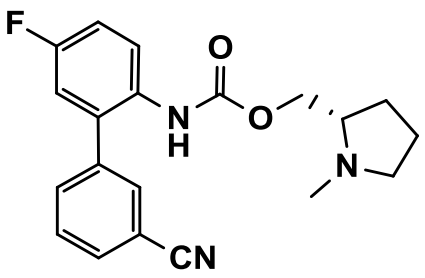
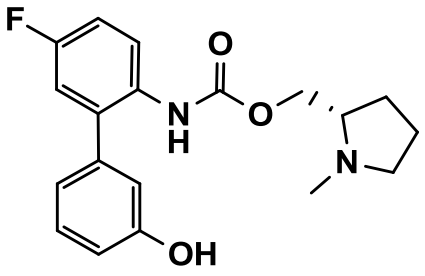
167	(2',4'-dicloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.11-8.09(d, 1H, J=8.0), 7.39-7.08(m, 5H), 6.92-6.88(m, 1H), 6.32(s, 1H), 4.27-4.12(m, 2H), 3.14-3.08(m, 1H), 2.57-2.53(m, 1H), 2.44(s, 3H), 2.31-2.21(m, 1H), 2.01-1.58(m, 4H)
168	(3'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.98-7.96(d, 1H, J=7.6), 7.30-7.26(m, 1H), 7.22-7.14(m, 2H), 7.11-7.05(m, 1H), 6.81-6.77(t, 2H, J=16.8), 6.73-6.71(t, 1H, J=4.4), 4.23-4.08(m, 2H), 3.09-3.05(m, 1H), 2.57-2.50(m, 1H), 2.38(s, 3H), 2.36-2.22(m, 1H), 1.99-1.59(m, 4H)

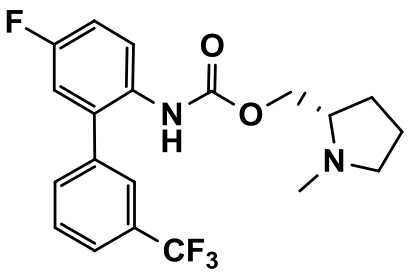
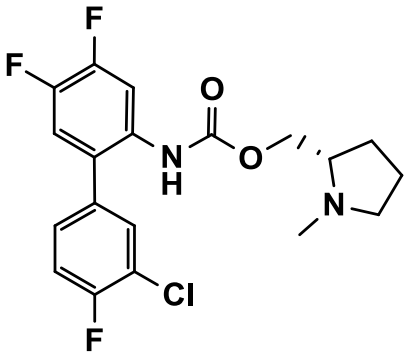
169	(3'-ciano-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.02-8.00(d, 1H, J=7.2), 7.68-7.65(m, 2H), 7.60-7.54(m, 2H), 7.41-7.37(m, 1H), 7.17-7.16(d, 2H, J=4.4), 6.42(s, 1H), 4.22-4.04(m, 2H), 3.06-3.02(m, 1H), 2.35(s, 3H), 2.30-2.24(q, 1H, J=16.0), 2.02-1.55(m, 4H)
170	(3'-amino-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.09-8.07(d, 1H, J=7.6), 7.41-7.15(m, 4H), 7.08-7.00(m, 1H), 6.94(s, 2H), 6.82(s, 1H), 6.42(s, 1H), 6.69-6.66(t, 1H, J=14.8), 6.61(s, 1H), 4.24-4.03(m, 2H), 3.11-3.02(m, 1H), 2.56-2.44(m, 1H), 2.40(s, 3H), 2.30-2.17(m, 1H), 1.96-1.58(m, 4H)

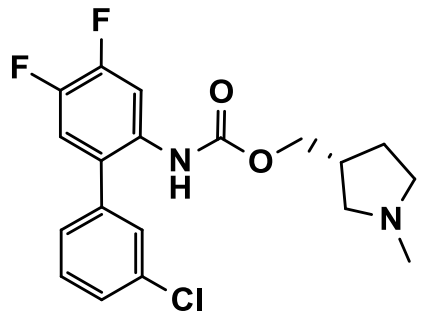
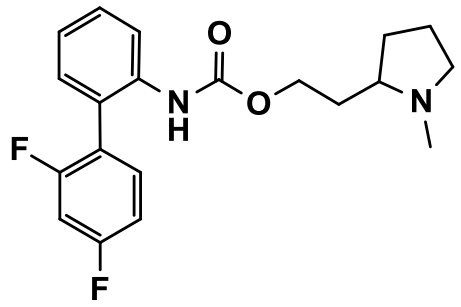
171	(3',4',5-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.75(s, 1H), 7.23-6.97(m, 4H), 6.90-6.85(m, 1H), 6.83(s, 1H), 4.31-4.15(m, 2H), 3.26(m, 1H), 2.81(m, 1H), 2.54(m, 1H), 2.47(s, 3H), 2.03-1.64(m, 4H)
172	(3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.88(s, 1H), 7.06-7.01(m, 2H), 6.90-6.78(m, 3H), 6.61(s, 1H), 4.18-3.94(m, 2H), 3.05-3.00(m, 1H), 2.45-2.36(m, 1H), 2.33(s, 3H), 2.28-2.12(m, 1H), 1.90-1.52(m, 4H)
173	(2',4',5,5'-tetrafluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.82(s, 1H), 7.16-6.98(m, 3H), 6.93-6.90(m, 1H), 6.60(s, 1H), 4.29-4.07(m, 2H), 3.24(m, 1H), 2.51-2.32(m, 2H), 2.15(s, 3H), 2.07-1.69(m, 4H)

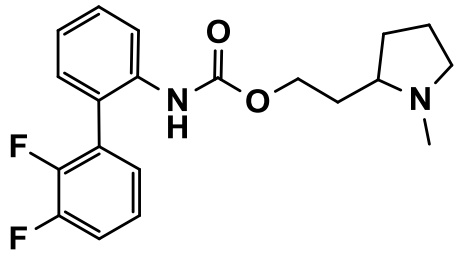
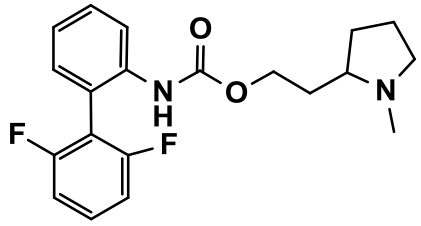
174	(3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.94(s, 1H), 7.23-7.16(m, 2H), 7.07-7.02(m, 2H), 6.92-6.89(m, 2H), 6.56(s, 1H), 4.20-4.04(m, 2H), 3.07-3.03(m, 1H), 2.48-2.39(m, 1H), 2.36(s, 3H), 2.31-2.19(m, 1H), 1.93-1.55(m, 4H)
175	(4'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.89(s, 1H), 7.24(s, 1H), 7.22(s, 1H), 7.03-6.98(m, 2H), 6.88-6.85(m, 2H), 6.55(s, 1H), 4.16-4.00(m, 2H), 3.04-3.00(m, 1H), 2.47-2.35(m, 1H), 2.32(s, 3H), 2.27-2.16(m, 1H), 1.90-1.51(m, 4H)

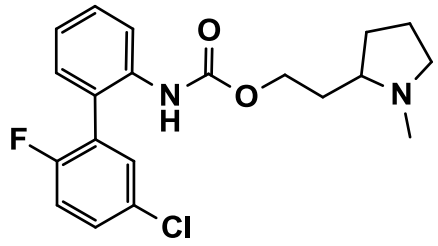
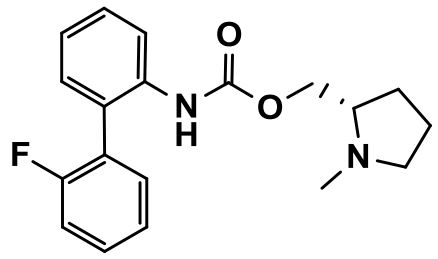
176	(2',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.89(s, 1H), 7.31-7.28(m, 1H), 7.18(s, 1H), 7.16(s, 1H), 7.13-7.04(m, 1H), 6.83-6.81(m, 1H), 6.30(s, 1H), 4.16-4.00(m, 2H), 3.04-3.00(m, 1H), 2.47-2.35(m, 1H), 2.32(s, 3H), 2.27-2.16(m, 1H), 1.90-1.51(m, 4H)
177	(3',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$) δ 7.88(s, 1H), 7.41-7.37(m, 1H), 7.21-7.16(m, 1H), 7.08-7.01(m, 2H), 6.91-6.88(m, 1H), 6.52(s, 1H), 4.24-4.05(m, 2H), 3.12-3.07(m, 1H), 2.53-2.44(m, 1H), 2.38(s, 3H), 2.36-2.22(m, 1H), 1.94-1.56(m, 4H)

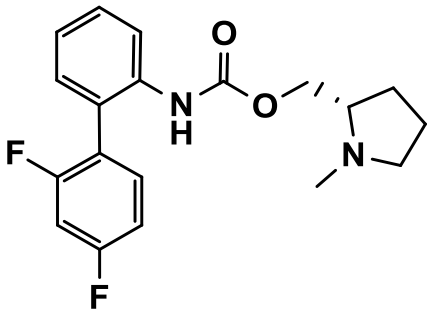
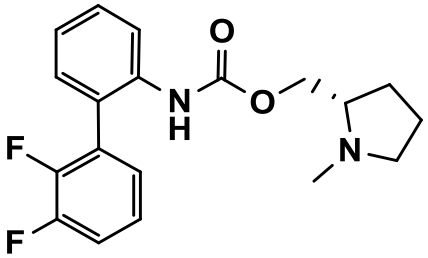
178	(3'-ciano-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.86(s, 1H), 7.53-7.49(m, 1H), 7.45-7.40(m, 2H), 7.11-7.05(m, 2H), 6.91-6.88(m, 1H), 6.42(s, 1H), 4.18-4.02(m, 2H), 3.06-3.02(m, 1H), 2.45-2.39(m, 1H), 2.34(s, 3H), 2.28-2.13(m, 1H), 1.91-1.53(m, 4H)
179	(3'-hidroxi-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.85(s, 1H), 7.26-7.19(m, 1H), 7.02-6.96(m, 1H), 6.93-6.90(m, 1H), 6.78-6.74(m, 3H), 6.71(s, 1H), 4.21-4.18(m, 2H), 3.15-3.11(m, 1H), 2.62-2.56(m, 1H), 2.41(s, 3H), 2.34-2.27(m, 1H), 1.98-1.62(m, 4H)

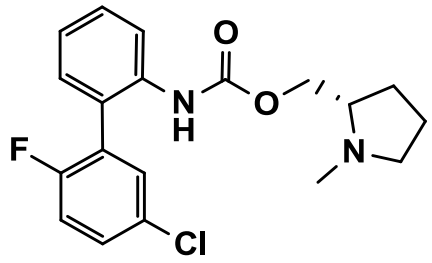
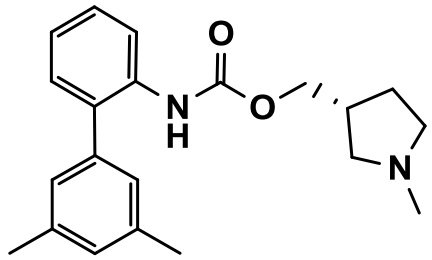
180	(5-fluoro-3'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.81(s, 1H), 7.25-7.22(m, 1H), 7.11(s, 1H), 7.07-6.91(m, 4H), 6.67(s, 1H), 4.30-4.09(m, 2H), 3.21-3.13(m, 1H), 2.71-2.58(m, 1H), 2.39(s, 3H), 2.03-1.56(m, 4H)
181	(3'-cloro-4,4',5-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.02(m, 1H), 7.39-7.38(dd, 1H, J=4.4), 7.27-7.25(m, 1H), 7.21-7.18(m, 1H), 7.01-6.98(dd, 1H, J=7.2), 6.50(s, 1H), 4.23-4.10(m, 2H), 3.10-3.07(m, 1H), 2.50-2.46(m, 1H), 2.39(s, 3H), 2.28-2.23(m, 1H), 1.95-1.60(m, 4H)

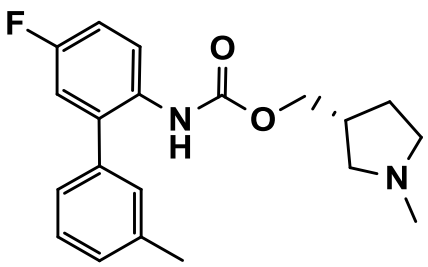
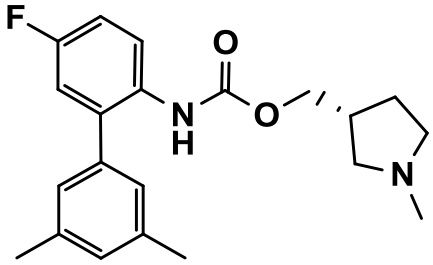
182	(3'-cloro-4,5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.00(m, 1H), 7.41-7.39(m, 1H), 7.28-7.23(m, 1H), 7.20-7.19(m, 1H), 7.00-6.96(dd, 1H, J=7.2), 6.61(s, 1H), 4.22-4.10(m, 2H), 3.11-3.09(m, 1H), 2.50-2.46(m, 1H), 2.38(s, 3H), 2.29-2.21(m, 1H), 1.95-1.59(m, 4H)
183	(2',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.96(m, 1H), 7.41-7.38(m, 1H), 7.30-7.26(m, 2H), 7.19-7.15(m, 2H), 7.01-6.93(m, 2H), 6.38(s, 1H), 4.21-4.14(m, 2H), 3.35(m, 1H), 3.00-2.64(m, 1H), 2.48(s, 3H), 2.26-2.03(m, 3H), 1.94-1.67(m, 4H)

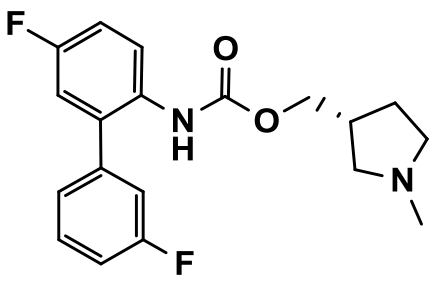
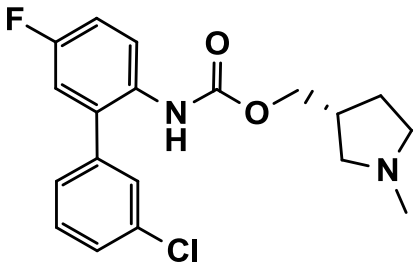
184	(2',3'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.90(m, 1H), 7.44-7.41(m, 1H), 7.26-7.19(m, 4H), 7.09-7.06(m, 1H), 6.46(s, 1H), 4.25(m, 2H), 3.80(m, 1H), 2.98(m, 1H), 2.73(s, 3H), 2.29-2.15(m, 3H), 2.02-1.57(m, 4H)
185	(2',6'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.94(m, 1H), 7.60-7.37(m, 2H), 7.26-7.21(m, 2H), 7.06-6.99(m, 2H), 6.40(s, 1H), 4.22-4.20(m, 2H), 3.83(m, 1H), 2.99(m, 1H), 2.73(s, 3H), 2.31-2.15(m, 3H), 2.02-1.59(m, 4H)

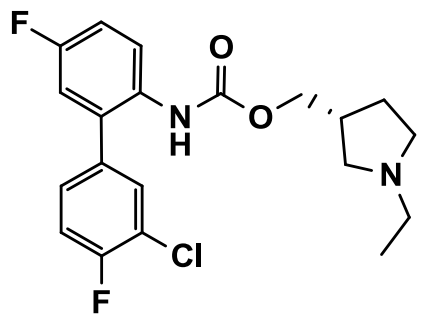
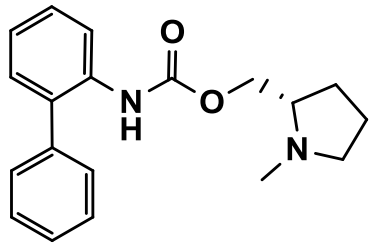
186	(5'-cloro-2'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo 	^{1}H NMR($CDCl_3$): δ 7.92(m, 1H), 7.42-7.39(m, 1H), 7.37-7.34(m, 1H), 7.29-7.28(m, 1H), 7.22-7.17(m, 2H), 7.14-7.11(m, 1H), 6.45(s, 1H), 4.22-4.14(m, 2H), 3.80(m, 1H), 3.47-3.45(m, 1H), 2.53(s, 3H), 2.16-2.11(m, 3H), 1.98-1.72(m, 4H)
187	(2'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.00(m, 1H), 7.41-7.37(m, 3H), 7.33-7.27(m, 1H), 7.25-7.20(m, 1H), 7.19-7.14(m, 2H), 6.61(s, 1H), 4.08-4.01(m, 2H), 2.88-2.79(m, 1H), 2.49-2.45(m, 1H), 2.40(s, 3H), 2.28-2.14(m, 1H), 1.94-1.61(m, 4H)

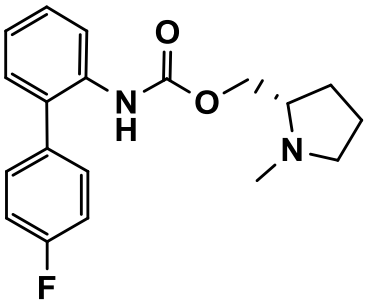
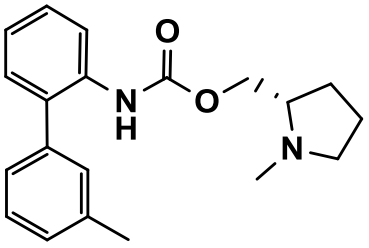
188	(2',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.98(m, 1H), 7.41-7.37(m, 1H), 7.29-7.23(m, 1H), 7.17-7.14(m, 2H), 6.99-6.89(m, 2H), 6.44(s, 1H), 4.23-4.05(m, 2H), 3.10-3.07(m, 1H), 2.49(m, 1H), 2.38(s, 3H), 2.28-2.22(m, 3H), 1.93-1.60(m, 4H)
189	(2',3'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.00(m, 1H), 7.38-7.34(m, 1H), 7.29-7.23(m, 2H), 7.20-7.14(m, 2H), 7.02-6.89(m, 1H), 6.51(s, 1H), 4.20-4.05(m, 2H), 3.08-3.05(m, 1H), 2.58-2.44(m, 1H), 2.39(s, 3H), 2.30-2.24(m, 3H), 1.99-1.64(m, 4H)

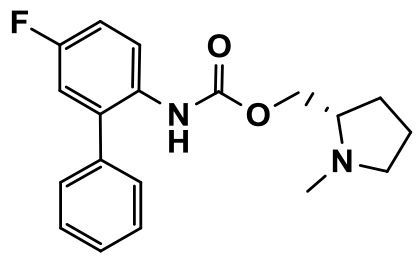
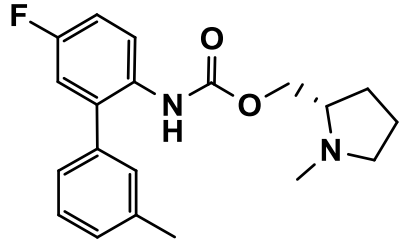
190	(3'-cloro-6'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.97(m, 1H), 7.43-7.39(m, 1H), 7.23-7.08(m, 4H), 7.04-6.98(m, 1H), 6.52(s, 1H), 4.27-4.15(m, 2H), 3.17-3.07(m, 1H), 2.62(m, 1H), 2.44(s, 3H), 2.34-2.30(m, 3H), 1.95-1.58(m, 4H)
191	(3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.07-8.05(m, 1H), 7.33-7.30(m, 1H), 7.18-7.16(m, 1H), 7.10-7.06(m, 1H), 7.03(s, 1H), 6.95(s, 2H), 6.69(s, 1H), 4.09-3.99(m, 2H), 2.69-2.65(t, 1H, J=17.2), 2.59-2.40(m, 3H), 2.35-2.27(m, 4H), 2.01-1.95(m, 1H), 1.54-1.48(m, 1H)

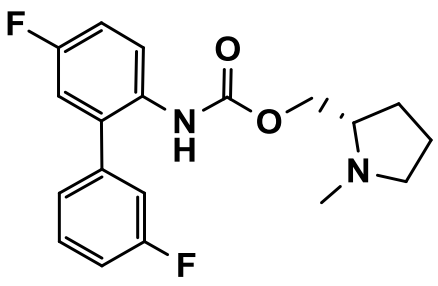
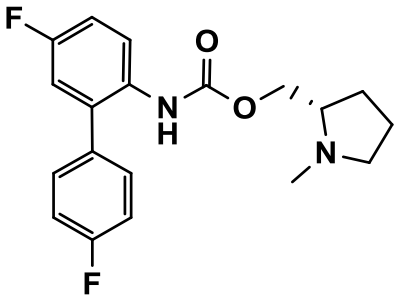
192	(5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.07-7.89(bs, 1H), 7.40-7.29(m, 1H), 7.29-7.19(m, 1H), 7.19-7.07(m, 2H), 7.07-6.97(m, 1H), 6.97-6.86(m, 1H), 6.61-6.45(bs, 1H), 4.13-3.92(m, 2H), 2.68-2.43(m, 4H), 2.39(s, 3H), 2.36-2.20(m, 4H), 2.04-1.88(m, 1H), 1.53-1.39(m, 1H)
193	(5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.98(m, 1H), 7.89-7.04(m, 6H), 6.55(s, 1H), 4.08-3.97(m, 2H), 2.63-2.59(t, 1H, J=17.2), 2.53-2.40(m, 2H), 2.35-2.31(m, 3H), 2.31(s, 1H), 2.27-2.23(m, 1H), 1.99-1.92(m, 1H), 1.51-1.44(m, 1H)

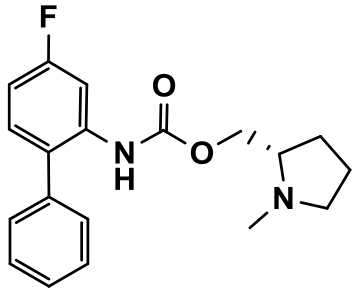
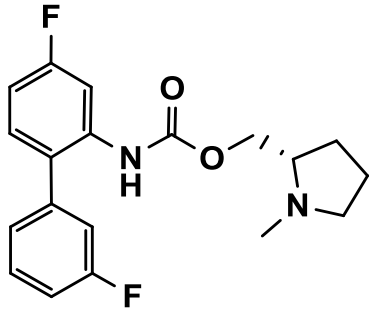
194	(3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.95(m, 1H), 7.47-7.41(m, 2H), 7.12-7.04(m, 4H), 6.93-6.91(m, 1H), 6.48(s, 1H), 4.08-3.97(m, 2H), 2.63-2.59(t, 1H, J=17.2), 2.52-2.49(m, 3H), 2.34-2.27(m, 4H), 2.00-1.93(m, 1H), 1.50-1.46(m, 1H)
195	(3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.92(m, 1H), 7.42-7.33(m, 2H), 7.23-7.21(m, 2H), 7.07-7.03(m, 1H), 6.93-6.90(m, 1H), 6.27(s, 1H), 4.08-3.97(m, 2H), 2.65-2.60(t, 1H, J=17.2), 2.53-2.45(m, 3H), 2.35-2.29(m, 4H), 2.01-1.93(m, 1H), 1.53-1.46(m, 1H)

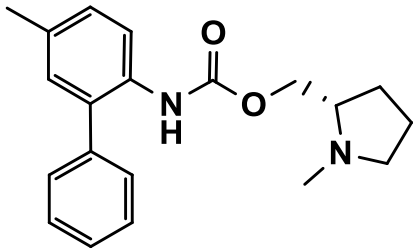
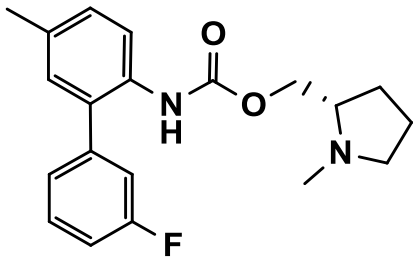
196	(3'-cloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-etilpirrolidin-3-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.87(s, 1H), 7.40-7.38(m, 1H), 7.25-7.21(m, 2H), 7.08-7.03(m, 1H), 6.90(dd, 1H, J=8.8, J=2.8), 6.50(s, 1H), 4.09-3.98(m, 2H), 2.72(t, 1H, J=8.8), 2.64-2.44(m, 5H), 2.36-2.33(m, 1H), 2.02-1.92(m, 1H), 1.55-1.47(m, 1H), 1.09(t, 3H, J=7.2)
197	[1,1'-bifenil]-2-ilcarbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.14-8.01(m, 1H), 7.51-7.29(m, 6H), 7.23-7.05(m, 2H), 6.75-6.60(bs, 1H), 4.24-4.00(m, 2H), 3.10-2.98(m, 1H) 2.53-2.29(m, 4H), 2.28-2.15(m, 1H), 1.97-1.52(m, 4H)

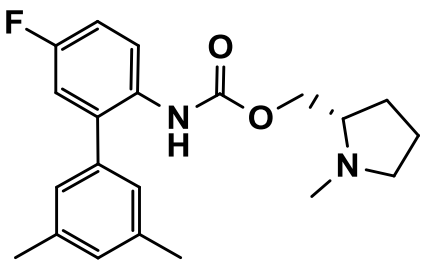
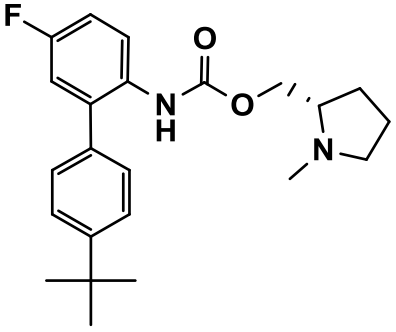
198	(4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.14-8.01(m, 1H), 7.51-7.29(m, 5H), 7.23-7.05(m, 2H), 6.75-6.60(bs, 1H), 4.24-4.00(m, 2H), 3.10-2.98(m, 1H) 2.53-2.29(m, 4H), 2.28-2.15(m, 1H), 1.97-1.52(m, 4H)
199	(3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.17-8.01(m, 1H), 7.41-7.27(m, 2H), 7.22-7.02(m, 5H), 6.76-6.63(bs, 1H), 4.22-4.00(m, 2H), 3.09-2.98(m, 1H) 2.52-2.30(m, 7H), 2.29-2.12(m, 1H), 1.97-1.80(m, 1H), 1.80-1.50(m, 3H)

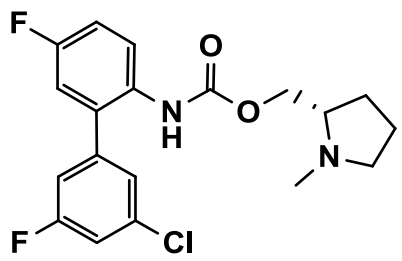
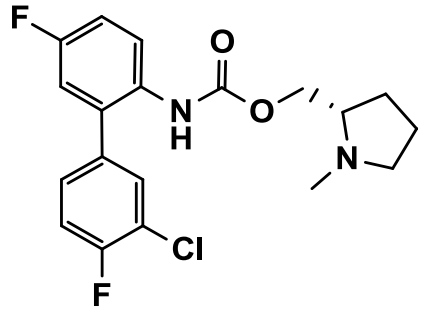
200	(5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.97(s, 1H), 7.45-7.37(m, 3H), 7.32-7.25(m, 3H), 7.05-7.00(m, 1H), 6.94-6.91(m, 1H), 6.59(s, 1H), 4.19-4.04(m, 2H), 3.06-3.04(m, 1H), 2.35(s, 3H), 2.28-2.18(m, 2H), 1.90-1.76(m, 2H), 1.61-1.57(m, 2H)
201	(5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.82(s, 1H), 7.30-7.11(m, 3H), 7.01-6.85(m, 3H), 4.30-4.07(m, 2H), 3.24-3.21(m, 1H), 2.43(s, 3H), 2.35(s, 3H), 1.96-1.84(m, 2H), 1.79-1.72(m, 2H), 1.67-1.51(m, 2H)

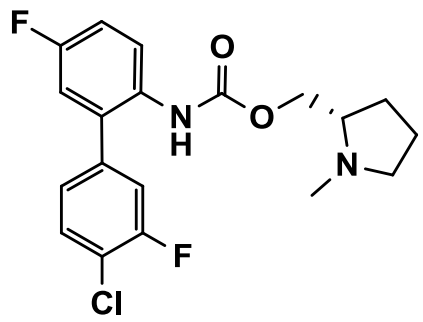
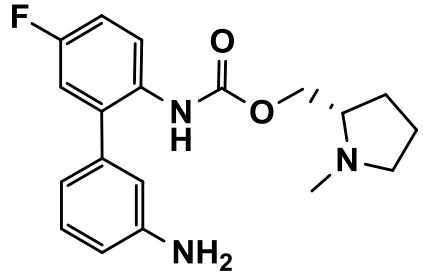
202	(3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.97(s, 1H), 7.43-7.39(m, 1H), 7.11-7.03(m, 4H), 6.91(d, 1H, J=8.4), 6.48(s, 1H), 4.19-4.04(m, 2H), 3.05-3.02(m, 1H), 2.35(s, 3H), 2.26-2.17(m, 2H), 1.88-1.83(m, 2H), 1.71-1.69(m, 2H)
203	(4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.97(s, 1H), 7.31-7.26(m, 1H), 7.22-7.12(m, 2H), 7.06-7.00(m, 2H), 6.91-6.88(m, 1H), 6.43(s, 1H), 4.21-4.03(m, 2H), 3.06-3.02(m, 1H), 2.35(s, 3H), 2.28-2.15(m, 2H), 1.95-1.83(m, 2H), 1.70-1.67(m, 2H)

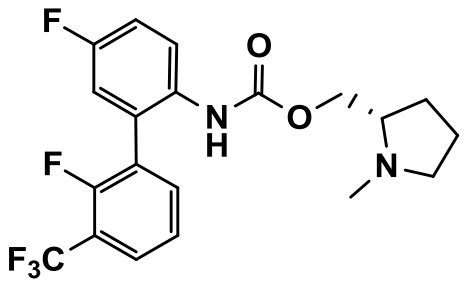
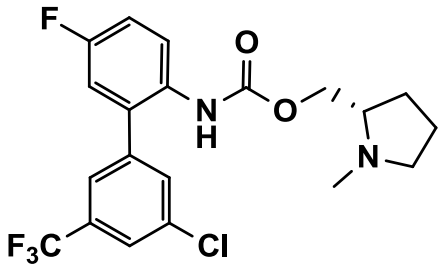
204	(4-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.96(s, 1H), 7.47-7.43(m, 2H), 7.40-7.36(m, 1H), 7.33-7.25(m, 2H), 7.18-7.10(m, 1H), 6.81-6.75(m, 2H), 4.18-4.05(m, 2H), 3.03-3.01(m, 1H), 2.35(s, 3H), 2.22-2.17(m, 2H), 1.93-1.86(m, 2H), 1.61-1.57(m, 2H)
205	(3',4-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.96(s, 1H), 7.45-7.39(m, 2H), 7.25-7.23(m, 1H), 7.16-7.07(m, 2H), 7.03-7.01(m, 1H), 6.83-6.78(m, 1H), 6.65(s, 1H), 4.19-4.06(m, 2H), 3.05-3.02(m, 1H), 2.36(s, 3H), 2.26-2.18(m, 2H), 1.93-1.84(m, 2H), 1.59-1.50(m, 2H)

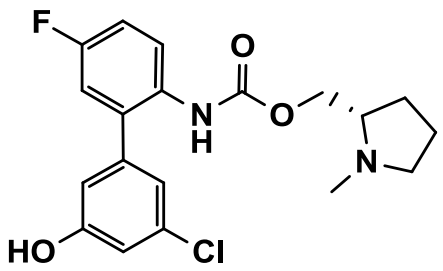
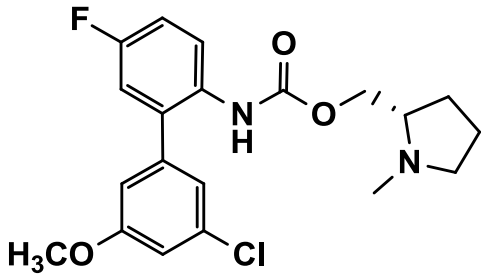
206	(5-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.92(s, 1H), 7.45-7.41(m, 2H), 7.33-7.25(m, 2H), 7.16-7.13(m, 1H), 7.02(s, 1H), 6.59(s, 1H), 4.21-4.05(m, 2H), 3.09-3.07(m, 1H), 2.38(s, 3H), 2.32(s, 3H), 2.27-2.23(m, 2H), 1.90-1.87(m, 2H), 1.78-1.72(m, 2H)
207	(3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.88(s, 1H), 7.42-7.36(m, 1H), 7.21-7.20(m, 1H), 7.17-7.15(m, 1H), 7.10-7.03(m, 2H), 7.00(m, 1H), 6.55(s, 1H), 4.22-4.06(m, 2H), 3.10-3.06(m, 1H), 2.38(s, 3H), 2.31(s, 3H), 2.27-2.21(m, 2H), 1.94-1.85(m, 2H), 1.78-1.69(m, 2H)

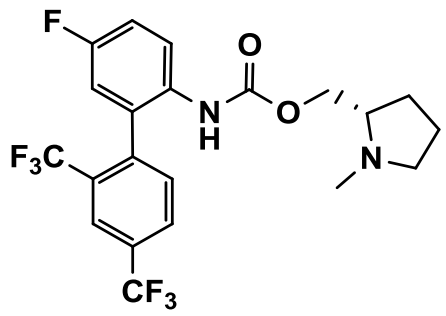
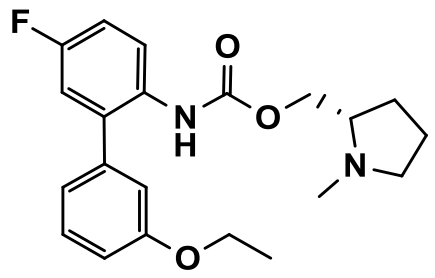
208	(5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.95(s, 1H), 7.15(m, 2H), 7.04-6.98(m, 2H), 6.93-6.90(m, 2H),, 6.72(s, 1H), 4.31-4.17(m, 2H), 3.14(m, 1H), 2.82(m, 1H), 2.61-2.03(m, 10H), 1.99-1.62(m, 4H)
209	(4'-(tert-butil)-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.83(s, 1H), 7.72-7.70(m, 2H), 7.67-7.62(m, 2H), 7.03-6.91(m, 2H), 6.76(s, 1H), 4.35-4.22(m, 2H), 3.20(m, 1H), 2.96(m, 1H), 2.68-2.65(m, 1H), 2.48(s, 3H), 1.99-1.63(m, 4H), 1.51-1.29(m, 9H)

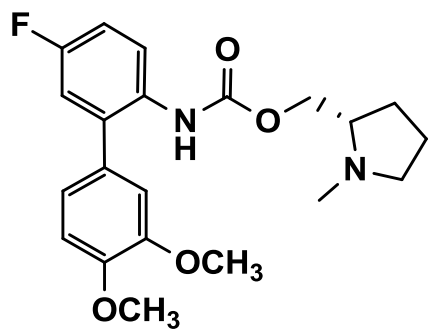
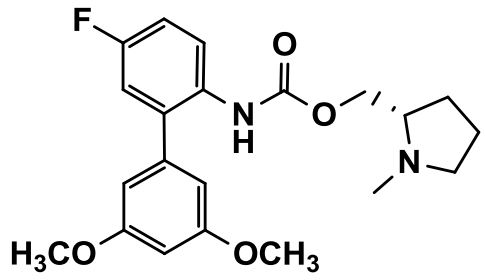
210	(3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.84(s, 1H), 7.24-7.15(m, 1H), 7.12-6.89(m, 4H), 6.64(s, 1H), 4.26-4.10(m, 2H), 3.16-3.15(m, 1H), 2.62(m, 1H), 2.42(s, 3H), 2.38-2.32(m, 1H), 1.99-1.60(m, 4H)
211	(3'-cloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.05(m, 1H), 7.57-7.48(m, 1H), 7.22-7.14(m, 2H), 7.12-7.00(m, 2H), 6.61(s, 1H), 4.23-4.16(m, 2H), 3.22-3.10(m, 1H), 2.58-2.47(m, 1H), 2.38(s, 3H), 2.35-2.30(m, 3H), 1.98-1.60(m, 4H)

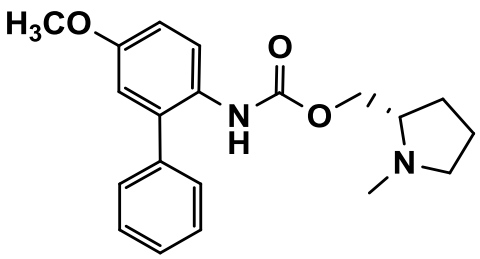
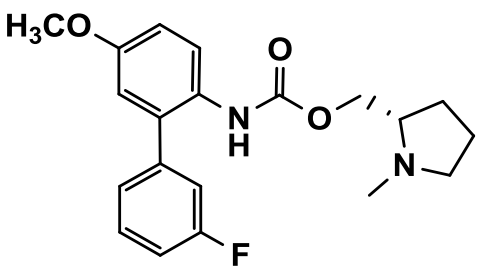
212	(4'-cloro-3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.39-7.31(m, 3H), 7.20-7.00(m, 2H), 6.98-6.88(d, 1H, J=2.8), 4.34-4.23(m, 2H), 3.45(m, 1H), 3.16(m, 1H), 2.57-2.54(m, 4H), 2.11-1.70(m, 4H).
213	(3'-amino-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.99(s, 1H), 7.23-7.19(m, 1H), 7.03-6.98(m, 1H), 6.93-6.90(m, 1H), 6.74(m, 1H), 6.70-6.66(m, 1H), 6.63(s, 1H), 4.24-4.07(m, 2H), 3.46(s, 1H), 3.14(m, 1H), 2.59(m, 1H), 2.42(s, 3H), 2.33-2.29(m, 1H), 1.98-1.63(m, 4H)

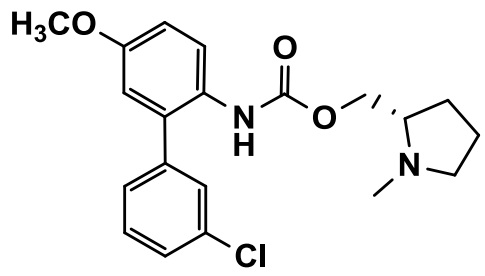
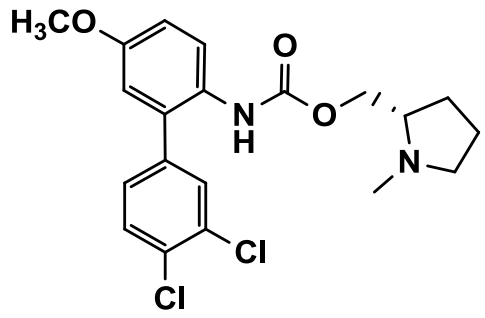
214	(2',5-difluoro-3'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.84(s, 1H), 7.69-7.66(m, 1H), 7.53-7.50(m, 1H), 7.37-7.33(m, 1H), 7.15-7.10(m, 1H), 6.98-6.95(m, 1H), 6.61(s, 1H), 4.29-4.15(m, 2H), 3.27(s, 1H), 2.78-2.70(m, 1H), 2.48-2.35(m, 4H), 1.98-1.70(m, 4H)
215	(3'-cloro-5-fluoro-5'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.96(s, 1H), 7.79(s, 1H), 7.61(s, 1H), 7.50-7.47(d, 1H, J=11.6), 7.11-7.06(m, 1H), 6.94-6.91(m, 1H), 6.58(s, 1H), 4.27-4.11(m, 2H), 3.22-3.17(m, 1H), 2.67-2.66(m, 1H), 2.42-2.32(m, 4H), 2.02-1.60(m, 4H)

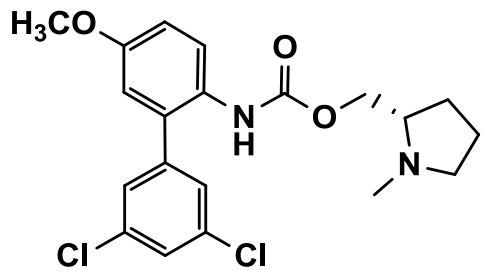
216	(3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.82(s, 1H), 7.02-6.64(m, 5H), 4.17-4.09(m, 2H), 3.10-3.06(m, 1H), 2.53(m, 1H), 2.37(s, 3H), 2.34-2.21(m, 1H), 1.96-1.62(m, 4H)
217	(3'-cloro-5-fluoro-5'-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.94(s, 1H), 7.66-7.44(m, 4H), 6.91-6.89(d, 1H, J=8.4), 6.62(s, 1H), 4.23-4.08(m, 2H), 3.86-3.85(m, 3H), 3.11(m, 1H), 2.53(m, 1H), 2.34(s, 3H), 2.29-2.28(m, 1H), 1.93-1.63(m, 4H)

218	(5-fluoro-2',4'-bis(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 8.11(m, 1H), 7.44-7.36(m, 1H), 7.20-7.17(m, 2H), 7.10-6.99(m, 2H), 6.54(s, 1H), 4.27-4.21(m, 2H), 3.31-3.15(m, 1H), 2.44-2.40(m, 1H), 2.39(s, 3H), 2.30-2.25(m, 3H), 2.01-1.55(m, 4H)
219	(3'-etoxi-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.58-7.53(m, 1H), 7.48-7.44(m, 2H), 7.29-7.15(m, 2H), 6.95-6.92(m, 1H), 6.84-6.79(m, 1H), 4.27-4.23(m, 2H), 4.14-4.07(q, 2H, J=6.8), 3.28(m, 1H), 2.89(m, 1H), 2.50(m, 4H), 1.98-1.59(m, 4H), 1.46-1.40(t, 3H, J=14.0)

220	(5-fluoro-3',4'-dimetoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.65-7.61(m, 1H), 7.54-7.52(m, 1H), 7.47-7.43(m, 2H), 7.33(m, 1H), 6.68-6.65(m, 1H), 4.29-4.15(m, 2H), 3.87(s, 6H), 3.28-3.25(m, 1H), 2.78-2.70(m, 1H), 2.48-2.35(m, 4H), 1.98-1.63(m, 4H)
221	(5-fluoro-3',5'-dimetoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.93(s, 1H), 7.03-6.91(m, 4H), 6.46-6.42(m, 1H), 6.38(s, 1H), 4.22-4.08(m, 2H), 3.77(s, 6H), 3.15(m, 1H), 2.61(m, 1H), 2.41(s, 3H), 2.36-2.24(m, 1H), 1.93-1.58(m, 4H)

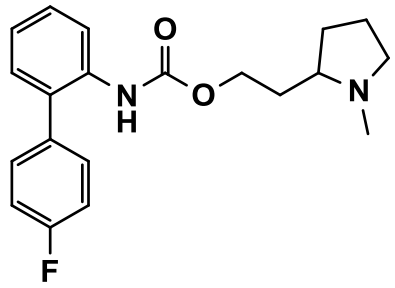
222	(5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.81(s, 1H), 7.43-7.28(m, 4H), 7.20-7.19(d, 1H, J=4.4), 6.87-6.86(dd, 1H, J=9.2), 6.76-6.75(d, 1H, J=2.8), 6.61(s, 1H), 4.20-4.06(m, 2H), 3.77(s, 3H), 3.13-3.10(m, 1H), 2.58-2.43(m, 1H), 2.38(s, 3H), 2.32-2.25(m, 1H), 1.92-1.56(m, 4H)
223	(3'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.74(s, 1H), 7.39-7.33(m, 1H), 7.10-7.01(m, 2H), 6.88-6.85(m, 1H), 6.73-6.72(m, 1H), 6.59(s, 1H), 4.17-4.03(m, 2H), 3.76(s, 3H), 3.76(m, 1H), 2.49(m, 1H), 2.36(s, 3H), 2.28-2.21(m, 1H), 1.99-1.56(m, 4H)

224	(3'-cloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.79(s, 1H), 7.37-7.33(m, 2H), 7.26-7.20(m, 2H), 6.91-6.88(m, 1H), 6.73-6.72(m, 1H), 6.38(s, 1H), 4.22-4.05(m, 2H), 3.79(s, 3H), 3.11-3.07(m, 1H), 2.50-2.38(m, 1H), 2.33(s, 3H), 2.29-2.22(m, 1H), 1.94-1.57(m, 4H)
225	(3',4'-dicloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.69(s, 1H), 7.48-7.43(m, 2H), 7.21-7.17(m, 1H), 6.90-6.87(m, 1H), 6.71-6.70(m, 1H), 6.51(s, 1H), 4.21-4.05(m, 2H), 3.78(s, 3H), 3.13(m, 1H), 2.52-2.45(m, 1H), 2.32(s, 3H), 2.30-2.22(m, 1H), 1.97-1.59(m, 4H)

226	(3',5'-dicloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo 	^{1}H NMR($CDCl_3$): δ 7.79(s, 1H), 7.64(m, 1H), 7.35-7.34(m, 1H), 7.23-7.22(m, 1H), 7.07-7.02(m, 1H), 6.90-6.87(m, 1H), 6.63(s, 1H), 4.26-4.05(m, 2H), 3.20-3.15(m, 1H), 2.66(m, 1H), 2.42-2.32(m, 4H), 1.99-1.61(m, 4H)

Ejemplo 1

Síntesis de (4'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-Metilpirrolidin-2-il)etilo



Ácido 4'-fluoro-[1,1'-bifenil]-2-carboxílico (747mg, 3.46mmol)(Ejemplo de la Síntesis 1) se disolvió en tolueno (20mL), y luego azida de bifenilfosforilo (958uL, 4.15mmol) y trietilamina (486uL, 3.46mmol) se agregaron al mismo. El mismo se agitó a temperatura ambiente por 30 minutos, y luego se agitó otra vez bajo reflujo por 1 hora. El reactivo se enfrió a temperatura ambiente. 2-(2-Hidroxietil)-1-

metilpirrolidina (558uL, 4.15mmol) se agregó al mismo y se agitó bajo reflujo por 12 horas. El reactivo se enfrió a temperatura ambiente. El solvente se removió al concentrarse bajo presión reducida, y luego el mismo se extrajo con agua y acetato de etilo. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (280mg, 24%).

Ejemplos 2-16

Los materiales de partida en la Tabla 7 se usaron en vez de ácido 4'-fluoro-[1,1'-bifenil]-2-carboxílico (747mg, 3.46mmol)(Ejemplo de Síntesis 1) para preparar los compuestos de los Ejemplos 2-16 de la misma manera que el Ejemplo 1.

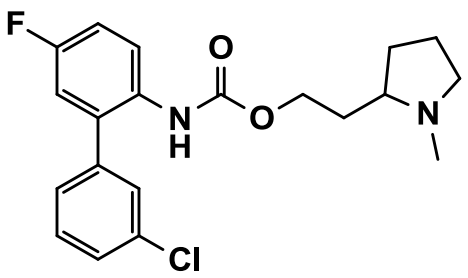
Tabla 7 Ejemplos 2-16

Ejemplo	Nombre Químico	Material de Partida
2	(3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-Metilpirrolidin-2-il)etilo (290mg, 23%)	ácido 3',5'-Difluoro-[1,1'-bifenil]-2-carboxílico (820mg) (Ejemplo de Síntesis 2)
3	(3',4',5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (300mg, 41%)	ácido 3',4',5'-trifluoro-[1,1'-bifenil]-2-carboxílico (492mg) (Ejemplo de Síntesis 3)

4	(3'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (326mg, 41%)	ácido 3'-fluoro-[1,1'-bifenil]-2-carboxílico (500mg) (Ejemplo de Síntesis 4)
5	(4'-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (350mg, 36%)	ácido 4'-metoxi-[1,1'-bifenil]-2-carboxílico (630mg) (Ejemplo de Síntesis 5)
6	[1,1'-bifenil]-2-ilcarbamato de 2-(1-metilpirrolidin-2-il)etilo (400mg, 50%)	Ácido [1,1'-Bifenil]-2-carboxílico (500mg)
7	(4'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (230mg, 30%)	ácido 4'-Cloro-[1,1'-bifenil]-2-carboxílico (500mg) (Ejemplo de Síntesis 6)
8	(3'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (170mg, 22%)	ácido 3'-Cloro-[1,1'-bifenil]-2-carboxílico (500mg) (Ejemplo de Síntesis 7)
9	(3',5'-dicloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (125mg, 28%)	ácido 3',5'-Dicloro-[1,1'-bifenil]-2-carboxílico (300mg) (Ejemplo de Síntesis 8)
10	(4'-trifluorometoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (370mg, 57%)	ácido 4'-Trifluorometoxi-[1,1'-bifenil]-2-carboxílico (450mg) (Ejemplo de Síntesis 9)

11	(4'-nitro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (410mg, 82%)	ácido 4'-Nitro-[1,1'-bifenil]-2-carboxílico (330mg) (Ejemplo de Síntesis 10)
12	(3'-trifluorometil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (476mg, 65%)	ácido 3'-trifluorometil-[1,1'-bifenil]-2-carboxílico (500mg) (Ejemplo de Síntesis 11)
13	(4'-trifluorometil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (45mg, 6%)	ácido 4'-trifluorometil-[1,1'-bifenil]-2-carboxílico (500mg) (Ejemplo de Síntesis 12)
14	((3'-fluoro-4'-metil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (306mg, 46%)	ácido 3'-Fluoro-4'-metil-[1,1'-bifenil]-2-carboxílico (430mg) (Ejemplo de Síntesis 13)
15	(3'-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (105mg, 16%)	ácido 3'-Metil-[1,1'-bifenil]-2-carboxílico (400mg) (Ejemplo de Síntesis 14)
16	(3'-etoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (250mg, 52%)	ácido 3'-Etoxi-[1,1'-bifenil]-2-carboxílico (315mg) (Ejemplo de Síntesis 15)

Ejemplo 17 Síntesis de (3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo



Ácido 3'-cloro-5-fluoro-[1,1'-bifenil]-2-carboxílico (300mg, 1.20mmol)(Ejemplo de Síntesis 16) se disolvió en tolueno (20mL), y luego azida de bifenilfosforilo (310uL, 1.44mmol) y trietilamina (202uL, 1.44mmol) se agregó al mismo. El mismo se agitó a temperatura ambiente por 30 minutos, y luego se agitó otra vez bajo reflujo por 1 hora. El reactivo se enfrió a temperatura ambiente. 2-(2-Hidroxietil)-1-metilpirrolidina (194uL, 1.44mmol) se agregó al mismo y luego se agitó bajo reflujo por 12 horas. El reactivo se enfrió a temperatura ambiente. El solvente se removió al concentrarse bajo presión reducida, y luego el mismo se extrajo con agua y acetato de etilo. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (93mg, 21%).

Ejemplos 18-27

Los materiales de partida en la Tabla 7 se usaron en vez

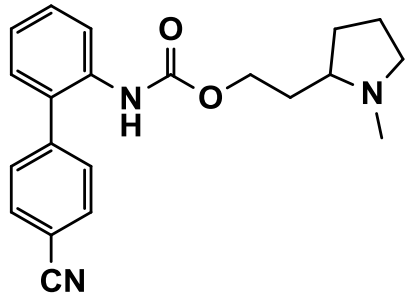
de ácido 3'-cloro-5-fluoro-[1,1'-bifenil]-2-carboxílico (300mg, 1.20mmol)(Ejemplo de Síntesis 16) para preparar los compuestos de los Ejemplos 18-27 de la misma manera que el Ejemplo 17.

Tabla 8 Ejemplos 18-27

Ejemplo	Nombre Químico	Material de Partida
18	(3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (465mg, 76%)	ácido 3',5-Difluoro-[1,1'-bifenil]-2-carboxílico (400mg, 1.71mmol) (Ejemplo de Síntesis 17)
19	(4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (184mg, 30%)	ácido 4',5-Difluoro-[1,1'-bifenil]-2-carboxílico (400mg, 1.71mmol) (Ejemplo de Síntesis 18)
20	(3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (362mg, 48%)	ácido 3',5,5'-Difluoro-[1,1'-bifenil]-2-carboxílico (500mg, 1.98mmol) (Ejemplo de Síntesis 19)
21	(5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (297mg, 19%)	ácido 5-Fluoro-[1,1'-bifenil]-2-carboxílico (1g, 4.63mmol) (Ejemplo de Síntesis 20)
22	(5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (152mg, 26%)	ácido 5-Fluoro-3'-metil-[1,1'-bifenil]-2-carboxílico (380mg, 1.65mmol) (Ejemplo de Síntesis 21)

23	(4-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (400mg, 51%)	ácido 4-Fluoro-[1,1'-bifenil]-2-carboxílico (500mg, 2.31mmol) (Ejemplo de Síntesis 22)
24	(3',4-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (84mg, 14%)	ácido 3',4-Difluoro-[1,1'-bifenil]-2-carboxílico (400mg, 1.71mmol) (Ejemplo de Síntesis 23)
25	(4-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (170mg, 34%)	ácido 4-Metoxi-[1,1'-bifenil]-2-carboxílico (320mg, 1.40mmol) (Ejemplo de Síntesis 24)
26	(5-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (123mg, 26%)	ácido 5-Metil-[1,1'-bifenil]-2-carboxílico (300mg, 1.41mmol) (Ejemplo de Síntesis 25)
27	(3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (279mg, 90%)	ácido 3'-Fluoro-5-metil-[1,1'-bifenil]-2-carboxílico (200mg, 0.87mmol) (Ejemplo de Síntesis 26)

Ejemplo 28 Síntesis de (4'-ciano-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo



(2-Yodofenil)carbamato de 2-(1-metilpirrolidin-2-il)etilo (600mg, 1.6mmol)(Ejemplo de Síntesis A) se disolvió en una solución mezclada de tolueno (20mL) y etanol (4mL). Ácido borónico de 4-cianofenilo (259mg, 1.76mmol), carbonato de potasio (442mg, 3.2mmol) y paladio de tetraquis trifenilfosfina (370mg, 0.32mmol) se agregaron al mismo. El reactivo se agitó a 110°C por 12 horas y se enfrió a temperatura ambiente. El mismo se filtró a través de Celite y el solvente se removió al concentrarse bajo presión reducida. El mismo se extrajo con agua y acetato de etilo, y luego la capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (193mg, 35%).

Ejemplos 29-32

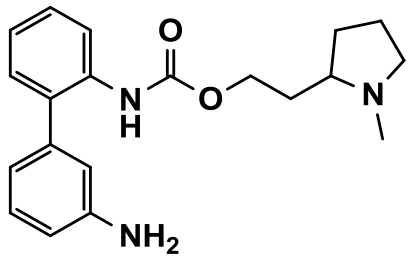
(2-Yodofenil)carbamato de 2-(1-metilpirrolidin-2-il)etilo del Ejemplo de la Síntesis A como un material de partida y los materiales de reacción en la Tabla 9 se usaron para preparar los compuestos de los Ejemplos 29-32 de la misma manera que el Ejemplo 28.

Tabla 9 Ejemplos 29-32

Ejemplo	Nombre Químico	Material de Partida (Ejemplo de Síntesis A)	Material de Reacción
29	(3'-(3-hidroxipropil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (52mg, 5%)	1g, 2.67mmol	ácido 3-(3-Hidroxipropil)fenil borónico (530mg, 2.94mmol)
30	(4'-(dimetilamino)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (71mg, 36%)	200mg, 0.53mmol	ácido 4-(Dimetilamino)fenil borónico (131mg, 0.80mmol)
31	(4'-(tert-butil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (33mg, 22%)	150mg, 0.40mmol	ácido 4-Tert-butilfenil borónico (110mg, 0.60mmol)
32	(2'-amino-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (37mg, 10%)	400mg, 1.07mmol	éster de pinacol de ácido 2-aminofenil borónico (353mg, 1.61mmol)

Ejemplo 33

Síntesis de (3'-amino-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo



(2-Yodofenil)carbamato de 2-(1-metilpirrolidin-2-il)etilo (1.36g, 3.63mmol)(Ejemplo de Síntesis A) se disolvió en una solución mezclada de acetonitrilo (15mL) y agua (15mL). Ácido 3-Aminofenil borónico (995mg, 7.26mmol), carbonato de sodio (772mg, 7.26mmol) y paladio de diclorobis trifenilfosfina (127mg, 0.18mmol) se agregaron al mismo. El reactivo se agitó a 110°C en un horno de microondas por 10 minutos y se enfrió a temperatura ambiente. El mismo se filtró a través de Celite y el solvente se removió al concentrarse bajo presión reducida. El mismo se extrajo con agua y acetato de etilo. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (192mg, 16%).

Ejemplos 34-41

(2-Yodofenil)carbamato de 2-(1-metilpirrolidin-2-il)etilo del Ejemplo de la Síntesis A como un material de

partida y los materiales de reacción en la Tabla 10 se usaron para preparar los compuestos de los Ejemplos 34-41 de la misma manera que el Ejemplo 33.

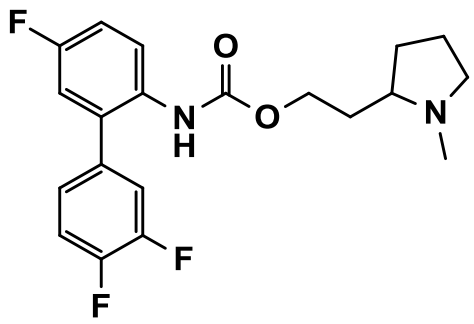
Tabla 10 Ejemplos 34-41

Ejemplo	Nombre Químico	Material de Partida (Ejemplo de Síntesis A)	Material de Reacción
34	(2'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (126mg, 30%)	400mg, 1.07mmol	ácido 2-Fluorofenil borónico (300mg, 2.14mmol)
35	(2'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (80mg, 18%)	400mg, 1.07mmol	ácido 2-Clorofenil borónico (335mg, 2.14mmol)
36	(2'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (65mg, 16%)	400mg, 1.07mmol	Éster de pinacol de ácido 2-Hidroxifenil borónico (471mg, 2.14mmol)
37	(3'-tert-butil-5'-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (155mg, 49%)	300mg, 0.80mmol	ácido (3-tert-Butil-5-metil)fenil borónico (307mg, 1.60mmol)

38	(4'-fluoro-3'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (66mg, 20%)	297mg, 0.79mmol	ácido (4-Fluoro-3-(trifluorometil) fenil)borónico (330mg, 1.58mmol)
39	(4'-amino-3'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (81mg, 27%)	300mg, 0.80mmol	Éster de pinacol de ácido (4-Amino-3-clorofenil) borónico (406mg, 1.6mmol)
40	(3'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (48mg, 9%)	300mg, 0.80mmol	ácido 3-Hidroxifenil borónico (221mg, 1.6mmol)
41	2-(1-Metilpirrolidin-2-il)etilo (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato (150mg, 43%)	300mg, 0.80mmol	ácido 3-Cloro-4-fluorofenil borónico (240mg, 1.38mmol)

Ejemplo 42

Síntesis de (3',4',5-trifluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo



(2-bromo-4-fluorofenil)carbamato de 2-(1-Metilpirrolidin-2-il)etilo (400mg, 1.16mmol)(Ejemplo de Síntesis B) se disolvió en tolueno (20mL). Ácido 3,4-Fluorofenil diborónico (280mg, 1.74mmol), carbonato de potasio (321mg, 2.32mmol) y paladio de tetraquis trifenilfosfina (140mg, 0.12mmol) se agregaron al mismo. El reactivo se agitó a 120°C por 12 horas y se enfrió a temperatura ambiente. El mismo se filtró a través de Celite y el solvente se removió al concentrarse bajo presión reducida. El mismo se extrajo con agua y acetato de etilo. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (15mg, 3%).

Ejemplos 43-46

(2-bromo-4-fluorofenil)carbamato de 2-(1-

Metilpirrolidin-2-il)etilo del Ejemplo de la Síntesis B como un material de partida y los materiales de reacción en la Tabla 11 se usaron para preparar los compuestos de los Ejemplos 43-46 de la misma manera que el Ejemplo 42.

Tabla 11 Ejemplos 43-46

Ejemplo	Nombre Químico	Material de Partida (Ejemplo de Síntesis B)	Material de Reacción
43	(3',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (24mg, 5%)	400mg, 1.16mmol	ácido 3,4-Diclorofenil borónico (332mg, 1.74mmol)
44	(3'-etil-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (40mg, 12%)	300mg, 0.87mmol	ácido 3-etilfenil borónico (200mg, 1.31mmol)
45	(5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (18mg, 4%)	400mg, 1.16mmol	ácido 3,5-Dimetilfenil borónico (261mg, 1.74mmol)
46	(3'-amino-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (50mg, 5%)	1g, 2.90mmol	ácido 3-Aminofenil borónico (600mg, 4.35mmol)

Ejemplos 47-51

(2-bromo-4-(trifluorometil)fenil)carbamato de 2-(1-Metilpirrolidin-2-il)etilo del Ejemplo de la Síntesis C como un material de partida en vez de (2-bromo-4-fluorofenil)carbamato de 2-(1-Metilpirrolidin-2-il)etilo del Ejemplo de la Síntesis B y los materiales de reacción en la Tabla 12 se usaron para preparar los compuestos de los Ejemplos 47-51 de la misma manera que el Ejemplo 42.

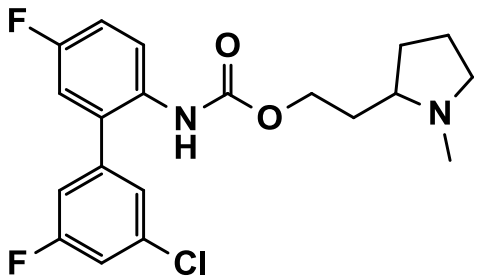
Tabla 12 Ejemplos 47-51

Ejemplo	Nombre Químico	Material de Partida (Ejemplo de Síntesis C)	Material de Reacción
47	(5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (26mg, 9%)	300mg, 0.76mmol	ácido Fenilborónico (102mg, 0.84mmol)
48	(4'-fluoro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (14mg, 4%)	300mg, 0.76mmol	ácido 4-Fluorofenilborónico (118mg, 0.84mmol)

49	(3'-fluoro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (19mg, 6%)	300mg, 0.76mmol	ácido 3-Fluorofenilborónico (118mg, 0.84mmol)
50	(3',5'-difluoro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (12mg, 4%)	260mg, 0.66mmol	ácido 3,5-Difluorofenilboróni co (115mg, 0.73mmol)
51	(3'-cloro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (14mg, 4%)	300mg, 0.76mmol	ácido 3-Clorofenilborónico (131mg, 0.84mmol)

Ejemplo 52

Síntesis de (3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo



(2-bromo-4-fluorofenil)carbamato de 2-(1-Metilpirrolidin-2-il)etilo (300mg, 0.87mmol)(Ejemplo de

Síntesis B) se disolvió en una solución mezclada de acetonitrilo (10mL) y agua (10mL). Ácido (3-Cloro-5-fluorofenil)borónico (303mg, 1.74mmol), carbonato de sodio (184mg, 1.74mmol) y paladio de diclorobis trifenilfosfina (31mg, 0.04mmol) se agregaron al mismo. El reactivo se agitó a 110°C en un horno de microondas por 10 minutos y se enfrió a temperatura ambiente. El mismo se filtró a través de Celite y el solvente se removió al concentrarse bajo presión reducida. El mismo se extrajo con agua y acetato de etilo. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (51mg, 15%).

Ejemplos 53-59

(2-bromo-4-fluorofenil)carbamato de 2-(1-Metilpirrolidin-2-il)etilo del Ejemplo de Síntesis B como un material de partida y los materiales de reacción en la Tabla 13 se usaron para preparar los compuestos de los Ejemplos 53-59 de la misma manera que el Ejemplo 52.

Tabla 13 Ejemplos 53-59

Ejemplo	Nombre Químico	Material de Partida (Ejemplo de Síntesis B)	Material de Reacción
53	(3'-cloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (81mg, 24%)	300mg, 0.87mmol	ácido (3-Cloro-4-fluorofenil)borónico (303mg, 1.74mmol)
54	(4'-cloro-3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (173mg, 38%)	400mg, 1.16mmol	ácido (3-Fluoro-4-clorofenil)borónico (405mg, 2.32mmol)
55	(3',5'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (71mg, 15%)	400mg, 1.16mmol	ácido 3,5-Diclorofenil borónico (443mg, 2.32mmol)

56	(3',5'-dicloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (99mg, 20%)	400mg, 1.16mmol	ácido 3,5-Dicloro-4-fluorofenil borónico (484mg, 2.32mmol)
57	(3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (97mg, 28%)	300mg, 0.87mmol	ácido (3-Cloro-5-hidroxifenil)borónico (300mg, 1.74mmol)
58	(3'-cloro-5-fluoro-4'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (176mg, 39%)	400mg, 1.16mmol	ácido (3-Cloro-4-hidroxifenil)borónico (400mg, 2.32mmol)
59	(5-fluoro-3',4'-dimetil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (129mg, 30%)	400mg, 1.16mmol	ácido (3,4-Dimetilfenil)borónico (348mg, 2.32mmol)

Ejemplos 60-65

(2-bromo-4-metoxifenil)carbamato de 2-(1-

Metilpirrolidin-2-il)etilo del Ejemplo de la Síntesis D en vez de (2-bromo-4-fluorofenil)carbamato de 2-(1-Metilpirrolidin-2-il)etilo del Ejemplo de la Síntesis B como un material de partida y los materiales de reacción en la Tabla 14 se usaron para preparar los compuestos de los Ejemplos 60-65 de la misma manera que el Ejemplo 52.

Tabla 14 Ejemplos 60-65

Ejemplo	Nombre Químico	Material de Partida (Ejemplo de Síntesis D)	Material de Reacción
60	(5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (25mg, 8%)	300mg, 0.84mmol	ácido Fenilborónico (154mg, 1.26mmol)
61	(3'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (112mg, 36%)	300mg, 0.84mmol	ácido 3-Fluorofenilborónico (176mg, 1.26mmol)
62	(3',5'-difluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (161mg, 37%)	400mg, 1.12mmol	ácido 3,5-Difluorofenil borónico (354mg, 2.24mmol)

63	(3'-cloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (112mg, 31%)	330mg, 0.92mmol	ácido 3-Clorofenilborónico (289mg, 1.85mmol)
64	(3',5'-dicloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (92mg, 19%)	400mg, 1.12mmol	ácido 3,5-Diclorofenil borónico (427mg, 2.24mmol)
65	(3'-cloro-4'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (155mg, 34%)	400mg, 1.12mmol	ácido (3-Cloro-4-fluoro)fenil borónico (390mg, 2.24mmol)

Ejemplos 66-73

(2-bromo-4-clorofenil)carbamato de 2-(1-Metilpirrolidin-2-il)etilo del Ejemplo de Síntesis E en vez de (2-bromo-4-fluorofenil)carbamato de 2-(1-Metilpirrolidin-2-il)etilo of Ejemplo de Síntesis B como un material de partida y los materiales de reacción en la Tabla 15 se usaron para preparar los compuestos de los Ejemplos 66-73 de la misma manera que el Ejemplo 52.

Tabla 15 Ejemplos 66-73

Ejemplo	Nombre Químico	Material de Partida (Ejemplo de Síntesis E)	Material de Reacción
66	(5-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (94mg, 24%)	400mg, 1.11mmol	ácido Fenilborónico (271mg, 2.22mmol)
67	(5-cloro-3'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (187mg, 45%)	400mg, 1.11mmol	ácido 3-Fluorofenil borónico (311mg, 2.22mmol)
68	(5-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (38mg, 9%)	400mg, 1.11mmol	ácido 4-Fluorofenil borónico (311mg, 2.22mmol)
69	(5-cloro-3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (162mg, 37%)	400mg, 1.11mmol	ácido 3,5-Difluorofenil borónico (351mg, 2.22mmol)
70	(3',5-dicloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (111mg, 25%)	400mg, 1.11mmol	ácido 3-Clorofenil borónico (347mg, 2.22mmol)

71	(3',5,5'-tricloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (58mg, 12%)	400mg, 1.11mmol	ácido 3,5-Diclorofenil borónico (424mg, 2.22mmol)
72	(3',5-dicloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (119mg, 26%)	400mg, 1.11mmol	ácido (3-Cloro-5-fluorofenil) borónico (387mg, 2.22mmol)
73	(3',5-dicloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (88mg, 19%)	400mg, 1.11mmol	ácido (3-Cloro-4-fluorofenil) borónico (387mg, 2.22mmol)

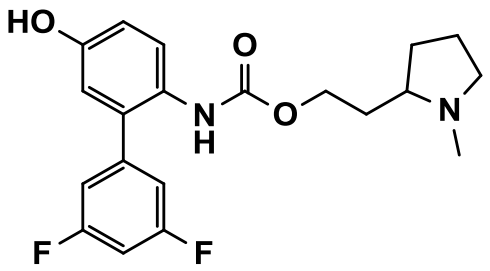
Ejemplo 74

Síntesis de (3'-fluoro-4'-formil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo

(2-bromofenil)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (220mg, 0.70mmol)(Ejemplo de Síntesis F) y ácido 3-fluoro-4-formilfenilborónico (237mg, 1.41mmol) se usaron como materiales de partida para preparar el compuesto del título (124mg, 50%) de la misma manera que el Ejemplo 52.

Ejemplo 75

Síntesis de (3',5'-difluoro-5-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo



(3',5'-difluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (130mg, 0.33mmol)(Ejemplo 62) se disolvió en diclorometano (10mL). Una solución de tricloruro de boro (1.0M diclorometano, 0.99ml, 0.99mmol) se agregó al mismo y se agitó a temperatura ambiente por 2 horas. Después de que la reacción se terminó, el reactivo se extrajo con agua y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (68mg, 55%).

Ejemplo 76

Síntesis de (3',5'-dicloro-5-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo

(3',5'-dicloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (90mg, 0.21mmol)(Ejemplo 64) se usó en vez de Ejemplo 62 para preparar el compuesto del título (10mg, 12%) de la misma manera que el Ejemplo 75.

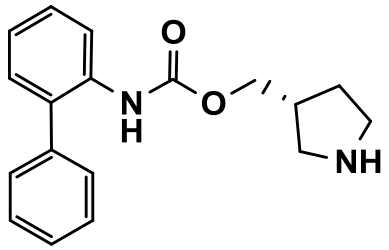
Ejemplo 77

Síntesis dw (3'-cloro-4'-fluoro-5-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo

(3'-cloro-4'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (140mg, 0.34mmol)(Ejemplo 65) se usó en vez de Ejemplo 62 para preparar el compuesto del título (130mg, 96%) de la misma manera que el Ejemplo 75.

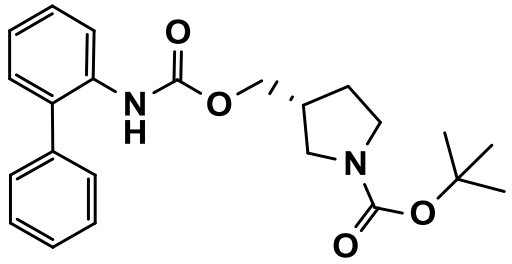
Ejemplo 78

Síntesis de [1,1'-bifenil]-2-ilcarbamato de (R)-pirrolidin-3-ilmetilo



Etapa 1

3-((([1,1'-bifenil]-2-ilcarbamoil)oxi)metil)pirrolidin-1-carboxilato de (R)-tert-butilo



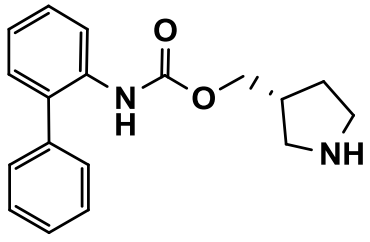
Ácido [1,1'-Bifenil]-2-carboxílico (2g, 10.09mmol) se disolvió en tolueno (50mL), y luego azida de bifenilfosforilo

(2.61mL, 12.11mmol) y trietilamina (1.42mL, 10.09mmol) se agregaron al mismo. El mismo se agitó a temperatura ambiente por 30 minutos y luego se agitó otra vez bajo reflujo por 1 hora. El reactivo se enfrió a temperatura ambiente. 3-(hidroximetil)pirrolidin-1-carboxilato de (R)-tert-butilo (2.44g, 12.11mmol) se agregó al mismo y se agitó bajo reflujo por 12 horas. El reactivo se enfrió a temperatura ambiente. El solvente se removió al concentrarse bajo presión reducida, y luego el mismo se extrajo con agua y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (3g, 75%).

^{1}H NMR($CDCl_3$): δ 8.15-7.97(bs, 1H), 7.55-7.26(m, 6H), 7.26-7.05(m, 2H), 6.67-6.52(bs, 1H), 4.19-3.90(m, 2H), 3.57-3.18(m, 2H), 3.13-2.73(bs, 1H), 2.57-2.38(m, 1H), 2.00-1.83(m, 1H), 1.70-1.53(m, 2H) 1.43(s, 9H)

Etapa 2

Síntesis de [1,1'-bifenil]-2-ilcarbamato de (R)-pirrolidin-3-ilmetilo



3-((([1,1'-bifenil]-2-ilcarbamoil)oxi)metil)pirrolidin-1-carboxilato de (R)-tert-butilo (3g, 7.57mmol) se disolvió en diclorometano (80mL). Ácido trifluoroacético (40mL) se agregó al mismo y se agitó a temperatura ambiente por 2 horas. El solvente se removió al concentrar el reactivo bajo presión reducida y el mismo se extrajo con solución de hidróxido de sodio 2N y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (1.73g, 77%).

Ejemplos 79-88

Los materiales de partida y los materiales de reacción en la Tabla 16 se usaron para preparar los compuestos de los Ejemplos 79-88 de la misma manera que el Ejemplo 78.

Tabla 16 Ejemplos 79-88

Ejemplo	Nombre Químico	Material de Partida	Material de Reacción
79	[1,1'-bifenil]-2-ilcarbamato de (S)-pirrolidin-3-ilmetilo (1.53g, 51%)	ácido [1,1'-Bifenil]-2-carboxílico (2g, 10.09mmol)	3-(hidroximetil) pirrolidin-1-carboxilato de (S)-tert-butilo (2.44g, 12.11mmol)

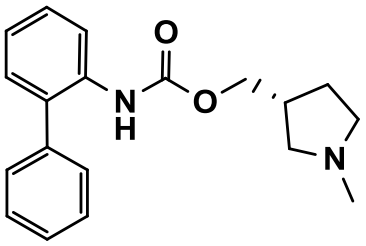
80	(3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo (435mg, 63%)	ácido 3',5'-Difluoro-[1,1'-bifenil]-2-carboxílico (500mg, 2.13mmol) (Ejemplo de Síntesis 2)	3-(hidroximetil) pirrolidin-1-carboxilato de (R)-tert-butilo (516mg, 2.56mmol)
81	(3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo (416mg, 59%)	ácido 3',5'-Difluoro-[1,1'-bifenil]-2-carboxílico (500mg, 2.13mmol) (Ejemplo de Síntesis 2)	3-(hidroximetil) pirrolidin-1-carboxilato de (S)-tert-butilo (516mg, 2.56mmol)
82	(5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo (712mg, 51%)	ácido 5-Fluoro-[1,1'-bifenil]-2-carboxílico (1g, 4.63mmol) (Ejemplo de Síntesis 20)	3-(hidroximetil) pirrolidin-1-carboxilato de (S)-tert-butilo (1,12g, 5.56mmol)

83	(5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo (260mg, 18%)	ácido 5-Fluoro-3'-metil-[1,1'-bifenil]-2-carboxílico (1g, 4.34mmol) (Ejemplo de Síntesis 21)	3-(hidroximetil) pirrolidin-1-carboxilato de (S)-tert-butilo (1,05g, 5.21mmol)
84	(3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo (470mg, 67%)	ácido 3',5,5'-Trifluoro-[1,1'-bifenil]-2-carboxílico (500mg, 1.98mmol) (Ejemplo de Síntesis 19)	3-(hidroximetil) pirrolidin-1-carboxilato de (R)-tert-butilo (479mg, 2.38mmol)
85	(3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo (400mg, 58%)	ácido 3',5,5'-Trifluoro-[1,1'-bifenil]-2-carboxílico (500mg, 1.98mmol) (Ejemplo de Síntesis 19)	3-(hidroximetil) pirrolidin-1-carboxilato de (S)-tert-butilo (479mg, 2.38mmol)

86	(5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo (222mg, 25%)	ácido 5-Metil-[1,1'-bifenil]-2-carboxílico (600mg, 2.83mmol) (Ejemplo de Síntesis 25)	3-(hidroximetil) pirrolidin-1-carboxilato de (R)-tert-butilo (684mg, 3.40mmol)
87	(3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo (346mg, 61%)	ácido 3'-Fluoro-5-metil-[1,1'-bifenil]-2-carboxílico (400mg, 1.74mmol) (Ejemplo de Síntesis 26)	3-(hidroximetil) pirrolidin-1-carboxilato de (R)-tert-butilo (420mg, 2.09mmol)
88	(4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-2-ilmetilo (915mg, 84%)	ácido 4'-Fluoro-[1,1'-bifenil]-2-carboxílico (750mg, 3.47mmol) (Ejemplo de Síntesis 1)	2-(hidroximetil) pirrolidin-1-carboxilato de (S)-tert-butilo (837mg, 4.16mmol)

Ejemplo 89

Síntesis de [1,1'-bifenil]-2-ilcarbamato de (R)-(1-metilpirrolidin-3-il)metilo



[1,1'-bifenil]-2-ilcarbamato de (R)-pirrolidin-3-ilmetilo (727mg, 2.45mmol)(Ejemplo 78) se disolvió en agua (50mL). Ácido acético (1mL), solución de formaldehido (3mL) y polvo de zinc (300mg) se agregaron secuencialmente al mismo y se agitó a temperatura ambiente por 12 horas. El reactivo se filtró, se neutralizó con hidróxido de sodio 2N y se extrajo con agua y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (209mg, 28%).

Ejemplos 90-99

Los materiales de partida en la Tabla 17 se usaron en vez de [1,1'-bifenil]-2-ilcarbamato de (R)-pirrolidin-3-ilmetilo para preparar los compuestos de los Ejemplos 90-99 de la misma manera que el Ejemplo 89.

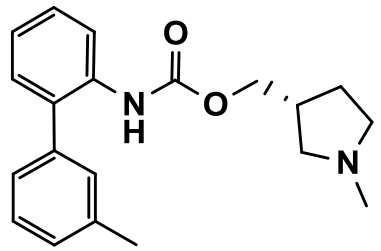
Tabla 17 Ejemplos 90-99

Ejemplo	Nombre Químico	Material de Partida
90	[1,1'-bifenil]-2-ilcarbamato de (S)-(1-metilpirrolidin-3-il)metilo (285mg, 52%)	[1,1'-bifenil]-2-ilcarbamato de (S)-pirrolidin-3-ilmetilo (523mg, 1.76mmol) (Ejemplo 79)
91	(3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (138mg, 33%)	(3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo (400mg, 1.2mmol) (Ejemplo 80)
92	(3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo (78mg, 19%)	(3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo (377mg, 1.13mmol) (Ejemplo 81)
93	(5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo (230mg, 67%)	(5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo (330mg, 1.05mmol) (Ejemplo 82)
94	(5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo (24mg, 9%)	(5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo (260mg, 0.79mmol) (Ejemplo 83)

95	(3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (58mg, 14%)	(3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo (400mg, 1.14mmol) (Ejemplo 84)
96	(3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo (144mg, 35%)	(3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo (400mg, 1.14mmol) (Ejemplo 85)
97	(5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (24mg, 16%)	(5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo (145mg, 0.47mmol) (Ejemplo 86)
98	(3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (15mg, 5%)	(3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo (320mg, 0.97mmol) (Ejemplo 87)
99	(4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (87mg, 10%)	(4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-2-ilmetilo (850mg, 2.70mmol) (Ejemplo 88)

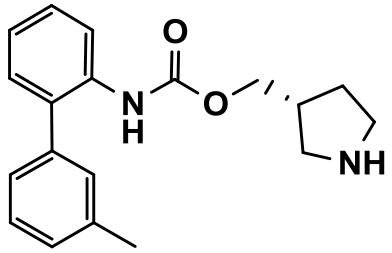
Ejemplo 100

Síntesis de (3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo



Etapa 1

Síntesis de (3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo

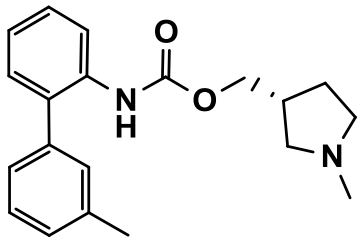


Ácido 3'-Metil-[1,1'-bifenil]-2-carboxílico (Ejemplo de Síntesis 14) y 3-(hidroximetil)pirrolidin-1-carboxilato de (R)-tert-butilo se usaron como materiales de partida para preparar el compuesto del título de la misma manera que el Ejemplo 78.

^{1}H NMR($CDCl_3$): δ 8.13-7.97(bs, 1H), 7.41-7.28(m, 2H), 7.26-7.02(m, 5H), 6.77-6.62(bs, 1H), 4.13-3.92(m, 2H), 3.09-2.82(m, 3H), 2.72-2.49(m, 2H), 2.47-2.30(m, 4H), 1.97-1.81(m, 1H), 1.50-1.36(m, 1H)

Etapa 2

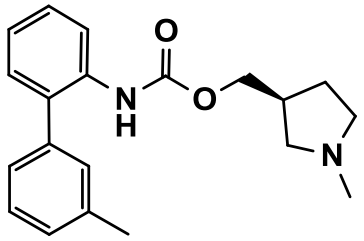
Síntesis de (3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo



(3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo (600mg, 1.93mmol) se preparó en la Etapa 1 se usó para preparar el título del compuesto (30mg, 5%) de la misma manera que el Ejemplo 89.

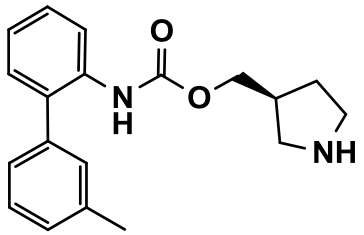
Ejemplo 101

Síntesis de (3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo



Etapa 1

Síntesis de (3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo

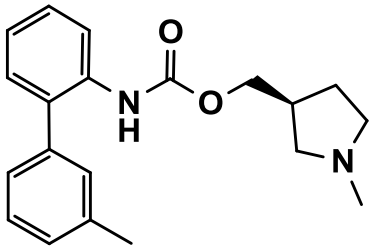


Ácido 3'-Metil-[1,1'-bifenil]-2-carboxílico (Ejemplo de Síntesis 14) y 3-(hidroximetil)pirrolidin-1-carboxilato de (S)-tert-butilo se usaron como materiales de partida para preparar el compuesto del título de la misma manera que el Ejemplo 78.

^{1}H NMR($CDCl_3$): δ 8.15-7.99(bs, 1H), 7.45-7.29(m, 2H), 7,27-7.06(m, 5H), 6.74-6.59(bs, 1H), 4.15-3.92(m, 2H), 3.07-2.79(m, 4H), 2.69-2.57(m, 1H), 2.39(s, 3H), 2.07-1.92(bs, 1H) 1.92-1.79(m, 1H), 1.48-1.33(m, 1H)

Etapa 2

Síntesis de (3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo

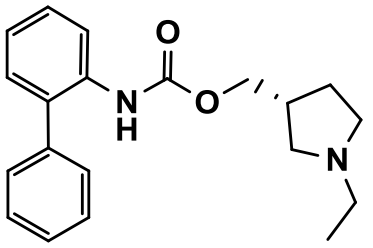


(3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-

pirrolidin-3-ilmetilo (900mg, 2.90mmol) preparado en la Etapa 1 se usó para preparar el compuesto del título (208mg, 22%) de la misma manera que el Ejemplo 89.

Ejemplo 102

Síntesis de [1,1'-bifenil]-2-ilcarbamato de (R)-(1-etilpirrolidin-3-il)metilo



[1,1'-bifenil]-2-ilcarbamato de (R)-pirrolidin-3-ilmetilo (1g, 3.37mmol)(Ejemplo 78) se disolvió es dimetilformamida (20mL). Carbamato de potasio (652mg, 4.72mmol), yoduro de potasio (112mg, 0.67mmol), trietilamina (1.42mL, 10.11mmol) y yodoetano (323uL, 4.04mmol) se agregaron secuencialmente al mismo y se agitó a 120°C por 12 horas. El reactivo se enfrió a temperatura ambiente y se extrajo con agua y acetato de etilo. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (142mg, 13%).

Ejemplos 103-105

Los materiales de partida en la Tabla 18 se usaron en

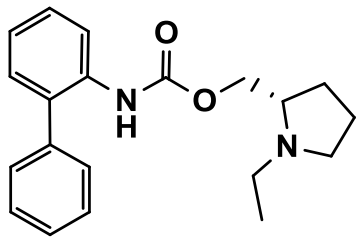
vez de [1,1'-bifenil]-2-ilcarbamato de (R)-pirrolidin-3-ilmetilo para preparar los compuestos de los Ejemplos 103-105 de la misma manera que el Ejemplo 102.

Tabla 18 Ejemplos 103-105

Ejemplo	Nombre Químico	Material de Partida
103	[1,1'-bifenil]-2-ilcarbamato de (S)-(1-etilpirrolidin-3-il)metilo (89mg, 8%)	[1,1'-bifenil]-2-ilcarbamato de (S)-pirrolidin-3-ilmetilo (1g, 3.37mmol) (Ejemplo 79)
104	(3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-etilpirrolidin-3-il)metilo (109mg, 16%)	(3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo (623mg, 2.01mmol) (Ejemplo 100, Etapa 1)
105	(3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-etilpirrolidin-3-il)metilo (40mg, 6%)	(3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo (600mg, 1.93mmol) (Ejemplo 101, Etapa 1)

Ejemplo 106

Síntesis de [1,1'-bifenil]-2-ilcarbamato de (S)-(1-etilpirrolidin-2-il)metilo

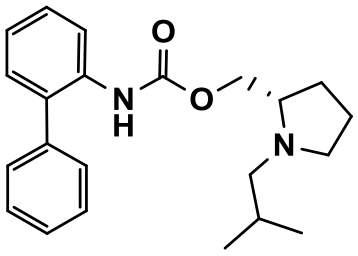


[1,1'-bifenil]-2-ilcarbamato de (S)-pirrolidin-2-

ilmetilo (1g, 3.37mmol) y 2-yodoetano (323uL, 4.04mmol) se usaron como materiales de partida para preparar el compuesto del título (385mg, 35%) de la misma manera que el Ejemplo 102.

Ejemplo 107

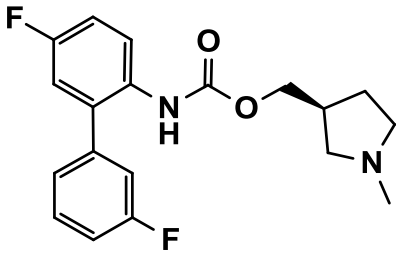
Síntesis de [1,1'-bifenil]-2-ilcarbamato de (S)-(1-isobutilpirrolidin-2-il)metilo



[1,1'-bifenil]-2-ilcarbamato de (S)-pirrolidin-2-ilmetilo (940mg, 3.17mmol) y 1-yodo-2-metilpropano (438uL, 3.08mmol) se usaron como materiales de partida para preparar el compuesto del título (47mg, 4%) de la misma manera que el Ejemplo 102.

Ejemplo 108

Síntesis de (3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo

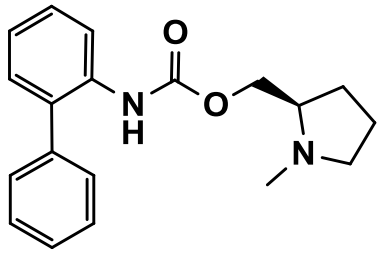


Ácido 3',5-Difluoro-[1,1'-bifenil]-2-carboxílico (800mg,

3.42mmol) (Ejemplo de Síntesis 17) y 3-(hidroximetil)pirrolidin-1-carboxilato de (S)-tert-butilo (825mg, 4.10mmol) se usaron como materiales de partida para preparar el compuesto del título (50mg, 5%) de la misma manera que el Ejemplo 78 y Ejemplo 89.

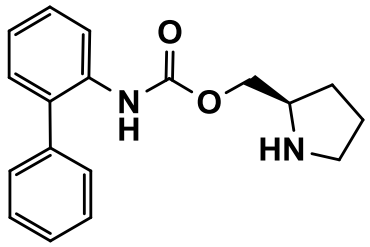
Ejemplo 109

Síntesis de [1,1'-bifenil]-2-ilcarbamato de (R)-(1-metilpirrolidin-2-il)metilo



Etapa 1

Síntesis de [1,1'-bifenil]-2-ilcarbamato de (R)-pirrolidin-2-ilmetilo

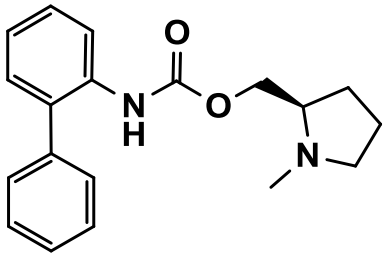


Ácido [1,1'-Bifenil]-2-carboxílico (821mg, 4.14mmol) y 2-(hidroximetil)pirrolidin-1-carboxilato de (R)-tert-butilo (1g, 4.97mmol) se usaron como materiales de partida para preparar el compuesto del título (730mg, 60%) de la misma manera que el Ejemplo 78.

^{1}H NMR ($CDCl_3$): δ 8.09-8.08(m, 1H), 7.49-7.47(m, 1H), 7.29-7.26(m, 1H), 7.17(m, 1H), 6.92-6.89(m, 1H), 4.15-4.04(m, 2H), 3.12-3.08(m, 1H), 2.99-2.94(m, 2H), 2.74-2.72(m, 1H), 2.51-2.44(m, 1H), 1.98-1.89(m, 1H), 1.51-1.44(m, 1H)

Etapa 2

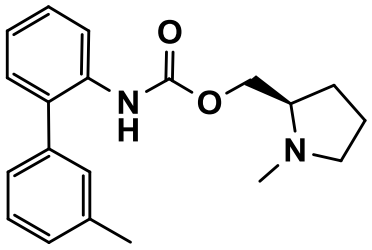
Síntesis de [1,1'-bifenil]-2-ilcarbamato de (R)-(1-metilpirrolidin-2-il)metilo



[1,1'-bifenil]-2-ilcarbamato de (R)-pirrolidin-2-ilmetilo (730mg, 2.46mmol) se usó como un material de partida para preparar el compuesto del título (183mg, 24%) de la misma manera que el Ejemplo 89.

Ejemplo 110

Síntesis de (3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-2-il)metilo

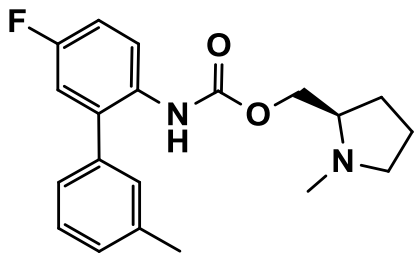


Ácido 3'-Metil-[1,1'-bifenil]-2-carboxílico (700mg, 3.3mmol)(Ejemplo de Síntesis 14) y 2-

(hidroximetil)pirrolidin-1-carboxilato de (R)-tert-butilo (797mg, 3.96mmol) se usaron como materiales de partida para preparar el compuesto del título (258mg, 24%) de la misma manera que el Ejemplo 78 y Ejemplo 89.

Ejemplo 111

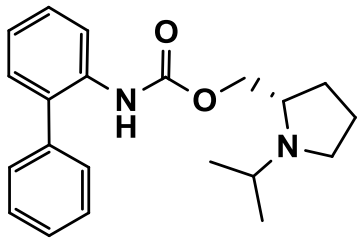
Síntesis de (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-2-il)metilo



Ácido 5-Fluoro-3'-metil-[1,1'-bifenil]-2-carboxílico (1g, 4.34mmol)(Ejemplo de Síntesis 21) y 2-(hidroximetil)pirrolidin-1-carboxilato de (R)-tert-butilo (1.05g, 5.21mmol) se usaron como materiales de partida para preparar el compuesto del título (52mg, 4%) de la misma manera que el Ejemplo 78 y Ejemplo 89.

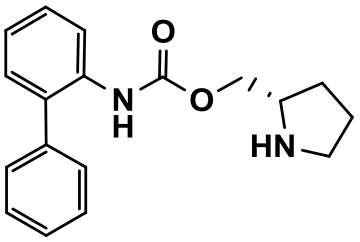
Ejemplo 112

Síntesis de [1,1'-bifenil]-2-ilcarbamato de (S)-(1-isopropilpirrolidin-2-il)metilo



Etapa 1

Síntesis de [1,1'-bifenil]-2-ilcarbamato de (S)-pirrolidin-2-ilmetilo

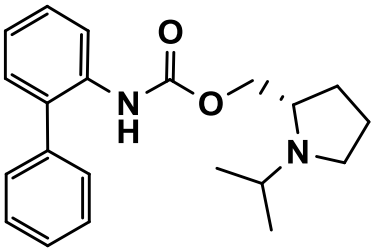


Ácido [1,1'-Bifenil]-2-carboxílico (2.5g, 12.61mmol) y 2-(hidroximetil)pirrolidin-1-carboxilato de (S)-tert-butilo (3.05g, 15.14mmol) se usaron como materiales de partida para preparar el compuesto del título (3.06g, 82%) de la misma manera que el Ejemplo 78.

^{1}H NMR ($CDCl_3$) δ 7.88(m, 1H), 7.48-7.42(m, 1H), 7.15-7.05(m, 4H), 7.04-6.92(m, 1H), 6.40(s, 1H), 4.78-4.76(m, 1H), 3.23-3.21(m, 1H), 2.87-2.73(m, 4H), 2.06-2.05(m, 3H), 2.04-1.67(m, 1H), 1.66-1.54(m, 1H), 1.53-1.35(m, 1H)

Etapa 2

Síntesis de [1,1'-bifenil]-2-ilcarbamato de (S)-(1-isopropilpirrolidin-2-il)metilo

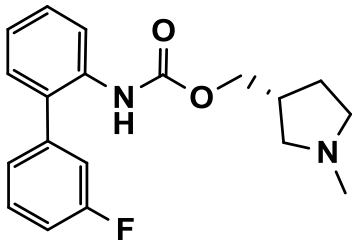


[1,1'-bifenil]-2-ilcarbamato de (S)-pirrolidin-2-

ilmetilo (1g, 3.37mmol) y 2-yodopropilo (404uL, 4.04mmol) se usaron como materiales de partida para preparar el compuesto del título (78mg, 7%) de la misma manera que el Ejemplo 102.

Ejemplo 113

Síntesis de (3'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo



(2-bromofenil)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (230mg, 0.73mmol)(Ejemplo de Síntesis F) se disolvió en una solución mezclada de etanol (5mL) y agua (5mL). Ácido 3-Fluorofenilborónico (123mg, 0.88mmol), carbonato de potasio (203mg, 1.47mmol), di(acetato)diciclohexilfenilfosfina paladio(II) y Polymer-bound FibreCat™ (30mg) se agregaron al mismo. El reactivo se agitó a 110°C por 12 horas y luego se enfrió a temperatura ambiente. El mismo se filtró a través de Celite y el solvente se removió al concentrarse bajo presión reducida. El mismo se extrajo con agua y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del

título (60mg, 25%).

Ejemplos 114-115

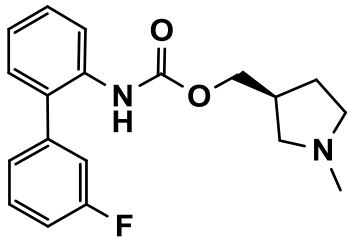
Los materiales de reacción en la Tabla 19 se usó en vez de ácido 3-fluorofenilborónico para preparar los compuestos de los Ejemplos 114-115.

Tabla 19 Ejemplo 114-115

Ejemplo	Nombre Químico	Material de Partida (Ejemplo de Síntesis F)	Material de Reacción
114	(4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (58mg, 24%)	230mg, 0.73mmol	ácido 4-Fluorofenilborónico (123mg, 0.88mmol)
115	(3',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (132mg, 55%)	220mg, 0.70mmol	ácido 3,4-Difluorofenil borónico (222mg, 1.40mmol)

Ejemplos 116

Síntesis de (3'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo



(2-bromofenil)carbamato de (S)-(1-metilpirrolidin-3-il)metilo (200mg, 0.64mmol)(Ejemplo de Síntesis G) se disolvió en tolueno (10mL). Ácido 3-Fluorofenilborónico (179mg, 1.28mmol), carbonato de potasio (177mg, 1.28mmol) y paladio de tetraquis trifenilfosfina (74mg, 0.064mmol) se agregaron al mismo. El reactivo se agitó a 110°C por 12 horas y se enfrió a temperatura ambiente. El mismo se filtró a través de Celite y el solvente se removió al concentrarse bajo presión reducida. El mismo se extrajo con agua y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (102mg, 49%).

Ejemplos 117-129

Los materiales de partida y los materiales de reacción en la Tabla 20 se usaron para preparar los compuestos de los Ejemplos 117-129 de la misma manera que el Ejemplo 116.

Tabla 20 Ejemplos 117-129

Ejemplo	Nombre Químico	Material de Partida	Material de Reacción
117	(3'-cloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (160mg, 63%)	(2-bromofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (230mg, 0.73mmol) (Ejemplo de Síntesis F)	ácido 3-Clorofenil borónico (138mg, 0.88mmol)
118	(3'-cloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo (130mg, 39%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-3-il)metilo (305mg, 0.97mmol) (Ejemplo de Síntesis G)	ácido 3-Clorofenil borónico (305mg, 1.95mmol)
119	(3',5'-dicloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo (170mg, 51%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-3-il)metilo (274mg, 0.88mmol) (Ejemplo de Síntesis G)	ácido 3,5-Diclorofenil borónico (334mg, 1.75mmol)

120	(3'-cloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo (66mg, 18%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-3-il)metilo (312mg, 1.00mmol) (Ejemplo de Síntesis G)	ácido 3-Cloro-5-fluorofenil borónico (348mg, 1.99mmol)
121	(3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo (107mg, 47%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-3-il)metilo (200mg, 0.63mmol) (Ejemplo de Síntesis G)	ácido (3-Cloro-4-fluoro)fenil borónico (223mg, 1.28mmol)
122	(5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo (160mg, 73%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-3-il)metilo (190mg, 0.57mmol) (Ejemplo de Síntesis I)	ácido 3,5-Dimetilfenil borónico (172mg, 1.15mmol)

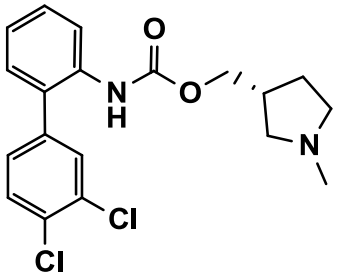
123	(3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo (150mg, 64%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-3-il)metilo (205mg, 0.62mmol) (Ejemplo de Síntesis I)	ácido (3-Cloro-5-hidroxifenil) borónico (213mg, 1.24mmol)
124	(4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo (78mg, 33%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-3-il)metilo (225mg, 0.68mmol) (Ejemplo de Síntesis I)	ácido 4-Fluorofenil borónico (114mg, 0.82mmol)
125	(3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo (153mg, 64%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-3-il)metilo (220mg, 0.66mmol) (Ejemplo de Síntesis I)	ácido 3-Clorofenil borónico (125mg, 0.80mmol)

126	(3',5'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo (74mg, 22%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-3-il)metilo (280mg, 0.85mmol) (Ejemplo de Síntesis I)	ácido 3,5-Diclorofenil borónico (460mg, 1.69mmol)
127	(4'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo (37mg, 17%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-3-il)metilo (195mg, 0.59mmol) (Ejemplo de Síntesis I)	ácido 4-Clorofenil borónico (111mg, 0.71mmol)
128	(3',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo (50mg, 19%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-3-il)metilo (220mg, 0.66mmol) (Ejemplo de Síntesis I)	ácido 3,4-Diclorofenil borónico (152mg, 0.80mmol)

129	(3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo (130mg, 54%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-3-il)metilo (210mg, 0.63mmol) (Ejemplo de Síntesis I)	ácido (3-Cloro-5-fluorofenil) borónico (221mg, 1.27mmol)

Ejemplo 130

Síntesis de (3',4'-dicloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo



(2-bromofenil)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (225mg, 0.72mmol)(Ejemplo de Síntesis F) se disolvió en una solución mezclada de etanol (5mL) y agua (5mL). Ácido 3,4-Diclorofenilborónico (274mg, 1.44mmol), carbonato de potasio (199mg, 1.44mmol) y paladio de tetraquis trifenilfosfina (83mg, 0.072mmol) se agregaron al mismo. El reactivo se agitó a 110°C por 6 horas y se enfrió a temperatura ambiente. El mismo se filtró a través de Celite y el solvente se removió al concentrarse bajo presión

reducida. El mismo se extrajo con agua y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (151mg, 56%).

Ejemplos 131-135

Los materiales de partida y los materiales de reacción en la Tabla 21 se usaron para preparar los compuestos de los Ejemplos 131-135 de la misma manera que el Ejemplo 130.

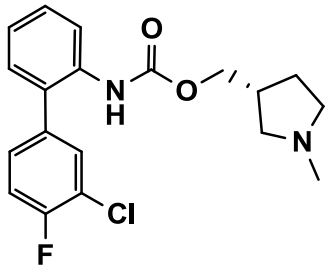
Tabla 21 Ejemplos 131-135

Ejemplo	Nombre Químico	Material de Partida	Material de Reacción
131	(3',5'-dicloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (101mg, 40%)	(2-bromofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (206mg, 0.66mmol) (Ejemplo de Síntesis F)	ácido 3,5-Diclorofenil borónico (251mg, 1.32mmol)
132	(3'-cloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo	(2-bromofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (206mg, 0.66mmol) (Ejemplo de Síntesis F)	ácido 3-Cloro-5-fluorofenil borónico (251mg, 1.32mmol)

133	(5-fluoro-3'-amino-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (63mg, 28%)	(2-bromo-4-fluorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (215mg, 0.65mmol) (Ejemplo de Síntesis H)	ácido 3-Aminofenil borónico (178mg, 1.30mmol)
134	(3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (143mg, 53%)	(2-bromo-4-fluorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (236mg, 0.71mmol) (Ejemplo de Síntesis H)	ácido (3-Cloro-5-hidroxifenil) borónico (246mg, 1.43mmol)
135	(3',5'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (65mg, 25%)	(2-bromo-4-fluorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (220mg, 0.66mmol) (Ejemplo de Síntesis H)	ácido 3,5-Diclorofenil borónico (254mg, 1.33mmol)

Ejemplo 136

Síntesis de (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo



(2-bromofenil)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (250mg, 0.80mmol)(Ejemplo de Síntesis F) se disolvió en una solución mezclada de acetonitrilo (6mL) y agua (6mL). Ácido (3-Cloro-4-fluorofenil)borónico (279mg, 1.60mmol), carbonato de sodio (170mg, 1.60mmol) y diclorobistrifenilfosfina paladio (28mg, 0.04mmol) se agregaron al mismo. El reactivo se agitó en un horno de microondas a 110°C por 30 minutos y se enfrió a temperatura ambiente. El mismo se filtró a través de Celite y el solvente se removió al concentrarse bajo presión reducida. El mismo se extrajo con agua y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (23mg, 70%).

Ejemplos 137-149

Los materiales de partida y los materiales de reacción

en la Tabla 22 se usaron para preparar los compuestos de los Ejemplos 137-149 de la misma manera que el Ejemplo 136.

Tabla 22 Ejemplos 137-149

Ejemplo	Nombre Químico	Material de Partida	Material de Reacción
137	(3'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (156mg, 65%)	(2-bromofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (230mg, 0.73mmol) (Ejemplo de Síntesis F)	ácido 3-Hidroxifenil borónico (111mg, 0.81mmol)
138	(3'-cloro-5'-(trifluoro metil)-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (208mg, 43%)	(2-bromofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (365mg, 0.17mmol) (Ejemplo de Síntesis F)	ácido (3-Cloro-5-(trifluorometil) fenil)borónico (523mg, 2.33mmol)

139	(3'-cloro-5-fluoro-5'-metoxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (184mg, 73%)	(2-bromo-4-fluorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (213mg, 0.64mmol) (Ejemplo de Síntesis H)	ácido (3-Cloro-5-metoxifenil) borónico (240mg, 1.29mmol)
140	(3'-cloro-5-fluoro-5'-(trifluoro metil)-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (135mg, 47%)	(2-bromo-4-fluorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (227mg, 0.69mmol) (Ejemplo de Síntesis H)	ácido (3-Cloro-5-(trifluorometil) fenil)borónico (307mg, 1.37mmol)
141	(4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (208mg, 62%)	(2-bromo-4-fluorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (320mg, 0.97mmol) (Ejemplo de Síntesis H)	ácido 4-Fluorofenil borónico (270mg, 1.93mmol)

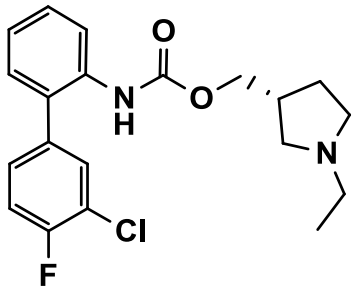
142	(3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (108mg, 42%)	(2-bromo-4-fluorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (226mg, 0.68mmol) (Ejemplo de Síntesis H)	ácido (3-Cloro-5-fluorofenil) borónico (238mg, 1.37mmol)
143	(3'-cloro-4', 5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (150mg, 54%)	(2-bromo-4-fluorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (240mg, 0.73mmol) (Ejemplo de Síntesis H)	ácido (3-Cloro-4-fluorofenil) borónico (253mg, 1.45mmol)
144	(2',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (134mg, 43%)	(2-bromo-4-fluorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (300mg, 0.91mmol) (Ejemplo de Síntesis H)	ácido 2-Fluorofenil borónico (254mg, 1.812mmol)

145	(3',5-dicloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (69mg, 22%)	(2-bromo-4-clorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (290mg, 0.84mmol) (Ejemplo de Síntesis J)	ácido 3-Clorofenil borónico (197mg, 1.26mmol)
146	(3',5-dicloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo	(2-bromo-4-clorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (300mg, 0.84mmol) (Ejemplo de Síntesis J)	ácido (3-Cloro-4-fluorofenil) borónico (300mg, 1.72mmol)
147	(3'-cloro-4'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo	(2-bromo-4-metoxifenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (270mg, 0.78mmol) (Ejemplo de Síntesis K)	ácido (3-Cloro-4-fluorofenil) borónico (274mg, 1.57mmol)

148	(3'-cloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (150mg, 65%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.64mmol) (Ejemplo de Síntesis M)	ácido (3-Cloro-5-fluorofenil) borónico (223mg, 1.28)
149	(3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (151mg, 26%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (500mg, 1.59mmol) (Ejemplo de Síntesis M)	ácido (3-Cloro-4-fluorofenil) borónico (555mg, 3.18mmol)

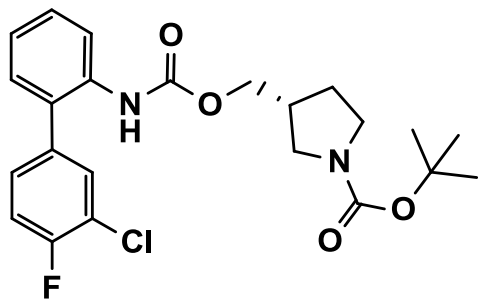
Ejemplo 150

Síntesis de (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-etilpirrolidin-3-il)metilo



Etapa 1

Síntesis de 3-((((3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamoil)oxi)metil)pirrolidin-1-carboxilato de (R)-tert-butilo

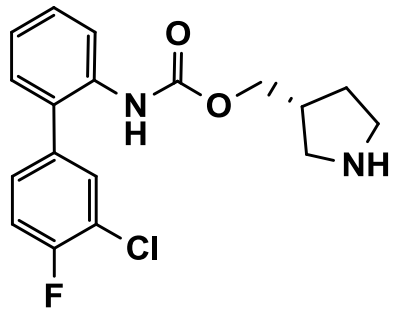


3-((((2-bromofenil)carbamoil)oxi)metil)pirrolidin-1-carboxilato de (R)-tert-butilo (4g, 10.02mmol)(Ejemplo de Síntesis F, Etapa 1) y ácido (3-cloro-4-fluoro)fenilborónico (3.5g, 20.04mmol) se usaron como materiales de partida para preparar el compuesto del título (3.4g, 76%) de la misma manera que el Ejemplo 42.

^{1}H NMR ($CDCl_3$): δ 8.01(s, 1H), 7.41-7.35(m, 2H), 7.31-7.22(m, 2H), 7.20-7.13(m, 2H), 6.34(s, 1H), 4.15-4.07(m, 2H), 3.48-3.29(m, 3H), 3.15-2.99(s, 1H), 2.51-2.48(m, 1H), 1.98-1.94(m, 1H), 1.44-1.38(m, 10H)

Etapa 2

Síntesis de (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo



3-((((3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamoil)oxi)metil)pirrolidin-1-carboxilato de (R)-tert-butilo (3.4g, 7.57mmol) preparado en la Etapa 1 se usó como un material de partida para preparar el compuesto del título (2.3g, 87%) de la misma manera que el Ejemplo 78.

^{1}H NMR ($CDCl_3$): δ 7.98(s, 1H), 7.41-7.34(m, 2H), 7.23-7.17(m, 2H), 7.16-7.11(m, 2H), 6.55(s, 1H), 4.10-4.01(m, 2H), 3.99-2.86(m, 3H), 2.70-2.66(s, 1H), 2.45-2.39(m, 1H), 1.95-1.86 (m, 1H), 1.47-1.41(m, 1H)

Etapa 3

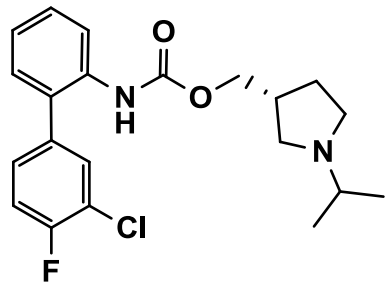
Síntesis de (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo

(3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo (345mg, 0.99mmol) preparado en la Etapa 2 se disolvió en tetrahidrofurano (20mL). Trietilamina (150uL, 1.09mmol) y bromoetano (118uL, 1.58mmol) se agregaron

secuencialmente al mismo y se agitó a temperatura ambiente por 3 días. El reactivo bajo presión reducida y se extrajo con agua y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (74mg, 20%).

Ejemplo 151

Síntesis de (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-isopropil pirrolidin-3-il)metilo

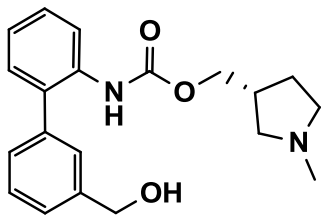


(3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo (347mg, 1.00mmol)(Ejemplo 150, Etapa 2) se disolvió en tetrahidrofurano (20mL). Trietilamina (150uL, 1.10mmol) y 2-bromopropano (100uL, 1.10mmol) se agregaron secuencialmente al mismo y se agitó a temperatura ambiente por 3 días. El reactivo se concentró bajo presión reducida y se extrajo con agua y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del

título (17mg, 4%).

Ejemplo 152

Síntesis de (3'-(hidroximetil)-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo



(2-bromofenil)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (395mg, 1.26mmol)(Ejemplo de Síntesis F) se disolvió en una solución mezclada de tolueno (15mL) y etanol (2mL). Ácido 3-(Hidroximetil)fenilborónico (211mg, 1.39mmol), carbonato de potasio (348mg, 2.52mmol) y paladio de tetraquis trifenilfosfina (146mg, 0.13mmol) se agregaron al mismo. El reactivo se agitó a 110°C por 12 horas y se enfrió a temperatura ambiente. El mismo se filtró a través de Celite y el solvente se removió al concentrarse bajo presión reducida. El mismo se extrajo con agua y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (126mg, 29%).

Ejemplos 153-190

Los materiales de partida y los materiales de

reacción en la Tabla 23 se usaron para preparar los compuestos de los Ejemplos 153-190 de la misma manera que el Ejemplo 152.

Tabla 23 Ejemplos 153-190

Ejemplo	Nombre Químico	Material de Partida	Material de Reacción
153	(3'-carbamoil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (125mg, 28%)	(2-bromofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (395mg, 1.26mmol) (Ejemplo de Síntesis F)	ácido (3-Carbamoilfenil) borónico (229mg, 1.39mmol)
154	(3'-amino-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (102mg, 45%)	(2-bromofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (220mg, 0.70mmol) (Ejemplo de Síntesis F)	ácido 3-Aminofenil borónico (115mg, 0.84mmol)
155	(3'-ciano-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (77mg, 34%)	(2-bromofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (210mg, 0.67mmol) (Ejemplo de Síntesis F)	ácido 3-Cianofenil borónico (118mg, 0.80mmol)

	156	(2'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (210mg, 67%)	(2-bromofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (300mg, 0.958mmol) (Ejemplo de Síntesis F)	ácido 2-Fluorofenil borónico (201mg, 1.437mmol)
	157	(2',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (115mg, 52%)	(2-bromofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (200mg, 0.639mmol) (Ejemplo de Síntesis F)	ácido 2,4-Difluorofenil borónico (202mg, 1.277mmol)
	158	(2',3'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (145mg, 66%)	(2-bromofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (200mg, 0.639mmol) (Ejemplo de Síntesis F)	ácido 2,3-Difluorofenil borónico (202mg, 1.277mmol)
	159	(3'-cloro-6'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (130mg, 56%)	(2-bromofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (200mg, 0.639mmol) (Ejemplo de Síntesis F)	ácido 3-Cloro-6-fluorofenil borónico (223mg, 1.277mmol)

	160	(3'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (183mg, 87%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.64mmol) (Ejemplo de Síntesis M)	ácido 3-Fluorofenil borónico (107mg, 0.77mmol)
	161	(3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (163mg, 74%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.64mmol) (Ejemplo de Síntesis M)	ácido 3,5-Difluorofenil borónico (121mg, 0.77mmol)
	162	(3',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (105mg, 95%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (100mg, 0.32mmol) (Ejemplo de Síntesis M)	ácido 3,4-Difluorofenil borónico (101mg, 0.64mmol)
	163	(2',4',5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (79mg, 68%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (100mg, 0.32mmol) (Ejemplo de Síntesis M)	ácido 2,4,5-Trifluorofenil borónico (113mg, 0.64mmol)

164	(4'-cloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (103mg, 94%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (100mg, 0.32mmol) (Ejemplo de Síntesis M)	ácido 4-Clorofenil borónico (100mg, 0.64mmol)
165	(3'-cloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (70mg, 64%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (100mg, 0.32mmol) (Ejemplo de Síntesis M)	ácido 3-Clorofenil borónico (100mg, 0.64mmol)
166	(3',4'-dicloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (96mg, 79%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (100mg, 0.32mmol) (Ejemplo de Síntesis M)	ácido 3,4-Diclorofenil borónico (122mg, 0.64mmol)
167	(2',4'-dicloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (83mg, 69%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (100mg, 0.32mmol) (Ejemplo de Síntesis M)	ácido 2,4-Diclorofenil borónico (122mg, 0.64mmol)

168	(3'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (160mg, 77%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.64mmol) (Ejemplo de Síntesis M)	ácido 3-Hidroxifenil borónico (106mg, 0.77mmol)
169	(3'-ciano-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (17mg, 13%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.64mmol) (Ejemplo de Síntesis M)	ácido 3-Cianofenil borónico (113mg, 0.77mmol)
170	(3'-amino-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (78mg, 38%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.64mmol) (Ejemplo de Síntesis M)	ácido 3-Aminofenil borónico (105mg, 0.77mmol)
171	(3',4',5-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (88mg, 81%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (100mg, 0.30mmol) (Ejemplo de Síntesis N)	ácido 3,4-Difluorofenil borónico (95mg, 0.60mmol)

172	(3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (180mg, 83%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.60mmol) (Ejemplo de Síntesis N)	ácido 3,5-Difluorofenil borónico (190mg, 1.20mmol)
173	(2',4',5,5'-tetrafluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (188mg, 82%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.60mmol) (Ejemplo de Síntesis N)	ácido 2,4,5-Trifluorofenil borónico (211mg, 1.20mmol)
174	(3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (171mg, 79%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.60mmol) (Ejemplo de Síntesis N)	ácido 3-Clorofenil borónico (188mg, 1.20mmol)

175	(4'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (198mg, 91%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.60mmol) (Ejemplo de Síntesis N)	ácido 4-Clorofenil borónico (188mg, 1.20mmol)
176	(2',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (146mg, 61%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.60mmol) (Ejemplo de Síntesis N)	ácido 2,4-Diclorofenil borónico (230mg, 1.20mmol)
177	(3',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (76mg, 64%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (100mg, 0.30mmol) (Ejemplo de Síntesis N)	ácido 3,4-Diclorofenil borónico (115mg, 0.60mmol)

178	(3'-ciano-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (117mg, 55%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.60mmol) (Ejemplo de Síntesis N)	ácido 3-Cianofenil borónico (176mg, 1.20mmol)
179	(3'-hidroxi-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (66mg, 64%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo(100mg, 0.30mmol) (Ejemplo de Síntesis N)	ácido 3-Hidroxifenil borónico (83mg, 0.60mmol)
180	(5-fluoro-3'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (43mg, 36%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (100mg, 0.30mmol) (Ejemplo de Síntesis N)	ácido 3-(Trifluorometil) fenilborónico (115mg, 0.60mmol)

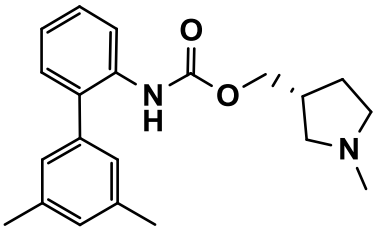
181	(3'-cloro-4,4',5-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (57mg, 25%)	(2-bromo-4,5-difluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.57mmol) (Ejemplo de Síntesis P)	ácido 3-Cloro-4-fluorofenil borónico (200mg, 1.15mmol)
182	(3'-cloro-4,5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (50mg, 25%)	(2-bromo-4,5-difluorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (180mg, 1.52mmol) (Ejemplo de Síntesis L)	ácido 3-Clorofenil borónico (161mg, 1.03mmol)
183	(2',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (50mg, 15%)	(2-yodofenil)carbamato de 2-(1-metilpirrolidin-2-il)etilo (300mg, 0.917mmol) (Ejemplo de Síntesis A)	ácido 2,4-Difluorofenil borónico (290mg, 1.834mmol)

	184	(2',3'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (50mg, 15%)	(2-yodofenil)carbamato de 2-(1-metilpirrolidin-2-il)etilo (300mg, 0.917mmol) (Ejemplo de Síntesis A)	ácido 2,3-Difluorofenil borónico (290mg, 1.834mmol)
	185	(2',6'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (50mg, 15%)	(2-yodofenil)carbamato de 2-(1-metilpirrolidin-2-il)etilo (300mg, 0.917mmol) (Ejemplo de Síntesis A)	ácido 2,6-Difluorofenil borónico (290mg, 1.834mmol)
	186	(5'-cloro-2'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo (160mg, 46%)	(2-yodofenil)carbamato de 2-(1-metilpirrolidin-2-il)etilo (300mg, 0.917mmol) (Ejemplo de Síntesis A)	ácido 5-Cloro-2-fluorofenil borónico (320mg, 1.834mmol)
	187	(2'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (205mg, 65%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (300mg, 0.958mmol) (Ejemplo de Síntesis M)	ácido 2-Fluorofenil borónico (268mg, 1.916mmol)

188	(2',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (250mg, 75%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (300mg, 0.958mmol) (Ejemplo de Síntesis M)	ácido 2,4-Difluorofenil borónico (303mg, 1.916mmol)
189	(2',3'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (100mg, 30%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (300mg, 0.958mmol) (Ejemplo de Síntesis M)	ácido 2,3-Difluorofenil borónico (303mg, 1.916mmol)
190	(3'-cloro-6'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (150mg, 43%)	(2-bromofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (300mg, 0.958mmol) (Ejemplo de Síntesis M)	ácido 3-Cloro-6-fluorofenil borónico (334mg, 1.916mmol)

Ejemplo 191

Síntesis de (3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo



(2-bromofenil)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (220mg, 0.70mmol)(Ejemplo de Síntesis F) se disolvió en una solución mezclada de etanol (5mL) y agua (5mL). Ácido 3,5-dimetilborónico (211mg, 1.41mmol), carbonato de potasio (194mg, 1.41mmol), di(acetato)diciclohexilfenilfosfina paladio(II) y FibreCat™ (28mg) unido a un polímero se agregaron al mismo. El reactivo se agitó en un horno de microondas a 110°C por 30 minutos y se enfrió a temperatura ambiente. El mismo se filtró a través de Celite y el solvente se removió al concentrarse bajo presión reducida. El mismo se extrajo con agua y diclorometano. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (134mg, 56%).

Ejemplos 192-195

Los materiales de partida y los materiales de reacción

en la Tabla 24 se usaron para preparar los compuestos de los Ejemplos 192-195 de la misma manera que el Ejemplo 191.

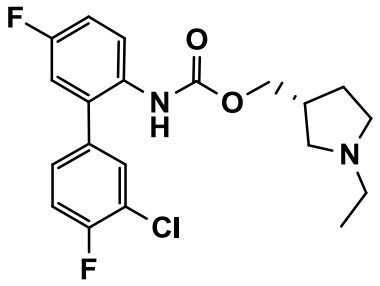
Tabla 24 Ejemplos 192-195

Ejemplo	Nombre Químico	Material de Partida	Material de Reacción
192	(5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (158mg, 73%)	(2-bromo-4-fluorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (210mg, 0.63mmol) (Ejemplo de Síntesis H)	ácido 3-Metilfenil borónico (172mg, 1.27mmol)
193	(5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (82mg, 39%)	(2-bromo-4-fluorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (206mg, 0.62mmol) (Ejemplo de Síntesis H)	ácido 3,5-Dimetilfenil borónico (187mg, 1.24mmol)

194	(3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (124mg, 55%)	(2-bromo-4-fluorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (215mg, 0.65mmol) (Ejemplo de Síntesis H)	ácido 3-Fluorofenil borónico (182mg, 1.30mmol)
195	(3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo (151mg, 66%)	(2-bromo-4-fluorofenil) carbamato de (R)-(1-metilpirrolidin-3-il)metilo (210mg, 0.63mmol) (Ejemplo de Síntesis H)	ácido 3-Clorofenil borónico (198mg, 1.27mmol)

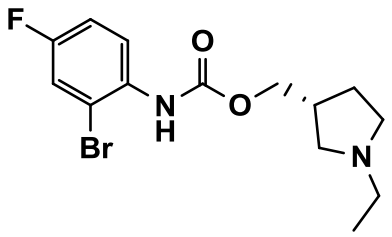
Ejemplo 196

Síntesis de (3'-cloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-etilpirrolidin-3-il)metilo



Etapa 1

Síntesis de (2-bromo-4-fluorofenil)carbamato de (R)-(1-etilpirrolidin-3-il)metilo

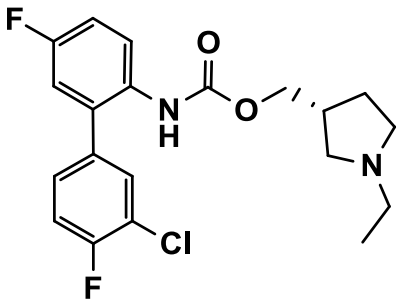


Ácido 2-bromo-4-fluorobenzoico (3g, 13.70mmol) y 3-(hidroximetil)pirrolidin-1-carboxilato de (R)-tert-butilo (3.31g, 16.44mmol) se usaron como materiales de partida para preparar el compuesto del título (4.5g, 79%) de la misma manera que el Ejemplo de Síntesis F.

^{1}H NMR ($CDCl_3$): δ 8.00(s, 1H), 7.28-7.24(m, 1H), 7.05-7.00(m, 1H), 4.21-4.10(m, 2H), 3.06-3.03(m, 1H), 2.90-2.87(m, 1H), 2.84-2.71(m, 5H), 2.17-2.12(m, 1H), 1.76-1.71(m, 1H), 1.24(t, 3H, J=7.2)

Etapa 2

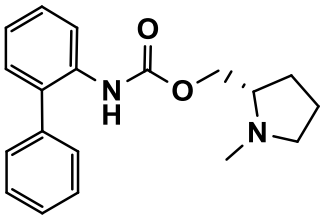
Síntesis de (3'-cloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-etilpirrolidin-3-il)metilo



(2-bromo-4-fluorofenil)carbamato de (R)-(1-etilpirrolidin-3-il)metilo (165mg, 0.48mmol) y ácido (3-cloro-4-fluorofenil)borónico (167mg, 0.96mmol) se usaron como materiales de partida para preparar el compuesto del título (143mg, 76%) de la misma manera que el Ejemplo 136.

Ejemplo 197

Síntesis de [1,1'-bifenil]-2-ilcarbamato de (S)-(1-metilpirrolidin-2-il)metilo



Ácido [1,1'-Bifenil]-2-carboxílico (1g, 5.05mmol) se disolvió en tolueno (20mL). Azida de bifenilfosforilo (1.4mL, 6.05mmol) y trietilamina (0.71mL, 5.05mmol) se agregaron al mismo. El mismo se agitó a temperatura ambiente por 30 minutos, y luego se agitó otra vez bajo reflujo a temperatura ambiente por 1 hora. El reactivo se enfrió a temperatura ambiente y (S)-(1-metilpirrolidin-2-il)metanol (0.72mL, 6.05mmol) se agregó al mismo, y luego se agitó bajo reflujo por 12 horas. El reactivo se enfrió a temperatura ambiente. El solvente se removió al concentrarse bajo presión reducida. El mismo se extrajo con agua y acetato de etilo. La capa orgánica se secó con sulfato de magnesio

anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (458mg, 29%).

Ejemplos 198-207

Los materiales de partida y los materiales de reacción en la Tabla 25 se usaron para preparar los compuestos de los Ejemplos 198-207 de la misma manera que el Ejemplo 197.

Tabla 25 Ejemplos 198-207

Ejemplo	Nombre Químico	Material de Partida	Material de Reacción
198	(4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (97mg, 13%)	ácido 4'-Fluoro-[1,1'-bifenil]-2-carboxílico (482mg, 2.23mmol) (Ejemplo de Síntesis 1)	(S)-(1-metilpirrolidin-2-il)metanol (318uL, 2.68mmol)
199	(3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (379mg, 51%)	ácido 3'-Metil-[1,1'-bifenil]-2-carboxílico (488mg, 2.3mmol) (Ejemplo de Síntesis 14)	(S)-(1-metilpirrolidin-2-il)metanol (328uL, 2.76mmol)

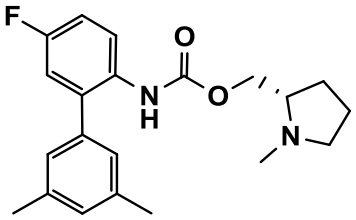
200	(5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (42mg, 7%)	ácido 5-Fluoro-[1,1'-bifenil]-2-carboxílico (400mg, 1.85mmol) (Ejemplo de Síntesis 20)	(S)-(1-metilpirrolidin-2-il)metanol (0.26mL, 2.22mmol)
201	(5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (98mg, 14%)	ácido 5-Fluoro-3'-metil-[1,1'-bifenil]-2-carboxílico (460mg, 2.0mmol) (Ejemplo de Síntesis 21)	(S)-(1-metilpirrolidin-2-il)metanol (0.29mL, 2.4mmol)
202	(3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (280mg, 47%)	ácido 3',5-Difluoro-[1,1'-bifenil]-2-carboxílico (400mg, 1.71mmol) (Ejemplo de Síntesis 17)	(S)-(1-metilpirrolidin-2-il)metanol (0.24mL, 2.05mmol)

203	(4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (312mg, 53%)	ácido 4',5-Difluoro-[1,1'-bifenil]-2-carboxílico (400mg, 1.71mmol) (Ejemplo de Síntesis 18)	(S)-(1-metilpirrolidin-2-il)metanol (0.24mL, 2.05mmol)
204	(4-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (140mg, 51%)	ácido 4-Fluoro-[1,1'-bifenil]-2-carboxílico (180mg, 0.83mmol) (Ejemplo de Síntesis 22)	(S)-(1-metilpirrolidin-2-il)metanol (0.12mL, 1.0mmol)
205	(3',4-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 34%)	ácido 3',4-Difluoro-[1,1'-bifenil]-2-carboxílico (400mg, 1.71mmol) (Ejemplo de Síntesis 23)	(S)-(1-metilpirrolidin-2-il)metanol (0.24mL, 2.05mmol)

206	(5-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (189mg, 41%)	ácido 5-Metil-[1,1'-bifenil]-2-carboxílico (300mg, 1.41mmol) (Ejemplo de Síntesis 25)	(S)-(1-metilpirrolidin-2-il)metanol (201uL, 1.7mmol)
207	(3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (265mg, 89%)	ácido 3'-Fluoro-5-metil-[1,1'-bifenil]-2-carboxílico (200mg, 0.87mmol) (Ejemplo de Síntesis 26)	(S)-(1-metilpirrolidin-2-il)metanol (124uL, 1.04mmol)

Ejemplo 208

Síntesis de (5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo



(2-bromo-4-fluorofenil)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.60mmol)(Ejemplo de Síntesis N) se disolvió en una solución mezclada de

acetonitrilo (3mL) y agua (3mL). Ácido 3,5-Dimetilfenilborónico (181mg, 1.20mmol), carbonato de sodio (95mg, 0.90mmol) y diclorobistrifenilfosfina paladio (2mg, 0.003mmol) se agregaron al mismo. El reactivo se agitó en un horno de microondas a 150°C por 10 minutos y se enfrió a temperatura ambiente. El mismo se filtró a través de Celite y el solvente se removió al concentrarse bajo presión reducida. El mismo se extrajo con agua y acetato de etilo. La capa orgánica se secó con sulfato de magnesio anhidro, se filtró y se concentró. El residuo resultante se purificó con cromatografía de columna para preparar el compuesto del título (98mg, 46%).

Ejemplos 209-226

Los materiales de partida y los materiales de reacción en la Tabla 26 se usaron para preparar los compuestos de los Ejemplos 209-226 de la misma manera que el Ejemplo 208.

Tabla 26 Ejemplos 209-226

Ejemplo	Nombre Químico	Material de Partida	Material de Reacción
209	(4'-(tert-butil)-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (68mg, 30%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.60mmol) (Ejemplo de Síntesis N)	ácido 4-tert-Butilfenil borónico (213mg, 1.20mmol)
210	(3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (55mg, 32%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (150mg, 0.45mmol) (Ejemplo de Síntesis N)	ácido (3-Cloro-5-fluoro)fenil borónico (158mg, 0.90mmol)

211	(3'-cloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (56mg, 16%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (300mg, 0.91mmol) (Ejemplo de Síntesis N)	ácido (3-Cloro-4-fluoro)fenil borónico (316mg, 1.81mmol)
212	(4'-cloro-3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (140mg, 40%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (300mg, 0.91mmol) (Ejemplo de Síntesis N)	ácido (3-Fluoro-4-cloro)fenil borónico (316mg, 1.81mmol)
213	(3'-amino-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (46mg, 45%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (150mg, 0.45mmol) (Ejemplo de Síntesis N)	ácido 3-Aminofenil borónico (68mg, 0.50mmol)

214	(2',5-difluoro-3'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (17mg, 10%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (150mg, 0.45mmol) (Ejemplo de Síntesis N)	ácido (2-Fluoro-3-(trifluorometil) fenil)borónico (187mg, 0.90mmol)
215	(3'-cloro-5-fluoro-5'-(trifluoro metil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (80mg, 41%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (150mg, 0.45mmol) (Ejemplo de Síntesis N)	ácido (3-Cloro-5-(trifluorometil) fenil)borónico (202mg, 0.90mmol)

216	(3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (35mg, 24%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (130mg, 0.39mmol) (Ejemplo de Síntesis N)	ácido (3-Cloro-5-hidroxifenil) borónico (135mg, 0.79mmol)
217	(3'-cloro-5-fluoro-5'-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (55mg, 31%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (150mg, 0.45mmol) (Ejemplo de Síntesis N)	ácido (3-Cloro-5-metoxifenil) borónico (168mg, 0.90mmol)

218	(5-fluoro-2',4'-bis(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (85mg, 41%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (150mg, 0.45mmol) (Ejemplo de Síntesis N)	ácido (2,4-Bis(trifluorometil)fenil) borónico (230mg, 0.90mmol)
219	(3'-etoxi-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (94mg, 42%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.60mmol) (Ejemplo de Síntesis N)	ácido 3-Etoxifenil borónico (200mg, 1.20mmol)
220	(5-fluoro-3',4'-dimetoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (54mg, 23%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.60mmol) (Ejemplo de Síntesis N)	ácido 3,4-Dimetoxifenil borónico (218mg, 1.20mmol)

221	(5-fluoro-3',5'-dimetoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (140mg, 60%)	(2-bromo-4-fluorofenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.60mmol) (Ejemplo de Síntesis N)	ácido 3,5-Dimetoxifenil borónico (218mg, 1.20mmol)
222	(5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (66mg, 34%)	(2-bromo-4-metoxifenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.58mmol) (Ejemplo de Síntesis O)	ácido Fenilborónico (142mg, 1.16mmol)
223	(3'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (99mg, 55%)	(2-bromo-4-metoxifenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.58mmol) (Ejemplo de Síntesis O)	ácido 3-Fluorofenil borónico (162mg, 1.16mmol)

224	(3'-cloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (117mg, 54%)	(2-bromo-4-metoxifenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.58mmol) (Ejemplo de Síntesis O)	ácido 3-Clorofenil borónico (181mg, 1.16mmol)
225	(3',4'-dicloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (90mg, 38%)	(2-bromo-4-metoxifenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.58mmol) (Ejemplo de Síntesis O)	ácido 3,4-Diclorofenil borónico (221mg, 1.16mmol)
226	(3',5'-dicloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo (110mg, 46%)	(2-bromo-4-metoxifenil) carbamato de (S)-(1-metilpirrolidin-2-il)metilo (200mg, 0.58mmol) (Ejemplo de Síntesis O)	ácido 3,5-Diclorofenil borónico (221mg, 1.16mmol)

Ejemplo Experimental 1

Ensayo de Unión en receptor muscarínico M3 humano

Las proteínas de la membrana celular (Perkin Elmer) donde el receptor muscarínico M3 humano se sobreexpresó, escopolamina de [^{3}H]-metilo y compuestos de prueba en varias concentraciones se cultivaron en 0.2 ml de solución amortiguadora de Tris-HCl a 25°C por 120 minutos. El mismo se filtró bajo succión a través de un filtro de fibra de vidrio (Whatman GF/B), y luego el filtrado se lavó 5 veces con 1 ml de solución amortiguadora de Tris-HCl. La radioactividad de escopolamina de [^{3}H]-metilo en el filtrado se midió por un contador de centelleo líquido. La unión no específica se evaluó bajo la existencia de 4 uM de atropina. La afinidad del compuesto de la presente invención al receptor muscarínico M3 se calculó como la Constante de disociación (K_i), la cual puede calcularse de la concentración (IC_{50}) de compuestos de prueba que inhiben el 50% de la unión de escopolamina de [^{3}H]-metilo (es decir, ligando marcado) de acuerdo a Cheng y Prusoff [Cheng y Prusoff, Biochem. Pharmacol., 22, 3099, 1973]. En la siguiente Tabla, los compuestos que tienen una Afinidad de Unión más fuerte al receptor muscarínico M3 humano tienen una menor Constante de disociación (K_i).

Tabla 27 Afinidad de Unión al receptor muscarínico M3 humano

Ejemplo	Afinidad de Unión al Receptor M3, K_i (nM)	Ejemplo	Afinidad de Unión al Receptor M3, K_i (nM)
1	4.42	115	7.49
2	8.69	116	12.60
3	11.58	117	1.60
4	2.93	118	2.42
5	1101.45	119	42.34
6	2.47	120	9.70
7	31.84	121	1.75
8	1.33	122	87.80
9	9.10	123	52.84
10	401.05	124	8.12
11	467.04	125	2.67
12	88.00	126	24.79
13	80.10	127	69.36
14	12.39	128	3.41
15	2.27	129	12.56
16	1056.28	130	2.10
17	1.00	131	12.01
18	6.98	132	4.64
19	4.17	133	34.48
20	20.72	134	46.90
21	2.25	135	24.15
22	3.79	136	1.59
23	6.40	137	27.02
24	31.01	138	>1000
25	115.46	139	82.67
26	18.52	140	>1000
27	56.72	141	7.57

28	844.79	142	4.88
29	931.06	143	1.12
30	830.16	144	17.16
31	311.47	145	14.27
32	>1000	146	6.85
33	16.84	147	77.41
34	19.64	148	10.20
35	434.72	149	1.57
36	>1000	150	5.60
37	>1000	151	14.95
38	574.03	152	147.11
39	28.04	153	>1000
40	118.89	154	16.67
41	2.45	155	>1000
42	9.21	156	10.63
43	1.48	157	29.63
44	95.47	158	119.82
45	69.57	159	5.13
46	37.51	160	4.29
47	136.47	161	8.92
48	257.54	162	5.34
49	303.01	163	16.13
50	>1000	164	36.92
51	101.48	165	0.63
52	10.02	166	9.04
53	1.34	167	67.35
54	125.95	168	22.86
55	38.76	169	282.30
56	12.52	170	9.23
57	34.83	171	16.93
58	26.31	172	6.15

59	6.42	173	42.74
60	118.72	174	0.61
61	217.94	175	22.49
62	>1000	176	>1000
63	58.09	177	6.32
64	>1000	178	>1000
65	71.32	179	241.05
66	6.98	180	9.15
67	16.32	181	3.29
68	13.23	182	>1000
69	108.98	183	18.91
70	8.17	184	63.46
71	134.09	185	46.09
72	58.83	186	4.68
73	4.84	187	10.66
74	>1000	188	13.73
75	471.30	189	65.59
76	>1000	190	2.17
77	22.00	191	30.78
78	4.62	192	4.60
80	27.38	193	45.83
81	30.35	194	6.30
82	18.89	195	1.08
83	18.29	196	7.67
84	34.94	197	0.78
86	111.04	198	1.87
87	94.38	199	0.80
88	99.67	200	2.03
89	2.43	201	2.70
90	1.97	202	2.18
91	4.50	203	2.36

92	10.66	204	3.53
93	4.12	205	7.95
94	6.18	206	7.32
95	6.27	207	13.45
96	17.57	208	110.05
97	35.17	209	>1000
98	46.18	210	4.60
99	8.10	211	9.91
100	2.43	212	>1000
101	3.79	213	53.03
102	12.86	214	>1000
103	12.96	215	>1000
104	14.18	216	60.13
105	19.55	217	222.89
106	0.80	218	>1000
107	752.18	219	>1000
108	3.95	220	>1000
109	5.33	221	>1000
110	9.13	222	28.27
111	10.79	223	120.66
112	3.77	224	15.14
113	1.92	225	53.65
114	4.23	226	16.71

Ejemplo Experimental 2

Ensayo de antagonismo en el receptor muscarínico M3 humano

El ensayo de antagonismo para varios compuestos de la presente invención se condujo en antagonismo al receptor humano M3 en células Cos-7 que fueron transfectadas con

receptor muscarínico M3 humano codificador de plásmidos. Los compuestos de prueba en varias concentraciones se pre-trataron a las células por 3 minutos, y luego los cambios de calcio intracelular se midieron después de tratar los mismos con carbacol (es decir, agonista del receptor muscarínico). El ensayo de Calcio 5 FLIPR® (Molecular Devices) y el dispositivo Flex3 (Molecular Devices) se usaron para medir la concentración del calcio. Las cantidades de calcio antes y después del tratamiento de carbacol se fijaron en 0% y 100% respectivamente. Las tasas de inhibición (%) por los compuestos para incrementar el calcio intracelular por carbacol se calcularon. La potencia antagonista de los compuestos de prueba en el receptor muscarínico M3 humano se calculó como la constante de unión funcional (K_b), la cual puede calcularse de la concentración (IC_{50}) del compuesto que inhibe el 50% de la actividad de carbacol de acuerdo con la ecuación de Cheng y Prusoff. Los compuestos usados en el experimento se identificaron como antagonistas para el receptor muscarínco M3 humano, y un menor valor de K_b significa una potencia antagonista superior.

Tabla 28 Potencia antagónica para el receptor muscarínico M3 humano

Ejemplo	Antagonismo para el receptor M3, K_b (nM)	Ejemplo	Antagonismo para el receptor M3, K_b (nM)
2	6.02	128	1.20
4	3.41	129	6.24
8	3.02	130	1.14
15	4.10	131	1.86
19	1.90	132	0.75
21	0.49	135	16.53
22	2.39	136	0.25
34	2.64	141	0.35
41	0.18	142	1.04
42	1.19	143	0.68
52	1.22	144	1.42
53	0.57	145	2.97
56	10.00	146	1.57
58	4.70	148	2.22
59	2.38	149	0.10
66	3.06	150	1.34
67	11.85	151	2.67
68	13.22	156	1.15
70	1.95	157	3.25
73	4.75	159	0.46
77	10.00	166	1.33
89	0.16	181	0.29
90	0.17	183	2.57
91	1.32	186	0.34
95	0.75	187	0.48
100	0.64	188	2.23

114	0.58	190	0.95
115	0.32	194	0.58
116	1.21	195	0.43
117	0.34	196	1.54
118	0.77	199	0.26
120	1.03	207	3.52
124	2.86	211	10.00
125	0.33	224	7.5
126	17.47	226	4.99

Ejemplo Experimental 3

Experimentación sobre las contracciones rítmicas de la vejiga en ratas (in vivo)

Una rata Sprague-Dawley hembra se anestesió por halotano, y un catéter de polietileno se insertó a través de la uretra fijada recta y fija. La orina en la vejiga se excretó a través del catéter al masajear gentilmente el abdomen de la rata, y luego se removió. Una llave de cierre de 3 vías se conectó al catéter y un transductor de presión se conectó a un lado de la llave de cierre de 3 vías para medir la presión, y una jeringa se instaló en el otro lado para inyectar una solución salina a 37°C. La solución salina se inyectó lentamente hasta que contracciones regulares de la vejiga ocurrieron repetidamente. Cuando las contracciones de la vejiga regulares ocurrieron establemente, los compuestos de prueba se administraron vía intravenosa a través de la

vena de la cola. El efecto inhibitorio de los compuestos de prueba se evaluó al medir el grado de reducción de amplitud de las contracciones de la vejiga. Los compuestos de la presente invención redujeron significativamente la amplitud de las contracciones de la vejiga cuando los compuestos se administraron al menos en 0.3 mg/kg o más.

Tabla 29 Contractibilidad Rítmica de la Vejiga de ratas

Ejemplo	Contractibilidad rítmica de la vejiga de ratas (%, 0.3 mpk)	Ejemplo	Contractibilidad rítmica de la vejiga de ratas (%, 0.3 mpk)
1	26.1±5.1	117	15.4±0.1
2	20.1±3.1	121	31.4±6.1
3	15.9±0.9	124	21.2±0.7
4	22.3±4.9	125	22.6±5.8
6	28.5±4.6	128	15.1±3.4
8	23.2±2.3	129	15.7±1.4
9	9.6±1.6	131	17.8±2.5
15	25.6±2.2	136	33.2±4.0
17	27.9±6.1	142	15.1±3.4
19	12.8±3.0	143	24.3±5.5
22	16.7±1.7	145	13.1±3.0
26	11.0±2.5	146	8.2±2.9
34	20.1±1.8	150	25.1±2.5
43	8.9±2.3	160	15.5±2.4
52	10.8±0.8	165	34.5±2.5
53	28.0±5.0	166	10.2±1.7
59	11.6±1.9	172	12.4±2.7
66	12.0±1.4	177	11.3±2.2

70	9.7±4.1	180	6.3±1.3
73	10.0±1.0	181	18.1±2.6
78	17.9±2.1	192	18.6±3.6
89	33.9±3.5	194	24.6±2.6
90	27.4±1.9	195	20.3±2.6
91	25.2±2.5	197	32.8±9.7
93	27.3±1.9	198	26.3±2.4
95	15.7±0.8	199	27.8±4.5
99	16.3±1.0	201	9.1±3.0
100	26.0±6.0	202	17.3±1.3
101	20.1±1.7	203	19.4±4.0
108	18.1±1.4	204	23.3±6.6
109	18.1±1.7	205	11.9±3.7
106	32.7±5.2	207	18.2±3.7
112	34.8±2.9		

Ejemplo Experimental 4

Prueba de Toxicidad Aguda para administración oral en ratas

A fin de confirmar la toxicidad aguda de los compuestos de la presente invención, se condujo el siguiente experimento. Un grupo de baja dosis, un grupo de dosis media y un grupo de alta dosis, donde los compuestos de los Ejemplos se administraron en 100 mg/kg, 300 mg/kg y 1000 mg/kg respectivamente, se prepararon. Una solución de celulosa de metilo (0.5%) se preparó y se administró oralmente a 3 ratas de cada grupo (es decir, ratas Sprague-Dawley (SD) de 6 semanas de edad de ambos sexos; ratas macho

en 142-143 g; ratas hembra en 126.3-127.3 g) en un volumen 10 mL/kg. La mortalidad, los signos clínicos y el peso y similares se midieron por 4 días, y se descubrió la Dosis Letal Aproximada (ADL) se explicaron en la Tabla 30 a continuación. Como se muestra en la Tabal 30, la Dosis Letal Aproximada de los compuestos de prueba fueron de 1000 mg/kg o más, por lo tanto los compuestos se determinaron como fármacos seguros.

Tabla 30 Dosis Letal Aproximada

Ejemplo	Dosis Letal Aproximada (ALD)	Ejemplo	Dosis Letal Aproximada (ALD)
15	>1000	100	>1000
53	>1000	136	>1000
89	>1000	143	>1000
90	>1000	150	>1000
91	>1000	199	>1000

Aplicabilidad Industrial

Los derivados de bifenilo novedosos, los isómeros o sales farmacéuticamente aceptables de los mismos de acuerdo con la presente invención actúan como un antagonista del receptor muscarínico M3, y por lo tanto pueden ser de utilidad para la prevención o tratamiento de un enfermedad del grupo que consiste de enfermedad pulmonar obstructiva crónica, asma, síndrome de intestino irritable, incontinencia urinaria, rinitis, colitis espasmódica, cistitis crónica,

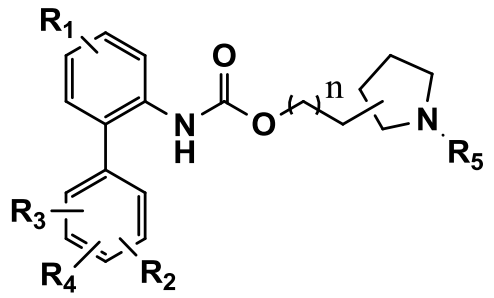
enfermedad de Alzheimer, demencia senil, glaucoma, esquizofrenia, enfermedad de reflujo gastroesofágico, arritmia cardiaca, y síndromes de hipersalivación.

NOVEDAD DE LA INVENCIÓN

Habiendo descrito la presente invención, se considera como novedad, y por lo tanto se reclama como propiedad lo contenido en las siguientes:

REIVINDICACIONES

1. Un derivado de bifenilo novedoso representado por la siguiente Fórmula 1, un isómero del mismo, o una sal farmacéuticamente aceptable del mismo:



caracterizado porque

R_1 es hidrógeno, halógeno, hidroxi, alquilo C_1-C_6 sustituido o no sustituido, o alcoxi C_1-C_6;

R_2, R_3 y R_4 son independientemente hidrógeno, halógeno, amino sustituido o no sustituido, nitro, ciano, hidroxi, alquilo C_1-C_6 sustituido o no sustituido, alcoxi C_1-C_6 sustituido o no sustituido, o $-C(O)R_6$;

R_5 es hidrógeno o alquilo C_1-C_6;

n es 0 o 1; y

R_6 es hidrógeno o amino.

2. El derivado de bifenilo novedoso, isómero del mismo o

sal farmacéuticamente aceptable del mismo de conformidad con la reivindicación 1, caracterizado porque R_1 es hidrógeno o halógeno; R_2, R_3 y R_4 son independientemente hidrógeno, halógeno, o alquilo C_1-C_6; y R_5 es alquilo C_1-C_6.

3. El derivado de bifenilo novedoso, isómero del mismo o sal farmacéuticamente aceptable del mismo de conformidad con la reivindicación 1, caracterizado porque R_1 es hidrógeno; R_2, R_3 y R_4 son de forma independiente hidrógeno o halógeno; R_5 es alquilo C_1-C_6; y n es 0 o 1.

4. El derivado de bifenilo novedoso, isómero del mismo o sal farmacéuticamente aceptable del mismo de conformidad con la reivindicación 1, caracterizado porque el derivado de bifenilo novedoso se selecciona del grupo que consiste de los siguientes compuestos:

1) (4'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

2) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

3) (3',4',5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

4) (3'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

5) (4'-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

6) [1,1'-bifenil]-2-ilcarbamato de 2-(1-metilpirrolidin-2-il)etilo;

7) (4'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

8) (3'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

9) (3',5'-dicloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

10) (4'-trifluorometoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

11) (4'-nitro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

12) (3'-trifluorometil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

13) (4'-trifluorometil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

14) ((3'-fluoro-4'-metil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

15) (3'-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

16) (3'-etoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

17) (3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

18) (3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

19) (4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

20) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

21) (5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

22) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

23) (4-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

24) (3',4-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

25) (4-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

26) (5-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

27) (3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

28) (4'-ciano-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

29) (3'-(3-hidroxipropil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

30) (4'-(dimetilamino)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

31) (4'-(tert-butil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

32) (2'-amino-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

33) (3'-amino-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

34) (2'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

35) (2'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

36) (2'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

37) (3'-tert-butil-5'-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

38) (4'-fluoro-3'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

39) (4'-amino-3'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

40) (3'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

41) (3'-cloro-4’-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

42) (3',4',5-trifluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

43) (3',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

44) (3'-etil-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

45) (5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

46) (3'-amino-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

47) (5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

48) (4'-fluoro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

49) (3'-fluoro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

50) (3',5'-difluoro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

51) (3'-cloro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

52) (3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

53) (3'-cloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

54) (4'-cloro-3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

55) (3',5'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

56) (3',5'-dicloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

57) (3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

58) (3'-cloro-5-fluoro-4'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

59) (5-fluoro-3',4'-dimetil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

60) (5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

61) (3'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

62) (3',5'-difluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

63) (3'-cloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

64) (3',5'-dicloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

65) (3'-cloro-4'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

66) (5-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

67) (5-cloro-3'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

68) (5-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

69) (5-cloro-3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

70) (3',5-dicloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

71) (3',5,5'-tricloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

72) (3',5-dicloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

73) (3',5-dicloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

74) (3'-fluoro-4'-formil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

75) (3',5'-difluoro-5-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

76) (3',5'-dicloro-5-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

77) (3'-cloro-4'-fluoro-5-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

78) [1,1'-bifenil]-2-ilcarbamato de (R)-pirrolidin-3-ilmetilo;

79) [1,1'-bifenil]-2-ilcarbamato de (S)-pirrolidin-3-ilmetilo;

80) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo;

81) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo;

82) (5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo;

83) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo;

84) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo;

85) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo;

86) (5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo;

87) (3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo;

88) (4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-2-ilmetilo;

89) [1,1'-bifenil]-2-ilcarbamato de (R)-(1-metilpirrolidin-3-il)metilo;

90) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-metilpirrolidin-3-il)metilo;

91) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

92) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

93) (5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

94) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

95) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

96) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

97) (5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

98) (3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

99) (4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

100) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

101) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

102) [1,1'-bifenil]-2-ilcarbamato de (R)-(1-etilpirrolidin-3-il)metilo;

103) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-etilpirrolidin-3-il)metilo;

104) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-etilpirrolidin-3-il)metilo;

105) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-etilpirrolidin-3-il)metilo;

106) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-etilpirrolidin-2-il)metilo;

107) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-isobutilpirrolidin-2-il)metilo;

108) (3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

109) [1,1'-bifenil]-2-ilcarbamato de (R)-(1-metilpirrolidin-2-il)metilo;

110) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-2-il)metilo;

111) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-2-il)metilo;

112) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-isopropilpirrolidin-2-il)metilo;

113) (3'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

114) (4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

115) (3',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

116) (3'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

117) (3'-cloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

118) (3'-cloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

119) (3',5'-dicloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

120) (3'-cloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

121) (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

122) (5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

123) (3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

124) (4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

125) (3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

126) (3',5'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

127) (4'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

128) (3',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

129) (3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

130) (3',4'-dicloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

131) (3',5'-dicloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

132) (3'-cloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

133) (5-fluoro-3'-amino-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

134) (3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

135) (3',5'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

136) (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

137) (3'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

138) (3'-cloro-5'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

139) (3'-cloro-5-fluoro-5'-metoxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

140) (3'-cloro-5-fluoro-5'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

141) (4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

142) (3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

143) (3'-cloro-4',5-dlfluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

144) (2',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

145) (3',5-dicloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

146) (3',5-dicloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

147) (3'-cloro-4'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

148) (3'-cloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

149) (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato

de (S)-(1-metilpirrolidin-2-il)metilo;

150) (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-etilpirrolidin-3-il)metilo;

151) (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-isopropilpirrolidin-3-il)metilo;

152) (3'-(hidroximetil)-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

153) (3'-carbamoil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

154) (3'-amino-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

155) (3'-ciano-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

156) (2'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

157) (2',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

158) (2',3'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

159) (3'-cloro-6'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

160) (3'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

161) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de

(S)-(1-metilpirrolidin-2-il)metilo;

162) (3',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

163) (2',4',5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

164) (4'-cloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

165) (3'-cloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

166) (3',4'-dicloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

167) (2',4'-dicloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

168) (3'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

169) (3'-ciano-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

170) (3'-amino-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

171) (3',4',5-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

172) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

173) (2',4',5,5'-tetrafluoro-[1,1'-bifenil]-2-

il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

174) (3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

175) (4'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

176) (2',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

177) (3',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

178) (3'-ciano-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

179) (3'-hidroxi-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

180) (5-fluoro-3'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

181) (3'-cloro-4,4',5-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

182) (3'-cloro-4,5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

183) (2',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

184) (2',3'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

185) (2',6'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-

(1-metilpirrolidin-2-il)etilo;

186) (5'-cloro-2'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

187) (2'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

188) (2',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

189) (2',3'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

190) (3'-cloro-6'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

191) (3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

192) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

193) (5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

194) (3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

195) (3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

196) (3'-cloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-etilpirrolidin-3-il)metilo;

197) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-

metilpirrolidin-2-il)metilo;

198) (4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

199) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

200) (5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

201) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

202) (3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

203) (4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

204) (4-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

205) (3',4-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

206) (5-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

207) (3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

208) (5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

209) (4'-(tert-butil)-5-fluoro-[1,1'-bifenil]-2-

il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

210) (3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

211) (3'-cloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

212) (4'-cloro-3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

213) (3'-amino-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

214) (2',5-difluoro-3'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

215) (3'-cloro-5-fluoro-5'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

216) (3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

217) (3'-cloro-5-fluoro-5'-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

218) (5-fluoro-2',4'-bis(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

219) (3'-etoxi-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

220) (5-fluoro-3',4'-dimetoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

221) (5-fluoro-3',5'-dimetoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

222) (5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

223) (3'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

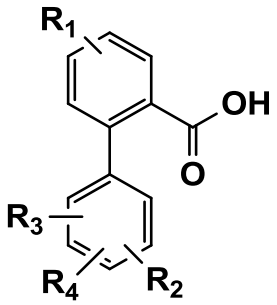
224) (3'-cloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

225) (3',4'-dicloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo; y

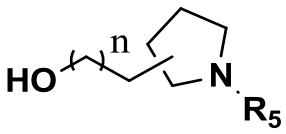
226) (3',5'-dicloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo.

5. Un método para preparar un compuesto de la siguiente Fórmula 1 o una sal farmacéuticamente aceptable del mismo, caracterizado porque el método comprende una etapa para hacer reaccionar un compuesto de la siguiente Fórmula 2 con un compuesto de la siguiente Fórmula 3 en presencia de un reactivo de síntesis de carbamato:

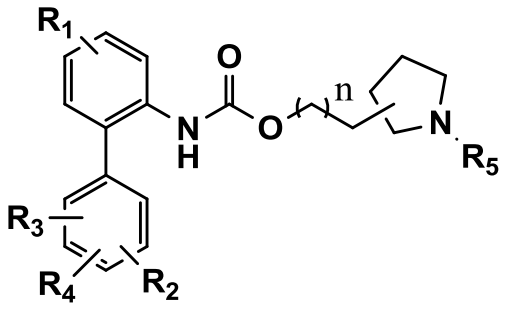
Fórmula 2



Fórmula 3



Fórmula 1



donde R_1 a R_5 y n son las mismas como se definen en la reivindicación 1.

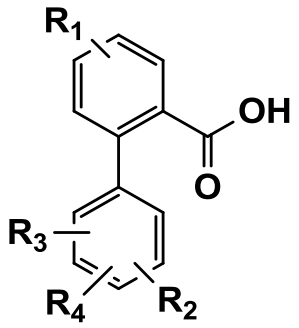
6. Un método para preparar un compuesto de la siguiente Fórmula 1 o una sal farmacéuticamente aceptable del mismo, caracterizado porque el método comprende las etapas de:

hacer reaccionar un compuesto de la siguiente Fórmula 2 con un compuesto de la siguiente Fórmula 3a en presencia de un reactivo de síntesis de carbamato para preparar un compuesto de la siguiente Fórmula 4;

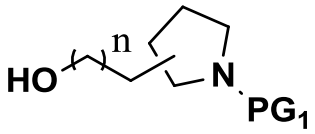
remover un grupo protector amina del compuesto de la Fórmula 4 para preparar un compuesto de la siguiente Fórmula 1a; e

introducir un sustituyente de R_5 al compuesto de la Fórmula 1a:

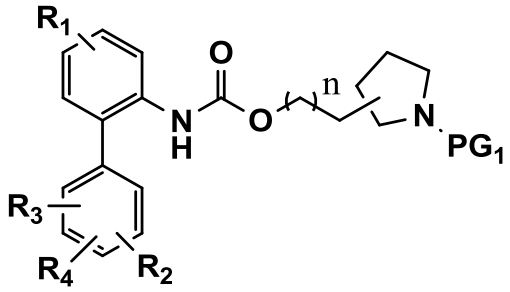
Fórmula 2



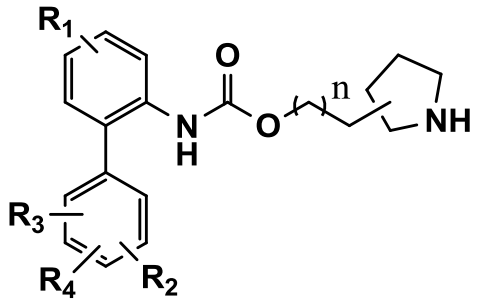
Fórmula 3a



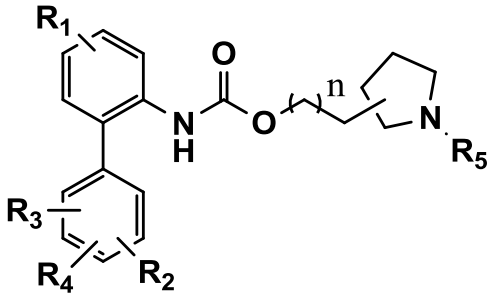
Fórmula 4



Fórmula 1a



Fórmula 1



donde R_1 a R_5 y n son las mismas como se definen en la reivindicación 1, y PG_1 es un grupo protector amina seleccionado del grupo que consiste de Boc (tert-butiloxicarbonilo), bencilo, tert-butilo, PMB (4-metoxibencilo), Fmoc (fluorenilmetiloxicarbonilo), Ts (tosilato), MOM (metoximetil), THP (tetrahidropiranilo), TBDMS (tert-butildimetilsililo), y TBDPS (tert-butildimetilsililo).

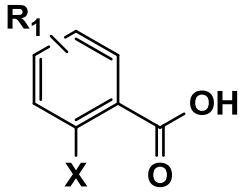
7. El método de conformidad con la reivindicación 5 o 6, caracterizado porque el compuesto de la Fórmula 2 se prepara por las etapas de:

hacer reaccionar un compuesto de la siguiente Fórmula 5 en presencia de un ácido para preparar un compuesto de la siguiente Fórmula 6, el cual tiene un grupo protector de ácido carboxílico introducido en el mismo;

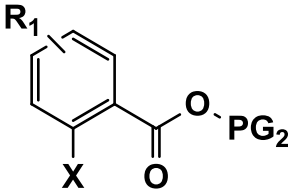
acoplar el compuesto de la Fórmula 6 con un compuesto de la siguiente Fórmula 7 para preparar un compuesto de la siguiente Fórmula 8; y

des-esterificar el compuesto de la Fórmula 8 en presencia de una base:

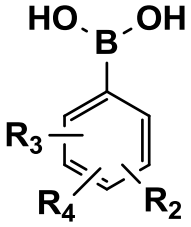
Fórmula 5



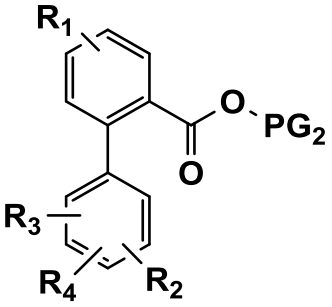
Fórmula 6



Fórmula 7



Fórmula 8



donde R_1 a R_5 y n son las mismas como se definen en la reivindicación 1; X es halógeno; y PG_2 es un grupo protector seleccionado del grupo que consiste de un grupo alquilo C_1-C_4,

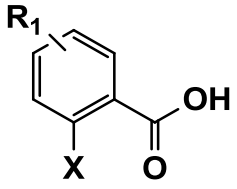
bencilo, PMB (4-metoxibencilo), THP (tetrahidropiranilo), TBDMS (tert-butildimetilsililo), y TBDPS (tert-butildimetilsililo).

8. Un método para preparar un compuesto de la siguiente Fórmula 1 o una sal farmacéuticamente aceptable del mismo, caracterizado porque el método comprende las etapas de:

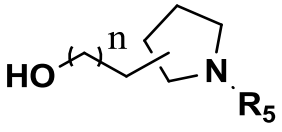
hacer reaccionar un compuesto de la siguiente Fórmula 5 con un compuesto de la siguiente Fórmula 3 en presencia de un reactivo de síntesis de carbamato para preparar un compuesto de la siguiente Fórmula 9; y

acoplar un compuesto de la siguiente Fórmula 7 al compuesto de la Fórmula 9:

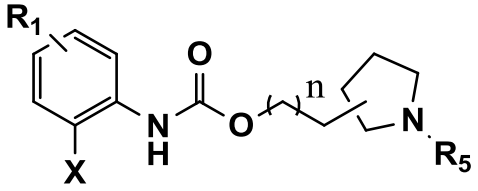
Fórmula 5



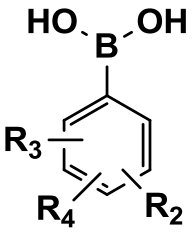
Fórmula 3



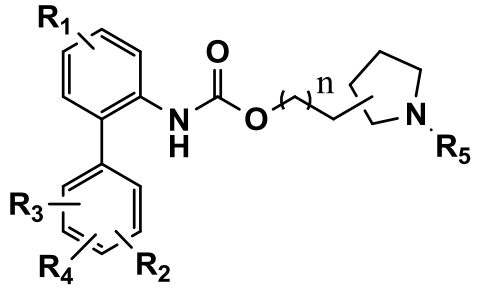
[Fórmula 9]



Fórmula 7



Fórmula 1



donde R_1 a R_5 y n son las mismas como se definen en la reivindicación 1, y X es halógeno.

9. Un método para preparar un compuesto de la siguiente Fórmula 1 o una sal farmacéuticamente aceptable del mismo, caracterizado porque el método comprende las etapas de:

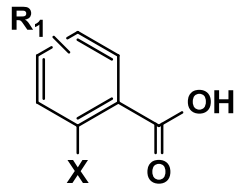
hacer reaccionar un compuesto de la siguiente Fórmula 5 con un compuesto de la siguiente Fórmula 3a en presencia de un reactivo de síntesis de carbamato para preparar un compuesto de la siguiente Fórmula 9a;

desproteger el compuesto de la Fórmula 9a para preparar un compuesto de la siguiente Fórmula 9b;

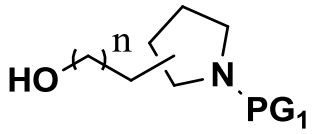
introducir un sustituyente de R_5 al compuesto de la Fórmula 9b para preparar un compuesto de la siguiente Fórmula 9; y

acoplar un compuesto de la siguiente Fórmula 7 al compuesto de la Fórmula 9:

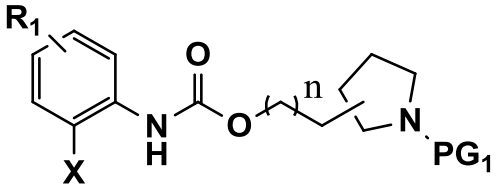
Fórmula 5



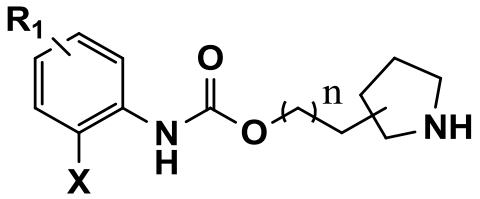
Fórmula 3a



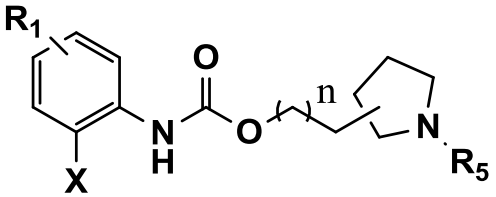
Fórmula 9a



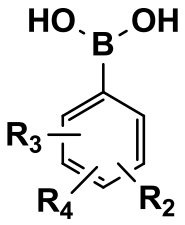
Fórmula 9b



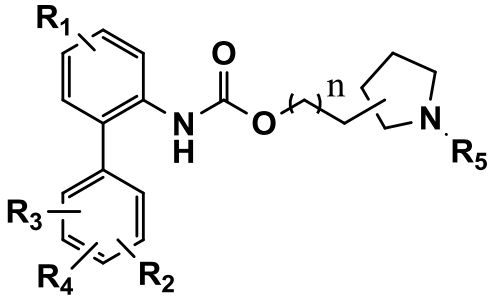
Fórmula 9



Fórmula 7



Fórmula 1



donde R_1 a R_5 y n son las mismas como se definen en la reivindicación 1; X es halógeno; y PG_1 es el mismo como se define en la reivindicación 6.

10. El método de conformidad con cualquiera de las reivindicaciones 5, 6, 8 y 9, caracterizado porque el reactivo de síntesis de carbamato comprende un compuesto de azida.

11. El método de conformidad con la reivindicación 10, caracterizado porque el reactivo de síntesis de carbamato es un mezcla de azida de difenilfosforilo (DPPA) y trietilamina, una mezcla de anhídrido propilfosfónico (T3P), azida de trimetilsililo ($TMSN_3$) y trietilamina, o una mezcla de azida de sodio (NaN_3), bromuro de tetrabutilamonio y triflato de zinc(II).

12. Un antagonista del receptor muscarínico M3 caracterizado porque contiene al compuesto de conformidad con la reivindicación 1, un isómero del mismo, o una sal farmacéuticamente aceptable del mismo como un ingrediente activo.

13. El antagonista del receptor muscarínico M3 de conformidad con la reivindicación 12, caracterizado porque sirve para prevenir o tratar una enfermedad seleccionada del grupo que consiste de enfermedad pulmonar obstructiva crónica, asma, síndrome de intestino irritable, incontinencia urinaria, rinitis, colitis espasmódica, cistitis crónica, enfermedad de Alzheimer, demencia senil, glaucoma, esquizofrenia, enfermedad de reflujo gastroesofágico, arritmia cardiaca, y síndromes de hipersalivación.

14. Un método para prevenir o tratar una enfermedad relacionada con el receptor muscarínico M3, caracterizado porque el método comprende administrar una composición que contiene el compuesto de conformidad con la reivindicación 1, un isómero del mismo, o una sal farmacéuticamente aceptable del mismo como un ingrediente activo a mamíferos incluyendo humanos en necesidad del mismo.

15. Uso de una composición que contiene el compuesto de conformidad de la reivindicación 1, un isómero del mismo, o una sal farmacéuticamente aceptable del mismo como un

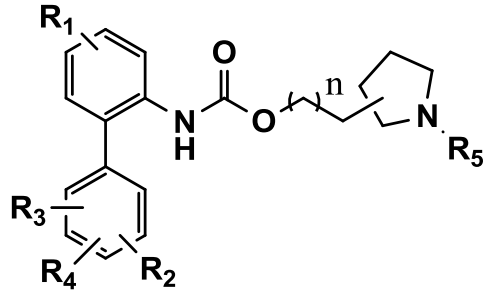
ingrediente activo para la preparación de un medicamente para prevenir o tratar una enfermedad relacionada con el receptor muscarínico M3.

RESUMEN DE LA INVENCIÓN

La presente invención proporciona derivados de bifenilo novedosos, isómeros de los mismos, o sales farmacéuticamente aceptables de los mismos, métodos para preparar los mismos, y una composición farmacéutica que contiene los mismos. Los derivados de bifenilo novedosos, isómeros de los mismos, o sales farmacéuticamente aceptables de los mismos, como se describe en la presente invención, actúan como antagonistas del receptor muscarínico M3, y de esta manera son útiles para la prevención o tratamiento de una enfermedad seleccionada del grupo que consiste de enfermedad pulmonar obstructiva crónica, asma, síndrome de intestino irritable, incontinencia urinaria, rinitis, colitis espasmódica, cistitis crónica, enfermedad de Alzheimer, demencia senil, glaucoma, esquizofrenia, enfermedad de reflujo gastroesofágico, arritmia cardiaca, y síndromes de hipersalivación.

REIVINDICACIONES

1. Un derivado de bifenilo novedoso representado por la siguiente Fórmula 1, un isómero del mismo, o una sal farmacéuticamente aceptable del mismo:



caracterizado porque

R_1 es hidrógeno, halógeno, hidroxi, alquilo C_1-C_6 sustituido o no sustituido, o alcoxi C_1-C_6;

R_2, R_3 y R_4 son independientemente hidrógeno, halógeno, amino sustituido o no sustituido, nitro, ciano, hidroxi, alquilo C_1-C_6 sustituido o no sustituido, alcoxi C_1-C_6 sustituido o no sustituido, o $-C(O)R_6$;

R_5 es hidrógeno o alquilo C_1-C_6;

n es 0 o 1; y

R_6 es hidrógeno o amino.

2. El derivado de bifenilo novedoso, isómero del mismo o

sal farmacéuticamente aceptable del mismo de conformidad con la reivindicación 1, caracterizado porque R_1 es hidrógeno o halógeno; R_2, R_3 y R_4 son independientemente hidrógeno, halógeno, o alquilo C_1-C_6; y R_5 es alquilo C_1-C_6.

3. El derivado de bifenilo novedoso, isómero del mismo o sal farmacéuticamente aceptable del mismo de conformidad con la reivindicación 1, caracterizado porque R_1 es hidrógeno; R_2, R_3 y R_4 son de forma independiente hidrógeno o halógeno; R_5 es alquilo C_1-C_6; y n es 0 o 1.

4. El derivado de bifenilo novedoso, isómero del mismo o sal farmacéuticamente aceptable del mismo de conformidad con la reivindicación 1, caracterizado porque el derivado de bifenilo novedoso se selecciona del grupo que consiste de los siguientes compuestos:

1) (4'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

2) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

3) (3',4',5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

4) (3'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

5) (4'-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

6) [1,1'-bifenil]-2-ilcarbamato de 2-(1-metilpirrolidin-2-il)etilo;

7) (4'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

8) (3'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

9) (3',5'-dicloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

10) (4'-trifluorometoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

11) (4'-nitro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

12) (3'-trifluorometil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

13) (4'-trifluorometil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

14) ((3'-fluoro-4'-metil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

15) (3'-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

16) (3'-etoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

17) (3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

18) (3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

19) (4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

20) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

21) (5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

22) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

23) (4-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

24) (3',4-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

25) (4-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

26) (5-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

27) (3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

28) (4'-ciano-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

29) (3'-(3-hidroxipropil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

30) (4'-(dimetilamino)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

31) (4'-(tert-butil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

32) (2'-amino-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

33) (3'-amino-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

34) (2'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

35) (2'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

36) (2'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

37) (3'-tert-butil-5'-metil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

38) (4'-fluoro-3'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

39) (4'-amino-3'-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

40) (3'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

41) (3'-cloro-4’-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

42) (3',4',5-trifluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

43) (3',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

44) (3'-etil-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

45) (5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

46) (3'-amino-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

47) (5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

48) (4'-fluoro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

49) (3'-fluoro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

50) (3',5'-difluoro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

51) (3'-cloro-5-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

52) (3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

53) (3'-cloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

54) (4'-cloro-3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

55) (3',5'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

56) (3',5'-dicloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

57) (3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

58) (3'-cloro-5-fluoro-4'-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

59) (5-fluoro-3',4'-dimetil-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

60) (5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

61) (3'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

62) (3',5'-difluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

63) (3'-cloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

64) (3',5'-dicloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

65) (3'-cloro-4'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

66) (5-cloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

67) (5-cloro-3'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

68) (5-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

69) (5-cloro-3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

70) (3',5-dicloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

71) (3',5,5'-tricloro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

72) (3',5-dicloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

73) (3',5-dicloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

74) (3'-fluoro-4'-formil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

75) (3',5'-difluoro-5-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

76) (3',5'-dicloro-5-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

77) (3'-cloro-4'-fluoro-5-hidroxi-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

78) [1,1'-bifenil]-2-ilcarbamato de (R)-pirrolidin-3-ilmetilo;

79) [1,1'-bifenil]-2-ilcarbamato de (S)-pirrolidin-3-ilmetilo;

80) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo;

81) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo;

82) (5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo;

83) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo;

84) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo;

85) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-3-ilmetilo;

86) (5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo;

87) (3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-pirrolidin-3-ilmetilo;

88) (4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-pirrolidin-2-ilmetilo;

89) [1,1'-bifenil]-2-ilcarbamato de (R)-(1-metilpirrolidin-3-il)metilo;

90) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-metilpirrolidin-3-il)metilo;

91) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

92) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

93) (5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

94) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

95) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

96) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

97) (5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

98) (3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

99) (4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

100) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

101) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

102) [1,1'-bifenil]-2-ilcarbamato de (R)-(1-etilpirrolidin-3-il)metilo;

103) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-etilpirrolidin-3-il)metilo;

104) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-etilpirrolidin-3-il)metilo;

105) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-etilpirrolidin-3-il)metilo;

106) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-etilpirrolidin-2-il)metilo;

107) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-isobutilpirrolidin-2-il)metilo;

108) (3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

109) [1,1'-bifenil]-2-ilcarbamato de (R)-(1-metilpirrolidin-2-il)metilo;

110) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-2-il)metilo;

111) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-2-il)metilo;

112) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-isopropilpirrolidin-2-il)metilo;

113) (3'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

114) (4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

115) (3',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

116) (3'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

117) (3'-cloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

118) (3'-cloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

119) (3',5'-dicloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

120) (3'-cloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

121) (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

122) (5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

123) (3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

124) (4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

125) (3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

126) (3',5'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

127) (4'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

128) (3',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

129) (3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-3-il)metilo;

130) (3',4'-dicloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

131) (3',5'-dicloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

132) (3'-cloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

133) (5-fluoro-3'-amino-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

134) (3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

135) (3',5'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

136) (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

137) (3'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

138) (3'-cloro-5'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

139) (3'-cloro-5-fluoro-5'-metoxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

140) (3'-cloro-5-fluoro-5'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

141) (4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

142) (3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

143) (3'-cloro-4',5-dlfluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

144) (2',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

145) (3',5-dicloro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

146) (3',5-dicloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

147) (3'-cloro-4'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

148) (3'-cloro-5'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

149) (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato

de (S)-(1-metilpirrolidin-2-il)metilo;

150) (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-etilpirrolidin-3-il)metilo;

151) (3'-cloro-4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-isopropilpirrolidin-3-il)metilo;

152) (3'-(hidroximetil)-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

153) (3'-carbamoil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

154) (3'-amino-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

155) (3'-ciano-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

156) (2'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

157) (2',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

158) (2',3'-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

159) (3'-cloro-6'-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

160) (3'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

161) (3',5'-difluoro-[1,1'-bifenil]-2-il)carbamato de

(S)-(1-metilpirrolidin-2-il)metilo;

162) (3',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

163) (2',4',5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

164) (4'-cloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

165) (3'-cloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

166) (3',4'-dicloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

167) (2',4'-dicloro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

168) (3'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

169) (3'-ciano-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

170) (3'-amino-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

171) (3',4',5-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

172) (3',5,5'-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

173) (2',4',5,5'-tetrafluoro-[1,1'-bifenil]-2-

il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

174) (3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

175) (4'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

176) (2',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

177) (3',4'-dicloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

178) (3'-ciano-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

179) (3'-hidroxi-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

180) (5-fluoro-3'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

181) (3'-cloro-4,4',5-trifluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

182) (3'-cloro-4,5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

183) (2',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

184) (2',3'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

185) (2',6'-difluoro-[1,1'-bifenil]-2-il)carbamato de 2-

(1-metilpirrolidin-2-il)etilo;

186) (5'-cloro-2'-fluoro-[1,1'-bifenil]-2-il)carbamato de 2-(1-metilpirrolidin-2-il)etilo;

187) (2'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

188) (2',4'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

189) (2',3'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

190) (3'-cloro-6'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

191) (3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

192) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

193) (5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

194) (3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

195) (3'-cloro-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-metilpirrolidin-3-il)metilo;

196) (3'-cloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (R)-(1-etilpirrolidin-3-il)metilo;

197) [1,1'-bifenil]-2-ilcarbamato de (S)-(1-

metilpirrolidin-2-il)metilo;

198) (4'-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

199) (3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

200) (5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

201) (5-fluoro-3'-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

202) (3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

203) (4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

204) (4-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

205) (3',4-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

206) (5-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

207) (3'-fluoro-5-metil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

208) (5-fluoro-3',5'-dimetil-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

209) (4'-(tert-butil)-5-fluoro-[1,1'-bifenil]-2-

il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

210) (3'-cloro-5,5'-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

211) (3'-cloro-4',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

212) (4'-cloro-3',5-difluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

213) (3'-amino-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

214) (2',5-difluoro-3'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

215) (3'-cloro-5-fluoro-5'-(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

216) (3'-cloro-5-fluoro-5'-hidroxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

217) (3'-cloro-5-fluoro-5'-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

218) (5-fluoro-2',4'-bis(trifluorometil)-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

219) (3'-etoxi-5-fluoro-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

220) (5-fluoro-3',4'-dimetoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

221) (5-fluoro-3',5'-dimetoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

222) (5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

223) (3'-fluoro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

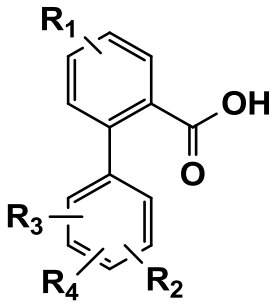
224) (3'-cloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo;

225) (3',4'-dicloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo; y

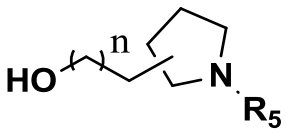
226) (3',5'-dicloro-5-metoxi-[1,1'-bifenil]-2-il)carbamato de (S)-(1-metilpirrolidin-2-il)metilo.

5. Un método para preparar un compuesto de la siguiente Fórmula 1 o una sal farmacéuticamente aceptable del mismo, caracterizado porque el método comprende una etapa para hacer reaccionar un compuesto de la siguiente Fórmula 2 con un compuesto de la siguiente Fórmula 3 en presencia de un reactivo de síntesis de carbamato:

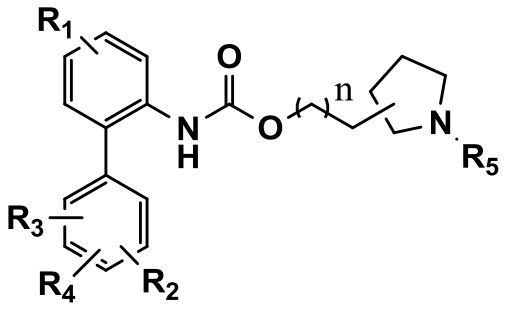
Fórmula 2



Fórmula 3



Fórmula 1



donde R_1 a R_5 y n son las mismas como se definen en la reivindicación 1.

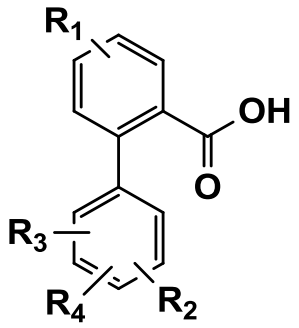
6. Un método para preparar un compuesto de la siguiente Fórmula 1 o una sal farmacéuticamente aceptable del mismo, caracterizado porque el método comprende las etapas de:

hacer reaccionar un compuesto de la siguiente Fórmula 2 con un compuesto de la siguiente Fórmula 3a en presencia de un reactivo de síntesis de carbamato para preparar un compuesto de la siguiente Fórmula 4;

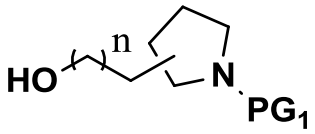
remover un grupo protector amina del compuesto de la Fórmula 4 para preparar un compuesto de la siguiente Fórmula 1a; e

introducir un sustituyente de R_5 al compuesto de la Fórmula 1a:

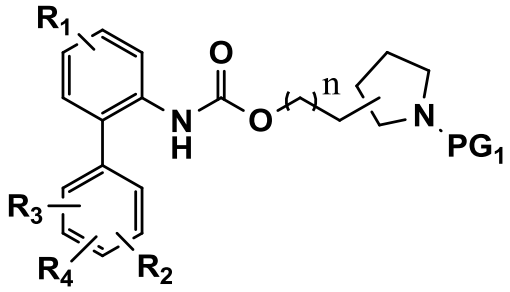
Fórmula 2



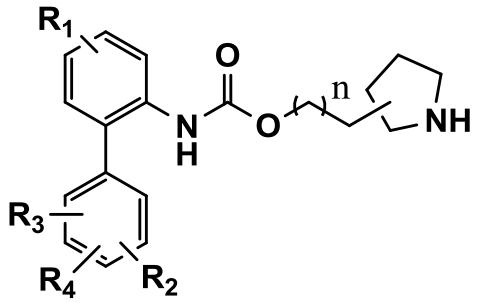
Fórmula 3a



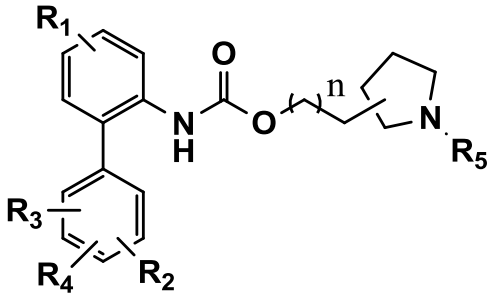
Fórmula 4



Fórmula 1a



Fórmula 1



donde R_1 a R_5 y n son las mismas como se definen en la reivindicación 1, y PG_1 es un grupo protector amina seleccionado del grupo que consiste de Boc (tert-butiloxicarbonilo), bencilo, tert-butilo, PMB (4-metoxibencilo), Fmoc (fluorenilmetiloxicarbonilo), Ts (tosilato), MOM (metoximetil), THP (tetrahidropiranilo), TBDMS (tert-butildimetilsililo), y TBDPS (tert-butildimetilsililo).

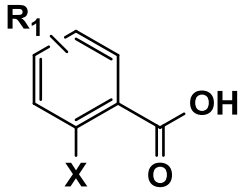
7. El método de conformidad con la reivindicación 5 o 6, caracterizado porque el compuesto de la Fórmula 2 se prepara por las etapas de:

hacer reaccionar un compuesto de la siguiente Fórmula 5 en presencia de un ácido para preparar un compuesto de la siguiente Fórmula 6, el cual tiene un grupo protector de ácido carboxílico introducido en el mismo;

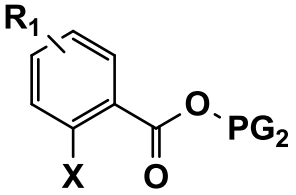
acoplar el compuesto de la Fórmula 6 con un compuesto de la siguiente Fórmula 7 para preparar un compuesto de la siguiente Fórmula 8; y

des-esterificar el compuesto de la Fórmula 8 en presencia de una base:

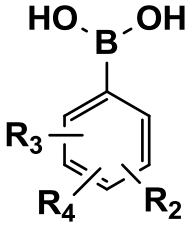
Fórmula 5



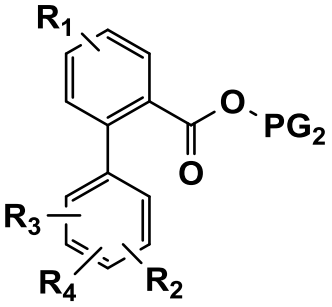
Fórmula 6



Fórmula 7



Fórmula 8



donde R_1 a R_5 y n son las mismas como se definen en la reivindicación 1; X es halógeno; y PG_2 es un grupo protector seleccionado del grupo que consiste de un grupo alquilo C_1-C_4,

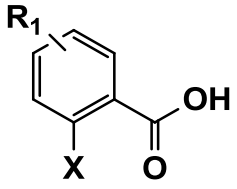
bencilo, PMB (4-metoxibencilo), THP (tetrahidropiranilo), TBDMS (tert-butildimetilsililo), y TBDPS (tert-butildimetilsililo).

8. Un método para preparar un compuesto de la siguiente Fórmula 1 o una sal farmacéuticamente aceptable del mismo, caracterizado porque el método comprende las etapas de:

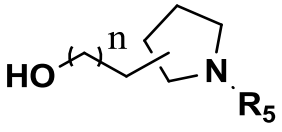
hacer reaccionar un compuesto de la siguiente Fórmula 5 con un compuesto de la siguiente Fórmula 3 en presencia de un reactivo de síntesis de carbamato para preparar un compuesto de la siguiente Fórmula 9; y

acoplar un compuesto de la siguiente Fórmula 7 al compuesto de la Fórmula 9:

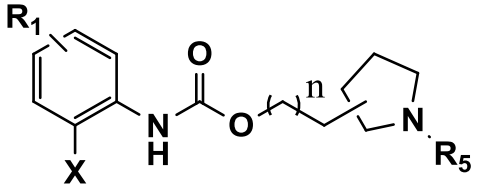
Fórmula 5



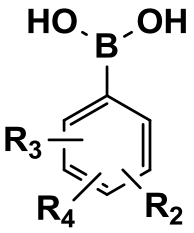
Fórmula 3



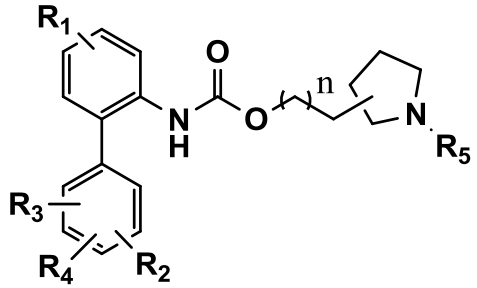
[Fórmula 9]



Fórmula 7



Fórmula 1



donde R_1 a R_5 y n son las mismas como se definen en la reivindicación 1, y X es halógeno.

9. Un método para preparar un compuesto de la siguiente Fórmula 1 o una sal farmacéuticamente aceptable del mismo, caracterizado porque el método comprende las etapas de:

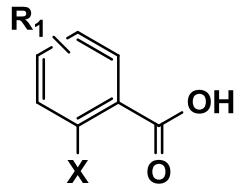
hacer reaccionar un compuesto de la siguiente Fórmula 5 con un compuesto de la siguiente Fórmula 3a en presencia de un reactivo de síntesis de carbamato para preparar un compuesto de la siguiente Fórmula 9a;

desproteger el compuesto de la Fórmula 9a para preparar un compuesto de la siguiente Fórmula 9b;

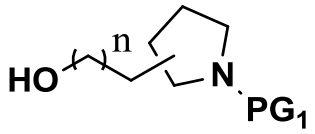
introducir un sustituyente de R_5 al compuesto de la Fórmula 9b para preparar un compuesto de la siguiente Fórmula 9; y

acoplar un compuesto de la siguiente Fórmula 7 al compuesto de la Fórmula 9:

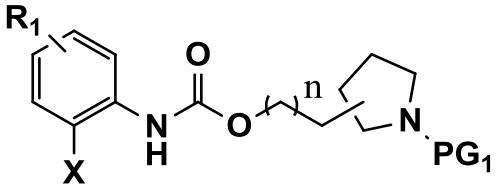
Fórmula 5



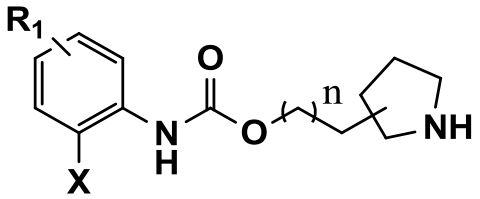
Fórmula 3a



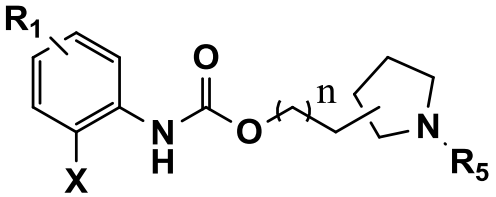
Fórmula 9a



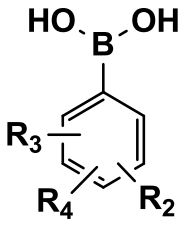
Fórmula 9b



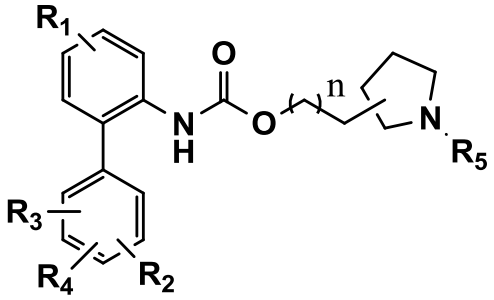
Fórmula 9



Fórmula 7



Fórmula 1



donde R_1 a R_5 y n son las mismas como se definen en la reivindicación 1; X es halógeno; y PG_1 es el mismo como se define en la reivindicación 6.

10. El método de conformidad con cualquiera de las reivindicaciones 5, 6, 8 y 9, caracterizado porque el reactivo de síntesis de carbamato comprende un compuesto de azida.

11. El método de conformidad con la reivindicación 10, caracterizado porque el reactivo de síntesis de carbamato es un mezcla de azida de difenilfosforilo (DPPA) y trietilamina, una mezcla de anhídrido propilfosfónico (T3P), azida de trimetilsililo ($TMSN_3$) y trietilamina, o una mezcla de azida de sodio (NaN_3), bromuro de tetrabutilamonio y triflato de zinc(II).

12. Un antagonista del receptor muscarínico M3 caracterizado porque contiene al compuesto de conformidad con la reivindicación 1, un isómero del mismo, o una sal farmacéuticamente aceptable del mismo como un ingrediente activo.

13. El antagonista del receptor muscarínico M3 de conformidad con la reivindicación 12, caracterizado porque sirve para prevenir o tratar una enfermedad seleccionada del grupo que consiste de enfermedad pulmonar obstructiva crónica, asma, síndrome de intestino irritable, incontinencia urinaria, rinitis, colitis espasmódica, cistitis crónica, enfermedad de Alzheimer, demencia senil, glaucoma, esquizofrenia, enfermedad de reflujo gastroesofágico, arritmia cardiaca, y síndromes de hipersalivación.

14. Un método para prevenir o tratar una enfermedad relacionada con el receptor muscarínico M3, caracterizado porque el método comprende administrar una composición que contiene el compuesto de conformidad con la reivindicación 1, un isómero del mismo, o una sal farmacéuticamente aceptable del mismo como un ingrediente activo a mamíferos incluyendo humanos en necesidad del mismo.

15. Uso de una composición que contiene el compuesto de conformidad de la reivindicación 1, un isómero del mismo, o una sal farmacéuticamente aceptable del mismo como un

ingrediente activo para la preparación de un medicamente para prevenir o tratar una enfermedad relacionada con el receptor muscarínico M3.

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Dr. Ahn International Patent Law Office
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Seocho-gu
Seoul 137-881
RÉPUBLIQUE DE CORÉE

Date of mailing *(day/month/year)* 30 September 2014 (30.09.2014)	
Applicant's or agent's file reference P14018-DONG	**IMPORTANT NOTIFICATION**
International application No. PCT/KR2014/006483	International filing date *(day/month/year)* 17 July 2014 (17.07.2014)
International publication date *(day/month/year)* **Not yet published**	Priority date *(day/month/year)* 30 July 2013 (30.07.2013)
Applicant DONG-A ST CO., LTD	

The applicant is hereby notified of the date of receipt (or of obtaining by the International Bureau) of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to the date of receipt, **the priority document concerned was submitted or transmitted to or obtained by the International Bureau in compliance with Rule 17.1(a), (b) or (b-*bis*)**. This Form replaces any previously issued notification concerning submission, transmittal or obtaining of priority documents.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
30 July 2013 (30.07.2013)	10-2013-0090175	KR	22 July 2014 (22.07.2014)

The letters "NR" denote a priority document which, on the date of mailing of this Form, had not yet been received or obtained by the International Bureau in compliance with Rule 17.1(a), (b) or (b-*bis*). Where the applicant has failed to either submit, request to prepare and transmit, or to request the International Bureau to obtain the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

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(12) 특허협력조약에 의하여 공개된 국제출원

(19) 세계지식재산권기구
국제사무국

(43) 국제공개일
2015 년 2 월 5 일 (05.02.2015)

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(21) 국제출원번호: PCT/KR2014/006483

(22) 국제출원일: 2014 년 7 월 17 일 (17.07.2014)

(25) 출원언어: 한국어

(26) 공개언어: 한국어

(30) 우선권정보:
10-2013-0090175 2013 년 7 월 30 일 (30.07.2013) KR

(71) 출원인: **동아에스티 주식회사 (DONG-A ST CO., LTD)** [KR/KR]; 130-823 서울시 동대문구 천호대로 64, Seoul (KR).

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(74) 대리인: **안소영 (AHN, So-Young)**; 137-881 서울시 서초구 서초대로 344, 4 층 안소영 국제특허법률사무소, Seoul (KR).

(81) 지정국 (별도의 표시가 없는 한, 가능한 모든 종류의 국내 권리의 보호를 위하여): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) 지정국 (별도의 표시가 없는 한, 가능한 모든 종류의 역내 권리의 보호를 위하여): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), 유라시아 (AM, AZ, BY, KG, KZ, RU, TJ, TM), 유럽 (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

공개:
— 국제조사보고서와 함께 (조약 제 21 조(3))

WO 2015/016511 A1

(54) **Title**: NOVEL BIPHENYL DERIVATIVE AND METHOD FOR PREPARING SAME

(54) **발명의 명칭** : 신규한 바이페닐 유도체 및 그의 제조방법

(57) **Abstract**: The present invention provides a novel biphenyl derivative, or an isomer or pharmaceutically acceptable salt thereof, a method for preparing the same, and a pharmaceutical composition containing the same. The novel biphenyl derivative, or the isomer or pharmaceutically acceptable salt thereof according to the present invention acts as a muscarinic M3 receptor antagonist, and thus can be useful for the prevention or treatment of a disease selected from the group consisting of chronic obstructive pulmonary disease, asthma, irritable bowel syndrome, urinary incontinence, rhinitis, spasmodic colitis, chronic cystitis, Alzheimer's disease, senile dementia, glaucoma, schizophrenia, gastroesophogeal reflux disease, cardiac arrhythmia, and hyper salivation syndrome.

(57) **요약서**: 본 발명은 신규한 바이페닐 유도체, 이의 이성질체 또는 이의 약학적으로 허용가능한 염, 이의 제조방법, 이를 포함하는 약학적 조성물을 제공한다. 본 발명에 따른 신규한 바이페닐 유도체, 이의 이성질체 또는 이의 약학적으로 허용가능한 염은 무스카린 M3 수용체 길항제로서 작용함으로써, 만성 폐쇄성 폐질환(Chronic obstructive pulmonary disease), 천식(asthma), 과민성 대장 증후군(irritable bowel syndrome), 요실금(urinary incontinence), 비염(rhinitis), 경련성 대장염(spasmodic colitis), 만성 방광염(chronic cystitis), 알츠하이머병(alzheimer's disease), 노인성 치매(senile dementia), 녹내장(glaucoma), 조현병(schizophrenia), 역류성 식도염(gastroesophogeal reflux disease), 심장 부정맥(cardiac arrhythmia), 타액분비항진증(hyper salivation syndromes)으로 이루어진 군으로부터 선택되는 질환의 예방 또는 치료에 유용하게 적용될 수 있다.

명세서

발명의 명칭: 신규한 바이페닐 유도체 및 그의 제조방법

기술분야

[1] 본 발명은 신규한 무스카린 M3 수용체 길항제(antagonist)에 관한 것으로, 더욱 상세하게는 무스카린 M3 수용체 길항제의 활성을 갖는 신규한 바이페닐 유도체, 그 이성질체, 약학적으로 허용가능한 염 또는 수화물, 이의 제조방법 및 이를 유효성분으로 포함하는 약학적 조성물에 관한 것이다.

배경기술

[2] 무스카린 수용체는 사람의 뇌에서부터 침샘에 이르기까지 전신에 다양하게 존재하며, 이 수용체는 G-단백질 커플링된 수용체의 구성원으로서, M1에서 M5까지 5개의 아형으로 세분화된다. 이들 중 M1, M2 및 M3 수용체는 동물 및 인간 조직에서 광범위하게 존재하며, 그 약리상 특징이 규명되어 있다. 무스카린 M1 수용체는 대뇌 피질에서 주로 발현되고, 고도의 인지 기능을 조절하는데 관여한다. M2 수용체는 심장 및 방광 평활근에서 주로 존재하며 심박 조절에 관여한다. M3 수용체는 많은 말초 조직에서 광범위하게 발현되며, 위장관 및 요로관 자극, 타액 분비에 관여하는 것으로 알려져 있다. M4 및 M5 수용체는 뇌에 존재하며 주로 M4 수용체는 운동에 관여하지만, M5 수용체의 역할에 대해서는 거의 알려진 바가 없다.

[3] 일반적으로, 무스카린 수용체 길항제들은 다양한 질환, 예를 들어 만성 폐쇄성 폐질환(Chronic obstructive pulmonary disease), 천식(asthma), 과민성 대장 증후군(irritable bowel syndrome), 요실금(urinary incontinence), 비염(rhinitis), 경련성 대장염(spasmodic colitis), 만성 방광염(chronic cystitis), 알츠하이머병(alzheimer's disease), 노인성 치매(senile dementia), 녹내장(glaucoma), 조현병(schizophrenia), 역류성 식도염(gastroesophogeal reflux disease), 심장 부정맥(cardiac arrhythmia), 타액분비항진증(hyper salivation syndromes) 등의 치료에 유용한 것으로 밝혀졌다 (Invest. Drugs, 1997, 6 (10), 1395-1411, Drugs Future, 1997, 22 (2) 135-137, Drugs Future, 1996, 21 (11), 1105-1108, Drugs Future, 1997, 22 (7), 733-737).

[4] 한편, 사람의 방광 내에는 무스카린 수용체 아형 중 M2 와 M3가 우세하게 존재하며 이들은 방광수축 기전을 조절하는 역할을 하고 있는 것으로 알려져 있다. M2 수용체는 방광에서 M3 수용체보다 3배 이상 많은 양이 존재하지만 이는 직접 방광수축에 관여하기 보다 베타수용체를 통해 방광이완을 억제하는 역할을 함으로써 방광수축에 가장 주도적인 역할을 수행하는 수용체는 M3 수용체로 간주되고 있다. 따라서 M3 수용체의 선택적 길항제가 무스카린성 방광 수축에 대해 우수한 억제 효과를 나타내게 되나 이와 동시에 이는 침샘 분비를 억제함으로써 입마름증을 유발하게 된다.

[5] 이에 본 발명자는 무스카린 M3 수용체에 선택적으로 결합하여 작용적 활성을 나타내며, 부작용을 최소화시킬 수 있는 신규한 유도체들을 제조함으로써 본 발명을 완성하였다.

발명의 상세한 설명

기술적 과제

[6] 본 발명은 신규한 바이페닐 유도체 또는 약학적으로 허용가능한 염을 제공하는 것을 목적으로 한다.

[7] 또한, 본 발명은 신규한 바이페닐 유도체 또는 약학적으로 허용가능한 염의 제조방법을 제공하는 것을 목적으로 한다.

[8] 또한, 본 발명은 신규한 바이페닐 유도체, 약학적으로 허용가능한 염 또는 수화물을 유효성분으로 함유하는 무스카린 M3 수용체 길항제를 제공하는 것을 목적으로 한다.

과제 해결 수단

[9] 본 발명은 신규한 바이페닐 유도체 또는 약학적으로 허용가능한 염을 제공한다.

[10] 또한, 본 발명은 신규한 바이페닐 유도체 또는 약학적으로 허용가능한 염의 제조방법을 제공한다.

[11] 또한, 본 발명은 신규한 바이페닐 유도체, 약학적으로 허용가능한 염 또는 수화물을 유효성분으로 함유하는 무스카린 M3 수용체 길항제를 제공한다.

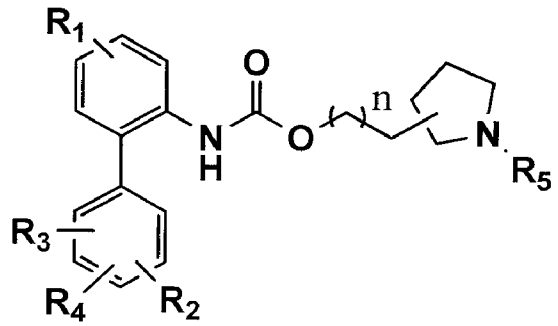
[12] 본 명세서에서, 용어 "알킬(alkyl)"은 직쇄상 또는 분지상의 탄화수소 라디칼을 의미한다. 예를 들어 C1~C6 알킬은 1 내지 6개의 탄소원자를 갖는 지방족 탄화수소로서, 메틸, 에틸, 프로필, n-부틸, n-펜틸, n-헥실, 이소프로필, 이소부틸, sec-부틸, tert-부틸, 네오펜틸, 이소펜틸 등을 모두 포함한다.

[13] 또한, 용어 "알콕시(alkoxy)"는 히드록시기의 수소 원자가 알킬로 치환된 라디칼을 의미하며, 예를 들어 C1~C6 알콕시는 메톡시, 에톡시, 프로폭시, n-부톡시, n-펜틸옥시, 이소프로폭시, sec-부톡시, tert-부톡시, 네오펜틸옥시, 이소펜틸옥시 등을 모두 포함한다.

[14] <u>신규한 바이페닐 유도체</u>

[15] 본 발명은 하기 화학식 1로 표시되는 신규한 바이페닐 유도체, 이의 약학적으로 허용가능한 염을 제공한다.

[16] [화학식 1]

[17] 

[18] 상기 화학식 1에서,

[19] R_1은 수소, 할로겐, 히드록시, 치환 또는 비치환된 C1~C6의 알킬, 또는 C1~C6의 알콕시이고,

[20] R_2, R_3, R_4는 각각 독립적으로 수소, 할로겐, 치환 또는 비치환된 아미노, 니트로, 시아노, 히드록시, 치환 또는 비치환된 C1~C6의 알킬, 치환 또는 비치환된 C1~C6의 알콕시, 또는 $-C(O)R_6$이고,

[21] R_5는 수소 또는 C1~C6의 알킬이고,

[22] n은 0 또는 1이며,

[23] R_6는 수소 또는 아미노이다.

[24] 또한, 본 발명의 바람직한 구체예에 따르면, 상기 화학식 1에서, R_1은 수소 또는 할로겐이고, R_2, R_3, R_4는 각각 독립적으로 수소, 할로겐, 또는 C1~C6의 알킬이고, R_5는 C1~C6의 알킬일 수 있다.

[25] 또한, 본 발명의 다른 바람직한 구체예에 따르면, 상기 화학식 1에서, R_1은 수소이고, R_2, R_3, R_4는 각각 독립적으로 수소 또는 할로겐이고, R_5는 C1~C6의 알킬이며, n은 0 또는 1일 수 있다.

[26] 본 발명에서, 약학적으로 허용가능한 염은 허용가능한 유리산(free acid)에 의해 형성된 산부가 염이 유용하다. 유리산으로는 무기산과 유기산을 사용할 수 있으며, 무기산으로는 염산, 브롬산, 황산, 인산 등을 사용할 수 있고, 유기산으로는 구연산, 초산, 젖산, 말레인산, 우마린산, 글루콘산, 메탄설폰산, 글리콘산, 숙신산, 4-톨루엔셀폰산, 트리플루오로아세트산, 갈룩투론산, 엠본산, 글루탐산, 또는 아스파르트산 등을 사용할 수 있다.

[27] 또한, 상기 화학식 1의 화합물, 또는 약학적으로 허용 가능한 염은 다형(polymorphism)을 나타낼 수 있고, 또한 용매화물 (예컨대, 수화물 등)로서 존재할 수 있다. 그리고 각 화합물들은 개별 입체 이성질체 또는 그 혼합물을 포함한다.

[28] 또한, 본 발명은 하기 화합물로부터 이루어진 군으로부터 선택되는 신규한 바이페닐 유도체에 관한 것이다.

[29] 1) 2-(1-메틸피롤리딘-2-일)에틸 (4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[30] 2) 2-(1-메틸피롤리딘-2-일)에틸 (3',
5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[31] 3) 2-(1-메틸피롤리딘-2-일)에틸

(3',4',5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[32] 4) 2-(1-메틸피롤리딘-2-일)에틸 (3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[33] 5) 2-(1-메틸피롤리딘-2-일)에틸 (4'-메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[34] 6) 2-(1-메틸피롤리딘-2-일)에틸 [1,1'-바이페닐]-2-일카바메이트;

[35] 7) 2-(1-메틸피롤리딘-2-일)에틸 (4'-클로로-[1,1'-바이페닐]-2-일)카바메이트;

[36] 8) 2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-[1,1'-바이페닐]-2-일)카바메이트;

[37] 9) 2-(1-메틸피롤리딘-2-일)에틸
(3',5'-디클로로-[1,1'-바이페닐]-2-일)카바메이트;

[38] 10) 2-(1-메틸피롤리딘-2-일)에틸
(4'-트리플루오로메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[39] 11) 2-(1-메틸피롤리딘-2-일)에틸 (4'-니트로-[1,1'-바이페닐]-2-일)카바메이트;

[40] 12) 2-(1-메틸피롤리딘-2-일)에틸
(3'-트리플루오로메틸-[1,1'-바이페닐]-2-일)카바메이트;

[41] 13) 2-(1-메틸피롤리딘-2-일)에틸
(4'-트리플루오로메틸-[1,1'-바이페닐]-2-일)카바메이트;

[42] 14) 2-(1-메틸피롤리딘-2-일)에틸
((3'-플루오로-4'-메틸)-[1,1'-바이페닐]-2-일)카바메이트;

[43] 15) 2-(1-메틸피롤리딘-2-일)에틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[44] 16) 2-(1-메틸피롤리딘-2-일)에틸 (3'-에톡시-[1,1'-바이페닐]-2-일)카바메이트;

[45] 17) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[46] 18) 2-(1-메틸피롤리딘-2-일)에틸
(3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[47] 19) 2-(1-메틸피롤리딘-2-일)에틸
(4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[48] 20) 2-(1-메틸피롤리딘-2-일)에틸
(3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[49] 21) 2-(1-메틸피롤리딘-2-일)에틸 (5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[50] 22) 2-(1-메틸피롤리딘-2-일)에틸
(5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[51] 23) 2-(1-메틸피롤리딘-2-일)에틸 (4-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[52] 24) 2-(1-메틸피롤리딘-2-일)에틸
(3',4-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[53] 25) 2-(1-메틸피롤리딘-2-일)에틸 (4-메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[54] 26) 2-(1-메틸피롤리딘-2-일)에틸 (5-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[55] 27) 2-(1-메틸피롤리딘-2-일)에틸
(3'-플루오로-5-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[56] 28) 2-(1-메틸피롤리딘-2-일)에틸 (4'-시아노-[1,1'-바이페닐]-2-일)카바메이트;

[57] 29) 2-(1-메틸피롤리딘-2-일)에틸
(3'-(3-히드록시프로필)-[1,1'-바이페닐]-2-일)카바메이트;

[58] 30) 2-(1-메틸피롤리딘-2-일)에틸
(4'-(디메틸아미노)-[1,1'-바이페닐]-2-일)카바메이트;

[59] 31) 2-(1-메틸피롤리딘-2-일)에틸
(4'-(tert-부틸)-[1,1'-바이페닐]-2-일)카바메이트;

[60] 32) 2-(1-메틸피롤리딘-2-일)에틸 (2'-아미노-[1,1'-바이페닐]-2-일)카바메이트;

[61] 33) 2-(1-메틸피롤리딘-2-일)에틸 (3'-아미노-[1,1'-바이페닐]-2-일)카바메이트;

[62] 34) 2-(1-메틸피롤리딘-2-일)에틸 (2'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[63] 35) 2-(1-메틸피롤리딘-2-일)에틸 (2'-클로로-[1,1'-바이페닐]-2-일)카바메이트;

[64] 36) 2-(1-메틸피롤리딘-2-일)에틸 (2'-히드록시-[1,1'-바이페닐]-2-일)카바메이트;

[65] 37) 2-(1-메틸피롤리딘-2-일)에틸
(3'-tert-부틸-5'-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[66] 38) 2-(1-메틸피롤리딘-2-일)에틸
(4'-플루오로-3'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;

[67] 39) 2-(1-메틸피롤리딘-2-일)에틸
(4'-아미노-3'-클로로-[1,1'-바이페닐]-2-일)카바메이트;

[68] 40) 2-(1-메틸피롤리딘-2-일)에틸 (3'-히드록시-[1,1'-바이페닐]-2-일)카바메이트;

[69] 41) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[70] 42) 2-(1-메틸피롤리딘-2-일)에틸
(3',4',5-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[71] 43) 2-(1-메틸피롤리딘-2-일)에틸
(3',4'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[72] 44) 2-(1-메틸피롤리딘-2-일)에틸
(3'-에틸-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[73] 45) 2-(1-메틸피롤리딘-2-일)에틸
(5-플루오로-3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트;

[74] 46) 2-(1-메틸피롤리딘-2-일)에틸
(3'-아미노-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[75] 47) 2-(1-메틸피롤리딘-2-일)에틸
(5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;

[76] 48) 2-(1-메틸피롤리딘-2-일)에틸
(4'-플루오로-5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;

[77] 49) 2-(1-메틸피롤리딘-2-일)에틸
(3'-플루오로-5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;

[78] 50) 2-(1-메틸피롤리딘-2-일)에틸
(3',5'-디플루오로-5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;

[79] 51) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;

[80] 52) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-5,5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[81] 53) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[82] 54) 2-(1-메틸피롤리딘-2-일)에틸
(4'-클로로-3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[83] 55) 2-(1-메틸피롤리딘-2-일)에틸
(3',5'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[84] 56) 2-(1-메틸피롤리딘-2-일)에틸
(3',5'-디클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[85] 57) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-5-플루오로-5'-히드록시-[1,1'-바이페닐]-2-일)카바메이트;

[86] 58) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-5-플루오로-4'-히드록시-[1,1'-바이페닐]-2-일)카바메이트;

[87] 59) 2-(1-메틸피롤리딘-2-일)에틸
(5-플루오로-3',4'-디메틸-[1,1'-바이페닐]-2-일)카바메이트;

[88] 60) 2-(1-메틸피롤리딘-2-일)에틸 (5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[89] 61) 2-(1-메틸피롤리딘-2-일)에틸
(3'-플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[90] 62) 2-(1-메틸피롤리딘-2-일)에틸
(3',5'-디플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[91] 63) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[92] 64) 2-(1-메틸피롤리딘-2-일)에틸
(3',5'-디클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[93] 65) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-4'-플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[94] 66) 2-(1-메틸피롤리딘-2-일)에틸 (5-클로로-[1,1'-바이페닐]-2-일)카바메이트;

[95] 67) 2-(1-메틸피롤리딘-2-일)에틸
(5-클로로-3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[96] 68) 2-(1-메틸피롤리딘-2-일)에틸
(5-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[97] 69) 2-(1-메틸피롤리딘-2-일)에틸
(5-클로로-3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[98] 70) 2-(1-메틸피롤리딘-2-일)에틸
(3',5-디클로로-[1,1'-바이페닐]-2-일)카바메이트;

[99] 71) 2-(1-메틸피롤리딘-2-일)에틸
(3',5,5'-트리클로로-[1,1'-바이페닐]-2-일)카바메이트;

[100] 72) 2-(1-메틸피롤리딘-2-일)에틸
(3',5-디클로로-5'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[101] 73) 2-(1-메틸피롤리딘-2-일)에틸
(3',5-디클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[102] 74) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-플루오로-4'-포밀-[1,1'-바이페닐]-2-일)카바메이트;

[103] 75) 2-(1-메틸피롤리딘-2-일)에틸
(3',5'-디플루오로-5-히드록시-[1,1'-바이페닐]-2-일)카바메이트;

[104] 76) 2-(1-메틸피롤리딘-2-일)에틸
(3',5'-디클로로-5-히드록시-[1,1'-바이페닐]-2-일)카바메이트;

[105] 77) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-4'-플루오로-5-히드록시-[1,1'-바이페닐]-2-일)카바메이트;

[106] 78) (R)-피롤린딘-3-일메틸 [1,1'-바이페닐]-2-일카바메이트;

[107] 79) (S)-피롤린딘-3-일메틸 [1,1'-바이페닐]-2-일카바메이트;

[108] 80) (R)-피롤리딘-3-일메틸 (3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[109] 81) (S)-피롤리딘-3-일메틸 (3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[110] 82) (S)-피롤린딘-3-일메틸 (5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[111] 83) (S)-피롤린딘-3-일메틸
(5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[112] 84) (R)-피롤린딘-3-일메틸
(3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[113] 85) (S)-피롤린딘-3-일메틸
(3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[114] 86) (R)-피롤리딘-3-일메틸 (5-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[115] 87) (R)-피롤리딘-3-일메틸
(3'-플루오로-5-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[116] 88) (S)-피롤리딘-2-일메틸 (4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[117] 89) (R)-(1-메틸피롤리딘-3-일)메틸 [1,1'-바이페닐]-2-일카바메이트;

[118] 90) (S)-(1-메틸피롤리딘-3-일)메틸 [1,1'-바이페닐]-2-일카바메이트;

[119] 91) (R)-(1-메틸피롤리딘-3-일)메틸
(3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[120] 92) (S)-(1-메틸피롤리딘-3-일)메틸
(3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[121] 93) (S)-(1-메틸피롤리딘-3-일)메틸
(5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[122] 94) (S)-(1-메틸피롤리딘-3-일)메틸

(5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[123] 95) (R)-(1-메틸피롤리딘-3-일)메틸
(3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[124] 96) (S)-(1-메틸피롤리딘-3-일)메틸
(3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[125] 97) (R)-(1-메틸피롤리딘-3-일)메틸 (5-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[126] 98) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-플루오로-5-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[127] 99) (S)-(1-메틸피롤리딘-2-일)메틸
(4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[128] 100) (R)-(1-메틸피롤리딘-3-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[129] 101) (S)-(1-메틸피롤리딘-3-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[130] 102) (R)-(1-에틸피롤리딘-3-일)메틸 [1,1'-바이페닐]-2-일카바메이트;

[131] 103) (S)-(1-에틸피롤리딘-3-일)메틸 [1,1'-바이페닐]-2-일카바메이트;

[132] 104) (R)-(1-에틸피롤리딘-3-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[133] 105) (S)-(1-에틸피롤리딘-3-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[134] 106) (S)-(1-에틸피롤리딘-2-일)메틸 [1,1'-바이페닐]-2-일카바메이트;

[135] 107) (S)-(1-이소부틸피롤리딘-2-일)메틸 [1,1'-바이페닐]-2-일카바메이트;

[136] 108) (S)-(1-메틸피롤리딘-3-일)메틸
(3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[137] 109) (R)-(1-메틸피롤리딘-2-일)메틸 [1,1'-바이페닐]-2-일카바메이트;

[138] 110) (R)-(1-메틸피롤리딘-2-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[139] 111) (R)-(1-메틸피롤리딘-2-일)메틸
(5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[140] 112) (S)-(1-이소프로필피롤리딘-2-일)메틸 [1,1'-바이페닐]-2-일카바메이트;

[141] 113) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[142] 114) (R)-(1-메틸피롤리딘-3-일)메틸
(4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[143] 115) (R)-(1-메틸피롤리딘-3-일)메틸
(3',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[144] 116) (S)-(1-메틸피롤리딘-3-일)메틸
(3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[145] 117) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-[1,1'-바이페닐]-2-일)카바메이트;

[146] 118) (S)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-[1,1'-바이페닐]-2-일)카바메이트;

[147] 119) (S)-(1-메틸피롤리딘-3-일)메틸

(3',5'-디클로로-[1,1'-바이페닐]-2-일)카바메이트;

[148] 120) (S)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[149] 121) (S)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[150] 122) (S)-(1-메틸피롤리딘-3-일)메틸
(5-플루오로-3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트;

[151] 123) (S)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5-플루오로-5'-히드록시-[1,1'-바이페닐]-2-일)카바메이트;

[152] 124) (S)-(1-메틸피롤리딘-3-일)메틸
(4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[153] 125) (S)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[154] 126) (S)-(1-메틸피롤리딘-3-일)메틸
(3',5'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[155] 127) (S)-(1-메틸피롤리딘-3-일)메틸
(4'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[156] 128) (S)-(1-메틸피롤리딘-3-일)메틸
(3',4'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[157] 129) (S)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5,5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[158] 130) (R)-(1-메틸피롤리딘-3-일)메틸
(3',4'-디클로로-[1,1'-바이페닐]-2-일)카바메이트;

[159] 131) (R)-(1-메틸피롤리딘-3-일)메틸
(3',5'-디클로로-[1,1'-바이페닐]-2-일)카바메이트;

[160] 132) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[161] 133) (R)-(1-메틸피롤리딘-3-일)메틸
(5-플루오로-3'-아미노-[1,1'-바이페닐]-2-일)카바메이트;

[162] 134) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5-플루오로-5'-히드록시-[1,1'-바이페닐]-2-일)카바메이트;

[163] 135) (R)-(1-메틸피롤리딘-3-일)메틸
(3',5'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[164] 136) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[165] 137) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-히드록시-[1,1'-바이페닐]-2-일)카바메이트;

[166] 138) (R)-(1-메틸피롤리딘-3-일)메틸

(3'-클로로-5'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;

[167] 139) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5-플루오로-5'-메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[168] 140) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5-플루오로-5'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;

[169] 141) (R)-(1-메틸피롤리딘-3-일)메틸
(4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[170] 142) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5,5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[171] 143) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[172] 144) (R)-(1-메틸피롤리딘-3-일)메틸
(2',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[173] 145) (R)-(1-메틸피롤리딘-3-일)메틸
(3',5-디클로로-[1,1'-바이페닐]-2-일)카바메이트;

[174] 146) (R)-(1-메틸피롤리딘-3-일)메틸
(3',5-디클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트

[175] 147) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-4'-플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[176] 148) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-5'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[177] 149) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[178] 150) (R)-(1-에틸피롤리딘-3-일)메틸
(3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[179] 151) (R)-(1-이소프로필피롤리딘-3-일)메틸
(3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[180] 152) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-(히드록시메틸)-[1,1'-바이페닐]-2-일)카바메이트;

[181] 153) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-카바모일-[1,1'-바이페닐]-2-일)카바메이트;

[182] 154) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-아미노-[1,1'-바이페닐]-2-일)카바메이트;

[183] 155) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-시아노-[1,1'-바이페닐]-2-일)카바메이트;

[184] 156) (R)-(1-메틸피롤리딘-3-일)메틸
(2'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[185] 157) (R)-(1-메틸피롤리딘-3-일)메틸

(2',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[186] 158) (R)-(1-메틸피롤리딘-3-일)메틸
(2',3'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[187] 159) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-6'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[188] 160) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[189] 161) (S)-(1-메틸피롤리딘-2-일)메틸
(3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[190] 162) (S)-(1-메틸피롤리딘-2-일)메틸
(3',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[191] 163) (S)-(1-메틸피롤리딘-2-일)메틸
(2',4',5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[192] 164) (S)-(1-메틸피롤리딘-2-일)메틸
(4'-클로로-[1,1'-바이페닐]-2-일)카바메이트;

[193] 165) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-[1,1'-바이페닐]-2-일)카바메이트;

[194] 166) (S)-(1-메틸피롤리딘-2-일)메틸
(3',4'-디클로로-[1,1'-바이페닐]-2-일)카바메이트;

[195] 167) (S)-(1-메틸피롤리딘-2-일)메틸
(2',4'-디클로로-[1,1'-바이페닐]-2-일)카바메이트;

[196] 168) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-히드록시-[1,1'-바이페닐]-2-일)카바메이트;

[197] 169) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-시아노-[1,1'-바이페닐]-2-일)카바메이트;

[198] 170) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-아미노-[1,1'-바이페닐]-2-일)카바메이트;

[199] 171) (S)-(1-메틸피롤리딘-2-일)메틸
(3',4',5-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[200] 172) (S)-(1-메틸피롤리딘-2-일)메틸
(3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[201] 173) (S)-(1-메틸피롤리딘-2-일)메틸
(2',4',5,5'-테트라플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[202] 174) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[203] 175) (S)-(1-메틸피롤리딘-2-일)메틸
(4'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[204] 176) (S)-(1-메틸피롤리딘-2-일)메틸

(2',4'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[205] 177) (S)-(1-메틸피롤리딘-2-일)메틸
(3',4'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[206] 178) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-시아노-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[207] 179) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-히드록시-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[208] 180) (S)-(1-메틸피롤리딘-2-일)메틸
(5-플루오로-3'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;

[209] 181) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-4,4',5-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[210] 182) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-4,5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[211] 183) 2-(1-메틸피롤리딘-2-일)에틸
(2',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[212] 184) 2-(1-메틸피롤리딘-2-일)에틸
(2',3'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[213] 185) 2-(1-메틸피롤리딘-2-일)에틸
(2',6'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[214] 186) 2-(1-메틸피롤리딘-2-일)에틸
(5'-클로로-2'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[215] 187) (S)-(1-메틸피롤리딘-2-일)메틸
(2'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[216] 188) (S)-(1-메틸피롤리딘-2-일)메틸
(2',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[217] 189) (S)-(1-메틸피롤리딘-2-일)메틸
(2',3'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[218] 190) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-6'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[219] 191) (R)-(1-메틸피롤리딘-3-일)메틸
(3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트;

[220] 192) (R)-(1-메틸피롤리딘-3-일)메틸
(5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[221] 193) (R)-(1-메틸피롤리딘-3-일)메틸
(5-플루오로-3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트;

[222] 194) (R)-(1-메틸피롤리딘-3-일)메틸
(3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[223] 195) (R)-(1-메틸피롤리딘-3-일)메틸

(3'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[224] 196) (R)-(1-에틸피롤리딘-3-일)메틸
(3'-클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[225] 197) (S)-(1-메틸피롤리딘-2-일)메틸 [1,1'-바이페닐]-2-일카바메이트;

[226] 198) (S)-(1-메틸피롤리딘-2-일)메틸
(4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[227] 199) (S)-(1-메틸피롤리딘-2-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[228] 200) (S)-(1-메틸피롤리딘-2-일)메틸
(5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[229] 201) (S)-(1-메틸피롤리딘-2-일)메틸
(5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[230] 202) (S)-(1-메틸피롤리딘-2-일)메틸
(3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[231] 203) (S)-(1-메틸피롤리딘-2-일)메틸
(4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[232] 204) (S)-(1-메틸피롤리딘-2-일)메틸
(4-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[233] 205) (S)-(1-메틸피롤리딘-2-일)메틸
(3',4-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[234] 206) (S)-(1-메틸피롤리딘-2-일)메틸 (5-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[235] 207) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-플루오로-5-메틸-[1,1'-바이페닐]-2-일)카바메이트;

[236] 208) (S)-(1-메틸피롤리딘-2-일)메틸
(5-플루오로-3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트;

[237] 209) (S)-(1-메틸피롤리딘-2-일)메틸
(4'-(tert-부틸)-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[238] 210) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-5,5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[239] 211) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[240] 212) (S)-(1-메틸피롤리딘-2-일)메틸
(4'-클로로-3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[241] 213) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-아미노-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[242] 214) (S)-(1-메틸피롤리딘-2-일)메틸
(2',5-디플루오로-3'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;

[243] 215) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-5-플루오로-5'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;

[244] 216) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-5-플루오로-5'-히드록시-[1,1'-바이페닐]-2-일)카바메이트;

[245] 217) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-5-플루오로-5'-메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[246] 218) (S)-(1-메틸피롤리딘-2-일)메틸
(5-플루오로-2',4'-비스(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;

[247] 219) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-에톡시-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

[248] 220) (S)-(1-메틸피롤리딘-2-일)메틸
(5-플루오로-3',4'-디메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[249] 221) (S)-(1-메틸피롤리딘-2-일)메틸
(5-플루오로-3',5'-디메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[250] 222) (S)-(1-메틸피롤리딘-2-일)메틸 (5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[251] 223) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[252] 224) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[253] 225) (S)-(1-메틸피롤리딘-2-일)메틸
(3',4'-디클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;

[254] 226) (S)-(1-메틸피롤리딘-2-일)메틸
(3',5'-디클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트.

[255]

[256] <u>신규한 바이페닐 유도체의 제조방법</u>

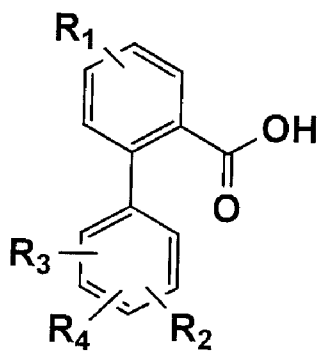
[257] 본 발명은 상기 화학식 1의 화합물 또는 이의 약학적으로 허용가능한 염의 제조방법(제조방법 1 내지 4)을 제공한다.

[258] <u>제조방법 1</u>

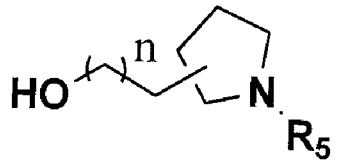
[259] 본 발명의 화학식 1의 화합물 또는 이의 약학적으로 허용가능한 염의 제조방법은 하기 화학식 2의 화합물과 하기 화학식 3의 화합물을 카바메이트 제조시약 존재 하에 반응시키는 단계를 포함할 수 있다.

[260] [화학식 2]

[261]



[262] [화학식 3]

[263] 

[264] 상기 화학식 2 및 3에서, R_1~R_5 및 n은 화학식 1에서 정의한 바와 같다.

[265] 상기 카바메이트 제조시약은 아지드 화합물을 포함하는 것이 바람직하다. 구체적으로, 다이페닐포스포릴 아지드 (DPPA) 및 트리에틸아민의 혼합액, 프로필포스포닉 언히드리드(T3P)와 트리메틸실릴 아지드 ($TMSN_3$) 및 트리에틸아민의 혼합액, 소듐 아지드(NaN_3), 테트라부틸암모늄 브로마이드, 징크 트리플레이트 (Zi(II) triflate)의 혼합액 등이 사용될 수 있다.

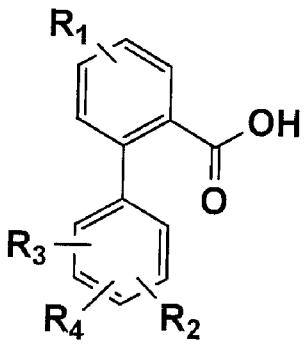
[266] 또한, 상기 카바메이트 제조 반응은 100 ~ 120℃의 범위에서 4 ~ 12시간 동안 수행될 수 있다.

[267]

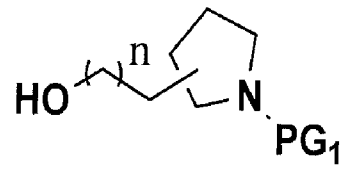
[268] 제조방법 2

[269] 또한, 본 발명의 화학식 1의 화합물 또는 이의 약학적으로 허용가능한 염의 제조방법은, 하기 화학식 2의 화합물과 하기 화학식 3a의 화합물을 카바메이트 제조시약 존재 하에 반응시켜 하기 화학식 4의 화합물을 제조하는 단계; 상기 화학식 4의 화합물의 아민 보호기 (Protecting Group)를 제거하여 하기 화학식 1a의 화합물을 제조하는 단계; 및 하기 화학식 1a의 화합물에 R_5 치환기를 도입하는 단계를 포함할 수 있다.

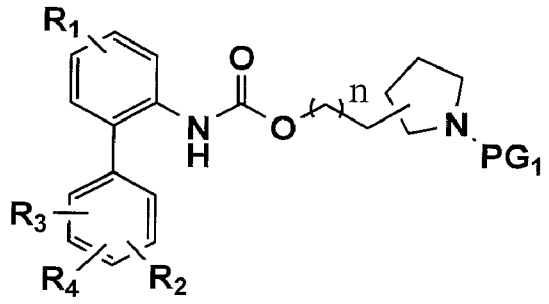
[270] [화학식 2]

[271] 

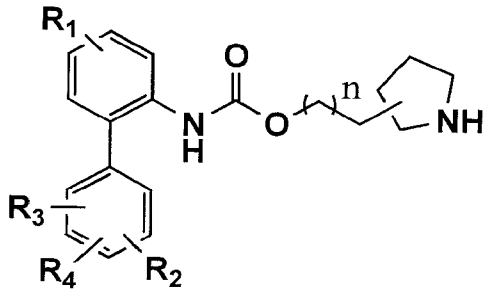
[272] [화학식 3a]

[273] 

[274] [화학식 4]

[275] 

[276] [화학식 1a]

[277] 

[278] 상기 화학식 2, 3a, 4 및 화학식 1a에서 R_1~R_4 및 n은 화학식 1에서 정의한 바와 같으며, PG_1은 아민 보호기로서 Boc(tert-butyloxycarbonyl), 벤질, tert-부틸, pmb(4-methoxybenzyl), Fmoc(Fluorenylmethyloxycarbonyl), Ts(tosylate), MOM(methoxymethyl), THP(tetrahydropyranyl), TBDMS(tert-butyldimethylsilyl), 및 TBDPS(tert-butyldimethylsilyl) 등으로 이루어진 군으로부터 선택될 수 있다.

[279] 상기 카바메이트 제조 시약 및 반응조건은 제조방법 1과 동일하다.

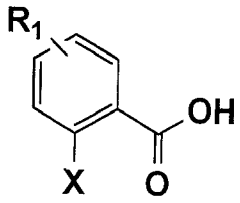
[280] 또한, 상기 아민 보호기 제거 반응은 트리플루오로 아세틱 애시드, 팔라듐-탄소(Pd-C), 황산, 브롬산 등의 강산, 피페리딘 등의 염기, 암모늄 세륨(IV) 니트레이트, 테트라-n-부틸 암모늄 플루오라이드 등이 사용될 수 있다. 반응은 상온에서 3 내지 12시간 동안 진행할 수 있다.

[281] 또한, R_5 치환기를 도입 반응은 포름알데히드 용액 및 아세트산, 아연을 사용하거나 알킬 할라이드, 포타슘카보네이트, 포타슘아이오다이드, 트리에틸아민을 사용할 수 있으며, 용매는 물 또는 디메틸포름아이드 등을 사용할 수 있다. 반응은 상온 내지 120℃에서 5~12 시간 동안 진행할 수 있다.

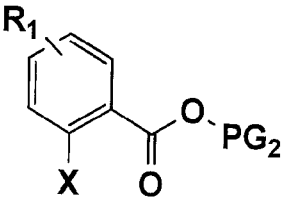
[282]

[283] 한편, 상기 화학식 2의 화합물은, 화학식 5의 화합물을 산 존재 하에 반응시켜 카르복실산 보호기 (Protecting Group)가 도입된 화학식 6의 화합물을 제조하는 단계; 화학식 6의 화합물과 화학식 7의 화합물을 커플링시켜 화학식 8의 화합물을 제조하는 단계; 화학식 8의 화합물을 염기 존재 하에 탈에스테르화하는 단계를 포함하는 방법으로 제조될 수 있다.

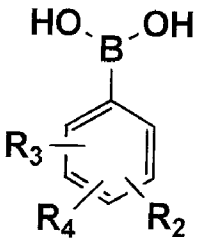
[284] [화학식 5]

[285] 

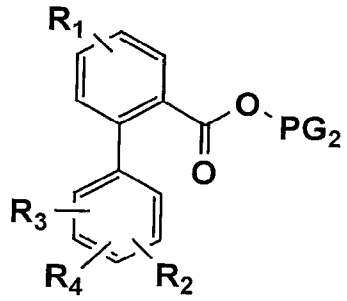
[286] [화학식 6]

[287] 

[288] [화학식 7]

[289] 

[290] [화학식 8]

[291] 

[292] 상기 화학식 5 내지 8에서 R_1~R_5 및 n은 화학식 1에서 정의한 바와 같으며, X는 할로겐이고, PG_2는 C1~C4의 알킬기, 벤질, pmb(4-methoxybenzyl), THP(tetrahydropyranyl), TBDMS(tert-butyldimethylsilyl), TBDPS(tert-butyldimethylsilyl) 등으로 이루어진 군으로부터 선택될 수 있는 보호기이다.

[293] 상기 카르복실산 보호기 도입 반응에서, 산은 싸이오닐 클로라이드 또는 황산을 사용하는 것이 바람직하며, 용매는 에탄올 또는 메탄올을 사용할 수 있고, 상기 반응은 80℃ 내지 100℃의 범위에서 4 내지 24시간 동안 진행할 수 있다.

[294] 또한, 상기 커플링 반응에서 염기는 포타슘카보네이트 또는 소듐카보네이트 중에서 선택되는 것이 바람직하며, 촉매는 테트라키스트리페닐포스핀 팔라듐 또는 디클로로비스트리페닐포스핀 팔라듐 등을 사용할 수 있고, 용매는 톨루엔, 톨루엔과 에탄올의 혼합용액, 에탄올과 물의 혼합용액, 아세토니트릴과 물의

혼합용액 등을 사용할 수 있다. 반응 온도는 100℃ 내지 120℃, 반응 시간은 10분 내지 12시간 동안 진행할 수 있다.

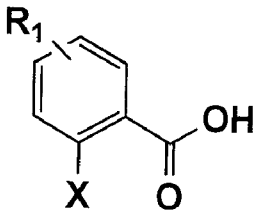
[295] 또한, 상기 탈에스테르화 반응에서, 염기는 소듐 히드록시드 또는 포타슘 히드록시드 중에서 선택하는 것이 바람직하며, 용매는 에탄올 또는 에탄올과 물의 혼합용액 등을 사용할 수 있고, 반응 온도는 100℃ 내지 120℃, 반응 시간은 2 내지 12시간 동안 진행할 수 있다.

[296]

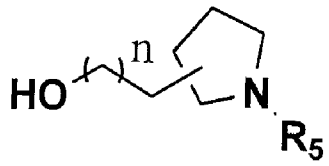
[297] 제조방법 3

[298] 또한, 본 발명의 화학식 1의 화합물 또는 이의 약학적으로 허용가능한 염의 제조방법은, 하기 화학식 5의 화합물을 하기 화학식 3의 화합물과 카바메이트 제조시약 존재 하에 반응시켜 하기 화학식 9의 화합물을 제조하는 단계; 및 상기 화학식 9의 화합물에 하기 화학식 7의 화합물을 커플링하는 단계를 포함할 수 있다.

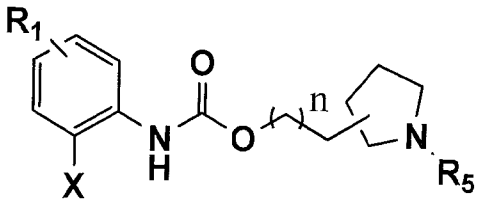
[299] [화학식 5]

[300] 

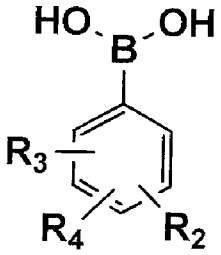
[301] [화학식 3]

[302] 

[303] [화학식 9]

[304] 

[305] [화학식 7]

[306] 

[307] 상기 화학식 3, 5, 7, 9에서 R_1~R_5 및 n은 화학식 1에서 정의한 바와 같으며, X는

할로겐이다.

[308] 상기 카바메이트 제조 시약 및 반응조건은 제조방법 1과 동일하다.

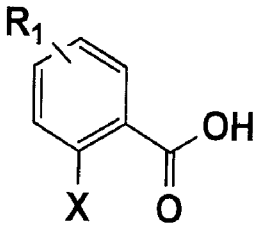
[309] 또한, 상기 커플링 반응의 시약 및 반응조건은 제조방법 2와 동일하다.

[310]

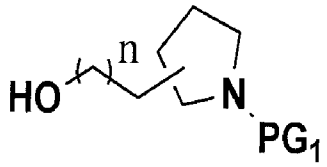
[311] 제조방법 4

[312] 또한, 본 발명의 화학식 1의 화합물 또는 이의 약학적으로 허용가능한 염의 제조방법은, 하기 화학식 5의 화합물을 하기 화학식 3a의 화합물과 카바메이트 제조시약 존재 하에 반응시켜 하기 화학식 9a의 화합물을 제조하는 단계; 상기 화학식 9a의 화합물을 탈보호화하여 하기 화학식 9b 화합물을 제조하는 단계; 상기 화학식 9b의 화합물에 R_5 치환기를 도입하여 하기 화학식 9의 화합물을 제조하는 단계; 및 상기 화학식 9의 화합물에 하기 화학식 7의 화합물을 커플링하는 단계를 포함할 수 있다.

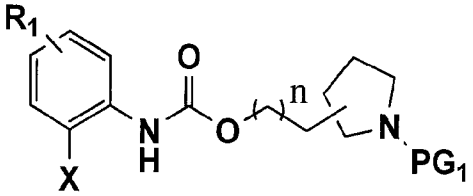
[313] [화학식 5]

[314] 

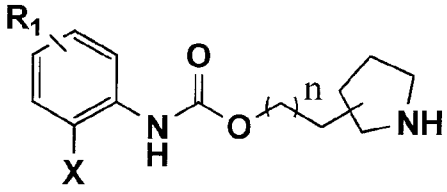
[315] [화학식 3a]

[316] 

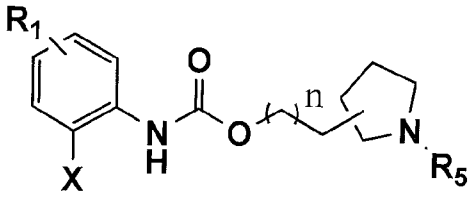
[317] [화학식 9a]

[318] 

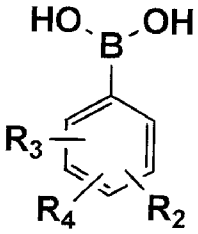
[319] [화학식 9b]

[320] 

[321] [화학식 9]

[322] 

[323] [화학식 7]

[324] 

[325] 상기 화학식 3a, 5, 7, 9, 9a 및 9b에서 R_1~R_5 및 n은 화학식 1에서 정의한 바와 같으며, X는 할로겐이고, PG_1은 제조방법 2에서 정의한 바와 같다

[326] 상기 카바메이트 제조 시약 및 반응조건은 제조방법 1과 동일하다.

[327] 또한, 상기 탈보호화 반응, R_5 치환기를 도입 반응 및 커플링 반응은 제조방법 2와 동일하다.

[328]

[329] <u>신규한 바이페닐 유도체를 포함하는 약학적 조성물</u>

[330] 본 발명은 화학식 1의 화합물, 이의 이성질체, 약학적으로 허용가능한 염 또는 수화물을 유효성분으로 함유하는 무스카린 M3 수용체 길항제를 제공한다.

[331] 본 발명에서, 무스카린 M3 수용체 길항제는 만성 폐쇄성 폐질환(Chronic obstructive pulmonary disease), 천식(asthma), 과민성 대장 증후군(irritable bowel syndrome), 요실금(urinary incontinence), 비염(rhinitis), 경련성 대장염(spasmodic colitis), 만성 방광염(chronic cystitis), 알츠하이머병(alzheimer's disease), 노인성 치매(senile dementia), 녹내장(glaucoma), 조현병(schizophrenia), 역류성 식도염(gastroesophogeal reflux disease), 심장 부정맥(cardiac arrhythmia), 타액분비항진증(hyper salivation syndromes에서 선택되는 질환의 예방 또는 치료용 조성물일 수 있다.

[332] 본 발명에서, 무스카린 M3 수용체 길항제는 본 발명의 화학식1의 화합물 또는 이의 약학적으로 허용 가능한 염에 추가하여 동일 또는 유사한 기능을 나타내는 유효성분을 1종 이상 함유할 수 있다.

[333] 또한, 본 발명은 투여를 위해서 상기 기재한 유효성분 이외에 추가로 약제학적으로 허용가능한 담체를 1종 이상 포함하여 제조되며, 약제학적으로 허용 가능한 담체는 식염수, 멸균수, 링거액, 완충 식염수, 덱스트로즈 용액, 말토덱스트린 용액, 글리세롤, 에탄올 및 이들 성분 중 1성분 이상을 혼합하여 사용할 수 있으며, 필요에 따라 항산화제, 완충액, 정균제 등 다른 통상의 첨가제를 첨가할 수 있다. 또한 희석제, 분산제, 계면활성제, 결합제 및 윤활제를 부가적으로 첨가하여 수용액, 현탁액, 유탁액 등과 같은 주사용 제형, 환약, 캡슐,

과립 또는 정제로 제제화 할 수 있다. 더 나아가 당분야의 적정한 방법으로 또는 Remington's Pharmaceutical Science, Merck Publishing Company, Easton PA에 개시되어 있는 방법을 이용하여 각 질환에 따라 또는 성분에 따라 바람직하게 제제화 할 수 있다.

[334] 또한, 본 발명의 무스카린 M3 수용체 길항제가 경구투여용인 경우, 본 발명의 화학식1의 화합물 또는 이의 약학적으로 허용되는 염은 제제 내 1 내지 95중량%으로 함유될 수 있으며, 바람직하게는 1내지 70중량% 함유될 수 있다.

[335] 본 발명에서 약제학적 조성물은 경구 투여하거나 주사제, 좌제, 경피제, 흡입제 또는 방광내 주입 형태로 비경구 투여할 수 있다.

[336] 본 발명은 또한 본 발명의 화학식 1의 화합물 또는 약학적으로 허용가능한 염을 유효성분으로 함유하는 무스카린 M3 수용체 길항제를 무스카린 M3 수용체 길항효과를 요하는 인간을 포함하는 포유류에게 투여하여 무스카린 M3 수용체 효과 저하로 인한 질환을 치료 또는 완화시키는 방법을 제공한다.

[337] 본 발명의 무스카린 M3 수용체 길항제는 무스카린 M3 수용체 효과 저하로 인한 질환의 예방 및 치료를 위하여 단독으로, 또는 수술, 호르몬 치료, 약물 치료 및 생물학적 반응 조절제를 사용하는 방법들과 병용하여 사용할 수 있다.

[338]

[339] **무스카린 M3 수용체 길항작용 관련 질환의 예방 또는 치료방법**

[340] 또한, 본 발명은 화학식 1의 화합물, 이의 이성질체, 약학적으로 허용가능한 염 또는 수화물을 유효성분으로 함유하는 조성물을 이를 필요로 하는 대상체에 투여하는 단계를 포함하는 무스카린 M3 수용체 길항작용 관련 질환, 예를 들어 만성 폐쇄성 폐질환(Chronic obstructive pulmonary disease), 천식(asthma), 과민성 대장 증후군(irritable bowel syndrome), 요실금(urinary incontinence), 비염(rhinitis), 경련성 대장염(spasmodic colitis), 만성 방광염(chronic cystitis), 알츠하이머병(alzheimer's disease), 노인성 치매(senile dementia), 녹내장(glaucoma), 조현병(schizophrenia), 역류성 식도염(gastroesophogeal reflux disease), 심장 부정맥(cardiac arrhythmia), 타액분비항진증(hyper salivation syndromes)에서 선택되는 질환의 예방 또는 치료방법을 제공한다.

[341] 본 발명의 예방 또는 치료방법에 사용되는 상기 조성물은 본 명세서에 기재된 약제학적 조성물을 포함한다.

[342] 또한, 본 발명의 예방 또는 치료방법으로 필요로 하는 상기 대상체는 포유류, 특히 인간을 포함한다.

발명의 효과

[343] 본 발명에 따른 바이페닐 유도체들은 무스카린 M3 수용체에 대한 친화성 및 선택성을 가지며, 독성이 낮아 M3 수용체가 관여하는 각종 질환, 특히 야뇨증, 신경성 빈뇨, 신경 원인성 방광, 불안정 방광, 만성 방광염, 방광 연축, 요실금, 빈뇨 등의 비뇨기 질환, 만성 폐쇄성 폐질환, 만성 기관지염, 천식과 비염 등의

호흡기 질환, 과민성 대장 증후군, 연축성 대장염 또는 게실염 등의 소화기 질환의 예방제 또는 치료제로서 유용하게 이용될 수 있다.

[344] 특히, 본 발명의 바이페닐 유도체들은 M2 수용체 및 평활근 및 선 조직 등에 존재하는 M3 수용체에 대한 선택성이 높기 때문에 부작용이 적은 M3 수용체 길항제이므로 요실금, 빈뇨, 만성 기관지염, 만성 폐쇄성 폐질환, 천식, 비염 등의 예방제 또는 치료제로서 그 유용성이 높다.

발명의 실시를 위한 형태

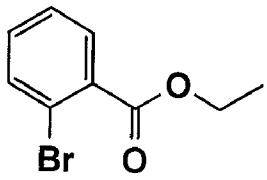
[345] 이하, 본 발명의 이해를 돕기 위하여 바람직한 합성예, 실시예 및 실험예를 제시한다. 그러나 하기의 합성예, 실시예 및 실험예는 본 발명을 보다 쉽게 이해하기 위하여 제공되는 것일 뿐, 실시예에 의해 본 발명의 내용이 한정되는 것은 아니다.

[346] 이하에서 사용된 시약은 별다른 언급이 없는 한 Aldrich Korea, Acros, Lancaster, TCI 등으로부터 구입 한 것이며, ^{1}H NMR은 Varian 400MHz, Microwave oven은 Anton Paar사의 Monowave 300을 사용하였다.

[347]

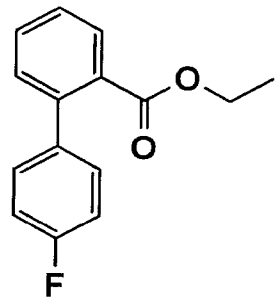
[348] **[합성예 1] 4'-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드의 합성**

[349] [단계 1] 에틸-2-브로모벤조에이트의 합성

[350] 

[351] 2-브로모벤조익 애시드(5g, 24.87mmol)를 에탄올(100mL)에 녹인 후, 황산(5mL)을 가하고 24시간 동안 환류교반하였다. 반응이 종결된 후 반응물의 온도를 상온으로 식히고, 감압 농축하여 용매를 제거한 후 물과 에틸아세테이트로 추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(4.9g, 86%)을 얻었다.

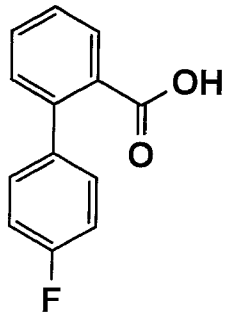
[352] [단계 2] 에틸 4'-플루오로-[1,1'-바이페닐]-2-카복실레이트의 합성

[353] 

[354] 단계 1에서 제조된 에틸-2-브로모벤조에이트(1g, 4.37mmol)를 톨루엔(20mL)과 에탄올(4mL) 혼합용액에 녹인 후 4-플루오로페닐 보로닉애시드(672mg, 4.80mmol), 포타슘카보네이트(1.21g, 8.73mmol),

테트라키스트리페닐포스핀팔라듐(504mg, 0.44mmol)을 가하였다. 반응물을 100℃에서 6시간 동안 교반한 후 온도를 상온으로 낮추고, 셀라이트 여과 후 감압 농축하여 용매를 제거하였다. 물과 에틸아세테이트로 추출한 후 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(948mg, 89%)을 얻었다.

[355] [단계 3] 4'-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드의 합성

[356] 

[357] 단계 2에서 제조된 에틸 4'-플루오로-[1,1'-바이페닐]-2-카복실레이트(948mg, 3.33mmol)를 에탄올(20mL)에 녹인 후 2N-수산화나트륨 용액(5.82mL, 11.64mmol)을 가하고 12시간 동안 환류교반하였다. 반응물의 온도를 상온으로 낮추고, 감압 농축하여 용매를 제거한 후 1N-염산 용액과 다이클로로메탄으로 추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 표제화합물(747mg, 89%)을 얻었다.

[358]

[359] **[합성예 2 - 15]**

[360] 출발물질로 2-브로모벤조익 애시드와 [표 1]의 반응물질을 사용하여 합성예 1과 동일한 방법으로 합성예 2 내지 15의 화합물을 제조하였다.

[361] [표 1] 합성예 1-15

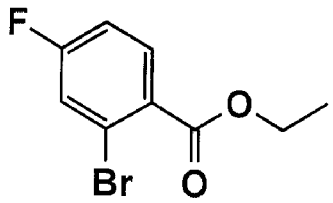
[362]

합성예	화학명	반응물질
1	4'-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드	4-플루오로페닐 보로닉애시드
2	3',5'-디플루오로-[1,1'-바이페닐]-2-카복실릭 애시드	3,5-디플루오로페닐 보로닉애시드
3	3',4',5'-트리플루오로-[1,1'-바이페닐]-2-카복실릭 애시드	3,4,5-트리플루오로페닐 보로닉애시드
4	3'-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드	3-플루오로페닐 보로닉애시드
5	4'-메톡시-[1,1'-바이페닐]-2-카복실릭 애시드	4-메톡시페닐 보로닉애시드
6	4'-클로로-[1,1'-바이페닐]-2-카복실릭 애시드	4-클로로페닐 보로닉애시드
7	3'-클로로-[1,1'-바이페닐]-2-카복실릭 애시드	3-클로로페닐 보로닉애시드
8	3',5'-디클로로-[1,1'-바이페닐]-2-카복실릭 애시드	3,5-디클로로페닐 보로닉애시드
9	4'-트리플루오로메톡시-[1,1'-바이페닐]-2-카복실릭 애시드	4-트리플루오로메톡시페닐 보로닉애시드
10	4'-니트로-[1,1'-바이페닐]-2-카복실릭 애시드	4-니트로페닐 보로닉애시드
11	3'-트리플루오로메틸-[1,1'-바이페닐]-2-카복실릭 애시드	3-트리플루오로메틸페닐 보로닉애시드
12	4'-트리플루오로메틸-[1,1'-바이페닐]-2-카복실릭 애시드	4-트리플루오로메틸페닐 보로닉애시드
13	3'-플루오로-4'-메틸-[1,1'-바이페닐]-2-카복실릭 애시드	3-플루오로-4-메틸페닐 보로닉애시드
14	3'-메틸-[1,1'-바이페닐]-2-카복실릭 애시드	3-메틸페닐 보로닉애시드
15	3'-에톡시-[1,1'-바이페닐]-2-카복실릭 애시드	3-에톡시페닐 보로닉애시드

[363]

[364] **[합성예 16] 3'-클로로-5-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드의 합성**

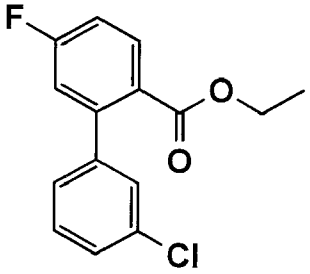
[365] [단계 1] 에틸 2-브로모-4-플루오로벤조에이트

[366] 

[367] 2-브로모-4-플루오로벤조익 애시드(2.37g, 10.82mmol)을 에탄올(100mL)에

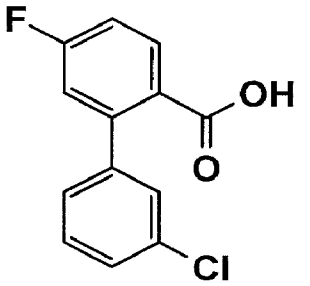
녹인 후, 싸이오닐클로라이드(1.57mL, 21.64mmol)을 가하고 24시간 동안 환류교반하였다. 반응이 종결된 후 반응물의 온도를 상온으로 식히고, 감압 농축하여 용매를 제거한 후 물과 에틸아세테이트로 추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(2.29g, 87%)을 얻었다.

[368] [단계 2] 에틸 3'-클로로-5-플루오로-[1,1'-바이페닐]-2-카복실레이트

[369] 

[370] 단계 1에서 제조된 에틸 2-브로모-4-플루오로벤조에이트(1.1g, 4.47mmol)을 톨루엔(20mL)에 녹인 후 3-클로로페닐 보로닉애시드(766mg, 4.90mmol), 포타슘카보네이트(1.23g, 8.90mmol), 테트라키스트리페닐포스핀팔라듐(520mg, 0.44mmol)을 가하였다. 반응물을 100℃에서 6시간 동안 교반한 후 온도를 상온으로 낮추고, 셀라이트 여과 후 감압 농축하여 용매를 제거하였다. 물과 에틸아세테이트로 추출한 후 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(850mg, 69%)을 얻었다.

[371] [단계 3] 3'-클로로-5-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드

[372] 

[373] 단계 2에서 제조된 에틸 3'-클로로-5-플루오로-[1,1'-바이페닐]-2-카복실레이트(850mg, 3.05mmol)을 에탄올(20mL)에 녹인 후 2N-수산화나트륨 용액(4.57mL, 9.15mmol)을 가하고 12시간 동안 환류교반하였다. 반응물의 온도를 상온으로 낮추고, 감압 농축하여 용매를 제거한 후 1N-염산 용액과 다이클로로메탄으로 추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 표제화합물(650mg, 85%)을 얻었다.

[374]

[375] **[합성예 17 - 26]**

[376] [표 2]의 출발물질 및 반응물질을 사용하여 합성예 16과 동일한 방법으로

합성예 17 내지 26의 화합물을 제조하였다.

[377] [표 2] 합성예 16-26

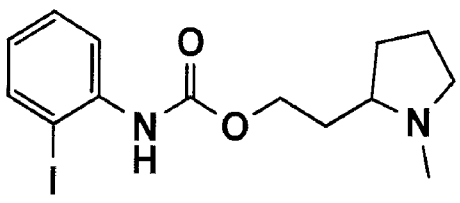
[378]

합성예	화학명	출발물질	반응물질
16	3'-클로로-5-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드	2-브로모-4-플루오로벤조익 애시드	3-클로로페닐 보로닉 애시드
17	3',5-디플루오로-[1,1'-바이페닐]-2-카복실릭 애시드	2-브로모-4-플루오로벤조익 애시드	3-플루오로페닐 보로닉애시드
18	4',5-디플루오로-[1,1'-바이페닐]-2-카복실릭 애시드	2-브로모-4-플루오로벤조익 애시드	4-플루오로페닐 보로닉애시드
19	3',5,5'-트리플루오로-[1,1'-바이페닐]-2-카복실릭 애시드	2-브로모-4-플루오로벤조익 애시드	3,5-디플루오로페닐 보로닉애시드
20	5-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드	2-브로모-4-플루오로벤조익 애시드	페닐 보로닉애시드
21	5-플루오로-3'-메틸-[1,1'-바이페닐]-2-카복실릭 애시드	2-브로모-4-플루오로벤조익 애시드	3-메틸페닐 보로닉애시드
22	4-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드	2-브로모-5-플루오로벤조익 애시드	페닐 보로닉애시드
23	3',4-디플루오로-[1,1'-바이페닐]-2-카복실릭 애시드	2-브로모-5-플루오로벤조익 애시드	3-플루오로페닐 보로닉애시드
24	4-메톡시-[1,1'-바이페닐]-2-카복실릭 애시드	2-브로모-5-메톡시벤조익 애시드	페닐 보로닉애시드
25	5-메틸-[1,1'-바이페닐]-2-카복실릭 애시드	2-브로모-4-메틸벤조익 애시드	페닐 보로닉애시드
26	3'-플루오로-5-메틸-[1,1'-바이페닐]-2-카복실릭 애시드	2-브로모-4-메틸벤조익 애시드	3-플루오로페닐 보로닉애시드

[379]

[380] **[합성예 A] 2-(1-메틸피롤리딘-2-일)에틸 (2-아이오도페닐)카바메이트의 합성**

[381]



[382] 2-아이오도벤조익 애시드(1g, 4.03mmol)를 톨루엔(50mL)에 녹인 후 바이페닐포스포릴 아지드(1.04mL, 4.84mmol)와 트리에틸아민(566uL, 4.03mmol)을 가하였다. 상온에서 30분간 교반 한 후 다시 1시간 동안 환류교반 하였다. 반응물의 온도를 상온으로 낮추고 2-(2-히드록시에틸)-1-메틸피롤리딘(651uL, 4.84mmol)을 가한 후 12시간 동안

환류교반하였다. 반응물의 온도를 상온으로 낮추고, 감압 농축하여 용매를 제거한 후 물과 에틸아세테이트로 추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(1.16g, 77%)을 얻었다.

[383]

[384] **[합성예 B - E]**

[385] 2-아이오도벤조익 애시드 대신 [표 3]의 출발물질을 사용하여 합성예 A와 동일한 방법으로 합성예 B 내지 E의 화합물을 제조하였다.

[386] [표 3] 합성예 A-E

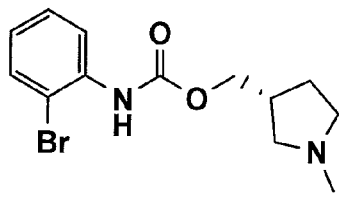
[387]

합성예	화학명	출발물질
A	2-(1-메틸피롤리딘-2-일)에틸 (2-아이오도페닐)카바메이트 (1.16g, 77%)	2-아이오도벤조익 애시드 (1g, 4.03mmol)
B	2-(1-메틸피롤리딘-2-일)에틸 (2-브로모-4-플루오로페닐)카바메이트 (3.7g, 94%)	2-브로모-4-플루오로벤조익 애시드 (2.5g, 11.42mmol)
C	2-(1-메틸피롤리딘-2-일)에틸 (2-브로모-4-(트리플루오로메틸)페닐)카바메이트 (1.72g, 94%)	2-브로모-4-(트리플루오로메틸)벤조익 애시드 (2g, 7.43mmol)
D	2-(1-메틸피롤리딘-2-일)에틸 (2-브로모-4-메톡시페닐)카바메이트 (2.5g, 81%)	2-브로모-4-메톡시벤조익 애시드 (2g, 7.43mmol)
E	2-(1-메틸피롤리딘-2-일)에틸 (2-브로모-4-클로로페닐)카바메이트 (38g, 99%)	2-브로모-4-클로로벤조익 애시드 (2.5g, 10.62mmol)

[388]

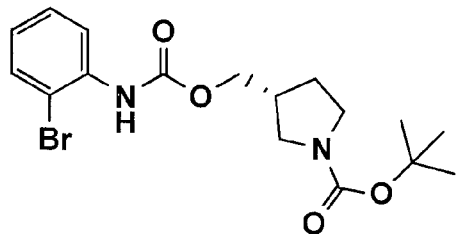
[389] **[합성예 F] (R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트의 합성**

[390]



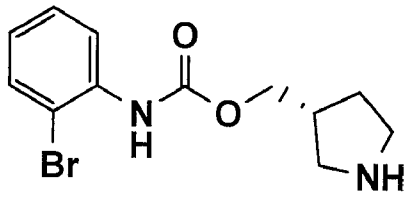
[391] [단계 1] (R)-tert-부틸 3-((((2-브로모페닐)카바모일)옥시)메틸)피롤리딘-1-카복실레이트의 합성

[392]



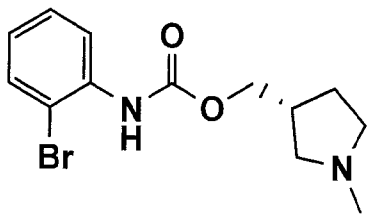
[393] 2-브로모벤조익 애시드(4.5g, 22.4mmol)를 톨루엔(100mL)에 녹인 후 바이페닐포스포릴 아지드(5.8mL, 26.9mmol)와 트리에틸아민(3.15mL, 22.4mmol)을 가하였다. 상온에서 30분간 교반 한 후 다시 1시간 동안 환류교반하였다. 반응물의 온도를 상온으로 낮추고 (R)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이트(5.41g, 26.9mmol)을 가한 후 12시간 동안 환류교반하였다. 반응물의 온도를 상온으로 낮추고, 감압 농축하여 용매를 제거한 후 물과 디클로로메탄으로 추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(8.1g, 91%)을 얻었다.

[394] [단계 2] ((R)-피롤리딘-3-일메틸 (2- 브로모페닐)카바메이트의 합성

[395] 

[396] 단계 1에서 제조된 (R)-tert-부틸 3-((((2-브로모페닐)카바모일)옥시)메틸)피롤리딘-1-카복실레이트(8.1g, 20.29mmol)를 디클로로메탄(100mL)에 녹인 후, 트리플루오로아세틱 애시드(50mL)를 가하고 상온에서 2시간 동안 교반하였다. 반응물을 감압농축하여 용매를 제거하고 2N-소듐히드록시드 용액과 디클로로메탄으로 추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(3.94g, 65%)을 얻었다.

[397] [단계 3] (R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트의 합성

[398] 

[399] 단계 2에서 제조된 (R)-피롤리딘-3-일메틸 (2-브로모페닐)카바메이트(3.94g, 13.13mmol)를 물(100mL)에 녹인 후, 아세틱애시드(5mL), 포름알데히드 용액(15mL), 징크 파우더(1.5g)를 순차적으로 가하고 상온에서 12시간 동안 교반하였다. 반응물을 여과한 후 2N-소듐히드록시드 용액으로 중화한 후 물과 디클로로메탄으로 추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(3.06g, 75%)을 얻었다.

[400]

[401] **[합성예 G - L]**

[402] [표 4]의 출발물질 및 반응물질을 사용하여 합성예 F와 동일한 방법으로 합성예

G 내지 L의 화합물을 제조하였다.

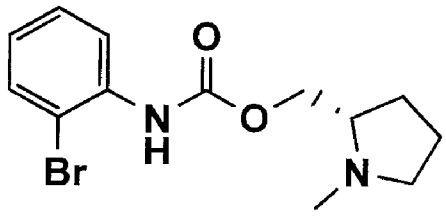
[403] [표 4] 합성예 F-L

[404]

합성예	화학명	출발물질	반응물질
F	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트 (3.06g, 75%)	2-브로모벤조익 애시드 (4.5g, 22.4mmol)	(R)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이드 (5.41g, 26.9mmol)
G	(S)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트	2-브로모벤조익 애시드	(S)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이드
H	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (2.29g, 30%)	2-브로모-4-플루오로벤조익 애시드(5g, 22.83mmol)	(R)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이드(5.51g, 27.4mmol)
I	(S)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트의 합성	2-브로모-4-플루오로벤조익 애시드	(S)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이드
J	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-클로로페닐)카바메이트 (2.5g, 34%)	2-브로모-4-클로로벤조익 애시드(5g, 21.23mmol)	(R)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이드(5.1g, 25.48mmol)
K	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-메톡시페닐)카바메이트 (2.3g, 52%)	2-브로모-4-메톡시벤조익 애시드(3g, 12.98mmol)	(R)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이드(3.9g, 19.47mmol)
L	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4,5-디플루오로페닐)카바메이트 (884mg, 40%)	2-브로모-4,5-디플루오로벤조익 애시드(1.5g, 6.33mmol)	(R)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이드(2.55g, 12.65mmol)

[405] **[합성예 M] (S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐)카바메이트의 합성**

[406]



[407] 2-브로모벤조익 애시드(2g, 9.95mmol)를 톨루엔(75mL)에 녹인 후 바이페닐포스포릴 아지드(2.57mL, 11.94mmol)와 트리에틸아민(1.4mL, 9.95mmol)을 가하였다. 상온에서 30분간 교반 한 후 다시 1시간 동안

환류교반하였다. 반응물의 온도를 상온으로 낮추고 (S)-(1-메틸피롤리딘-2-일)메탄올(1.42mL, 11.94mmol)을 가한 후 4시간 동안 환류교반하였다. 반응물의 온도를 상온으로 낮추고, 감압 농축하여 용매를 제거한 후 물과 디클로로메탄으로 추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(1.4g, 45%)을 얻었다.

[408]

[409] **[합성예 N - P]**

[410] [표 5]의 출발물질 및 반응물질을 사용하여 합성예 M와 동일한 방법으로 합성예 N 내지 P의 화합물을 제조하였다.

[411] [표 5] 합성예 M-P

[412]

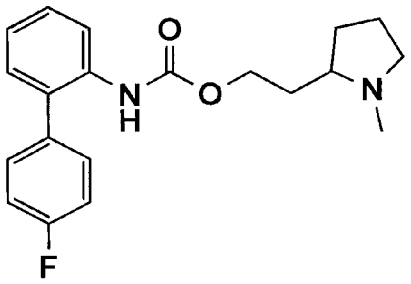
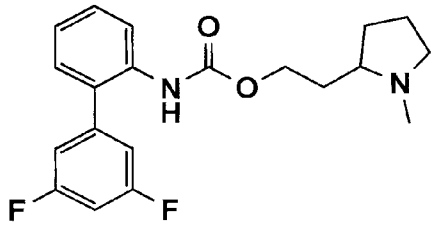
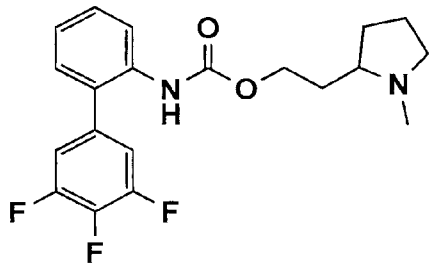
합성예	화학명	출발물질	반응물질
M	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐)카바메이트 (1.4g, 45%)	2-브로모벤조익 애시드 (2g, 9.95mmol)	(S)-(1-메틸피롤리딘-2-일)메탄올 (1.42mL, 11.94mmol)
N	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (2.86g, 47%)	2-브로모-4-플루오로벤조익 애시드 (4g, 18.26mmol)	(S)-(1-메틸피롤리딘-2-일)메탄올 (2.6mL, 21.91mmol)
O	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-메톡시페닐)카바메이트 (600mg, 67%)	2-브로모-4-메톡시벤조익 애시드 (600mg, 2.60mmol)	(S)-(1-메틸피롤리딘-2-일)메탄올 (463uL, 3.90mmol)
P	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4,5-디플루오로페닐) 카바메이트 (737mg, 50%)	2-브로모-4,5-디플루오로벤조익 애시드 (1g, 4.22mmol)	(S)-(1-메틸피롤리딘-2-일)메탄올(730mg, 6.33mmol)

[413]

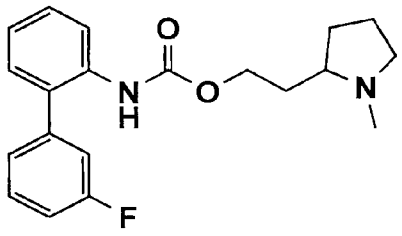
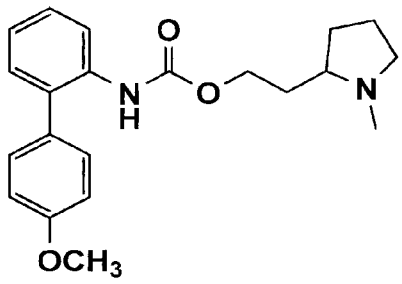
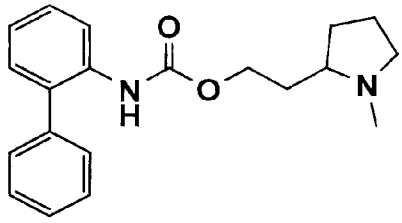
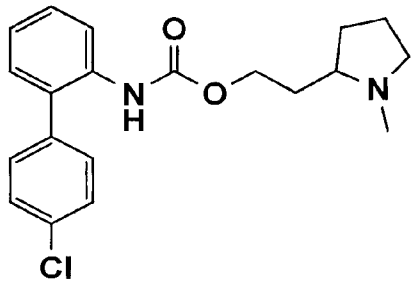
[414] **실시예**

[415] [표 6] 실시예 화합물

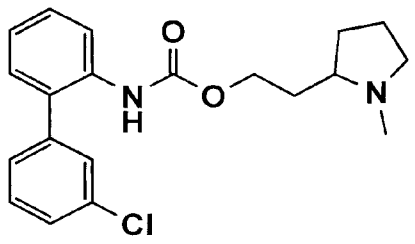
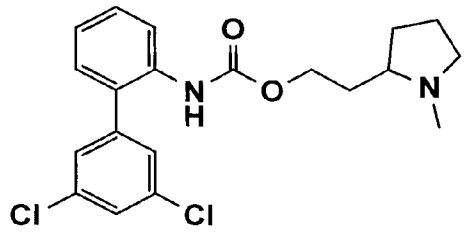
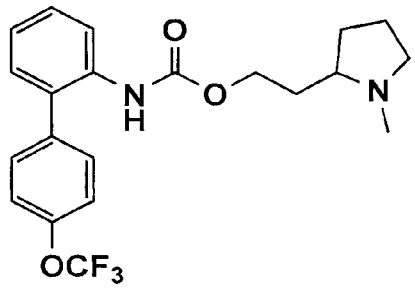
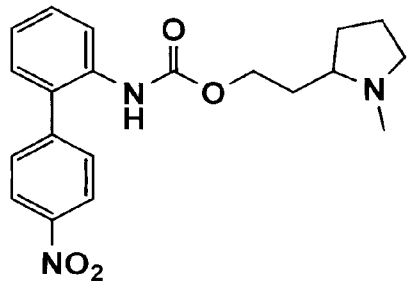
[416]

실시예	화합물	NMR 값
1	2-(1-메틸피롤리딘-2-일)에틸 (4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.10-7.99(m, 1H), 7.38-7.26(m, 3H), 7.20-7.06(m, 4H), 6.52-6.41(bs, 1H), 4.21-4.08(m, 2H), 3.12-2.99(m, 1H), 2.29(m, 3H), 2.20-1.87(m, 4H), 1.83-1.61(m, 2H), 1.61-1.40(m, 2H)
2	2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.11-7.96(m, 1H), 7.45-7.32(m, 1H), 7.21-7.07(m, 2H), 6.98-6.79(m, 3H), 6.55-6.39(bs, 1H), 4.27-4.10(m, 2H), 3.14-2.99(m, 1H) 2.30(s, 3H), 2.21-1.85(m, 4H), 1.85-1.41(m, 4H)
3	2-(1-메틸피롤리딘-2-일)에틸 (3',4',5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.00-7.88(m, 1H), 7.43-7.30(m, 1H), 7.29-7.08(m, 2H), 7.05-6.91(m, 2H), 6.69-6.52(bs, 1H), 4.25-4.06(m, 2H), 3.25-3.08(m, 1H), 2.47-2.17(m, 5H) 2.14-1.91(m, 2H), 1.90-1.45(m, 4H)

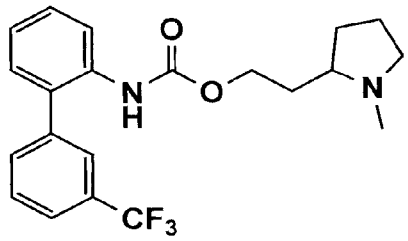
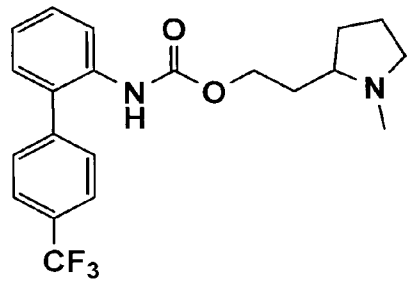
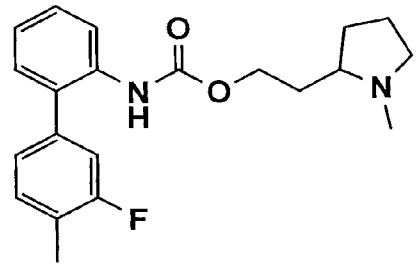
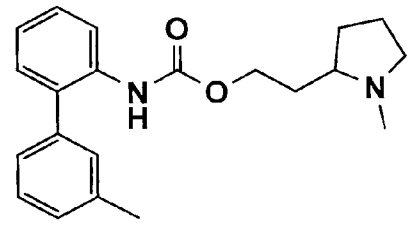
[417]

4	2-(1-메틸피롤리딘-2-일)에틸 (3'-플루오-로[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.13-7.96(m, 1H), 7.50 7.28(m, 2H), 7.22-7.00(m, 5H), 6.60-6.45(bs, 1H), 4.25-4.07(m, 2H), 3.13 2.99(m, 1H), 2.31(s, 3H), 2.22-1.41(m, 8H)
5	2-(1-메틸피롤리딘-2-일)에틸 (4'-메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.13-7.99(m, 1H), 7.35-7.22(m, 4H), 7.20-7.14(m, 1H), 7.12-7.06(m, 1H), 7.03-6.95(m, 2H), 6.63-6.56(bs, 1H), 4.23-4.10(m, 2H), 3.85(s, 3H), 3.10-3.01(m, 1H), 2.28(s, 3H) 2.17-1.88(m, 4H), 1.84-1.62(m, 2H), 1.62-1.41(m, 2H)
6	2-(1-메틸피롤리딘-2-일)에틸 [1,1'-바이페닐]-2-일카바메이트 	^{1}H NMR($CDCl_3$): δ 8.11(s, 1H), 7.45(t, 1H), 7.38(d, 1H), 7.34(dd, 2H), 7.21(dd, 2H), 7.12(t, 1H), 6.99(t, 1H), 6.64(s, 1H), 4.18-4.14(m, 2H), 3.09-3.01(m, 1H), 2.40(s, 3H), 2.34(m, 3H), 2.12-2.06 (m, 2H), 1.91-1.82(m, 1H), 1.78-1.66(m, 2H), 1.60-1.56(m, 1H)
7	2-(1-메틸피롤리딘-2-일)에틸 (4'-클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.11-7.94(m, 1H), 7.55-6.97(m, 7H), 6.55-6.35(bs, 1H), 4.25-3.98(m, 2H), 3.14-2.94(m, 1H) 2.29(s, 3H), 2.20-1.84(m, 4H), 1.81-1.37(m, 4H)

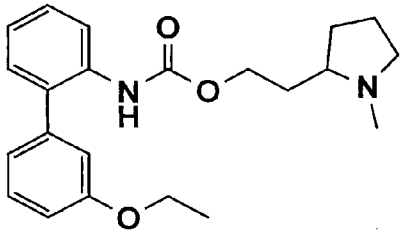
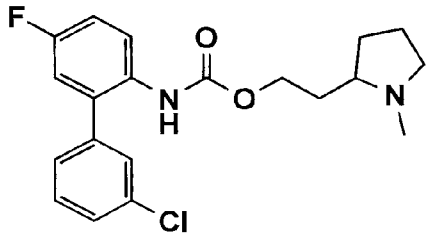
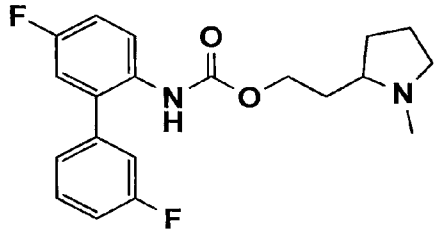
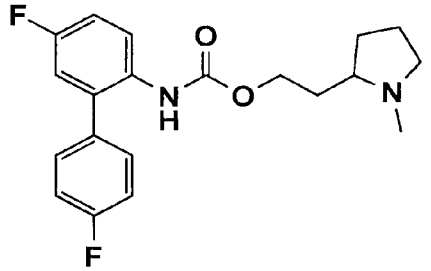
[418]

8	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.06(s, 1H), 7.41-7.35(m, 4H), 7.26-7.22(m, 1H), 7.19-7.16(m, 1H), 7.14-7.10(m, 1H), 6.47(s, 1H), 4.22-4.15(m, 2H), 3.07-3.02(m, 1H), 2.29(s, 3H), 2.16-2.06(m, 2H), 2.03-1.91(m, 2H), 1.78-1.62(m, 2H), 1.60-1.47(m, 2H)
9	2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.01(s, 1H), 7.39-7.35(m, 2H), 7.22-7.20(m, 2H), 7.17-7.11(m, 2H), 6.42(s, 1H), 4.22-4.13(m, 2H), 3.10-3.01(s, 1H), 2.30(s, 3H), 2.08-2.04(m, 2H), 2.03-1.90(m, 2H), 1.78-1.60(m, 2H), 1.58-1.42(m, 2H)
10	2-(1-메틸피롤리딘-2-일)에틸 (4'-트리플루오로메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.03(s, 1H), 7.39-7.34(m, 3H), 7.31-7.291(m, 2H), 7.19-7.11(m, 2H), 6.44(s, 1H), 4.24-4.15(m, 2H), 3.04-3.00(m, 1H), 2.27(s, 3H), 2.04-2.01(m, 2H), 2.00-1.88(m, 2H), 1.80-1.63(m, 2H), 1.59-1.44(m, 2H)
11	2-(1-메틸피롤리딘-2-일)에틸 (4'-니트로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.27-8.24(m, 1H), 7.55-7.52(m, 1H), 7.41-7.37(m, 1H), 7.22-7.00(m, 3H), 7.01-6.97(m, 1H), 4.14-4.05(m, 2H), 3.37-3.35(m, 1H), 2.50(s, 3H), 2.10-2.04(m, 2H), 1.93-1.88(m, 2H), 1.81-1.77(m, 2H), 1.66-1.62(m, 2H)

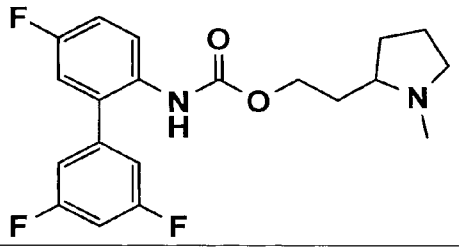
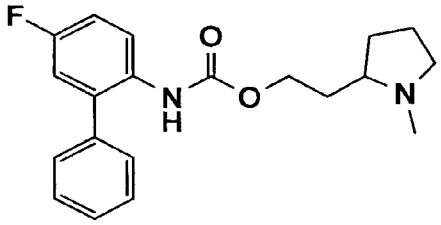
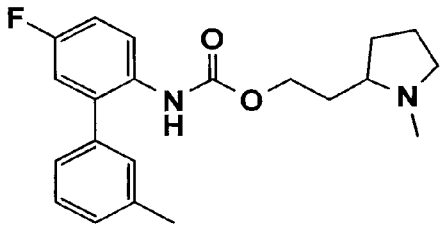
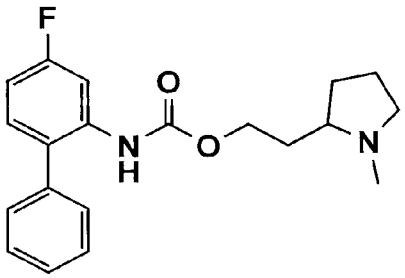
[419]

12	2-(1-메틸피롤리딘-2-일)에틸 (3'-트리플루오로메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.10-7.92(m, 1H), 7.73-7.46(m, 3H), 7.44-7.31(m, 1H), 7.31-7.05(m, 2H), 6.55-6.34(bs, 1H), 4.26-4.02(m, 2H), 3.20-3.00(m, 1H), 2.31(s, 3H), 2.25-1.88(m, 4H) 1.86-1.40(m, 4H)
13	2-(1-메틸피롤리딘-2-일)에틸 (4'-트리플루오로메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.04(s, 1H), 7.72(d, 2H, *J*=8.0), 7.48(d, 2H, *J*=8.4), 7.41-7.36(m, 1H), 7.20-7.13(m, 2H), 6.41(s, 1H), 4.18-4.14(m, 2H), 3.06-3.01(s, 1H), 2.27(s, 3H), 2.18-2.04(m, 2H), 2.02-1.87(m, 2H), 1.77-1.68(m, 2H), 1.57-1.43(m, 2H)
14	2-(1-메틸피롤리딘-2-일)에틸 ((3'-플루오로-4'-메틸)-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.11-7.99(m, 1H), 7.39-7.30(m, 1H), 7.30-7.14(m, 2H), 7.14-7.07(m, 1H), 7.06-6.95(m, 2H), 6.64-6.54(bs, 1H), 4.26-4.08(m, 2H), 3.30-3.09(m, 1H), 2.36(s, 3H), 2.32(s, 3H), 2.30-2.14(m, 2H) 2.13-1.92(m, 2H), 1.92-1.46(m, 4H)
15	2-(1-메틸피롤리딘-2-일)에틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.10(s, 1H), 7.38-7.33(m, 2H), 7.26-7.17(m, 3H), 7.15-7.09(m, 1H), 6.66(s, 1H), 4.19-4.16(m, 2H), 3.21-3.01 (s, 1H), 2.41(s, 3H), 2.28(s, 3H), 2.23-2.12(m, 2H), 2.10-1.91(m, 2H), 1.83-1.63(m, 2H), 1.60-1.43(m, 2H)

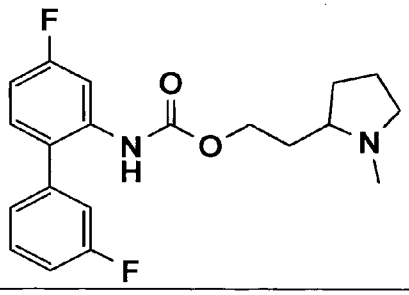
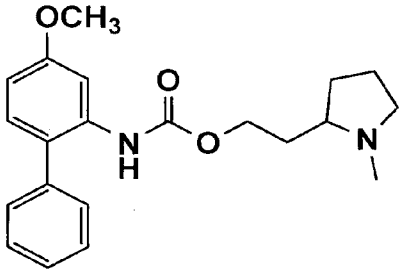
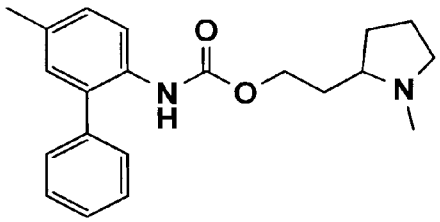
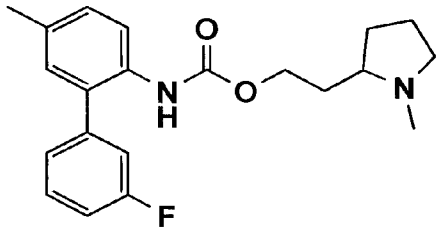
[420]

16	2-(1-메틸피롤리딘-2-일)에틸 (3'-에톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.10(s, 1H), 7.37-7.31(m, 2H), 7.23-7.18(m, 2H), 7.11-7.08(m, 1H), 7.00-6.86(m, 2H), 6.70(s, 1H), 4.17-4.01(m, 4H), 3.18-3.15(m, 1H), 2.36(s, 3H), 2.23-2.16(m, 2H), 2.08-1.91(m, 2H), 1.81-1.71(m, 2H), 1.63-1.41(m, 2H), 1.40-1.38(m, 3H)
17	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.94(s, 1H), 7.41-7.36(m, 2H), 7.32(s, 1H), 7.22-7.20(m, 1H), 7.07-7.02(m, 1H), 6.92-6.89(m, 1H), 6.38(s, 1H), 4.17-4.13(m, 2H), 3.04-3.00(m, 1H), 2.27(s, 3H), 2.15-2.03(m, 2H), 2.00-1.87(m, 2H), 1.80-1.64(m, 2H), 1.56-1.40(m, 2H)
18	2-(1-메틸피롤리딘-2-일)에틸 (3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.86(s, 1H), 7.44-7.39(m, 1H), 7.26-7.22(m, 1H), 7.17-7.08(m, 1H), 7.06-7.02(m, 1H), 7.01-6.91(m, 2H), 6.75(s, 1H), 4.15-4.06(m, 2H), 3.30-3.27(m, 1H), 2.47(s, 3H), 2.10-1.93(m, 2H), 1.87-1.73(m, 2H), 1.70-1.54(m, 2H)
19	2-(1-메틸피롤리딘-2-일)에틸 (4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.97(s, 1H), 7.32-7.26(m, 1H), 7.24-7.21(m, 1H), 7.19-7.13(m, 2H), 7.07-7.00(m, 1H), 6.92-6.90(m, 1H), 6.48(s, 1H), 4.16-4.10(m, 2H), 3.20-3.17(m, 1H), 2.26(s, 3H), 2.17-2.15(m, 2H), 2.07-1.96(m, 2H), 1.83-1.72(m, 2H), 1.69-1.65(m, 2H)

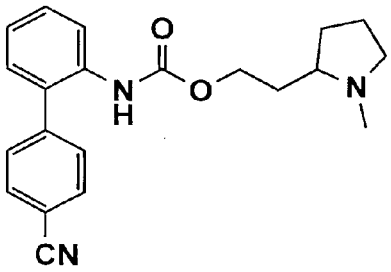
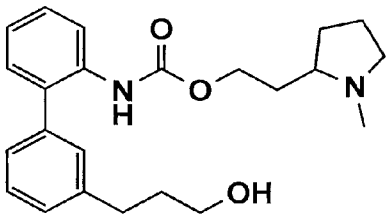
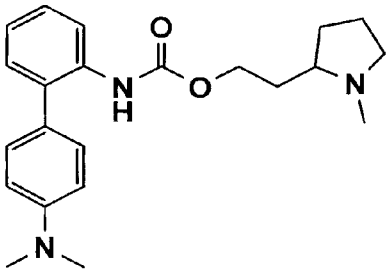
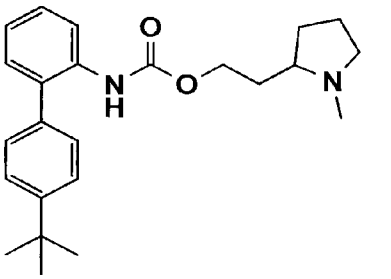
[421]

20	2-(1-메틸피롤리딘-2-일)에틸 (3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.82-7.66(bs, 1H), 7.12-6.75(m, 5H), 4.27-3.99(m, 2H), 3.51-3.30(bs, 1H) 2.75-2.34(m, 5H), 2.20-1.55(m, 6H)
21	2-(1-메틸피롤리딘-2-일)에틸 (5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.98(s, 1H), 7.50-7.39(m, 3H), 7.34-7.27(m, 2H), 7.06-7.01(m, 1H), 6.98-6.92(m, 1H), 6.45(s, 1H), 4.17-4.07(m, 2H), 3.05-3.01(m, 1H), 2.27(s, 3H), 2.22-2.02(m, 2H), 2.01-1.80(m, 2H), 1.78-1.61(m, 2H), 1.58-1.40(m, 2H)
22	2-(1-메틸피롤리딘-2-일)에틸 (5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.01(s, 1H), 7.36-7.32(m, 1H), 7.27-7.21(m, 2H), 7.13-7.11(m, 1H), 7.05-7.00(m, 1H), 6.96-6.90(m, 1H), 6.51(s, 1H), 4.16-4.09(m, 2H), 3.06-3.02(m, 1H), 2.39(s, 3H), 2.28(s, 3H), 2.18-2.07(m, 2H), 2.05-1.88(m, 2H), 1.81-1.62(m, 2H), 1.58-1.44(m, 2H)
23	2-(1-메틸피롤리딘-2-일)에틸 (4-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.97(s, 1H), 7.48-7.45(m, 2H), 7.42-7.40(m, 1H), 7.32-7.30(m, 2H), 7.15-7.11(m, 1H), 6.82-6.79(m, 1H), 6.66(s, 1H), 4.18-4.14(m, 2H), 3.06-3.04(m, 1H), 2.30(s, 3H), 2.15-2.00(m, 2H), 1.99-1.91(m, 2H), 1.69-1.58(m, 2H), 1.56-1.48(m, 2H)

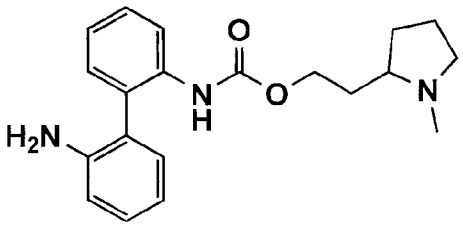
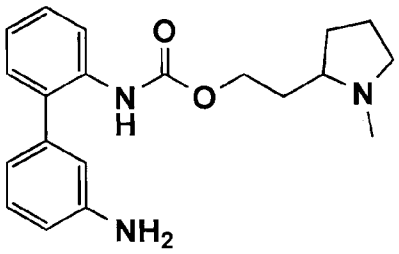
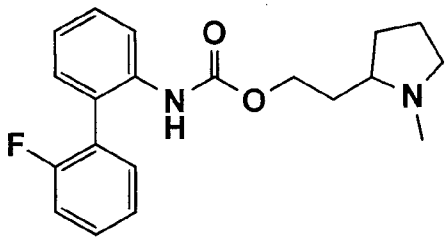
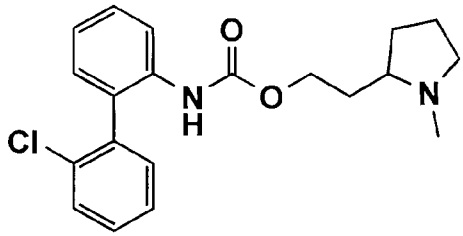
[422]

24	2-(1-메틸피롤리딘-2-일)에틸 (3',4-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.97(s, 1H), 7.48-7.44(m, 1H), 7.28-7.17(m, 2H), 7.15-7.11(m, 1H), 7.05-6.97(m, 1H), 6.86-6.80(m, 1H), 6.68(s, 1H), 4.19-4.13(m, 2H), 3.31-3.28(m, 1H), 2.48(s, 3H), 2.19-2.07(m, 2H), 1.95-1.88(m, 2H), 1.85-1.70(m, 2H), 1.67-1.54(m, 2H)
25	2-(1-메틸피롤리딘-2-일)에틸 (4-메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.80(s, 1H), 7.44-7.36(m, 1H), 7.34-7.29(m, 3H), 7.09-7.07(m, 1H), 6.68-6.64(m, 2H), 4.20-4.14(m, 2H), 3.82(s, 3H), 3.04-3.00(m, 1H), 2.26(s, 3H), 2.14-2.00(m, 2H), 2.13-1.87(m, 2H), 1.79-1.59(m, 2H), 1.56-1.40 (m, 2H)
26	2-(1-메틸피롤리딘-2-일)에틸 (5-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.91 (s, 1H), 7.46-7.42(m, 2H), 7.38-7.29(m, 2H), 7.22-7.18(m, 1H), 7.02(s, 1H), 6.54(s, 1H), 4.18-4.10(m, 2H), 3.21-3.10(m, 1H), 2.32(s, 3H), 2.31(s, 3H), 2.22-2.16(m, 2H), 2.12-1.91(m, 2H), 1.81-1.68(m, 2H), 1.65-1.48(m, 2H)
27	2-(1-메틸피롤리딘-2-일)에틸 (3'-플루오로-5-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.92 (s, 1H), 7.44-7.38(m, 2H), 7.20-7.15(m, 1H), 7.13-7.09(m, 1H), 7.07-6.97(m, 2H), 6.55(s, 1H), 4.17-4.07(m, 2H), 3.30-3.23(m, 1H), 2.49(s, 3H), 2.37(s, 3H), 2.15-2.05(m, 2H), 1.93-1.90(m, 2H), 1.79-1.76(m, 2H), 1.63-1.61(m, 2H)

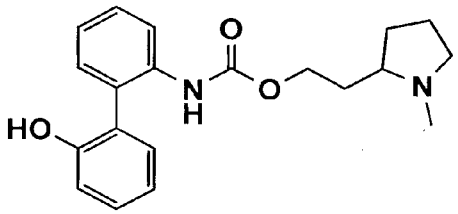
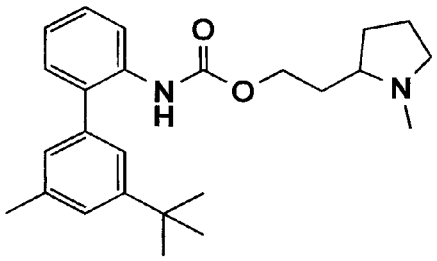
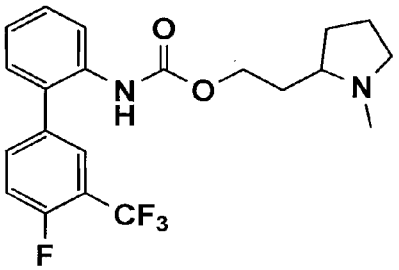
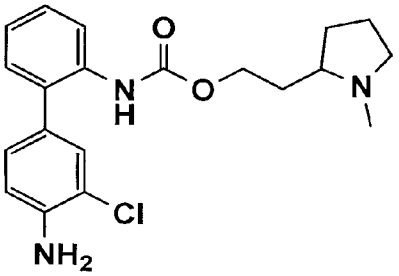
[423]

28	2-(1-메틸피롤리딘-2-일)에틸 (4'-시아노-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.06-7.93(m, 1H), 7.75(d, 8.4Hz, 2H), 7.49(d, J=8.0, 2H), 7.44-7.33(m, 1H), 7.21-7.09(m, 2H), 6.42-6.38(bs, 1H), 4.22-4.07(m, 2H), 3.11-2.98(m, 1H), 2.29(s, 3H), 2.19-1.85(m, 3H) 1.85-1.39(m, 5H)
29	2-(1-메틸피롤리딘-2-일)에틸 (3'-(3-하드록시프로펜)-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.03(s, 1H), 7.39-7.28(m, 3H), 7.23-7.11(m, 3H), 7.05-7.01(m, 1H), 6.67(s, 1H), 4.23-4.14(m, 2H), 3.66-3.60(m, 2H), 3.17-3.03(m, 1H), 2.75-2.71(m, 2H), 2.32(s, 3H), 2.24-2.10(m, 2H), 2.05-1.96 (m, 2H), 1.94-1.83 (m, 2H), 1.81-1.69(m, 2H), 1.61-1.46(m, 2H)
30	2-(1-메틸피롤리딘-2-일)에틸 (4'-(디메틸아미노)-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.11(s, 1H), 7.28(t, 1H, J=7.2), 7.23-7.19(m, 2H), 7.19-7.17(m, 1H), 7.07(t, 1H, J=7.6), 6.81(t, 2H, J=2.8), 6.74(s, 1H), 4.18-4.14(m, 2H), 3.09-3.01(m, 1H), 3.00(s, 9H), 2.14(s, 3H), 2.12-2.06(m, 2H), 2.01-1.92(m, 2H), 1.79-1.66(m, 2H), 1.58-1.46(m, 2H)
31	2-(1-메틸피롤리딘-2-일)에틸 (4'-(tert-부틸)-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.04(s, 1H), 7.48-7.46(m, 2H), 7.35-7.27(m, 3H), 7.24-7.19(m, 1H), 7.12-7.08(m, 1H), 6.67(s, 1H), 4.17-4.13(m, 2H), 3.10-3.07(m, 1H), 2.30(s, 3H), 2.18-1.99(m, 2H), 1.98-1.90(m, 2H), 1.80-1.62(m, 2H), 1.44-1.36(m, 2H), 1.36(s, 9H)

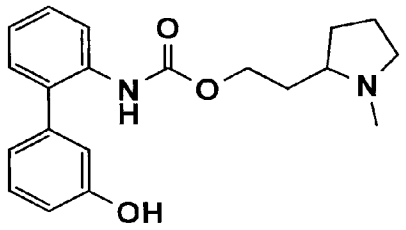
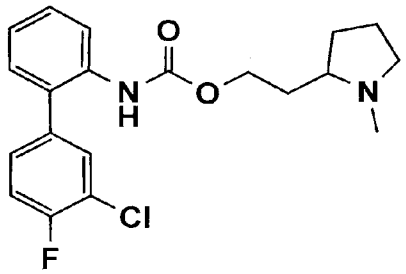
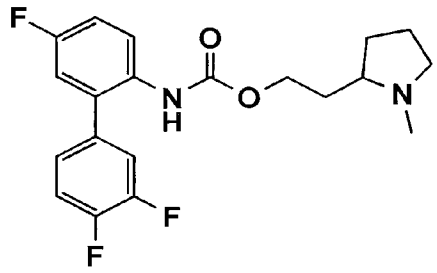
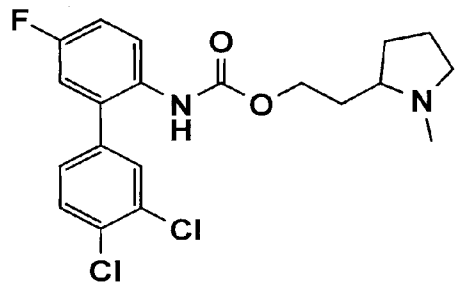
[424]

32	2-(1-메틸피롤리딘-2-일)에틸 (2'-아미노-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.11(s, 1H), 7.37(t, 1H, J=8.0), 7.22-7.20(m, 2H), 7.13(t, 1H, J=7.6), 7.06(d, 1H, J=7.6), 6.86-6.78(m, 2H), 4.15-4.11(m, 2H), 3.08-3.04(s, 1H), 2.25(s, 3H), 2.17-2.10(m, 2H), 2.02-1.90(m, 2H), 1.78-1.66(m, 2H), 1.58-1.46(m, 2H)
33	2-(1-메틸피롤리딘-2-일)에틸 (3'-아미노-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR(CD_3OD): δ 7.83(s, 1H), 7.29-7.15(m, 3H), 7.06-7.00(m, 2H), 6.80-6.77(m, 2H), 4.14-4.10(m, 2H), 3.30(s, 3H), 3.20-3.15(m, 1H), 2.45-2.43(m, 2H), 2.10-2.00 (m, 2H), 1.84-1.81(m, 2H), 1.62-1.47(m, 2H)
34	2-(1-메틸피롤리딘-2-일)에틸 (2'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.96(s, 1H), 7.42-7.36(m, 3H), 7.31-7.14(m, 3H), 6.99-6.97(m, 1H), 6.45(s, 1H), 4.15-4.08(m, 2H), 3.26-3.22(s, 1H), 2.39(s, 3H), 2.35-2.25(m, 2H), 2.09-1.96(m, 2H), 1.88-1.64(m, 2H), 1.60-1.53(m, 2H)
35	2-(1-메틸피롤리딘-2-일)에틸 (2'-클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.01(s, 1H), 7.51-7.48(m, 1H), 7.41-7.34(m, 2H), 7.28-7.13(m, 3H), 6.96-6.93(m, 1H), 6.26(s, 1H), 4.18-4.05(m, 2H), 3.22-3.20(s, 1H), 2.37(s, 3H), 2.35-2.28(m, 2H), 2.07-1.93(m, 2H), 1.84-1.63(m, 2H), 1.57-1.52(m, 2H)

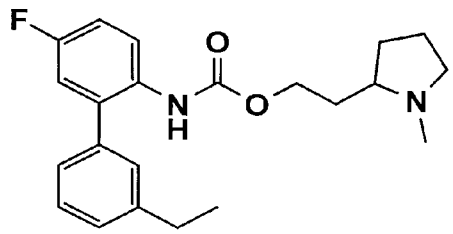
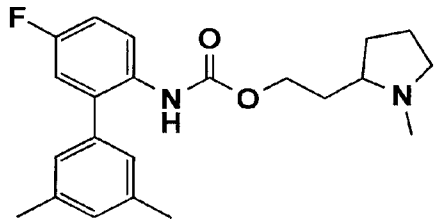
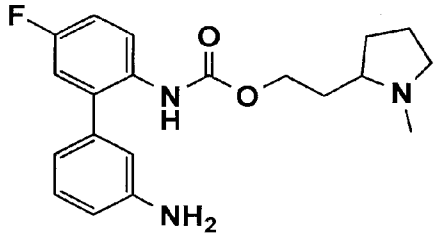
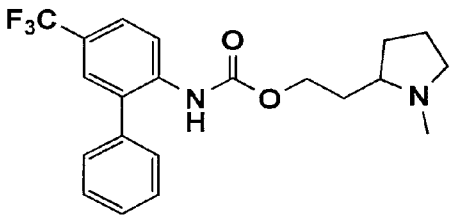
[425]

36	2-(1-메틸피롤리딘-2-일)에틸 (2'-히드록시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.84(s, 1H), 7.39-7.33(m, 1H), 7.31-7.12(m, 4H), 7.05-7.01(m, 1H), 6.96-6.90(m, 1H), 4.21-4.09(m, 2H), 3.21-3.14(s, 1H), 2.40(s, 3H), 2.36-2.26(m, 2H), 2.13-1.96(m, 2H), 1.84-1.66(m, 2H), 1.64-1.53(m, 2H)
37	2-(1-메틸피롤리딘-2-일)에틸 (3'-tert-부틸-5'-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.11(s, 1H), 7.35-7.27(m, 1H), 7.23-7.21(m, 2H), 7.18(s, 1H), 7.13-7.09(m, 1H), 6.99(s, 1H), 6.74(s, 1H), 4.17-4.12(m, 2H), 3.12-3.09(m, 1H), 2.39(s, 3H), 2.30(s, 3H), 2.23-2.11(m, 2H), 2.01-1.98(m, 2H), 1.79-1.66(m, 2H), 1.58-1.46(m, 2H), 1.32(m, 9H)
38	2-(1-메틸피롤리딘-2-일)에틸 (4'-플루오로-3'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.99(s, 1H), 7.60-7.58(m, 1H), 7.56-7.53(m, 1H), 7.41-7.36(m, 1H), 7.32-7.27(m, 1H), 7.20-7.14(m, 2H), 6.37(s, 1H), 4.18-4.13(m, 2H), 3.14-3.12(m, 1H), 2.34(s, 3H), 2.34-2.21(m, 2H), 2.06-1.93(m, 2H), 1.76-1.68(m, 2H), 1.64-1.46(m, 2H)
39	2-(1-메틸피롤리딘-2-일)에틸 (4'-아미노-3'-클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.04(s, 1H), 7.30(t, 1H, J=8.0), 7.15-7.12(m, 2H), 7.07-7.03(m, 2H), 6.82(d, 1H, J=8.4), 6.59(s, 1H), 4.18-4.09(m, 2H), 3.08-3.04(m, 1H), 2.30(s, 3H), 2.25-2.10 (m, 2H), 2.08-1.91(m, 2H), 1.81-1.57(m, 2H), 1.56-1.43(m, 2H)

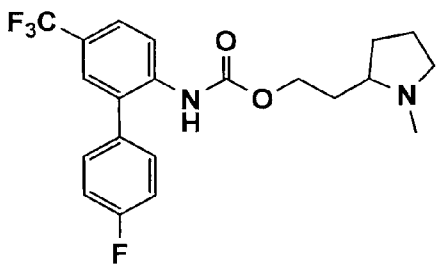
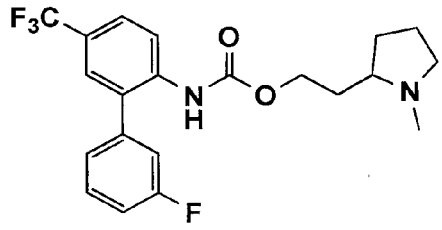
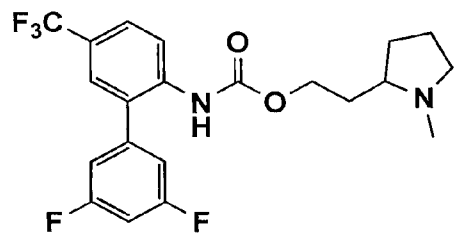
[426]

40	2-(1-메틸피롤리딘-2-일)에틸 (3'-히드록시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR(CD_3OD): δ 7.84(s, 1H), 7.31-7.18(m, 3H), 7.06-7.02(m, 2H), 6.82-6.79(m, 2H), 4.11-4.08(m, 2H), 3.30(s, 3H), 3.21-3.18(m, 1H), 2.45-2.43(m, 2H), 2.08-2.01(m, 2H), 1.84-1.82(m, 2H), 1.61-1.45(m, 2H)
41	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.06-7.93(bs, 1H), 7.41-7.38(m, 1H), 7.38-7.34(m, 1H), 7.23-7.19(m, 3H), 7.17-7.10(m, 2H), 6.51-6.44(bs, 1H), 4.20-4.12(m, 2H), 3.16-3.07(bs, 1H) 2.33(s, 3H), 2.25-2.13(m, 2H), 2.07-1.92(m, 2H), 1.84-1.65(m, 2H), 1.65-1.46(m, 2H)
42	2-(1-메틸피롤리딘-2-일)에틸 (3',4',5-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.98(s, 1H), 7.29-7.28(m, 1H), 7.17-7.14(m, 1H), 7.08-7.03(m, 2H), 6.90(dd, 1H, *J*=8.8, *J*=2.8), 6.33(s, 1H), 4.17-4.13(m, 2H), 3.05-3.03(m, 1H), 2.28(s 3H), 2.08-2.03(m, 2H), 2.02-1.89(m, 2H), 1.79-1.63(m, 2H), 1.60-1.42(m, 2H)
43	2-(1-메틸피롤리딘-2-일)에틸 (3',4'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.94(s, 1H), 7.54(d, 1H, *J*=8.4), 7.44(d, 1H, *J*=2.0), 7.19(dd, 1H, *J*=8.4, *J*=2.0), 7.09-7.05(m, 1H), 6.91(dd, 1H, *J*=8.4, *J*=2.8), 6.38(s, 1H), 4.20-4.14(m, 2H), 3.17-3.16(m, 1H), 2.36(s, 3H), 2.07-1.96(m, 2H), 1.83-1.80(m, 2H), 1.77-1.71(m, 2H), 1.58-1.54(m, 2H)

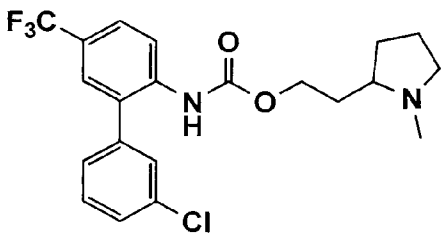
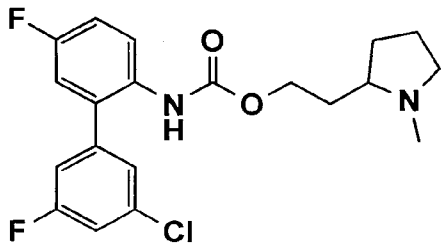
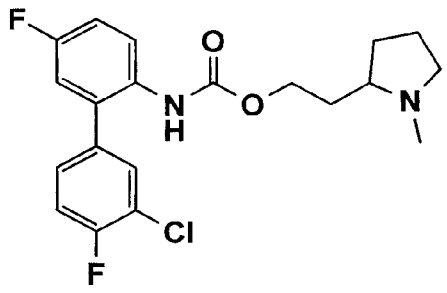
[427]

44	2-(1-메틸피롤리딘-2-일)에틸 (3'-에틸-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.01(s, 1H), 7.38(t, 1H, J=8.0), 7.25-7.23(m, 1H), 7.16-7.13(m, 2H), 7.05-7.00(m, 1H), 6.95-6.92(m, 1H), 6.53(s, 1H), 4.17-4.12(m, 2H), 3.05-3.03(m, 1H), 2.68(q, 2H, J=7.6), 2.28(s, 3H), 2.16-2.02(m, 2H), 2.00-1.88(m, 2H), 1.78-1.62(m, 2H), 1.59-1.41(m, 2H), 1.25(t, 3H, J=7.6)
45	2-(1-메틸피롤리딘-2-일)에틸 (5-플루오로-3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.01(s, 1H), 7.03-6.98(m, 2H), 6.93-6.89(m, 2H), 6.55(s, 1H), 4.20-4.14(m, 2H), 3.03-3.01(m, 1H), 2.38(s, 6H), 2.35(s, 3H), 2.09-2.04(m, 2H), 2.03-1.90(m, 2H), 1.79-1.63(m, 2H), 1.59-1.44(m, 2H)
46	2-(1-메틸피롤리딘-2-일)에틸 (3'-아미노-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.02(s, 1H), 7.25-7.21(m, 2H), 7.03-6.99(m, 1H), 6.92-6.89(m, 1H), 6.71-6.67(m, 2H), 6.60(s, 2H), 4.16-4.12(m, 2H), 3.04-3.01(m, 1H), 2.28(s, 3H), 2.02-1.97(m, 2H), 1.96-1.89(m, 2H), 1.78-1.63(m, 2H), 1.57-1.41(m, 2H)
47	2-(1-메틸피롤리딘-2-일)에틸 (5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.29(d, 1H, J=8.8), 7.59(d, 1H, J=8.8), 7.52-7.49(m, 2H), 7.46-7.44(m, 2H), 7.36-7.34(m, 2H), 6.78(s, 1H), 4.19-4.16(m, 2H), 3.12-3.10(m, 1H), 2.33(s, 3H), 2.17-2.05(m, 2H), 2.03-1.93(m, 2H), 1.78-1.64(m, 2H), 1.53-1.51(m, 2H)

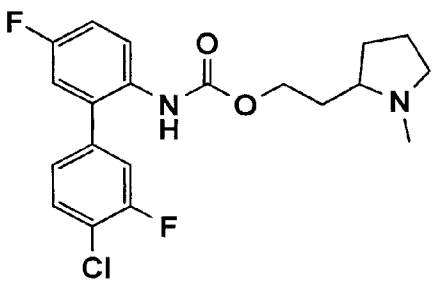
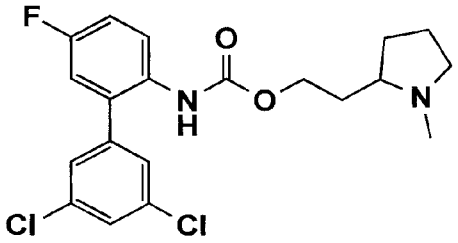
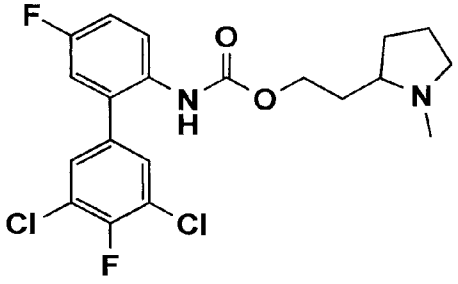
[428]

48	2-(1-메틸피롤리딘-2-일)에틸 (4'-플루오로-5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.27(d, 1H, J=8.4), 7.59(d, 1H, J=8.8), 7.41(d, 1H, J=1.2), 7.34-7.31 (m, 2H), 7.22-7.18(m, 2H), 6.70(s, 1H), 4.22-4.16(m, 2H), 3.26-3.24(m, 1H), 2.41(s, 3H), 2.35-2.29(m, 2H), 2.13-1.98(m, 2H), 1.88-1.77(m, 2H), 1.62-1.59(m, 2H)
49	2-(1-메틸피롤리딘-2-일)에틸 (3'-플루오로-5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.29(d, 1H, J=8.8), 7.61(d, 1H, J=8.8), 7.51-7.45(m, 1H), 7.43(s, 1H), 7.18-7.13(m, 2H), 7.08-7.06(m, 1H), 6.71(s, 1H), 4.21-4.17(m, 2H), 3.12-3.10(m, 1H), 2.33(s, 3H), 2.19-2.15(m, 2H), 2.07-1.92(m, 2H), 1.74-1.71(m, 2H), 1.53-1.50(m, 2H)
50	2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디플루오로-5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.26(d, 1H, J=8.8), 7.62(d, 1H, J=8.8), 7.43(s, 1H), 6.93-6.89(m, 3H), 6.78(s, 1H), 4.24-4.19(m, 2H), 3.28-3.21(m, 1H), 2.45(s, 3H), 2.15-2.04(m, 2H), 1.89-1.87(m, 2H), 1.82-1.80(m, 2H), 1.67-1.63(m, 2H)

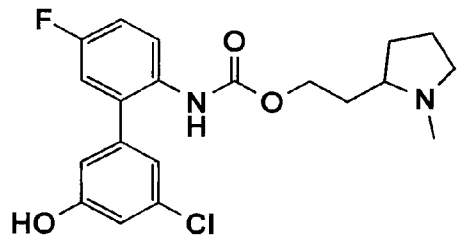
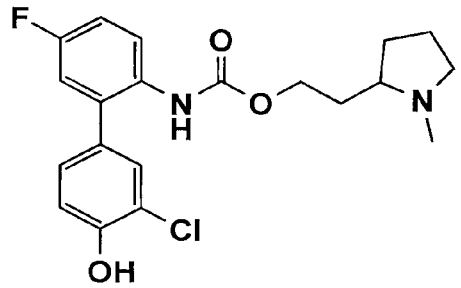
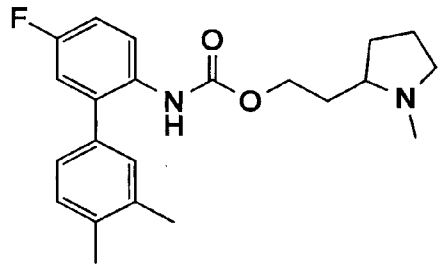
[429]

51	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.27(d, 1H, J=8.4), 7.61(d, 1H, J=8.8), 7.47-7.43(m, 3H), 7.35(s, 1H), 7.25-7.23(m, 1H), 6.75(s, 1H), 4.23-4.17(m, 2H), 3.34-3.32(m, 1H), 2.42(s, 3H), 2.11-2.05(m, 2H), 2.02-1.91(m, 2H), 1.90-1.83(m, 2H), 1.83-1.80(m, 2H)
52	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-5,5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.91(s, 1H), 7.22-7.20(m, 1H), 7.15-7.13(m, 1H), 7.10-7.05(m, 1H), 6.99-6.97(m, 1H), 6.92(dd, 1H, J=8.8, J=2.8), 6.44(s, 1H), 4.21-4.14(m, 2H), 3.22-3.19(m, 1H), 2.40(s, 3H), 2.32-2.28(m, 2H), 2.10-2.02(m, 2H), 1.86-1.59(m, 2H), 1.26-1.22(m, 2H)
53	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.91(s, 1H), 7.39(dd, 1H, J=7.2, J=2.0), 7.23-7.19(m, 2H), 7.08-7.04(m, 1H), 6.90(dd, 1H, J=8.4, J=2.8), 6.37(s, 1H), 4.18-4.13(m, 2H), 3.14-3.10(m, 1H), 2.33(s, 3H), 2.23-2.16(m, 2H), 2.06-1.91(m, 2H), 1.82-1.65(m, 2H), 1.60-1.51(m, 2H)

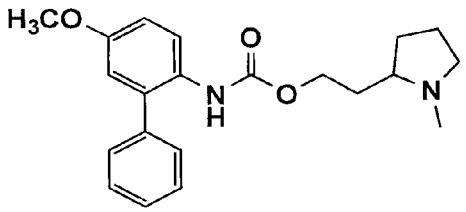
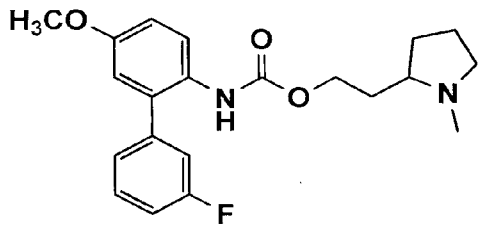
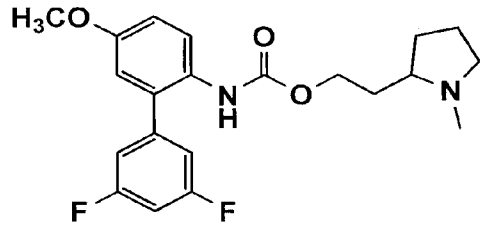
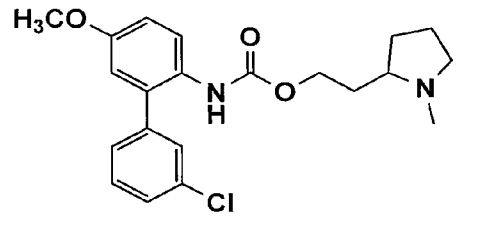
[430]

54	2-(1-메틸피롤리딘-2-일)에틸 (4'-클로로-3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.81(s, 1H), 7.47-7.43(m, 1H), 7.19-7.11(m, 2H), 7.11-6.95(m, 1H), 6.90(dd, 1H, *J*=8.8, *J*=3.2) 6.62(s, 1H), 4.14-4.04(m, 2H), 3.21-3.16(m, 1H), 2.37(s, 3H), 2.04-1.95(m, 2H), 1.84-1.69(m, 2H), 1.67-1.61(m, 1H), 1.57-1.48(m, 2H)
55	2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.90(s, 1H), 7.41-7.40(m, 1H), 7.25-7.22(m, 2H), 7.10-7.05(m, 1H), 6.91(dd, 1H, *J*=8.8, *J*=2.8), 6.38(s, 1H), 4.20-4.16(m, 2H), 3.16-3.12(m, 1H), 2.36(s, 3H), 2.23-2.21(m, 2H), 2.09-1.94(m, 2H), 1.80-1.64(m, 2H), 1.56-1.52(m, 2H)
56	2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.81(s, 1H), 7.31-7.30(m, 1H), 7.19-7.18(m, 1H), 7.09-7.04(m, 1H), 6.91-6.62(m, 1H), 6.61(s, 1H), 4.20-4.11(m, 2H), 3.26-3.22(m, 1H), 2.42-2.30(m, 4H), 2.11-1.93(m, 2H), 1.88-1.63(m, 2H), 1.61-1.54(m, 2H)

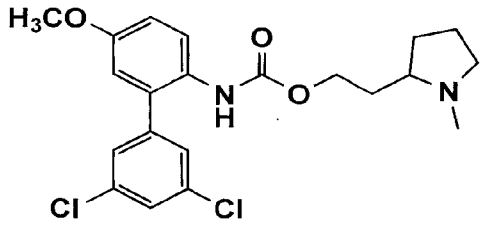
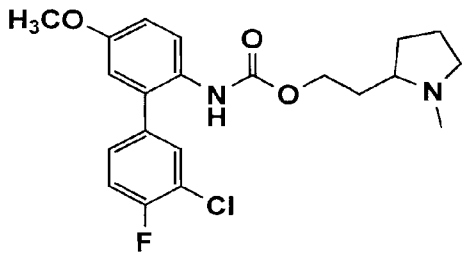
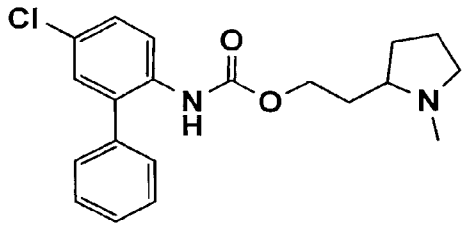
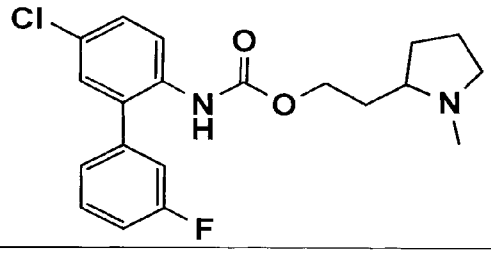
[431]

57	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-5-플루오로-5'-히드록시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.83(s, 1H), 7.03-6.95(m, 1H), 6.91-6.88(m, 1H), 6.80(s, 1H), 6.73-6.66(m, 2H), 4.12-4.07(m, 2H), 3.21-3.17(m, 1H), 2.35(s, 3H), 2.28-2.24(m, 2H), 1.82-1.65(m, 2H), 1.62-1.55(m, 2H), 1.25-1.21(m, 2H)
58	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-5-플루오로-4'-히드록시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.83(s, 1H), 7.25-7.20(m, 1H), 7.05-6.92(m, 3H), 6.88(dd, 1H, J=8.8, J=2.8), 6.57(s, 1H), 4.14-4.06(m, 2H), 3.22-3.17(m, 1H), 2.40(s, 3H), 2.39-2.29(m, 2H), 2.10-1.97(m, 2H), 1.86-1.66(m, 2H), 1.65-1.54(m, 2H)
59	2-(1-메틸피롤리딘-2-일)에틸 (5-플루오로-3',4'-디메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.99(s, 1H), 7.22-7.20(m, 1H), 7.08-6.97(m, 3H), 6.90(dd, 1H, J=9.2, J=2.8), 6.57(s, 1H), 4.15-4.13(m, 2H), 3.16-3.12(m, 1H), 2.31(s, 3H), 2.29(s, 6H), 2.02-2.17(m, 2H), 2.00-1.89(m, 2H), 1.76-1.55(m, 2H), 1.53-1.42(m, 2H)

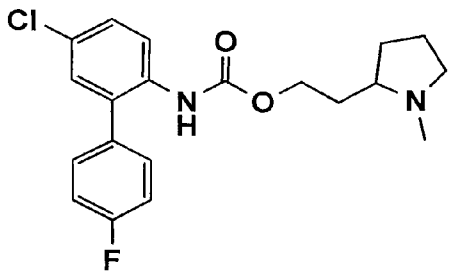
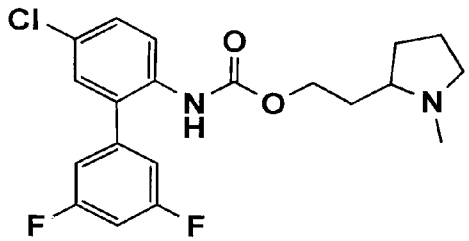
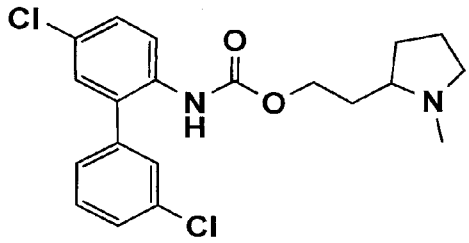
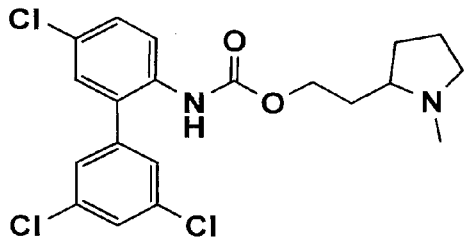
[432]

60	2-(1-메틸피롤리딘-2-일)에틸 (5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.93(s, 1H), 7.46-7.40(m, 2H), 7.39-7.36(m, 1H), 7.35-7.33(m, 2H), 6.89(dd, 1H, J=8.8, J=2.8), 6.77(d, 1H, J=2.8), 6.38(s, 1H), 4.15-4.10(m, 2H), 3.86(s, 3H), 3.14-3.11(m, 1H), 2.35(m, 3H), 2.26-2.16(m, 2H), 2.06-1.91(m, 2H), 1.82-1.62(m, 2H), 1.60-1.45(m, 2H)
61	2-(1-메틸피롤리딘-2-일)에틸 (3'-플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.82(s, 1H), 7.42-7.39(m, 1H), 7.14-7.10(m, 1H), 7.07-7.05(m, 2H), 6.90(dd, 1H, J=8.8, J=3.2), 6.75(d, 1H, J=3.2), 6.37(s, 1H), 4.17-4.13(m, 2H), 3.79(s, 3H), 3.21-3.18(m, 1H), 2.38(s, 3H), 2.30-2.26(m, 2H), 2.09-1.99(m, 2H), 1.74-1.70(m, 2H), 1.56-1.53(m, 2H)
62	2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.72(s, 1H), 7.28-7.26(m, 1H), 6.92-6.79(m, 3H), 6.74-6.73(m, 1H), 6.29(s, 1H), 4.15-4.10(m, 2H), 3.75(s, 3H), 3.15-3.10(m, 1H), 2.34(s, 3H), 2.27-2.25(m, 2H), 2.06-1.96(m, 2H), 1.78-1.69(m, 2H), 1.63-1.50(m, 2H)
63	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.82(s, 1H), 7.38-7.34(m, 2H), 7.23-7.21(m, 2H), 6.90(dd, 1H, J=9.2, J=2.8), 6.74(d, 1H, J=2.8), 6.28(s, 1H), 4.17-4.12(m, 2H), 3.78(s, 3H), 3.16-3.14(m, 1H), 2.35(s, 3H), 2.23-2.18(m, 2H), 2.21-1.93(m, 2H), 1.79-1.64(m, 2H), 1.60-1.50(m, 2H)

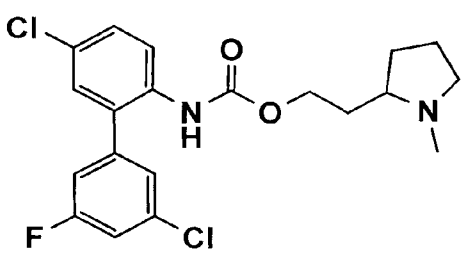
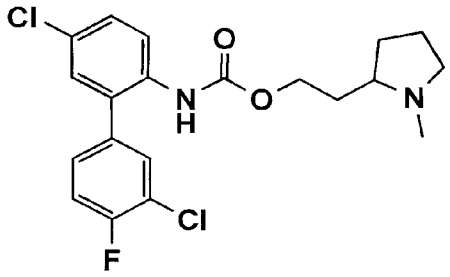
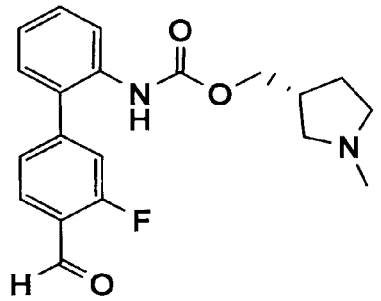
[433]

64	2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.70(s, 1H), 7.36-7.35(m, 1H), 7.23-7.20(m, 2H), 6.90(dd, 1H, *J*=8.8, *J*=2.8), 6.73-6.72(m, 1H), 6.58(s, 1H), 4.16-4.08(m, 2H), 3.75(s, 3H), 3.28-3.26(m, 1H), 2.43(s, 3H), 2.40-2.38(m, 2H), 2.08-2.02(m, 2H), 1.85-1.72(m, 2H), 1.60-1.57(m, 2H)
65	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-4'-플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.70(s, 1H), 7.39-7.38(m, 1H), 7.21-7.19(m, 2H), 6.90(dd, 1H, *J*=8.8, *J*=2.8), 6.72-6.71(m, 1H), 6.21(s, 1H), 4.15-4.09(m, 2H), 3.76(s, 3H), 3.13-3.11(m, 1H), 2.37(s, 3H), 2.30-2.23(m, 2H), 2.02-1.97(m, 2H), 1.79-1.71(m, 2H), 1.62-1.56(m, 2H)
66	2-(1-메틸피롤리딘-2-일)에틸 (5-클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.04(s, 1H), 7.48-7.45(m, 2H), 7.43-7.39(m, 1H), 7.32-7.28(m, 3H), 7.23-7.18(m, 1H), 6.56(s, 1H), 4.16-4.12(m, 2H), 3.06-3.02(m, 1H), 2.28(s, 3H), 2.12-1.96(m, 2H), 1.94-1.87(m, 2H), 1.76-1.64(m, 2H), 1.57-1.44(m, 2H)
67	2-(1-메틸피롤리딘-2-일)에틸 (5-클로로-3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.03(s, 1H), 7.44(q, 1H, *J*=8.0), 7.31(dd, 1H, *J*=8.8, *J*=2.4), 7.14-7.10(m, 2H), 7.05-7.03(m, 1H), 6.49(s, 1H), 4.17-4.13(m, 2H), 3.03-3.01(m, 2H), 2.29(s, 3H), 2.13-1.98(m, 2H), 1.97-1.88(m, 2H), 1.77-1.64(m, 2H), 1.59-1.42(m, 2H)

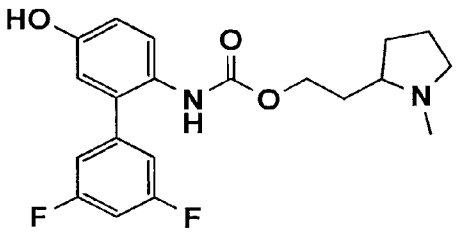
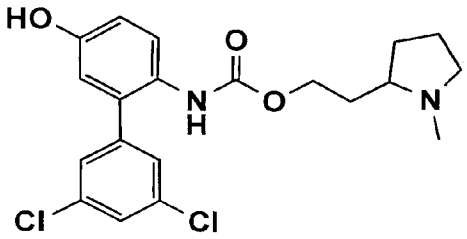
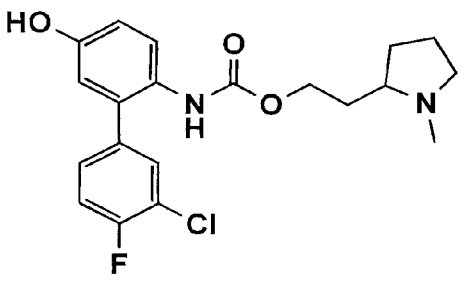
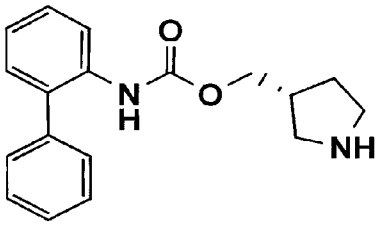
[434]

68	2-(1-메틸피롤리딘-2-일)에틸 (5-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.02(s, 1H), 7.31-7.28(m, 3H), 7.18-7.14(m, 3H), 6.44(s, 1H), 4.17-4.13(m, 2H), 3.04-3.01(m, 1H), 2.28(s, 3H), 2.10-2.00(m, 2H), 1.98-1.87(m, 2H), 1.78-1.65(m, 2H), 1.57-1.44(m, 2H)
69	2-(1-메틸피롤리딘-2-일)에틸 (5-클로로-3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.99(s, 1H), 7.34-7.31(m, 2H), 7.17-7.16(m, 1H), 6.88-6.84(m, 2H), 6.51(s, 1H), 4.18-4.10(m, 2H), 3.16-3.13(m, 1H), 2.36(s, 3H), 2.32-2.29(m, 2H), 2.08-1.96(m, 2H), 1.82-1.61(m, 2H), 1.57-1.49(m, 2H)
70	2-(1-메틸피롤리딘-2-일)에틸 (3',5-디클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.01(s, 1H), 7.43-7.38(m, 2H), 7.32-7.30(m, 2H), 7.23-7.21(m, 1H), 7.17(d, 1H, *J*=2.4), 6.47(s, 1H), 4.18-4.13(m, 2H), 3.06-3.04(m, 1H), 2.25(s, 3H), 2.19-2.06(m, 2H), 2.05-1.90(m, 2H), 1.80-1.59(m, 2H), 1.58-1.44(m, 2H)
71	2-(1-메틸피롤리딘-2-일)에틸 (3',5,5'-트리클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.98(s, 1H), 7.41(s, 1H), 7.33(dd, 1H, *J*=8.8, *J*=2.4), 7.23-7.22(m, 2H), 7.15(d, 1H, *J*=2.4), 6.39(s, 1H), 4.19-4.14(m, 2H), 3.09-3.05(m, 1H), 2.30(s, 3H), 2.19-2.07(m, 2H), 2.04-1.91(m, 2H), 1.77-1.61(m, 2H), 1.59-1.43(m, 2H)

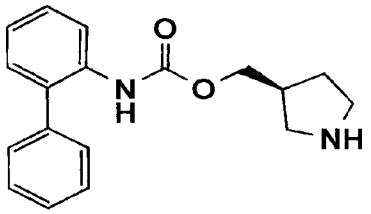
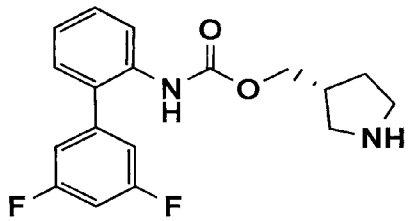
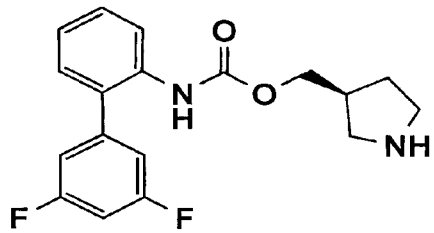
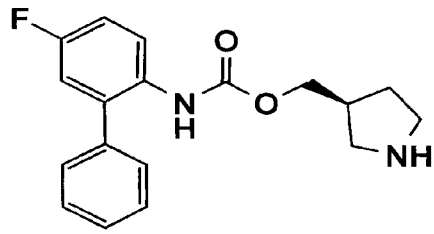
[435]

72	2-(1-메틸피롤리딘-2-일)에틸 (3',5-디클로로-5'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.99(s, 1H), 7.33(dd, 1H, *J*=8.8, *J*=2.4), 7.21-7.13(m, 3H), 6.96(dd, 1H, *J*=8.8, *J*=2.4), 6.46(s, 1H), 4.20-4.12(m, 2H), 3.11-3.07(m, 1H), 2.32(s, 3H), 2.20-2.14(m, 2H), 2.06-1.91(m, 2H), 1.79-1.62(m, 2H), 1.60-1.45(m, 2H)
73	2-(1-메틸피롤리딘-2-일)에틸 (3',5-디클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.98(s, 1H), 7.39-7.37(m, 1H), 7.32-7.26(m, 1H), 7.23-7.21(m, 2H), 7.19(d, 1H, *J*=2.8), 6.41(s, 1H), 4.17-4.13(m, 2H), 3.06-3.03(m, 1H), 2.26(s, 3H), 2.39-2.10(m, 2H), 2.03-1.89(m, 2H), 1.80-1.59(m, 2H), 1.57-1.43(m, 2H)
74	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-플루오로-4'-포밀-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.00-7.93(m, 2H), 7.41-7.37(t, 1H, *J*=15.2), 7.29-7.27(d, 1H, *J*=8.0), 7.23-7.15(m, 3H), 6.51(s, 1H), 4.08-3.97(m, 2H), 2.60-2.56(t, 1H, *J*=17.2), 2.49-2.45(m, 3H), 2.29-2.24(m, 4H), 1.96-1.91(m, 1H), 1.48-1.43(m, 1H)

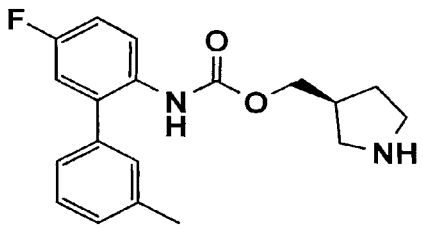
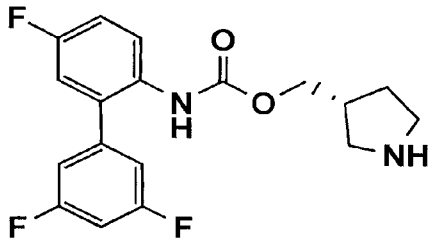
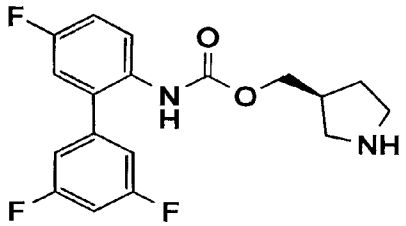
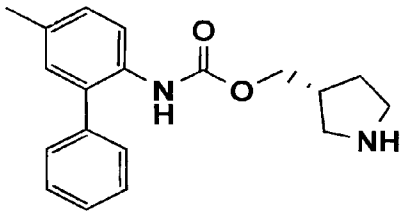
[436]

75	2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디플루오로-5-히드록시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR(CD_3OD): δ 7.19-7.17(m, 1H), 6.92-6.90(m, 2H), 6.85-6.76(m, 2H), 6.72-6.71(m, 1H), 4.10-4.02(m, 2H), 3.70-3.61(m, 1H), 3.16-3.10(m, 2H), 2.83(s, 3H), 2.27-2.13(m, 2H), 2.13-2.02(m, 2H), 1.77-1.72(m, 2H)
76	2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디클로로-5-히드록시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR(CD_3OD): δ 7.33-7.32(m, 1H), 7.27-7.23(m, 1H), 7.17-7.15(m, 1H), 7.05-7.01(m, 1H), 6.82-6.79(m, 1H), 6.72-6.71(m, 1H), 4.11-4.07(m, 2H), 3.50-3.47(m, 1H), 3.04-3.01(m, 2H), 2.70(s, 3H), 2.20-2.16(m, 2H), 1.95-1.90(m, 2H), 1.75-1.70(m, 2H)
77	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-4'-플루오로-5-히드록시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR(CD_3OD): δ 7.44-7.42(m, 1H), 7.27-7.22(m, 2H), 7.16-7.14(m, 1H), 6.77-6.75(m, 1H), 6.70-6.69(m, 1H), 4.08-4.02(m, 2H), 3.64-3.57(m, 1H), 3.13-3.09(m, 2H), 2.86(s, 3H), 2.27-2.22(m, 2H), 1.97-1.93(m, 2H), 1.75-1.70(m, 2H)
78	(R)-피롤린딘-3-일메틸 [1,1'-바이페닐]-2-일 카바메이트 	^{1}H NMR($CDCl_3$): δ 8.17-7.98(bs, 1H), 7.60-7.29(m, 6H), 7.26-7.06(m, 2H), 6.78-6.61(bs, 1H), 4.17-3.94(m, 2H), 3.09-2.81(m, 3H) 2.75-2.59(m, 1H), 2.56-2.33(m, 2H), 1.98-1.80(m, 1H), 1.54-1.35(m, 1H)

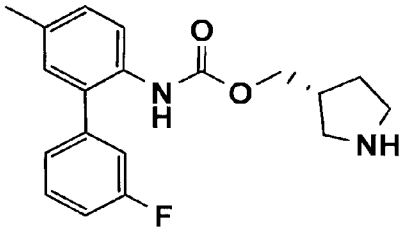
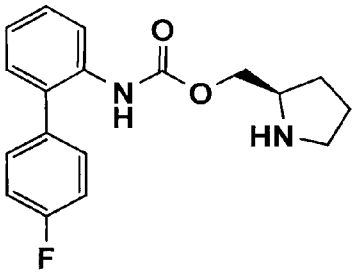
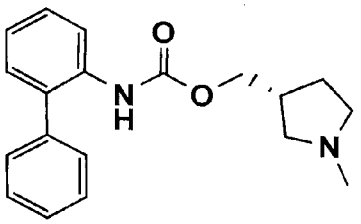
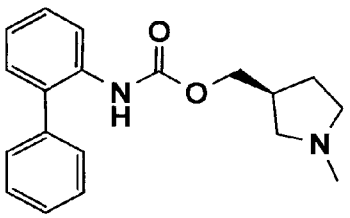
[437]

79	(S)-피롤린딘-3-일메틸 [1,1'-바이페닐]-2-일 카바메이트 	^{1}H NMR($CDCl_3$): δ 8.07-7.89(bs, 1H), 7.58-7.32(m, 6H), 7.32-7.13(m, 2H) 7.01-6.85(bs, 1H), 4.28-3.98(m, 3H), 3.47-3.17(m, 3H), 3.13-2.95(m, 1H), 2.80-2.62(m, 1H), 2.25-2.08(m, 1H), 1.89-1.70(m, 1H)
80	(R)-피롤리딘-3-일메틸 (3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.10-7.93(bs, 1H), 7.45-7.30(m, 1H), 7.21-7.08(m, 2H), 6.98-6.79(m, 3H), 6.67-6.51(bs, 1H), 4.15-3.90(m, 2H), 3.11-2.76(m, 3H), 2.71-2.53(m, 8H), 2.48-2.29(m, 1H), 2.02-2.72(m, 2H), 1.49-1.29(m, 1H)
81	(S)-피롤리딘-3-일메틸 (3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.10-7.89(m, 1H), 7.49-7.30(m, 1H), 7.22-7.04(m, 2H), 6.98-6.75(m, 3H), 6.68-6.50(bs, 1H), 4.19-3.85(m, 2H), 3.12-2.75(m, 3H) 2.72-2.52(bs, 1H), 2.52-2.27(m, 1H), 2.07-1.72(m, 2H), 1.50-1.31(m, 1H)
82	(S)-피롤린딘-3-일메틸 (5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.81(s, 1H), 7.45-7.36(m, 3H), 7.33-7.26(m, 2H), 7.06-7.01(m, 1H), 6.97-6.94(m, 1H), 4.12-4.06(m, 2H), 3.35-3.27(m, 1H), 3.23-3.16(m, 1H), 3.05-3.02(m, 1H), 2.69-2.65(m, 1H), 2.17-2.12(m, 1H), 1.82-1.78(m, 2H)

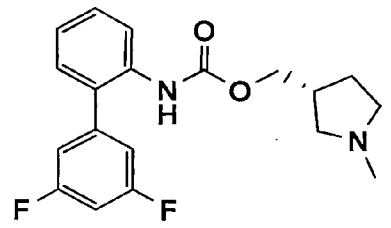
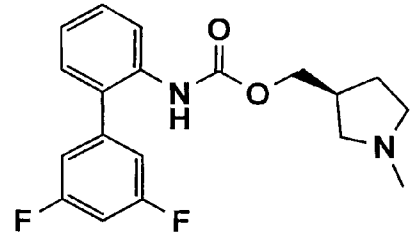
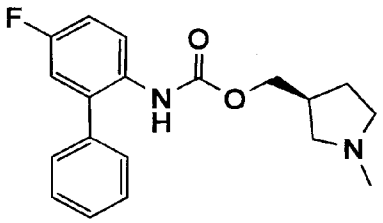
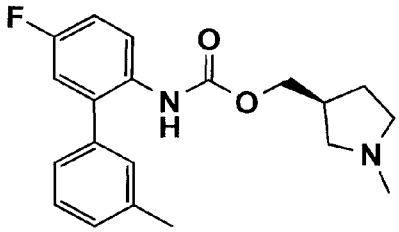
[438]

83	(S)-피롤린딘-3-일메틸 (5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.82(s, 1H), 7.35-7.31(m, 1H), 7.20-7.18(m, 1H), 7.18-7.14(m, 1H), 7.13-7.11(m, 1H), 7.07-6.98(m, 1H), 6.95-6.92(m, 1H), 4.13-4.07(m, 2H), 3.38-3.33(m, 2H), 3.25-3.22(m, 1H), 3.09-3.05(m, 1H), 2.69-2.65(m, 1H), 2.38(s, 3H), 2.15-2.13(m, 1H), 1.80-1.76(m, 1H)
84	(R)-피롤린딘-3-일메틸 (3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.98-7.79(bs, 1H), 7.14-7.00(m, 1H), 7.00-6.78(m, 4H), 6.61-6.45(bs, 1H), 4.18-3.90(m, 2H), 3.13-2.80(m, 3H), 2.70-2.57(m, 1H), 2.51-2.21(m, 2H), 1.94-1.80(m, 1H), 1.49-1.35(m, 1H)
85	(S)-피롤린딘-3-일메틸 (3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.96-7.77(bs, 1H), 7.13-6.99(m, 1H), 6.99-6.76(m, 4H), 6.68-6.50(bs, 1H), 4.15-3.92(m, 2H), 3.16-2.90(bs, 3H), 2.90-2.30(m, 3H), 1.99-1.81(m, 1H), 1.53-1.35(m, 1H)
86	(R)-피롤리딘-3-일메틸 (5-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.77 (s, 1H), 7.44-7.40(m, 2H), 7.37-7.31(m, 2H), 7.20-7.13(m, 2H), 7.04(s, 1H), 6.85(s, 1H), 4.13-4.04(m, 2H), 2.78-2.62(m, 3H), 2.32(s, 3H), 2.16-2.09(m, 2H), 2.03(s, 1H), 1.79-1.70(m, 2H)

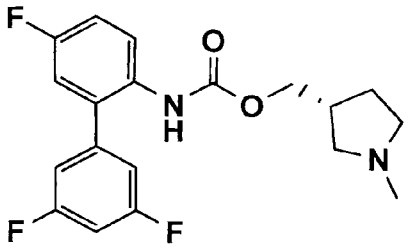
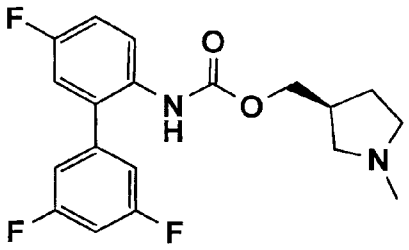
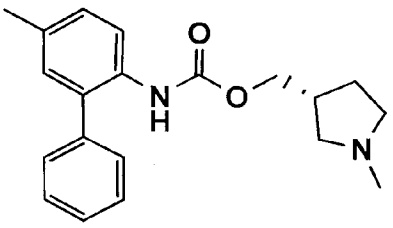
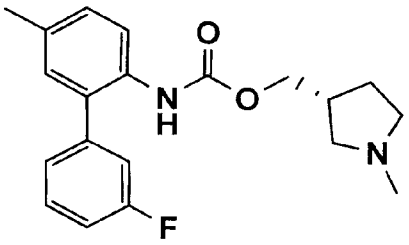
[439]

87	(R)-피롤리딘-3-일메틸 (3'-플루오로-5-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.84 (s, 1H), 7.43-7.38(m, 1H), 7.17-7.08(m, 2H), 7.04-7.02(m, 2H), 7.01(s, 1H), 6.55(s, 1H), 4.08-3.97(m, 2H), 2.47-2.33(m, 3H), 2.32(s, 3H), 1.94-1.80(m, 2H), 1.51-1.40(m, 2H)
88	(S)-피롤리딘-2-일메틸 (4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.13-7.94(m, 1H), 7.41-7.23(m, 3H), 7.20-7.02(m, 4H), 6.75-6.57(bs, 1H), 4.23-4.04(m, 1H), 4.02-3.85(m, 1H), 3.47-3.30(m, 1H), 3.02-2.81(m, 2H), 2.57-2.25(bs, 1H), 1.95-1.59(m, 3H), 1.50-1.32(m, 1H)
89	(R)-(1-메틸피롤리딘-3-일)메틸 [1,1'-바이페닐]-2-일카바메이트 	^{1}H NMR($CDCl_3$): δ 8.13-7.94(bs, 1H), 7.55-7.27(m, 6H), 7.26-7.03(m, 2H), 6.77-6.59(bs, 1H), 4.18-3.94(m, 2H), 3.00-2.57(m, 4H), 2.54-2.49(m, 1H), 2.47(s, 3H), 2.10-1.98(m, 1H) 1.67-1.55(m, 1H)
90	(S)-(1-메틸피롤리딘-3-일)메틸 [1,1'-바이페닐]-2-일카바메이트 	^{1}H NMR($CDCl_3$): δ 8.09-7.94(bs, 1H), 7.56-7.31(m, 6H), 7.30-7.12(m, 2H), 6.86-6.72(bs, 1H), 4.19-4.02(m, 1H), 3.41-3.05(m, 3H), 2.97-2.77(m, 2H) 2.74(s, 3H), 2.29-2.15(m, 1H), 1.89-1.74(m, 1H)

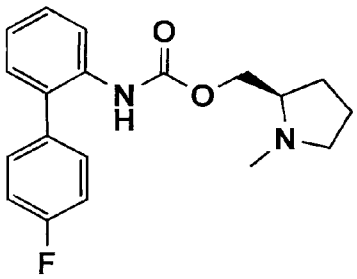
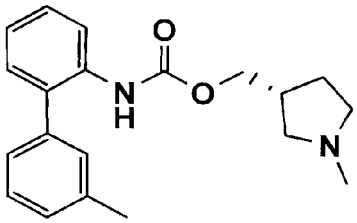
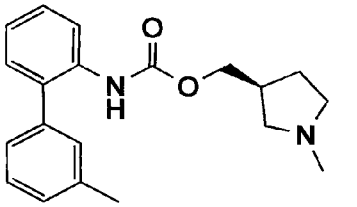
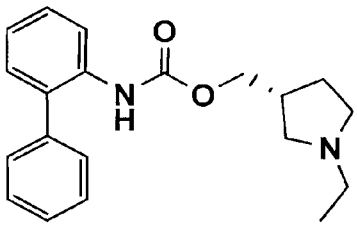
[440]

91	(R)-(1-메틸피롤리딘-3-일)메틸 (3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.08-7.95(bs, 1H), 7.42-7.33(m, 1H), 7.21-7.08(m, 2H), 6.98-6.79(m, 3H), 6.59-6.48(bs, 1H), 4.13-3.95(m, 2H), 2.69-2.43(m, 3H), 2.40-2.14(m, 5H), 2.05-1.90(m, 1H), 1.57-1.42(m, 1H)
92	(S)-(1-메틸피롤리딘-3-일)메틸 (3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.08-7.95(bs, 1H), 7.42-7.33(m, 1H), 7.21-7.08(m, 2H), 6.98-6.79(m, 3H), 6.59-6.48(bs, 1H), 4.13-3.95(m, 2H), 2.69-2.43(m, 3H), 2.40-2.14(m, 5H), 2.05-1.90(m, 1H), 1.57-1.42(m, 1H)
93	(S)-(1-메틸피롤리딘-3-일)메틸 (5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.98(s, 1H), 7.49-7.39(m, 3H), 7.34-7.32(m, 2H), 7.06-7.01(m, 1H), 6.94-6.91(m, 1H), 6.49(s, 1H), 4.08-3.96(m, 2H), 2.61-2.57(m, 1H), 2.53-2.44(m, 3H), 2.30(s, 3H), 2.27-2.22(m, 1H), 1.98-1.89(m, 1H), 1.49-1.41(m, 1H)
94	(S)-(1-메틸피롤리딘-3-일)메틸 (5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.97(s, 1H), 7.37-7.33(m, 1H), 7.30-7.21(m, 2H), 7.13-7.11(m, 1H), 7.04-7.00(m, 1H), 6.95-6.91(m, 1H), 6.58(s, 1H), 4.08-3.98(m, 2H), 2.71-2.66(m, 1H), 2.59-2.46(m, 3H), 2.46-2.33(m, 7H), 2.01-1.97(m, 1H), 1.55-1.48(m, 1H)

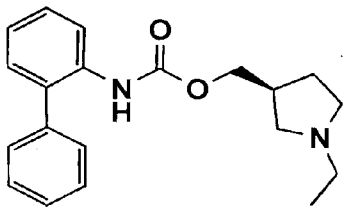
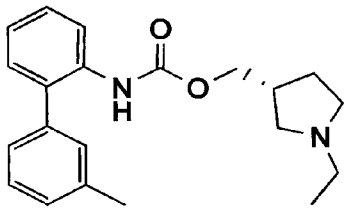
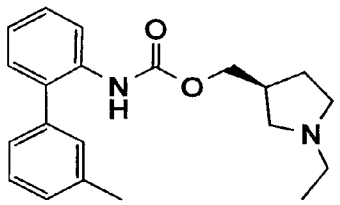
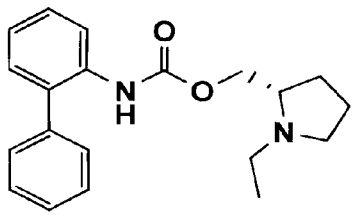
[441]

95	(R)-(1-메틸피롤리딘-3-일)메틸 (3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.97-7.81(bs, 1H), 7.13-7.01(m, 1H), 6.99-6.78(m, 4H). 6.57-6.41(bs, 1H), 4.13-3.94(m, 2H), 2.70-2.42(m, 4H), 2.05-2.88(m, 1H), 1.58-1.41(m, 4H)
96	(S)-(1-메틸피롤리딘-3-일)메틸 (3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.97-7.78(bs, 1H), 7.14-7.00(m, 1H), 6.99-6.78(m, 4H). 6.63-6.45(bs, 1H), 4.14-3.93(m, 2H), 2.71-2.42(m, 4H), 2.40-2.23(bs, 4H), 2.05-1.88(m, 1H), 1.59-1.41(m, 1H)
97	(R)-(1-메틸피롤리딘-3-일)메틸 (5-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.89 (s, 1H), 7.47-7.43(m, 2H), 7.39-7.31(m, 2H), 7.22-7.13(m, 2H), 7.02(s, 1H), 6.63(s, 1H), 4.09-4.01(m, 2H), 2.67-2.58(m, 3H), 2.52(s, 3H), 2.32(s, 3H), 2.11-2.01(m, 2H), 1.65-1.58(m, 2H)
98	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-플루오로-5-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.88 (s, 1H), 7.44-7.38(m, 1H), 7.17-7.10(m, 2H), 7.09-7.05(m, 2H), 7.01(s, 1H), 6.55(s, 1H), 4.09-3.98(m, 2H), 2.38(s, 3H), 2.32(s, 3H), 2.61-2.40(m, 3H), 2.15-1.97(m, 2H), 1.56-1.51(m, 2H)

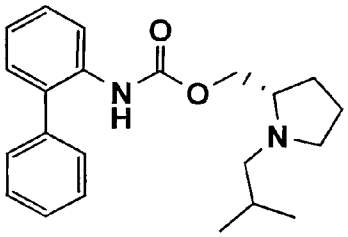
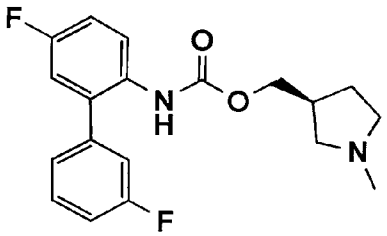
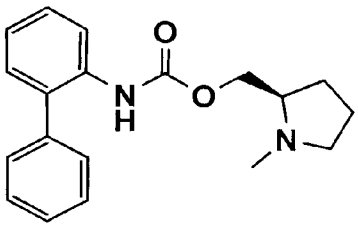
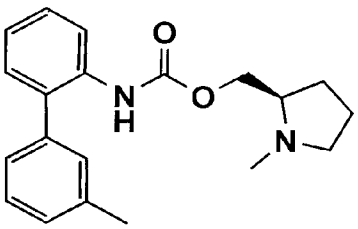
[442]

99	(S)-(1-메틸피롤리딘-2-일)메틸 (4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.13-7.96(m, 1H), 7.41-7.23(m, 3H), 7.20-7.02(m, 4H), 6.62-6.45(bs, 1H), 4.24-3.97(m, 2H), 3.10-2.96(m, 1H), 2.50-2.27(m, 4H), 2.27-2.13(m, 1H) 1.96-1.80(m, 1H), 1.80-1.51(m, 3H)
100	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.13-7.96(bs, 1H), 7.41-7.30(m, 2H), 7.30-7.03(m, 5H), 6.71-6.59(bs, 1H), 4.13-3.95(m, 2H), 2.72-2.59(m, 1H), 2.59-2.43(m, 3H), 2.40(s, 3H), 2.14-2.22(m, 4H) 2.06-1.87(m, 1H), 1.55-1.42(m, 1H)
101	(S)-(1-메틸피롤리딘-3-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.15-7.99(bs, 1H), 7.46-7.29(m, 2H), 7,28-7.02(m, 5H), 6.74-6.58(bs, 1H), 4.15-3.93(m, 2H), 2.70-2.43(m, 4H), 2.40(s, 3H), 2.31(s, 3H), 2.15-2.17(m, 1H) 2.03-1.86(m, 1H), 1.57-1.40(m, 1H)
102	(R)-(1-에틸피롤리딘-3-일)메틸 [1,1'-바이페닐]-2-일카바메이트 	^{1}H NMR($CDCl_3$): δ 8.13-7.96(bs, 1H), 7.54-7.26(m, 6H), 7,25-7.02(m, 2H), 6.72-6.55(bs, 1H), 4.15-3.92(m, 2H), 2.91-2.69(m, 1H), 2.69-2.35(m, 5H), 2.33-2.17(m, 1H), 2.04-1.87(m, 1H) 1.60-1.42(m, 1H), 1.00(t, 3H, *J*=7.2)

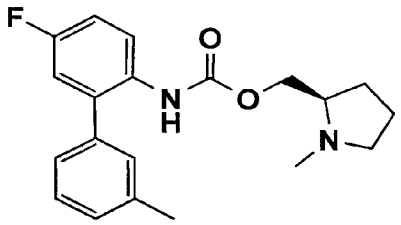
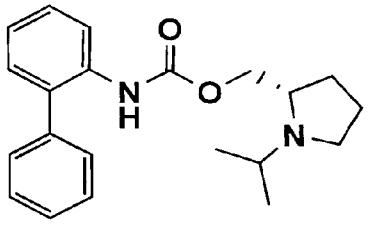
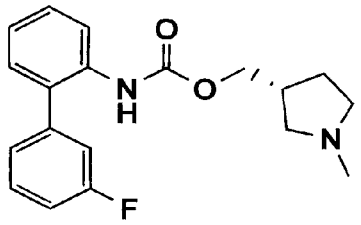
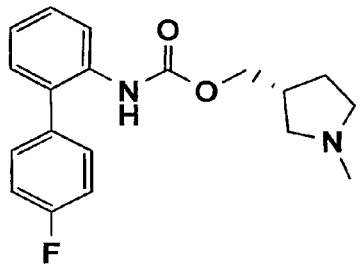
[443]

103	(S)-(1-에틸피롤리딘-3-일)메틸 [1,1'-바이페닐]-2-일카바메이트 	^{1}H NMR($CDCl_3$): δ 8.15-7.97(bs, 1H), 7.55-7.27(m, 6H), 7,24-7.05(m, 2H), 6.72-6.59(bs, 1H), 4.14-3.94(m, 2H), 2.92-2.71(bs, 1H), 2.71-2.39(m, 5H), 2.38-2.22(m, 1H), 2.04-1.86(m, 1H), 1.59-1.44(m, 1H), 1.11(t, 3H, *J*=7.2)
104	(R)-(1-에틸피롤리딘-3-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.13-8.00(bs, 1H), 7.42-7.27(m, 2H), 7.25-7.03(m, 5H), 6.69-6.59(bs, 1H), 4.13-3.95(m, 2H), 2.80-2.68(m, 1H), 2.68-2.32(m, 9H) 2.30-2.17(m, 1H), 2.03-1.89(m, 1H), 1.58-1.41(m, 1H), 1.18-1.04(t, 3H, *J*=7.6)
105	(S)-(1-에틸피롤리딘-3-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.13-7.99(m, 1H), 7.43-7.27(m, 2H), 7.27-7.02(m, 5H), 6.72-6.58(bs, 1H), 4.13-3.94(m, 2H), 2.89-2.66(m, 1H), 2.66-2.15(m, 9H), 2.06-1.87(m, 1H), 1.57-1.40(m, 1H), 1.09(t, 3H, *J*=7.6)
106	(S)-(1-에틸피롤리딘-2-일)메틸 [1,1'-바이페닐]-2-일카바메이트 	^{1}H NMR($CDCl_3$): δ 8.15-8.01(m, 1H), 7.54-7.26(m, 6H), 7,22-7.05(m, 2H), 6.72-6.58(bs, 1H), 4.22-4.07(m, 1H), 4.07-3.93(m, 1H), 3.21-3.02(m, 1H), 2.92-2.59(m, 2H), 2.41-2.12(m, 2H) 1.95-1.50(m, 5H), 1.08(t, 3H, J=7.2)

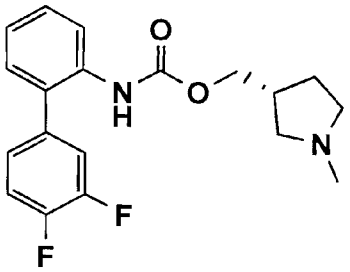
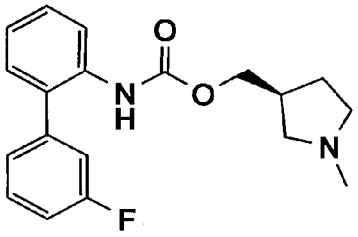
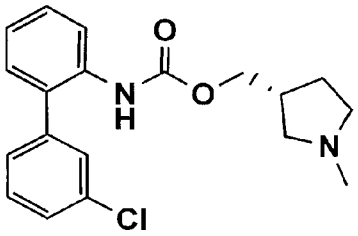
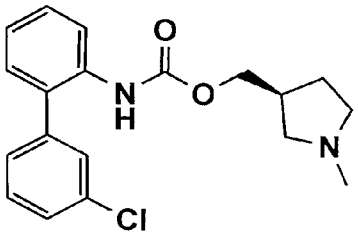
[444]

107	(S)-(1-이소부틸피롤리딘-2-일)메틸 [1,1'-바이페닐]-2-일카바메이트 	^{1}H NMR($CDCl_3$): δ 8.18-8.02(m, 1H), 7.53-7.27(m, 6H), 7,22-7.03(m, 2H). 6.69-6.54(bs, 1H), 4.18-3.83(m, 2H), 3.15-2.95(bs, 1H), 2.71-2.53(bs, 1H), 2.48-2.30(m, 1H), 2.23-2.02(m, 2H), 1.92-1.45(m, 5H), 0.84(t, 6H, J=6.8)
108	(S)-(1-메틸피롤리딘-3-일)메틸 (3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.85(s, 1H), 7.46-7.41(m, 1H), 7.15-7.03(m, 4H), 6.96-6.93(m, 1H), 4.11-4.03(m, 2H), 2.92-2.90(m, 1H), 2.82-2.68(m, 2H), 2.42(s, 3H), 2.12-2.10(m, 2H), 1.71-1.69(m, 2H)
109	(R)-(1-메틸피롤리딘-2-일)메틸 [1,1'-바이페닐]-2-일카바메이트 	^{1}H NMR($CDCl_3$): δ 8.18-7.99(m, 1H), 7.49-7.27(m, 6H), 7.22-7.15(m, 1H), 7.15-7.06(m, 1H), 6.72-6.60(bs, 1H), 4.24-3.98(m, 2H), 3.10-2.95(m, 1H), 2.52-2.40(m, 1H), 2.35(s, 3H) 2.26-2.12(m, 1H), 1.97-1.50(m, 4H)
110	(R)-(1-메틸피롤리딘-2-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.18-7.97(bs, 1H), 7.41-7.28(m, 2H), 7,23-7.01(m, 5H), 6.78-6.62(bs, 1H), 4.12-3.97(m, 2H), 3.05-2.90(m, 1H), 2.52-2.11(m, 8H), 1.95-1.47(m, 4H)

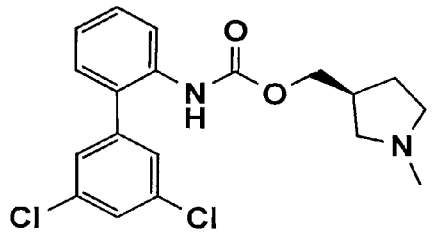
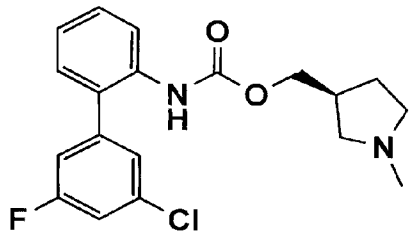
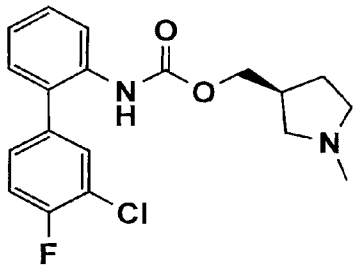
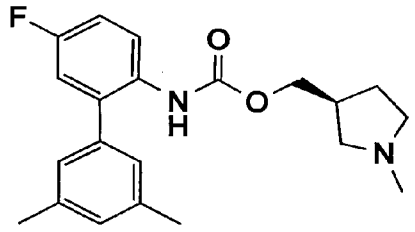
[445]

111	(R)-(1-메틸피롤리딘-2-일)메틸 (5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.00(s, 1H), 7.34-7.31(m, 1H), 7.21-7.19(m, 1H), 7.12-7.06(m, 2H), 7.04-6.99(m, 1H), 6.92-6.89(m, 1H), 6.59(s, 1H), 4.18-4.04(m, 2H), 3.06-3.02(m, 1H), 2.38(s, 3H), 2.35(s, 3H), 2.22-2.15(m, 2H), 1.92-1.76(m, 2H), 1.68-1.54(m, 2H)
112	(S)-(1-이소프로필피롤리딘-2-일)메틸 [1,1'-바이페닐]-2-일카바메이트 	^{1}H NMR($CDCl_3$): δ 8.15-8.01(m, 1H), 7.51-7.27(m, 6H), 7.21-7.06(m, 2H), 6.69-6.56(bs, 1H), 4.12-4.00(m, 1H), 3.87-3.76(m, 1H), 3.04-2.78(m, 3H) 2.53-2.40(m, 1H), 1.80-1.62(m, 4H), 1.08(d, 3H, *J*=6.4), 0.99(d, 3H, *J*=6.4)
113	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.13-7.98(m, 1H), 7.50-7.31(m, 2H), 7.21-7.00(m, 5H), 6.62-6.49(bs, 1H), 4.14-3.95(m, 2H), 2.75-2.42(m, 4H) 2.42-2.22(m, 4H), 2.03-1.87(m, 1H), 1.58-1.42(m, 1H)
114	(R)-(1-메틸피롤리딘-3-일)메틸 (4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.11-7.97(bs, 1H), 7.42-7.27(m, 3H), 7.01-7.03(m, 4H), 6.57-6.42(bs, 1H), 4.13-3.92(m, 2H), 2.70-2.41(m, 4H), 2.41-2.20(m, 4H), 2.06-1.94(m, 1H), 1.56-1.41(m, 1H)

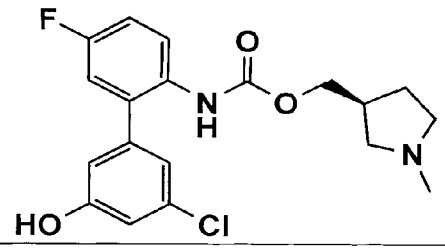
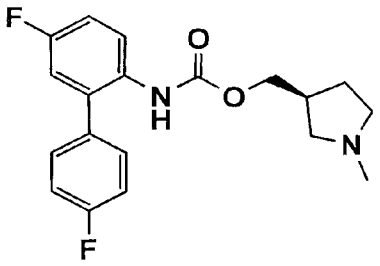
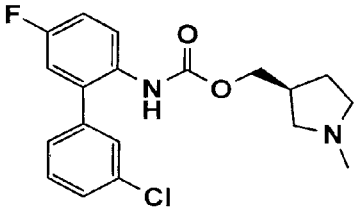
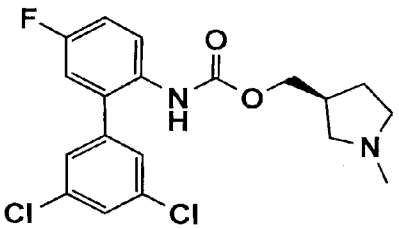
[446]

115	(R)-(1-메틸피롤리딘-3-일)메틸 (3',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 8.02-8.01(m, 1H), 7.38-7.06(m, 5H), 6.47(s, 1H), 4.09-3.98(m, 2H), 2.62-2.58(t, 1H, J=17.2), 2.55-2.46(m, 3H), 2.37-2.25(m, 4H), 2.04-1.91(m, 2H), 1.51-1.43(m, 1H)
116	(S)-(1-메틸피롤리딘-3-일)메틸 (3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.12-7.98(bs, 1H), 7.50-7.31(m, 2H), 7.24-7.02(m, 5H), 6.70-6.54(bs, 1H), 4.16-3.97(m, 2H), 2.77-2.65(m, 1H) 2.64-2.47(m, 3H), 2.45-2.28(m, 4H), 2.06-1.93(m, 1H), 1.61-1.47(m, 1H)
117	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.08-7.93(bs, 1H), 7.47-7.27(m, 4H), 7.21-7.05(m, 3H), 6.67-6.53(bs, 1H), 4.15-3.93(m, 2H), 2.80-2.50(m, 4H), 2.50-2.24(bs, 4H), 2.09-1.92(m, 1H), 1.62-1.46(m, 1H)
118	(S)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.07-7.92(bs, 1H), 7.42-7.31(m, 4H), 7.27-7.21(m, 1H), 7.20-7.09(m, 2H), 6.66-6.56(bs, 1H), 4.13-3.97(m, 2H), 2.85-2.53(m, 4H), 2.52-2.35(m, 4H), 2.08-1.97(m, 1H), 1.63-1.52(m, 1H)

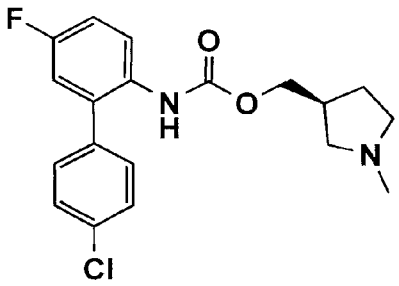
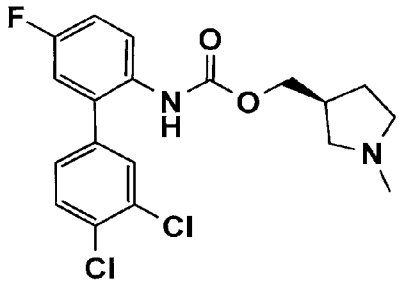
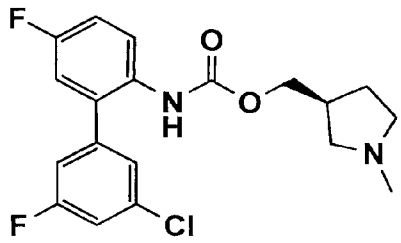
[447]

119	(S)-(1-메틸피롤리딘-3-일)메틸 (3',5'-디클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.02-7.83(bs, 1H), 7.48-7.32(m, 2H), 7.33-7.21(m, 2H), 7.20-7.08(m, 2H), 6.77-6.56(bs, 1H), 4.15-3.95(m, 2H), 2.80-2.54(m, 4H) 2.54-2.30(m, 4H), 2.12-1.92(m, 1H), 1.67-1.49(m, 1H)
120	(S)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.03-7.89(bs, 1H), 7.45-7.33(m, 1H), 7.23-7.07(m, 4H), 7.05-6.95(m, 1H), 6.72-6.56(bs, 1H), 4.16-3.96(m, 2H), 2.78-2.50(m, 4H) 2.50-2.29(m, 4H), 2.10-1.92(m, 1H), 1.65-1.47(m, 1H)
121	(S)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.06-7.96(bs, 1H), 7.49-7.32(m, 2H), 7.25-7.19(m, 2H), 7.18-7.10(m, 2H), 6.65-6.47(bs, 1H), 4.17-3.95(m, 2H), 2.78-2.50(m, 4H) 2.50-2.25(m, 4H), 2.08-1.91(m, 1H), 1.62-1.47(m, 1H)
122	(S)-(1-메틸피롤리딘-3-일)메틸 (5-플루오로-3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.03-7.88(bs, 1H), 7.05-6.96(m, 2H), 6.95-6.87(m, 3H), 6.64-6.58(bs, 1H), 4.12-3.92(m, 2H), 2.68-2.57(m, 1H) 2.57-2.43(m, 3H), 2.34(s, 6H), 2.33-2.15(m, 4H), 2.00-1.77(m, 1H), 1.55-1.45(m, 1H)

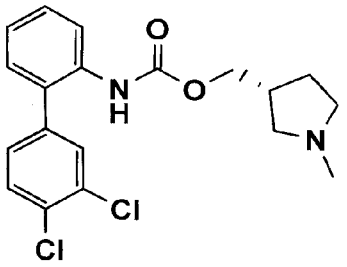
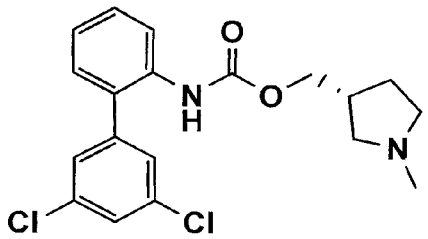
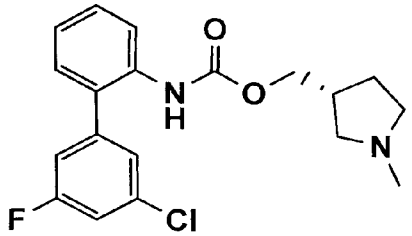
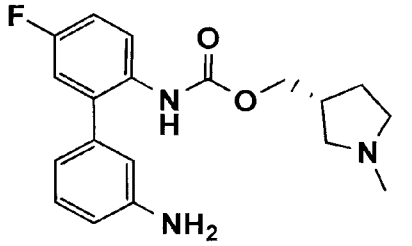
[448]

123	(S)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5-플루오로-5'-히드록시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.77-7.60(bs, 1H), 7.13-6.86(m, 3H), 6.79(s, 1H), 6.70(s, 1H), 6.53(s, 1H), 5.03-4.50(bs, 1H), 4.33-4.18(m, 1H), 4.18-3.98(m, 1H), 3.08-2.95(bs, 1H), 2.95-2.78(bs, 1H) 2.70-2.31(m, 5H), 2.08-1.90(bs, 1H), 1.90-1.70(bs, 1H)
124	(S)-(1-메틸피롤리딘-3-일)메틸 (4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.00-7.85(bs, 1H), 7.38-7.25(m, 2H), 7.20-7.19(m, 2H), 7.03(td, 1H, *J*=8.4, 2.8), 6.90(dd, 1H, *J*=8.8, 2.8), 6.51-6.39(bs, 1H), 4.12-3.90(m, 2H), 2.63-2.55(m, 1H) 2.55-2.39(m, 3H), 2.37-2.18(m, 4H), 1.99-1.85(m, 1H), 1.54-1.38(m, 1H)
125	(S)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.02-7.81(bs, 1H), 7.53-7.30(m, 3H), 7.26-7.19(m, 1H), 7.05(td, 1H, *J*=8.0, 2.8), 6.91(dd, 1H, J=8.8, 2.8), 6.54-6.45(bs, 1H), 4.13-3.86(m, 2H), 2.65-2.54(m, 1H) 2.54-2.42(m, 3H), 2.37-2.19(m, 4H), 2.00-1.86(m, 1H), 1.55-1.37(m, 1H)
126	(S)-(1-메틸피롤리딘-3-일)메틸 (3',5'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.92-7.76(bs, 1H), 7.42-7.36(m, 1H), 7.28-7.17(m, 2H), 7.06(td, 1h, *J*=8.8, 2.8), 6.90(dd, 1H, *J*=8.8, 2.8), 6.51-6.39(bs, 1H), 4.12-3.90(m, 2H), 2.63-2.55(m, 1H) 2.55-2.39(m, 3H), 2.37-2.18(m, 4H), 2.00-1.85(m, 1H), 1.54-1.38(m, 1H)

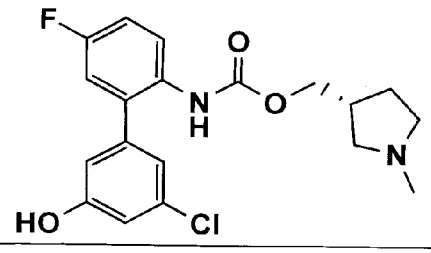
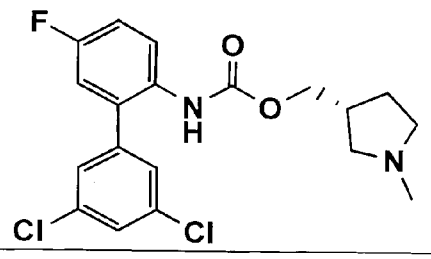
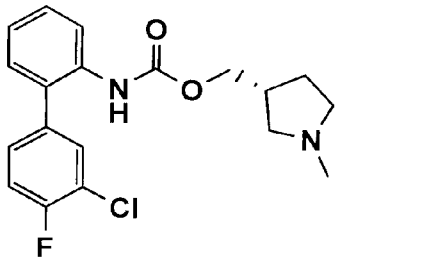
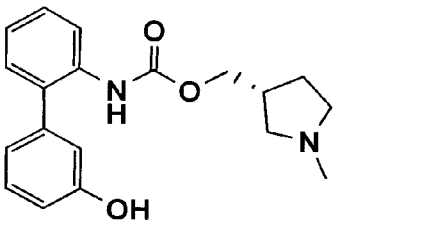
[449]

127	(S)-(1-메틸피롤리딘-3-일)메틸 (4'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.98-7.82(bs, 1H), 7.49-7.38(m, 2H), 7.34-7.20(m, 2H), 7.03(td, 1H, J=8.4, 2.8), 6.90(dd, 1H, J=8.8, 2.8), 6.60-6.49(bs, 1H), 4.14-3.87(m, 2H), 2.66-2.59(m, 1H) 2.59-2.45(m, 3H), 2.42-2.15(m, 4H), 2.04-1.89(m, 1H), 1.57-1.42(m, 1H)
128	(S)-(1-메틸피롤리딘-3-일)메틸 (3',4'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.86-7.65(bs, 1H), 7.58-7.39(m, 2H), 7.26-7.16(m, 1H), 7.04(td, 1H, J=8.4, 3.2), 6.89(dd, 1H, J=8.8, 3.2), 6.89-6.79(bs, 1H), 4.15-3.94(m, 2H), 2.90-2.73(m, 2H) 2.73-2.54(m, 3H), 2.52-2.19(m, 3H), 2.14-1.96(m, 1H), 1.70-1.54(m, 1H)
129	(S)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5,5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.97-7.76(bs, 1H), 7.18-7.02(m, 3H), 7.03-6.86(m, 2H), 6.54-6.42(bs, 1H), 4.03-3.85(m, 2H), 2.65-2.57(m, 1H) 2.57-2.41(m, 3H), 2.37-2.18(m, 4H), 2.02-1.87(m, 1H), 1.55-1.41(m, 1H)

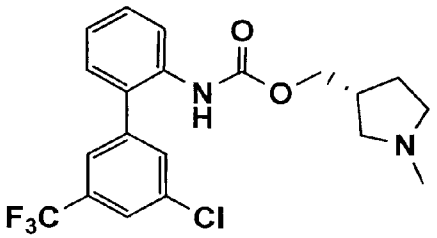
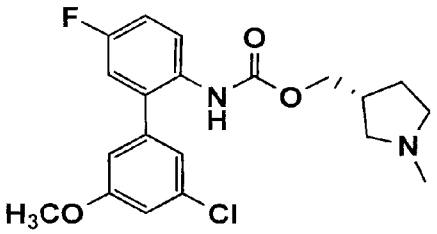
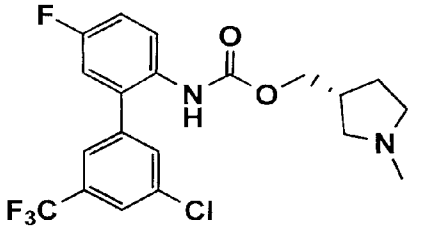
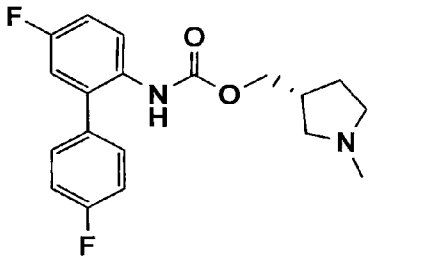
[450]

130	(R)-(1-메틸피롤리딘-3-일)메틸 (3',4'-디클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 8.01-7.99(m, 1H), 7.54-7.51(d, 1H, J=8Hz), 7.46(m, 1H), 7.38-7.34(m, 1H), 7.21-7.11(m, 2H), 6.46(s, 1H), 4.09-3.98(m, 2H), 2.63-2.59(t, 1H, J=17.2), 2.54-2.47(m, 3H), 2.36-2.26(m, 4H), 2.00-1.93(m, 1H), 1.50-1.45(m, 1H)
131	(R)-(1-메틸피롤리딘-3-일)메틸 (3',5'-디클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 8.01-7.97(m, 1H), 7.43-7.35(m, 2H), 7.26-7.25(m, 2H), 7.18-7.11(m, 2H), 6.46(s, 1H), 4.10-3.99(m, 2H), 2.67-2.61(t, 1H, J=17.2), 2.57-2.50(m, 3H), 2.38-2.28(m, 4H), 2.01-1.93(m, 1H), 1.52-1.48(m, 1H)
132	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 8.01-7.99(m, 1H), 7.39-7.35(m, 1H), 7.18-7.11(m, 3H), 6.99-6.97(m, 1H), 6.48(s, 1H), 4.10-3.99(m, 2H), 2.63-2.59(t, 1H, J=17.2), 2.53-2.48(m, 3H), 2.36-2.27(m, 4H), 2.00-1.92(m, 1H), 1.51-1.46(m, 1H)
133	(R)-(1-메틸피롤리딘-3-일)메틸 (5-플루오로-3'-아미노-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 8.03(m, 1H), 7.25-7.21(m, 1H), 7.03-6.98(m, 1H), 6.92-6.90(m, 1H), 6.72-6.61(m, 3H), 4.08-3.97(m, 2H),3.80(s, 1H), 2.66-2.62(t, 1H, J=17.2), 2.53-2.46(m, 3H), 2.33-2.28(m, 4H), 2.01-1.93(m, 1H), 1.51-1.48(m, 1H)

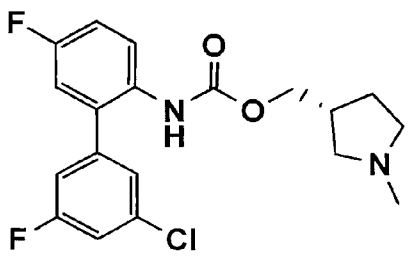
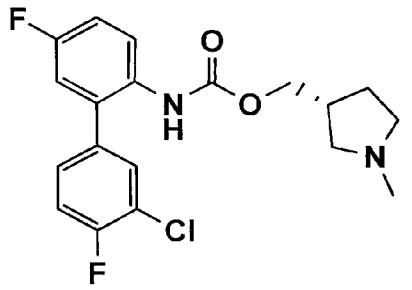
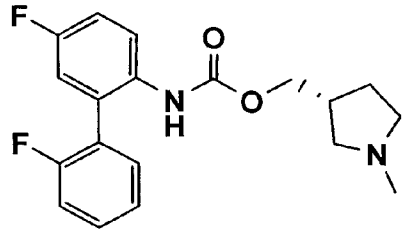
[451]

134	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5-플루오로-5'-히드록시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 7.67(m, 1H), 7.06-7.01(m, 1H), 6.97-6.94(m, 3H), 6.73-6.72(m, 1H), 6.54(s, 1H), 4.35-4.05(m, 2H), 3.01-3.00(m, 1H), 2.89-2.88(m, 1H), 2.59-2.57(m, 2H), 2.47-2.41(m, 4H), 1.97-1.96(m, 1H), 1.80(m, 1H)
135	(R)-(1-메틸피롤리딘-3-일)메틸 (3',5'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 7.85(s, 1H), 7.41-7.40(t, 1H, *J*=4.0), 7.23(s, 2H), 7.10-7.05(m, 2H), 6.93-6.90(m, 2H), 6.36(s, 1H), 4.09-3.99(m, 2H), 2.63-2.59(t, 1H, J=17.2), 2.56-2.45(m, 3H), 2.32-2.28(m, 4H), 2.01-1.93(m, 1H), 1.50-1.46(m, 1H)
136	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 8.03-7.98(m, 1H), 7.41-7.34(m, 2H), 7.26-7.21(m, 2H), 7.17-7.10(m, 2H), 6.49(s, 1H), 4.09-3.98(m, 2H), 2.63-2.59(t, 1H, *J*=17.2), 2.51-2.46(m, 3H), 2.36-2.26(m, 4H), 2.00-1.91(m, 1H), 1.51-1.46(m, 1H)
137	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-히드록시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.95-7.81(m, 1H), 7.40-7.19(m, 3H), 7.18-7.06(m, 1H), 6.89-6.65(m, 4H), 4.34-4.18(m, 1H), 4.09-3.94(m, 1H), 2.89-2.51(m, 5H), 2.42(s, 3H), 2.07-1.95(m, 1H), 1.78-1.60(m, 1H)

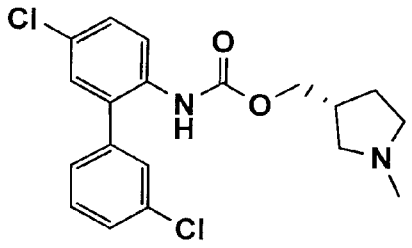
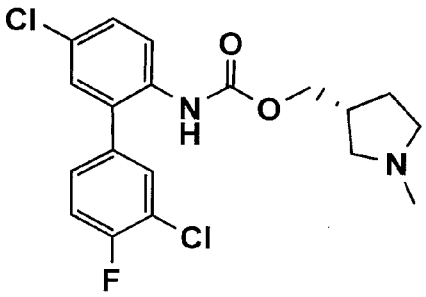
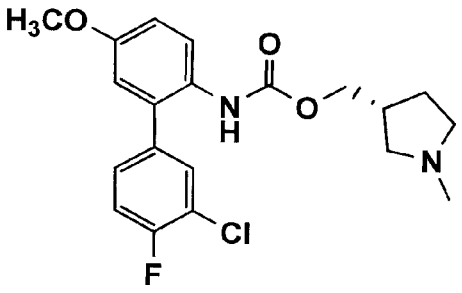
[452]

138	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 7.96-7.94(m, 1H), 7.63(s, 1H), 7.55-7.52(m, 2H), 7.42-7.37(m, 2H), 7.21-7.17(m, 2H), 6.40(s, 1H), 4.09-3.99(m, 2H), 2.64-2.60(t, 1H, J=17.2), 2.55-2.47(m, 3H), 2.36-2.31(m, 4H), 2.00-1.91(m, 1H), 1.51-1.46(m, 1H)
139	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5-플루오로-5'-메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 7.97(m, 1H), 7.07-7.03(m, 1H), 6.94-6.89(m, 2H), 6.74-6.73(m, 1H), 6.45(s, 1H), 4.08-3.99(m, 2H), 3.83-3.79(m, 3H), 2.63-2.59(t, 1H, J=17.2), 2.54-2.47(m, 3H), 2.36-2.27(m, 4H), 2.00-1.91(m, 1H), 1.49-1.45(m, 1H)
140	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5-플루오로-5'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 7.82(m, 1H), 7.65(s, 1H), 7.54-7.51(m, 2H), 7.13-7.08(m, 1H), 6.96-6.93(m, 2H), 6.34(s, 1H), 4.07-3.97(m, 2H), 2.60-2.56(t, 1H, J=17.2), 2.53-2.43(m, 3H), 2.34-2.35(m, 4H), 1.98-1.90(m, 1H), 1.49-1.44(m, 1H)
141	(R)-(1-메틸피롤리딘-3-일)메틸 (4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 7.93(m, 1H), 7.31-7.29(m, 2H), 7.23-7.13(m, 2H), 7.06-7.01(m, 1H), 6.91-6.89(m, 1H), 6.42(s, 1H), 4.07-3.96(m, 2H), 2.61-2.56(t, 1H, J=17.2), 2.53-2.43(m, 3H), 2.35-2.25(m, 4H), 2.00-1.89(m, 1H), 1.51-1.41(m, 1H)

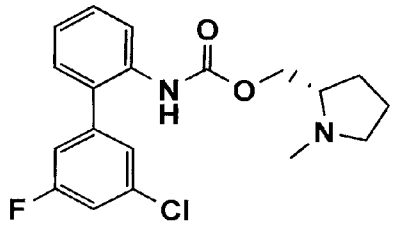
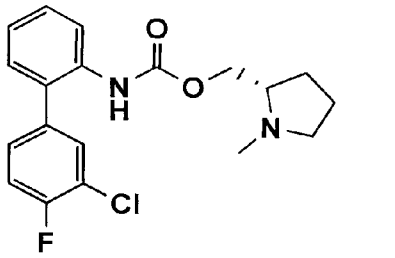
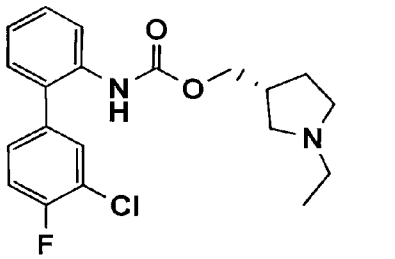
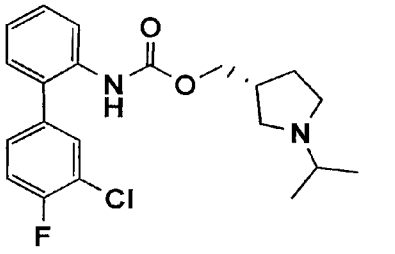
[453]

142	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5,5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 7.85(m, 1H), 7.14-7.13(m, 2H), 7.10-7.05(m, 1H), 6.98-6.96(m, 1H), 6.93-6.90(m, 1H), 6.43(s, 1H), 4.09-3.99(m, 2H), 2.65-2.60(t, 1H, *J*=17.2), 2.55-2.47(m, 3H), 2.36-2.31(m, 4H), 2.02-1.95(m, 1H), 1.52-1.47(m, 1H)
143	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 7.85(m, 1H), 7.40-7.38(m, 1H), 7.26-7.19(m, 2H), 7.08-7.03(m, 1H), 6.91-6.88(m, 1H), 6.34(s, 1H), 4.08-3.97(m, 2H), 2.61-2.57(t, 1H, *J*=17.2), 2.55-2.47(m, 3H), 2.36-2.25(m, 4H), 2.00-1.90(m, 1H), 1.51-1.44(m, 1H)
144	(R)-(1-메틸피롤리딘-3-일)메틸 (2',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 8.05(m, 1H), 7.44-7.40(m, 1H), 7.31-7.23(m, 2H), 7.21-7.17(m, 2H), 6.98-6.96(m, 1H), 4.13-4.07(m, 2H), 3.10-3.08(m, 1H), 2.49-2.45(m, 1H), 2.39(s, 3H), 2.29-2.21(m, 1H), 1.95-1.59(m, 4H)

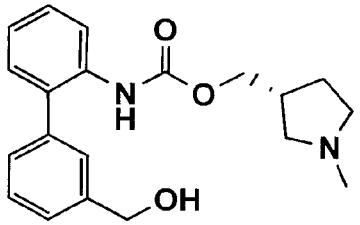
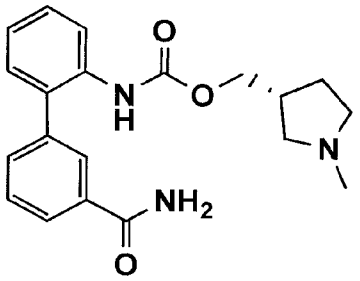
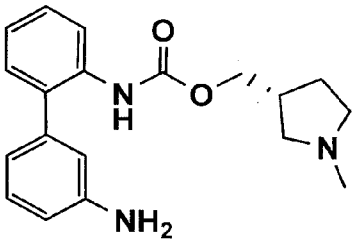
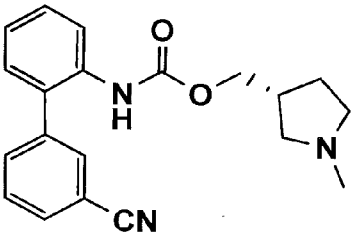
[454]

145	(R)-(1-메틸피롤리딘-3-일)메틸 (3',5-디클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 7.87-7.85(m, 1H), 7.55-7.17(m, 5H), 6.99(m, 1H), 6.55(s, 1H), 4.11-4.02(m, 2H), 3.06-3.02(m, 2H), 2.95-2.89(m, 1H), 2.85-2.81(m, 1H), 2.76-2.66(m, 1H), 2.62(s, 3H), 2.18-2.09(m, 1H), 1.78-1.69(m, 1H)
146	(R)-(1-메틸피롤리딘-3-일)메틸 (3',5-디클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 7.86-7.83(m, 1H), 7.53-7.15(m, 4H), 6.99(m, 1H), 6.50(s, 1H), 4.10-4.02(m, 2H), 3.05-3.02(m, 2H), 2.97-2.90(m, 1H), 2.84-2.82(m, 1H), 2.77-2.67(m, 1H), 2.60(s, 3H), 2.18-2.10(m, 1H), 1.79-1.69(m, 1H)
147	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-4'-플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 7.70(s, 1H), 7.44-7.42(d, 1H, J=7.2), 7.26-7.20(m, 2H), 6.93-6.90(m, 1H), 6.75(m, 1H), 6.66(s, 1H), 4.15-4.00(m, 2H), 3.81(s, 3H), 3.42-3.40(m, 1H), 2.81-2.47(m, 2H), 2.34(s, 3H), 2.06-1.60(m, 4H)

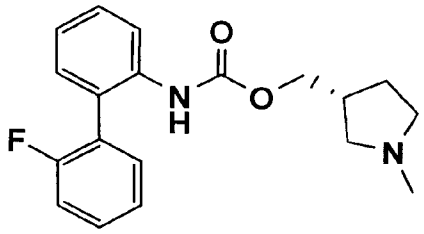
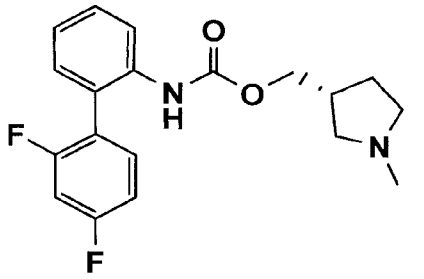
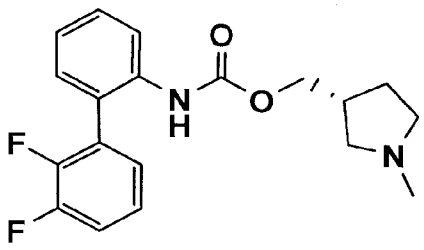
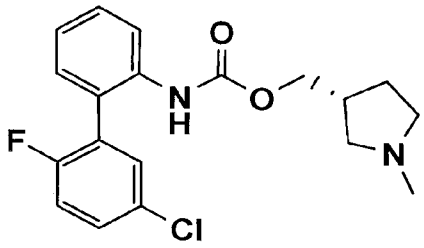
[455]

148	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-5'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 7.92(s, 1H), 7.43-7.27(m, 2H), 7.23-7.08(m, 3H), 7.03-6.95(m, 1H), 6.79(s, 1H), 4.33-4.19(m, 2H), 3.28-3.26(m, 1H), 2.75(m, 1H), 2.49-2.28(m, 4H), 1.98-1.59(m, 4H)
149	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$) δ 7.90(s, 1H), 7.39-7.31(m, 2H), 7.22-7.05(m, 3H), 7.03-6.97(m, 1H), 6.72(s, 1H), 4.26-4.11(m, 2H), 3.19-3.14(m, 1H), 2.70-2.64(m, 1H), 2.42-2.30(m, 4H), 1.99-1.58(m, 4H)
150	(R)-(1-에틸피롤리딘-3-일)메틸 (3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.97(s, 1H), 7.41-7.33(m, 2H), 7.23-7.21(m, 2H), 7.16-7.10(m, 2H), 6.60(s, 1H), 4.10-4.01(m, 2H), 2.74-2.72(m, 1H), 2.65-2.45 (m, 5H), 2.37-2.34(m, 1H), 2.02-1.93(m, 1H), 1.57-1.49(m, 1H), 1.11(t, 3H, *J*=7.2)
151	(R)-(1-이소프로필피롤리딘-3-일)메틸 (3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.95(s, 1H), 7.41-7.34(m, 2H), 7.23-7.21(m, 2H), 7.18-7.12(m, 2H), 6.68(s, 1H), 4.14-4.04(m, 2H), 3.07-3.05(m, 1H), 2.93-2.90(m, 1H), 2.76-2.74(m, 1H), 2.67-2.64(m, 2H), 2.09-2.02(m, 1H), 1.70-1.65(m, 2H), 1.23(s, 6H)

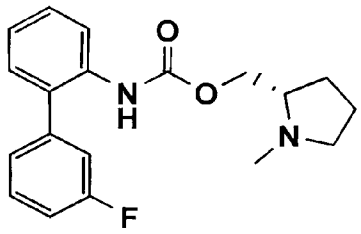
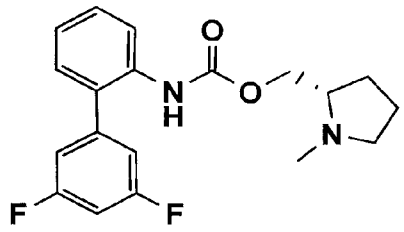
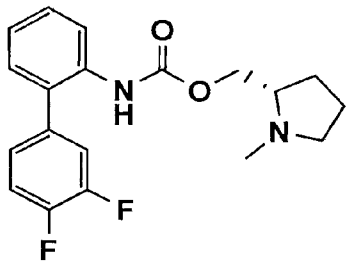
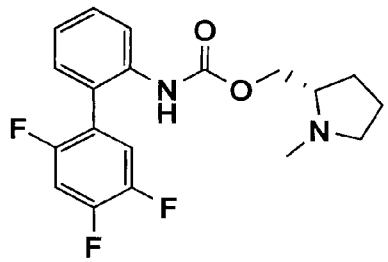
[456]

152	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-(히드록시메틸)-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.10-7.92(bs, 1H), 7.57-6.90(m, 7H), 4.71(s, 1H), 4.21-3.91(m, 3H), 2.73-2.16(m, 9H) 2.08-1.84(m, 1H), 1.64-1.39(m, 1H)
153	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-카바모일-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR(DMSO): δ 8.78(s, 1H), 8.20-7.78(m, 3H), 7.78-7.20(m, 7H), 3.99-3.65(bs, 2H), 3.55-3.26(bs, 1H), 2.60-1.97(m, 7H), 1.88-1.63(bs, 1H), 1.41-1.14(bs, 1H)
154	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-아미노-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.15-8.00(bs, 1H), 7.43-7.13(m, 3H), 7.12-6.99(m, 1H), 6.82-6.55(m, 4H), 4.18-3.93(m, 2H), 3.87-3.67(bs, 2H), 2.72-2.41(m, 4H) 2.41-2.19(m, 4H), 2.03-1.83(m, 1H), 1.55-1.40(m, 1H)
155	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-시아노-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.03-7.85(m, 1H), 7.74-7.50(m, 4H), 7,47-7.32(m, 1H), 7.26-7.08(m, 2H), 6.71-6.47(bs, 1H), 4.15-3.90(m, 2H), 2.77-2.48(m, 4H), 2.48-2.25(bs, 4H), 2.09-1.88(m, 1H), 1.63-1.44(m, 1H)

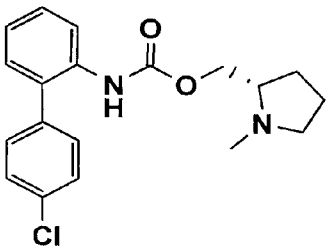
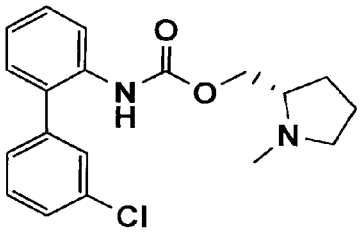
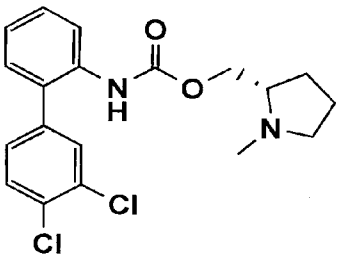
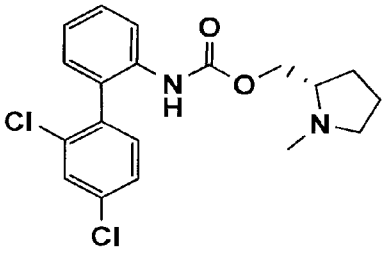
[457]

156	(R)-(1-메틸피롤리딘-3-일)메틸 (2'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.98(m, 1H), 7.43-7.38(m, 3H), 7.31-7.29(m, 1H), 7.26-7.25(m, 1H), 7.23-7.16(m, 2H), 6.48(s, 1H), 4.11-4.02(m, 2H), 2.94-2.80(m, 1H), 2.51-2.48(m, 1H), 2.44(s, 3H), 2.14-2.01(m, 1H), 1.89-1.55(m, 4H)
157	(R)-(1-메틸피롤리딘-3-일)메틸 (2',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.91(m, 1H), 7.39-7.36(m, 1H), 7.30-7.26(m, 1H), 7.19-7.17(m, 2H), 7.00-6.97(m, 2H), 6.95-6.92(m, 1H), 6.70(s, 1H), 4.12-4.06(m, 2H), 3.00-2.97(m, 1H), 2.75-2.70(m, 1H), 2.60(s, 3H), 2.18-2.14(m, 1H), 1.90-1.52(m, 4H)
158	(R)-(1-메틸피롤리딘-3-일)메틸 (2',3'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.84(m, 1H), 7.41-7.39(m, 1H), 7.23-7.17(m, 4H), 7.09-7.07(m, 1H), 4.18-4.11(m, 2H), 3.27-3.14(m, 1H), 2.89-2.85(m, 1H), 2.74(s, 3H), 2.28-2.23(m, 1H), 1.93-1.48(m, 4H)
159	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-6'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.94(m, 1H), 7.55-7.42(m, 1H), 7.30-7.22(m, 2H), 7.19-7.15(m, 2H), 7.04-7.00(m, 1H), 4.20-4.08(m, 2H), 3.29-3.17(m, 1H), 2.88-2.85(m, 1H), 2.54(s, 3H), 2.33-2.28(m, 1H), 2.01-1.66(m, 4H)

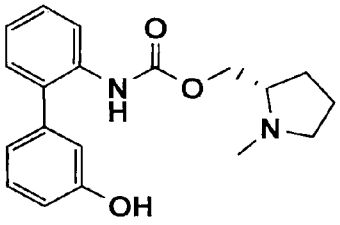
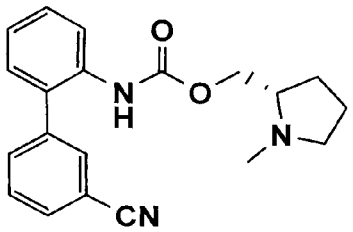
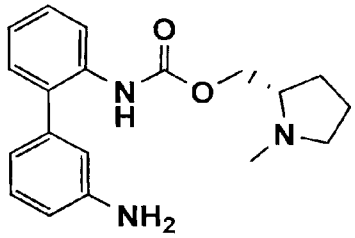
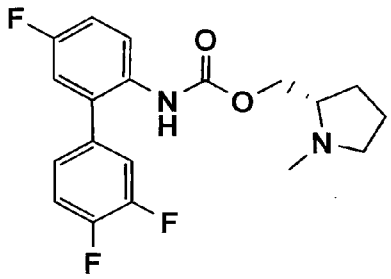
[458]

160	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.10-8.03(m, 1H), 7.36-7.02(m, 6H), 6.89-6.85(m, 1H), 6.63(s, 1H), 4.22-4.02(m, 2H), 3.07-2.98(m, 1H), 2.51-2.41(m, 1H), 2.39(s, 3H), 2.49-2.14(m, 1H), 1.96-1.52(m, 4H)
161	(S)-(1-메틸피롤리딘-2-일)메틸 (3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.02-8.00(m, 1H), 7.37-7.25(m, 2H), 7.17-7.08(m, 2H), 6.90-6.78(m, 2H), 6.60(s, 1H), 4.23-4.03(m, 2H), 3.08-2.99(m, 1H), 2.51-2.36(m, 1H), 2.34(s, 3H), 2.29-2.15(m, 1H), 1.99-1.54(m, 4H)
162	(S)-(1-메틸피롤리딘-2-일)메틸 (3',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.10-8.08(d, 1H, *J*=8.0), 7.39-7.10(m, 3H), 6.92-6.83(m, 1H), 6.66-6.61(m, 1H), 6.59(s, 1H), 6.52-6.48(m, 1H), 4.28-4.08(m, 2H), 3.14-3.07(m, 1H), 2.59-2.47(m, 1H), 2.38(s, 3H), 2.33-2.21(m, 1H), 2.02-1.58(m, 4H)
163	(S)-(1-메틸피롤리딘-2-일)메틸 (2',4',5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.11-8.09(d, 1H, *J*=8.0), 7.33-7.23(m, 2H), 7.18-7.14(m, 1H), 7.13-7.10(m, 1H), 6.91-6.87(m, 1H), 6.48(s, 1H), 4.26-4.06(m, 2H), 3.12-3.08(m, 1H), 2.53-2.43(m, 1H), 2.37(s, 3H), 2.30-2.20(m, 1H), 1.98-1.63(m, 4H)

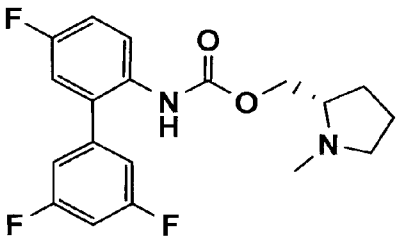
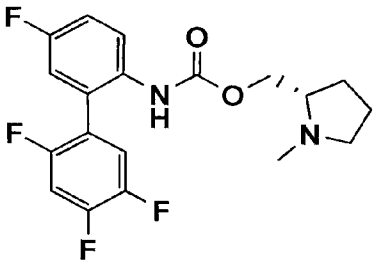
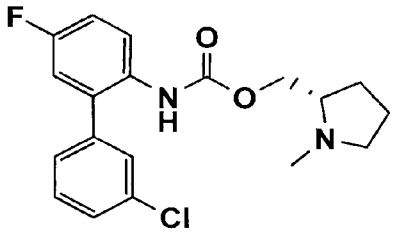
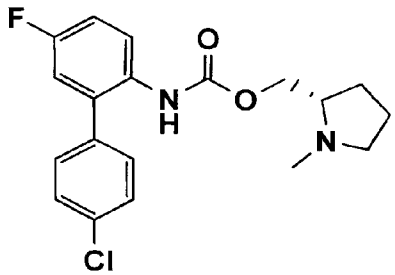
[459]

164	(S)-(1-메틸피롤리딘-2-일)메틸 (4'-클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.02-8.00(d, 1H, J=7.6), 7.30-7.23(m, 2H), 7.21-7.09(m, 1H), 7.06-7.04(d, 2H, J=8.8), 6.77-6.75(d, 2H, J=8.8), 6.60(s, 1H), 4.28-4.08(m, 2H), 3.13-3.06(m, 1H), 2.57-2.45(m, 1H), 2.38(s, 3H), 2.33-2.22(m, 1H), 1.99-1.59(m, 4H)
165	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.12-7.99(m, 1H), 7.49-7.28(m, 4H), 7.28-7.02(m, 3H), 6.62-6.49(bs, 1H), 4.26-3.99(m, 2H), 3.12-2.98(m, 1H), 2.53-2.40(m, 1H), 2.36(s, 3H), 2.27-2.14(m, 1H), 1.98-1.81(m, 1H) 1.80-1.55(m, 2H)
166	(S)-(1-메틸피롤리딘-2-일)메틸 (3',4'-디클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.10-8.08(d, 1H, J=8.0), 7.65-7.61(dd, 2H, J=12.0), 7.55-7.42(m, 3H), 7.19-7.10(m, 1H), 6.57(s, 1H), 4.27-4.07(m, 2H), 3.13-3.05(m, 1H), 2.57-2.47(m, 1H), 2.38(s, 3H), 2.33-2.21(m, 1H), 2.01-1.60(m, 4H)
167	(S)-(1-메틸피롤리딘-2-일)메틸 (2',4'-디클로로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.11-8.09(d, 1H, J=8.0), 7.39-7.08(m, 5H), 6.92-6.88(m, 1H), 6.32(s, 1H), 4.27-4.12(m, 2H), 3.14-3.08(m, 1H), 2.57-2.53(m, 1H), 2.44(s, 3H), 2.31-2.21(m, 1H), 2.01-1.58(m, 4H)

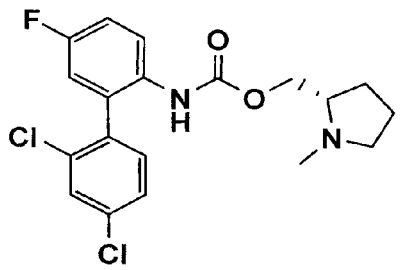
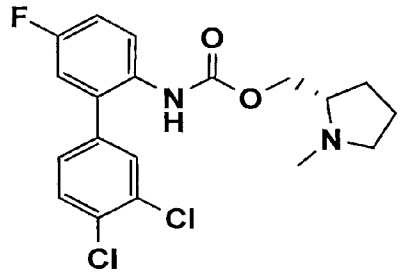
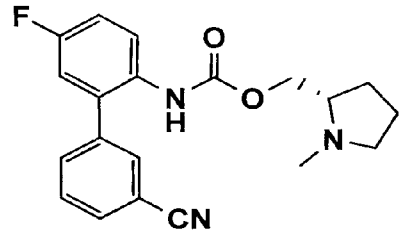
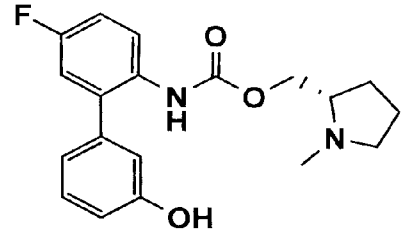
[460]

168	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-히드록시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.98-7.96(d, 1H, J=7.6), 7.30-7.26(m, 1H), 7.22-7.14(m, 2H), 7.11-7.05(m, 1H), 6.81-6.77(t, 2H, J=16.8), 6.73-6.71(t, 1H, J=4.4), 4.23-4.08(m, 2H), 3.09-3.05(m, 1H), 2.57-2.50(m, 1H), 2.38(s, 3H), 2.36-2.22(m, 1H), 1.99-1.59(m, 4H)
169	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-시아노-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.02-8.00(d, 1H, J=7.2), 7.68-7.65(m, 2H), 7.60-7.54(m, 2H), 7.41-7.37(m, 1H), 7.17-7.16(d, 2H, J=4.4), 6.42(s, 1H), 4.22-4.04(m, 2H), 3.06-3.02(m, 1H), 2.35(s, 3H), 2.30-2.24(q, 1H, J=16.0), 2.02-1.55(m, 4H)
170	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-아미노-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.09-8.07(d, 1H, J=7.6), 7.41-7.15(m, 4H), 7.08-7.00(m, 1H), 6.94(s, 2H), 6.82(s, 1H), 6.42(s, 1H), 6.69-6.66(t, 1H, J=14.8), 6.61(s, 1H), 4.24-4.03(m, 2H), 3.11-3.02(m, 1H), 2.56-2.44(m, 1H), 2.40(s, 3H), 2.30-2.17(m, 1H), 1.96-1.58(m, 4H)
171	(S)-(1-메틸피롤리딘-2-일)메틸 (3',4',5-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.75(s, 1H), 7.23-6.97(m, 4H), 6.90-6.85(m, 1H), 6.83(s, 1H), 4.31-4.15(m, 2H), 3.26(m, 1H), 2.81(m, 1H), 2.54(m, 1H), 2.47(s, 3H), 2.03-1.64(m, 4H)

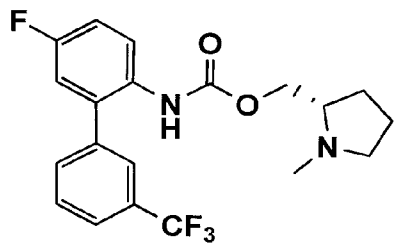
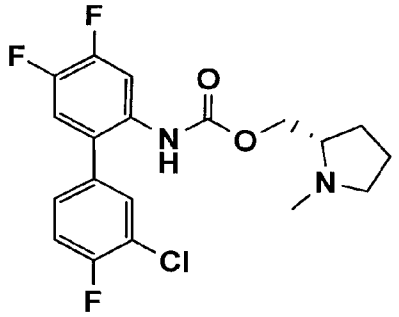
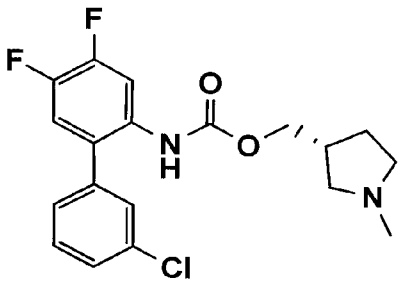
[461]

172	(S)-(1-메틸피롤리딘-2-일)메틸 (3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.88(s, 1H), 7.06-7.01(m, 2H), 6.90-6.78(m, 3H), 6.61(s, 1H), 4.18-3.94(m, 2H), 3.05-3.00(m, 1H), 2.45-2.36(m, 1H), 2.33(s, 3H), 2.28-2.12(m, 1H), 1.90-1.52(m, 4H)
173	(S)-(1-메틸피롤리딘-2-일)메틸 (2',4',5,5'-테트라플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.82(s, 1H), 7.16-6.98(m, 3H), 6.93-6.90(m, 1H), 6.60(s, 1H), 4.29-4.07(m, 2H), 3.24(m, 1H), 2.51-2.32(m, 2H), 2.15(s, 3H), 2.07-1.69(m, 4H)
174	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.94(s, 1H), 7.23-7.16(m, 2H), 7.07-7.02(m, 2H), 6.92-6.89(m, 2H), 6.56(s, 1H), 4.20-4.04(m, 2H), 3.07-3.03(m, 1H), 2.48-2.39(m, 1H), 2.36(s, 3H), 2.31-2.19(m, 1H), 1.93-1.55(m, 4H)
175	(S)-(1-메틸피롤리딘-2-일)메틸 (4'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.89(s, 1H), 7.24(s, 1H), 7.22(s, 1H), 7.03-6.98(m, 2H), 6.88-6.85(m, 2H), 6.55(s, 1H), 4.16-4.00(m, 2H), 3.04-3.00(m, 1H), 2.47-2.35(m, 1H), 2.32(s, 3H), 2.27-2.16(m, 1H), 1.90-1.51(m, 4H)

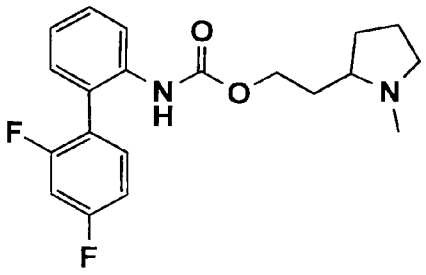
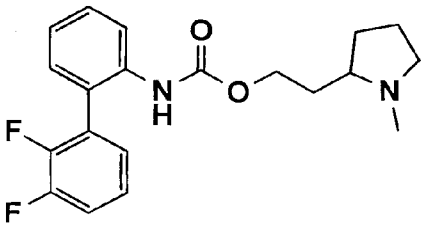
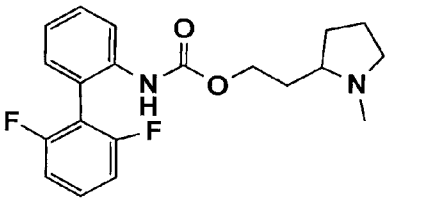
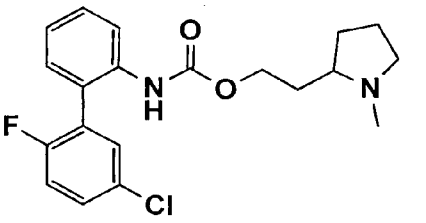
[462]

176	(S)-(1-메틸피롤리딘-2-일)메틸 (2',4'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.89(s, 1H), 7.31-7.28(m, 1H), 7.18(s, 1H), 7.16(s, 1H), 7.13-7.04(m, 1H), 6.83-6.81(m, 1H), 6.30(s, 1H), 4.16-4.00(m, 2H), 3.04-3.00(m, 1H), 2.47-2.35(m, 1H), 2.32(s, 3H), 2.27-2.16(m, 1H), 1.90-1.51(m, 4H)
177	(S)-(1-메틸피롤리딘-2-일)메틸 (3',4'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR(CDCl3) δ 7.88(s, 1H), 7.41-7.37(m, 1H), 7.21-7.16(m, 1H), 7.08-7.01(m, 2H), 6.91-6.88(m, 1H), 6.52(s, 1H), 4.24-4.05(m, 2H), 3.12-3.07(m, 1H), 2.53-2.44(m, 1H), 2.38(s, 3H), 2.36-2.22(m, 1H), 1.94-1.56(m, 4H)
178	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-시아노-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.86(s, 1H), 7.53-7.49(m, 1H), 7.45-7.40(m, 2H), 7.11-7.05(m, 2H), 6.91-6.88(m, 1H), 6.42(s, 1H), 4.18-4.02(m, 2H), 3.06-3.02(m, 1H), 2.45-2.39(m, 1H), 2.34(s, 3H), 2.28-2.13(m, 1H), 1.91-1.53(m, 4H)
179	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-히드록시-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.85(s, 1H), 7.26-7.19(m, 1H), 7.02-6.96(m, 1H), 6.93-6.90(m, 1H), 6.78-6.74(m, 3H), 6.71(s, 1H), 4.21-4.18(m, 2H), 3.15-3.11(m, 1H), 2.62-2.56(m, 1H), 2.41(s, 3H), 2.34-2.27(m, 1H), 1.98-1.62(m, 4H)

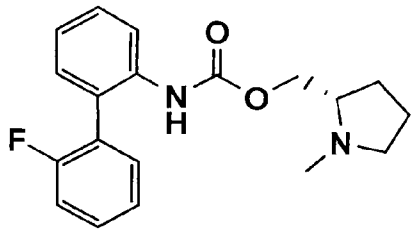
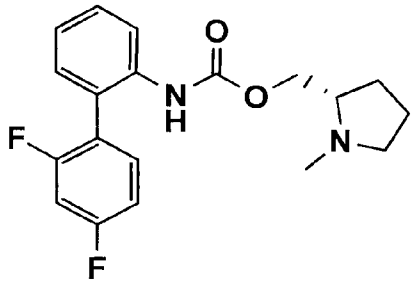
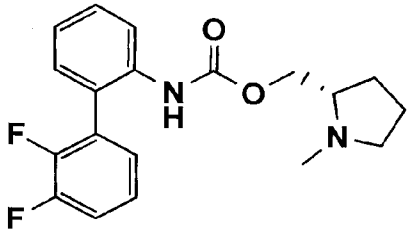
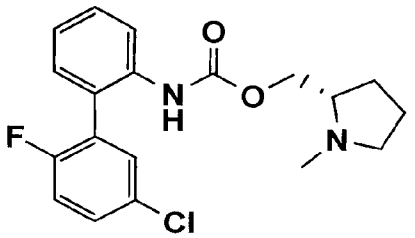
[463]

180	(S)-(1-메틸피롤리딘-2-일)메틸 (5-플루오로-3'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.81(s, 1H), 7.25-7.22(m, 1H), 7.11(s, 1H), 7.07-6.91(m, 4H), 6.67(s, 1H), 4.30-4.09(m, 2H), 3.21-3.13(m, 1H), 2.71-2.58(m, 1H), 2.39(s, 3H), 2.03-1.56(m, 4H)
181	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-4,4',5-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.02(m, 1H), 7.39-7.38(dd, 1H, *J*=4.4), 7.27-7.25(m, 1H), 7.21-7.18(m, 1H), 7.01-6.98(dd, 1H, *J*=7.2), 6.50(s, 1H), 4.23-4.10(m, 2H), 3.10-3.07(m, 1H), 2.50-2.46(m, 1H), 2.39(s, 3H), 2.28-2.23(m, 1H), 1.95-1.60(m, 4H)
182	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-4,5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.00(m, 1H), 7.41-7.39(m, 1H), 7.28-7.23(m, 1H), 7.20-7.19(m, 1H), 7.00-6.96(dd, 1H, *J*=7.2), 6.61(s, 1H), 4.22-4.10(m, 2H), 3.11-3.09(m, 1H), 2.50-2.46(m, 1H), 2.38(s, 3H), 2.29-2.21(m, 1H), 1.95-1.59(m, 4H)

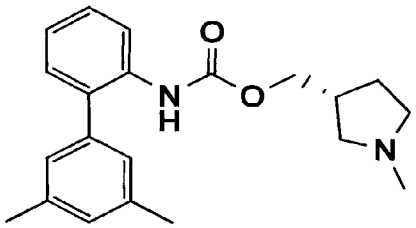
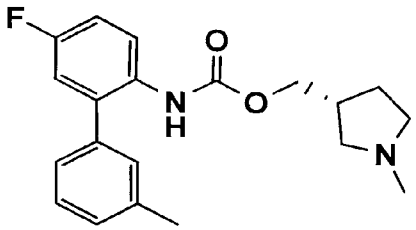
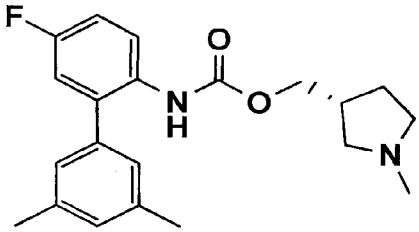
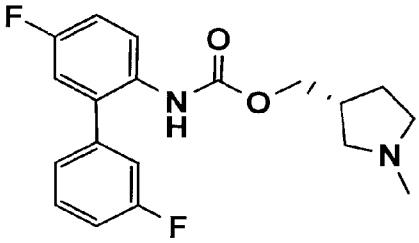
[464]

183	2-(1-메틸피롤리딘-2-일)에틸 (2',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.96(m, 1H), 7.41-7.38(m, 1H), 7.30-7.26(m, 2H), 7.19-7.15(m, 2H), 7.01-6.93(m, 2H), 6.38(s, 1H), 4.21-4.14(m, 2H), 3.35(m, 1H), 3.00-2.64(m, 1H), 2.48(s, 3H), 2.26-2.03(m, 3H), 1.94-1.67(m, 4H)
184	2-(1-메틸피롤리딘-2-일)에틸 (2',3'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.90(m, 1H), 7.44-7.41(m, 1H), 7.26-7.19(m, 4H), 7.09-7.06(m, 1H), 6.46(s, 1H), 4.25(m 2H), 3.80(m, 1H), 2.98(m, 1H), 2.73(s, 3H), 2.29-2.15(m, 3H), 2.02-1.57(m, 4H)
185	2-(1-메틸피롤리딘-2-일)에틸 (2',6'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.94(m, 1H), 7.60-7.37(m, 2H), 7.26-7.21(m, 2H), 7.06-6.99(m, 2H), 6.40(s, 1H), 4.22-4.20(m, 2H), 3.83(m, 1H), 2.99(m 1H), 2.73(s, 3H), 2.31-2.15(m, 3H), 2.02-1.59(m, 4H)
186	2-(1-메틸피롤리딘-2-일)에틸 (5'-클로로-2'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.92(m, 1H), 7.42-7.39(m, 1H), 7.37-7.34(m, 1H), 7.29-7.28(m, 1H), 7.22-7.17(m, 2H), 7.14-7.11(m, 1H), 6.45(s, 1H), 4.22-4.14(m, 2H), 3.80(m, 1H), 3.47-3.45(m, 1H), 2.53(s, 3H), 2.16-2.11(m, 3H), 1.98-1.72(m, 4H)

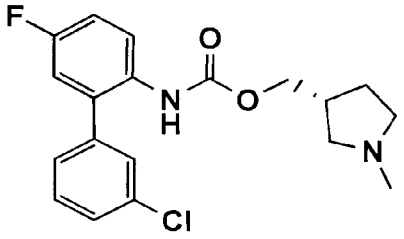
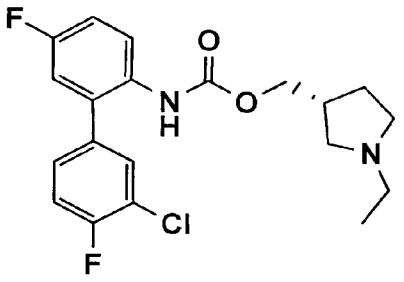
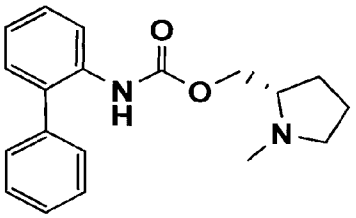
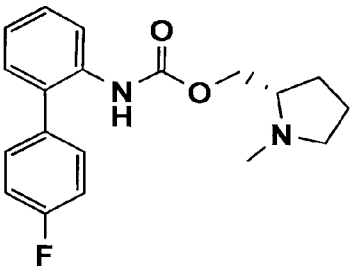
[465]

187	(S)-(1-메틸피롤리딘-2-일)메틸 (2'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.00(m, 1H), 7.41-7.37(m, 3H), 7.33-7.27(m, 1H), 7.25-7.20(m, 1H), 7.19-7.14(m, 2H), 6.61(s, 1H), 4.08-4.01(m, 2H), 2.88-2.79(m, 1H), 2.49-2.45(m, 1H), 2.40(s, 3H), 2.28-2.14(m, 1H), 1.94-1.61(m, 4H)
188	(S)-(1-메틸피롤리딘-2-일)메틸 (2',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.98(m, 1H), 7.41-7.37(m, 1H), 7.29-7.23(m, 1H), 7.17-7.14(m, 2H), 6.99-6.89(m, 2H), 6.44(s, 1H), 4.23-4.05(m, 2H), 3.10-3.07(m, 1H), 2.49(m, 1H), 2.38(s, 3H), 2.28-2.22(m, 3H), 1.93-1.60(m, 4H)
189	(S)-(1-메틸피롤리딘-2-일)메틸 (2',3'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.00(m, 1H), 7.38-7.34(m, 1H), 7.29-7.23(m, 2H), 7.20-7.14(m, 2H), 7.02-6.89(m, 1H), 6.51(s, 1H), 4.20-4.05(m, 2H), 3.08-3.05(m, 1H), 2.58-2.44(m, 1H), 2.39(s, 3H), 2.30-2.24(m, 3H), 1.99-1.64(m, 4H)
190	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-6'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.97(m, 1H), 7.43-7.39(m, 1H), 7.23-7.08(m, 4H), 7.04-6.98(m, 1H), 6.52(s, 1H), 4.27-4.15(m, 2H), 3.17-3.07(m, 1H), 2.62(m, 1H), 2.44(s, 3H), 2.34-2.30(m, 3H), 1.95-1.58(m, 4H)

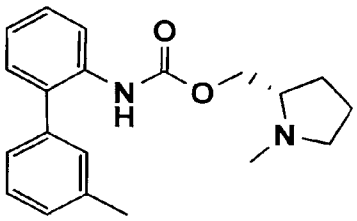
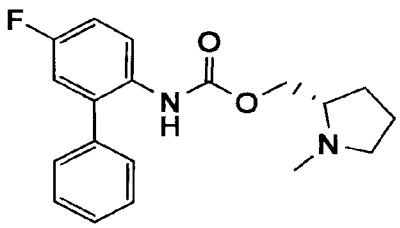
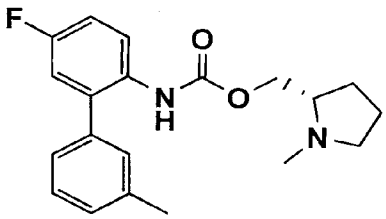
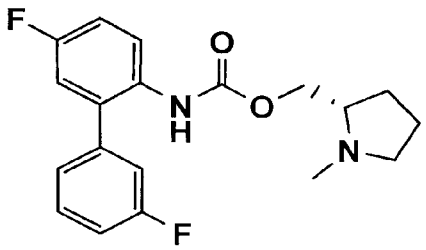
[466]

191	(R)-(1-메틸피롤리딘-3-일)메틸 (3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.07-8.05(m, 1H), 7.33-7.30(m, 1H), 7.18-7.16(m, 1H), 7.10-7.06(m, 1H), 7.03(s, 1H), 6.95(s, 2H), 6.69(s, 1H), 4.09-3.99(m, 2H), 2.69-2.65(t, 1H, J=17.2), 2.59-2.40(m, 3H), 2.35-2.27(m, 4H), 2.01-1.95(m, 1H), 1.54-1.48(m, 1H)
192	(R)-(1-메틸피롤리딘-3-일)메틸 (5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.07-7.89(bs, 1H), 7.40-7.29(m, 1H), 7.29-7.19(m, 1H), 7.19-7.07(m, 2H), 7.07-6.97(m, 1H), 6.97-6.86(m, 1H), 6.61-6.45(bs, 1H), 4.13-3.92(m, 2H), 2.68-2.43(m, 4H), 2.39(s, 3H), 2.36-2.20(m, 4H), 2.04-1.88(m, 1H), 1.53-1.39(m, 1H)
193	(R)-(1-메틸피롤리딘-3-일)메틸 (5-플루오로-3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.98(m, 1H), 7.89-7.04(m, 6H), 6.55(s, 1H), 4.08-3.97(m, 2H), 2.63-2.59(t, 1H, J=17.2), 2.53-2.40(m, 2H), 2.35-2.31(m, 3H), 2.31(s, 1H), 2.27-2.23(m, 1H), 1.99-1.92(m, 1H), 1.51-1.44(m, 1H)
194	(R)-(1-메틸피롤리딘-3-일)메틸 (3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.95(m, 1H), 7.47-7.41(m, 2H), 7.12-7.04(m, 4H), 6.93-6.91(m, 1H), 6.48(s, 1H), 4.08-3.97(m, 2H), 2.63-2.59(t, 1H, J=17.2), 2.52-2.49(m, 3H), 2.34-2.27(m, 4H), 2.00-1.93(m, 1H), 1.50-1.46(m, 1H)

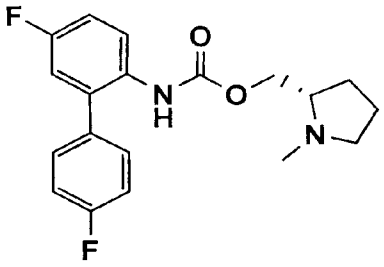
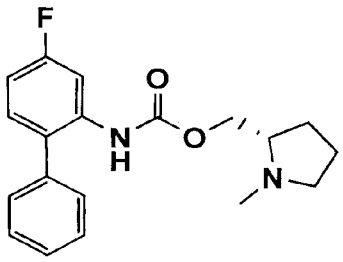
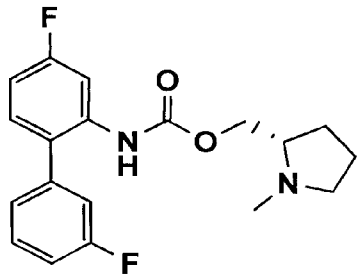
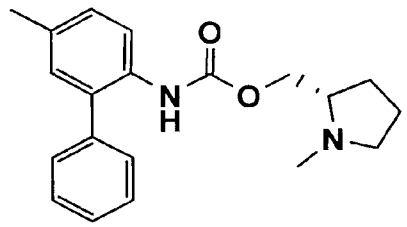
[467]

195	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.92(m, 1H), 7.42-7.33(m, 2H), 7.23-7.21(m, 2H), 7.07-7.03(m, 1H), 6.93-6.90(m, 1H), 6.27(s, 1H), 4.08-3.97(m, 2H), 2.65-2.60(t, 1H, *J*=17.2), 2.53-2.45(m, 3H), 2.35-2.29(m, 4H), 2.01-1.93(m, 1H), 1.53-1.46(m, 1H)
196	(R)-(1-에틸피롤리딘-3-일)메틸 (3'-클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.87(s, 1H), 7.40-7.38(m, 1H), 7.25-7.21(m, 2H), 7.08-7.03(m, 1H), 6.90(dd, 1H, *J*=8.8, *J*=2.8), 6.50(s, 1H), 4.09-3.98(m, 2H), 2.72(t, 1H, *J*=8.8), 2.64-2.44(m, 5H), 2.36-2.33(m, 1H), 2.02-1.92(m, 1H), 1.55-1.47(m, 1H), 1.09(t, 3H, *J*=7.2)
197	(S)-(1-메틸피롤리딘-2-일)메틸 [1,1'-바이페닐]-2-일카바메이트 	^{1}H NMR($CDCl_3$): δ 8.14-8.01(m, 1H), 7.51-7.29(m, 6H), 7.23-7.05(m, 2H), 6.75-6.60(bs, 1H), 4.24-4.00(m, 2H), 3.10-2.98(m, 1H) 2.53-2.29(m, 4H), 2.28-2.15(m, 1H), 1.97-1.52(m, 4H)
198	(S)-(1-메틸피롤리딘-2-일)메틸 (4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.14-8.01(m, 1H), 7.51-7.29(m, 5H), 7.23-7.05(m, 2H), 6.75-6.60(bs, 1H), 4.24-4.00(m, 2H), 3.10-2.98(m, 1H) 2.53-2.29(m, 4H), 2.28-2.15(m, 1H), 1.97-1.52(m, 4H)

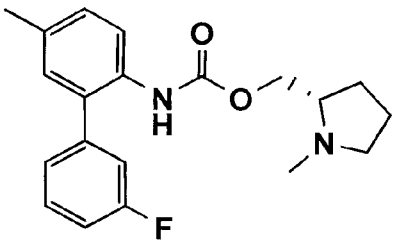
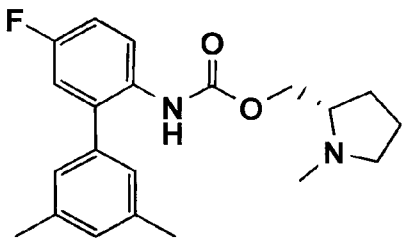
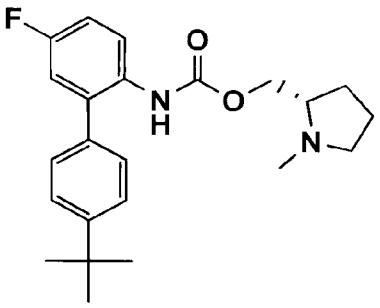
[468]

199	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.17-8.01(m, 1H), 7.41-7.27(m, 2H), 7.22-7.02(m, 5H), 6.76-6.63(bs, 1H), 4.22-4.00(m, 2H), 3.09-2.98(m, 1H) 2.52-2.30(m, 7H), 2.29-2.12(m, 1H), 1.97-1.80(m, 1H), 1.80-1.50(m, 3H)
200	(S)-(1-메틸피롤리딘-2-일)메틸 (5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.97(s, 1H), 7.45-7.37(m, 3H), 7.32-7.25(m, 3H), 7.05-7.00(m, 1H), 6.94-6.91(m, 1H), 6.59(s, 1H), 4.19-4.04(m, 2H), 3.06-3.04(m, 1H), 2.35(s, 3H), 2.28-2.18(m, 2H), 1.90-1.76(m, 2H), 1.61-1.57(m, 2H)
201	(S)-(1-메틸피롤리딘-2-일)메틸 (5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.82(s, 1H), 7.30-7.11(m, 3H), 7.01-6.85(m, 3H), 4.30-4.07(m, 2H), 3.24-3.21(m, 1H), 2.43(s, 3H), 2.35(s, 3H), 1.96-1.84(m, 2H), 1.79-1.72(m, 2H), 1.67-1.51(m, 2H)
202	(S)-(1-메틸피롤리딘-2-일)메틸 (3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.97(s, 1H), 7.43-7.39(m, 1H), 7.11-7.03(m, 4H), 6.91(d, 1H, *J*=8.4), 6.48(s, 1H), 4.19-4.04(m, 2H), 3.05-3.02(m, 1H), 2.35(s, 3H), 2.26-2.17(m, 2H), 1.88-1.83(m, 2H), 1.71-1.69(m, 2H)

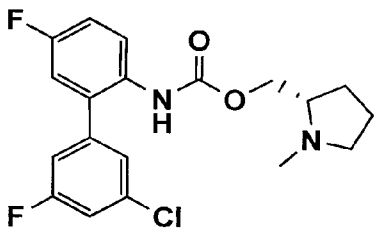
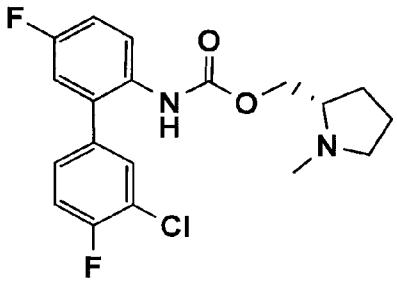
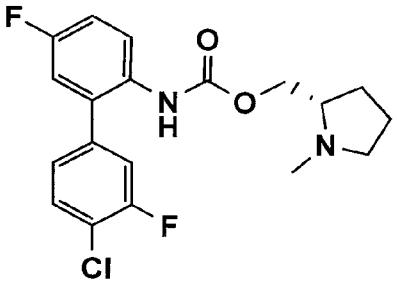
[469]

203	(S)-(1-메틸피롤리딘-2-일)메틸 (4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.97(s, 1H), 7.31-7.26(m, 1H), 7.22-7.12(m, 2H), 7.06-7.00(m, 2H), 6.91-6.88(m, 1H), 6.43(s, 1H), 4.21-4.03(m, 2H), 3.06-3.02(m, 1H), 2.35(s, 3H), 2.28-2.15(m, 2H), 1.95-1.83(m, 2H), 1.70-1.67(m, 2H)
204	(S)-(1-메틸피롤리딘-2-일)메틸 (4-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.96(s, 1H), 7.47-7.43(m, 2H), 7.40-7.36(m, 1H), 7.33-7.25(m, 2H), 7.18-7.10(m, 1H), 6.81-6.75(m, 2H), 4.18-4.05(m, 2H), 3.03-3.01(m, 1H), 2.35(s, 3H), 2.22-2.17(m, 2H), 1.93-1.86(m, 2H), 1.61-1.57(m, 2H)
205	(S)-(1-메틸피롤리딘-2-일)메틸 (3',4-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.96(s, 1H), 7.45-7.39(m, 2H), 7.25-7.23(m, 1H), 7.16-7.07(m, 2H), 7.03-7.01(m, 1H), 6.83-6.78(m, 1H), 6.65(s, 1H), 4.19-4.06(m, 2H), 3.05-3.02(m, 1H), 2.36(s, 3H), 2.26-2.18(m, 2H), 1.93-1.84(m, 2H), 1.59-1.50(m, 2H)
206	(S)-(1-메틸피롤리딘-2-일)메틸 (5-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.92(s, 1H), 7.45-7.41(m, 2H), 7.33-7.25(m, 2H), 7.16-7.13(m, 1H), 7.02(s, 1H), 6.59(s, 1H), 4.21-4.05(m, 2H), 3.09-3.07(m, 1H), 2.38(s, 3H), 2.32(s, 3H), 2.27-2.23(m, 2H), 1.90-1.87(m, 2H), 1.78-1.72(m, 2H)

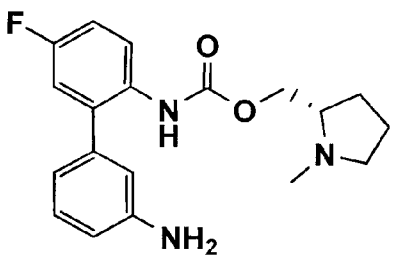
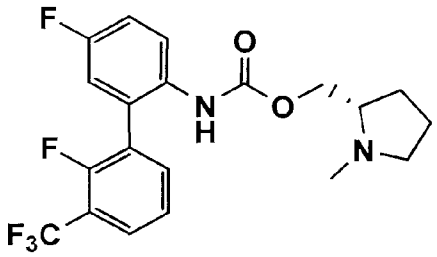
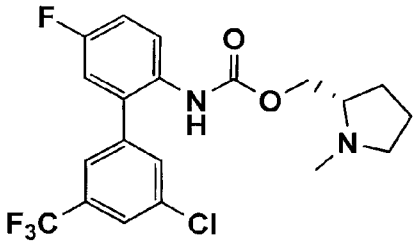
[470]

207	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-플루오로-5-메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.88(s, 1H), 7.42-7.36(m, 1H), 7.21-7.20(m, 1H), 7.17-7.15(m, 1H), 7.10-7.03(m, 2H), 7.00(m, 1H), 6.55(s, 1H), 4.22-4.06(m, 2H), 3.10-3.06(m, 1H), 2.38(s, 3H), 2.31(s, 3H), 2.27-2.21(m, 2H), 1.94-1.85(m, 2H), 1.78-1.69(m, 2H)
208	(S)-(1-메틸피롤리딘-2-일)메틸 (5-플루오로-3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.95(s, 1H), 7.15(m, 2H), 7.04-6.98(m, 2H), 6.93-6.90(m, 2H),, 6.72(s, 1H), 4.31-4.17(m, 2H), 3.14(m, 1H), 2.82(m, 1H) 2.61-2.03(m, 10H), 1.99-1.62(m, 4H)
209	(S)-(1-메틸피롤리딘-2-일)메틸 (4'-(tert-부틸)-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.83(s, 1H), 7.72-7.70(m, 2H), 7.67-7.62(m, 2H), 7.03-6.91(m, 2H), 6.76(s, 1H), 4.35-4.22(m, 2H), 3.20(m, 1H), 2.96(m, 1H), 2.68-2.65(m, 1H), 2.48(s, 3H), 1.99-1.63(m, 4H), 1.51-1.29(m, 9H)

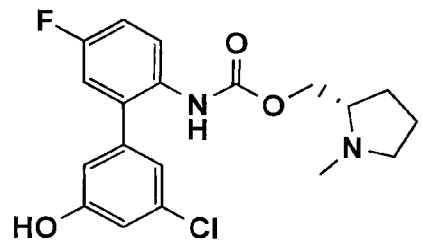
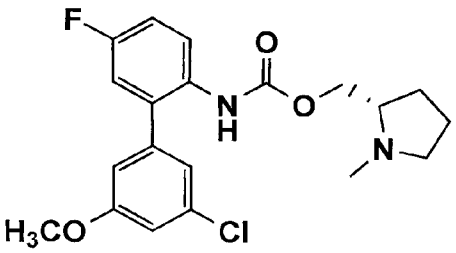
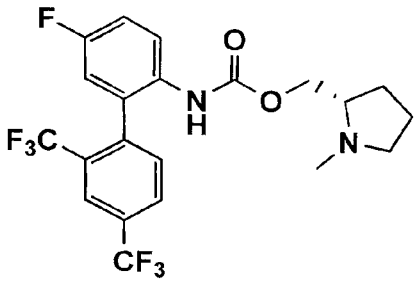
[471]

210	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-5,5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.84(s, 1H), 7.24-7.15(m, 1H), 7.12-6.89(m, 4H), 6.64(s, 1H), 4.26-4.10(m, 2H), 3.16-3.15(m, 1H), 2.62(m, 1H), 2.42(s, 3H), 2.38-2.32(m, 1H), 1.99-1.60(m, 4H)
211	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.05(m, 1H), 7.57-7.48(m, 1H), 7.22-7.14(m, 2H), 7.12-7.00(m, 2H), 6.61(s, 1H), 4.23-4.16(m, 2H), 3.22-3.10(m, 1H), 2.58-2.47(m, 1H), 2.38(s, 3H), 2.35-2.30(m, 3H), 1.98-1.60(m, 4H)
212	(S)-(1-메틸피롤리딘-2-일)메틸 (4'-클로로-3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.39-7.31(m, 3H), 7.20-7.00(m, 2H), 6.98-6.88(d, 1H, *J*=2.8), 4.34-4.23(m, 2H), 3.45(m 1H), 3.16(m, 1H), 2.57-2.54(m, 4H), 2.11-1.70(m, 4H).

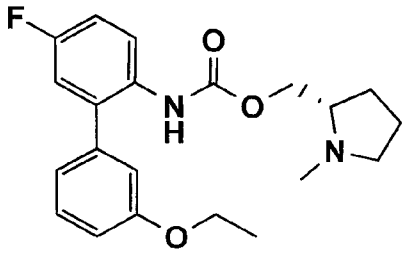
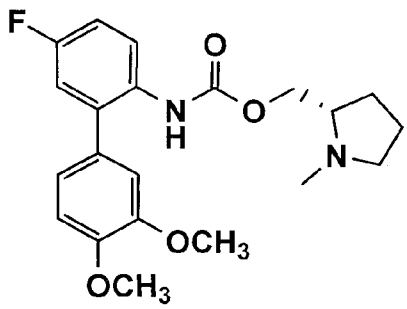
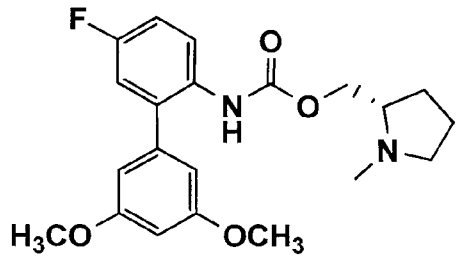
[472]

213	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-아미노-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.99(s, 1H), 7.23-7.19(m, 1H), 7.03-6.98(m, 1H), 6.93-6.90(m, 1H), 6.74(m, 1H), 6.70-6.66(m, 1H), 6.63(s, 1H), 4.24-4.07(m, 2H), 3.46(s, 1H), 3.14(m, 1H), 2.59(m, 1H), 2.42(s, 3H), 2.33-2.29(m, 1H), 1.98-1.63(m, 4H)
214	(S)-(1-메틸피롤리딘-2-일)메틸 (2',5-디플루오로-3'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.84(s, 1H), 7.69-7.66(m, 1H), 7.53-7.50(m, 1H), 7.37-7.33(m, 1H), 7.15-7.10(m, 1H), 6.98-6.95(m, 1H), 6.61(s, 1H), 4.29-4.15(m, 2H), 3.27(s, 1H), 2.78-2.70(m, 1H), 2.48-2.35(m, 4H), 1.98-1.70(m, 4H)
215	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-5-플루오로-5'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.96(s, 1H), 7.79(s, 1H), 7.61(s, 1H), 7.50-7.47(d, 1H, J=11.6), 7.11-7.06(m, 1H), 6.94-6.91(m, 1H), 6.58(s, 1H), 4.27-4.11(m, 2H), 3.22-3.17(m, 1H), 2.67-2.66(m, 1H), 2.42-2.32(m, 4H), 2.02-1.60(m, 4H)

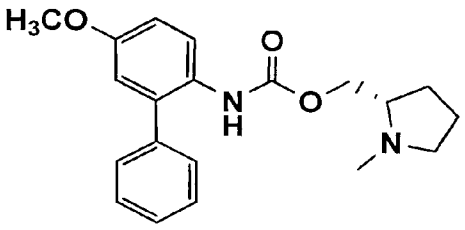
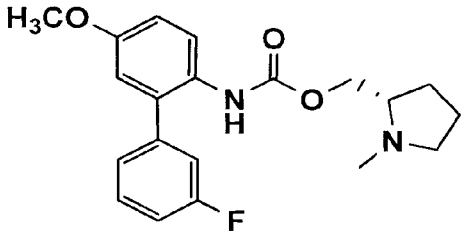
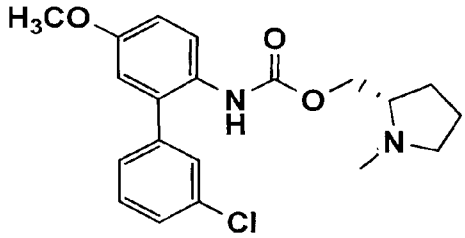
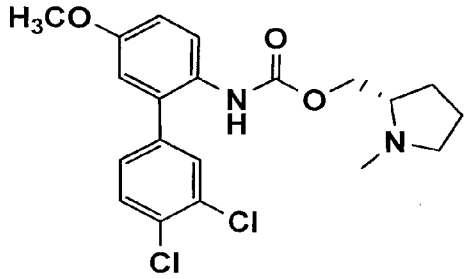
[473]

216	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-5-플루오로-5'-히드록시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.82(s, 1H), 7.02-6.64(m, 5H), 4.17-4.09(m, 2H), 3.10-3.06(m, 1H), 2.53(m, 1H), 2.37(s, 3H), 2.34-2.21(m, 1H), 1.96-1.62(m, 4H)
217	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-5-플루오로-5'-메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.94(s, 1H), 7.66-7.44(m, 4H), 6.91-6.89(d, 1H, J=8.4), 6.62(s, 1H), 4.23-4.08(m, 2H), 3.86-3.85(m, 3H), 3.11(m, 1H), 2.53(m, 1H), 2.34(s, 3H), 2.29-2.28(m, 1H), 1.93-1.63(m, 4H)
218	(S)-(1-메틸피롤리딘-2-일)메틸 (5-플루오로-2',4'-비스(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 8.11(m, 1H), 7.44-7.36(m, 1H), 7.20-7.17(m, 2H), 7.10-6.99(m, 2H), 6.54(s, 1H), 4.27-4.21(m, 2H), 3.31-3.15(m, 1H), 2.44-2.40(m, 1H), 2.39(s, 3H), 2.30-2.25(m, 3H), 2.01-1.55(m, 4H)

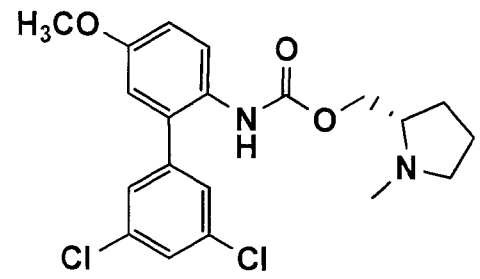
[474]

219	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-에톡시-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.58-7.53(m, 1H), 7.48-7.44(m, 2H), 7.29-7.15(m, 2H), 6.95-6.92(m, 1H), 6.84-6.79(m, 1H), 4.27-4.23(m, 2H), 4.14-4.07(q, 2H, J=6.8), 3.28(m, 1H), 2.89(m, 1H), 2.50(m, 4H), 1.98-1.59(m, 4H), 1.46-1.40(t, 3H, J=14.0)
220	(S)-(1-메틸피롤리딘-2-일)메틸 (5-플루오로-3',4'-디메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.65-7.61(m, 1H), 7.54-7.52(m, 1H), 7.47-7.43(m, 2H), 7.33(m, 1H), 6.68-6.65(m, 1H), 4.29-4.15(m, 2H), 3.87(s, 6H), 3.28-3.25(m, 1H), 2.78-2.70(m, 1H), 2.48-2.35(m, 4H), 1.98-1.63(m, 4H)
221	(S)-(1-메틸피롤리딘-2-일)메틸 (5-플루오로-3',5'-디메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.93(s, 1H), 7.03-6.91(m, 4H), 6.46-6.42(m, 1H), 6.38(s, 1H), 4.22-4.08(m, 2H), 3.77(s, 6H), 3.15(m, 1H), 2.61(m, 1H), 2.41(s, 3H), 2.36-2.24(m, 1H), 1.93-1.58(m, 4H)

[475]

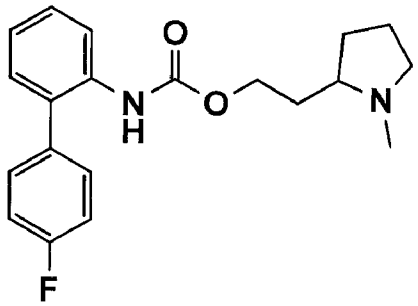
222	(S)-(1-메틸피롤리딘-2-일)메틸 (5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.81(s, 1H), 7.43-7.28(m, 4H), 7.20-7.19(d, 1H, *J*=4.4), 6.87-6.86(dd, 1H, *J*=9.2), 6.76-6.75(d, 1H, *J*=2.8), 6.61(s, 1H), 4.20-4.06(m, 2H), 3.77(s, 3H), 3.13-3.10(m, 1H), 2.58-2.43(m, 1H), 2.38(s, 3H), 2.32-2.25(m, 1H), 1.92-1.56(m, 4H)
223	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.74(s, 1H), 7.39-7.33(m, 1H), 7.10-7.01(m, 2H), 6.88-6.85(m, 1H), 6.73-6.72(m, 1H), 6.59(s, 1H), 4.17-4.03(m, 2H), 3.76(s, 3H), 3.76(m, 1H), 2.49(m, 1H), 2.36(s, 3H), 2.28-2.21(m, 1H), 1.99-1.56(m, 4H)
224	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.79(s, 1H), 7.37-7.33(m, 2H), 7.26-7.20(m, 2H), 6.91-6.88(m, 1H), 6.73-6.72(m, 1H), 6.38(s, 1H), 4.22-4.05(m, 2H), 3.79(s, 3H), 3.11-3.07(m, 1H), 2.50-2.38(m, 1H), 2.33(s, 3H), 2.29-2.22(m, 1H), 1.94-1.57(m, 4H)
225	(S)-(1-메틸피롤리딘-2-일)메틸 (3',4'-디클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.69(s, 1H), 7.48-7.43(m, 2H), 7.21-7.17(m, 1H), 6.90-6.87(m, 1H), 6.71-6.70(m, 1H), 6.51(s, 1H), 4.21-4.05(m, 2H), 3.78(s, 3H), 3.13(m, 1H), 2.52-2.45(m, 1H), 2.32(s, 3H), 2.30-2.22(m, 1H), 1.97-1.59(m, 4H)

[476]

226	(S)-(1-메틸피롤리딘-2-일)메틸 (3',5'-디클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 	^{1}H NMR($CDCl_3$): δ 7.79(s, 1H), 7.64(m, 1H), 7.35-7.34(m, 1H), 7.23-7.22(m, 1H), 7.07-7.02(m, 1H), 6.90-6.87(m, 1H), 6.63(s, 1H), 4.26-4.05(m, 2H), 3.20-3.15(m, 1H), 2.66(m, 1H), 2.42-2.32(m, 4H), 1.99-1.61(m, 4H)

[477]

[478] **[실시예 1] 2-(1-메틸피롤리딘-2-일)에틸 (4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[479] 

[480] 4'-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드(747mg, 3.46mmol)(합성예1)를 톨루엔(20mL)에 녹인 후 바이페닐포스포릴 아지드(958μL, 4.15mmol)와 트리에틸아민(486μL, 3.46mmol)을 가하였다. 상온에서 30분간 교반 한 후 다시 1시간 동안 환류교반하였다. 반응물의 온도를 상온으로 낮추고 2-(2-히드록시에틸)-1-메틸피롤리딘(558μL, 4.15mmol)을 가한 후 12시간 동안 환류교반하였다. 반응물의 온도를 상온으로 낮추고, 감압 농축하여 용매를 제거한 후 물과 에틸아세테이트로 추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(280mg, 24%)을 얻었다.

[481]

[482] **[실시예 2-16]**

[483] 4'-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드(747mg, 3.46mmol)(합성예1) 대신 [표 7]의 출발물질을 사용하여 실시예 1과 동일한 방법으로 실시예 2 내지 16의 화합물을 제조하였다.

[484] [표 7] 실시예 2-16

[485]

실시예	화학명	출발물질
2	2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (290mg, 23%)	3',5'-다이플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (820mg) (합성예2)
3	2-(1-메틸피롤리딘-2-일)에틸 (3',4',5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 (300mg, 41%)	3',4',5'-트리플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (492mg) (합성예3)
4	2-(1-메틸피롤리딘-2-일)에틸 (3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (326mg, 41%)	3'-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (500mg) (합성예4)
5	2-(1-메틸피롤리딘-2-일)에틸 (4'-메톡시-[1,1'-바이페닐]-2-일)카바메이트 (350mg, 36%)	4'-메톡시-[1,1'-바이페닐]-2-카복실릭 애시드 (630mg) (합성예5)
6	2-(1-메틸피롤리딘-2-일)에틸 [1,1'-바이페닐]-2-일카바메이트 (400mg, 50%)	[1,1'-바이페닐]-2-카복실릭 애시드 (500mg)
7	2-(1-메틸피롤리딘-2-일)에틸 (4'-클로로-[1,1'-바이페닐]-2-일)카바메이트 (230mg, 30%)	4'-클로로-[1,1'-바이페닐]-2-카복실릭 애시드 (500mg) (합성예6)
8	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-[1,1'-바이페닐]-2-일)카바메이트 (170mg, 22%)	3'-클로로-[1,1'-바이페닐]-2-카복실릭 애시드 (500mg) (합성예7)
9	2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디클로로-[1,1'-바이페닐]-2-일)카바메이트 (125mg, 28%)	3',5'-디클로로-[1,1'-바이페닐]-2-카복실릭 애시드 (300mg) (합성예8)
10	2-(1-메틸피롤리딘-2-일)에틸 (4'-트리플루오로메톡시-[1,1'-바이페닐]-2-일)카바메이트 (370mg, 57%)	4'-트리플루오로메톡시-[1,1'-바이페닐]-2-카복실릭 애시드 (450mg) (합성예9)
11	2-(1-메틸피롤리딘-2-일)에틸 (4'-니트로-[1,1'-바이페닐]-2-일)카바메이트 (410mg, 82%)	4'-니트로-[1,1'-바이페닐]-2-카복실릭 애시드 (330mg) (합성예10)

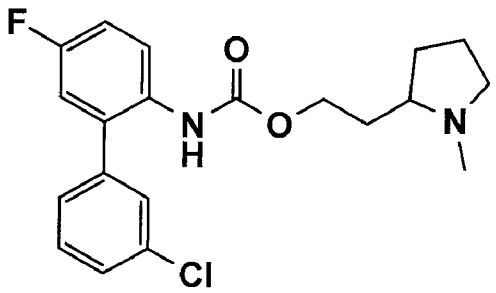
[486]

12	2-(1-메틸피롤리딘-2-일)에틸 (3'-트리플루오로메틸-[1,1'-바이페닐]-2-일)카바메이트 (476mg, 65%)	3'-트리플루오로메틸-[1,1'-바이페닐]-2-카복실릭 애시드 (500mg) (합성예11)
13	2-(1-메틸피롤리딘-2-일)에틸 (4'-트리플루오로메틸-[1,1'-바이페닐]-2-일)카바메이트 (45mg, 6%)	4'-트리플루오로메틸-[1,1'-바이페닐]-2-카복실릭 애시드 (500mg) (합성예12)
14	2-(1-메틸피롤리딘-2-일)에틸 ((3'-플루오로-4'-메틸)-[1,1'-바이페닐]-2-일)카바메이트 (306mg, 46%)	3'-플루오로-4'-메틸-[1,1'-바이페닐]-2-카복실릭 애시드 (430mg) (합성예13)
15	2-(1-메틸피롤리딘-2-일)에틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 (105mg, 16%)	3'-메틸-[1,1'-바이페닐]-2-카복실릭 애시드 (400mg) (합성예14)
16	2-(1-메틸피롤리딘-2-일)에틸 (3'-에톡시-[1,1'-바이페닐]-2-일)카바메이트 (250mg, 52%)	3'-에톡시-[1,1'-바이페닐]-2-카복실릭 애시드 (315mg) (합성예15)

[487]

[488] **[실시예 17] 2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[489]



[490] 3'-클로로-5-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드(300mg, 1.20mmol)(합성예 16)을 톨루엔(20mL)에 녹인 후 바이페닐포스포릴 아지드(310μL, 1.44mmol)와 트리에틸아민(202μL, 1.44mmol)을 가하였다. 상온에서 30분간 교반 한 후 다시 1시간 동안 환류교반하였다. 반응물의 온도를 상온으로 낮추고 2-(2-히드록시에틸)-1-메틸피롤리딘(194μL, 1.44mmol)을 가한 후 12시간 동안 환류교반하였다. 반응물의 온도를 상온으로 낮추고, 감압 농축하여 용매를 제거한 후 물과 에틸아세테이트로 추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(93mg, 21%)을 얻었다.

[491]

[492] **[실시예 18-27]**

[493] 3'-클로로-5-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드(300mg,

1.20mmol)(합성예 16) 대신 [표 7]의 출발물질을 사용하여 실시예 17과 동일한 방법으로 실시예 18 내지 27의 화합물을 제조하였다.

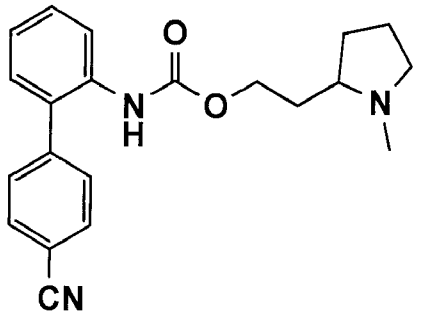
[494] [표 8] 실시예 18-27

[495]

실시예	화학명	출발물질
18	2-(1-메틸피롤리딘-2-일)에틸 (3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (465mg, 76%)	3',5-디플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (400mg, 1.71mmol) (합성예 17)
19	2-(1-메틸피롤리딘-2-일)에틸 (4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (184mg, 30%)	4',5-디플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (400mg, 1.71mmol) (합성예 18)
20	2-(1-메틸피롤리딘-2-일)에틸 (3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 (362mg, 48%)	3',5,5'-디플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (500mg, 1.98mmol) (합성예 19)
21	2-(1-메틸피롤리딘-2-일)에틸 (5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (297mg, 19%)	5-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (1g, 4.63mmol) (합성예 20)
22	2-(1-메틸피롤리딘-2-일)에틸 (5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 (152mg, 26%)	5-플루오로-3'-메틸-[1,1'-바이페닐]-2-카복실릭 애시드 (380mg, 1.65mmol) (합성예 21)
23	2-(1-메틸피롤리딘-2-일)에틸 (4-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (400mg, 51%)	4-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (500mg, 2.31mmol) (합성예 22)
24	2-(1-메틸피롤리딘-2-일)에틸 (3',4-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (84mg, 14%)	3',4-디플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (400mg, 1.71mmol) (합성예 23)
25	2-(1-메틸피롤리딘-2-일)에틸 (4-메톡시-[1,1'-바이페닐]-2-일)카바메이트 (170mg, 34%)	4-메톡시-[1,1'-바이페닐]-2-카복실릭 애시드 (320mg, 1.40mmol) (합성예 24)
26	2-(1-메틸피롤리딘-2-일)에틸 (5-메틸-[1,1'-바이페닐]-2-일)카바메이트 (123mg, 26%)	5-메틸-[1,1'-바이페닐]-2-카복실릭 애시드 (300mg, 1.41mmol) (합성예 25)
27	2-(1-메틸피롤리딘-2-일)에틸 (3'-플루오로-5-메틸-[1,1'-바이페닐]-2-일)카바메이트 (279mg, 90%)	3'-플루오로-5-메틸-[1,1'-바이페닐]-2-카복실릭 애시드 (200mg, 0.87mmol) (합성예 26)

[496]

[497] **[실시예 28] 2-(1-메틸피롤리딘-2-일)에틸 (4'-시아노-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[498] 

[499] 2-(1-메틸피롤리딘-2-일)에틸 (2-아이오도페닐)카바메이트(600mg, 1.6mmol)(합성예 A)를 톨루엔(20mL)과 에탄올(4mL) 혼합용액에 녹인 후 4-시아노페닐 보로닉애시드(259mg, 1.76mmol), 포타슘카보네이트(442mg, 3.2mmol), 테트라키스트리페닐포스핀팔라듐(370mg, 0.32mmol)을 가하였다. 반응물을 110℃에서 12시간 동안 교반한 후 온도를 상온으로 낮추고, 셀라이트 여과 후 감압 농축하여 용매를 제거하였다. 물과 에틸아세테이트로 추출한 후 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(193mg, 35%)을 얻었다.

[500]

[501] **[실시예 29-32]**

[502] 출발물질로 합성예 A의 2-(1-메틸피롤리딘-2-일)에틸 (2-아이오도페닐)카바메이트와 [표 9]의 반응물질을 사용하여 실시예 28과 동일한 방법으로 실시예 29 내지 32의 화합물을 제조하였다.

[503] [표 9] 실시예 29-32

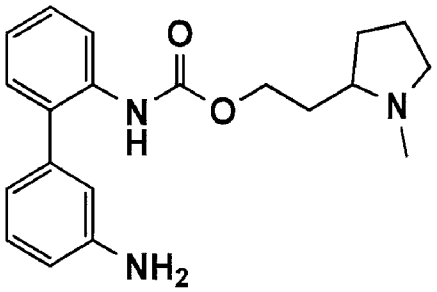
[504]

실시예	화학명	출발물질 (합성예 A)	반응물질
29	2-(1-메틸피롤리딘-2-일)에틸 (3'-(3-히드록시프로필)-[1,1'-바이페닐]-2-일)카바메이트 (52mg, 5%)	1g, 2.67mmol	3-(3-히드록시프로필)페닐 보로닉애시드 (530mg, 2.94mmol)
30	2-(1-메틸피롤리딘-2-일)에틸 (4'-(디메틸아미노)-[1,1'-바이페닐]-2-일)카바메이트 (71mg, 36%)	200mg, 0.53mmol	4-(디메틸아미노)페닐 보로닉애시드 (131mg, 0.80mmol)
31	2-(1-메틸피롤리딘-2-일)에틸 (4'-(tert-부틸)-[1,1'-바이페닐]-2-일)카바메이트 (33mg, 22%)	150mg, 0.40mmol	4-tert-부틸페닐 보로닉애시드 (110mg, 0.60mmol)
32	2-(1-메틸피롤리딘-2-일)에틸 (2'-아미노-[1,1'-바이페닐]-2-일)카바메이트 (37mg, 10%)	400mg, 1.07mmol	2-아미노페닐 보로닉애시드 피나콜 에스터(353mg, 1.61mmol)

[505]

[506] **[실시예 33] 2-(1-메틸피롤리딘-2-일)에틸**

(3'-아미노-[1,1'-바이페닐]-2-일)카바메이트의 합성

[507] 

[508] 2-(1-메틸피롤리딘-2-일)에틸 (2-아이오도페닐)카바메이트(1.36g, 3.63mmol)(합성예 A)를 아세토니트릴(15mL)과 물(15mL)의 혼합용액에 녹인 후 3-아미노페닐 보로닉애시드(995mg, 7.26mmol), 소듐카보네이트(772mg, 7.26mmol), 디클로로비스트리페닐포스핀 팔라듐(127mg, 0.18mmol)을 가하였다. 반응물을 Microwave oven에서 110℃로 10분간 교반한 후 온도를 상온으로 낮추고, 셀라이트 여과 후 감압 농축하여 용매를 제거하였다. 물과 에틸아세테이트로 추출한 후 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(192mg, 16%)을 얻었다.

[509]

[510] **[실시예 34-41]**

[511] 출발물질로 합성예 A의 2-(1-메틸피롤리딘-2-일)에틸 (2-아이오도페닐)카바메이트와 [표 10]의 반응물질을 사용하여 실시예 33와 동일한 방법으로 실시예 34 내지 41의 화합물을 제조하였다.

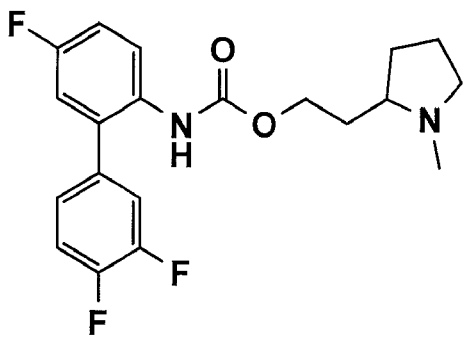
[512] [표 10] 실시예 34-41

[513]

실시예	화학명	출발물질 (합성예 A)	반응물질
34	2-(1-메틸피롤리딘-2-일)에틸 (2'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (126mg, 30%)	400mg, 1.07mmol	2-플루오로페닐보로닉애시드 (300mg, 2.14mmol)
35	2-(1-메틸피롤리딘-2-일)에틸 (2'-클로로-[1,1'-바이페닐]-2-일)카바메이트 (80mg, 18%)	400mg, 1.07mmol	2-클로로페닐보로닉애시드 (335mg, 2.14mmol)
36	2-(1-메틸피롤리딘-2-일)에틸 (2'-히드록시-[1,1'-바이페닐]-2-일)카바메이트 (65mg, 16%)	400mg, 1.07mmol	2-히드록시페닐보로닉애시드 피나콜 에스터 (471mg, 2.14mmol)
37	2-(1-메틸피롤리딘-2-일)에틸 (3'-tert-부틸-5'-메틸-[1,1'-바이페닐]-2-일)카바메이트 (155mg, 49%)	300mg, 0.80mmol	(3-tert-부틸-5-메틸)페닐보로닉애시드(307mg, 1.60mmol)
38	2-(1-메틸피롤리딘-2-일)에틸 (4'-플루오로-3'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 (66mg, 20%)	297mg, 0.79mmol	(4-플루오로-3-(트리플루오로메틸)페닐)보로닉애시드 (330mg, 1.58mmol)
39	2-(1-메틸피롤리딘-2-일)에틸 (4'-아미노-3'-클로로-[1,1'-바이페닐]-2-일)카바메이트 (81mg, 27%)	300mg, 0.80mmol	(4-아미노-3-클로로페닐)보로닉애시드 피나콜 에스터 (406mg, 1.6mmol)
40	2-(1-메틸피롤리딘-2-일)에틸 (3'-히드록시-[1,1'-바이페닐]-2-일)카바메이트 (48mg, 9%)	300mg, 0.80mmol	3-히드록시페닐보로닉애시드 (221mg, 1.6mmol)
41	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (150mg, 43%)	300mg, 0.80mmol	3-클로로-4-플루오로페닐보로닉 애시드 (240mg, 1.38mmol)

[514]

[515] **[실시예 42] 2-(1-메틸피롤리딘-2-일)에틸 (3',4',5-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[516] 

[517] 2-(1-메틸피롤리딘-2-일)에틸 (2-브로모-4-플루오로페닐)카바메이트(400mg, 1.16mmol)(합성예 B)를 톨루엔(20mL)에 녹인 후 3,4-디플루오로페닐 보로닉애시드(280mg, 1.74mmol), 포타슘카보네이트(321mg, 2.32mmol), 테트라키스트리페닐포스핀팔라듐(140mg, 0.12mmol)을 가하였다. 반응물을 120℃에서 12시간 동안 교반한 후 온도를 상온으로 낮추고, 셀라이트 여과 후 감압 농축하여 용매를 제거하였다. 물과 에틸아세테이트로 추출한 후 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(15mg, 3%)을 얻었다.

[518]

[519] **[실시예 43-46]**

[520] 출발물질로 합성예 B의 2-(1-메틸피롤리딘-2-일)에틸 (2-브로모-4-플루오로페닐)카바메이트와 [표 11]의 반응물질을 사용하여 실시예 42와 동일한 방법으로 실시예 43 내지 46의 화합물을 제조하였다.

[521] [표 11] 실시예 43-46

[522]

실시예	화학명	출발물질 (합성예 B)	반응물질
43	2-(1-메틸피롤리딘-2-일)에틸 (3',4'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (24mg, 5%)	400mg, 1.16mmol	3,4-디클로로페닐 보로닉 애시드(332mg, 1.74mmol)
44	2-(1-메틸피롤리딘-2-일)에틸 (3'-에틸-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트(40mg, 12%)	300mg, 0.87mmol	3-에틸페닐 보로닉애시드 (200mg, 1.31mmol)
45	2-(1-메틸피롤리딘-2-일)에틸 (5-플루오로-3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트 (18mg, 4%)	400mg, 1.16mmol	3,5-디메틸페닐 보로닉애시드 (261mg, 1.74mmol)
46	2-(1-메틸피롤리딘-2-일)에틸 (3'-아미노-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (50mg, 5%)	1g, 2.90mmol	3-아미노페닐 보로닉애시드 (600mg, 4.35mmol)

[523]

[524] **[실시예 47-51]**

[525] 출발물질로 합성예 B의 2-(1-메틸피롤리딘-2-일)에틸 (2-브로모-4-플루오로페닐)카바메이트 대신 합성예 C의 2-(1-메틸피롤리딘-2-일)에틸 (2-브로모-4-(트리플루오로메틸)페닐)카바메이트와 [표 12]의 반응물질을 사용하여 실시예 42와 동일한 방법으로 실시예 47 내지 51의 화합물을 제조하였다.

[526] [표 12] 실시예 47-51

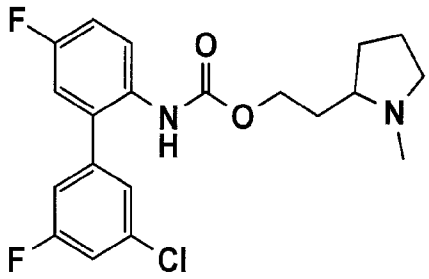
[527]

실시예	화학명	출발물질 (합성예 C)	반응물질
47	2-(1-메틸피롤리딘-2-일)에틸 (5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 (26mg, 9%)	300mg, 0.76mmol	페닐보로닉 애시드 (102mg, 0.84mmol)
48	2-(1-메틸피롤리딘-2-일)에틸 (4'-플루오로-5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 (14mg, 4%)	300mg, 0.76mmol	4-플루오로페닐보로닉 애시드 (118mg, 0.84mmol)
49	2-(1-메틸피롤리딘-2-일)에틸 (3'-플루오로-5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 (19mg, 6%)	300mg, 0.76mmol	3-플루오로페닐보로닉 애시드 (118mg, 0.84mmol)
50	2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디플루오로-5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 (12mg, 4%)	260mg, 0.66mmol	3,5-디플루오로페닐보로닉 애시드 (115mg, 0.73mmol)
51	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 (14mg, 4%)	300mg, 0.76mmol	3-클로로페닐보로닉 애시드 (131mg, 0.84mmol)

[528]

[529] **[실시예 52] 2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-5,5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[530]



[531] 2-(1-메틸피롤리딘-2-일)에틸 (2-브로모-4-플루오로페닐)카바메이트(300mg, 0.87mmol)(합성예 B)를 아세토니트릴(10mL)과 물(10mL)의 혼합용액에 녹인 후 (3-클로로-5-플루오로페닐)보로닉애시드(303mg, 1.74mmol), 소듐카보네이트(184mg, 1.74mmol), 디클로로비스트리페닐포스핀 팔라듐(31mg, 0.04mmol)을 가하였다. 반응물을 Microwave oven에서 110oC로 10분간 교반한 후 온도를 상온으로 낮추고, 셀라이트 여과 후 감압 농축하여 용매를 제거하였다. 물과 에틸아세테이트로 추출한 후 유기층을 무수 황산마그네슘으로 건조하고,

여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(51mg, 15%)을 얻었다.

[532]

[533] **[실시예 53-59]**

[534] 출발물질로 합성예 B의 2-(1-메틸피롤리딘-2-일)에틸 (2-브로모-4-플루오로페닐)카바메이트와 [표 13]의 반응물질을 사용하여 실시예 52과 동일한 방법으로 실시예 53 내지 59의 화합물을 제조하였다.

[535] [표 13] 실시예 53-59

[536]

실시예	화학명	출발물질 (합성예 B)	반응물질
53	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (81mg, 24%)	300mg, 0.87mmol	(3-클로로-4-플루오로페닐)보로닉애시드 (303mg, 1.74mmol)
54	2-(1-메틸피롤리딘-2-일)에틸 (4'-클로로-3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (173mg, 38%)	400mg, 1.16mmol	(3-플루오로-4-클로로페닐)보로닉애시드 (405mg, 2.32mmol)
55	2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (71mg, 15%)	400mg, 1.16mmol	3,5-디클로로페닐 보로닉 애시드 (443mg, 2.32mmol)
56	2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (99mg, 20%)	400mg, 1.16mmol	3,5-디클로로-4-플루오로페닐 보로닉애시드 (484mg, 2.32mmol)
57	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-5-플루오로-5'-히드록시-[1,1'-바이페닐]-2-일)카바메이트 (97mg, 28%)	300mg, 0.87mmol	(3-클로로-5-히드록시페닐)보로닉애시드 (300mg, 1.74mmol)
58	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-5-플루오로-4'-히드록시-[1,1'-바이페닐]-2-일)카바메이트 (176mg, 39%)	400mg, 1.16mmol	(3-클로로-4-히드록시페닐)보로닉애시드 (400mg, 2.32mmol)
59	2-(1-메틸피롤리딘-2-일)에틸 (5-플루오로-3',4'-디메틸-[1,1'-바이페닐]-2-일)카바메이트 (129mg, 30%)	400mg, 1.16mmol	(3,4-디메틸페닐)보로닉애시드 (348mg, 2.32mmol)

[537]

[538] **[실시예 60-65]**

[539] 출발물질로 합성예 B의 2-(1-메틸피롤리딘-2-일)에틸 (2-브로모-4-플루오로페닐)카바메이트 대신 합성예 D의 2-(1-메틸피롤리딘-2-일)에틸 (2-브로모-4-메톡시페닐)카바메이트와 [표 14]의 반응물질을 사용하여 실시예 52과 동일한 방법으로 실시예 60 내지 65의 화합물을 제조하였다.

[540] [표 14] 실시예 60-65

[541]

실시예	화학명	출발물질 (합성예 D)	반응물질
60	2-(1-메틸피롤리딘-2-일)에틸 (5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 (25mg, 8%)	300mg, 0.84mmol	페닐보로닉 애시드 (154mg, 1.26mmol)
61	2-(1-메틸피롤리딘-2-일)에틸 (3'-플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 (112mg, 36%)	300mg, 0.84mmol	3-플루오로페닐보로닉 애시드 (176mg, 1.26mmol)
62	2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 (161mg, 37%)	400mg, 1.12mmol	3,5-디플루오로페닐보로닉 애시드 (354mg, 2.24mmol)
63	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 (112mg, 31%)	330mg, 0.92mmol	3-클로로페닐보로닉 애시드 (289mg, 1.85mmol)
64	2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 (92mg, 19%)	400mg, 1.12mmol	3,5-디클로로페닐보로닉 애시드 (427mg, 2.24mmol)
65	2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-4'-플루오로-5-메톡시-[1,1'-바이페닐]-2-일) 카바메이트 (155mg, 34%)	400mg, 1.12mmol	(3-클로로-4-플루오로)페닐보로닉 애시드 (390mg, 2.24mmol)

[542]

[543] **[실시예 66-73]**

[544] 출발물질로 합성예 B의 2-(1-메틸피롤리딘-2-일)에틸 (2-브로모-4-플루오로페닐)카바메이트 대신 합성예 E의 2-(1-메틸피롤리딘-2-일)에틸 (2-브로모-4-클로로페닐)카바메이트와 [표 15]의 반응물질을 사용하여 실시예 52와 동일한 방법으로 실시예 66 내지 73의 화합물을 제조하였다.

[545] [표 15] 실시예 66-73

[546]

실시예	화학명	출발물질 (합성예 E)	반응물질
66	2-(1-메틸피롤리딘-2-일)에틸 (5-클로로-[1,1'-바이페닐]-2-일)카바메이트 (94mg, 24%)	400mg, 1.11mmol	페닐보로닉 애시드 (271mg, 2.22mmol)
67	2-(1-메틸피롤리딘-2-일)에틸 (5-클로로-3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (187mg, 45%)	400mg, 1.11mmol	3-플루오로페닐보로닉 애시드 (311mg, 2.22mmol)
68	2-(1-메틸피롤리딘-2-일)에틸 (5-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (38mg, 9%)	400mg, 1.11mmol	4-플루오로페닐보로닉 애시드 (311mg, 2.22mmol)
69	2-(1-메틸피롤리딘-2-일)에틸 (5-클로로-3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (162mg, 37%)	400mg, 1.11mmol	3,5-디플루오로페닐보로닉 애시드 (351mg, 2.22mmol)
70	2-(1-메틸피롤리딘-2-일)에틸 (3',5-디클로로-[1,1'-바이페닐]-2-일)카바메이트 (111mg, 25%)	400mg, 1.11mmol	3-클로로페닐보로닉 애시드 (347mg, 2.22mmol)
71	2-(1-메틸피롤리딘-2-일)에틸 (3',5,5'-트리클로로-[1,1'-바이페닐]-2-일)카바메이트 (58mg, 12%)	400mg, 1.11mmol	3,5-디클로로페닐보로닉 애시드 (424mg, 2.22mmol)
72	2-(1-메틸피롤리딘-2-일)에틸 (3',5-디클로로-5'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (119mg, 26%)	400mg, 1.11mmol	(3-클로로-5-플루오로페닐)보로닉 애시드 (387mg, 2.22mmol)
73	2-(1-메틸피롤리딘-2-일)에틸 (3',5-디클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (88mg, 19%)	400mg, 1.11mmol	(3-클로로-4-플루오로페닐)보로닉 애시드 (387mg, 2.22mmol)

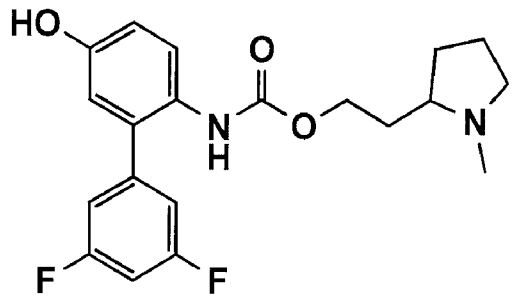
[547]

[548] **[실시예 74] (R)-(1-메틸피롤리딘-3-일)메틸 (3'-플루오로-4'-포밀-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[549] 출발물질로 (R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트(220mg, 0.70mmol)(합성예 F)와 3-플루오로-4-포밀페닐보로닉 애시드(237mg, 1.41mmol)을 사용하여 실시예 52와 같은 방법으로 표제화합물(124mg, 50%)을 얻었다.

[550]

[551] **[실시예 75] 2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디플루오로-5-히드록시-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[552] 

[553] 2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트(130mg, 0.33mmol)(실시예 62)를 디클로로메탄 (10ml)에 녹인 후 보론 트리클로라이드 용액(1.0M 디클로로메탄, 0.99ml, 0.99mmol)을 가하고 상온에서 2시간 동안 교반하였다. 반응이 종결된 후 반응물을 물과 디클로로메탄으로 추출하고 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(68mg, 55%)을 얻었다.

[554]

[555] **[실시예 76] 2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디클로로-5-히드록시-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[556] 실시예 62 대신 2-(1-메틸피롤리딘-2-일)에틸 (3',5'-디클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 (90mg, 0.21mmol)(실시예 64)를 사용하여 실시예 75와 동일한 방법으로 표제화합물(10mg, 12%)을 얻었다.

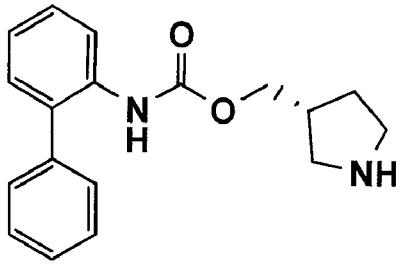
[557]

[558] **[실시예 77] 2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-4'-플루오로-5-히드록시-[1,1'-바이페닐]-2-일)카바메이트의 합성**

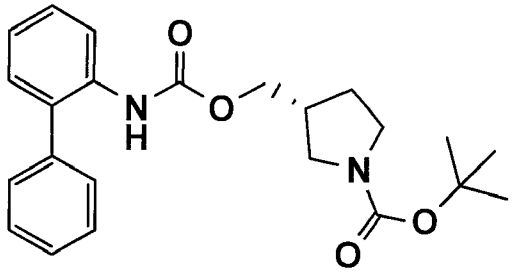
[559] 실시예 62 대신 2-(1-메틸피롤리딘-2-일)에틸 (3'-클로로-4'-플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트(140mg, 0.34mmol)(실시예 65)를 사용하여 실시예 75와 동일한 방법으로 표제화합물 (130mg, 96%)을 얻었다.

[560]

[561] **[실시예 78] (R)-피롤린딘-3-일메틸 [1,1'-바이페닐]-2-일카바메이트의 합성**

[562] 

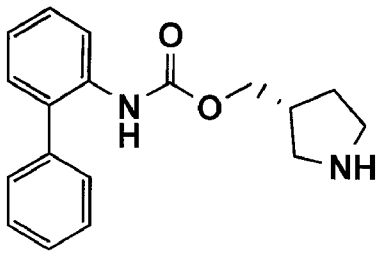
[563] [단계 1] (R)-tert-부틸 3-((([1,1'-바이페닐]-2-일카바모일)옥시)메틸)피롤리딘-1-카복실레이트의 합성

[564] 

[565] [1,1'-바이페닐]-2-카복실릭 애시드(2g, 10.09mmol)를 톨루엔(50mL)에 녹인 후 바이페닐포스포릴 아지드(2.61mL, 12.11mmol)과 트리에틸아민(1.42mL, 10.09mmol)을 가하였다. 상온에서 30분간 교반한 후 다시 1시간 동안 환류교반하였다. 반응물의 온도를 상온으로 낮추고 (R)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이트(2.44g, 12.11mmol)를 가한 후 12시간 동안 환류교반하였다. 반응물의 온도를 상온으로 낮추고, 감압 농축하여 용매를 제거한 후 물과 디클로로메탄으로 추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(3g, 75%)을 얻었다.

[566] ^{1}H NMR($CDCl_3$): δ 8.15-7.97(bs, 1H), 7.55-7.26(m, 6H), 7.26-7.05(m, 2H), 6.67-6.52(bs, 1H), 4.19-3.90(m, 2H), 3.57-3.18(m, 2H), 3.13-2.73(bs, 1H), 2.57-2.38(m, 1H), 2.00-1.83(m, 1H), 1.70-1.53(m, 2H) 1.43(s, 9H)

[567] [단계 2] (R)-피롤린딘-3-일메틸 [1,1'-바이페닐]-2-일카바메이트의 합성

[568] 

[569] (R)-tert-부틸 3-((([1,1'-바이페닐]-2-일카바모일)옥시)메틸)피롤리딘-1-카복실레이트(3g, 7.57mmol)를 디클로로메탄(80mL)에 녹인 후, 트리플루오로아세틱 애시드(40mL)를 가하고 상온에서 2시간 동안 교반하였다. 반응물을

감압농축하여 용매를 제거하고 2N-소듐히드록시드 용액과 디클로로메탄으로 추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(1.73g, 77%)을 얻었다.

[570]

[571] **[실시예 79-88]**

[572] [표 16]의 출발물질 및 반응물질을 사용하여 실시예 78과 동일한 방법으로 실시예 79 내지 88의 화합물을 제조하였다.

[573] [표 16] 실시예 79-88

[574]

실시예	화학명	출발물질	반응물질
79	(S)-피롤린딘-3-일메틸 [1,1'-바이페닐]-2-일카바메이트 (1.53g, 51%)	[1,1'-바이페닐]-2-카복실릭 애시드 (2g, 10.09mmol)	(S)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이드 (2.44g, 12.11mmol)
80	(R)-피롤리딘-3-일메틸 (3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (435mg, 63%)	3',5'-디플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (500mg, 2.13mmol) (합성예 2)	(R)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이드 (516mg, 2.56mmol)
81	(S)-피롤리딘-3-일메틸 (3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (416mg, 59%)	3',5'-디플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (500mg, 2.13mmol) (합성예 2)	(S)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이드 (516mg, 2.56mmol)
82	(S)-피롤린딘-3-일메틸 (5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (712mg, 51%)	5-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (1g, 4.63mmol) (합성예 20)	(S)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이드 (1,12g, 5.56mmol)
83	(S)-피롤린딘-3-일메틸 (5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 (260mg, 18%)	5-플루오로-3'-메틸-[1,1'-바이페닐]-2-카복실릭 애시드 (1g, 4.34mmol) (합성예 21)	(S)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이드 (1,05g, 5.21mmol)
84	(R)-피롤린딘-3-일메틸 (3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 (470mg, 67%)	3',5,5'-트리플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (500mg, 1.98mmol) (합성예 19)	(R)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이드 (479mg, 2.38mmol)
85	(S)-피롤린딘-3-일메틸 (3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 (400mg, 58%)	3',5,5'-트리플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (500mg, 1.98mmol) (합성예 19)	(S)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이드 (479mg, 2.38mmol)
86	(R)-피롤리딘-3-일메틸 (5-메틸-[1,1'-바이페닐]-2-일)카바메이트 (222mg, 25%)	5-메틸-[1,1'-바이페닐]-2-카복실릭 애시드 (600mg, 2.83mmol) (합성예 25)	(R)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이드 (684mg, 3.40mmol)

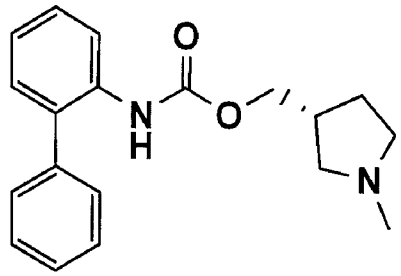
[575]

87	(R)-피롤리딘-3-일메틸 (3'-플루오로-5-메틸-[1,1'-바이페닐]-2-일)카바메이트 (346mg, 61%)	3'-플루오로-5-메틸-[1,1'-바이페닐]-2-카복실릭 애시드 (400mg, 1.74mmol) (합성예 26)	(R)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이드 (420mg, 2.09mmol)
88	(S)-피롤리딘-2-일메틸 (4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (915mg, 84%)	4'-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (750mg, 3.47mmol) (합성예 1)	(S)-tert-부틸 2-(히드록시메틸)피롤리딘-1-카복실레이드 (837mg, 4.16mmol)

[576]

[577] **[실시예 89] (R)-(1-메틸피롤리딘-3-일)메틸 [1,1'-바이페닐]-2-일카바메이트의 합성**

[578]



[579] (R)-피롤린딘-3-일메틸 [1,1'-바이페닐]-2-일카바메이트(727mg, 2.45mmol)(실시예 78)를 물(50mL)에 녹인 후, 아세틱애시드(1mL), 포름알데히드 용액(3mL), 징크 파우더 (300mg)를 순차적으로 가하고 상온에서 12시간 동안 교반하였다. 반응물을 여과한 후 2N-소듐히드록시드 용액으로 중화한 후 물과 디클로로메탄으로 추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(209mg, 28%)을 얻었다.

[580]

[581] **[실시예 90-99]**

[582] (R)-피롤린딘-3-일메틸 [1,1'-바이페닐]-2-일카바메이트 대신 [표 17]의 출발물질을 사용하여 실시예 89와 동일한 방법으로 실시예 90 내지 99의 화합물을 제조하였다.

[583] [표 17] 실시예 90-99

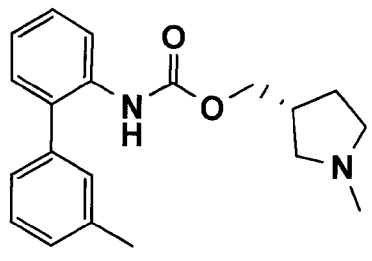
[584]

실시예	화학명	출발물질
90	(S)-(1-메틸피롤리딘-3-일)메틸 [1,1'-바이페닐]-2-일카바메이트 (285mg, 52%)	(S)-피롤린딘-3-일메틸 [1,1'-바이페닐]-2-일카바메이트 (523mg, 1.76mmol) (실시예 79)
91	(R)-(1-메틸피롤리딘-3-일)메틸 (3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (138mg, 33%)	(R)-피롤리딘-3-일메틸 (3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (400mg, 1.2mmol) (실시예 80)
92	(S)-(1-메틸피롤리딘-3-일)메틸 (3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (78mg, 19%)	(S)-피롤리딘-3-일메틸 (3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (377mg, 1.13mmol) (실시예 81)
93	(S)-(1-메틸피롤리딘-3-일)메틸 (5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (230mg, 67%)	(S)-피롤린딘-3-일메틸 (5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (330mg, 1.05mmol) (실시예 82)
94	(S)-(1-메틸피롤리딘-3-일)메틸 (5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 (24mg, 9%)	(S)-피롤린딘-3-일메틸 (5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 (260mg, 0.79mmol) (실시예 83)
95	(R)-(1-메틸피롤리딘-3-일)메틸 (3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 (58mg, 14%)	(R)-피롤린딘-3-일메틸 (3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 (400mg, 1.14mmol) (실시예 84)
96	(S)-(1-메틸피롤리딘-3-일)메틸 (3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 (144mg, 35%)	(S)-피롤린딘-3-일메틸 (3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 (400mg, 1.14mmol) (실시예 85)
97	(R)-(1-메틸피롤리딘-3-일)메틸 (5-메틸-[1,1'-바이페닐]-2-일)카바메이트 (24mg, 16%)	(R)-피롤리딘-3-일메틸 (5-메틸-[1,1'-바이페닐]-2-일)카바메이트 (145mg, 0.47mmol) (실시예 86)
98	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-플루오로-5-메틸-[1,1'-바이페닐]-2-일)카바메이트 (15mg, 5%)	(R)-피롤리딘-3-일메틸 (3'-플루오로-5-메틸-[1,1'-바이페닐]-2-일)카바메이트 (320mg, 0.97mmol) (실시예 87)
99	(S)-(1-메틸피롤리딘-2-일)메틸 (4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (87mg, 10%)	(S)-피롤리딘-2-일메틸 (4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (850mg, 2.70mmol) (실시예 88)

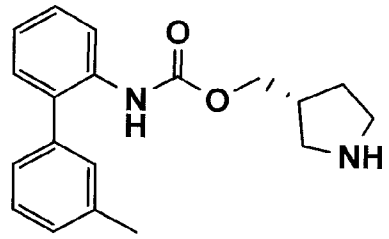
[585]

[586] **[실시예 100] (R)-(1-메틸피롤리딘-3-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[587]



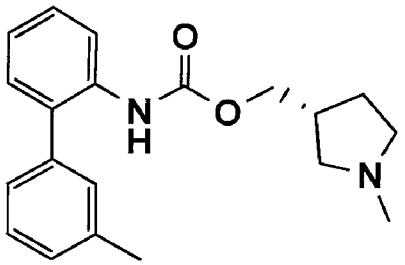
[588] [단계 1] (R)-피롤리딘-3-일메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트의 합성

[589] 

[590] 출발물질로 3'-메틸-[1,1'-바이페닐]-2-카복실릭 애시드(합성예 14)와 (R)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이트를 사용하여 실시예 78과 같은 방법으로 표제화합물을 얻었다.

[591] ^{1}H NMR($CDCl_3$): δ 8.13-7.97(bs, 1H), 7.41-7.28(m, 2H), 7.26-7.02(m, 5H), 6.77-6.62(bs, 1H), 4.13-3.92(m, 2H), 3.09-2.82(m, 3H), 2.72-2.49(m, 2H), 2.47-2.30(m, 4H), 1.97-1.81(m, 1H), 1.50-1.36(m, 1H)

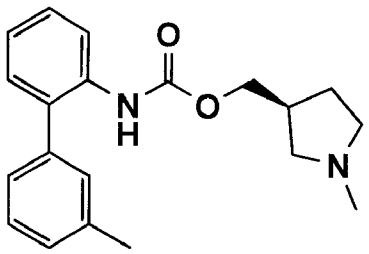
[592] [단계 2] (R)-(1-메틸피롤리딘-3-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트의 합성

[593] 

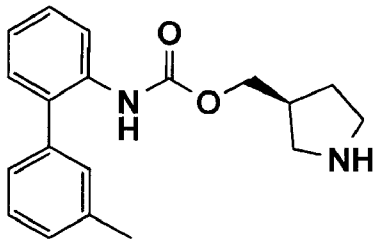
[594] 단계 1에서 제조된 (R)-피롤리딘-3-일메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트(600mg, 1.93mmol)를 사용하여 실시예 89와 같은 방법으로 표제화합물(30mg, 5%)을 얻었다.

[595]

[596] **[실시예 101] (S)-(1-메틸피롤리딘-3-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[597] 

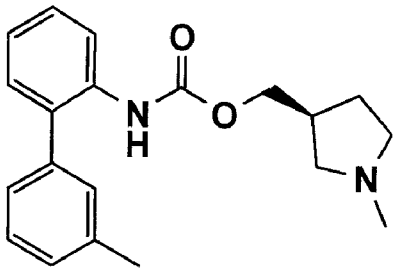
[598] [단계 1] (S)-피롤리딘-3-일메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트의 합성

[599] 

[600] 출발물질로 3'-메틸-[1,1'-바이페닐]-2-카복실릭 애시드(합성예 14)와 (S)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이트를 사용하여 실시예 78과 같은 방법으로 표제화합물을 얻었다.

[601] ^{1}H NMR($CDCl_3$): δ 8.15-7.99(bs, 1H), 7.45-7.29(m, 2H), 7,27-7.06(m, 5H), 6.74-6.59(bs, 1H), 4.15-3.92(m, 2H), 3.07-2.79(m, 4H), 2.69-2.57(m, 1H), 2.39(s, 3H), 2.07-1.92(bs, 1H) 1.92-1.79(m, 1H), 1.48-1.33(m, 1H)

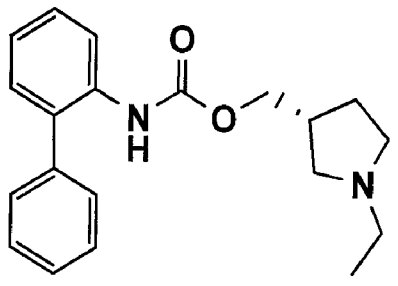
[602] [단계 2] (S)-(1-메틸피롤리딘-3-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트의 합성

[603] 

[604] 단계 1에서 제조된 (S)-피롤리딘-3-일메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트(900mg, 2.90mmol)를 사용하여 실시예 89와 같은 방법으로 표제화합물(208mg, 22%)을 얻었다.

[605]

[606] **[실시예 102] (R)-(1-에틸피롤리딘-3-일)메틸 [1,1'-바이페닐]-2-일카바메이트의 합성**

[607] 

[608] (R)-피롤린딘-3-일메틸 [1,1'-바이페닐]-2-일카바메이트(1g, 3.37mmol)(실시예 78)를 디메틸포름아미드(20mL)에 녹인 후, 포타슘카바메이트(652mg, 4.72mmol), 포타슘아이오다이드(112mg, 0.67mmol), 트리에틸아민(1.42mL, 10.11mmol), 아이오도에탄(323uL, 4.04mmol)을 순차적으로 가하고, 120℃에서 12시간 동안 교반하였다. 반응물의 온도를 상온으로 낮추고 물과 에틸아세테이트로

추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(142mg, 13%)을 얻었다.

[609]

[610] **[실시예 103-105]**

[611] (R)-피롤린딘-3-일메틸 [1,1'-바이페닐]-2-일카바메이트 대신 [표 18]의 출발물질을 사용하여 실시예 102와 동일한 방법으로 실시예 103-105의 화합물을 제조하였다.

[612] [표 18] 실시예 103-105

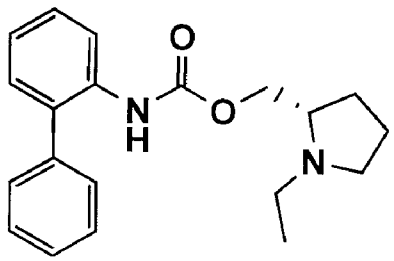
[613]

실시예	화학명	출발물질
103	(S)-(1-에틸피롤리딘-3-일)메틸 [1,1'-바이페닐]-2-일카바메이트 (89mg, 8%)	(S)-피롤린딘-3-일메틸 [1,1'-바이페닐]-2-일카바메이트 (1g, 3.37mmol) (실시예 79)
104	(R)-(1-에틸피롤리딘-3-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 (109mg, 16%)	(R)-피롤리딘-3-일메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 (623mg, 2.01mmol) (실시예 100, 단계 1)
105	(S)-(1-에틸피롤리딘-3-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 (40mg, 6%)	(S)-피롤리딘-3-일메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 (600mg, 1.93mmol) (실시예 101, 단계 1)

[614]

[615] **[실시예 106] (S)-(1-에틸피롤리딘-2-일)메틸 [1,1'-바이페닐]-2-일카바메이트의 합성**

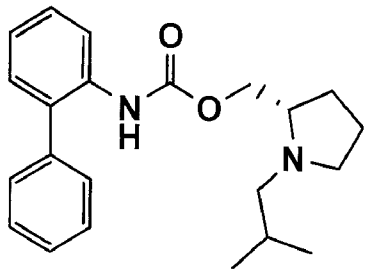
[616]



[617] 출발물질로 (S)-피롤리딘-2-일메틸 [1,1'-바이페닐]-2-일카바메이트(1g, 3.37mmol)와 2-아이오도에탄(323μL, 4.04mmol)을 사용하여 실시예 102와 같은 방법으로 표제화합물(385mg, 35%)을 얻었다.

[618]

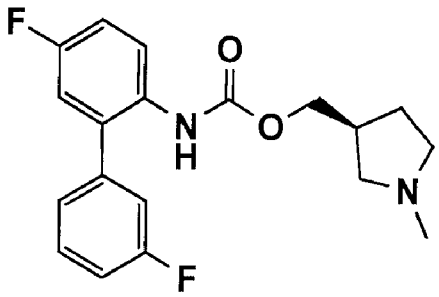
[619] **[실시예 107] (S)-(1-이소부틸피롤리딘-2-일)메틸 [1,1'-바이페닐]-2-일카바메이트의 합성**

[620] 

[621] 출발물질로 (S)-피롤리딘-2-일메틸 [1,1'-바이페닐]-2-일카바메이트(940mg, 3.17mmol)와 1-아이오도-2-메틸프로판(438μL, 3.08mmol)을 사용하여 실시예 102와 같은 방법으로 표제화합물(47mg, 4%)을 얻었다.

[622]

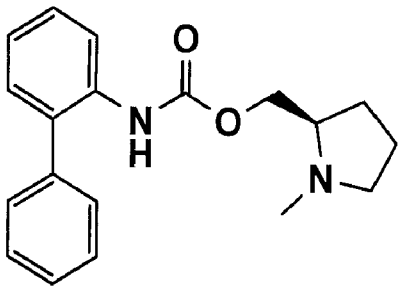
[623] **[실시예 108] (S)-(1-메틸피롤리딘-3-일)메틸 (3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[624] 

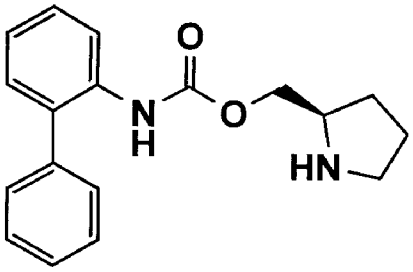
[625] 출발물질로 3',5-디플루오로-[1,1'-바이페닐]-2-카복실릭 애시드(800mg, 3.42mmol) (합성예 17)와 (S)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이트(825mg, 4.10mmol)를 사용하여 실시예 78 및 실시예 89와 같은 방법으로 표제화합물(50mg, 5%)을 얻었다.

[626]

[627] **[실시예 109] (R)-(1-메틸피롤리딘-2-일)메틸 [1,1'-바이페닐]-2-일카바메이트의 합성**

[628] 

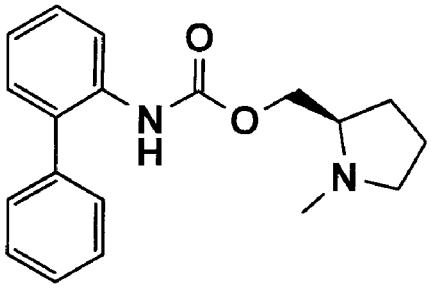
[629] [단계 1] (R)-피롤리딘-2-일메틸 [1,1'-바이페닐]-2-일카바메이트의 합성

[630] 

[631] 출발물질로 [1,1'-바이페닐]-2-카복실릭 애시드(821mg, 4.14mmol)와 (R)-tert-부틸 2-(히드록시메틸)피롤리딘-1-카복실레이트(1g, 4.97mmol)를 사용하여 실시예 78과 같은 방법으로 표제화합물(730mg, 60%)을 얻었다.

[632] ^{1}H NMR ($CDCl_3$): δ 8.09-8.08(m, 1H), 7.49-7.47(m, 1H), 7.29-7.26(m, 1H), 7.17(m, 1H), 6.92-6.89(m, 1H), 4.15-4.04(m, 2H), 3.12-3.08(m, 1H), 2.99-2.94(m, 2H), 2.74-2.72(m, 1H), 2.51-2.44(m, 1H), 1.98-1.89(m, 1H), 1.51-1.44(m, 1H)

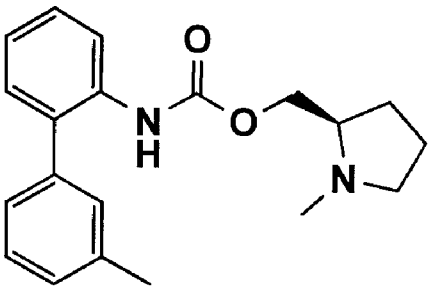
[633] [단계 2] (R)-(1-메틸피롤리딘-2-일)메틸 [1,1'-바이페닐]-2-일카바메이트의 합성

[634] 

[635] 출발물질로 (R)-피롤리딘-2-일메틸 [1,1'-바이페닐]-2-일카바메이트(730mg, 2.46mmol)를 사용하여 실시예 89와 같은 방법으로 표제화합물 (183mg, 24%)을 얻었다.

[636]

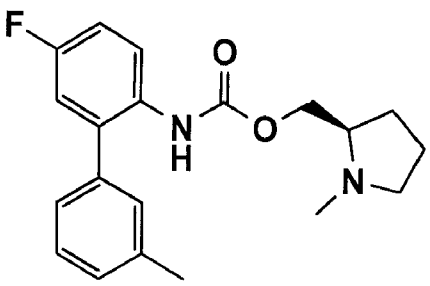
[637] **[실시예 110] (R)-(1-메틸피롤리딘-2-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[638] 

[639] 출발물질로 3'-메틸-[1,1'-바이페닐]-2-카복실릭 애시드(700mg, 3.3mmol)(합성예 14)와 (R)-tert-부틸 2-(히드록시메틸)피롤리딘-1-카복실레이트(797mg, 3.96mmol)를 사용하여 실시예 78 및 실시예 89와 같은 방법으로 표제화합물(258mg, 24%)을 얻었다.

[640]

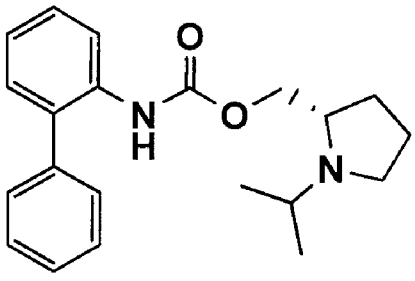
[641] **[실시예 111] (R)-(1-메틸피롤리딘-2-일)메틸 (5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[642] 

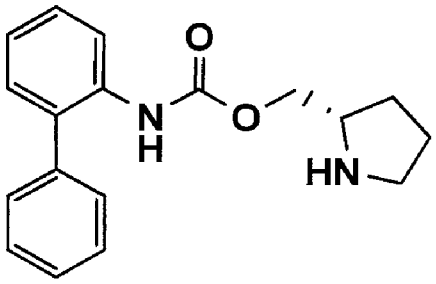
[643] 출발물질로 5-플루오로-3'-메틸-[1,1'-바이페닐]-2-카복실릭 애시드(1g, 4.34mmol)(합성예 21)와 (R)-tert-부틸 2-(히드록시메틸)피롤리딘-1-카복실레이트(1.05g, 5.21mmol)를 사용하여 실시예 78 및 실시예 89와 같은 방법으로 표제화합물(52mg, 4%)을 얻었다.

[644]

[645] **[실시예 112] (S)-(1-이소프로필피롤리딘-2-일)메틸 [1,1'-바이페닐]-2-일카바메이트의 합성**

[646] 

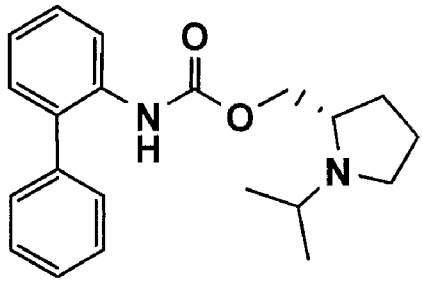
[647] [단계 1] (S)-피롤리딘-2-일메틸 [1,1'-바이페닐]-2-일카바메이트의 합성

[648] 

[649] 출발물질로 [1,1'-바이페닐]-2-카복실릭 애시드(2.5g, 12.61mmol)와 (S)-tert-부틸 2-(히드록시메틸)피롤리딘-1-카복실레이트(3.05g, 15.14mmol)을 사용하여 실시예 78과 같은 방법으로 표제화합물(3.06g, 82%)을 얻었다.

[650] ^{1}H NMR ($CDCl_3$) δ 7.88(m, 1H), 7.48-7.42(m, 1H), 7.15-7.05(m, 4H), 7.04-6.92(m, 1H), 6.40(s, 1H), 4.78-4.76(m, 1H), 3.23-3.21(m, 1H), 2.87-2.73(m, 4H), 2.06-2.05(m, 3H), 2.04-1.67(m, 1H), 1.66-1.54(m, 1H), 1.53-1.35(m, 1H)

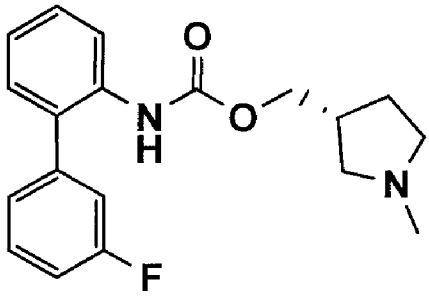
[651] [단계 2] (S)-(1-이소프로필피롤리딘-2-일)메틸 [1,1'-바이페닐]-2-일카바메이트의 합성

[652] 

[653] 출발물질로 (S)-피롤리딘-2-일메틸 [1,1'-바이페닐]-2-일카바메이트(1g, 3.37mmol)와 2-아이오도프로필(404μL, 4.04mmol)을 사용하여 실시예 102와 같은 방법으로 표제화합물(78mg, 7%)을 얻었다.

[654]

[655] **[실시예 113] (R)-(1-메틸피롤리딘-3-일)메틸 (3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[656] 

[657] (R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트(230mg, 0.73mmol)(합성예 F)를 에탄올(5mL)과 물(5mL) 혼합용액에 녹인 후 3-플루오로페닐보로닉 애시드(123mg, 0.88mmol), 포타슘카보네이트(203mg, 1.47mmol), 디(아세테이토)디씨클로헥시페닐포스핀팔라듐(II), Polymer-bound FibreCat™(30mg)을 가하였다. 반응물을 110℃에서 12시간 동안 교반한 후 온도를 상온으로 낮추고, 셀라이트 여과 후 감압 농축하여 용매를 제거하였다. 물과 디클로로메탄로 추출한 후 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(60mg, 25%)을 얻었다.

[658]

[659] **[실시예 114-115]**

[660] 반응물질로 3-플루오로페닐보로닉 애시드 대신 [표 19]를 사용하여 실시예 114-115의 화합물을 제조하였다.

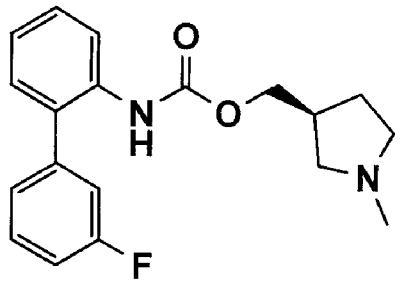
[661] [표 19] 실시예 114-115

[662]

실시예	화학명	출발물질 (합성예 F)	반응물질
114	(R)-(1-메틸피롤리딘-3-일)메틸 (4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (58mg, 24%)	230mg, 0.73mmol	4-플루오로페닐보로닉 애시드 (123mg, 0.88mmol)
115	(R)-(1-메틸피롤리딘-3-일)메틸 (3',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (132mg, 55%)	220mg, 0.70mmol	3,4-디플루오로페닐보로닉 애시드 (222mg, 1.40mmol)

[663] **[실시예 116] (S)-(1-메틸피롤리딘-3-일)메틸 (3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[664]



[665] (S)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트(200mg, 0.64mmol)(합성예 G)를 톨루엔 (10mL)에 녹인 후 3-플루오로페닐보로닉 애시드(179mg, 1.28mmol), 포타슘카보네이트(177mg, 1.28mmol), 테트라키스트리페닐포스핀팔라듐(74mg, 0.064mmol)을 가하였다. 반응물을 110℃에서 12시간 동안 교반한 후 온도를 상온으로 낮추고, 셀라이트 여과 후 감압 농축하여 용매를 제거하였다. 물과 디클로로메탄로 추출한 후 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(102mg, 49%)을 얻었다.

[666]

[667] **[실시예 117-129]**

[668] 출발물질 및 반응물질로 [표 20]를 사용하여 실시예 116과 동일한 방법으로 실시예 117-129의 화합물을 제조하였다.

[669] [표 20] 실시예 117-129

[670]

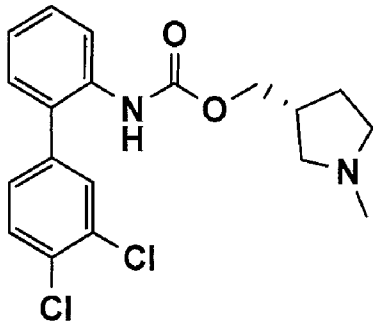
실시예	화학명	출발물질	반응물질
117	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-[1,1'-바이페닐]-2-일)카바메이트(160mg, 63%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트 (230mg, 0.73mmol) (합성예 F)	3-클로로페닐보로닉 애시드 (138mg, 0.88mmol)
118	(S)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-[1,1'-바이페닐]-2-일)카바메이트 (130mg, 39%)	(S)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트 (305mg, 0.97mmol) (합성예 G)	3-클로로페닐보로닉 애시드 (305mg, 1.95mmol)
119	(S)-(1-메틸피롤리딘-3-일)메틸 (3',5'-디클로로-[1,1'-바이페닐]-2-일)카바메이트 (170mg, 51%)	(S)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트 (274mg, 0.88mmol) (합성예 G)	3,5-디클로로페닐보로닉 애시드 (334mg, 1.75mmol)
120	(S)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (66mg, 18%)	(S)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트 (312mg, 1.00mmol) (합성예 G)	3-클로로-5-플루오로페닐보로닉 애시드 (348mg, 1.99mmol)
121	(S)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (107mg, 47%)	(S)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트 (200mg, 0.63mmol) (합성예 G)	(3-클로로-4-플루오로)페닐보로닉 애시드 (223mg, 1.28mmol)
122	(S)-(1-메틸피롤리딘-3-일)메틸 (5-플루오로-3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트 (160mg, 73%)	(S)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (190mg, 0.57mmol) (합성예 I)	3,5-디메틸페닐보로닉 애시드 (172mg, 1.15mmol)

[671]

123	(S)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5-플루오로-5'-히드록시-[1,1'-바이페닐]-2-일)카바메이트 (150mg, 64%)	(S)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (205mg, 0.62mmol) (합성예 I)	(3-클로로-5-히드록시페닐)보로닉 애시드 (213mg, 1.24mmol)
124	(S)-(1-메틸피롤리딘-3-일)메틸 (4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (78mg, 33%)	(S)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오르페닐)카바메이트 (225mg, 0.68mmol) (합성예 I)	4-플루오로페닐보로닉 애시드 (114mg, 0.82mmol)
125	(S)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (153mg, 64%)	(S)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (220mg, 0.66mmol) (합성예 I)	3-클로로페닐보로닉 애시드 (125mg, 0.80mmol)
126	(S)-(1-메틸피롤리딘-3-일)메틸 (3',5'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (74mg, 22%)	(S)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (280mg, 0.85mmol) (합성예 I)	3,5-디클로로페닐보로닉 애시드 (460mg, 1.69mmol)
127	(S)-(1-메틸피롤리딘-3-일)메틸 (4'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (37mg, 17%)	(S)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (195mg, 0.59mmol) (합성예 I)	4-클로로페닐보로닉 애시드 (111mg, 0.71mmol)
128	(S)-(1-메틸피롤리딘-3-일)메틸 (3',4'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (50mg, 19%)	(S)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (220mg, 0.66mmol) (합성예 I)	3,4-디클로로페닐보로닉 애시드 (152mg, 0.80mmol)
129	(S)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5,5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (130mg, 54%)	(S)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (210mg, 0.63mmol) (합성예 I)	(3-클로로-5-플루오로페닐)보로닉 애시드 (221mg, 1.27mmol)

[672]

[673] **[실시예 130] (R)-(1-메틸피롤리딘-3-일)메틸 (3',4'-디클로로-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[674] 

[675] (R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트(225mg, 0.72mmol)(합성예 F)를 에탄올(5mL)과 물(5mL)의 혼합용액에 녹인 후 3,4-디클로로페닐보로닉 애시드(274mg, 1.44mmol), 포타슘카보네이트(199mg, 1.44mmol), 테트라키스트리페닐포스핀팔라듐(83mg, 0.072mmol)을 가하였다. 반응물을 110℃에서 6시간 동안 교반한 후 온도를 상온으로 낮추고, 셀라이트 여과 후 감압 농축하여 용매를 제거하였다. 물과 디클로로메탄로 추출한 후 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(151mg, 56%)을 얻었다.

[676]

[677] **[실시예 131-135]**

[678] 출발물질 및 반응물질로 [표 21]를 사용하여 실시예 130과 동일한 방법으로 실시예 131-135의 화합물을 제조하였다.

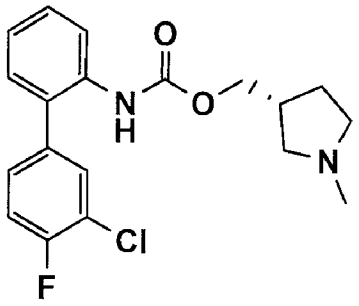
[679] [표 21] 실시예 131-135

[680]

실시예	화학명	출발물질	반응물질
131	(R)-(1-메틸피롤리딘-3-일)메틸 (3',5'-디클로로-[1,1'-바이페닐]-2-일)카바메이트 (101mg, 40%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트 (206mg, 0.66mmol) (합성예 F)	3,5-디클로로페닐보로닉 애시드 (251mg, 1.32mmol)
132	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5'-플루오로-[1,1'-바이페닐]-2-일)카바메이트	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트 (206mg, 0.66mmol) (합성예 F)	3-클로로-5-플루오로페닐보로닉 애시드 (251mg, 1.32mmol)
133	(R)-(1-메틸피롤리딘-3-일)메틸 (5-플루오로-3'-아미노-[1,1'-바이페닐]-2-일)카바메이트 (63mg, 28%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (215mg, 0.65mmol) (합성예 H)	3-아미노페닐보로닉 애시드 (178mg, 1.30mmol)
134	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5-플루오로-5'-히드록시-[1,1'-바이페닐]-2-일)카바메이트 (143mg, 53%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (236mg, 0.71mmol) (합성예 H)	(3-클로로-5-히드록시페닐)보로닉 애시드 (246mg, 1.43mmol)
135	(R)-(1-메틸피롤리딘-3-일)메틸 (3',5'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (65mg, 25%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (220mg, 0.66mmol) (합성예 H)	3,5-디클로로페닐보로닉 애시드 (254mg, 1.33mmol)

[681] **[실시예 136] (R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[682]



[683] (R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트(250mg, 0.80mmol)(합성예 F)를 아세토니트릴(6mL)과 물(6mL)의 혼합용액에 녹인 후 (3-클로로-4-플루오로페닐)보로닉애시드(279mg, 1.60mmol), 소듐카보네이트(170mg, 1.60mmol), 디클로로비스트리페닐포스핀 팔라듐(28mg, 0.04mmol)을 가하였다. 반응물을 Microwave oven에서 110℃로 30분간 교반한 후

온도를 상온으로 낮추고, 셀라이트 여과 후 감압 농축하여 용매를 제거하였다. 물과 디클로로메탄으로 추출한 후 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(23mg, 70%)을 얻었다.

[684]

[685] **[실시예 137-149]**

[686] 출발물질 및 반응물질로 [표 22]를 사용하여 실시예 136와 동일한 방법으로 실시예 137-149의 화합물을 제조하였다.

[687] [표 22] 실시예 137-149

[688]

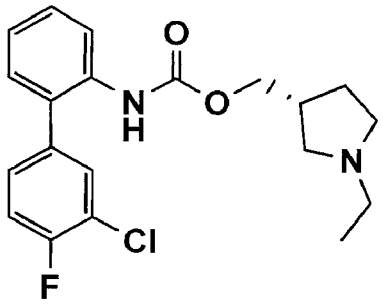
실시예	화학명	출발물질	반응물질
137	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-히드록시-[1,1'-바이페닐]-2-일)카바메이트 (156mg, 65%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트 (230mg, 0.73mmol) (합성예 F)	3-히드록시페닐보로닉 애시드 (111mg, 0.81mmol)
138	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 (208mg, 43%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트 (365mg, 0.17mmol) (합성예 F)	(3-클로로-5-(트리플루오로메틸)페닐)보로닉 애시드 (523mg, 2.33mmol)
139	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5-플루오로-5'-메톡시-[1,1'-바이페닐]-2-일)카바메이트 (184mg, 73%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (213mg, 0.64mmol) (합성예 H)	(3-클로로-5-메톡시페닐)보로닉 애시드 (240mg, 1.29mmol)
140	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5-플루오로-5'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 (135mg, 47%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (227mg, 0.69mmol) (합성예 H)	(3-클로로-5-(트리플루오로메틸)페닐)보로닉 애시드 (307mg, 1.37mmol)
141	(R)-(1-메틸피롤리딘-3-일)메틸 (4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (208mg, 62%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (320mg, 0.97mmol) (합성예 H)	4-플루오로페닐보로닉 애시드 (270mg, 1.93mmol)
142	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5,5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (108mg, 42%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (226mg, 0.68mmol) (합성예 H)	(3-클로로-5-플루오로페닐)보로닉 애시드 (238mg, 1.37mmol)

[689]

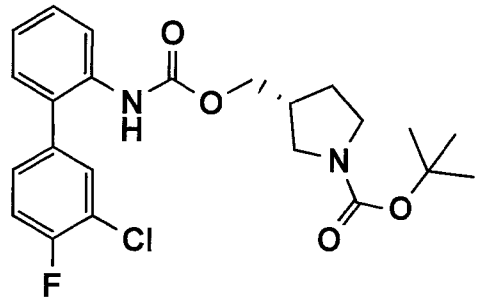
143	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (150mg, 54%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (240mg, 0.73mmol) (합성예 H)	(3-클로로-4-플루오로페닐)보로닉 애시드 (253mg, 1.45mmol)
144	(R)-(1-메틸피롤리딘-3-일)메틸 (2',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (134mg, 43%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (300mg, 0.91mmol) (합성예 H)	2-플루오로페닐 보로닉애시드 (254mg, 1.812mmol)
145	(R)-(1-메틸피롤리딘-3-일)메틸 (3',5-디클로로-[1,1'-바이페닐]-2-일)카바메이트 (69mg, 22%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-클로로페닐)카바메이트 (290mg, 0.84mmol) (합성예 J)	3-클로로페닐보로닉 애시드 (197mg, 1.26mmol)
146	(R)-(1-메틸피롤리딘-3-일)메틸 (3',5-디클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-클로로페닐)카바메이트 (300mg, 0.84mmol) (합성예 J)	(3-클로로-4-플루오로페닐)보로닉 애시드 (300mg, 1.72mmol)
147	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-4'-플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-메톡시페닐)카바메이트 (270mg, 0.78mmol) (합성예 K)	(3-클로로-4-플루오로페닐)보로닉 애시드 (274mg, 1.57mmol)
148	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-5'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (150mg, 65%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐)카바메이트 (200mg, 0.64mmol) (합성예 M)	(3-클로로-5-플루오로페닐)보로닉 애시드 (223mg, 1.28)
149	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (151mg, 26%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐)카바메이트 (500mg, 1.59mmol) (합성예 M)	(3-클로로-4-플루오로페닐)보로닉 애시드 (555mg, 3.18mmol)

[690]

[691] **[실시예 150] (R)-(1-에틸피롤리딘-3-일)메틸 (3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[692] 

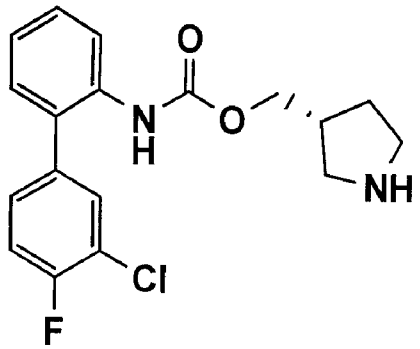
[693] [단계 1] (R)-tert-부틸 3-((((3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바모일)옥시)메틸)피롤리딘-1-카복실레이트의 합성

[694] 

[695] 출발물질로 (R)-tert-부틸 3-((((2-브로모페닐)카바모일)옥시)메틸)피롤리딘-1-카복실레이트(4g, 10.02mmol)(합성예 F, 단계 1)와 (3-클로로-4-플루오로)페닐보로닉 애시드(3.5g, 20.04mmol)를 사용하여 실시예 42와 같은 방법으로 표제화합물(3.4g, 76%)을 얻었다.

[696] ^{1}H NMR ($CDCl_3$): δ 8.01(s, 1H), 7.41-7.35(m, 2H), 7.31-7.22(m, 2H), 7.20-7.13(m, 2H), 6.34(s, 1H), 4.15-4.07(m, 2H), 3.48-3.29(m, 3H), 3.15-2.99(s, 1H), 2.51-2.48(m, 1H), 1.98-1.94(m, 1H), 1.44-1.38(m, 10H)

[697] [단계 2] (R)-피롤리딘-3-일메틸 (3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트의 합성

[698] 

[699] 출발물질로 단계 1에서 제조된 (R)-tert-부틸 3-((((3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바모일)옥시)메틸)피롤리딘-1-카복실레이트(3.4g, 7.57mmol)을 사용하여 실시예 78과 같은 방법으로

표제화합물(2.3g, 87%)을 얻었다.

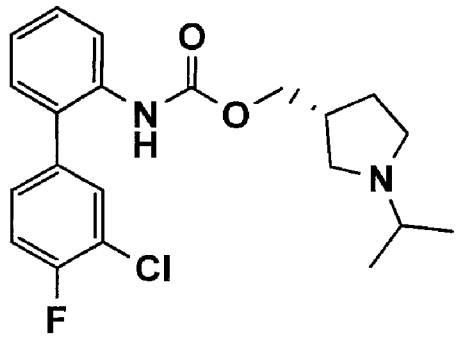
[700] ^{1}H NMR ($CDCl_3$): δ 7.98(s, 1H), 7.41-7.34(m, 2H), 7.23-7.17(m, 2H), 7.16-7.11(m, 2H), 6.55(s, 1H), 4.10-4.01(m, 2H), 3.99-2.86(m, 3H), 2.70-2.66(s, 1H), 2.45-2.39(m, 1H), 1.95-1.86 (m, 1H), 1.47-1.41(m, 1H)

[701] [단계 3] (R)-피롤리딘-3-일메틸 (3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트의 합성

[702] 단계 2에서 제조된 (R)-피롤리딘-3-일메틸 (3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트(345mg, 0.99mmol)를 테트라히드로퓨란(20mL)에 녹인 후, 트리에틸아민(150μL, 1.09mmol), 브로모에탄(118μL, 1.58mmol)을 순차적으로 가하고, 실온에서 3일 동안 교반하였다. 반응물을 감압 농축한 후, 물과 디클로로메탄으로 추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(74mg, 20%)을 얻었다.

[703]

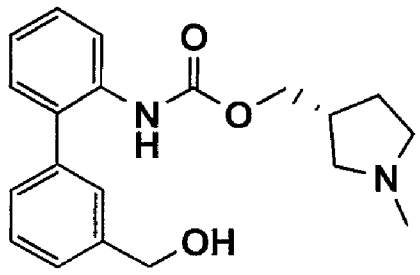
[704] **[실시예 151] (R)-(1-이소프로필피롤리딘-3-일)메틸 (3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[705] 

[706] (R)-피롤리딘-3-일메틸 (3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트(347mg, 1.00mmol)(실시예 150, 단계 2)를 테트라히드로퓨란(20mL)에 녹인 후, 트리에틸아민(150μL, 1.10mmol), 2-브로모프로판(100μL, 1.10mmol)을 순차적으로 가하고, 실온에서 3일 동안 교반하였다. 반응물을 감압 농축한 후, 물과 디클로로메탄으로 추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(17mg, 4%)을 얻었다.

[707]

[708] **[실시예 152] (R)-(1-메틸피롤리딘-3-일)메틸 (3'-(히드록시메틸)-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[709] 

[710] (R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트 (395mg, 1.26mmol)(합성예 F)를 톨루엔(15mL)과 에탄올(2mL) 혼합용액에 녹인 후 3-(히드록시메틸)페닐 보로닉애시드(211mg, 1.39mmol), 포타슘카보네이트 (348mg, 2.52mmol), 테트라키스트리페닐포스핀팔라듐(146mg, 0.13mmol)을 가하였다. 반응물을 110℃에서 12시간 동안 교반한 후 온도를 상온으로 낮추고, 셀라이트 여과 후 감압 농축하여 용매를 제거하였다. 물과 디클로로메탄으로 추출한 후 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(126mg, 29%)을 얻었다.

[711]

[712] **[실시예 153-190]**

[713] 출발물질 및 반응물질로 [표 23]를 사용하여 실시예 152과 동일한 방법으로 실시예 153-190의 화합물을 제조하였다.

[714] [표 23] 실시예 153-190

[715]

실시예	화학명	출발물질	반응물질
153	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-카바모일-[1,1'-바이페닐]-2-일)카바메이트 (125mg, 28%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트 (395mg, 1.26mmol) (합성예 F)	(3-카바모일페닐)보로닉 애시드(229mg, 1.39mmol)
154	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-아미노-[1,1'-바이페닐]-2-일)카바메이트 (102mg, 45%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트 (220mg, 0.70mmol) (합성예 F)	3-아미노페닐보로닉 애시드 (115mg, 0.84mmol)
155	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-시아노-[1,1'-바이페닐]-2-일)카바메이트 (77mg, 34%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트 (210mg, 0.67mmol) (합성예 F)	3-시아노페닐보로닉 애시드 (118mg, 0.80mmol)
156	(R)-(1-메틸피롤리딘-3-일)메틸 (2'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (210mg, 67%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트 (300mg, 0.958mmol) (합성예 F)	2-플루오로페닐 보로닉애시드 (201mg, 1.437mmol)
157	(R)-(1-메틸피롤리딘-3-일)메틸 (2',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (115mg, 52%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트 (200mg, 0.639mmol) (합성예 F)	2,4-디플루오로페닐 보로닉애시드 (202mg, 1.277mmol)
158	(R)-(1-메틸피롤리딘-3-일)메틸 (2',3'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (145mg, 66%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트 (200mg, 0.639mmol) (합성예 F)	2,3-디플루오로페닐 보로닉애시드 (202mg, 1.277mmol)

[716]

159	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-6'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (130mg, 56%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐) 카바메이트 (200mg, 0.639mmol) (합성예 F)	3-클로로-6-플루오로페닐보로닉애시드 (223mg, 1.277mmol)
160	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-플루오로-[1,1'-바이페닐]-2-일) 카바메이트 (183mg, 87%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐) 카바메이트 (200mg, 0.64mmol) (합성예 M)	3-플루오로페닐보로닉 애시드 (107mg, 0.77mmol)
161	(S)-(1-메틸피롤리딘-2-일)메틸 (3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (163mg, 74%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐) 카바메이트 (200mg, 0.64mmol) (합성예 M)	3,5-디플루오로페닐보로닉 애시드 (121mg, 0.77mmol)
162	(S)-(1-메틸피롤리딘-2-일)메틸 (3',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (105mg, 95%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐) 카바메이트 (100mg, 0.32mmol) (합성예 M)	3,4-디플루오로페닐보로닉 애시드 (101mg, 0.64mmol)
163	(S)-(1-메틸피롤리딘-2-일)메틸 (2',4',5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 (79mg, 68%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐) 카바메이트 (100mg, 0.32mmol) (합성예 M)	2,4,5-트리플루오로페닐보로닉 애시드 (113mg, 0.64mmol)
164	(S)-(1-메틸피롤리딘-2-일)메틸 (4'-클로로-[1,1'-바이페닐]-2-일) 카바메이트 (103mg, 94%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐) 카바메이트 (100mg, 0.32mmol) (합성예 M)	4-클로로페닐보로닉 애시드 (100mg, 0.64mmol)
165	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-[1,1'-바이페닐]-2-일) 카바메이트 (70mg, 64%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐) 카바메이트 (100mg, 0.32mmol) (합성예 M)	3-클로로페닐보로닉 애시드 (100mg, 0.64mmol)

[717]

166	(S)-(1-메틸피롤리딘-2-일)메틸 (3',4'-디클로로-[1,1'-바이페닐]-2-일)카바메이트 (96mg, 79%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐) 카바메이트 (100mg, 0.32mmol) (합성예 M)	3,4-디클로로페닐보로닉 애시드(122mg, 0.64mmol)
167	(S)-(1-메틸피롤리딘-2-일)메틸 (2',4'-디클로로-[1,1'-바이페닐]-2-일)카바메이트 (83mg, 69%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐) 카바메이트 (100mg, 0.32mmol) (합성예 M)	2,4-디클로로페닐보로닉 애시드(122mg, 0.64mmol)
168	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-히드록시-[1,1'-바이페닐]-2-일) 카바메이트 (160mg, 77%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐) 카바메이트 (200mg, 0.64mmol) (합성예 M)	3-히드록시페닐보로닉 애시드 (106mg, 0.77mmol)
169	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-시아노-[1,1'-바이페닐]-2-일) 카바메이트 (17mg, 13%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐) 카바메이트 (200mg, 0.64mmol) (합성예 M)	3-시아노페닐보로닉 애시드 (113mg, 0.77mmol)
170	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-아미노-[1,1'-바이페닐]-2-일) 카바메이트 (78mg, 38%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐) 카바메이트 (200mg, 0.64mmol) (합성예 M)	3-아미노페닐보로닉 애시드 (105mg, 0.77mmol)
171	(S)-(1-메틸피롤리딘-2-일)메틸 (3',4',5-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 (88mg, 81%)	(S) (1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (100mg, 0.30mmol) (합성예 N)	3,4-디플루오로페닐보로닉 애시드 (95mg, 0.60mmol)
172	(S)-(1-메틸피롤리딘-2-일)메틸 (3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 (180mg, 83%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (200mg, 0.60mmol) (합성예 N)	3,5-디플루오로페닐보로닉 애시드 (190mg, 1.20mmol)

[718]

173	(S)-(1-메틸피롤리딘-2-일)메틸 (2',4',5,5'-테트라플루오로-[1,1'-바이페닐]-2-일)카바메이트 (188mg, 82%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (200mg, 0.60mmol) (합성예 N)	2,4,5-트리플루오로페닐보로닉 애시드 (211mg, 1.20mmol)
174	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (171mg, 79%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (200mg, 0.60mmol) (합성예 N)	3-클로로페닐보로닉 애시드 (188mg, 1.20mmol)
175	(S)-(1-메틸피롤리딘-2-일)메틸 (4'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (198mg, 91%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (200mg, 0.60mmol) (합성예 N)	4-클로로페닐보로닉 애시드 (188mg, 1.20mmol)
176	(S)-(1-메틸피롤리딘-2-일)메틸 (2',4'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (146mg, 61%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (200mg, 0.60mmol) (합성예 N)	2,4-디클로로페닐보로닉 애시드(230mg, 1.20mmol)
177	(S)-(1-메틸피롤리딘-2-일)메틸 (3',4'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (76mg, 64%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (100mg, 0.30mmol) (합성예 N)	3,4-디클로로페닐보로닉 애시드(115mg, 0.60mmol)
178	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-시아노-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (117mg, 55%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (200mg, 0.60mmol) (합성예 N)	3-시아노페닐보로닉 애시드 (176mg, 1.20mmol)
179	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-히드록시-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (66mg, 64%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (100mg, 0.30mmol) (합성예 N)	3-히드록시페닐보로닉 애시드 (83mg, 0.60mmol)

[719]

180	(S)-(1-메틸피롤리딘-2-일)메틸 (5-플루오로-3'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 (43mg, 36%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (100mg, 0.30mmol) (합성예 N)	3-(트리플루오로메틸)페닐보로닉 애시드 (115mg, 0.60mmol)
181	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-4,4',5-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트 (57mg, 25%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4,5-디플루오로페닐)카바메이트 (200mg, 0.57mmol) (합성예 P)	3-클로로-4-플루오로페닐보로닉애시드 (200mg, 1.15mmol)
182	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-4,5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (50mg, 25%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4,5-디플루오로페닐)카바메이트 (180mg, 1.52mmol) (합성예 L)	3-클로로페닐 보로닉애시드 (161mg, 1.03mmol)
183	2-(1-메틸피롤리딘-2-일)에틸 (2',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (50mg, 15%)	2-(1-메틸피롤리딘-2-일)에틸 (2-아이오도페닐)카바메이트 (300mg, 0.917mmol) (합성예 A)	2,4-디플루오로페닐 보로닉애시드 (290mg, 1.834mmol)
184	2-(1-메틸피롤리딘-2-일)에틸 (2',3'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (50mg, 15%)	2-(1-메틸피롤리딘-2-일)에틸 (2-아이오도페닐)카바메이트 (300mg, 0.917mmol) (합성예 A)	2,3-디플루오로페닐 보로닉애시드 (290mg, 1.834mmol)
185	2-(1-메틸피롤리딘-2-일)에틸 (2',6'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (50mg, 15%)	2-(1-메틸피롤리딘-2-일)에틸 (2-아이오도페닐)카바메이트 (300mg, 0.917mmol) (합성예 A)	2,6-디플루오로페닐 보로닉애시드 (290mg, 1.834mmol)
186	2-(1-메틸피롤리딘-2-일)에틸 (5'-클로로-2'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (160mg, 46%)	2-(1-메틸피롤리딘-2-일)에틸 (2-아이오도페닐)카바메이트 (300mg, 0.917mmol) (합성예 A)	5-클로로-2-플루오로페닐 보로닉애시드 (320mg, 1.834mmol)

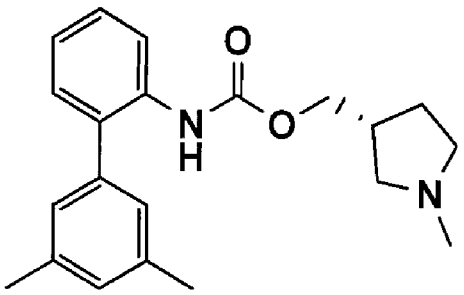
[720]

187	(S)-(1-메틸피롤리딘-2-일)메틸 (2'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (205mg, 65%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐)카바메이트 (300mg, 0.958mmol) (합성예 M)	2-플루오로페닐 보로닉애시드 (268mg, 1.916mmol)
188	(S)-(1-메틸피롤리딘-2-일)메틸 (2',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (250mg, 75%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐)카바메이트 (300mg, 0.958mmol) (합성예 M)	2,4-디플루오로페닐 보로닉애시드 (303mg, 1.916mmol)
189	(S)-(1-메틸피롤리딘-2-일)메틸 (2',3'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (100mg, 30%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐)카바메이트 (300mg, 0.958mmol) (합성예 M)	2,3-디플루오로페닐 보로닉애시드 (303mg, 1.916mmol)
190	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-6'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (150mg, 43%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모페닐)카바메이트 (300mg, 0.958mmol) (합성예 M)	3-클로로-6-플루오로페닐 보로닉애시드 (334mg, 1.916mmol)

[721]

[722] **[실시예 191] (R)-(1-메틸피롤리딘-3-일)메틸 (3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[723]



[724] (R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모페닐)카바메이트(220mg, 0.70mmol)(합성예 F)를 에탄올(5mL)과 물(5mL)의 혼합용액에 녹인 후 3,5-디메틸페닐보로닉 애시드(211mg, 1.41mmol), 포타슘카보네이트(194mg, 1.41mmol), 디(아세테이토)디씨클로헥시페닐포스핀팔라듐(II), Polymer-bound FibreCat™(28mg)을 가하였다. 반응물을 Microwave oven에서 110℃로 30분간 교반한 후 온도를 상온으로 낮추고, 셀라이트 여과 후 감압 농축하여 용매를 제거하였다. 물과 디클로로메탄로 추출한 후 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여

표제화합물(134mg, 56%)을 얻었다.

[725]

[726] **[실시예 192-195]**

[727] 출발물질 및 반응물질로 [표 24]를 사용하여 실시예 191과 동일한 방법으로 실시예 192-195의 화합물을 제조하였다.

[728] [표 24] 실시예 192-195

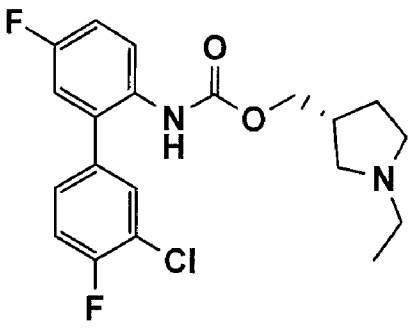
[729]

실시예	화학명	출발물질	반응물질
192	(R)-(1-메틸피롤리딘-3-일)메틸 (5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 (158mg, 73%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (210mg, 0.63mmol) (합성예 H)	3-메틸페닐보로닉 에시드 (172mg, 1.27mmol)
193	(R)-(1-메틸피롤리딘-3-일)메틸 (5-플루오로-3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트 (82mg, 39%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (206mg, 0.62mmol) (합성예 H)	3,5-디메틸페닐보로닉 에시드 (187mg, 1.24mmol)
194	(R)-(1-메틸피롤리딘-3-일)메틸 (3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (124mg, 55%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (215mg, 0.65mmol) (합성예 H)	3-플루오로페닐보로닉 에시드 (182mg, 1.30mmol)
195	(R)-(1-메틸피롤리딘-3-일)메틸 (3'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (151mg, 66%)	(R)-(1-메틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (210mg, 0.63mmol) (합성예 H)	3-클로로페닐보로닉 에시드 (198mg, 1.27mmol)

[730]

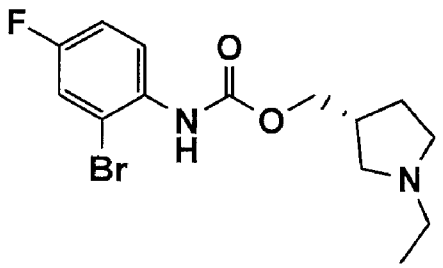
[731] **[실시예 196] (R)-(1-에틸피롤리딘-3-일)메틸 (3'-클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[732]



[733] [단계 1] (R)-(1-에틸피롤리딘-3-일)메틸

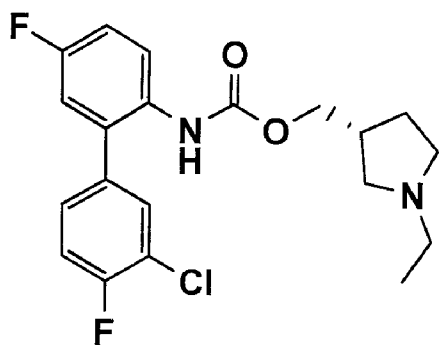
(2-브로모-4-플루오로페닐)카바메이트의 합성

[734] 

[735] 출발물질로 2-브로모-4-플루오로벤조익 애시드(3g, 13.70mmol)와 (R)-tert-부틸 3-(히드록시메틸)피롤리딘-1-카복실레이트(3.31g, 16.44mmol)를 사용하여 합성예 F와 같은 방법으로 표제화합물(4.5g, 79%)을 얻었다.

[736] ^{1}H NMR ($CDCl_3$): δ 8.00(s, 1H), 7.28-7.24(m, 1H), 7.05-7.00(m, 1H), 4.21-4.10(m, 2H), 3.06-3.03(m, 1H), 2.90-2.87(m, 1H), 2.84-2.71(m, 5H), 2.17-2.12(m, 1H), 1.76-1.71(m, 1H), 1.24(t, 3H, J=7.2)

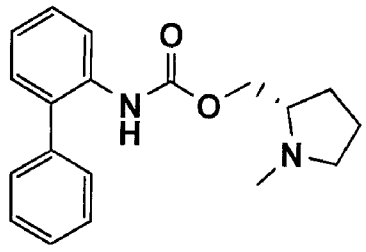
[737] [단계 2] (R)-(1-에틸피롤리딘-3-일)메틸 (3'-클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트의 합성

[738] 

[739] 출발물질로 (R)-(1-에틸피롤리딘-3-일)메틸 (2-브로모-4-플루오로페닐)카바메이트(165mg, 0.48mmol)와 (3-클로로-4-플루오로페닐)보로닉 애시드(167mg, 0.96mmol)를 사용하여 실시예 136과 같은 방법으로 표제화합물(143mg, 76%)을 얻었다.

[740]

[741] **[실시예 197] (S)-(1-메틸피롤리딘-2-일)메틸 [1,1'-바이페닐]-2-일카바메이트의 합성**

[742] 

[743] [1,1'-바이페닐]-2-카복실릭 애시드(1g, 5.05mmol)를 톨루엔(20mL)에 녹인 후 바이페닐포스포릴 아지드(1.4mL, 6.05mmol)과 트리에틸아민(0.71mL,

5.05mmol)을 가하였다. 상온에서 30분간 교반한 후 다시 1시간 동안 환류교반하였다. 반응물의 온도를 상온으로 낮추고 (S)-(1-메틸피롤리딘-2-일)메탄올(0.72mL, 6.05mmol)을 가한 후 12시간 동안 환류교반하였다. 반응물의 온도를 상온으로 낮추고, 감압 농축하여 용매를 제거한 후 물과 에틸아세테이트로 추출하였다. 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(458mg, 29%)을 얻었다.

[744]

[745] **[실시예 198-207]**

[746] 출발물질 및 반응물질로 [표 25]를 사용하여 실시예 197과 동일한 방법으로 실시예 198-207의 화합물을 제조하였다.

[747] [표 25] 실시예 198-207

[748]

실시예	화학명	출발물질	반응물질
198	(S)-(1-메틸피롤리딘-2-일)메틸 (4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (97mg, 13%)	4'-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (482mg, 2.23mmol) (합성예 1)	(S)-(1-메틸피롤리딘-2-일)메탄올 (318uL, 2.68mmol)
199	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 (379mg, 51%)	3'-메틸-[1,1'-바이페닐]-2-카복실릭 애시드 (488mg, 2.3mmol) (합성예 14)	(S)-(1-메틸피롤리딘-2-일)메탄올 (328uL, 2.76mmol)
200	(S)-(1-메틸피롤리딘-2-일)메틸 (5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (42mg, 7%)	5-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (400mg, 1.85mmol) (합성예 20)	(S)-(1-메틸피롤리딘-2-일)메탄올 (0.26mL, 2.22mmol)
201	(S)-(1-메틸피롤리딘-2-일)메틸 (5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트 (98mg, 14%)	5-플루오로-3'-메틸-[1,1'-바이페닐]-2-카복실릭 애시드 (460mg, 2.0mmol) (합성예 21)	(S)-(1-메틸피롤리딘-2-일)메탄올 (0.29mL, 2.4mmol)
202	(S)-(1-메틸피롤리딘-2-일)메틸 (3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (280mg, 47%)	3',5-디플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (400mg, 1.71mmol) (합성예 17)	(S)-(1-메틸피롤리딘-2-일)메탄올 (0.24mL, 2.05mmol)
203	(S)-(1-메틸피롤리딘-2-일)메틸 (4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (312mg, 53%)	4',5-디플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (400mg, 1.71mmol) (합성예 18)	(S)-(1-메틸피롤리딘-2-일)메탄올 (0.24mL, 2.05mmol)
204	(S)-(1-메틸피롤리딘-2-일)메틸 (4-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (140mg, 51%)	4-플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (180mg, 0.83mmol) (합성예 22)	(S)-(1-메틸피롤리딘-2-일)메탄올 (0.12mL, 1.0mmol)

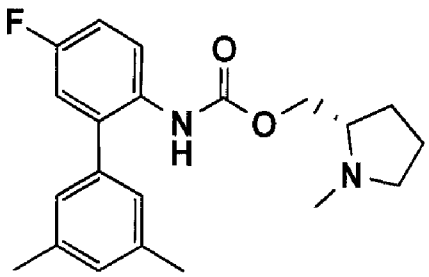
[749]

205	(S)-(1-메틸피롤리딘-2-일)메틸 (3',4-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (200mg, 34%)	3',4-디플루오로-[1,1'-바이페닐]-2-카복실릭 애시드 (400mg, 1.71mmol) (합성예 23)	(S)-(1-메틸피롤리딘-2-일)메탄올 (0.24mL, 2.05mmol)
206	(S)-(1-메틸피롤리딘-2-일)메틸 (5-메틸-[1,1'-바이페닐]-2-일)카바메이트 (189mg, 41%)	5-메틸-[1,1'-바이페닐]-2-카복실릭 애시드 (300mg, 1.41mmol) (합성예 25)	(S)-(1-메틸피롤리딘-2-일)메탄올 (201uL, 1.7mmol)
207	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-플루오로-5-메틸-[1,1'-바이페닐]-2-일)카바메이트 (265mg, 89%)	3'-플루오로-5-메틸-[1,1'-바이페닐]-2-카복실릭 애시드 (200mg, 0.87mmol) (합성예 26)	(S)-(1-메틸피롤리딘-2-일)메탄올 (124uL, 1.04mmol)

[750]

[751] **[실시예 208] (S)-(1-메틸피롤리딘-2-일)메틸 (5-플루오로-3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트의 합성**

[752]



[753] (S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트(200mg, 0.60mmol)(합성예 N)를 아세토니트릴(3mL)과 물(3mL)의 혼합용액에 녹인 후 3,5-디메틸페닐보로닉 애시드(181mg, 1.20mmol), 소듐카보네이트(95mg, 0.90mmol), 디클로로비스트리페닐포스핀 팔라듐(2mg, 0.003mmol)을 가하였다. 반응물을 Microwave oven에서 150℃로 10분간 교반한 후 온도를 상온으로 낮추고, 셀라이트 여과 후 감압 농축하여 용매를 제거하였다. 물과 에틸아세테이트로 추출한 후 유기층을 무수 황산마그네슘으로 건조하고, 여과, 농축하여 얻어진 잔류물을 컬럼크로마토그래피로 정제하여 표제화합물(98mg, 46%)을 얻었다.

[754]

[755] **[실시예 209-226]**

[756] 출발물질 및 반응물질로 [표 26]의 물질을 사용하여 실시예 208과 동일한 방법으로 실시예 209-226의 화합물을 제조하였다.

[757] [표 26] 실시예 209-226

[758]

실시예	화학명	출발물질	반응물질
209	(S)-(1-메틸피롤리딘-2-일)메틸 (4'-(tert-부틸)-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (68mg, 30%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (200mg, 0.60mmol) (합성예 N)	4-tert-부틸페닐보로닉 에시드 (213mg, 1.20mmol)
210	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-5,5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (55mg, 32%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (150mg, 0.45mmol) (합성예 N)	(3-클로로-5-플루오로)페닐보로닉 에시드 (158mg, 0.90mmol)
211	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (56mg, 16%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (300mg, 0.91mmol) (합성예 N)	(3-클로로-4-플루오로)페닐보로닉 에시드 (316mg, 1.81mmol)
212	(S)-(1-메틸피롤리딘-2-일)메틸 (4'-클로로-3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트 (140mg, 40%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (300mg, 0.91mmol) (합성예 N)	(3-플루오로-4-클로로)페닐보로닉 에시드 (316mg, 1.81mmol)
213	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-아미노-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (46mg, 45%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (150mg, 0.45mmol) (합성예 N)	3-아미노페닐보로닉 에시드 (68mg, 0.50mmol)
214	(S)-(1-메틸피롤리딘-2-일)메틸 (2',5-디플루오로-3'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 (17mg, 10%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (150mg, 0.45mmol) (합성예 N)	(2-플루오로-3-(트리플루오로메틸)페닐)보로닉 에시드 (187mg, 0.90mmol)

[759]

215	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-5-플루오로-5'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 (80mg, 41%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (150mg, 0.45mmol) (합성예 N)	(3-클로로-5-(트리플루오로메틸)페닐)보로닉 애시드 (202mg, 0.90mmol)
216	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-5-플루오로-5'-히드록시-[1,1'-바이페닐]-2-일)카바메이트 (35mg, 24%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (130mg, 0.39mmol) (합성예 N)	(3-클로로-5-히드록시페닐)보로닉 애시드 (135mg, 0.79mmol)
217	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-5-플루오로-5'-메톡시-[1,1'-바이페닐]-2-일)카바메이트 (55mg, 31%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (150mg, 0.45mmol) (합성예 N)	(3-클로로-5-메톡시페닐)보로닉 애시드 (168mg, 0.90mmol)
218	(S)-(1-메틸피롤리딘-2-일)메틸 (5-플루오로-2',4'-비스(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트 (85mg, 41%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (150mg, 0.45mmol) (합성예 N)	(2,4-비스(트리플루오로메틸)페닐)보로닉 애시드 (230mg, 0.90mmol)
219	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-에톡시-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트 (94mg, 42%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (200mg, 0.60mmol) (합성예 N)	3-에톡시페닐보로닉 애시드 (200mg, 1.20mmol)
220	(S)-(1-메틸피롤리딘-2-일)메틸 (5-플루오로-3',4'-디메톡시-[1,1'-바이페닐]-2-일)카바메이트 (54mg, 23%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (200mg, 0.60mmol) (합성예 N)	3,4-디메톡시페닐보로닉 애시드 (218mg, 1.20mmol)

[760]

221	(S)-(1-메틸피롤리딘-2-일)메틸 (5-플루오로-3',5'-디메톡시-[1,1'-바이페닐]-2-일)카바메이트 (140mg, 60%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-플루오로페닐)카바메이트 (200mg, 0.60mmol) (합성예 N)	3,5-디메톡시페닐보로닉 애시드 (218mg, 1.20mmol)
222	(S)-(1-메틸피롤리딘-2-일)메틸 (5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 (66mg, 34%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-메톡시페닐)카바메이트 (200mg, 0.58mmol) (합성예 O)	페닐보로닉 애시드 (142mg, 1.16mmol)
223	(S) (1-메틸피롤리딘-2-일)메틸 (3'-플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 (99mg, 55%)	(S) (1-메틸피롤리딘-2-일)메틸 (2-브로모-4-메톡시페닐)카바메이트 (200mg, 0.58mmol) (합성예 O)	3-플루오로페닐보로닉 애시드 (162mg, 1.16mmol)
224	(S)-(1-메틸피롤리딘-2-일)메틸 (3'-클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 (117mg, 54%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-메톡시페닐)카바메이트 (200mg, 0.58mmol) (합성예 O)	3-클로로페닐보로닉 애시드 (181mg, 1.16mmol)
225	(S)-(1-메틸피롤리딘-2-일)메틸 (3',4'-디클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 (90mg, 38%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-메톡시페닐)카바메이트 (200mg, 0.58mmol) (합성예 O)	3,4-디클로로페닐보로닉 애시드 (221mg, 1.16mmol)
226	(S)-(1-메틸피롤리딘-2-일)메틸 (3',5'-디클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트 (110mg, 46%)	(S)-(1-메틸피롤리딘-2-일)메틸 (2-브로모-4-메톡시페닐)카바메이트 (200mg, 0.58mmol) (합성예 O)	3,5-디클로로페닐보로닉 애시드 (221mg, 1.16mmol)

[761]

[762] **[실험예 1] 인체 무스카린 M3 수용체 결합 시험**

[763] 인체 무스카린성 M3 수용체가 과발현된 세포막 단백질(Perkin Elmer), [^{3}H]-메틸스코폴아민(methyl scopolamine) 및 여러 농도의 피시험 화합물을 0.2ml의 Tris-HCl 완충액 속에 25℃에서 120분간 배양하고, 유리 필터(Whatman GF/B)로 흡인 여과한 다음, 1ml의 Tris-HCl 완충액으로 필터를 5회 세척한다. 필터에 흡착된 [^{3}H]-메틸스코폴아민의 방사능을 액체 신틸레이션 카운터로 측정한다. 비특이성 결합은 5uM의 아트로핀 존재 하에 평가한다. 본 발명 화합물의 무스카린 M3 수용체에 대한 친화성은 쳉과 프루스프 [참조: Cheng and Prusoff, Biochem. Pharmacol., 22, 3099, 1973]에 따라 표지 리간드인 [^{3}

H]-메틸스코폴아민의 결합을 50% 억제하는 피험 화합물의 농도(IC_{50})로부터 산출하는 해리 상수 (K_i)로써 구한다. 하기 표에 제시한 해리 상수 (K_i)가 낮은 값일수록 인체 무스카린 M3 수용체에 대한 결합능이 강한 화합물을 의미한다.

[764] [표 27] 인체 무스카린 M3 수용체 결합능

[765]

실시예	M3 수용체 결합능, K_i (nM)	실시예	M3 수용체 결합능, K_i (nM)
1	4.42	115	7.49
2	8.69	116	12.60
3	11.58	117	1.60
4	2.93	118	2.42
5	1101.45	119	42.34
6	2.47	120	9.70
7	31.84	121	1.75
8	1.33	122	87.80
9	9.10	123	52.84
10	401.05	124	8.12
11	467.04	125	2.67
12	88.00	126	24.79
13	80.10	127	69.36
14	12.39	128	3.41
15	2.27	129	12.56
16	1056.28	130	2.10
17	1.00	131	12.01
18	6.98	132	4.64
19	4.17	133	34.48
20	20.72	134	46.90
21	2.25	135	24.15
22	3.79	136	1.59
23	6.40	137	27.02
24	31.01	138	>1000
25	115.46	139	82.67
26	18.52	140	>1000
27	56.72	141	7.57
28	844.79	142	4.88
29	931.06	143	1.12
30	830.16	144	17.16
31	311.47	145	14.27
32	>1000	146	6.85

[766]

33	16.84	147	77.41
34	19.64	148	10.20
35	434.72	149	1.57
36	>1000	150	5.60
37	>1000	151	14.95
38	574.03	152	147.11
39	28.04	153	>1000
40	118.89	154	16.67
41	2.45	155	>1000
42	9.21	156	10.63
43	1.48	157	29.63
44	95.47	158	119.82
45	69.57	159	5.13
46	37.51	160	4.29
47	136.47	161	8.92
48	257.54	162	5.34
49	303.01	163	16.13
50	>1000	164	36.92
51	101.48	165	0.63
52	10.02	166	9.04
53	1.34	167	67.35
54	125.95	168	22.86
55	38.76	169	282.30
56	12.52	170	9.23
57	34.83	171	16.93
58	26.31	172	6.15
59	6.42	173	42.74
60	118.72	174	0.61
61	217.94	175	22.49
62	>1000	176	>1000
63	58.09	177	6.32
64	>1000	178	>1000
65	71.32	179	241.05
66	6.98	180	9.15
67	16.32	181	3.29

[767]

68	13.23	182	>1000
69	108.98	183	18.91
70	8.17	184	63.46
71	134.09	185	46.09
72	58.83	186	4.68
73	4.84	187	10.66
74	>1000	188	13.73
75	471.30	189	65.59
76	>1000	190	2.17
77	22.00	191	30.78
78	4.62	192	4.60
80	27.38	193	45.83
81	30.35	194	6.30
82	18.89	195	1.08
83	18.29	196	7.67
84	34.94	197	0.78
86	111.04	198	1.87
87	94.38	199	0.80
88	99.67	200	2.03
89	2.43	201	2.70
90	1.97	202	2.18
91	4.50	203	2.36
92	10.66	204	3.53
93	4.12	205	7.95
94	6.18	206	7.32
95	6.27	207	13.45
96	17.57	208	110.05
97	35.17	209	>1000
98	46.18	210	4.60
99	8.10	211	9.91
100	2.43	212	>1000
101	3.79	213	53.03
102	12.86	214	>1000
103	12.96	215	>1000
104	14.18	216	60.13

[768]

105	19.55	217	222.89
106	0.80	218	>1000
107	752.18	219	>1000
108	3.95	220	>1000
109	5.33	221	>1000
110	9.13	222	28.27
111	10.79	223	120.66
112	3.77	224	15.14
113	1.92	225	53.65
114	4.23	226	16.71

[769]

[770] **[실험예 2] 인체 무스카린 M3 수용체 길항 작용 시험**

[771] 본 발명의 여러 다른 화합물들은 인체 무스카린성 M3 수용체로 코드된 플라스미드로 형질이입(形質移入:transfected)된 Cos-7 세포에서 M3 수용체에 대한 길항 작용 평가 시험을 수행한다. 여러 농도의 피험 화합물을 상기 세포에 3분간 전처리한 다음, 무스카린 수용체 효능제인 카르바콜(carbachol)을 처치하여 세포내 칼슘 변화량을 측정한다. 칼슘 농도는 FLIPR® Calcium 5 assay법(Molecular devices)과 Flex3 기기(Melecular devices)를 사용한다. 카르바콜만 처치 전과 후의 칼슘양을 각각 0%와 100%로 하여, 카르바콜에 의한 세포 내 칼슘 증가에 대하여 화합물에 의한 억제율(%)을 계산한다. 피험 화합물들의 인체 무스카린 M3 수용체에 대한 길항작용의 효능은 쳉과 프루스프의 식에 따라 카르바콜의 활성을 50% 억제하는 화합물의 농도(IC_{50})로부터 산출하는 기능적 결합 상수(K_b)로써 나타낸다. 시험에 사용된 화합물은 인체 무스카린 M3 수용체의 길항제로 판명되었으며 K_b가 낮을수록 길항 작용이 우수한 화합물을 의미한다.

[772] [표 28] 인체 무스카린 M3 수용체 길항능

[773]

실시예	M3 수용체 길항능, K_b (nM)	실시예	M3 수용체 길항능, K_b (nM)
2	6.02	128	1.20
4	3.41	129	6.24
8	3.02	130	1.14
15	4.10	131	1.86
19	1.90	132	0.75
21	0.49	135	16.53
22	2.39	136	0.25
34	2.64	141	0.35
41	0.18	142	1.04
42	1.19	143	0.68
52	1.22	144	1.42
53	0.57	145	2.97
56	10.00	146	1.57
58	4.70	148	2.22
59	2.38	149	0.10
66	3.06	150	1.34
67	11.85	151	2.67
68	13.22	156	1.15
70	1.95	157	3.25
73	4.75	159	0.46
77	10.00	166	1.33
89	0.16	181	0.29
90	0.17	183	2.57
91	1.32	186	0.34
95	0.75	187	0.48
100	0.64	188	2.23
114	0.58	190	0.95
115	0.32	194	0.58
116	1.21	195	0.43
117	0.34	196	1.54
118	0.77	199	0.26
120	1.03	207	3.52

[774]

124	2.86	211	10.00
125	0.33	224	7.5
126	17.47	226	4.99

[775]

[776] **[실험예 3] 래트의 율동적 방광 수축에 대한 시험(생체 내)**

[777] 암컷 Sprague Dawley계 래트를 할로탄 마취를 하고 반듯하게 눕혀놓은 요도를

통해 폴리에틸렌 카테터를 삽관하고 고정시킨다. 복부를 부드럽게 맛사지하여 방광 안에 있는 뇨를 카테터를 통해 배출하여 제거한다. 카테터에 쓰리웨이 스탑콕을 연결하여 한쪽에는 압력을 측정하기 위해 압력트랜스듀서를 연결하고 한쪽에는 37℃의 생리식염수을 주입하기 위해 주사기를 설치한다. 서서히 생리식염수를 규칙적인 방광수축이 반복적으로 일어날 때까지 주입시킨다. 규칙적인 방광수축이 안정적으로 발생하면 꼬리정맥을 통해 시험화합물을 투여한다. 시험화합물의 억제 효과는 방광 수축의 진폭감소정도를 측정하여 평가된다. 본 발명의 화합물들은 적어도 0.3mg/kg 이상의 투여량에서 방광 수축의 진폭을 유의적으로 감소시켰다.

[778] [표 29] 래트 율동적 방광 수축능

[779]

실시예	래트 율동적 방광 수축능 (%, 0.3mpk)	실시예	래트 율동적 방광 수축능 (%, 0.3mpk)
1	26.1±5.1	117	15.4±0.1
2	20.1±3.1	121	31.4±6.1
3	15.9±0.9	124	21.2±0.7
4	22.3±4.9	125	22.6±5.8
6	28.5±4.6	128	15.1±3.4
8	23.2±2.3	129	15.7±1.4
9	9.6±1.6	131	17.8±2.5
15	25.6±2.2	136	33.2±4.0
17	27.9±6.1	142	15.1±3.4
19	12.8±3.0	143	24.3±5.5
22	16.7±1.7	145	13.1±3.0
26	11.0±2.5	146	8.2±2.9
34	20.1±1.8	150	25.1±2.5
43	8.9±2.3	160	15.5±2.4
52	10.8±0.8	165	34.5±2.5
53	28.0±5.0	166	10.2±1.7
59	11.6±1.9	172	12.4±2.7
66	12.0±1.4	177	11.3±2.2
70	9.7±4.1	180	6.3±1.3
73	10.0±1.0	181	18.1±2.6
78	17.9±2.1	192	18.6±3.6
89	33.9±3.5	194	24.6±2.6
90	27.4±1.9	195	20.3±2.6
91	25.2±2.5	197	32.8±9.7
93	27.3±1.9	198	26.3±2.4
95	15.7±0.8	199	27.8±4.5
99	16.3±1.0	201	9.1±3.0
100	26.0±6.0	202	17.3±1.3

[780]

101	20.1±1.7	203	19.4±4.0
108	18.1±1.4	204	23.3±6.6
109	18.1±1.7	205	11.9±3.7
106	32.7±5.2	207	18.2±3.7
112	34.8±2.9		

[781]

[782] **[실험예 4] 래트에 대한 경구투여 급성독성 시험**

[783] 본 발명에 의한 화합물의 급성독성을 알아보기 위하여 하기와 같이 실험을 수행하였다. 실시예 화합물 저용량군 100mg/kg, 중용량군 300mg/kg 및 고용량군 1000mg/kg에 0.5% Methyl cellulose solution을 조제하여 군별로 6주령의 암수 Sprague-Dawley (SD) 래트(수컷 142g~143g, 암컷 126.3g~127.3g) 각 3마리에 10mL/kg으로 경구투여하고, 4일간 사망률, 임상증상, 체중 등을 관찰하여 개략치사량 (ALD, Approximate Lethal Dose)을 조사하여 그 결과를 [표 30]에 나타내었다. 표의 급성독성시험 결과에서 알 수 있듯이 시험에 사용된 화합물의 개략치사량이 1000mg/kg 이상이므로 안전한 약물로 판단된다.

[784] [표 30] 개략치사량

[785]

실시예	개략치사량 (ALD)	실시예	개략치사량 (ALD)
15	>1000	100	>1000
53	>1000	136	>1000
89	>1000	143	>1000
90	>1000	150	>1000
91	>1000	199	>1000

[786]

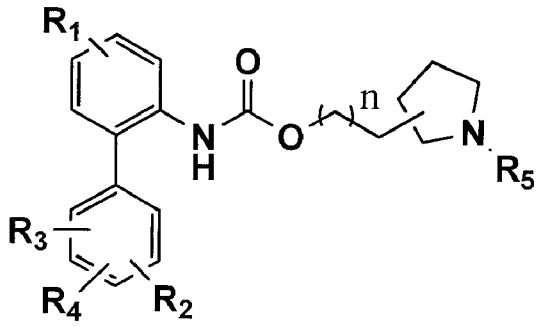
산업상 이용가능성

[787] 본 발명에 따른 화합물, 화학식 1로 표시되는 신규한 바이페닐 유도체, 이의 이성질체 또는 이의 약학적으로 허용가능한 염은 무스카린 M3 수용체 길항작용을 통하여 만성 폐쇄성 폐질환(Chronic obstructive pulmonary disease), 천식(asthma), 과민성 대장 증후군(irritable bowel syndrome), 요실금(urinary incontinence), 비염(rhinitis), 경련성 대장염(spasmodic colitis), 만성 방광염(chronic cystitis), 알츠하이머병(alzheimer's disease), 노인성 치매(senile dementia), 녹내장(glaucoma), 조현병(schizophrenia), 역류성 식도염(gastroesophogeal reflux disease), 심장 부정맥(cardiac arrhythmia), 타액분비항진증(hyper salivation syndromes)으로 이루어진 군으로부터 선택되는 질환의 예방 또는 치료에 유용하게 적용될 수 있다.

청구범위

[청구항 1] 하기 화학식 1로 표시되는 신규한 바이페닐 유도체, 이의 이성질체 또는 이의 약학적으로 허용가능한 염:

[화학식 1]



상기 화학식 1에서,

R_1은 수소, 할로겐, 히드록시, 치환 또는 비치환된 C1~C6의 알킬, 또는 C1~C6의 알콕시이고,

R_2, R_3, R_4는 각각 독립적으로 수소, 할로겐, 치환 또는 비치환된 아미노, 니트로, 시아노, 히드록시, 치환 또는 비치환된 C1~C6의 알킬, 치환 또는 비치환된 C1~C6의 알콕시, 또는 $-C(O)R_6$이고,

R_5는 수소 또는 C1~C6의 알킬이고,

n은 0 또는 1이며,

R_6는 수소 또는 아미노이다.

[청구항 2] 제1항에 있어서, R_1은 수소 또는 할로겐이고, R_2, R_3, R_4는 각각 독립적으로 수소, 할로겐, 또는 C1~C6의 알킬이고, R_5는 C1~C6의 알킬인 신규한 바이페닐 유도체, 이의 이성질체 또는 이의 약학적으로 허용가능한 염.

[청구항 3] 제1항에 있어서, R_1은 수소이고, R_2, R_3, R_4는 각각 독립적으로 수소 또는 할로겐이고, R_5는 C1~C6의 알킬이며, n은 0 또는 1인, 신규한 바이페닐 유도체, 이의 이성질체 또는 이의 약학적으로 허용가능한 염.

[청구항 4] 제1항에 있어서, 하기 화합물들로 이루어진 군으로부터 선택되는 것인 신규한 바이페닐 유도체, 이의 이성질체, 또는 이들의 약학적으로 허용되는 염:

1) 2-(1-메틸피롤리딘-2-일)에틸 (4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

2) 2-(1-메틸피롤리딘-2-일)에틸 (3', 5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

3) 2-(1-메틸피롤리딘-2-일)에틸 (3', 4', 5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;

4) 2-(1-메틸피롤리딘-2-일)에틸
(3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
5) 2-(1-메틸피롤리딘-2-일)에틸
(4'-메톡시-[1,1'-바이페닐]-2-일)카바메이트;
6) 2-(1-메틸피롤리딘-2-일)에틸 [1,1'-바이페닐]-2-일카바메이트;
7) 2-(1-메틸피롤리딘-2-일)에틸
(4'-클로로-[1,1'-바이페닐]-2-일)카바메이트;
8) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-[1,1'-바이페닐]-2-일)카바메이트;
9) 2-(1-메틸피롤리딘-2-일)에틸
(3',5'-디클로로-[1,1'-바이페닐]-2-일)카바메이트;
10) 2-(1-메틸피롤리딘-2-일)에틸
(4'-트리플루오로메톡시-[1,1'-바이페닐]-2-일)카바메이트;
11) 2-(1-메틸피롤리딘-2-일)에틸
(4'-니트로-[1,1'-바이페닐]-2-일)카바메이트;
12) 2-(1-메틸피롤리딘-2-일)에틸
(3'-트리플루오로메틸-[1,1'-바이페닐]-2-일)카바메이트;
13) 2-(1-메틸피롤리딘-2-일)에틸
(4'-트리플루오로메틸-[1,1'-바이페닐]-2-일)카바메이트;
14) 2-(1-메틸피롤리딘-2-일)에틸
((3'-플루오로-4'-메틸)-[1,1'-바이페닐]-2-일)카바메이트;
15) 2-(1-메틸피롤리딘-2-일)에틸
(3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;
16) 2-(1-메틸피롤리딘-2-일)에틸
(3'-에톡시-[1,1'-바이페닐]-2-일)카바메이트;
17) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
18) 2-(1-메틸피롤리딘-2-일)에틸
(3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
19) 2-(1-메틸피롤리딘-2-일)에틸
(4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
20) 2-(1-메틸피롤리딘-2-일)에틸
(3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;
21) 2-(1-메틸피롤리딘-2-일)에틸
(5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
22) 2-(1-메틸피롤리딘-2-일)에틸
(5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;
23) 2-(1-메틸피롤리딘-2-일)에틸

(4-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
24) 2-(1-메틸피롤리딘-2-일)에틸
(3',4-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
25) 2-(1-메틸피롤리딘-2-일)에틸
(4-메톡시-[1,1'-바이페닐]-2-일)카바메이트;
26) 2-(1-메틸피롤리딘-2-일)에틸
(5-메틸-[1,1'-바이페닐]-2-일)카바메이트;
27) 2-(1-메틸피롤리딘-2-일)에틸
(3'-플루오로-5-메틸-[1,1'-바이페닐]-2-일)카바메이트;
28) 2-(1-메틸피롤리딘-2-일)에틸
(4'-시아노-[1,1'-바이페닐]-2-일)카바메이트;
29) 2-(1-메틸피롤리딘-2-일)에틸
(3'-(3-히드록시프로필)-[1,1'-바이페닐]-2-일)카바메이트;
30) 2-(1-메틸피롤리딘-2-일)에틸
(4'-(디메틸아미노)-[1,1'-바이페닐]-2-일)카바메이트;
31) 2-(1-메틸피롤리딘-2-일)에틸
(4'-(tert-부틸)-[1,1'-바이페닐]-2-일)카바메이트;
32) 2-(1-메틸피롤리딘-2-일)에틸
(2'-아미노-[1,1'-바이페닐]-2-일)카바메이트;
33) 2-(1-메틸피롤리딘-2-일)에틸
(3'-아미노-[1,1'-바이페닐]-2-일)카바메이트;
34) 2-(1-메틸피롤리딘-2-일)에틸
(2'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
35) 2-(1-메틸피롤리딘-2-일)에틸
(2'-클로로-[1,1'-바이페닐]-2-일)카바메이트;
36) 2-(1-메틸피롤리딘-2-일)에틸
(2'-히드록시-[1,1'-바이페닐]-2-일)카바메이트;
37) 2-(1-메틸피롤리딘-2-일)에틸
(3'-tert-부틸-5'-메틸-[1,1'-바이페닐]-2-일)카바메이트;
38) 2-(1-메틸피롤리딘-2-일)에틸
(4'-플루오로-3'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;
39) 2-(1-메틸피롤리딘-2-일)에틸
(4'-아미노-3'-클로로-[1,1'-바이페닐]-2-일)카바메이트;
40) 2-(1-메틸피롤리딘-2-일)에틸
(3'-히드록시-[1,1'-바이페닐]-2-일)카바메이트;
41) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

42) 2-(1-메틸피롤리딘-2-일)에틸
(3',4',5-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;
43) 2-(1-메틸피롤리딘-2-일)에틸
(3',4'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
44) 2-(1-메틸피롤리딘-2-일)에틸
(3'-에틸-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
45) 2-(1-메틸피롤리딘-2-일)에틸
(5-플루오로-3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트;
46) 2-(1-메틸피롤리딘-2-일)에틸
(3'-아미노-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
47) 2-(1-메틸피롤리딘-2-일)에틸
(5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;
48) 2-(1-메틸피롤리딘-2-일)에틸
(4'-플루오로-5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;
49) 2-(1-메틸피롤리딘-2-일)에틸
(3'-플루오로-5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;
50) 2-(1-메틸피롤리딘-2-일)에틸
(3',5'-디플루오로-5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;
51) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-5-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;
52) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-5,5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
53) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
54) 2-(1-메틸피롤리딘-2-일)에틸
(4'-클로로-3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
55) 2-(1-메틸피롤리딘-2-일)에틸
(3',5'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
56) 2-(1-메틸피롤리딘-2-일)에틸
(3',5'-디클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
57) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-5-플루오로-5'-히드록시-[1,1'-바이페닐]-2-일)카바메이트;
58) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-5-플루오로-4'-히드록시-[1,1'-바이페닐]-2-일)카바메이

트;
59) 2-(1-메틸피롤리딘-2-일)에틸
(5-플루오로-3',4'-디메틸-[1,1'-바이페닐]-2-일)카바메이트;
60) 2-(1-메틸피롤리딘-2-일)에틸
(5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;
61) 2-(1-메틸피롤리딘-2-일)에틸
(3'-플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;
62) 2-(1-메틸피롤리딘-2-일)에틸
(3',5'-디플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;
63) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;
64) 2-(1-메틸피롤리딘-2-일)에틸
(3',5'-디클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;
65) 2-(1-메틸피롤리딘-2-일)에틸
(3'-클로로-4'-플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;
66) 2-(1-메틸피롤리딘-2-일)에틸
(5-클로로-[1,1'-바이페닐]-2-일)카바메이트;
67) 2-(1-메틸피롤리딘-2-일)에틸
(5-클로로-3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
68) 2-(1-메틸피롤리딘-2-일)에틸
(5-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
69) 2-(1-메틸피롤리딘-2-일)에틸
(5-클로로-3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
70) 2-(1-메틸피롤리딘-2-일)에틸
(3',5-디클로로-[1,1'-바이페닐]-2-일)카바메이트;
71) 2-(1-메틸피롤리딘-2-일)에틸
(3',5,5'-트리클로로-[1,1'-바이페닐]-2-일)카바메이트;
72) 2-(1-메틸피롤리딘-2-일)에틸
(3',5-디클로로-5'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
73) 2-(1-메틸피롤리딘-2-일)에틸
(3',5-디클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
74) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-플루오로-4'-포밀-[1,1'-바이페닐]-2-일)카바메이트;
75) 2-(1-메틸피롤리딘-2-일)에틸
(3',5'-디플루오로-5-히드록시-[1,1'-바이페닐]-2-일)카바메이트;
76) 2-(1-메틸피롤리딘-2-일)에틸
(3',5'-디클로로-5-히드록시-[1,1'-바이페닐]-2-일)카바메이트;
77) 2-(1-메틸피롤리딘-2-일)에틸

(3'-클로로-4'-플루오로-5-히드록시-[1,1'-바이페닐]-2-일)카바메이트;
78) (R)-피롤린딘-3-일메틸 [1,1'-바이페닐]-2-일카바메이트;
79) (S)-피롤린딘-3-일메틸 [1,1'-바이페닐]-2-일카바메이트;
80) (R)-피롤리딘-3-일메틸
(3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
81) (S)-피롤리딘-3-일메틸
(3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
82) (S)-피롤린딘-3-일메틸
(5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
83) (S)-피롤린딘-3-일메틸
(5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;
84) (R)-피롤린딘-3-일메틸
(3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;
85) (S)-피롤린딘-3-일메틸
(3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;
86) (R)-피롤리딘-3-일메틸
(5-메틸-[1,1'-바이페닐]-2-일)카바메이트;
87) (R)-피롤리딘-3-일메틸
(3'-플루오로-5-메틸-[1,1'-바이페닐]-2-일)카바메이트;
88) (S)-피롤리딘-2-일메틸
(4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
89) (R)-(1-메틸피롤리딘-3-일)메틸
[1,1'-바이페닐]-2-일카바메이트;
90) (S)-(1-메틸피롤리딘-3-일)메틸
[1,1'-바이페닐]-2-일카바메이트;
91) (R)-(1-메틸피롤리딘-3-일)메틸
(3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
92) (S)-(1-메틸피롤리딘-3-일)메틸
(3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
93) (S)-(1-메틸피롤리딘-3-일)메틸
(5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
94) (S)-(1-메틸피롤리딘-3-일)메틸
(5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;
95) (R)-(1-메틸피롤리딘-3-일)메틸
(3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;
96) (S)-(1-메틸피롤리딘-3-일)메틸
(3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;

97) (R)-(1-메틸피롤리딘-3-일)메틸
(5-메틸-[1,1'-바이페닐]-2-일)카바메이트;
98) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-플루오로-5-메틸-[1,1'-바이페닐]-2-일)카바메이트;
99) (S)-(1-메틸피롤리딘-2-일)메틸
(4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
100) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;
101) (S)-(1-메틸피롤리딘-3-일)메틸
(3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;
102) (R)-(1-에틸피롤리딘-3-일)메틸
[1,1'-바이페닐]-2-일카바메이트;
103) (S)-(1-에틸피롤리딘-3-일)메틸
[1,1'-바이페닐]-2-일카바메이트;
104) (R)-(1-에틸피롤리딘-3-일)메틸
(3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;
105) (S)-(1-에틸피롤리딘-3-일)메틸
(3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;
106) (S)-(1-에틸피롤리딘-2-일)메틸
[1,1'-바이페닐]-2-일카바메이트;
107) (S)-(1-이소부틸피롤리딘-2-일)메틸
[1,1'-바이페닐]-2-일카바메이트;
108) (S)-(1-메틸피롤리딘-3-일)메틸
(3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
109) (R)-(1-메틸피롤리딘-2-일)메틸
[1,1'-바이페닐]-2-일카바메이트;
110) (R)-(1-메틸피롤리딘-2-일)메틸
(3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;
111) (R)-(1-메틸피롤리딘-2-일)메틸
(5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;
112) (S)-(1-이소프로필피롤리딘-2-일)메틸
[1,1'-바이페닐]-2-일카바메이트;
113) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
114) (R)-(1-메틸피롤리딘-3-일)메틸
(4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
115) (R)-(1-메틸피롤리딘-3-일)메틸
(3',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;

116) (S)-(1-메틸피롤리딘-3-일)메틸
(3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
117) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-[1,1'-바이페닐]-2-일)카바메이트;
118) (S)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-[1,1'-바이페닐]-2-일)카바메이트;
119) (S)-(1-메틸피롤리딘-3-일)메틸
(3',5'-디클로로-[1,1'-바이페닐]-2-일)카바메이트;
120) (S)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
121) (S)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
122) (S)-(1-메틸피롤리딘-3-일)메틸
(5-플루오로-3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트;
123) (S)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5-플루오로-5'-히드록시-[1,1'-바이페닐]-2-일)카바메이트;
124) (S)-(1-메틸피롤리딘-3-일)메틸
(4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
125) (S)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
126) (S)-(1-메틸피롤리딘-3-일)메틸
(3',5'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
127) (S)-(1-메틸피롤리딘-3-일)메틸
(4'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
128) (S)-(1-메틸피롤리딘-3-일)메틸
(3',4'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
129) (S)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5,5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
130) (R)-(1-메틸피롤리딘-3-일)메틸
(3',4'-디클로로-[1,1'-바이페닐]-2-일)카바메이트;
131) (R)-(1-메틸피롤리딘-3-일)메틸
(3',5'-디클로로-[1,1'-바이페닐]-2-일)카바메이트;
132) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
133) (R)-(1-메틸피롤리딘-3-일)메틸
(5-플루오로-3'-아미노-[1,1'-바이페닐]-2-일)카바메이트;
134) (R)-(1-메틸피롤리딘-3-일)메틸

(3'-클로로-5-플루오로-5'-히드록시-[1,1'-바이페닐]-2-일)카바메이트;
135) (R)-(1-메틸피롤리딘-3-일)메틸
(3',5'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
136) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
137) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-히드록시-[1,1'-바이페닐]-2-일)카바메이트;
138) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;
139) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5-플루오로-5'-메톡시-[1,1'-바이페닐]-2-일)카바메이트;
140) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5-플루오로-5'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;
141) (R)-(1-메틸피롤리딘-3-일)메틸
(4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
142) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5,5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
143) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
144) (R)-(1-메틸피롤리딘-3-일)메틸
(2',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
145) (R)-(1-메틸피롤리딘-3-일)메틸
(3',5-디클로로-[1,1'-바이페닐]-2-일)카바메이트;
146) (R)-(1-메틸피롤리딘-3-일)메틸
(3',5-디클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트
147) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-4'-플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;
148) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-5'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
149) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
150) (R)-(1-에틸피롤리딘-3-일)메틸
(3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
151) (R)-(1-이소프로필피롤리딘-3-일)메틸
(3'-클로로-4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;

152) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-(히드록시메틸)-[1,1'-바이페닐]-2-일)카바메이트;
153) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-카바모일-[1,1'-바이페닐]-2-일)카바메이트;
154) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-아미노-[1,1'-바이페닐]-2-일)카바메이트;
155) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-시아노-[1,1'-바이페닐]-2-일)카바메이트;
156) (R)-(1-메틸피롤리딘-3-일)메틸
(2'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
157) (R)-(1-메틸피롤리딘-3-일)메틸
(2',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
158) (R)-(1-메틸피롤리딘-3-일)메틸
(2',3'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
159) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-6'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
160) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
161) (S)-(1-메틸피롤리딘-2-일)메틸
(3',5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
162) (S)-(1-메틸피롤리딘-2-일)메틸
(3',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
163) (S)-(1-메틸피롤리딘-2-일)메틸
(2',4',5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;
164) (S)-(1-메틸피롤리딘-2-일)메틸
(4'-클로로-[1,1'-바이페닐]-2-일)카바메이트;
165) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-[1,1'-바이페닐]-2-일)카바메이트;
166) (S)-(1-메틸피롤리딘-2-일)메틸
(3',4'-디클로로-[1,1'-바이페닐]-2-일)카바메이트;
167) (S)-(1-메틸피롤리딘-2-일)메틸
(2',4'-디클로로-[1,1'-바이페닐]-2-일)카바메이트;
168) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-히드록시-[1,1'-바이페닐]-2-일)카바메이트;
169) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-시아노-[1,1'-바이페닐]-2-일)카바메이트;
170) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-아미노-[1,1'-바이페닐]-2-일)카바메이트;

171) (S)-(1-메틸피롤리딘-2-일)메틸
(3',4',5-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;
172) (S)-(1-메틸피롤리딘-2-일)메틸
(3',5,5'-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;
173) (S)-(1-메틸피롤리딘-2-일)메틸
(2',4',5,5'-테트라플루오로-[1,1'-바이페닐]-2-일)카바메이트;
174) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
175) (S)-(1-메틸피롤리딘-2-일)메틸
(4'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
176) (S)-(1-메틸피롤리딘-2-일)메틸
(2',4'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
177) (S)-(1-메틸피롤리딘-2-일)메틸
(3',4'-디클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
178) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-시아노-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
179) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-히드록시-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
180) (S)-(1-메틸피롤리딘-2-일)메틸
(5-플루오로-3'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;
181) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-4,4',5-트리플루오로-[1,1'-바이페닐]-2-일)카바메이트;
182) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-4,5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
183) 2-(1-메틸피롤리딘-2-일)에틸
(2',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
184) 2-(1-메틸피롤리딘-2-일)에틸
(2',3'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
185) 2-(1-메틸피롤리딘-2-일)에틸
(2',6'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
186) 2-(1-메틸피롤리딘-2-일)에틸
(5'-클로로-2'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
187) (S)-(1-메틸피롤리딘-2-일)메틸
(2'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
188) (S)-(1-메틸피롤리딘-2-일)메틸
(2',4'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
189) (S)-(1-메틸피롤리딘-2-일)메틸

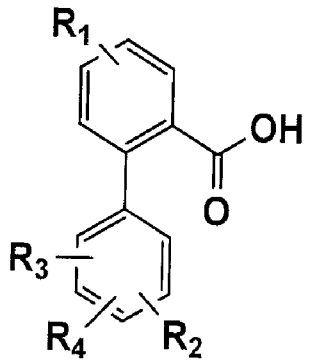
(2',3'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
190) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-6'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
191) (R)-(1-메틸피롤리딘-3-일)메틸
(3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트;
192) (R)-(1-메틸피롤리딘-3-일)메틸
(5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;
193) (R)-(1-메틸피롤리딘-3-일)메틸
(5-플루오로-3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트;
194) (R)-(1-메틸피롤리딘-3-일)메틸
(3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
195) (R)-(1-메틸피롤리딘-3-일)메틸
(3'-클로로-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
196) (R)-(1-에틸피롤리딘-3-일)메틸
(3'-클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
197) (S)-(1-메틸피롤리딘-2-일)메틸
[1,1'-바이페닐]-2-일카바메이트;
198) (S)-(1-메틸피롤리딘-2-일)메틸
(4'-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
199) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;
200) (S)-(1-메틸피롤리딘-2-일)메틸
(5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
201) (S)-(1-메틸피롤리딘-2-일)메틸
(5-플루오로-3'-메틸-[1,1'-바이페닐]-2-일)카바메이트;
202) (S)-(1-메틸피롤리딘-2-일)메틸
(3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
203) (S)-(1-메틸피롤리딘-2-일)메틸
(4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
204) (S)-(1-메틸피롤리딘-2-일)메틸
(4-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
205) (S)-(1-메틸피롤리딘-2-일)메틸
(3',4-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
206) (S)-(1-메틸피롤리딘-2-일)메틸
(5-메틸-[1,1'-바이페닐]-2-일)카바메이트;
207) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-플루오로-5-메틸-[1,1'-바이페닐]-2-일)카바메이트;
208) (S)-(1-메틸피롤리딘-2-일)메틸

(5-플루오로-3',5'-디메틸-[1,1'-바이페닐]-2-일)카바메이트;
209) (S)-(1-메틸피롤리딘-2-일)메틸
(4'-(tert-부틸)-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
210) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-5,5'-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
211) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-4',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
212) (S)-(1-메틸피롤리딘-2-일)메틸
(4'-클로로-3',5-디플루오로-[1,1'-바이페닐]-2-일)카바메이트;
213) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-아미노-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
214) (S)-(1-메틸피롤리딘-2-일)메틸
(2',5-디플루오로-3'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;
215) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-5-플루오로-5'-(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;
216) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-5-플루오로-5'-히드록시-[1,1'-바이페닐]-2-일)카바메이트;
217) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-5-플루오로-5'-메톡시-[1,1'-바이페닐]-2-일)카바메이트;
218) (S)-(1-메틸피롤리딘-2-일)메틸
(5-플루오로-2',4'-비스(트리플루오로메틸)-[1,1'-바이페닐]-2-일)카바메이트;
219) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-에톡시-5-플루오로-[1,1'-바이페닐]-2-일)카바메이트;
220) (S)-(1-메틸피롤리딘-2-일)메틸
(5-플루오로-3',4'-디메톡시-[1,1'-바이페닐]-2-일)카바메이트;
221) (S)-(1-메틸피롤리딘-2-일)메틸
(5-플루오로-3',5'-디메톡시-[1,1'-바이페닐]-2-일)카바메이트;
222) (S)-(1-메틸피롤리딘-2-일)메틸
(5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;
223) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-플루오로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;
224) (S)-(1-메틸피롤리딘-2-일)메틸
(3'-클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트;
225) (S)-(1-메틸피롤리딘-2-일)메틸

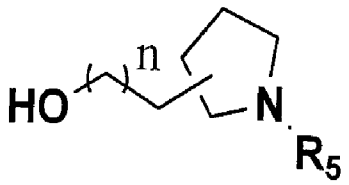
(3',4'-디클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트; 및
226) (S)-(1-메틸피롤리딘-2-일)메틸 (3',
5'-디클로로-5-메톡시-[1,1'-바이페닐]-2-일)카바메이트.

[청구항 5] 하기 화학식 2의 화합물과 하기 화학식 3의 화합물을 카바메이트 제조시약 존재 하에 반응시키는 단계를 포함하는 하기 화학식 1의 화합물 또는 이의 약학적으로 허용가능한 염의 제조방법:

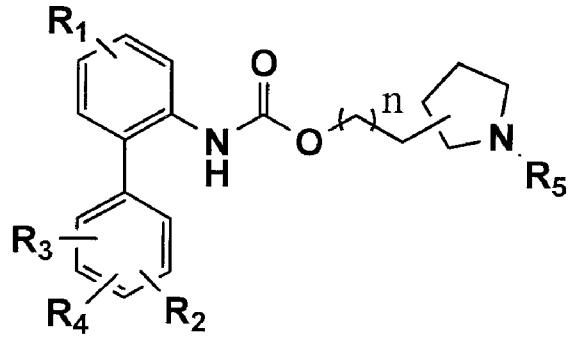
[화학식 2]



[화학식 3]



[화학식 1]



상기 화학식 1, 2 및 3에서, R_1~R_5 및 n은 제1항에서 정의한 바와 같다.

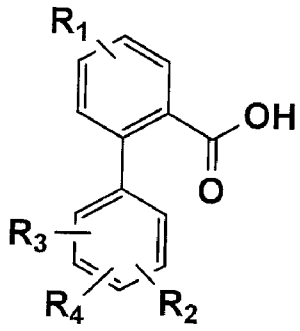
[청구항 6] 하기 화학식 2의 화합물과 하기 화학식 3a의 화합물을 카바메이트 제조시약 존재 하에 반응시켜 하기 화학식 4의 화합물을 제조하는 단계;

상기 화학식 4의 화합물의 아민 보호기 (Protecting Group)를 제거하여 하기 화학식 1a의 화합물을 제조하는 단계; 및

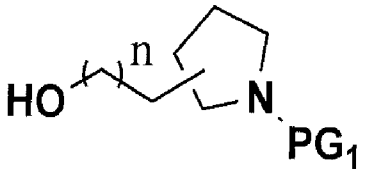
상기 화학식 1a의 화합물에 R_5 치환기를 도입하는 단계를

포함하는 하기 화학식 1의 화합물 또는 이의 약학적으로 허용가능한 염의 제조방법:

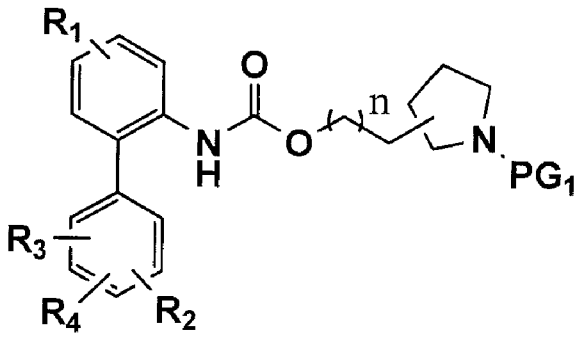
[화학식 2]



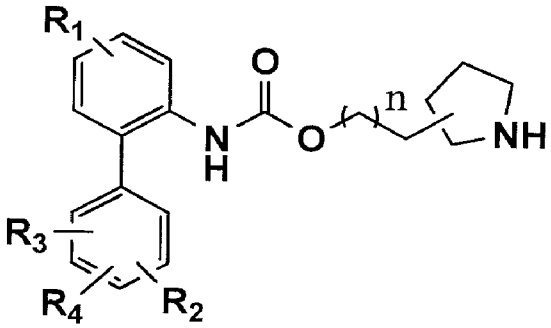
[화학식 3a]



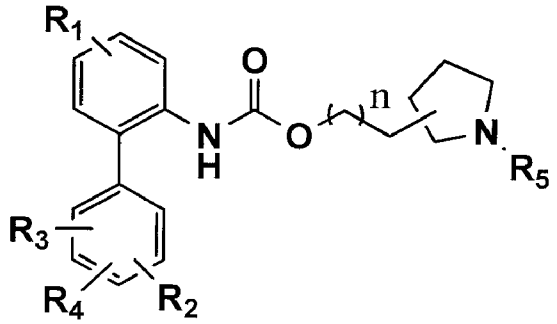
[화학식 4]



[화학식 1a]



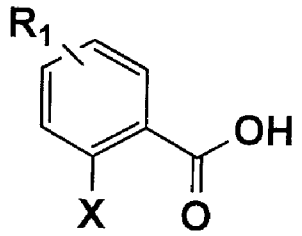
[화학식 1]



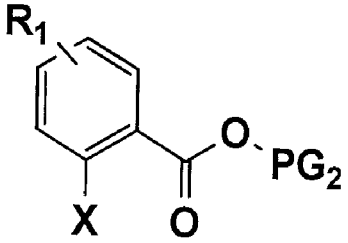
상기 화학식 1, 1a, 2, 3a 및 4에서 R_1~R_5 및 n은 제1항에서 정의한 바와 같으며, PG_1은 아민 보호기로서 Boc(tert-butyloxycarbonyl), 벤질, tert-부틸, pmb(4-methoxybenzyl), Fmoc(Fluorenylmethyloxycarbonyl), Ts(tosylate), MOM(methoxymethyl), THP(tetrahydropyranyl), TBDMS(tert-butyldimethylsilyl), TBDPS(tert-butyldimethylsilyl)로 이루어진 군으로부터 선택된다.

[청구항 7] 제5항 또는 제6항에 있어서, 상기 화학식 2의 화합물은,
하기 화학식 5의 화합물을 산 존재 하에 반응시켜 카르복실산 보호기 (Protecting Group)가 도입된 하기 화학식 6의 화합물을 제조하는 단계;
상기 화학식 6의 화합물과 하기 화학식 7의 화합물을 커플링시켜 하기 화학식 8의 화합물을 제조하는 단계; 및
하기 화학식 8의 화합물을 염기 존재 하에 탈에스테르화하는 단계를 통하여 제조되는 것을 특징으로 하는 화학식 1의 화합물 또는 이의 약학적으로 허용가능한 염의 제조방법:

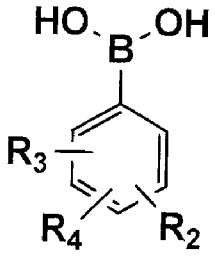
[화학식 5]



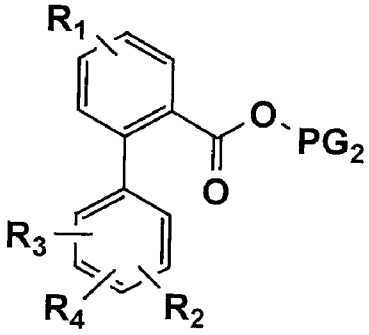
[화학식 6]



[화학식 7]



[화학식 8]



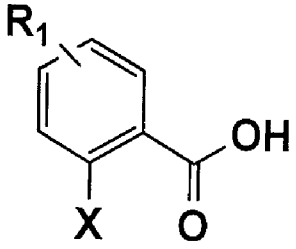
상기 화학식 5 내지 8에서, R_1~R_5 및 n은 제1항에서 정의한 바와 같으며, X는 할로겐이고, PG_2는 C1~C4의 알킬기, 벤질, pmb(4-methoxybenzyl), THP(tetrahydropyranyl), TBDMS(tert-butyldimethylsilyl), TBDPS(tert-butyldimethylsilyl)로 이루어진 군으로부터 선택되는 보호기이다.

[청구항 8]

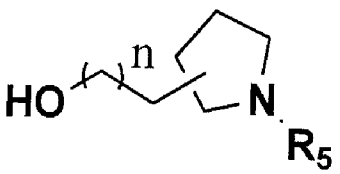
하기 화학식 5의 화합물을 하기 화학식 3의 화합물과 카바메이트 제조시약 존재 하에 반응시켜 하기 화학식 9의 화합물을 제조하는 단계; 및

상기 화학식 9의 화합물에 하기 화학식 7의 화합물을 커플링하는 단계를 포함하는 하기 화학식 1의 화합물 또는 이의 약학적으로 허용가능한 염의 제조방법.

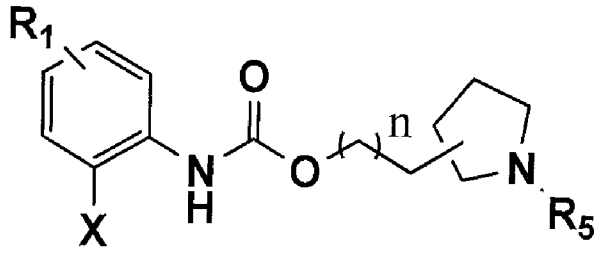
[화학식 5]



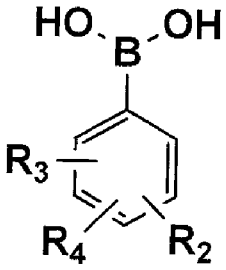
[화학식 3]



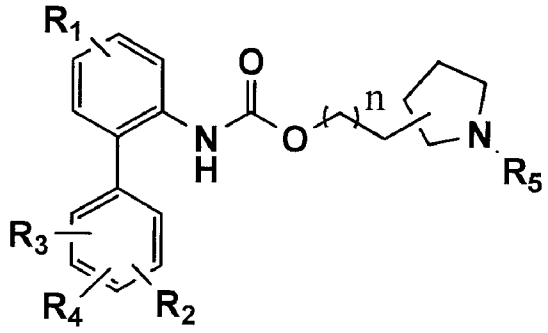
[화학식 9]



[화학식 7]



[화학식 1]



상기 화학식 1, 3, 5, 7 및 9에서 R_1~R_5 및 n은 제1항에서 정의한 바와 같으며, X는 할로겐이다.

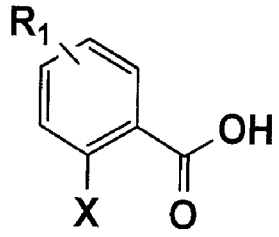
[청구항 9] 하기 화학식 5의 화합물을 하기 화학식 3a의 화합물과 카바메이트 제조시약 존재 하에 반응시켜 하기 화학식 9a의 화합물을 제조하는 단계;

하기 화학식 9a의 화합물을 탈보호화하여 하기 화학식 9b 화합물을 제조하는 단계;

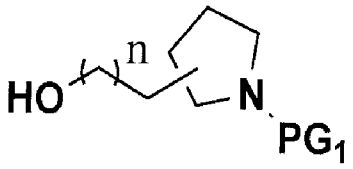
상기 화학식 9b의 화합물에 R_5 치환기를 도입하여 하기 화학식 9의 화합물을 제조하는 단계; 및

상기 화학식 9의 화합물에 하기 화학식 7의 화합물을 커플링하는 단계를 포함하는 하기 화학식 1의 화합물 또는 이의 약학적으로 허용가능한 염의 제조방법:

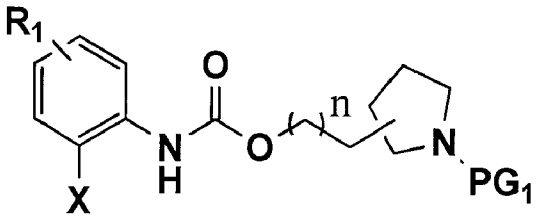
[화학식 5]



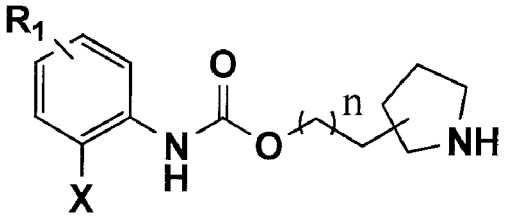
[화학식 3a]



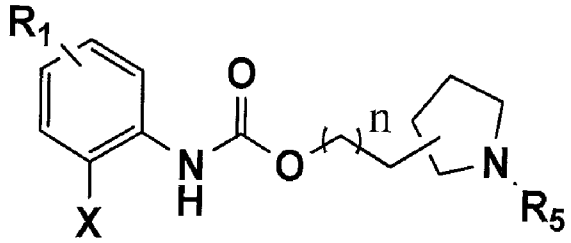
[화학식 9a]



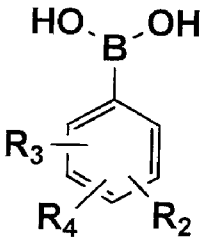
[화학식 9b]



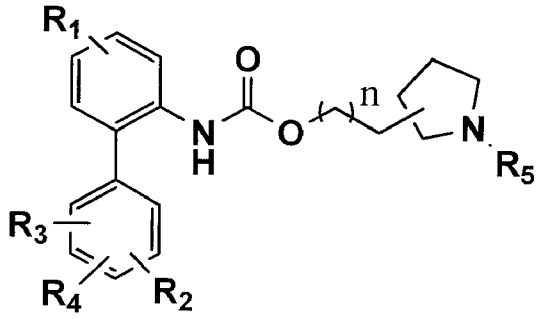
[화학식 9]



[화학식 7]



[화학식 1]



상기 화학식 1, 3a, 5, 7, 9, 9a 및 9b에서 R_1~R_5 및 n은 제1항에서 정의한 바와 같으며, X는 할로겐이고, PG_1은 제6항에서 정의한 바와 같다.

[청구항 10] 제5항, 제6항, 제8항 또는 제9항 중 어느 한 항에 있어서, 상기 카바메이트 제조시약은 아지드 화합물을 포함하는 것을 특징으로 하는 화학식 1의 화합물 또는 이의 약학적으로 허용가능한 염의 제조방법.

[청구항 11] 제10항에 있어서, 상기 카바메이트 제조시약은 다이페닐포스포릴 아지드 (DPPA) 및 트리에틸아민의 혼합액, 프로필포스포닉 언히드리드(T3P)와 트리메틸실릴 아지드 ($TMSN_3$) 및 트리에틸아민의 혼합액, 소듐 아지드(NaN_3), 테트라부틸암모늄 브로마이드, 징크 트리플레이트 (Zi(II) triflate)의 혼합액인 것을 특징으로 하는 화학식 1의 화합물 또는 이의 약학적으로 허용가능한 염의 제조방법.

[청구항 12] 제1항의 화합물, 이의 이성질체, 또는 이들의 약제학적으로 허용되는 염을 유효성분으로 포함하는 무스카린 M3 수용체 길항제.

[청구항 13] 제12항에 있어서, 만성 폐쇄성 폐질환(Chronic obstructive pulmonary disease), 천식(asthma), 과민성 대장 증후군(irritable bowel syndrome), 요실금(urinary incontinence), 비염(rhinitis), 경련성 대장염(spasmodic colitis), 만성 방광염(chronic cystitis), 알츠하이머병(alzheimer's disease), 노인성 치매(senile dementia), 녹내장(glaucoma), 조현병(schizophrenia), 역류성 식도염(gastroesophogeal reflux disease), 심장 부정맥(cardiac arrhythmia), 타액분비항진증(hyper salivation syndromes)으로 이루어진 군으로부터 선택되는 질환의 예방 또는 치료용 무스카린 M3 수용체 길항제.

[청구항 14] 제1항의 화합물, 이의 이성질체, 또는 이들의 약제학적으로 허용되는 염을 유효성분으로 포함하는 조성물을 이를 필요로 하는 인간을 포함하는 포유류에 투여함으로써, 무스카린 M3 수용체

길항작용 관련 질환를 예방 또는 치료하는 방법.

[청구항 15] 무스카린 M3 수용체 길항작용 관련 질환의 예방 또는 치료용 약제의 제조를 위한 제1항의 화합물, 이의 이성질체, 또는 이들의 약제학적으로 허용되는 염을 유효성분으로 포함하는 조성물의 용도.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2014/006483

A. CLASSIFICATION OF SUBJECT MATTER

C07D 207/06(2006.01)i, C07D 207/08(2006.01)i, A61K 31/40(2006.01)i, A61P 11/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 207/06; C07D 451/02; C07D 211/46; C07D 401/06; A61K 31/439; C07D 453/02; A61K 31/40; C07D 207/08; A61P 11/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Utility models and applications for Utility models: IPC as above
Japanese Utility models and applications for Utility models: IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS (KIPO internal), STN(REG, CAplus), PubMed, JPO, USPTO, Google & Keywords: biphenyl, carbamate, muscarine M3 receptor

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0747355 A1 (YAMANOUCHI PHARMACEUTICAL CO. LTD.) 11 December 1996 See abstract, claims 1-12	1-13,15
A	KR 10-2006-0129017 A (GLAXO GROUP LIMITED) 14 December 2006 See abstract, claims 1-3	1-13,15
A	US 2010-0105658 A1 (NAGASHIMA, Shinya et al.) 29 April 2010 See abstract, claims 1-16	1-13,15

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 OCTOBER 2014 (27.10.2014)	**28 OCTOBER 2014 (28.10.2014)**
Name and mailing address of the ISA/**KR** Korean Intellectual Property Office Government Complex-Daejeon, 189 Seonsa-ro, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2014/006483

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **14**
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 14 pertains to a method for treatment of the human by surgery or therapy, or to a diagnostic method, and thus pertains to subject matter on which the International Searching Authority is not required to carry out an international search under the provisions of PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

International application No.
PCT/KR2014/006483

Patent document cited in search report	Publication date	Patent family member	Publication date
EP 0747355 A1	11/12/1996	AU 1590995 A	29/08/1995
		AU 685225 B2	15/01/1998
		CA 2182568 A1	17/08/1995
		CN1140447 A0	15/01/1997
		EP 0747355 A4	09/04/1997
		HU76289A2	28/07/1997
		HU960218800	28/10/1996
		HUT76289A	28/07/1997
		KR 10-1997-0701174 A	17/03/1997
		WO 95-21820 A1	17/08/1995
KR 10-2006-0129017 A	14/12/2006	AU 2005-204935 A1	28/07/2005
		CA 2552880 A1	28/07/2005
		CN1929844 A	14/03/2007
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		EP 1711183 A2	18/10/2006
		JP 2007-518740A	12/07/2007
		US 2008-0249127 A1	09/10/2008
		WO 2005-067537 A2	28/07/2005
		WO 2005-067537 A3	18/05/2006
US 2010-0105658 A1	29/04/2010	AU 2008-212171 A1	14/08/2008
		BR PI0806972A2	08/04/2014
		CA 2678193 A1	14/08/2008
		CN101605784 A	16/12/2009
		CN101605784 B	10/04/2013
		EP 2119716 A1	18/11/2009
		EP 2119716 A4	01/06/2011
		IL200152D0	15/04/2010
		JP 05-293192B2	18/09/2013
		KR 10-2009-0107567 A	13/10/2009
		MX2009008509 A	20/08/2009
		RU2009133781 A	20/03/2011
		RU2441868 C2	10/02/2012
		US 8367696 B2	05/02/2013
		WO 2008-096870 A1	14/08/2008

국 제 조 사 보 고 서

국제출원번호
PCT/KR2014/006483

A. 발명이 속하는 기술분류(국제특허분류(IPC))

C07D 207/06(2006.01)i, C07D 207/08(2006.01)i, A61K 31/40(2006.01)i, A61P 11/00(2006.01)i

B. 조사된 분야

조사된 최소문헌(국제특허분류를 기재)

C07D 207/06; C07D 451/02; C07D 211/46; C07D 401/06; A61K 31/439; C07D 453/02; A61K 31/40; C07D 207/08; A61P 11/00

조사된 기술분야에 속하는 최소문헌 이외의 문헌

한국등록실용신안공보 및 한국공개실용신안공보: 조사된 최소문헌란에 기재된 IPC
일본등록실용신안공보 및 일본공개실용신안공보: 조사된 최소문헌란에 기재된 IPC

국제조사에 이용된 전산 데이터베이스(데이터베이스의 명칭 및 검색어(해당하는 경우))

eKOMPASS(특허청 내부 검색시스템), STN(REG, CAplus), PubMed, JPO, USPTO, Google & 키워드: 바이페닐, 카바메이트, 무스카린 M3 수용체

C. 관련 문헌

카테고리*	인용문헌명 및 관련 구절(해당하는 경우)의 기재	관련 청구항
A	EP 0747355 A1 (YAMANOUCHI PHARMACEUTICAL CO. LTD.) 1996.12.11. 요약, 청구항 1-12항 참조	1-13,15
A	KR 10-2006-0129017 A (글락소그룹 리미티드) 2006.12.14. 요약, 청구항 1-3항 참조	1-13,15
A	US 2010-0105658 A1 (NAGASHIMA SHINYA 외 5명) 2010.04.29. 요약, 청구항 1-16항 참조	1-13,15

☐ 추가 문헌이 C(계속)에 기재되어 있습니다.

☒ 대응특허에 관한 별지를 참조하십시오.

* 인용된 문헌의 특별 카테고리:

"A" 특별히 관련이 없는 것으로 보이는 일반적인 기술수준을 정의한 문헌

"E" 국제출원일보다 빠른 출원일 또는 우선일을 가지나 국제출원일 이후에 공개된 선출원 또는 특허 문헌

"L" 우선권 주장에 의문을 제기하는 문헌 또는 다른 인용문헌의 공개일 또는 다른 특별한 이유(이유를 명시)를 밝히기 위하여 인용된 문헌

"O" 구두 개시, 사용, 전시 또는 기타 수단을 언급하고 있는 문헌

"P" 우선일 이후에 공개되었으나 국제출원일 이전에 공개된 문헌

"T" 국제출원일 또는 우선일 후에 공개된 문헌으로, 출원과 상충하지 않으며 발명의 기초가 되는 원리나 이론을 이해하기 위해 인용된 문헌

"X" 특별한 관련이 있는 문헌. 해당 문헌 하나만으로 청구된 발명의 신규성 또는 진보성이 없는 것으로 본다.

"Y" 특별한 관련이 있는 문헌. 해당 문헌이 하나 이상의 다른 문헌과 조합하는 경우로 그 조합이 당업자에게 자명한 경우 청구된 발명은 진보성이 없는 것으로 본다.

"&" 동일한 대응특허문헌에 속하는 문헌

국제조사의 실제 완료일	국제조사보고서 발송일
2014년 10월 27일 (27.10.2014)	2014년 10월 28일 (28.10.2014)

ISA/KR의 명칭 및 우편주소
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(302-701) 대전광역시 서구 청사로 189, 4동 (둔산동, 정부대전청사)
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국 제 조 사 보 고 서

국제출원번호
PCT/KR2014/006483

제2기재란 일부 청구항을 조사할 수 없는 경우의 의견(첫 번째 용지의 2의 계속)

PCT 제17조(2)(a)의 규정에 따라 다음과 같은 이유로 일부 청구항에 대하여 본 국제조사보고서가 작성되지 아니하였습니다.

1. ☒ 청구항: 제14항
이 청구항은 본 기관이 조사할 필요가 없는 대상에 관련됩니다. 즉,
청구항 제14항은 수술 또는 치료에 의한 사람의 치료 및 진단방법에 관한 것이므로 PCT 조약 제17조(2)(a)(i) 및 PCT 규칙 39.1(iv)의 규정에 의하여 국제조사기관이 국제 조사할 의무가 없는 대상에 해당됩니다.

2. ☐ 청구항:
이 청구항은 유효한 국제조사를 수행할 수 없을 정도로 소정의 요건을 충족하지 아니하는 국제출원의 부분과 관련됩니다. 구체적으로는,

3. ☐ 청구항:
이 청구항은 종속청구항이나 PCT규칙 6.4(a)의 두 번째 및 세 번째 문장의 규정에 따라 작성되어 있지 않습니다.

제3기재란 발명의 단일성이 결여된 경우의 의견(첫 번째 용지의 3의 계속)

본 국제조사기관은 본 국제출원에 다음과 같이 다수의 발명이 있다고 봅니다.

1. ☐ 출원인이 모든 추가수수료를 기간 내에 납부하였으므로, 본 국제조사보고서는 모든 조사 가능한 청구항을 대상으로 합니다.

2. ☐ 추가수수료 납부를 요구하지 않고도 모든 조사 가능한 청구항을 조사할 수 있었으므로, 본 기관은 추가수수료 납부를 요구하지 아니하였습니다.

3. ☐ 출원인이 추가수수료의 일부만을 기간 내에 납부하였으므로, 본 국제조사보고서는 수수료가 납부된 청구항만을 대상으로 합니다. 구체적인 청구항은 아래와 같습니다.

4. ☐ 출원인이 기간 내에 추가수수료를 납부하지 아니하였습니다. 따라서 본 국제조사보고서는 청구범위에 처음 기재된 발명에 한정되어 있으며, 해당 청구항은 아래와 같습니다.

이의신청에 관한 기재

☐ 출원인의 이의신청 및 이의신청료 납부(해당하는 경우)와 함께 추가수수료가 납부되었습니다.

☐ 출원인의 이의신청과 함께 추가수수료가 납부되었으나 이의신청료가 보정요구서에 명시된 기간 내에 납부되지 아니하였습니다.

☐ 이의신청 없이 추가수수료가 납부되었습니다.

국제조사보고서
대응특허에 관한 정보

국제출원번호
PCT/KR2014/006483

국제조사보고서에서 인용된 특허문헌	공개일	대응특허문헌	공개일
EP 0747355 A1	1996/12/11	AU 1590995 A	1995/08/29
		AU 685225 B2	1998/01/15
		CA 2182568 A1	1995/08/17
		CN1140447 A0	1997/01/15
		EP 0747355 A4	1997/04/09
		HU76289A2	1997/07/28
		HU9602188D0	1996/10/28
		HUT76289A	1997/07/28
		KR 10-1997-0701174 A	1997/03/17
		WO 95-21820 A1	1995/08/17
KR 10-2006-0129017 A	2006/12/14	AU 2005-204935 A1	2005/07/28
		CA 2552880 A1	2005/07/28
		CN1929844 A	2007/03/14
		CN1929844 C0	2007/03/14
		EP 1711183 A2	2006/10/18
		JP 2007-518740A	2007/07/12
		US 2008-0249127 A1	2008/10/09
		WO 2005-067537 A2	2005/07/28
		WO 2005-067537 A3	2006/05/18
US 2010-0105658 A1	2010/04/29	AU 2008-212171 A1	2008/08/14
		BR PI0806972A2	2014/04/08
		CA 2678193 A1	2008/08/14
		CN101605784 A	2009/12/16
		CN101605784 B	2013/04/10
		EP 2119716 A1	2009/11/18
		EP 2119716 A4	2011/06/01
		IL200152D0	2010/04/15
		JP 05-293192B2	2013/09/18
		KR 10-2009-0107567 A	2009/10/13
		MX2009008509 A	2009/08/20
		RU2009133781 A	2011/03/20
		RU2441868 C2	2012/02/10
		US 8367696 B2	2013/02/05
		WO 2008-096870 A1	2008/08/14

RESUMEN DE LA INVENCIÓN

La presente invención proporciona derivados de bifenilo novedosos, isómeros de los mismos, o sales farmacéuticamente aceptables de los mismos, métodos para preparar los mismos, y una composición farmacéutica que contiene los mismos. Los derivados de bifenilo novedosos, isómeros de los mismos, o sales farmacéuticamente aceptables de los mismos, como se describe en la presente invención, actúan como antagonistas del receptor muscarínico M3, y de esta manera son útiles para la prevención o tratamiento de una enfermedad seleccionada del grupo que consiste de enfermedad pulmonar obstructiva crónica, asma, síndrome de intestino irritable, incontinencia urinaria, rinitis, colitis espasmódica, cistitis crónica, enfermedad de Alzheimer, demencia senil, glaucoma, esquizofrenia, enfermedad de reflujo gastroesofágico, arritmia cardiaca, y síndromes de hipersalivación.