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División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. **EXPEDIENTE No.** 04-52563

54 **TITULO** DERIVADOS DE α-(N-SULFONAMIDO) ACETAMIDA COMO INHIBIDORES DEL PEPTIDO β-AMILOIDEO

51 **CLASIFICACION INTERNACIONAL** A61K 31/18

71 **SOLICITANTE** BRISTOL - MYERS SQUIBB COMPANY

DOMICILIO PRINCETON, NEW JERSEY ESTADOS UNIDOS DE AMERICA

74 **APODERADO** RAMIRO CASTRO DUQUE

22 **SANTAFE DE BOGOTA, D.C.** 18/06/2004

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Oficina de Comunicaciones

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Industria y Comercio
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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

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ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)	Nombre: **BRISTOL – MYERS SQUIBB COMPANY** Dirección: P.O. Box 4000, Route 206 and provinceline Road, Princeton, NJ 08543-4000, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual____ Número 170.322 TP 1003
4 INVENTOR (ES) (72)	Nombre: Michael F. Parker, Katharine E. Mcelhone, Robert A. Mate, Joanne J. Bronson, Yonghua Gai, Carl P. Bergstrom, Lawrence R. Marcin, John E. Macor Dirección: 45 Brainard Hill Road, Higganum, CT 06441, US; 25 Midway Drive, Cromwell, CT 06416, US; 380-91 Hitchcock Road, Waterbury, CT 06705, US; 230 Parmelee Hill Road, Durham, CT 06422, US; 12 Linnea Lane, Killingworth, CT 06419, US; 22 Paper Mill Drive, Madison, CT 06443, US; 40 Ridgewood Drive, Bethany, CT 06437, US; 644 Moose Hill Road, Guilford, CT 06437, Estados Unidos de América (Respectivamente) Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente)	

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6 Título (54): DERIVADOS DE α-(N-SULFONAMIDO) ACETAMIDA COMO INHIBIDORES DEL PÉPTIDO β-AMILOIDEO

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2

10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $422.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Protocolo No. 19358
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] Otros - Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente.

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

C.C. 170.322 de Bogotá T.P. 1003 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

3

SUPERINDUSTRIA Y COMERCIO

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***** C O N S I G N A C I O N *****

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CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-41-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
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(71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P. O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000 (US).

(72) Inventors: PARKER, Michael, F.; 45 Brainard Hill Road, Higganum, CT 06441 (US). MCELHONE, Katharine, E.; 25 Midway Drive, Cromwell, CT 06416 (US). MATE, Robert, A.; 380-91 Hitchcock Road, Waterbury, CT 06705 (US). BRONSON, Joanne, J.; 230 Parmalee Hill Road, Durham, CT 06422 (US). GAI, Yonghua; 12 Linnea Lane, Killingworth, CT 06419 (US). BERGSTROM, Carl, P.; 22 Paper Mill Drive, Madison, CT 06443 (US). MARCIN, Lawrence, R.; 40 Ridgewood Drive, Bethany, CT 06437 (US). MACOR, John, E.; 644 Moose Hill Road, Guilford, CT 06437 (US).

(74) Agents: BABAJKO, Suzanne et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

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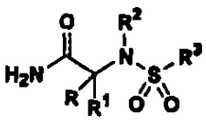
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(54) Title: α-(N-SULPHONAMIDO)ACETAMIDE DERIVATIVES AS β-AMYLOID INHIBITORS



(I)

(57) Abstract: There is provided a series of novel α-(N-sulfonamido)acetamide compounds of the Formula (I) wherein R, R^1, R^2 and R^3 are defined herein, which are inhibitors of β-amyloid peptide (β-AP) production and are useful in the treatment of Alzheimer's Disease and other conditions affected by anti-amyloid activity.

α-(N-SULFONAMIDO)ACETAMIDE DERIVATIVES AS β-AMYLOID INHIBITORS

FIELD OF THE INVENTION

This invention provides novel α-(N-sulfonamido)acetamide compounds having drug and bio-affecting properties, their pharmaceutical compositions and method of use. In particular, the invention is concerned with α-(N-arylsulfonamido)acetamides. These compounds possess unique inhibition of the β-amyloid peptide (β-AP) production, thereby acting to prevent the accumulation of amyloid protein deposits in the brain. More particularly, the present invention relates to the treatment of Alzheimer's Disease (AD).

BACKGROUND OF THE INVENTION

Alzheimer's Disease is a progressive, neurodegenerative disorder characterized by memory impairment and cognitive dysfunction. AD is characterized pathologically by the accumulation of senile (neuritic) plaques, neurofibrillary tangles, amyloid deposition in neural tissues and vessels, synaptic loss, and neuronal death. It is the most common form of dementia and it now represents the third leading cause of death after cardiovascular disorders and cancer. The cost of Alzheimer's Disease is enormous (in the U.S., greater than $100 billion annually) and includes the suffering of the patients, the suffering of families, and the lost productivity of patients and caregivers. As the longevity of society increases, the occurrence of AD will markedly increase. It is estimated that more than 10 million Americans will suffer from AD by the year 2020, if methods for prevention and treatment are not found. Currently, AD is estimated to afflict 10% of the population over age 65 and up to 50% of those over the age

of 85. No treatment that effectively prevents AD or reverses the clinical symptoms and underlying pathophysiology is currently available (for review see Selkoe, D.J. *Ann. Rev. Cell Biol.*, 1994, 10: 373-403).

There have been many theories relating to the etiology and pathogenesis of AD. These theories were either based on analogies with other diseases and conditions (e.g., slow virus and aluminum theories), or based on pathologic observations (e.g., cholinergic, amyloid, or tangle theories). Genetic analysis can potentially differentiate between competing theories. The identification of mutations in the β-amyloid precursor protein (β-APP) of individuals prone to early onset forms of AD and related disorders strongly supports the amyloidogenic theories.

Histopathological examination of brain tissue derived upon autopsy or from neurosurgical specimens in affected individuals reveals the occurrence of amyloid plaques and neurofibrillar tangles in the cerebral cortex of such patients. Similar alterations are observed in patients with Trisomy 21 (Down's syndrome). Biochemical and immunological studies reveal that the dominant proteinaceous component of the amyloid plaque is an approximately 4.2 kilodalton (kD) protein of about 39 to 43 amino acids. This protein is designated Aβ, β-amyloid peptide, and sometimes β/A4; referred to herein as Aβ. In addition to its deposition in amyloid plaques, Aβ is also found in the walls of meningeal and parenchymal arterioles, small arteries, capillaries, and sometimes, venules. Compelling evidence accumulated during the last decade reveals that Aβ is an internal polypeptide derived from a type 1 integral membrane protein, termed β-amyloid precursor protein (APP) (Selkoe, D. *Physiol. Rev.* 2001, 81, 741-766; Wolfe, M. *J. Med. Chem.* 2001, 44, 2039-2060). βAPP is normally produced by many cells both in vivo and in cultured cells, derived from various animals and humans. Several proteolytic fragments of APP are generated by proteinases referred to as secretases. A subset of these proteolytic fragments, designated β-amyloid peptide (Aβ), contains 39 to 43 amino acids and is generated by the combined action of β-secretase and γ-secretase. β-secretase is a membrane-bound, aspartyl protease

that forms the N-terminus of the Aβ peptide. The C-terminus of the Aβ peptide is formed by γ-secretase, an apparently oligomeric complex that includes presenilin-1 and/or presenilin-2. Presenilin-1 and presenilin-2 are polytopic membrane-spanning proteins that may contain the catalytic components of γ-secretase (Seiffert, D.; Bradley, J. et al. *J. Biol. Chem.* 2000, 275, 34086-34091).

Multiple lines of evidence together strongly suggest that a reduction in brain Aβ levels will prevent the onset and progression of AD. First, Aβ is a major constituent of the parenchemyal plaques observed in all AD patients and the cerebral vasculature amyloid deposits observed in 90% AD patients (reviewed in Selkoe, D. *Physiol. Rev.* 2001, 81, 741-766; Wolfe, M. *J. Med. Chem.* 2001, 44, 2039-2060). These plaques are formed from the aggregation of soluble Aβ whose brain levels are highly correlated with the severity of AD neurodegeneration (McLean, C., Cherny, R. et al. *Ann. Neurol.* 1999, 46, 860-866). Second, mutations in three genes (APP, PS-1, or PS-2) that increase Aβ cause familial AD (FAD), where AD onset is accelerated by at least a decade. Included in the mutations that increase Aβ are chromosome 21 Trisomy that causes Down's syndrome. Third, transgenic mice that express one or more of the mutant FAD genes have increased Aβ levels, form parenchymal plaques and cerebral vascular deposits containing Aβ, exhibit memory deficits (Chapman, P.; White, G. et al. *Nature Neurosci.* 1999, 2, 271-276) and enhance neurofibrillary degeneration in mice that also overexpress mutant tau (Lewis, J.; Dickson, D. et al. *Science* 2001, 293, 1487-1491). Fourth, Aβ is toxic to cultured cells (Dahlgren, K.; Manelli, A. et al. *J. Biol. Chem.* 2002 277, 32046-32053), induces neurofibrillary tangles in mice with mutant tau (Gotz, J., Chen, F. et al. *Science* 2001, 293, 1491-1495) and interferes with long-term potentiation, a likely component of memory (Walsh, D., Klyubin, I. et al. *Nature* 2002, 416, 535-539 and references therein). Taken together, these data lead one skilled in the art to conclude that excess Aβ production and/or reduced Aβ clearance cause AD. From this it follows that reducing brain Aβ levels by inhibition of γ-secretase will prevent the onset and progression of AD.

In addition to AD, excess production and/or reduced clearance of Aβ causes cerebral amyloid angiopathy (CAA) (reviewed in Thal, D., Gherbremedhin, E. et al. *J. Neuropath. Exp. Neuro.* 2002, 61, 282-293). In these patients, vascular amyloid deposits cause degeneration of vessel walls and aneurysms that may be responsible for 10-15% hemorrhagic strokes in elderly patients. As in AD, mutations in the gene encoding Aβ lead to an early onset form of CAA, referred to as cerebral hemorrhage with amyloidosis of the Dutch type, and mice expressing this mutant protein develop CAA that is similar to patients.

It is hypothesized that inhibiting the production of Aβ will prevent and reduce neurological degeneration, reducing neurotoxicity and, generally, mediating the pathology associated with Aβ production. Methods of treatment could target the formation of Aβ through the enzymes involved in the proteolytic processing of β-amyloid precursor protein. Compounds that inhibit β- or γ-secretase activity, either directly or indirectly, could control the production of Aβ. Advantageously, compounds that specifically target γ-secretases, could control the production of Aβ. Such inhibition of β- or γ-secretases could thereby reduce production of Aβ which, could reduce or prevent the neurological disorders associated with Aβ protein.

Smith, et al. in International Application WO 00/50391, published August 31, 2000, disclose a series of sulfonamide compounds that can act to modulate production of amyloid β protein as a means of treating a variety of diseases, especially Alzheimer's Disease and other diseases relating to the deposition of amyloid. Japanese Patent No.11343279, published December 14, 1999 discloses a series of sulfonamide derivatives which are TNF-alpha inhbitors useful for treating autoimmune diseases.

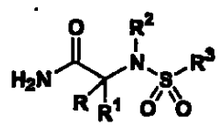
Nothing in these references can be construed to disclose or suggest the novel compounds of this invention and their use to inhibit β-AP production.

SUMMARY OF THE INVENTION

A series of α-(N-sulfonamido)acetamide derivatives have been synthesized. These compounds specifically inhibit the production of β-amyloid peptide (β-AP) from ß-amyloid precursor protein (β-APP). The pharmacologic action of these compounds makes them useful for treating conditions responsive to the inhibition of β-AP in a patient; e.g., Alzheimer's Disease (AD) and Down's Syndrome. Therapy utilizing administration of these compounds to patients suffering from, or susceptible to, these conditions involves reducing β-AP available for accumulation and deposition in brains of these patients.

DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises compounds of Formula I, their pharmaceutical formulations, and their use in inhibiting β-AP production in patients suffering from or susceptible to AD or other disorders resulting from β-AP accumulation in brain tissue. The compounds of Formula I which include nontoxic pharmaceutically acceptable salts and/or hydrates thereof have the following formula and meanings:



I

wherein:

R^1 is selected from the group consisting of

(a) a straight or branched-chain C_{1-6} alkyl or C_{2-6}alkenyl optionally substituted with substituents selected from the group consisting of hydroxy, C_{3-7} cycloalkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, and halogen;

(b) C_{3-7} cycloalkyl optionally substituted with hydroxy or halogen;

R is hydrogen or R^1 and R taken together is C_{2-5}alkylene;

R^2 is selected from the group consisting of

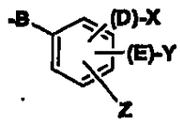
(a) a straight or branched-chain C_{1-6}alkyl or C_{3-6}alkenyl optionally substituted with substituents selected from the group consisting of halogen, C_{1-4}alkoxy, and NR^4R^5;

(b) C_{3-7}cycloalkylmethyl optionally substituted with substituents selected from the group consisting of amino, $(C_{1-4}alkyl)NH$-, $di(C_{1-4}alkyl)N$-, $C_{1-4}alkylC(=O)NH$-, and $C_{1-4}alkylOC(=O)NH$-;

(c) a straight or branched-chain C_{1-6}alkyl-C(=O)-A;

(d) -B-naphthyl;

(e)



D and E are each independently a direct bond, a straight or branched-chain C_{1-6}alkyl, C_{2-6}alkenyl, or C_{3-7}cycloalkyl;

Z is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halogen, cyano, hydroxy, $-OCHF_2$, $-OCF_3$, $-CF_3$, and $-CHF_2$;

X and Y are each independently selected from the group consisting of hydrogen, hydroxy, halogen, $(halogen)_3C$-, $(halogen)_2CH$-, $C_{1-4}alkylS$-, $C_{1-4}alkylS(O)$-, $C_{1-4}alkylSO_2$-, nitro, F_3S-, and cyano; $-OR^6$; $-NR^4R^5$; $-NR^7C(=O)R^8$; $-NR^7C(=O)OR^8$; $-NHSO_2C_{1-4}alkyl$; $-N(SO_2C_{1-4}alkyl)_2$; -C(=O)W wherein W is selected from the group consisting of hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, phenoxy, and $-NR^4R^5$; $-OC(=O)C_{1-4}alkyl$; -phenyl in which said phenyl is optionally substituted with cyano, halogen, C_{1-4}alkoxy, $C_{1-4}alkylS$-, $CH_3C(=O)$, $C_{1-4}alkylS(O)$-, or $C_{1-4}alkylSO_2$-; and heterocyclic group, in which said heterocyclic group is selected from the group consisting of furanyl, thiofuranyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, oxadiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, and thiazolyl, wherein said heterocyclic group is optionally substituted

with substituents selected from the group consisting of cyano, halogen, C_{1-4}alkyl, (halogen)C_{1-4}alkyl, and CO_2C_{1-4}alkyl;

(f) -B-(heterocycle), in which said heterocycle is selected from the group consisting of furanyl, thiofuranyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, oxadiazolyl, oxazolyl, isoxazolyl, thiadiazolyl and thiazolyl wherein said heterocycle is optionally substituted with substituents selected from the group consisting of cyano, halogen, C_{1-4}alkyl, CO_2C_{1-4}alkyl, amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and 4-(C_{1-6}alkyl)piperazin-1-yl;

(g) -B-(piperidin-4-yl), in which said piperidin-4-yl is optionally substituted with substituents selected from the group consisting of a straight or branched-chain C_{1-6}alkyl, $CH_2C(=O)$phenyl, phenyl and phenylmethyl in which said C_{1-6}alkyl and said phenyl are optionally substituted with substituents selected from the group consisting of cyano, halogen, benzimidazol-2-yl, pyridyl and tetrahydrofuran-2-yl; and -C(=O)W' wherein W' is selected from the group consisting of C_{1-4}alkoxy, R^9, and $-NR^4R^5$;

A is hydroxy, C_{1-4}alkoxy or NR^4R^5;

B is a straight or branched-chain C_{1-6}alkyl or C_{3-6}alkenyl;

R^3 is phenyl or pyridyl optionally substituted with substituents selected from the group consisting of halogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkyl, $(halogen)_3C-$, $(halogen)_2CH-$, and $halogenCH_2-$;

R^4 and R^5 each are independently hydrogen, a straight or branched-chain C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylmethyl, C_{1-4}alkoxy, phenyl, benzyl, pyridyl, piperidin-4-yl, indan-1-yl, indan-2-yl, tetrahydrofuran-3-yl, or pyrrolidin-3-yl; in which each is optionally substituted with substituents selected from the group consisting of hydroxy, cyano, halogen, $(halogen)_3C-$, $(halogen)_2CH-$, $halogenCH_2-$, hydroxymethyl, benzyloxymethyl, phenyl, pyridyl, C_{1-4}alkyl, C_{1-4}alkoxy,

(halogen)$_3$C-O-, (halogen)$_2$CH-O-, C_{1-4}alkylthio, amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, 4-(C_{1-6}alkyl)piperazin-1-yl, 4-phenylpiperazin-1-yl, 4-benzylpiperazin-1-yl, 4-pyridylpiperazin-1-yl, CO_2H, CO_2C_{1-4}alkyl, C(=O)NHC_{1-4}alkyl, and C(=O)N(C_{1-4}alkyl)$_2$;

R^4 and R^5 taken together may be morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, decahydroquinolin-1-yl, piperidin-1-yl, piperazin-1-yl, [1,4]-oxazepan-4-yl, azetidin-1-yl, 2,3-dihydro-1*H*-isoindol-2-yl, or 2,3-dihydro-1*H*-indol-1-yl; in which each is optionally substituted with substituents selected from the group consisting of hydroxy, cyano, halogen, (halogen)$_3$C-, (halogen)$_2$CH-, halogenCH_2-, phenyl, pyridyl, benzyl, C_{1-6}alkyl, C_{3-7} cycloalkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, CO_2H, CO_2C_{1-4}alkyl, C(=O)NHC_{1-4}alkyl, and C(=O)N(C_{1-4}alkyl)$_2$;

R^6 is a straight or branched-chain C_{1-6}alkyl, C_{3-6} alkenyl, benzyl, or phenyl in which each is optionally substituted with substituents selected from the group consisting of halogen, C_{1-4}alkyl, C_{1-4}alkoxy, amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, (C_{1-4}alkyl)(phenyl)N-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and 4-(C_{1-6}alkyl)piperazin-1-yl;

R^7 is hydrogen, a straight or branched-chain C_{1-6} alkyl;

R^8 is a straight or branched-chain C_{1-6}alkyl, C_{3-7} cycloalkyl, phenyl, pyridyl, or furanyl; in which each is optionally substituted with substituents selected from the group consisting of halogen, C_{1-4}alkyl, C_{1-4}alkoxy, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and 4-(C_{1-6}alkyl)piperazin-1-yl;

R^9 is a straight or branched-chain C_{1-6}alkyl, C_{3-6} alkenyl, benzyl, phenyl, oxazolyl or pyridyl; in which each is optionally substituted with substituents selected from the group consisting of halogen, (halogen)$_3$C-, (halogen)$_2$CH-, halogenCH_2-, C_{1-4}alkyl, C_{1-4}alkoxy, amino, (C_{1-4}alkyl)NH-,

di(C_{1-4}alkyl)N-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and 4-(C_{1-6}alkyl)piperazin-1-yl;

or a non-toxic pharmaceutically acceptable salt thereof.

The present invention also provides a method for the treatment or alleviation of disorders associated with β-amyloid peptide, especially Alzheimer's Disease, which comprises administering together with a conventional adjuvant, carrier or diluent a therapeutically effective amount of a compound of formula I or a nontoxic pharmaceutically acceptable salt, solvate or hydrate thereof.

The term "C_{1-6} alkyl" as used herein and in the claims (unless the context indicates otherwise) means straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, 3-methylbutyl, hexyl and the like. The term "C_{2-6} alkenyl" used herein and in the claims (unless the context indicates otherwise) means straight or branched chain alkenyl groups such as ethenyl (i.e. vinyl), propenyl, allyl, butenyl, 3-methylbutenyl, pentenyl, hexenyl and the like. Unless otherwise specified, the term "halogen" as used herein and in the claims is intended to include bromine, chlorine, iodine and fluorine while the term "halide" is intended to include bromide, chloride and iodide anion.

The term "C_{3-7} cycloalkyl" means a carbon cyclic ring system such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "C_{1-4} haloalkyl" means a straight or branched chain C_{1-4} alkyl group containing from 1 to 3 halogen atoms such as trifluoromethyl, fluoroethyl, 1,2-dichloroethyl, trichloroethyl and the like.

The term "C_{2-5} alkylene" means a straight or branched chain alkylene group such as methylene, ethylene, propylene, methylethylene, butylene, methylpropylene, pentylene, methylbutylene and ethylpropylene.

As the compounds of the present invention possess an asymmetric carbon atom, the present invention includes the racemate as well as the individual enantiometric forms of the compounds of Formula I as described herein and in the claims. The use of a single designation such as (R) or (S) is intended to

include mostly one stereoisomer. Mixtures of isomers can be separated into individual isomers according to methods which are known per se, e.g. fractional crystallization, adsorption chromatography or other suitable separation processes. Resulting racemates can be separated into antipodes in the usual manner after introduction of suitable salt-forming groupings, e.g. by forming a mixture of diastereosiomeric salts with optically active salt-forming agents, separating the mixture into diastereomeric salts and converting the separated salts into the free compounds. The possible enantiomeric forms may also be separated by fractionation through chiral high pressure liquid chromatography columns.

The term "nontoxic pharmaceutically acceptable salt" as used herein and in the claims is intended to include nontoxic base addition salts. Suitable salts include those derived from organic and inorganic acids such as, without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, tartaric acid, lactic acid, sulfinic acid, citric acid, maleic acid, fumaric acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, and the like.

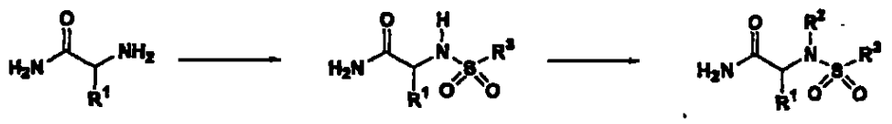
In the method of the present invention, the term "therapeutically effective amount" means the total amount of each active component of the method that is sufficient to show a meaningful patient benefit, i.e., healing of acute conditions characterized by inhibition of β-amyloid peptide production. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. The terms "treat, treating, treatment" as used herein and in the claims means preventing or ameliorating diseases associated with β-amyloid peptide.

General Reaction Schemes

The general procedures used to synthesize the compounds of Formula I are described in Reaction Schemes 1-23. Reasonable variations of the described

procedures, which would be evident to one skilled in the art, are intended to be within the scope of the present invention.

Reaction Scheme 1



II III I

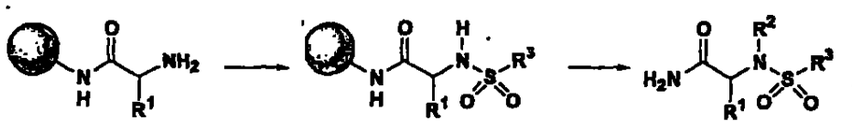
The starting (α-amino)acetamides of Formula II are used in racemic or in enantiomerically pure form and are commercially available or are prepared by well-known literature procedures from commercially available (α-amino)acids (general reference for amide preparation.: R.C. Larock "Comprehensive Organic Transformations, VCH Publishers, New York, 1989, pp. 972 – 976; see also Reaction Scheme 18 for the conversion of the acid of Formula XLVIII to the amide of Formula XLIX). The compound of Formula II is treated with a suitable base and a sulfonylating reagent such as a sulfonyl chloride in an aprotic solvent such as CH_2Cl_2 at room temperature to generate the (α-sulfonamido)acetamide of Formula III. Suitable bases include triethylamine and pyridine.

In one method for conversion of the compound of Formula III to the sulfonamide of Formula I, the compound of Formula III is treated with a suitable base and an alkylating agent in an aprotic solvent with or without heating. Suitable bases for this reaction include potassium carbonate and cesium carbonate. Alkylating agents include alkyl halides (e.g., alkyl chloride, alkyl bromide, or alkyl iodide) and alkyl sulfonates (tosylates, mesylates, trifluoromethanesulfonates). Preferred solvents include DMF and acetonitrile. The temperature range for the reaction is typically 20 °C to 100 °C.

An alternative method for conversion of the compound of Formula III to the compound of Formula I involves treatment of the compound of Formula III

with triphenyl phosphine, a dialkyl azodicarboxylate, and an alcohol in an inert solvent with or without heating.

Reaction Scheme 1-solid support

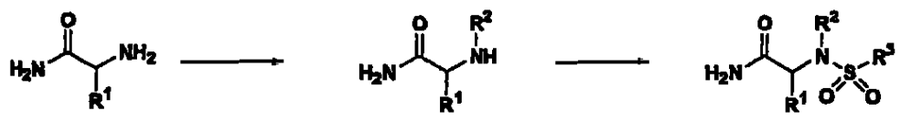


IV V I

The compounds of Formula I can also be prepared using solid phase methodology. For example, FMOC-protected Rink amide resin is treated with piperidine in DMF to effect removal of the FMOC group. The resin is then coupled with an amino-protected (α-amino)acid in the presence of a coupling agent such as 1-hydroxybenzotriazole and a dialkyl carbodiimide in an inert solvent such as DMF with or without heating. Deprotection of the α-amino group affords the polymer-bound amide of Formula IV. In the case of an FMOC-protected amino acid, the deprotection can be accomplished by treatment with piperidine in DMF.

Reaction of the compound of Formula IV with an appropriate base such as pyridine and a sulfonylating agent such as a sulfonyl chloride in an inert solvent provides the resin-linked sulfonamide of Formula V. Alkylation of the compound of Formula V with an alkyl halide (e.g., alkyl chloride, alkyl bromide, or alkyl iodide) or alkyl sulfonate (e.g., mesylate, tosylate, or trifluoromethanesulfonate) is carried out in the presence of a base in an inert solvent at room temperature. A preferred base is 2-*t*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diasaphosphorine. Cleavage from the resin provides the sulfonamide of Formula I. In the case of the Rink amide resin, the cleavage is preferably carried out using trifluoroacetic acid in an inert solvent such as CH_2Cl_2.

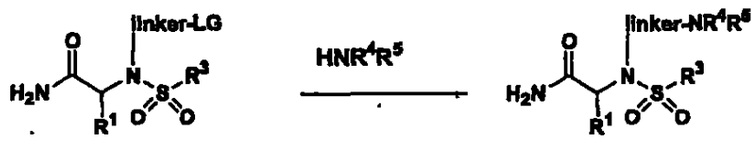
Reaction Scheme 2



II VI I

The compounds of Formula I can also be prepared as shown in Reaction Scheme 2. Reductive alkylation of the amine of Formula I to provide the amine of Formula VI is effected by treatment with an aldehyde and a hydride reducing agent in the presence of an acid catalyst with or without heating. A preferred reducing agent is sodium cyanoborohydride. A preferred acid catalyst is a Lewis acid such as $ZnCl_2$. The reaction solvent is preferably methanol. The amine of Formula VI is then treated with a sulfonylating agent such as a sulfonyl chloride in the presence of an amine such as triethylamine. This reaction is carried out in an inert solvent such as CH_2Cl_2 with or without heating to afford the product of Formula I. The reaction is typically carried out at room temperature.

Reaction Scheme 3

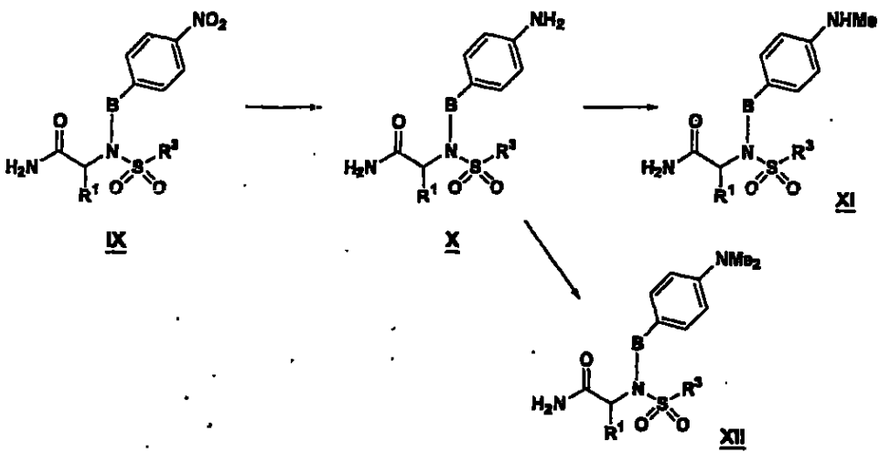


VII VIII

wherein linker = straight-chain or branched C_{1-6}alkyl or C_{3-6}alkenyl;
LG = leaving group

Preparation of compounds of Formula VIII is accomplished as shown in Reaction Scheme 3 by reaction of the compound of Formula VII with an amine in the presence of an acid scavenger such as triethylamine in an inert solvent such as CH_2Cl_2 with or without heating. The compound of Formula VII is prepared by the sequence shown in Reaction Scheme 1 or Reaction Scheme 2.

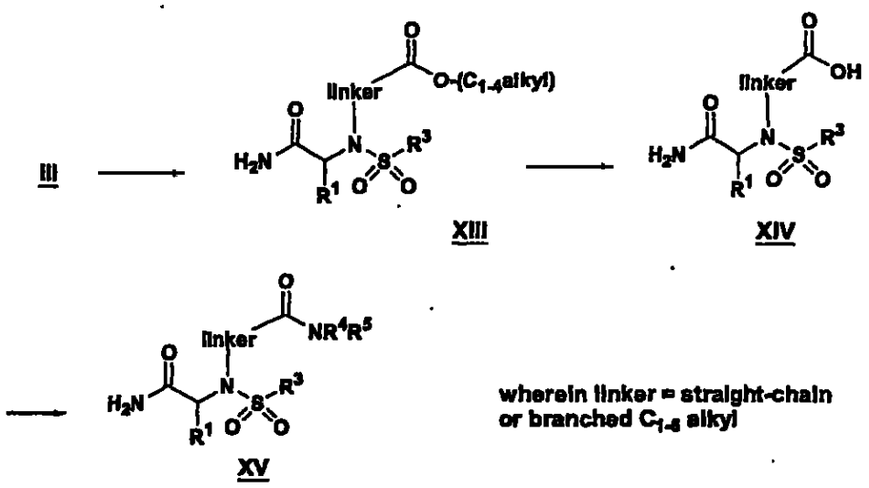
Reaction Scheme 4



IX X XI XII

The compounds of Formula XI and XII are prepared as shown in Reaction Scheme 4. Reduction of the nitro group of the compound of Formula IX (prepared by the sequence shown in Reaction Scheme 1 or 2) with hydrogen gas under pressure in the presence of a palladium catalyst, acid, and in a solvent such as methanol provided the aniline derivative of Formula X. Monomethylation of the compound of Formula X to provide the compound of Formula XI is accomplished by reaction with 1.1 equivalents of a methyl halide or a methyl sulfonate, for example dimethylsulfate, in the presence of a base such as triethylamine and in an inert solvent such as DMF. The monomethylation reaction is typically carried out between 20 °C and 40 °C. Preparation of the dimethylaniline of Formula XII is effected by treatment of the aniline of Formula X with an excess of a methyl halide such as methyl iodide or a methyl sulfonate in the presence of a base, for example cesium carbonate, in a solvent such as DMF, with or without heating.

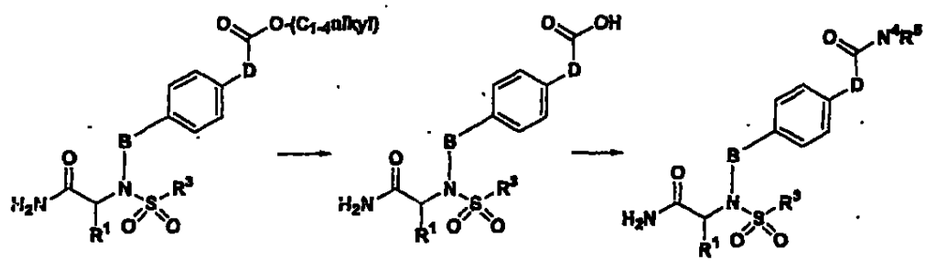
Reaction Scheme 5



Reaction Scheme 5 outlines the synthesis of esters of Formula XIII, acids of Formula XIV, and amides of Formula XV. Reaction of a compound of Formula III with a haloalkylcarboxylate ester, for example *t*-butyl bromoacetate, in the presence of a base such as potassium carbonate and in an inert solvent such as DMF affords the ester of Formula XIII. Deprotection of the ester is effected by methods known to those skilled in the art (ref.: T.W. Greene and P.G.M. Wuts, "Protecting Groups in Organic Synthesis", Wiley Interscience, New York, 1999, pp. 373 - 442). For example, for *t*-butyl esters, cleavage to the acid of Formula XIV is accomplished by treatment with trifluoroacetic acid in a solvent such as CH_2Cl_2. Conversion of the acid to the amide of Formula XV is carried out using common amide coupling procedures well known to those skilled in the art (ref.: R.C. Larock "Comprehensive Organic Transformations, VCH Publishers, New York, 1989, pp. 972 – 976). In a preferred procedure, the acid of Formula XIV is treated with a primary or secondary amine in the presence of 1-hydroxybenzotriazole and 1,3-dicyclohexylcarbodiimide in an aprotic solvent such as CH_2Cl_2 or DMF.

12

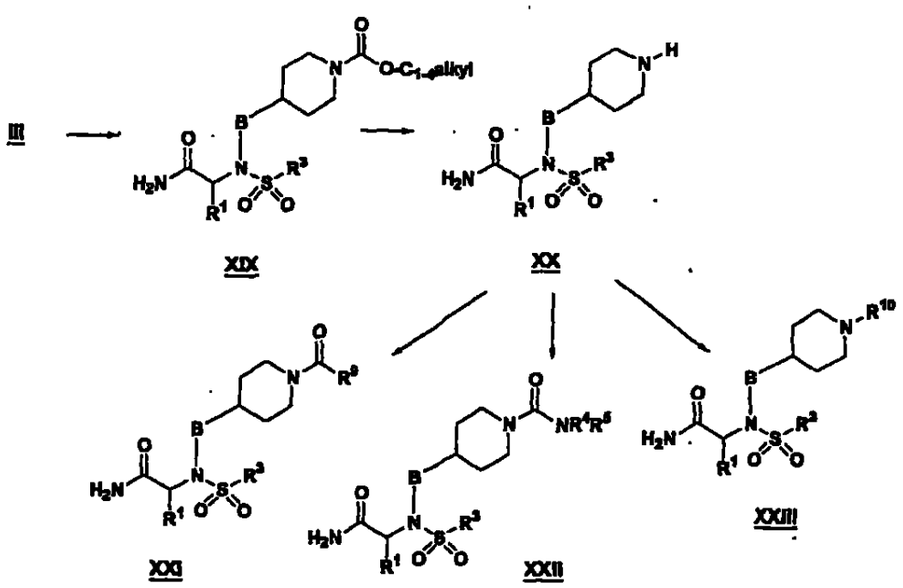
Reaction Scheme 6



XVI XVII XVIII

The preparation of acids of Formula XVII and amides of Formula XVIII is shown in Reaction Scheme 6. Conversion of an ester of Formula XVI (prepared as shown in Reaction Schemes 1 or 2) to an acid of Formula XVII is accomplished using standard ester cleavage conditions well known to those skilled in the art (ref.: T.W. Greene and P.G.M. Wuts, "Protecting Groups in Organic Synthesis", Wiley Interscience, New York, 1999, pp. 373 - 442). In the case of a methyl ester of Formula XVI, treatment with aqueous sodium hydroxide in a solvent such a methanol or a methanol/THF mixture at 20 °C to 40 °C provides the acid of Formula XVII. Conversion of the acid of Formula XVII to the amide of Formula XVIII is achieved using common amide coupling procedures well known to those skilled in the art (ref.: R.C. Larock "Comprehensive Organic Transformations, VCH Publishers, New York, 1989, pp. 972 – 976). In a preferred procedure, the acid of Formula XVII is treated with a primary or secondary amine in the presence of 1-hydroxybenzotriazole and a carbodiimide, for example 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, in a solvent such as DMF or CH_2Cl_2. A base such a diisopropylethylamine can be added as an acid scavenger.

Reaction Scheme 7

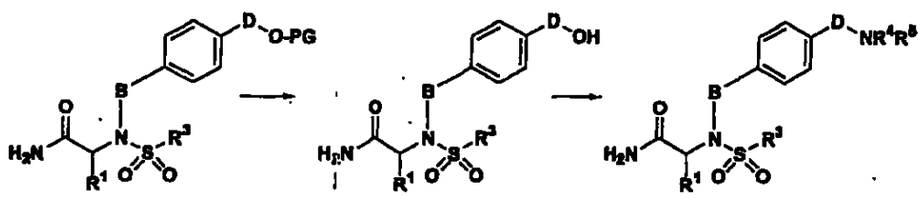


The synthesis of piperidine derivatives of Formula XIX, XX, XXI, XXII, and XXIII is described in Reaction Scheme 7. Reaction of a compound of Formula III with an N-protected piperidine substituted with a 4-haloalkyl or 4-sulfonyloxyalkyl group, such as 4-(toluenesulfonyloxymethyl)-1-(*t*-butoxycarbonyl)piperidine, in the presence of a base such as cesium carbonate in a solvent such as DMF, with or without heating, provides the carbamate of Formula XIX. Cleavage of the carbamate group in the compound of Formula XIX is carried out under standard conditions well known to those skilled in the art (ref.: T.W. Greene and P.G.M. Wuts, "Protecting Groups in Organic Synthesis", Wiley Interscience, New York, 1999, pp. 503-550) to provide the piperidine of Formula XX. In the case of a (*t*-butoxycarbonyl)piperidine derivative, the cleavage is effected by treatment with trifluoroacetic acid in CH_2Cl_2.

Conversion of the piperidine of Formula XX to an amide of Formula XXI is carried out using amide-coupling procedures well known to those skilled in the art (ref.: R.C. Larock "Comprehensive Organic Transformations, VCH

Publishers, New York, 1989, pp. 972 – 976). In a preferred method, the piperidine of Formula XX is treated with an acyl chloride in the presence of an amine such as triethylamine and in an inert solvent such as CH_2Cl_2 with or without heating. Alternatively, the piperidine of Formula XX may be coupled with an acid in the presence of coupling agents such as hydroxybenzotriazole and a carbodiimide to provide an amide of Formula XXI. Preparation of the urea of Formula XXII is achieved by treatment of the amine of Formula XX with an isocyanate and a base such as triethylamine in a solvent such as CH_2Cl_2 with or without heating. Alkylation of the piperidine of Formula XX provides N-substituted piperidines of Formula XXIII. In a typical procedure, the piperidine is treated with an alkyl halide or an alkyl sulfonate in the presence of a base such as triethylamine and in a solvent such as CH_2Cl_2.

Reaction Scheme 8



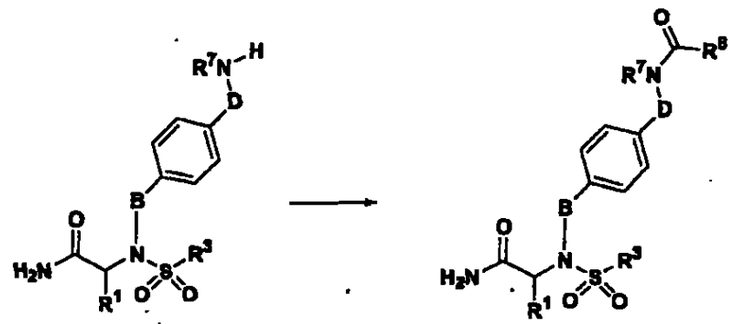
XXIV XXV XXVI

PG = an alcohol protecting group
D is other than a bond

Alcohols of Formula XXV and amines of Formula XXVI are synthesized by the sequence shown in Reaction Scheme 8. A protected alcohol of Formula XXIV is prepared by the procedure shown in Reaction Schemes 1 or 2. Deprotection of the alcohol under the appropriate conditions for the chosen protecting group (ref.: T.W. Greene and P.G.M. Wuts, "Protecting Groups in Organic Synthesis", Chapter 2) provides the alcohol of Formula XXV. For example, when the protecting group is a tetrahydropyranyl moiety, the alcohol is liberated by treatment of the compound of Formula XXIV with *p*-toluenesulfonic acid in a solvent such as methanol. The alcohol of Formula XXV is converted to

a leaving group (e.g., a halide or sulfonate) and then treated with a primary or secondary amine to afford an amine of Formula XXVI. For example, the alcohol may be converted to a mesylate derivative by reaction with methanesulfonyl chloride and a base such as triethylamine in CH_2Cl_2. Subsequent reaction of the mesylate with a primary or secondary amine in the presence of a base such as triethylamine in a solvent such as CH_2Cl_2 provides the amine of Formula XXVI.

Reaction Scheme 9

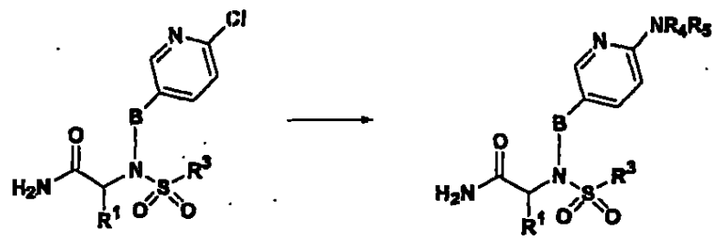


XXVII XXVIII

Amides of Formula XXVIII are prepared from amines of Formula XXVII as shown in Reaction Scheme 9. Amines of Formula XXVII wherein D is a direct bond are prepared as in Reaction Scheme 1 or 4. Amines of Formula XXVII wherein D is other than a direct bond are prepared as in Reaction Scheme 8. Conversion of the amines of Formula XXVII to the amides of Formula XXVIII is carried out using amide-coupling conditions well known to those skilled in the art (ref.: R.C. Larock "Comprehensive Organic Transformations, VCH Publishers, New York, 1989, pp. 972 – 976). For example, reaction of the amine of Formula XXVII with an acid chloride in the presence of a base such as triethylamine in a solvent such as CH_2Cl_2 provides the amide of Formula XXVIII. Conversion of the amines of Formula XXVII to carbamate derivatives can be carried out using conditions well known to those skilled in the art. (ref.: T.W. Greene and P.G.M. Wuts, "Protecting Groups in Organic Synthesis", P. 503 -

550). Preparation of sulfonamide derivatives from an amine of Formula XXVII can also be achieved using methods such as that described for the conversion of the intermediate of Formula II to the sulfonamide of Formula III.

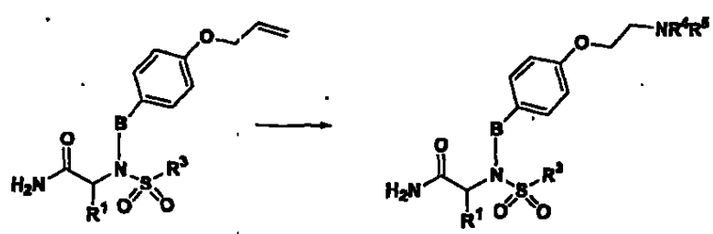
Reaction Scheme 10



XXIX XXX

The synthesis of pyridine derivatives of Formula XXX is accomplished as shown in Reaction Scheme 10. The chloropyridine derivative of Formula XXIX is prepared using the chemistry described in Reaction Schemes 1 or 2. Treatment of the compound of Formula XXIX with a primary or secondary amine in a solvent such as THF at temperatures from 20 °C to 100 °C, using sealed, pressurized vessel as appropriate, provides the aminopyridine of Formula XXX.

Reaction Scheme 11

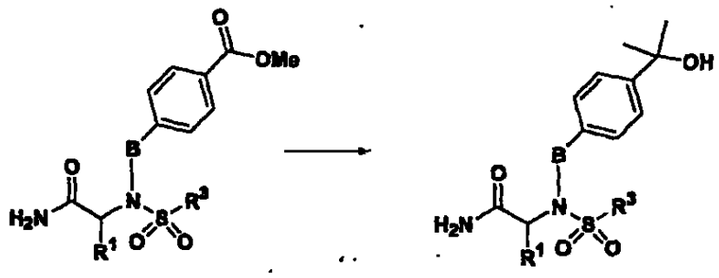


XXXI XXXII

Amine-substituted phenol ethers of Formula XXXII are prepared from (O-allyl)phenols as indicated in Reaction Scheme 11. The starting allyl ethers of

Formula XXXI are prepared as shown in Reaction Schemes 1 or 2. Treatment of the compound of Formula XXXI with osmium tetroxide and trimethylamine N-oxide in a solvent such as acetone followed by treatment with sodium periodate gives an intermediate aldehyde that is typically used without purification. Reaction of the unpurified aldehyde with a primary or secondary amine and a reducing agent such as sodium triacetoxyborohydride in a solvent such as ethanol with or without heating affords the amine of Formula XXXII.

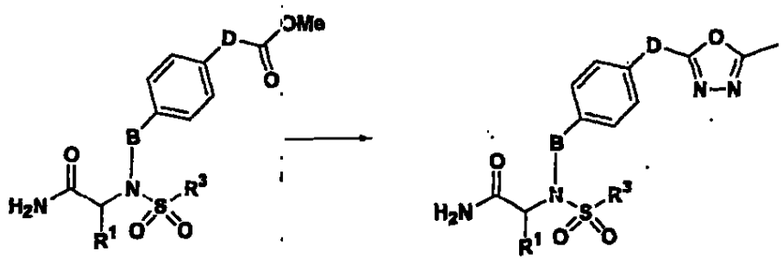
Reaction Scheme 12



XXXIII XXXIV

Conversion of the ester of Formula XXXIII to the tertiary alcohol of Formula XXXIV is carried out as shown in Reaction Scheme 12. Reaction of the ester of Formula XXXIII with an excess of a methyl organometallic reagent such as methyl magnesium bromide in a solvent such as THF at a temperature ranging from 0 °C to 25 °C yields the alcohol of Formula XXXIV.

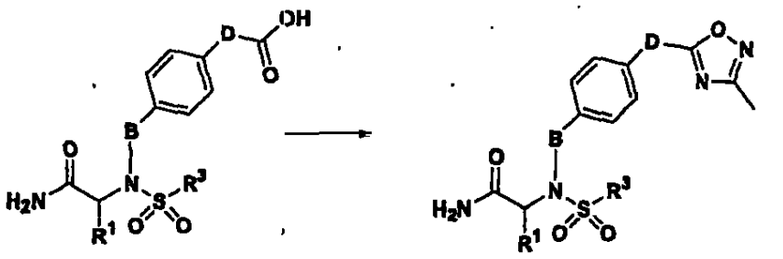
Reaction Scheme 13



XXXV XXXVI

Preparation of the 1,3,4-oxadiazole of Formula XXXVI is carried out as shown in Reaction Scheme 13 using methods well known to those skilled in the art (ref: Joule, J.A.; Mills, K.; Smith, G.F. Heterocyclic Chemistry, 3rd ed., Chapman & Hall: London, 1995; 452-456 and references cited therein). For example, the ester of Formula XXXV is treated with hydrazine in methanol with heating up to the reflux point. The resulting acyl hydrazide intermediate is used without purification in a subsequent reaction with an alkyl acetimidate in pyridine with heating at reflux to provide the oxadiazole of Formula XXXVI.

Reaction Scheme 14

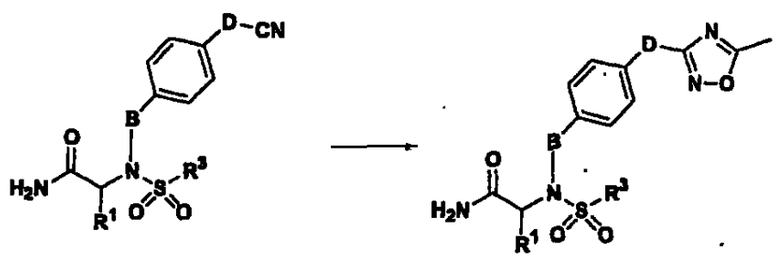


XVII XXXVII

Synthesis of the 1,2,4-oxadiazole of Formula XXXVII is achieved as shown in Reaction Scheme 14 using methods well known to those skilled in the art (ref: Joule, J.A.; Mills, K.; Smith, G.F. Heterocyclic Chemistry, 3rd ed.,

Chapman & Hall: London, 1995; 452-456 and references cited therein). For example, treatment of the acid of Formula XVII with hydroxbenzotriazole, a carbodiimide, and acetamidoxime (N-hydroxy ethanimidamide) in the presence of a base such as triethylamine provides an intermediate that is heated in refluxing pyridine to provide the oxadiazole of Formula XXXVII.

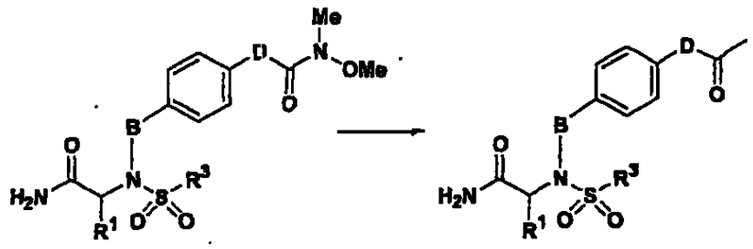
Reaction Scheme 15



XXXVIII XXXIX

The 1,2,4-oxadiazole of Formula XXXIX is prepared from the nitrile of Formula XXXVIII (Reaction Scheme 15) using methods well-known to those skilled in the art (ref: Joule, J.A.; Mills, K.; Smith, G.F. Heterocyclic Chemistry, 3rd ed., Chapman & Hall: London, 1995; 452-456 and references cited therein). For example, reaction of the nitrile of Formula XXXVIII with hydroxylamine in a solvent such as ethanol at temperatures up to reflux provides an intermediate N-hydroxyamidine that is subsequently treated with acetyl chloride in the presence of a base such as triethylamine in a solvent such as CH_2Cl_2 to provide the 1,2,4-oxadiazole of Formula XXXIX.

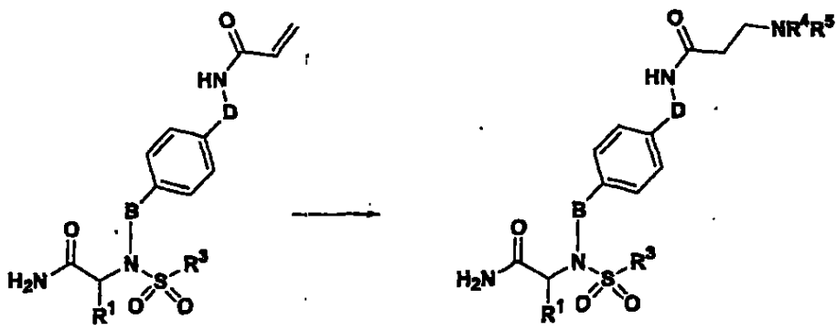
Reaction Scheme 16



XL XLI

Reaction Scheme 16 shows the transformation of the amide of Formula XL to the ketone of Formula XLI. The amide of Formula XL, which is prepared as described in Reaction Scheme 6, is treated with a methyl organometallic reagent such as methyl magnesium bromide in a solvent such as THF to provide the ketone of Formula XLI. The range of the reaction temperature is from –20 °C to 25 °C.

Reaction Scheme 17

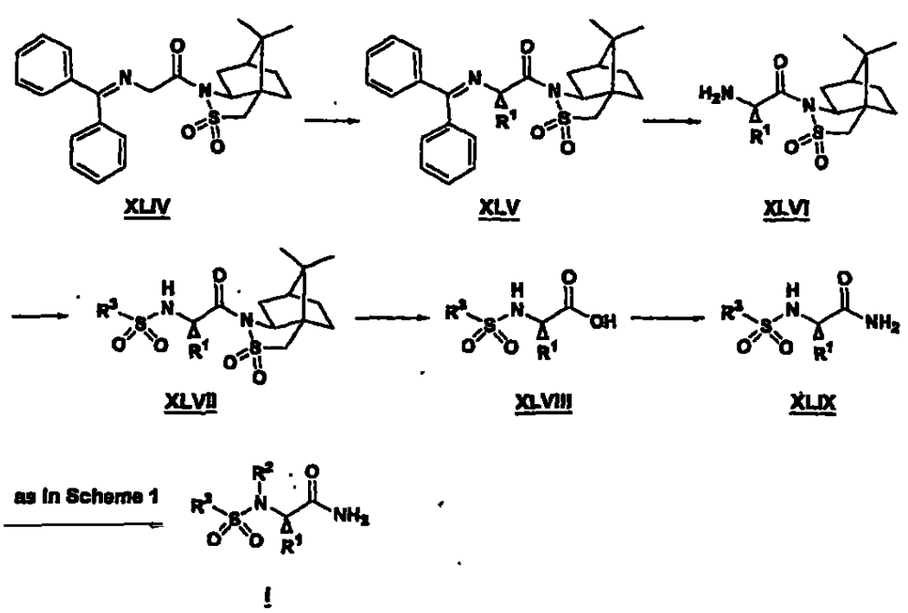


XLII XLIII

β-Amino amides of Formula XLIII are prepared from acrylamides of Formula XLII as shown in Reaction Scheme 17. For example, an acrylamide of Formula XLII, which is prepared as described in Reaction Scheme 9, is treated

with a primary or secondary amine in a solvent such as toluene to provide the β-amino amide of Formula XLIII.

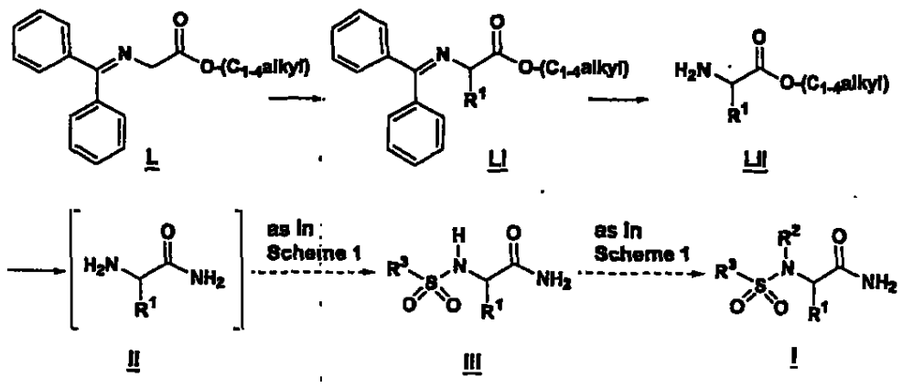
Reaction Scheme 18



Preparation of the sulfonamide intermediate of Formula XLIX (a single enantiomer of the compound of Formula III) is outlined in Reaction Scheme 18. Reaction of the α-anion of the intermediate of Formula XLIV (ref: Josien, H.; Martin, A.; Chassaing, G. Tetrahedron Lett. 1991, 32, 6547) with an alkylating agent such as an alkyl halide (e.g., an alkyl chloride, alkyl bromide, or alkyl iodide) or an alkyl sulfonate (e.g., an alkyl mesylate, alkyl tosylate, or alkyl trifluoromethanesulfonate) provides the intermediate of Formula XLV. The α-anion of the compound of Formula XLIV is formed by treatment with a strong base such as an alkyl lithium (e.g., n-BuLi) or a dialkylamide (e.g., lithium diisopropylamide) in a solvent such as THF with or without a co-solvent such as HMPA. The reaction temperature is typically between –78 °C and 25 °C. Removal of the benzhydrylidene protecting group of the compound of Formula

XLV is carried out under conditions well known to those skilled in the art (ref.: T.W. Greene and P.G.M. Wuts, "Protecting Groups in Organic Synthesis", Wiley Interscience, New York, 1999, pp. 587- 588). For example, the compound of Formula XLV is treated with an acid such as HCl in water in a solvent such as THF to effect hydrolysis of the benzhydrylidene protecting group. The resulting amine of Formula XLVI is treated with a sulfonylating agent as described for Reaction Scheme 1 to provide the sulfonamide of Formula XLVII. Hydrolysis of the acylsulfonamide of Formula XLVII to afford the acid of Formula XLVIII is carried out by treatment with hydroxide ion, for example in the form of lithium hydroxide, in the presence of additives such as lithium bromide and tetrabutylammonium bromide. The acid of Formula XLVIII is converted to the amide of formula XLIX under conditions that are well known to those skilled in the art (general ref for amide preparation.: R.C. Larock "Comprehensive Organic Transformations, VCH Publishers, New York, 1989, pp. 972 – 976). For example, reaction of the compound of Formula XLVIII with ammonium chloride in the presence of 1-hydroxybenzotriazole, a carbodiimide reagent, and an amine base such as diisopropylethylamine provides the amide of Formula XLIX. This reaction is typically run in a polar solvent such as DMF and at a reaction temperature from 0 °C to 40 °C. The amide of Formula XLIX is converted to the compounds of Formula I by the method described in Reaction Scheme 1.

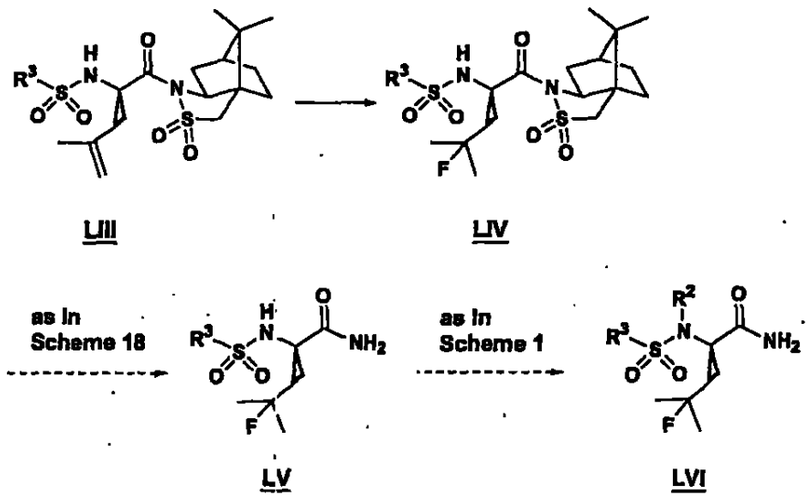
Reaction Scheme 19



Reaction Scheme 19 illustrates one method for synthesis of an α-substituted (N-sulfonamido)acetamide intermediate of Formula III starting with an activated glycine derivative of Formula L. Reaction of the compound of Formula L (ref.: Haufe, G.; Laue, K.W.; Triller, M.U.; Takeuchi, Y.; Shibata, N. *Tetrahedron* 1998, 54, p. 5929-5938; Kroger, S.; Haufe, G. *Amino Acids* 1997, 12, p. 363-372) with an alkylating agent such as an alkyl halide (e.g., an alkyl chloride, alkyl bromide, or alkyl iodide) or an alkyl sulfonate (e.g., an alkyl mesylate, an alkyl tosylate, or an alkyl trifluoromethanesulfonate) in the presence of a base such as potassium carbonate and an additive such as tetrabutylammonium bromide and in an inert solvent such as acetonitrile at a reaction temperature of between 25 °C and 70 ° C provides the compound of Formula LI. Removal of the benzhydrylidene protecting group is carried out under conditions well known to those skilled in the art (ref.: T.W. Greene and P.G.M. Wuts, "Protecting Groups in Organic Synthesis", Wiley Interscience, New York, 1999, pp. 587- 588). For example, a solution of the compound of Formula LI in a solvent such as diethyl ether is treated with aqueous acid (e.g., aqueous HCl), typically at a reaction temperature of between 0 °C and 30 °C, to provide the amine ester of Formula LII. Conversion of the ester of Formula LII to the amide of Formula II is carried out using procedures well known to those skilled in the art. For example, when the compound of Formula LII is an ethyl ester, hydrolysis of the ester is achieved by treatment of an ethereal solution with an acid such as HCl, typically with heating of the reaction mixture in refluxing solvent. The resulting acid intermediate is then converted to a methyl ester of Formula LII by transformation to the acid chloride under standard conditions, (e.g., treatment with thionyl-chloride and methanol), followed by reaction with aqueous ammonia in a solvent such as toluene (ref.: R.C. Larock "Comprehensive Organic Transformations, VCH Publishers, New York, 1989, pp. 972 – 976).. The amine of Formula II is converted to the compound of Formula I as described in Reaction Scheme 1.

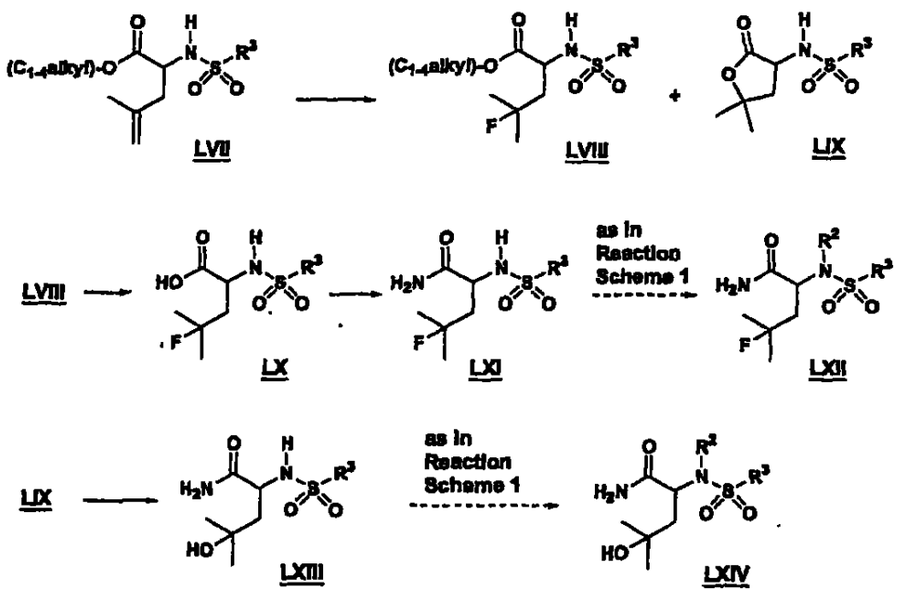
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Reaction Scheme 20



Preparation of the compound of Formula LVII is shown in Reaction Scheme 20. Alkene LIII is prepared as described in Reaction Scheme 18 from an intermediate of Formula XLIV and 1-bromo-2-methyl-2-propene). Treatment of the alkene of Formula LIII with HF•pyridine in a solvent such as THF at a reaction temperature between 0 °C and 25 °C affords the fluoroalkyl compound of Formula LIV. Conversion of the compound of Formula LIV to the amide of Formula LV is accomplished as described in Reaction Scheme 18. Transformation of the amide of Formula LV to the compound of Formula LVI is carried out as described in Reaction Scheme I.

Reaction Scheme 21



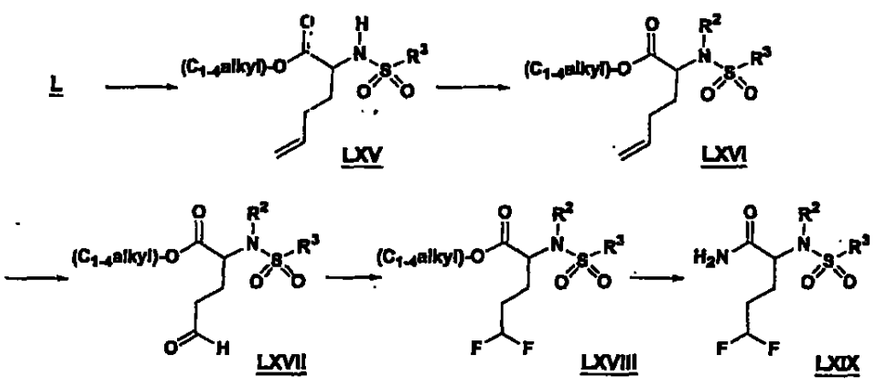
The syntheses of the compounds of Formula LXII and Formula LXIV are outlined in Reaction Scheme 21. Ethyl 2-amino-4-methyl-4-pentenoate (prepared as in Reaction Scheme 19 from (benzhydrylideneamino)acetic acid ethyl ester and 1-bromo-2-methyl-2-propene) is treated with a sulfonylating agent such as a sulfonyl chloride in the presence of a base such as triethylamine in an inert solvent such as CH_2Cl_2 to afford the ester of Formula LVII. Reaction of the ester of Formula LVII with HF•pyridine in a solvent such as THF and at a reaction temperature of between 0 °C and 25 °C provides a mixture of the fluoroalkyl derivative of Formula LVIII and the lactone of Formula LIX. These products are separated and carried on individually into subsequent reactions.

The ester of Formula LVIII is hydrolyzed to the acid of Formula LX using methods well known to those skilled in the art (ref.: T.W. Greene and P.G.M. Wuts, "Protecting Groups in Organic Synthesis", Wiley Interscience, New York, 1999, pp. 373 - 442). For example, treatment of the ester of Formula LVIII with aqueous sodium hydroxide in a solvent such as methanol affords the acid of

Formula LX. The acid of Formula LX is converted to the amide of Formula LXI using the procedure described in Reaction Scheme 18 for the preparation of the amide of Formula XLIX. Preparation of the amide of Formula LXII from the compound of Formula LXI is achieved as described in Reaction Scheme 1.

For the lactone of Formula LIX, treatment with aqueous ammonia provides the amide of Formula LXIII. This reaction is typically carried out with heating in a sealed tube. The reaction temperature is between 40 °C and 80 °C. Further conversion of the intermediate of Formula LXIII to the sulfonamide of Formula LXIV proceeded as described in Reaction Scheme 1.

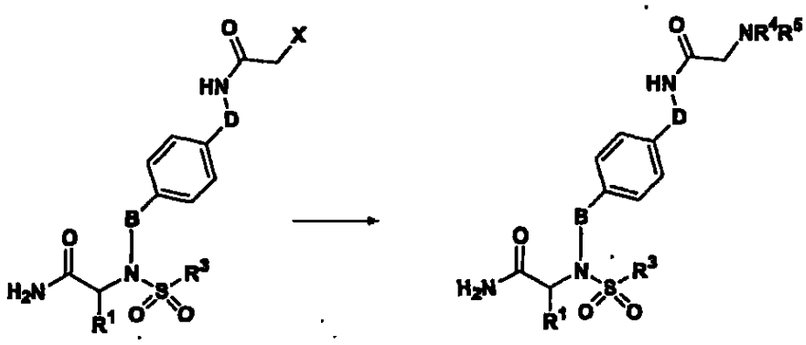
Reaction Scheme 22



The synthetic sequence for preparation of a difluoroalkyl amide of Formula LXIX is shown in Reaction Scheme 22. The compound of Formula L is treated with 4-bromo-1-butene in the presence of a base such potassium carbonate in the presence of a tetraalkylammonium halide salt such as tetrabutylammonium bromide in a solvent such as CH_3CN at a temperature from 20 °C to 70 °C. Removal of the benzhydrylidene protecting group as described in Reaction Scheme 19 provides an intermediate amine that is then treated with a sulfonylating reagent such as a sulfonyl chloride to provide the ester of Formula LXV. Alkylation of the sulfonamide nitrogen is accomplished using the procedure described in Reaction Scheme 1 to afford the compound of Formula

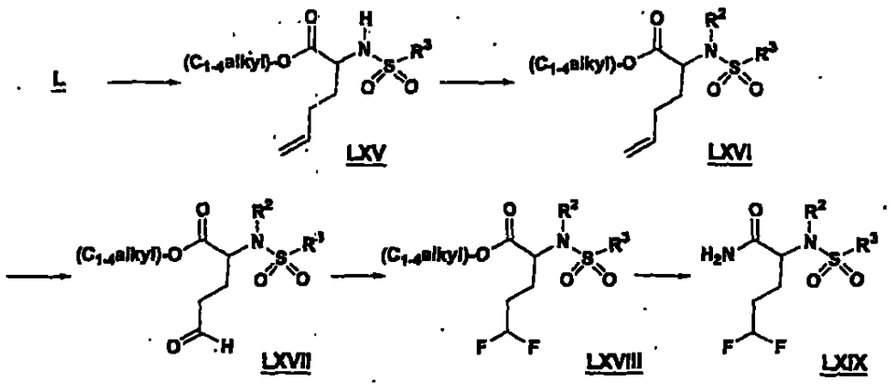
LXVI. Conversion of the alkene of Formula LXVI to the aldehyde of Formula LXVII is achieved by reaction of the alkene with osmium tetroxide and trimethylamine N-oxide in a solvent such as acetone, followed by treatment with sodium periodate. The reaction temperature is typically 20 °C to 40 °C. Reaction of the aldehyde of Formula LXVII with a fluorinating agent such as DAST in a solvent such as CH_2Cl_2 yields the difluoroalkyl derivative of Formula LXVIII. The compound of Formula LXVIII is converted to the amide of Formula LXIX by hydrolysis of the ester to an acid using an base such as sodium hydroxide in a solvent such as methanol. The intermediate acid was converted to the amide using conditions well known to those skilled in the art (ref.: R.C. Larock "Comprehensive Organic Transformations, VCH Publishers, New York, 1989, pp. 972 – 976). For example, reaction of the acid with ammonium chloride in the presence of hydroxybenzotriazole and a carbodiimide reagent and an amine base such as diisopropylethylamine provided the amide of Formula LXIX. This reaction is typically run in a polar solvent such as DMF and at a reaction temperature from 0° C to 40° C.

Reaction Scheme 23

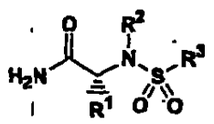


The α-amino amide of Formula LXXI is prepared using the reaction showed in Reaction Scheme 23. The amide of Formula LXX is prepared as

described in Reaction Scheme 9. Treatment of the compound of Formula LXX with a secondary or tertiary amine in a solvent such as THF at a reaction temperature between 20 °C and 40 °C affords the amine of Formula LXXI.



In a preferred embodiment, the present invention includes compounds of Formula Ia or a pharmaceutically acceptable salt thereof



Ia

wherein:

R^1 is selected from the group consisting of

(a) a straight or branched-chain C_{1-6} alkyl or C_{2-6}alkenyl optionally substituted with substituents selected from the group consisting of hydroxy, C_{3-7} cycloalkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, and halogen;

(b) C_{3-7} cycloalkyl optionally substituted with hydroxy or halogen;

R^2 is selected from the group consisting of

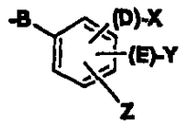
(a) a straight or branched-chain C_{1-6}alkyl or C_{2-6}alkenyl optionally substituted with substituents selected from the group consisting of halogen, C_{1-4}alkoxy, and NR^4R^5;

(b) C_{3-7} cycloalkylmethyl optionally substituted with substituents selected from the group consisting of amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, C_{1-4}alkylC(=O)NH-, and C_{1-4}alkylOC(=O)NH-;

(c) a straight or branched-chain C_{1-6}alkyl-C(=O)-A;

(d) -B-naphthyl;

(e)



D and B are each independently a direct bond, a straight or branched-chain C_{1-6}alkyl, C_{2-6} alkenyl, or C_{3-7} cycloalkyl;

Z is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halogen, cyano, hydroxy, -$OCHF_2$, -OCF_3, -CF_3, and -CHF_2;

X and Y are each independently selected from the group consisting of hydrogen, hydroxy, halogen, (halogen)$_3$C-, (halogen)$_2$CH-, C_{1-4}alkylS-, C_{1-4}alkylS(O)-, C_{1-4}alkylSO$_2$-, nitro, F_3S-, and cyano;

-OR^6;

-NR^4R^5;

-$NR^7C(=O)R^8$;

-$NR^7C(=O)OR^8$;

-$NHSO_2C_{1-4}$alkyl;

-$N(SO_2C_{1-4}alkyl)_2$;

-C(=O)W wherein W is selected from the group consisting of hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, phenoxy, and -NR^4R^5;

-$OC(=O)C_{1-4}$alkyl;

-phenyl in which said phenyl is optionally substituted with cyano, halogen, C_{1-4}alkoxy, C_{1-4}alkylS-, $CH_3C(=O)$, C_{1-4}alkylS(O)-, or C_{1-4}alkylSO$_2$-; and

heterocyclic group, in which said heterocyclic group is selected from the group consisting of furanyl, thiofuranyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, oxadiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, and thiazolyl, wherein said heterocyclic group is optionally substituted with substituents selected from the group consisting of cyano, halogen, C_{1-4}alkyl, (halogen)C_{1-4}alkyl, and CO_2C_{1-4}alkyl;

(f) -B-(heterocycle), in which said heterocycle is selected from the group consisting of furanyl, thiofuranyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, oxadiazolyl, oxazolyl, isoxazolyl, thiadiazolyl and thiazolyl wherein said heterocycle is optionally substituted with substituents selected from the group consisting of cyano, halogen, C_{1-4}alkyl, CO_2C_{1-4}alkyl, amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and 4-(C_{1-6}alkyl)piperazin-1-yl;

(g) -B-(piperidin-4-yl), in which said piperidin-4-yl is optionally substituted with substituents selected from the group consisting of a straight or branched-chain C_{1-6}alkyl, $CH_2C(=O)$phenyl, phenyl and phenylmethyl in which said C_{1-6}alkyl and said phenyl are optionally substituted with substituents selected from the group consisting of cyano, halogen, benzimidazol-2-yl, pyridyl and tetrahydrofuran-2-yl; and -C(=O)W' wherein W' is selected from the group consisting of C_{1-4}alkoxy, R^9, and $-NR^4R^5$;

A is hydroxy, C_{1-4}alkoxy or NR^4R^5;

B is a straight or branched-chain C_{1-6}alkyl or C_{3-6}alkenyl;

R^3 is phenyl or pyridyl optionally substituted with substituents selected from the group consisting of halogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkyl, $(halogen)_3C-$, $(halogen)_2CH-$, and $halogenCH_2-$;

R^4 and R^5 each are independently hydrogen, a straight or branched-chain C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylmethyl,

C_{1-4}alkoxy, phenyl, benzyl, pyridyl, piperidin-4-yl, indan-1-yl, indan-2-yl, tetrahydrofuran-3-yl, or pyrrolidin-3-yl; in which each is optionally substituted with substituents selected from the group consisting of hydroxy, cyano, halogen, $(halogen)_3C$-, $(halogen)_2CH$-, halogenCH_2-, hydroxymethyl, benzyloxymethyl, phenyl, pyridyl, C_{1-4}alkyl, C_{1-4}alkoxy, $(halogen)_3C$-O-, $(halogen)_2CH$-O-, C_{1-4}alkylthio, amino, $(C_{1-4}alkyl)NH$-, $di(C_{1-4}alkyl)N$-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, 4-(C_{1-6}alkyl)piperazin-1-yl, 4-phenylpiperazin-1-yl, 4-benzylpiperazin-1-yl, 4-pyridylpiperazin-1-yl, CO_2H, CO_2C_{1-4}alkyl, $C(=O)NHC_{1-4}$alkyl, and $C(=O)N(C_{1-4}alkyl)_2$;

R^4 and R^5 taken together may be morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, decahydroquinolin-1-yl, piperidin-1-yl, piperazin-1-yl, [1,4]-oxazepan-4-yl, azetidin-1-yl, 2,3-dihydro-1*H*-isoindol-2-yl, or 2,3-dihydro-1*H*-indol-1-yl; in which each is optionally substituted with substituents selected from the group consisting of hydroxy, cyano, halogen, $(halogen)_3C$-, $(halogen)_2CH$-, halogenCH_2-, phenyl, pyridyl, benzyl, C_{1-6}alkyl, C_{3-7} cycloalkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, amino, $(C_{1-4}alkyl)NH$-, $di(C_{1-4}alkyl)N$-, CO_2H, CO_2C_{1-4}alkyl, $C(=O)NHC_{1-4}$alkyl, and $C(=O)N(C_{1-4}alkyl)_2$;

R^6 is a straight or branched-chain C_{1-6}alkyl, C_{3-6} alkenyl, benzyl, or phenyl in which each is optionally substituted with substituents selected from the group consisting of halogen, C_{1-4}alkyl, C_{1-4}alkoxy, amino, $(C_{1-4}alkyl)NH$-, $di(C_{1-4}alkyl)N$-, $(C_{1-4}alkyl)(phenyl)N$-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and 4-(C_{1-4}alkyl)piperazin-1-yl;

R^7 is hydrogen, a straight or branched-chain C_{1-6} alkyl;

R^8 is a straight or branched-chain C_{1-6}alkyl, C_{3-7} cycloalkyl, phenyl, pyridyl, or furanyl; in which each is optionally substituted with substituents selected from the group consisting of halogen, C_{1-4}alkyl, C_{1-4}alkoxy, $(C_{1-4}alkyl)NH$-, $di(C_{1-4}alkyl)N$-, morpholin-4-yl, thiomorpholin-4-yl,

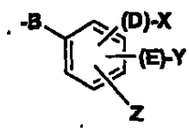
pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and 4-(C_{1-6}alkyl)piperazin-1-yl;

R^9 is a straight or branched-chain C_{1-6}alkyl, C_{1-6} alkenyl, benzyl, phenyl, oxazolyl or pyridyl; in which each is optionally substituted with substituents selected from the group consisting of halogen, (halogen)$_3$C-, (halogen)$_2$CH-, halogenCH_2-, C_{1-4}alkyl, C_{1-4}alkoxy, amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and 4-(C_{1-6}alkyl)piperazin-1-yl;

or a non-toxic pharmaceutically acceptable salt thereof.

In another preferred embodiment, the invention includes compounds of Formula Ia or a pharmaceutically acceptable salt thereof wherein R^3 is phenyl optionally substituted with substituents selected from the group consisting of halogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkyl, (halogen)$_3$C-, (halogen)$_2$CH-, and halogenCH_2-.

In yet another preferred embodiment, the invention includes compounds of Formula Ia or a pharmaceutically acceptable salt thereof wherein R^2 is



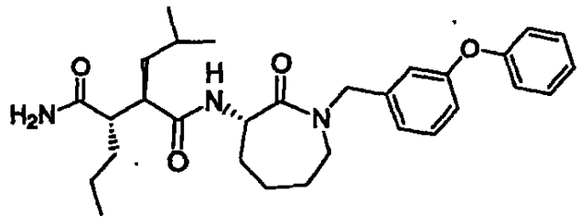
BIOLOGICAL TESTING METHODS

Compounds of Formula (I) are expected to possess γ-secretase inhibitory activity. The detection of γ-secretase activity requires assays capable of reliable, accurate and expedient detection of γ-secretase cleavage products, particularly Aβ. The γ-secretase inhibitory activity of the compounds of the present invention is demonstrated using assays for such activity, for example, using the assays described below. Compounds within the scope of the present invention have been shown to inhibit the activity of γ-secretase, as determined using assays for such activity.

Compounds provided by this invention should also be useful as standards and reagents in determining the ability of a potential pharmaceutical to inhibit Aβ production. These would be provided in commercial kits comprising a compound of this invention.

In vitro binding assay to identify γ-secretase inhibitors.

Competitive binding assays can be used to identify molecules that inhibit the binding of a radiolabeled γ-secretase inhibitor and therefore inhibit γ-secretase activity. For example, [^{3}H]-Compound A can be used for binding assays with membranes from THP-1 cells (Seiffert, D.; Bradley, J. et al., *J. Biol. Chem.* 2000, 275, 34086-34091). Compound A is (2R,3S) N1-[(3S)-hexahydro-1-(3-phenoxybenzyl)-2-oxo-1H-azepin-3-yl]-2-(2-methylpropyl)-3-(propyl)-butanediamide, the synthesis of which is described in U.S. patent US6331408 (12/18/2001); PCT Publication WO 00/28331; PCT Publication WO 00/07995; and Seiffert, D., Bradley, J. et al., *J. Biol. Chem.* 2000, 275. 34086-34091.



Compound A

For these assays, THP-1 cells were grown in spinner cultures in RPMI 1640 containing L-glutamine and 10 μM β-mercaptoethanol to a density of 5 x 10^5 cells/mL. Cells were harvested by centrifugation and cell pellets were quick frozen in dry ice/ethanol and stored at - 70 °C prior to use. The pellets of approximately 2 x 10^4 THP-1 cells were homogenized using a Brinkman Polytron at setting 6 for 10 sec. The homogenate was centrifuged at 48,000 x g for 12 min, and the resulting pellet was washed by repeating the homogenization

and centrifugation. The final cell pellet was resuspended in buffer to yield a protein concentration of approximately 0.5 mg/ml. Assays were initiated by the addition of 150 µl of membrane suspension to 150 µl of assay buffer containing 0.064 µCi of radioligand and various concentrations of unlabeled compounds. Binding assays were performed in duplicate in polypropylene 96-well plates in a final volume of 0.3 ml containing 50 mM Hepes, pH 7.0, and 5% dimethyl sulfoxide. Nonspecific binding was defined using incubations with 300 nM compound A (Seiffert, D., Bradley, J. et al., *J. Biol. Chem.* 2000, 275, 34086-34091). After incubating at 23 °C for 1.3 hr, bound ligand was separated from free radioligand by filtration over GFF glass fiber filters presoaked in 0.3% ethyleneimine polymer solution. Filters were washed three times with 0.3 ml of ice cold phosphate-buffered saline, pH 7.0, containing 0.1% Triton X-100. Filter-bound radioactivity was measured by scintillation counting. IC_{50} values were then determined and used to calculate K_i values using the Cheng-Prusoft correction for IC_{50} values. Compounds were scored as active γ-secretase inhibitors if K_i values were less than 10 µM.

Examples of the results obtained when the invention compounds are subjected to the above described assay are shown in Table 1. In the table, an inhibitory concentration (IC_{50}) of less than or equal to 50 nM is represented by +++; between 50 nM and 500 nM by ++; between 500 nM and 10000 nM by +.

TABLE 1: Examples of activity in the *in vitro* binding Assay

EXAMPLE	ACTIVITY RATING[a]
96	+++
123	+++
159	+++
315	++
341	++
357	++

EXAMPLE	ACTIVITY RATING[a]
362	+++
365	+++
366	+++
367	+
376	++
379	+++
385	+++
389	+++
394	+++
403	++
405	+++
408	+
409	++
437	+++
441	+++
443	++
445	+++
447	+++
450	++
451	+
452	++
457	++
464	+
474	+++
476	+++
479	++
486	+++

[a] Activity based on IC_{50} values:

+++	=	<50 nM
++	=	50 - 500 nM
+	=	>500 nM and <10,000 nM

In vitro assay to identify γ-secretase inhibitor based on the inhibition of Aß formation from membrane preparations.

An isolated membrane fraction which contains functionally active γ-secretase and β-APP substrates can generate γ-secretase cleavage products including Aβ (Roberts, S.B.; Hendrick, J. P.; Vinitsky, A.; Lewis, M.; Smith, D.W.; Pak, R. PCT Publication WO 01/0175435; Fechteler, K.; Kostka, M.; Fuchs, M. Patent Application No. DB 99-19941039; Shearman, M.; Beher, D. et al., *Biochemistry*, 2000, 39, 8698-8704; Zhang, L. Song, L. et al., *Biochemistry* 2001, 40, 5049-5055). An isolated membrane fraction can be prepared from human derived cell lines such as HeLa and H4 which have been transfected with wild type or mutant forms of β-APP or a human alkaline phosphatase β-APP fusion construct, and stably express high levels of γ-secretase substrates. The endogenous γ-secretase present in the isolated membranes prepared at 0-4 °C cleaves the β-APP substrates when the membranes are shifted from 0-4 to 37 °C. Detection of the cleavage products including Aβ can be monitored by standard techniques such as immunoprecipitation (Citron, M.; Diehl, T.S. et al., *Proc. Natl. Acad. Sci. USA*, 1996, 93,13170-13175), western blot (Klafki, H.-W.; Ambramowski, D. et al., *J. Biol. Chem.*, 1996, 271, 28655-28659), enzyme linked immunosorbent assay (ELISA) as demonstrated by Seubert, P.; Vigo-Pelfrey, C. et al., *Nature*, 1992, 359, 325-327, or by a preferred method using time-resolved fluorescence of the homogeneous sample containing membranes and Aβ (Roberts, S.B.; Hendrick, J. P.; Vinitsky, A.; Lewis, M.; Smith, D.W.; Pak, R. PCT Publication WO 01/0175435; Shearman, M.; Beher, D. et al., *Biochemistry*, 2000, 39, 8698-8704). The Aβ present in a homogeneous sample containing membranes can be detected by time-resolved fluorescence with two antibodies that recognize different epitopes of Aβ. One of the antibodies

recognizes an epitope that is present in Aβ but not present in the precursor fragments; preferably the antibody binds the carboxyl terminus of Aβ generated by the γ-secretase cleavage. The second antibody binds to any other epitope present on Aβ. For example, antibodies that bind the N-terminal region (e.g., 26D6-B2-B3 ® SIBIA Neurosciences, La Jolla, CA) or bind the C-terminal end (e.g., 9S3.2 ® antibody, Biosolutions, Newark, DE) of the Aβ peptide are known. The antibodies are labeled with a pair of fluorescent adducts that transfer fluorescent energy when the adducts are brought in close proximity as a result of binding to the N- and C-terminal ends or regions of Aβ. A lack of fluorescence is indicative of the absence of cleavage products, resulting from inhibition of γ-secretase. The isolated membrane assay can be used to identify candidate agents that inhibit the activity of γ-secretase cleavage and Aβ production.

A typical membrane-based assay requires 45 μg membrane protein per well in a 96- or 384-well format. Membranes in a neutral buffer are combined with the test compound and shifted from 0-4 to 37 °C. Test agents may typically consist of synthetic compounds, secondary metabolites from bacterial or fungal fermentation extracts, or extracts from plant or marine samples. All synthetic agents are initially screened at doses ranging from 10-100 μM or in the case of extracts at sufficient dilution to minimize cytotoxicity. Incubation of the membranes with the test agent will continue for approximately 90 minutes at which time fluorescence labeled antibodies are added to each well for Aβ quantitation. The time-resolved fluorescence detection and quantitation of Aβ is described elsewhere (Roberts, S.B.; Hendrick, J. P.; Vinitsky, A.; Lewis, M.; Smith, D.W.; Pak, R. PCT Publication WO 01/0175435; Shearman, M.; Beher, D. et al., *Biochemistry,* 2000. 39, 8698-8704). Results are obtained by analysis of the plate in a fluorescence plate reader and comparison to the mock treated membranes and samples in which known amounts of Aβ were added to construct a standard concentration curve. A positive acting compound is one that inhibits the Aβ relative to the control sample by at least 50% at the initial tested concentration. If a compound is found to be active then a dose response

experiment is performed to determine the lowest dose of compound necessary to elicit the inhibition of the production of Aβ. Compounds were scored as active γ-secretase inhibitors if K_i values were less than 10 μM.

Examples of the results obtained when the invention compounds are subjected to the above described assay are shown in Table 2. In the table, an inhibitory concentration (IC_{50}) of less than or equal to 50 nM is represented by +++; between 50 nM and 500 nM by ++; between 500 nM and 10000 nM by +.

TABLE 2: Examples of activity in the *in vitro* assay based on the inhibition of Aβ formation from membrane preparations

EXAMPLE	ACTIVITY RATING[a]
1	+++
2	+++
3	+++
4	+++
5	+++
6	+++
7	+++
8	+++
9	+++
10	+++
11	+++
12	+++
13	+++
14	+++
15	+++
16	+++
17	+++

EXAMPLE	ACTIVITY RATING[a]
18	++
19	++
20	++
21	+++
22	+++
23	+++
24	+++
25	+++
26	+++
27	++
28	++
29	+++
30	++
31	++
32	+++
33	+++
34	+++
35	++
36	++
37	+++
38	+++
39	+++
40	+++
41	+++
42	+++
43	+++
44	+++
45	+++

EXAMPLE	ACTIVITY RATING[a]
46	+++
47	+++
48	+++
49	++
50	+++
51	+++
52	+++
59	++
61	+++
83	+
85	+
87	+++
89	+++
95	+++
103	+++
113	++
122	+
133	+++
153	++

[a] Activity based on IC_{50} values:

+++ = <50 nM

++ = 50 - 500 nM

+ = >500 nM and <10,000 nM

In vitro assays to identify γ-secretase inhibitor based on the inhibition of Aβ formation in cultured cells.

Cultured human cell lines, such as HEK293 and H4 cells, which express APP and γ-secretase activity or transfected derivative cell lines that overexpress

wild-type APP, mutant APP, or APP fusion proteins will secrete Aβ peptides into the culture media that can be quantified as previously outlined (Dovey, H., John, V. et al., *J. Neurochem.* 2001, 76, 173-181). The incubation of these cultured cells with γ-secretase inhibitors decreases the production of Aβ peptides. For instance, H4 cells stably transfected to overexpress the HPLAP-APP fusion protein described above were grown as above, detached, and adjusted to 2 x 10^5 cells/ml. 100 µl of the resulting suspension was then added to each well of a 96-well plate. After 4 hrs, the media was removed and replaced with 100 µl serum-free media containing various dilutions of the test compound. Plates were then incubated for 18 hrs at 37 °C and a 100 µl aliquot of the tissue culture supernatant was removed for determination of Aβ levels using time-resolved fluorescence of the homogenous sample as outlined above. Alternately, the other methods described above for Aβ determination could be used. The extent of Aβ inhibition was used to calculate the IC_{50} value for the test compound. Compounds of the present invention are considered active when tested in the above assay if the IC_{50} value for the test compound is less than 50 µM.

Examples of the results obtained when the invention compounds are subjected to the above described assay are shown in Table 3. In the table, an inhibitory concentration (IC_{50}) of less than or equal to 50 nM is represented by +++; between 50 nM and 500 nM by ++; between 500 nM and 50000 nM by +.

TABLE 3: Examples of activity in the *in vitro* assay based on the inhibition of Aβ formation in cultured cells

EXAMPLE	ACTIVITY RATING[a]
1	+++
5	+++
19	++
26	+++

EXAMPLE	ACTIVITY RATING[a]
38	+++
41	+++
51	+++
55	+++
61	+++
72	+++
80	+++
89	+++
96	+++
101	+++
123	+++
127	++
143	+++
147	++
158	+++
171	++
193	+++
203	+++
205	++
207	+++
245	+++
246	+++
249	++
254	+++
256	+++
260	+++
272	+++
280	++

EXAMPLE	ACTIVITY RATING[a]
282	+++
288	++
301	++
302	+++
321	++
322	+++
329	+++
330	++
331	+
340	+++
341	++
342	+++
349	+++
352	++
358	++
359	+++
366	+++
367	+
378	+++
383	+++
394	+++
403	++
416	+++
418	+++
424	+++
433	+++
434	+++
439	+++

EXAMPLE	ACTIVITY RATING[a]
442	+++
472	+++
481	+
492	++
495	+++
497	+++

[a] Activity based on IC_{50} values:

+++ = <50 nM

++ = 50 - 500 nM

+ = >500 nM and <10,000 nM

Compounds of the present invention have been demonstrated to have an IC_{50} value less than 10 μM in one or all of the above assays. Therefore, the compounds of Formula I or pharmaceutical compositions thereof are useful in the treatment, alleviation or elimination of disorders or other disorders associated with the inhibition of β-amyloid peptide.

In addition to cleaving APP, γ-secretase cleaves other substrates, including: the Notch family of transmembrane receptors (reviewed in: Selkoe, D. *Physiol. Rev.* 2001, 81, 741-766; Wolfe, M. *J. Med. Chem.* 2001 44, 2039-2060); LDL receptor-related protein (May, P., Reddy, Y.K., Herz, J. *J. Biol. Chem.* 2002, 277, 18736-18743); ErbB-4 (Ni, C.Y., Murphy, M.P., Golde, T.E., Carpenter, G. *Science* 2001, 294, 2179-2181); E-cadherin (Marambaud, P., Shioi, J., et al., *EMBO J.* 2002, 21,1948-1956); and CD44 (Okamoto, I., Kawano, Y., et al., *J. Cell Biol.* 2001, 155, 755-762). If inhibition of cleavage of non-APP substrates causes undesirable effects in humans, then desired γ-secretase inhibitors would preferentially inhibit APP cleavage relative to unwanted substrates. Notch cleavage can be monitored directly by measuring the amount of cleavage product or indirectly by measuring the effect of the cleavage product on

transcription (Mizutani, T., Taniguchi, Y., et al. *Proc. Natl. Acad. Sci. USA* 2001, 98, 9026-9031).

In vivo assays for the determination of Aβ reduction by γ-secretase inhibitors.

In vivo assays are available to demonstrate the inhibition of γ-secretase activity. In these assays, animals, such as mice, that express normal levels of APP and γ-secretase or are engineered to express higher levels of APP and hence Aβ can be used to demonstrate the utility of γ-secretase inhibitors (Dovey, H., John, V., et al., *J. Neurochem.* 2001, 76, 173-181). In these assays, γ-secretase inhibitors were administered to animals and Aβ levels in multiple compartments, such as plasma, cerebral spinal fluid, and brain extracts, were monitored for Aβ levels using methods previously outlined. For instance, Tg2576 mice, which overexpress human APP, was administered γ-secretase inhibitors by oral gavage at doses that will cause measurable Aβ lowering, typically less than 100 mg/kg. Three hours after dosing plasma, brain, and CSF were collected, frozen in liquid nitrogen, and stored at –80 °C until analysis. For Aβ detection, plasma was diluted 15-fold in PBS with 0.1% Chaps while CSF was diluted 15-fold in 1% Chaps with protease inhibitors (5 μg/ml leupeptin, 30 μg/ml aprotinin, 1 mM phenylmethylsulfonylfluoride, 1 μM pepstatin). Brains were homogenized in 1% Chaps with protease inhibitors using 24 ml solution/g brain tissue. Homogenates were then centrifuged at 100,000 x g for 1 hr at 4 °C. The resulting supernatants were then diluted 10-fold in 1% Chaps with protease inhibitors. Aβ levels in the plasma, CSF, and brain lysate were measured using time-resolved fluorescence of the homogenous sample or one of the other methods previously described.

A γ-secretase inhibitor is considered active in one of the above in vivo assays if it reduces Aβ by at least 50% at a dosage of 100 mg/kg.

Therefore, the compounds of Formula I or pharmaceutical compositions thereof are useful in the treatment, alleviation or elimination of disorders or other disorders associated with the inhibition of β-amyloid peptide.

In another embodiment, this invention includes pharmaceutical compositions comprising at least one compound of Formula I in combination with a pharmaceutical adjuvant, carrier or diluent.

In still another embodiment, this invention relates to a method of treatment or prevention of disorders responsive to the inhibition of β-amyloid peptide in a mammal in need thereof, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I or a nontoxic pharmaceutically acceptable salt, solvate or hydrate thereof.

In yet another embodiment, this invention relates to a method for treating Alzheimer's Disease and Down's Syndrome in a mammal in need thereof, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I or a non-toxic pharmaceutically acceptable salt, solvate or hydrate thereof.

For therapeutic use, the pharmacologically active compounds of Formula I will normally be administered as a pharmaceutical composition comprising as the (or an) essential active ingredient at least one such compound in association with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically acceptable adjuvants and excipients employing standard and conventional techniques.

The pharmaceutical compositions include suitable dosage forms for oral, parenteral (including subcutaneous, intramuscular, intradermal and intravenous) bronchial or nasal administration. Thus, if a solid carrier is used, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form, or in the form of a troche or lozenge. The solid carrier may contain conventional excipients such as binding agents, fillers, tableting lubricants, disintegrants, wetting agents and the like. The tablet may, if desired, be film coated by conventional techniques. If a liquid carrier is employed, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule, sterile vehicle for injection, an aqueous or non-aqueous liquid suspension, or may be a dry product for reconstitution with water or other suitable vehicle before use. Liquid preparations may contain conventional additives such as suspending agents, emulsifying

agents, wetting agents, non-aqueous vehicle (including edible oils), preservatives, as well as flavoring and/or coloring agents. For parenteral administration, a vehicle normally will comprise sterile water, at least in large part, although saline solutions, glucose solutions and like may be utilized. Injectable suspensions also may be used, in which case conventional suspending agents may be employed. Conventional preservatives, buffering agents and the like also may be added to the parenteral dosage forms. The pharmaceutical compositions are prepared by conventional techniques appropriate to the desired preparation containing appropriate amounts of the active ingredient, that is, the compound of Formula I according to the invention. See, for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, 17th edition, 1985.

The dosage of the compounds of Formula I to achieve a therapeutic effect will depend not only on such factors as the age, weight and sex of the patient and mode of administration, but also on the degree of β-AP inhibition desired and the potency of the particular compound being utilized for the particular disorder of disease concerned. It is also contemplated that the treatment and dosage of the particular compound may be administered in unit dosage form and that the unit dosage form would be adjusted accordingly by one skilled in the art to reflect the relative level of activity. The decision as to the particular dosage to be employed (and the number of times to be administered per day) is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect.

A suitable dose of a compound of Formula I or pharmaceutical composition thereof for a mammal, including man, suffering from, or likely to suffer from any condition related to β-AP production as described herein, generally the daily dose will be from about 0.05 mg/kg to about 10 mg/kg and preferably, about 0.1 to 2 mg/kg when administered parenterally. For oral administration, the dose may be in the range from about 1 to about 75 mg/kg and preferably from 0.1 to 10 mg/kg body weight. The active ingredient will preferably be administered in equal doses from one to four times a day. However, usually a small dosage is administered, and the dosage is gradually

increased until the optimal dosage for the host under treatment is determined. In accordance with good clinical practice, it is preferred to administer the instant compounds at a concentration level that will produce an effective anti-amyloid effect without causing any harmful or untoward side effects. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances including the condition to be treated, the choice of compound of be administered, the chosen route of administration, the age, weight, and response of the individual patient, and the severity of the patient's symptoms.

The following examples are given by way of illustration and are not to be construed as limiting the invention in any way inasmuch as many variations of the invention are possible within the spirit of the invention.

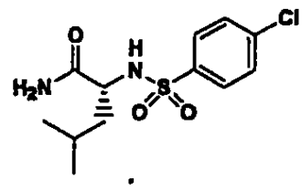
DESCRIPTION OF THE SPECIFIC EMBODIMENTS

In the following examples, all temperatures are given in degrees Centigrade. Melting points were recorded on a Thomas Scientific Unimelt capillary melting point apparatus and are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance 300, a Bruker Avance 400, or a Bruker Avance 500 spectrometer. All spectra were determined in the solvents indicated and chemical shifts are reported in δ units downfield from the internal standard tetramethylsilane (TMS) and interproton coupling constants are reported in Hertz (Hz). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak; dd, doublet of doublet; br d, broad doublet; dt, doublet of triplet; br s, broad singlet; dq, doublet of quartet. Infrared (IR) spectra using potassium bromide (KBr) or sodium chloride film were determined on a Jasco FT/IR-410 or a Perkin Elmer 2000 FT-IR spectrometer from 4000 cm^{-1} to 400 cm^{-1}, calibrated to 1601 cm^{-1} absorption of a polystyrene film and reported in reciprocal centimeters (cm^{-1}). Optical rotations $[\alpha]_D$ were determined on a Rudolph Scientific Autopol IV polarimeter in the solvents indicated; concentrations are given in mg/mL. Low resolution mass

spectra (MS) and the apparent molecular (MH^+) or $(M-H)^+$ was determined on a Finnegan SSQ7000. High resolution mass spectra were determined on a Finnegan MAT900. Liquid chromatography (LC)/mass spectra were run on a Shimadzu LC coupled to a Water Micromass ZQ.

The following abbreviations are used: DMF (dimethylformamide); THF (tetrahydrofuran); DMSO (dimethylsulfoxide), Leu (leucine); TFA (trifluoroacetic acid); DAST [(diethylamino)sulfur trifluoride], HPLC (high pressure liquid chromatography); rt (room temperature); aq. (aqueous).

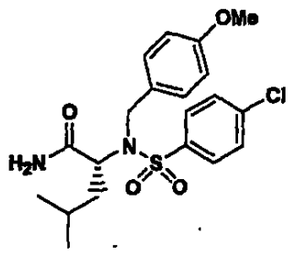
Exemplification of Reaction Scheme 1



(2*R*)-2-(4-Chlorobenzenesulfonylamino)-4-methylpentanoic acid amide:

To a solution of (*D*)-leucinamide hydrochloride (0.25 g, 1.5 mmol), and Et_3N (0.43 mL, 3.0 mmol) in CH_2Cl_2 (150 mL) was added 4-chlorobenzene-sulfonyl chloride (380 mg, 1.8 mmol). The resulting solution was stirred at rt for 18 h. The reaction was then diluted with CH_2Cl_2 (200 mL) and washed with H_2O, 0.5 N HCl, brine, and dried over $MgSO_4$, to afford the titled compound (410 mg) as a white solid in 90% yield. MS (ESI), $(M+H)^+$ 305.2; ^1H NMR (DMSO-d_6) δ 7.77 (d, 2H, J = 8.7), 7.62 (d, 2H, J = 8.7), 6.90 (br s, 1H), 3.67 (m, 1H), 1.54 (m, 1H), 1.31 (m, 2H), 0.81 (d, 3H, J = 7.0), 0.71 (d, 3H, J = 7.0).

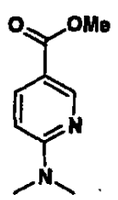
Method A for conversion of III to I:



(2*R*)-2-[N-(4-Chlorobenzenesulfonyl)-N-(4-methoxybenzyl)amino]-4-methylpentanoic acid amide (**Example 1**):

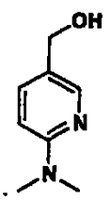
(2*R*)-2-(4-Chlorobenzenesulfonylamino)-4-methylpentanoic acid amide (300 mg, 1 mmol), K_2CO_3 (170 mg, 1.2 mmol), and 4-methoxybenzyl chloride (170 mg, 1.1 mmol) in DMF (25 mL) was heated to 60 °C for 18 h. The reaction was then diluted with EtOAc (150 mL) and washed with H_2O, brine, dried over $MgSO_4$ and concentrated to give a crude white wax. Further purification by flash chromatography (SiO_2, 25% EtOAc/hexanes) afforded the titled compound (297 mg) as a white solid in 70% yield. $[\alpha]_D = +44.2$ (c 1.00, MeOH); MS (ESI), $(M-H)^-$ 422.9; ^1H NMR ($CDCl_3$) δ 7.63 (d, 2H, $J = 7.0$), 7.42 (d, 2H, $J = 7.0$), 7.25 (d, 2H , $J = 8.0$), 6.79 (d, 2H, $J = 8.0$), 6.25 (br s, 1H), 5.35 (br s, 1H), 4.36 (dd, 2H, $J = 50$, 15), 4.26 (t, 1H, $J = 7.2$), 3.78 (s, 3H), 1.83 (m, 1H), 1.18-1.34 (m, 2H), 0.75 (d, 3H, $J = 7.0$), 0.67 (d, 3H, $J = 7.0$); IR (KBr) 3480, 2959, 1693, 1674, 1514, 1333, 1158 cm^{-1}.

Method B for conversion of III to I:



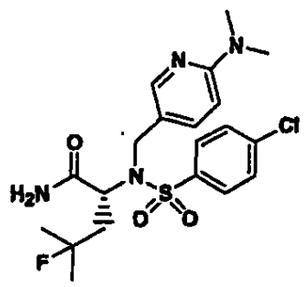
Methyl 6-dimethylaminonicotinate:

A solution of methyl 6-chloronicotinate (4.0 g, 23 mmol) in dimethylamine/MeOH (2 M, 80 mL, 160 mmol) in a pressure vessel was stirred at 95 °C for 2 h, cooled to rt and concentrated. The residue was dissolved in EtOAc (250mL), washed with water (2 x 150 mL), dried over Na_2SO_4, and concentrated to afford the title compound as a tan solid (4.1 g, 98%). MS (ESI), $(M+H)^+$ 181.24; ^1H NMR ($CDCl_3$) δ 8.79 (s, 1H), 7.99 (d, 1H, J = 9.2), 6.45 (d, 1H, J = 9.2), 3.85 (s, 3H), 3.15 (s, 6H).



2-Dimethylamino-5-hydroxymethylpyridine:

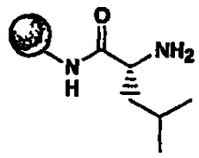
A solution of methyl 6-dimethylamino-nicotinate (4.14 g, 23.0 mmol) in anhydrous ether (80 mL) at 0 °C was treated with lithium aluminum hydride (1 M in ether, 20 mL, 20 mmol). The mixture was stirred at rt for 0.5 h, cooled again to 0 °C and quenched slowly with sat. aq. $NaHCO_3$ (10 mL). The resulting mixture was stirred at rt for 0.5 h, filtered, and washed with ether. The combined filtrates were dried over Na_2SO_4 and concentrated to give the title compound as a beige waxy solid (3.5 g, 100%). MS (ESI), $(M+H)^+$ 153.4; ^1H NMR ($CDCl_3$) δ 8.06 (d, 1H, J = 2.4), 7.47 (dd, 1H, J = 2.4, 8.8), 6.45 (d, 1H, J = 8.8), 4.50 (s, 2H), 3.06 (s, 6H), 1.98 (br s, 1H).



(2*R*)-2-[N-(4-Chlorobenzenesulfonyl)-N-(2-dimethylaminopyridin-5-yl)amino]-4-fluoro-4-methylpentanoic acid amide TFA salt (**Example 459**):

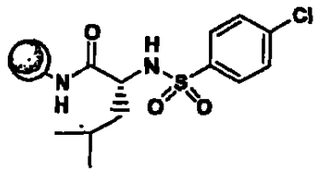
To a cloudy solution of (2*R*)-2-[(4-chlorobenzenesulfonylamino)-4-fluoro-4-methylpentanoic acid amide (prepared as in Reaction Scheme 20 or from γ-fluoro-D-Leu-OH methyl ester, Papageorgiou et. al., Bioorg. & Med. Chem. Lett. 1994, Vol. 4, p.p. 267-272; 0.060 g, 0.18 mmol), 2-dimethylamino-5-hydroxymethylpyridine (71 mg, 0.46 mmol), triphenylphosphine (122 mg, 0.464 mmol) in CH_2Cl_2 (9.5 mL) at rt was added dropwise diisopropyl azodicarboxylate (75 μL, 0.46 mmol). The resulting pale yellow solution was stirred at rt for 2 h and concentrated under vacuum. The residue was dissolved in methanol an purified by reverse phase preparative HPLC (YMC S5, ODS, MeOH-water-TFA) to afford the title compound as a white foam (90 mg, 85%). MS (ESI), $(M+H)^+$ 457.2; ^1H NMR ($CDCl_3$) δ 8.11 (s, 1H), 7.95 (d, 1H, J = 9.6), 7.77 (d, 2H, J = 6.8), 7.51 (d, 2H, J = 6.8), 6.76 (d, 2H, J = 9.6), 6.34 (s, 1H), 6.02 (s, 1H), 4.58(br d, 1H, J = 8.4), 4.46 (d, 1H, J = 16.0), 4.06 (d, 1H, J = 16), 3.29 (s, 6H), 2.50 (m, 1H), 1.39 (m, 1H), 1.25 (d, 3H, J = 22.0), 1.17 (d, 3H, J = 22.0).

Exemplification of Reaction Scheme 1 – Solid Support



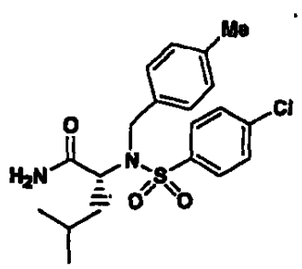
Polymer-bound D-Leu-NH_2: FMOC-protected Rink amide resin (30 g, 0.61 mmol/g, 18 mmol) was treated with piperidine/DMF solution (250 mL). The mixture was shaken at rt for 24 h, drained, washed with DMF (5 x 200mL), CH_2Cl_2 (5 x 200 mL) and dried under vacuum. The resin was then treated with FMOC-D-Leu-OH (22 g, 62 mmol), 1-hydroxybenzotriazole hydrate (2.5 g, 18 mmol), 1,3-diisopropylcarbodiimide (9.8 mL, 62 mmol), and DMF (250 mL).

The mixture was shaken for 20 h, drained, washed with DMF (4 x 200 mL), DMF-water (1:1, 3 x 200 mL), DMF (3 x 200 mL), MeOH (3 x 200 mL), CH_2Cl_2 (3 x 200mL) and dried. The completion of reaction and the loading of the resin-bound FMOC-D-Leu-NH_2 (0.56 mmol/g) were determined by the treatment of 52 mg of the resin with 10% (v/v) TFA/CH_2Cl_2 (2 mL) to give 11 mg of FMOC-D-Leu-NH_2. The resin-bound FMOC-D-Leu-NH_2 was deprotected with 20% (v/v) piperidine/DMF solution (250 mL) to give polymer-bound D-Leu-NH_2 (20 g).



Polymer-bound (R)-2-(4-Chlorobenzenesulfonylamino)-4-methylpentanoic acid amide:

The above polymer-bound D-Leu-NH_2 (20 g) was treated with CH_2Cl_2 (150 mL), pyridine (100 mL) and 4-chlorophenylsulfonyl chloride (20.0 g, 94.8 mmol). The mixture was shaken for 24 h, drained, washed with DMF (4 x 200 mL), CH_2Cl_2 (4 x 200 mL) and concentrated to give polymer-bound (R)-2-(4-chlorobenzenesulfonylamino)-4-methylpentanoic acid amide as a yellow resin (22 g). The completion of the reaction and the loading of the resin (0.57 mmol/g) were determined by the treatment of 50 mg of the resin with 10% (v/v) TFA/CH_2Cl_2 (2 mL) to give 8.7 mg of (R)-2-(4-chlorobenzenesulfonylamino)-4-methylpentanoic acid amide.



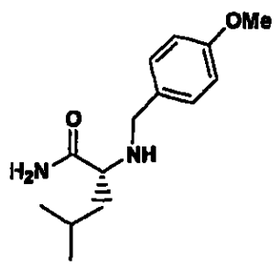
33

(2*R*)-2-[N-(4-Chlorobenzenesulfonyl)-N-(4-methylbenzyl)amino]-4-methylpentanoic acid amide (**Example 60**):

To a mixture of polymer-bound (2*R*)-2-[N-(4-chlorobenzenesulfonyl)amino]-4-methylpentanoic acid amide (loading 0.45 mmol/g, 50.0 mg, 0.0225 mmol), 4-methylbenzyl bromide (44 mg, 0.24 mmol) and DMF (1.5 mL) was added 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diaza-phosphorine (0.10 mL, 0.34 mmol). The resulting mixture was shaken at rt for 2 days, then was drained and washed with DMF (4 x 2 mL), MeOH (4 x 2 mL) and CH_2Cl_2 (4 x 2 mL).

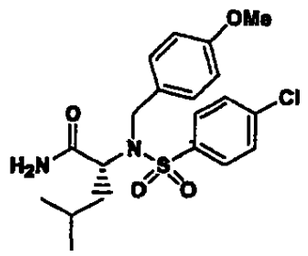
The resin was then treated with 10% (v/v) TFA/CH_2Cl_2. The mixture was shaken for 1 h, filtered and washed with CH_2Cl_2 (2 x 0.5 mL). The combined filtrates were concentrated under vacuum to afford the title compound as a beige solid (7.7 mg, 100%, HPLC purity > 95%). HRMS (ESI), $(M-H)^-$ for $C_{20}H_{24}SClN_2O_3$ calcd: 407.1206, found: 407.1201; ^1H NMR ($CDCl_3$) δ 7.64 (d, 2H, J = 8.0), 7.44 (d, 2H, J = 8.0), 7.22 (d, 2H, J = 8.0), 7.08 (d, 2H, J = 8.0), 6.29 (br s, 1H), 5.34 (br s, 1H), 4.53 (d, 1H, J = 15.2), 4.34 (d, 1H, J = 15.2), 4.27 (t, 1H, J = 7.2), 2.32 (s, 3H), 1.84 (m, 1H), 1.30 (m, 1H), 1.21 (m, 1H), 0.75 (d, 3H, J = 6.8), 0.67 (d, 3H, J = 6.8); IR (KBr) 3467, 3367, 2956, 2869, 1694, 1670, 1340, 1160 cm^{-1}.

Exemplification of Reaction Scheme 2



(2*R*)-2-(4-Methoxybenzylamino)-4-methylpentanoic acid amide:

A solution of *D*-leucinamide hydrochloride (2.8 g, 16.8 mmol), and p-anisaldehyde (2.29 g, 16.8 mmol) in methanol (150 mL) was treated with anhydrous $ZnCl_2$ (538 mg, 5 mmol). The resulting suspension was then treated with $NaCNBH_3$ (1.05 g, 16.8 mmol) portion wise and heated at reflux for 3 h. The reaction was cooled to rt, quenched with saturated $NaHCO_3$ (3 mL), diluted with EtOAc (500 mL), and washed with brine. Concentration afforded the crude benzyl amine as a white wax, which was carried on without further purification (3.57 g, 84%). MS (ESI), $(M+H)^+$ 251.4; ^1H NMR ($CDCl_3$) δ 7.20 (d, 2H, *J* = 6.6), 7.10 (br s, 2H), 6.88 (d, 2H, *J* = 8.4), 5.30 (br s, 1H), 3.80 (s, 3H), 3.63 (dd, 2H, *J* = 4.5, 12), 1.44-1.65 (m, 3H), 0.95 (d, 3H, *J* = 6.3), 0.80 (d, 3H, *J* = 6.3).

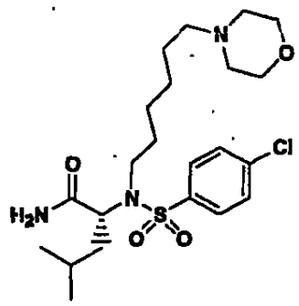


(2*R*)-2-[N-(4-Chlorobenzenesulfonyl)-N-(4-methoxybenzyl)amino]-4-methylpentanoic acid amide (Example 1):

(2*R*)-2-[N-(4-Methoxybenzy)lamino]-4-methylpentanoic acid amide (3.57 g , 14.3 mmol) was dissolved in CH_2Cl_2 (100 mL) and treated with Et_3N (4.2 mL, 29 mmol) and 4-chlorobenzenesulfonyl chloride (3.6 g, 17 mmol) at rt for 18 h. The solvents were removed and the residue was taken into EtOAc (500 mL). The organic solution was washed with H_2O, brine, dried over $MgSO_4$, and concentrated. The resulting material was then further purified by flash chromatography (SiO_2, 1% MeOH/CH_2Cl_2) to afford the title compound (2.4 g) as a slightly colored solid in 40% yield. MS (ESI), $(M-H)^-$ 422.9; ^1H NMR ($CDCl_3$) δ 7.63 (d, 2H, *J* = 7.0), 7.42 (d, 2H, *J* = 7.0), 7.25 (d, 2H, *J* = 8.0), 6.79 (d, 2H, *J* = 8.0), 6.25 (br s, 1H), 5.35 (br s, 1H), 4.36 (dd, 2H, *J* = 5.0, 15), 4.26 (t, 1H, *J* =

7.2), 3.78 (s, 3H), 1.83 (m, 1H), 1.18-1.34 (m, 2H), 0.75 (d, 3H, J = 7.0), 0.67 (d, 3H, J = 7.0); IR (KBr) 3480, 2959, 1693, 1674, 1514, 1333, 1158 cm^{-1}.

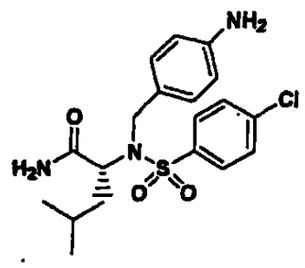
Exemplification of Reaction Scheme 3



(2*R*)-2-[N-(4-Morpholinohexyl)-N-(4-chlorobenzenesulfonyl)amino]-4-methylpentanoic acid amide (**Example 25**):

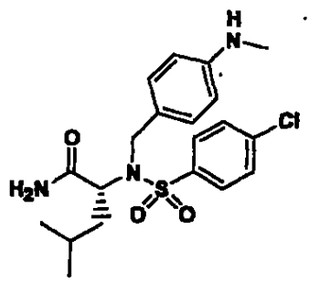
A solution of (2*R*)-2-[N-(4-bromohexyl)-N-(4-chlorobenzenesulfonyl)amino]-4-methylpentanoic acid amide (Example 24; prepared as described in Reaction Scheme 1; 0.20 g, 0.44 mmol), Et_3N (0.25 mL, 1.7 mmol), and morpholine (150 mg, 1.7 mmol) in CH_2Cl_2 (2 mL) was stirred at rt for 18 h. The reaction was then concentrated to give a crude white wax which was purified by flash chromatography (SiO_2, 85% EtOAc/5% hexanes/10% MeOH) to afford the title compound (112 mg) as a white solid in 54% yield. MS (ESI), $(M+H)^+$ 474.4; ^1H NMR (DMSO-d_6) δ 7.82 (d, 2H, J = 8.0), 7.64 (d, 2H, J = 8.0), 7.42 (br s, 1H) 6.99 (s, 1H), 4.25 (m, 1H), 3.51-3.60 (br s, 4H), 3.18-3.41 (m, 2H), 2.25-2.35 (br s, 4H), 2.27 (m, 2H)1.15-1.62 (m, 9H), 0.80 (d, 6H, J = 6.0).

Exemplification of Reaction Scheme 4



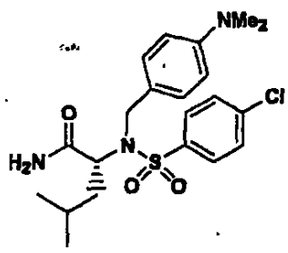
(2*R*)-2-[N-(4-Chlorobenzenesulfonyl)-N-(4-aminobenzyl)amino]-4-methylpentanoic acid amide (**Example 48**):

(2*R*)-(2-[N-(4-Chlorobenzenesulfonyl)-N-(4-nitrobenzyl)amino]-4-methylpentanoic acid amide (Compound of Example 24; prepared as described in Reaction Scheme 1; 2.8 g, 6.6 mmol) was suspended with 10% Pd/C (1 g) and conc. HCl (1 mL) in MeOH (100 mL) and placed under a hydrogen atmosphere at 40 psi for 1 h. The suspension was filtered through Celite and then concentrated to give the title compound as a tan solid (2.4 g, 88% yield). MS (ESI), $(M+H)^+$ 410.1; ^1H NMR ($CDCl_3$) δ 7.80 (d, 2H, J = 8.5), 7.63 (d, 2H, J = 8.5), 7.52 (br s, 1H), 7.46 (d, 1H, J = 8.0), 7.26 (d, 1H, J = 8.0), 7.02 (br s, 1H), 4.70 (dd, 2H, J = 50, 18), 4.30-4.41 (m, 1H), 3.67 (br s, 2H), 1.28-1.33 (m, 3H), 0.86 (d, 3H, J = 7.0), 0.57 (d, 3H, J = 7.0).



(2*R*)-2-[N-(4-Chlorobenzenesulfonyl)-N-(4-methylaminobenzyl)amino]-4-methylpentanoic acid amide (**Example 51**):

A solution of (2*R*)-2-[N-(4-chlorobenzenesulfonyl)-N-(4-aminobenzyl)amino]-4-methyl-pentanoic acid amide (Example 48, 400 mg, 1 mmol), Et_3N (0.16 mL, 1.1 mmol), dimethylsulfate (139 mg, 1.1 mmol) in 25 mL of toluene was stirred at rt for 18 h. The reaction was concentrated, then taken into EtOAc and washed with H_2O, brine, dried over K_2CO_3 and concentrated to give a crude mixture of starting material and product. The material was further purified by flash chromatography (SiO_2, 35% EtOAc/hexanes) to afford the title compound, 195 mg, in 46% yield. MS (ESI), $(M+H)^+$ 424.1; ^1H NMR ($CDCl_3$) δ 7.65 (d, 2H, J = 8.0), 7.58 (d, 2H, J = 8.2), 7.47 (d, 2H, J = 8.0), 7.31 (d, 2H, J = 8.5), 6.24 (br s, 1H), 5.16 (br s, 1H), 4.50(dd, 2H, J = 50, 17), 4.27 (t, 1H, J = 10), 2.44 (s, 3H), 1.74-1.83 (m, 1H), 1.25-1.33 (m, 1H), 0.93-1.01 (m, 1H), 0.74 (d, 3H, J = 7.0), 0.63 (d, 3H, J = 7.0).

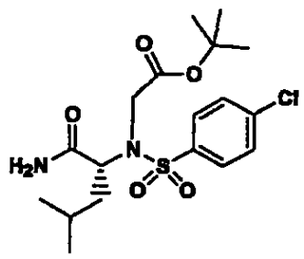


(2*R*)-2-[N-(4-Chlorobenzenesulfonyl)-N-(4-dimethylaminobenzyl)amino]-4-methylpentanoic acid amide (**Example 65**):

(2*R*)-2-[N-(4-Chlorobenzene-sulfonyl)-N-(4-aminobenzyl)amino]-4-methyl-pentanoic acid amide (Example 48, 0.10 g, 0.22 mmol) was dissolved in DMF (5 mL). To this solution was added iodomethane (62 mg, 0.44 mmol), and cesium carbonate (220 mg, 0.66 mmol). The reaction was then stirred at 40 °C for 18 h. The reaction was poured into EtOAc and water. The organic was collected, dried over $MgSO_4$, and concentrated to an oily residue. The residue was further purified (Biotage 40S, loaded in CH_2Cl_2, eluted in 25% EtOAc/hexanes) to yield a yellow powder (15 mg, 16%). MS(ESI), $(M+H)^+$ 438.1; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.74 (dd, 2H, J = 1.9, 6.7), 7.54 (dd, 2H, J = 1.9, 6.8), 7.43 (s, 1H),

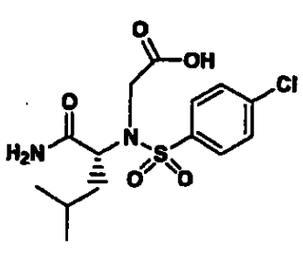
7.16 (d, 2H, J = 8.6), 7.01 (s, 1H), 6.61 (d, 2H, J = 8.8), 4.59 (q, 2H, J = 16, 25), 4.34 (dd, 1H, J = 5.0, 9.3), 2.85 (s, 6H), 1.27-1.47 (m, 3H), 0.80 (d, 3H, J = 5.9), 0.52 (d, 3H, J = 6.1).

Exemplification of Reaction Scheme 5



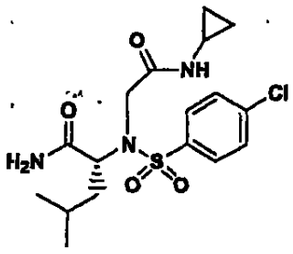
{N-[(1*R*)-1-Carbamoyl-3-methyl-butyl]-N-(4-chlorobenzenesulfonyl)amino}acetic acid tert-butyl ester (**Example 46**):

(2*R*)-2-(4-Chlorobenzenesulfonylamino)-4-methylpentanoic acid amide (3.00 g, 9.87 mmol) was dissolved in DMF (50 mL). To the solution was added potassium carbonate (6.0 g, 39 mmol) and bromoacetic acid *tert*-butyl ester (6.0 mL, 39 mmol). The solution was heated to 70 °C for 3 h. The reaction was quenched with EtOAc and saturated $NaHCO_3$. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude oil was further purified on a Biotage 40M (loaded in CH_2Cl_2, eluted in 30% EtOAc/hexanes) to afford a white powder (1.2 g, 35%). MS(ESI), $(M+H)^+$ 446.3; ^1H NMR ($CDCl_3$) δ 7.76 (d, 2H, J = 8.0), 7.52 (d, 2H, J = 8.0), 6.61 (br s, 1H) 5.45 (s, 1H), 4.15-4.18 (m, 1H), 3.09-3.24 (m, 2H), 2.50-2.58 (m, 4H), 2.31-2.39 (m, 2H), 1.92-1.99 (m, 1H), 1.15-1.59 (m, 8H), 1.00-1.04 (m, 7H), 0.71-0.74 (m, 6H).



{N-[(1*R*)-1-Carbamoyl-3-methyl-butyl]-N-(4-chlorobenzenesulfonyl)amino}acetic acid (**Example 59**):

Trifluoroacetic acid (15 mL) was added to a solution of {N-[(1*R*)-1-carbamoyl-3-methyl-butyl]-N-(4-chlorobenzenesulfonyl)amino}acetic acid tert-butyl ester (0.50 g, 1.2 mmol) in CH_2Cl_2 (15 mL). The reaction was stirred at rt for 4 h. The reaction was then concentrated to a white solid (0.40 g, 92%), which was used without further purification. MS(ESI), $(M+H)^+$ 363.1; ^1H NMR (DMSO-d_6, 500MHz) δ 7.90 (dd, 2H, J = 2.0, 6.8), 7.65 (dd, 2H, J = 2.0, 6.8), 7.60 (s, 1H), 7.06 (s, 1H), 4.32 (d, 1H, J = 18), 4.12 (t, 1H, J = 8.0), 4.02 (d, 1H, J = 18), 1.55-1.65 (m, 1H), 1.35-1.45 (m, 2H), 0.78 (d, 3H, J = 6.1), 0.73 (d, 3H, J = 6.1).

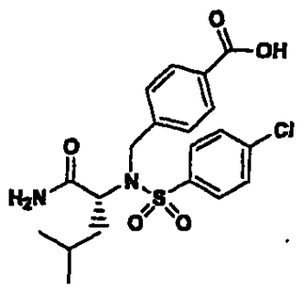


(2*R*)-2-[N-(4-Chlorobenzenesulfonyl)-N-(cyclopropylcarbamoylmethyl)amino]-4-methyl-pentanoic acid amide (**Example 88**):

To a solution of {N-[(1*R*)-1-carbamoyl-3-methyl-butyl]-N-(4-chlorobenzenesulfonyl)amino}acetic acid (Example 59, 175 mg, 0.480 mmol), cyclopropylamine (41 uL, 0.58 mmol) in CH_2Cl_2 (3 mL) was added 1-hydroxybenzotriazole (47 mg, 0.72 mmol), and 1,3-dicyclohexylcarbodiimide (144 mg, 0.720 mmol). The reaction was stirred for 18 h at rt, and then was poured into an EtOAc/water mixture. The organic layer was separated, dried over $MgSO_4$, and concentrated to a clear oil residue. The residue was further purified by Biotage 40S (eluted in 40% EtOAc in hexanes) to afford a white solid (54 mg, 29%). MS(ESI), $(M+H)^+$ 402.2; ^1H NMR ($CDCl_3$, 500MHz) δ 7.85 (dd, 2H, J = 1.9, 8.9), 7.50 (dd, 2H, J = 2.0, 8.7), 7.40 (br s, 1H), 6.55 (br s, 1H), 6.30 (br s,

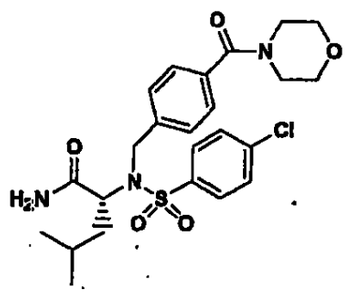
1H), 4.23 (dd, 1H, J = 2.9, 8.9), 3.92 (d, 1H, J = 17), 3.83 (d, 1H, J = 17), 2.68-2.73 (m, 1H), 1.75-1.83 (m, 1H), 1.50-1.57 (m, 1H), 1.40-1.49 (m, 1H), 0.88 (d, 3H, J = 6.4), 0.87 (d, 3H, J = 6.7), 0.80 (d, 2H, J = 7.0), 0.51 (t, 2H, J = 4.0).

Exemplification of Reaction Scheme 6



4-{[N-((1*R*)-1-Carbamoyl-3-methyl-butyl)-N-(4-chlorobenzenesulfonyl)amino]-methyl}-benzoic acid (**Example 89**):

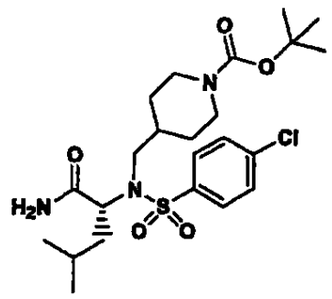
A solution of the compound of Example 61 [4-{[N-((1*R*)-1-carbamoyl-3-methyl-butyl)-N-(4-chlorobenzenesulfonyl)amino]-methyl}-benzoic acid methyl ester, 354 mg, 0.782 mmol] was dissolved in methanol (4 mL). A solution of 5 N NaOH (1 mL) was added, followed by enough THF (1 mL) to achieve homogeneity. After 1 h, an additional aliquot of 5 N NaOH (1 mL) was added, and stirring was continued for 2.5 h. The solution was acidified to pH 2 with 1 N HCl and extracted with $CHCl_3$ (2x). The combined organic layers were dried (Na_2SO_4) and concentrated to give a white solid (343 mg, 100%). MS (ESI), $(M+H)^+$ 439.17; ^1H NMR ($CDCl_3$, 300MHz) δ 7.91 (d, 2H, J = 8.2), 7.81-7.84 (m, 3H), 7.56 (d, 2H, J = 8.6), 7.49 (d, 2H, J = 8.2), 6.55 (br s, 1H), 5.10 (d, 1H, J = 15.4), 4.23 (dd, 1H, J = 4.6, 9.7), 4.05 (d, 1H, J = 15.4), 2.04-2.14 (m, 1H), 1.20-1.31 (m, 1H), 0.80-0.89 (m, 1H), 0.74 (d, 3H, J = 6.6), 0.68 (d, 3H, J = 6.6).



(2*R*)-2-{N-(4-Chlorobenzenesulfonyl)-N-[4-(morpholine-4-carbonyl)-benzyl]amino}-4-methyl-pentanoic acid amide (**Example 101**):

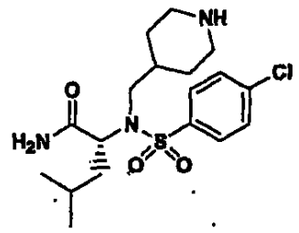
To a 0 °C solution of 4-{[N-((1*R*)-1-carbamoyl-3-methyl-butyl)-N-(4-chlorobenzenesulfonyl)amino]-methyl}benzoic acid (50.0 mg, 0.114 mmol) in DMF (0.3 mL) was added morpholine (12.9 mg, 0.148 mmol), followed by 1-hydroxybenzotriazole (18.5 mg, 0.137 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (26.2 mg, 0.137 mmol), and iPr$_2$NEt (26 μL, 0.15 mmol). After 2 h, the solution was warmed to rt. After 4 h, the solution was poured into 10% aq. citric acid and extracted with EtOAc (2x). The combined organic layers were washed sequentially with water and sat. aq. $NaHCO_3$, then dried ($MgSO_4$) and concentrated. Flash column chromatography (SiO_2, 40 to 100% EtOAc/hexanes) gave the title compound as a white solid (46.0 mg, 79%). MS (ESI), $(M+H)^+$ 508.22; ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.68 (d, 2H, J = 8.6), 7.29-7.47 (m, 6H), 6.38 (br s, 1H), 5.75 (br s, 1H), 4.65 (d, 1H, J = 16.0), 4.42 (d, 1H, J = 16.0), 4.32 (t, 1H, J = 7.5), 3.30-3.85 (br m, 8H), 1.69-1.78 (m, 1H), 1.28-1.37 (m, 1H), 1.08-1.14 (m, 1H), 0.76 (d, 3H, J = 6.5), 0.63 (d, 3H, J = 6.6).

Exemplification of Reaction Scheme 7



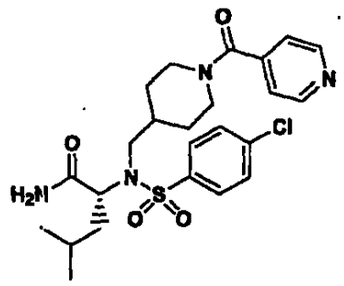
4-{[N-((1*R*)-1-Carbamoyl-3-methyl-butyl)-N-(4-chlorobenzenesulfonyl)amino]-methyl}-piperidine-1-carboxylic acid tert-butyl ester (**Example 92**):

To a solution of (2*R*)-2-(4-chlorobenzenesulfonylamino)-4-methylpentanoic acid amide (4.2 grams, 14 mmol) in DMF (50 mL) was added cesium carbonate (13.6 grams, 417 mmol). To this reaction was added 4-(toluene-4-sulfonyloxymethyl)-piperidine 1-carboxylic acid *tert*-butyl ester (ref.: Gilissen, C.; Bormans, G.; De Groot, T.; Verbruggen, A. *J. Labeled Cmpd. Radiopharm.* 1999, *42*, 1289; 10.4 g, 282 mmol). The reaction was stirred at 70 °C for 18 h. The reaction was then quenched with sat. aq. $NaHCO_3$ and extracted with EtOAc. The organic layer was collected, washed with brine, dried over $MgSO_4$, and concentrated to a clear oil. The oil was then purified on a Biotage 40S (eluted with 30% EtOAc in hexanes) to afford a white solid (3.0 g, 44%). MS(ESI), $(M+H)^+$ 502.1; ^1H NMR (DMSO-*d6*, 500MHz) δ 7.86 (dd, 2H, *J* = 2.0, 6.8), 7.65 (dd, 2H, *J* = 2.0, 6.8) 7.37 (br s, 1H), 7.07 (br s, 1H), 4.19 (t, 1H, *J* = 7.6), 3.92 (br s, 2H), 3.35 (dd, 1H, *J* = 15, 6.8), 3.05 (dd, 1H, *J* = 15, 8.1), 1.85 (br s, 1H), 1.50-1.70 (m, 4H), 1.38 (s, 9H), 1.10-1.20 (m, 1H), 0.80-1.00 (m, 3H), 0.82 (d, 6H, *J* = 7.6).



(2*R*)-2-[N-(4-Chlorobenzenesulfonyl)-N-(piperidin-4-ylmethyl)amino]-4-methyl-pentanoic acid amide (**Example 126**):

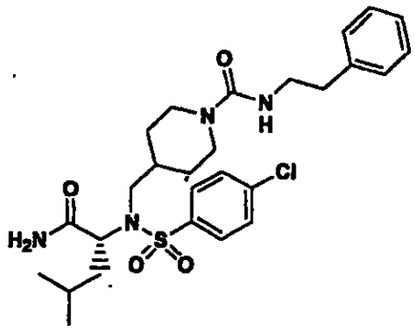
To a solution of 4-{[N-((1*R*)-1-carbamoyl-3-methyl-butyl)-N-(4-chlorobenzenesulfonyl)amino]-methyl}-piperidine-1-carboxylic acid *tert*-butyl ester (Example 92, 2.6 grams, 5.2 mmol) in CH_2Cl_2 (25 mL) was added trifluoroacetic acid (10 mL). The reaction was stirred at rt for 1 h and then was concentrated to give a white solid (1.6 grams, 84%). MS(ESI), $(M+H)^+$ 402.15; ^1H NMR (DMSO-*d6*, 500MHz), δ 7.87 (d, 2H, J = 8.5), 7.66 (d, 2H, J = 8.6), 7.41 (s, 1H), 7.04 (s, 1H), 4.17 (t, 1H, J = 7.3), 3.40-3.50 (m, 1H), 3.20-3.25 (m, 1H), 3.03-3.10 (m, 1H), 2.65-2.80 (m, 2H), 1.85-2.00 (m, 1H), 1.20-1.85 (m, 2H), 1.45-1.60 (m, 1H), 1.30-1.40 (m, 1H), 1.10-1.30 (m, 4H), 0.75-0.90 (m, 1H), 0.82 (d, 3H, J = 7.3), 0.80 (d, 3H, J = 7.0).



(2*R*)-2-{N-(4-Chlorobenzenesulfonyl)-N-[1-(pyridine-4-carbonyl)-piperidin-4-ylmethyl]-amino}-4-methyl-pentanoic acid amide (**Example 278**):

To a solution of (2*R*)-2-[N-(4-chlorobenzenesulfonyl)-N-(piperidin-4-ylmethyl)amino]-4-methyl-pentanoic acid amide (Example 126, 0.10 g, 0.22 mmol) and Et_3N (0.06 mL, 0.5 mmol) in CH_2Cl_2 (3.0 mL) was added

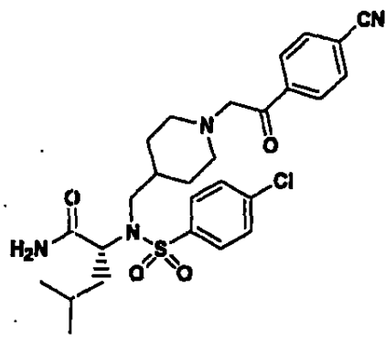
isonicotinoyl chloride hydrochloride (56 mg, 0.32 mmol). The reaction was stirred at rt for 18 h and then was poured into a mixture of EtOAc and sat. aq. $NaHCO_3$. The organic solution was separated and washed with brine, dried over $MgSO_4$, and concentrated to an oily residue. The residue was purified on a Biotage 10M (eluted with 80% EtOAc/hexanes) to give a white solid (36 mg, 30%). MS(ESI), $(M+H)^+$ 509.20; ^1H NMR ($CDCl_3$, 500MHz) δ 8.66 (br s, 2H), 7.80 (d, 1H, J = 8.6), 7.73 (d, 2H, J = 8.5), 7.51 (d, 2H, J = 7.6), 7.41 (br s, 1H), 6.64 (br s, 1H), 5.35 (br s, 1H), 4.70 (br s, 1H), 4.10 (br s, 1H), 3.71 (br s, 1H), 3.33 (br s, 1H), 3.02 (dd, 2H, J = 4.8, 16), 2.70-2.85 (br s, 1H), 1.50-2.09 (m, 5H), 1.18-1.33 (m, 4H), 0.73 (d, 3H, J = 6.7), 0.68 (d, 3H, J = 6.5).



4-{[N-((1*R*)-1-Carbamoyl-3-methyl-butyl)-N-(4-chlorobenzenesulfonyl)amino]-methyl}-piperidine-1-carboxylic acid phenethylamide (Example 256):

To a solution of (2*R*)-2-[N-(4-chlorobenzenesulfonyl)-N-(piperidin-4-ylmethyl)amino]-4-methyl-pentanoic acid amide (Example 126, 0.10 g, 0.22 mmol) and Et_3N (32 μL, 0.25 mmol) in CH_2Cl_2 (3.0 mL) was added (2-isocyanato-ethyl)-benzene (0.040 mL, 0.30 mmol). The reaction was stirred at rt for 18 h and then was poured into sat. aq. $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to an oily residue. The residue was further purified on a Biotage system (eluted with 75% EtOAc/hexanes) to afford the desired product as a white solid (67 mg, 52 %). MS(ESI), $(M+H)^+$ 549.00; ^1H NMR ($CDCl_3$, 500MHz) δ 7.71 (d, 2H, J = 8.6), 7.71 (d, 2H, J = 8.9), 7.15-7.35 (m, 5H), 6.64 (s, 1H), 5.86 (s, 1H), 4.15 (dd,

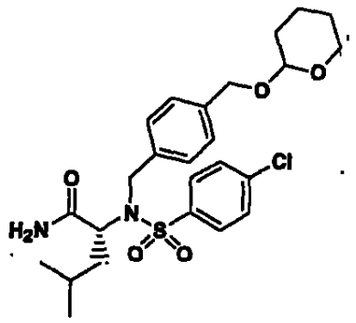
1H, J = 5.2, 9.5), 3.88 (d, 1H, J = 13), 3.76 (d, 1H, J = 13), 3.46 (t, 2H, J = 6.7), 3.21-3.29 (m, 1H), 2.97 (dd, 1H, J = 4.6, 14), 2.65-2.85 (m, 4H), 1.75-1.95 (m, 3H), 1.00-1.30 (m, 5H), 0.75-0.80 (m, 1H), 0.72 (d, 3H, J = 6.7), 0.67 (d, 3H, J = 6.7).



(2*R*)-2-(N-(4-Chlorobenzenesulfonyl)-N-{1-[2-(4-cyanophenyl)-2-oxo-ethyl]-piperidin-4-ylmethyl}-amino)-4-methyl-pentanoic acid amide (**Example 286**):

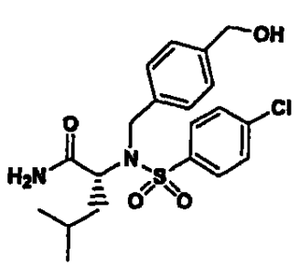
To a solution of (2*R*)-2-[N-(4-chlorobenzenesulfonyl)-N-(piperidin-4-ylmethyl)amino]-4-methyl-pentanoic acid amide (Example 126, 0.050 g, 0.12 mmol) and Et_3N (0.040 mL, 0.30 mmol) in CH_2Cl_2 (2.0 mL) was added 4-(2-chloro-acetyl)-benzonitrile (55 mg, 0.30 mmol). The reaction was stirred at rt for 18 h and then was concentrated to residue. The residue was purified on a Biotage system (eluted with 80% EtOAc/hexanes) to produce 29 mg (48%) of the desired product as a white solid. MS(ESI), $(M+H)^+$ 545.16; ^1H NMR ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, J = 8.5), 7.50-7.65 (m, 2H), 7.50 (d, 2H, J = 7.0), 7.35-7.45 (m, 2H), 6.67 (s, 1H), 5.32 (s, 1H), 4.14 (dd, 1H, J = 5.0, 9.0), 3.52 (br s, 1H), 3.28 (t, 1H, J = 14), 2.97 (dd, 1H, J = 3.5, 14), 2.82 (br s, 1H), 1.00-2.00 (m, 10H), 0.71 (d, 3H, J = 6.5), 0.66 (d, 3H, J = 6.5).

Exemplification of Reaction Scheme 8



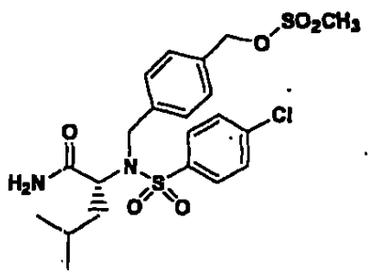
(2*R*)-2-{N-(4-Chlorobenzenesulfonyl)-N-[4-(tetrahydro-pyran-2-yloxymethyl)-benzyl]-amino}-4-methyl-pentanoic acid amide:

(2*R*)-2-(4-Chlorobenzenesulfonylamino)-4-methylpentanoic acid amide (6.35 g, 196 mmol), Cs_2CO_3 (5.62 g, 196 mmol), and 2-[(4-bromomethyl)benzyl]oxy)tetrahydropyran (5.62 g, 196 mmol) in acetonitrile (200 mL) were heated to reflux for 1 h. The reaction was filtered hot with suction through Celite. The filtrate was reduced *in vacuo* to a white foam (9.5 g, 96%). The foam was used as is in the next reaction. MS (ESI), $(M+H)^+$ 510.9, ^1H NMR ($CDCl_3$) δ 7.83 (d, 2H, J = 8.0), 7.75 (d, 2H, J = 8.0), 7.39 (d, 2H, J = 8.0), 7.24 (d, 2H, J = 8.0), 6.25 (br s, 1H), 5.35 (br s, 1H), 4.82 (d, 1H, J_{ab} = 12), 4.65 (m, 1H), 4.52 (d, 1H, J_{ab} = 12), 4.30 (d, 1H, J_{ab} = 16), 4.20 (d, 1H, J_{ab} = 16), 3.74 (m, 2H), 3.46 (m, 1H), 1.89 (m, 1H), 1.66 (m, 6H), 0.97 (d, 3H, J = 7.0), 0.94 (d, 3H, J = 7.0).



(2*R*)-2-[N-(4-Chlorobenzenesulfonyl)-N-(4-hydroxymethyl)benzylamino]-4-methyl-pentanoic acid amide (**Example 95**):

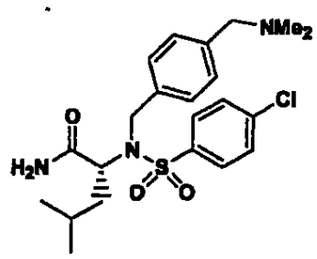
To a solution of (2*R*)-2-[N-(4-chlorobenzenesulfonyl)-N-[4-(tetrahydropyran-2-yloxymethyl)benzylamino]-4-methyl-pentanoic acid amide (9.5 g, 186 mmol) in methanol (200 mL) was added a catalytic amount of p-toluenesulfonic acid. The mixture was stirred overnight at rt. The solvent was removed *in vacuo*. The resulting foam was dissolved in CH_2Cl_2 (100 mL) washed with 1 N NaOH, H_2O, brine, and dried over $MgSO_4$. The filtrate solvent was removed *in vacuo*. The resulting foam was crystallized from hot hexane affording the product as a white solid (7.7g) in 92 % yield. MS (ESI), $(M+H)^+$ 425.17, ^1H NMR ($CDCl_3$) δ 7.68 (d, 2H, J = 7.0), 7.46 (d, 2H, J = 7.0), 7.33 (d, 2H, J = 8.0), 7.28 (d, 2H, J = 8.0), 6.26 (br s, 1H), 5.35 (br s, 1H), 4.67 (br s, 2H), 4.59 (d, 1H, J_{ab} = 16), 4.37 (d, 1H, J_{ab} = 16), 4.26 (t, 1H, 7.0), 1.86-1.80 (m, 2H), 1.34-1.28 (m, 1H), 1.16-1.10 (m, 1H), 0.96 (d, 3H, J = 7.0), 0.93 (d, 3H, J = 7.0).



Methanesulfonic acid 4-{[N-((1*R*)-1-carbamoyl-3-methyl-butyl)-N-(4-chlorobenzene-sulfonyl)-amino]methyl}benzyl ester:

To a stirred solution of (2*R*)-2-[N-(4-chloro-benzenesulfonyl)-N-(4-hydroxymethyl-benzyl)amino]-4-methyl-pentanoic acid amide (1.5 g, 3.5 mmol) in CH_2Cl_2 (15 mL) cooled to 0 °C was added Et_3N (0.74 mL, 5.3 mmol). A solution of methanesulfonyl chloride (0.29 mL, 3.5 mmol) in 5 mL CH_2Cl_2 was added dropwise and the reaction was allowed to stir at 0 °C for 1 h. The reaction mixture was diluted with 25 mL CH_2Cl_2, quickly washed with 1 N HCl, brine, and dried by passing the organic phase through a cotton plug. The solvent was

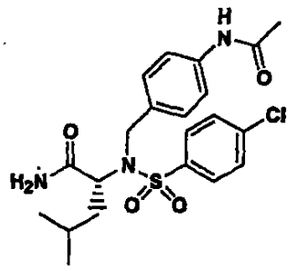
removed *in vacuo* affording the title compound in quantitative yield. The resulting foam was used as is in subsequent reactions. MS (ESI), $(M-95)^+$, 409.15 ^{1}H NMR ($CDCl_3$) δ 7.70 (d, 2H, J = 8.0), 7.48 (d, 2H, J = 8.0), 7.41 (d, 2H, J = 8.0), 7.38 (d, 2H, J = 8.0), 6.27 (br s, 1H), 5.32 (br s, 1H), 5.24 (s, 2H), 4.64 (d, 1H, J_{ab} = 16), 4.43 (d, 1H, J_{ab} = 16), 4.33 (t, 1H, J = 6), 2.90 (s, 3H), 1.90 (m, 1H), 1.60 (m, 2H), 0.96 (d, 3H, J = 7.0), 0.91 (d, 3H, J = 7.0)



(2*R*)-2-[N-(4-Chlorobenzenesulfonyl)-N-(4-dimethylaminomethyl-benzyl)amino]-4-methyl-pentanoic acid amide (**Example 110**):

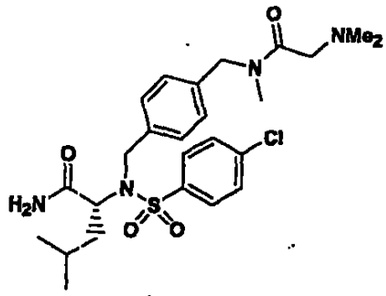
To a stirred solution of methanesulfonic acid 4-{[N-((1*R*)-1-carbamoyl-3-methyl-butyl)-N-(4-chlorobenzenesulfonyl)amino]-methyl}-benzyl ester (150 mg, 0.298 mmol) in (3 mL) CH_2Cl_2 at 0 °C was added 1 equivalent of Et_3N, followed by dimethylamine (0.3 mL, 2 M in THF). The reaction was stirred overnight at rt. The mixture was diluted with CH_2Cl_2, washed with H_2O, brine, dried over $MgSO_4$, and concentrated to give an amber glass. Purification by flash chromatography (SiO_2, 10% MeOH/CH_2Cl_2) afforded the title compound (95 mg) in 71 % yield. MS (ESI), $(M+H)^+$ 452.23, ^{1}H NMR ($CDCl_3$) δ 7.94 (d, 2H, J = 8.0), 7.74 (d, 2H, J = 8.0), 7.63 (d, 2H, J = 8.0) 7.38 (d, 2H, J = 8.0), 6.23 (br s, 1H), 5.35 (br s, 1H), 4.22 (d, 1H, J_{ab} = 16), 4.14 (d, 1H, J_{ab} = 16), 3.28-3.23 (m, 3H), 2.17 (br s, 6H), 1.95 (m, 1H), 1.55 (m, 2H), 0.96 (d, 3H, J = 7.0), 0.93 (d, 3H, J = 7.0).

Exemplification of Reaction Scheme 9



(2*R*)-2-[N-(4-Acetylaminobenzyl)-N-(4-chlorobenzenesulfonyl)amino]-4-methyl-pentanoic acid amide **(Example 163):**

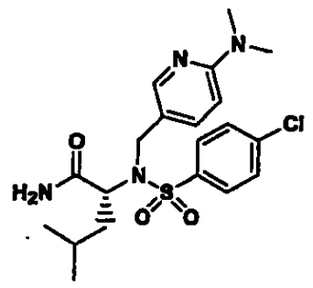
A solution of the compound of Example 48 [(2*R*)-2-[N-(4-chlorobenzenesulfonyl)-N-(4-aminobenzyl)amino]-4-methyl-pentanoic acid amide (250 mg, 0.60 mmol) and Et_3N (120 mg, 1.2 mmol) in CH_2Cl_2 (20 mL) was treated with acetyl chloride (56 mg, 0.72 mmol). After stirring for 18 h, the reaction was concentrated, chromatographed using silica gel flash chromatography (1% methanol/CH_2Cl_2) to afford the titled compound (110 mg, 41%). MS (ESI), $(M-H)^-$ 422.9; ^1H NMR ($CDCl_3$) δ 7.67 (d, 2H, J = 8.0), 7.28-7.46 (m, 6H), 7.12 (br s, 1H), 6.24 (br s, 1H), 5.19 (br s, 1H), 4.48 (dd, 2H, J = 50, 15), 4.27 (t, 1H, J = 7.0), 2.18 (s, 3H), 1.80-2.01 (m, 1H), 1.12-1.32 (m, 2H), 0.75 (d, 3H, J = 7.0), 0.67 (d, 3H, J = 7.0).



(2*R*)-2-[N-(4-Chlorobenzenesulfonyl)-N-(4-{[(2-dimethylamino-acetyl)-methyl-amino]-methyl}-benzyl)-amino]-4-methyl-pentanoic acid amide (**Example 272**):

(2*R*)-2-[N-(4-Chlorobenzenesulfonyl)-N-(4-methylaminomethyl-benzyl)-amino]-4-methyl-pentanoic acid amide (75 mg, 0.17 mmol), (α-dimethylamino)acetic acid (18 mg, 0.17 mmol), 1-hydroxybenzotriazole (24 mg, 0.17 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (33 mg, 0.17 mmol) were combined in 3 mL CH_2Cl_2 and stirred overnight. The reaction mixture was diluted with 5 mL CH_2Cl_2 and washed with 1 N NaOH and brine. The organic phase was dried by filtering through cotton and the solvent was removed *in vacuo*. Purification via preparative HPLC afforded the title compound (61 mg) in 68% yield. MS (ESI), 523.4 $(M+H)^+$ ^1H NMR ($CDCl_3$) δ 8.02 (d, 2H, J = 8.0), 7.71 (d, 2H, J = 8.0), 7.37 (d, 2H, J = 8.0), 7.28 (d, 2H, J = 8.0), 6.23 (br s, 1H), 5.51 (br s, 1H), 4.46 (s, 2H), 4.70 (d, 1H, J_{ab} = 16), 4.33 (d, 1H, J_{ab} = 16), 3.25 (t, 1H, J = 6.0), 2.69 (s, 3H), 2.63 (s, 2H), 2.20 (s, 6H), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J = 7.0), 0.94 (d, 3H, J = 7.0).

Exemplification of Reaction Scheme 10

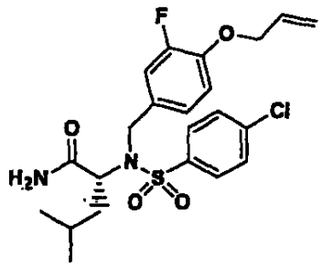


(2*R*)-2-[N-(4-Chlorobenzenesulfonyl)-N-(2-dimethylaminopyridin-5-ylmethyl)amino]-4-methylpentanoic acid amide TFA salt (**Example 254**):

A solution of (2*R*)-2-[N-(4-chlorobenzenesulfonyl)-N-(2-chloropyridin-5-ylmethyl)amino]-4-methylpentanoic acid amide (prepared via Reaction Scheme 1, 18 mg, 41 mmol) in dimethylamine/THF (2 M, 20 mL, 40 mmol) was stirred at 95 °C for 30 h in a pressure vessel. Five mL of reaction mixture (25% of total

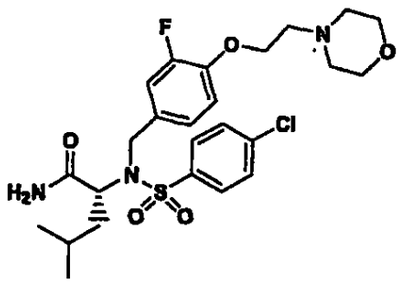
reaction volume) was purified by reverse phase preparative HPLC (YMC S5, ODS, MeOH-water-TFA) to afford the title compound as a white foam (17 mg, 30% yield). HRMS (ESI), $(M-H)^-$ for $C_{20}H_{25}SClN_4O_3$ calcd: 437.1426, found: 437.1420; ^1H NMR ($CDCl_3$): δ 8.04 (s, 1H), 8.03 (d, 1H, J= 9.8), 7.76 (d, 2H, J= 7.6), 7.54 (d, 2H, J= 7.6), 6.83 (d, 1H, J= 9.8), 6.62 (br s, 1H), 6.40 (br s, 1H), 4.64 (d, 1H, J= 15.9), 4.29 (m, 1H), 4.18 (d, 1H, J= 15.9), 3.30 (s, 6H), 1.84 (m, 1H), 1.29 (m, 1H), 0.93 (m, 1H), 0.77 (d, 3H, J= 6.5), 0.72 (d, 3H, J= 6.5).

Exemplification of Reaction Scheme 11



(2*R*)-2-[N-(4-Allyloxy-3-fluorobenzyl)-N-(4-chlorobenzenesulfonyl)amino]-4-methyl-pentanoic acid amide:

To a solution of (2*R*)-2-(4-chlorobenzenesulfonylamino)-4-methyl-pentanoic acid amide (1.00 g, 3.29 mmol), and Cs_2CO_3 (1.29 g, 3.95 mmol) in DMF (25 mL) was added 1-allyloxy-4-bromomethyl-2-fluorobenzene (ref.: Graham, Samuel L; et al., Eur. Pat. Appl. (1992): EP 487270; 0.88 g, 3.67 mmol). The resulting solution was stirred at rt for 18 h. The reaction was then diluted with 9:1 EtOAc:hexanes (350 mL) and washed with H_2O (4 x 200 mL), brine, and dried over Na_2SO_4, to afford the titled compound (393 mg) as a white solid in 26% yield. MS (ESI), $(M+H)^+$ 469.1; ^1H NMR ($CDCl_3$) δ 7.66 (d, 2H, J= 8.1), 7.45 (d, 2H, J= 8.1), 7.11 (d, 1H, J= 12.0), 6.98 (m, 1H), 6.84 (t, 1H, J= 8.0), 6.22 (br s, 1H), 6.04 (m, 2H), 5.42 (m, 1H), 5.16 (br s, 1H), 4.59 (m, 2H), 4.40 (m, 3H), 1.83 (m, 1H), 1.32 (m, 1H), 1.14 (m, 1H), 0.76 (d, 3H, J= 7.0), 0.68 (d, 3H, J= 7.0).

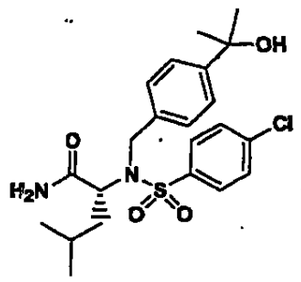


(2*R*)-2-{N-(4-Chlorobenzenesulfonyl)-N-[3-fluoro-4-(2-morpholin-4-yl-ethoxy)-benzyl]-amino}-4-methyl-pentanoic acid amide (**Example 427**):

A mixture of the allyloxy intermediate (0.39 g, 0.84 mmol) from above, osmium tetraoxide (0.01 g, 0.04 mmol), and trimethylamine N-oxide (0.140 g, 1.81 mmol) was dissolved in acetone (10 mL) and stirred for 4 h at rt. The solution was concentrated *in vacuo* and redissolved in 1.5:1 dioxane:H_2O (15 mL). Sodium periodate (0.22 g, 1.0 mmol) was added and the solution was stirred at rt for 18 h. The reaction was then diluted with EtOAc (200 mL) and washed with H_2O, brine, dried over Na_2SO_4 and concentrated to give (2*R*)-{N-(4-chloro-benzenesulfonyl)-N-[3-fluoro-4-(2-oxo-ethoxy)-benzyl]-amino}-4-methyl-pentanoic acid amide as a crude beige solid. This crude material was taken onto the next step without further purification. (2*R*)-2-{N-(4-Chlorobenzenesulfonyl)-N-[3-fluoro-4-(2-oxo-ethoxy)-benzyl]-amino}-4-methyl-pentanoic acid amide (0.16 g, 0.34 mmol) and morpholine (0.090 g, 1.0 mmol) was dissolved in EtOH (5 mL) and heated to 80 °C for approximately 15 min. The oil bath was removed and sodium triacetoxyborohydride (0.290 g, 1.36 mmol) was added and the slurry was stirred at rt for 16h. The solution was concentrated to dryness, taken up in brine, extracted with EtOAc (2 x 100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a crude orange residue. Further purification by Prep HPLC (20 x 100mm YMC S5 ODS C-18 column, 25 mL/min, 0-100 % MeOH/H_2O 0.1 % TFA 15 min) afforded as a TFA salt the titled compound (69.5 mg) as a pale yellow solid in 31 % yield. $[\alpha]_D$ +23 (c 6.4, CH_2Cl_2); LCMS $(M+H)^+$ 542.25; ^1H NMR ($CDCl_3$) δ 7.71 (d, 2H, J = 8.0), 7.50 (d, 2H, J = 8.0), 7.16 (d, 1H, J =

12.0), 7.05 (d, 1H, J = 8.0), 6.87 (t, 1H, J = 8.0), 6.38 (br s, 1H), 5.91 (br s, 1H), 4.41 (ABq, 2H, J = 16, J_{ab} = 176), 4.45 (m, 2H), 4.27 (t, 1H, J = 8.0), 4.03 (m, 4H), 3.70 (m, 2H), 3.51 (m, 2H), 3.10 (m, 2H), 1.83 (m, 1H), 1.29 (m, 1H), 1.05 (m, 1H), 0.75 (d, 3H, J = 8.0), 0.68 (d, 3H, J = 8.0).

Exemplification of Reaction Scheme 12

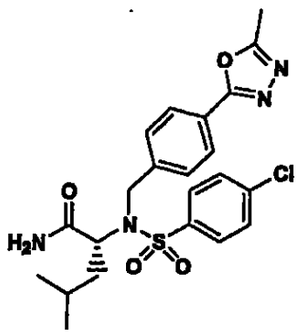


(2*R*)-2-{N-(4-Chlorobenzenesulfonyl)-N-[4-(1-hydroxy-1-methyl-ethyl)-benzyl]-amino}-4-methyl-pentanoic acid amide (**Example 287**):

A solution of the compound of Example 61 [4-{[N-((1*R*)-1-carbamoyl-3-methyl-butyl)-N-(4-chlorobenzenesulfonyl)amino]-methyl}-benzoic acid methyl ester, 101 mg, 0.221 mmol] was cooled to 0 °C in THF (2 mL). A solution of methyl magnesium bromide (1.4 M in toluene/THF, 0.50 mL, 0.71 mmol) was added dropwise. The dark yellow solution was stirred at 0 °C, and after 30 min, additional methyl magnesium bromide solution (0.25 mL, 0.353 mmol) was added. After 1 h, the solution was allowed to warm to rt. After 3.5 h, the reaction was quenched by the addition of sat. aq. NH_4Cl, and the mixture was extracted with EtOAc (2x). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash column chromatography (SiO_2, 20 to 100% EtOAc/hexanes) provided the title compound as a white foam (62 mg, 62%). MS (ESI), $(M+H)^+$ 453.16; ^1H NMR ($CDCl_3$, 300MHz) δ 7.61 (d, 2H, J = 8.7), 7.40 (d, 2H, J = 8.7), 7.37 (d, 2H, J = 8.4), 7.26 (d, 2H, J = 8.4), 6.28 (br s, 1H), 5.25 (br s, 1H), 4.49 (d, 1H, J = 15.9), 4.41 (d, 1H, J = 15.9), 4.33 (t, 1H, J = 6.6), 1.73-1.80 (m, 1H),

1.55 (s, 6H), 1.28-1.35 (m, 1H), 1.20-1.25 (m, 1H), 0.77 (d, 3H, J = 6.5), 0.66 (d, 3H, J = 6.6).

Exemplification of Reaction Scheme 13



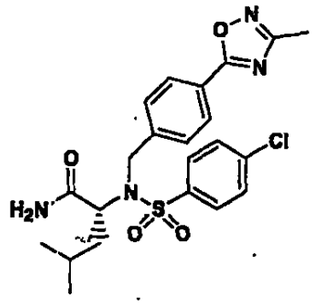
(2*R*)-2-{N-(4-Chlorobenzenesulfonyl)-[4-(5-methyl-[1, 3, 4]oxadiazol-2-yl)-benzyl]-amino}-4-methyl-pentanoic acid amide (**Example 436**):

Step 1: A solution of the compound of Example 61 [4-{[N-((1*R*)-1-carbamoyl-3-methyl-butyl)-N-(4-chlorobenzenesulfonyl)amino]-methyl}-benzoic acid methyl ester, 0.500 g, 1.10 mmol] was diluted with methanol (10 mL) and hydrazine (2 mL) was added. The starting material slowly dissolved over 5 min. After 30 min, the solution was heated at reflux. After 22 h, the solution was cooled to rt. Water (15 mL) was added, and a white precipitate formed. The mixture was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give the corresponding acyl hydrazide as a white foam, which was carried directly on to the cyclization step without purification.

Step 2: The crude acyl hydrazide (0.150 g, 0.331 mmol) was dissolved in pyridine (2.2 mL) and ethyl acetimidate hydrochloride (60.0 mg, 0.364 mmol) was added. The mixture was heated at reflux for 1.25 h. The solution was cooled to rt and concentrated to remove pyridine. The residue was taken up in EtOAc, and was washed sequentially with water, 1 N HCl (2x), sat. aq. $NaHCO_3$, and brine. The solution was dried ($MgSO_4$) and concentrated. Flash column chromatography (SiO_2, 50 to 100% EtOAc/hexanes) provided the listed

compound as a white solid (138 mg, 88% for 2 steps). $[\alpha]_D$ +11.1 (c 7.0 mg/ml, $CHCl_3$); MS (ESI), $(M+H)^+$ 477.22; ^1H NMR ($CDCl_3$, 300MHz) δ 7.94 (dd, 2H, *J* = 1.8, 8.4), 7.69 (dd, 2H, *J* = 1.8, 8.7), 7.45-7.50 (m, 4H), 6.23 (br s, 1H), 5.19 (br s, 1H), 4.65 (d, 1H, *J* = 15.9), 4.46 (d, 1H, *J* = 15.9), 4.31 (dd, 1H, *J* = 6.6, 7.8), 2.61 (s, 3H), 1.75-1.85 (m, 1H), 1.28-1.35 (m, 1H), 1.08-1.15 (m, 1H), 0.76 (d, 3H, *J* = 6.6), 0.64 (d, 3H, *J* = 6.6).

Exemplification of Reaction Scheme 14

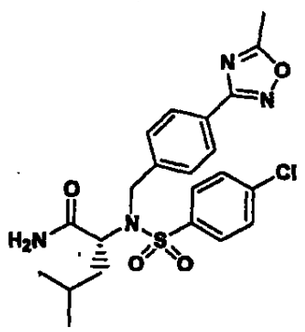


(2*R*)-2-{N-(4-Chlorobenzenesulfonyl)-N-[4-(3-methyl-[1, 2, 4]oxadiazol-5-yl)-benzyl]-amino}-4-methyl-pentanoic acid amide (**Example 437**):

Step 1: To a rt solution of the compound of Example 89 [4-{[N-((1*R*)-1-carbamoyl-3-methyl-butyl)-N-(4-chlorobenzene-sulfonyl)-amino]-methyl}-benzoic acid, 520 mg, 1.2 mmol] in DMF (2.4 mL) and CH_2Cl_2 (7.1 mL) was added 1-hydroxybenzotriazole (192 mg, 1.42 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (272 mg, 1.42 mmol), and iPr_2NEt (0.31 mL, 1.8 mmol). *N*-Hydroxyacetamide (105 mg, 1.42 mmol) was also added. After 21 h, starting material was evident, so additional portions of all reagents were added periodically to push the reaction forward. After 3 d, the mixture was concentrated and partitioned between sat. aq. $NaHCO_3$ and EtOAc (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to a yellow oil, which was carried on to the next step without purification.

Step 2: The crude acetamidoxime was dissolved in toluene (10 mL) and the solution was heated at reflux. After 1 h, pyridine (2 mL) was added and heating was continued for another 15 h. The mixture was concentrated and diluted with EtOAc. The organic phase was washed sequentially with water, 1 N HCl (2x), sat. aq. $NaHCO_3$, and brine, then was dried ($MgSO_4$) and concentrated. Flash column chromatography (SiO_2, 10 to 40% EtOAc/hexanes) gave the title compound as a pale yellow solid (238 mg, 42% for two steps). $[\alpha]^{23}_D$ +9.30 (*c* 5.93, $CHCl_3$); MS (ESI), $(M+H)^+$ 477.18; ^1H NMR ($CDCl_3$, 300MHz) δ 8.04 (d, 2H, *J* = 8.4), 7.70 (dd, 2H, *J* = 1.8, 8.4), 7.45-7.52 (m, 4H), 6.23 (br s, 1H), 5.19 (br s, 1H), 4.67 (d, 1H, *J* = 16.2), 4.47 (d, 1H, *J* = 15.9), 4.31 (t, 1H, *J* = 7.2), 2.47 (s, 3H), 1.75-1.85 (m, 1H), 1.28-1.35 (m, 1H), 1.08-1.15 (m, 1H), 0.76 (d, 3H, *J* = 6.6), 0.64 (d, 3H, *J* = 6.6).

Exemplification of Reaction Scheme 15

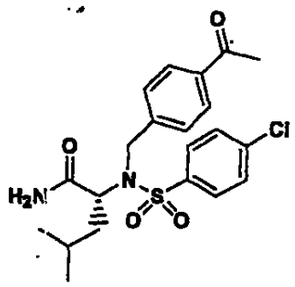


(2*R*)-2-{N-(4-Chlorobenzenesulfonyl)-N-[4-(5-methyl-[1, 2, 4]oxadiazol-3-yl)-benzyl]-amino}-4-methyl-pentanoic acid amide (Example 465):

A solution of the compound of Example 6 [(2*R*)-2-[N-(4-chlorobenzenesulfonyl)-N-(4-cyanobenzyl)amino]-4-methyl-pentanoic acid amide (0.20 g, 0.47 mmol) in ethanol (6 mL) was treated with hydroxylamine (50% solution in water, 0.050 mL, 0.71 mmol). The reaction was heated to 80 °C for 18 h. The reaction was concentrated to a residue and recrystallized from EtOAc/hexanes to produce a white solid (136 mg, 51%). This solid (0.18 mmol)

was then dissolved in chloroform and treated with Et_3N (0.030 mL, 0.24 mmol) and acetyl chloride (0.020 mL, 0.18 mmol). The reaction was stirred at rt for 2 h and then was poured into EtOAc and brine. The organic layer was separated, dried over $MgSO_4$, and concentrated to residue. The residue was taken up in toluene and heated at reflux for 24 h. The reaction was concentrated to a residue and purified on a Biotage system (eluted in 1:1 EtOAc/hexanes) to afford the desired product as a white solid (35 mg, 39% yield). MS(ESI), $(M+H)^+$ 477.13; ^1H NMR ($CDCl_3$, 500MHz) δ 7.98 (d, 2H, J = 8.2), 7.68 (d, 2H, J = 8.9), 7.45 (d, 4H, J = 8.5), 6.21 (s, 1H), 5.19 (s, 1H), 4.62 (d, 1H, J = 15), 4.48 (d, 1H, J = 16), 4.31 (t, 1H, J = 7.0), 2.65 (s, 3H), 1.75-1.85 (m, 1H), 1.20-1.35 (m, 4H), 1.10-1.17 (m, 1H), 0.85-0.90 (m, 1H), 0.75 (d, 3H, J = 6.7), 0.64 (d, 3H, J = 6.4).

Exemplification of Reaction Scheme 16

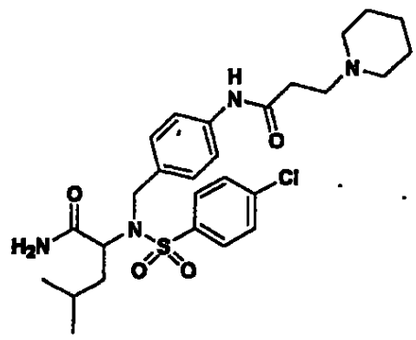


(2*R*)-2-[N-(4-Acetylbenzyl)-N-(4-chlorobenzenesulfonyl)amino]-4-methyl-pentanoic acid amide (**Example 273**):

A solution of the compound of Example 251 [4-{[N-((1*S*)-1-carbamoyl-3-methyl-butyl)-N-(4-chlorobenzenesulfonyl)-amino]-methyl}-N-methoxy-N-methyl-benzamide, 0.100 g, 0.207 mmol] was cooled to 0 °C in THF (2.1 mL). A solution of methyl magnesium bromide (1.4 M in toluene/THF, 0.178 mL, 0.249 mmol) was added dropwise. The resulting solution was stirred at 0 °C for 3 h, at which time additional methyl magnesium bromide solution (0.178 mL, 0.249 mmol) was added. After another 30 min, a final portion of MeMgBr solution (0.3 mL) was added. After a final 15 min, the reaction was quenched by the addition

of sat. aq. NH_4Cl and 1 N HCl, and the mixture was extracted with EtOAc (2x). The combined organic layers were washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. Flash column chromatography (SiO_2, 20 to 60% EtOAc/hexanes) gave the desired compound as an off-white foam (79 mg, 87%). $[\alpha]^{23}_D$ +20.4 (*c* 7.57, $CHCl_3$); MS (ESI), $(M+H)^+$ 437.13; ^1H NMR ($CDCl_3$, 300MHz) δ 7.87 (d, 2H, *J* = 8.4), 7.67 (dd, 2H, *J* = 1.8, 8.7), 7.42-7.46 (m, 4H), 6.21 (br s, 1H), 5.28 (br s, 1H), 4.64 (d, 1H, *J* = 15.9), 4.45 (d, 1H, *J* = 15.9), 4.31 (t, 1H, *J* = 6.6), 2.58 (s, 3H), 1.73-1.80 (m, 1H), 1.25-1.35 (m, 1H), 1.05-1.14 (m, 1H), 0.74 (d, 3H, *J* = 6.5), 0.65 (d, 3H, *J* = 6.6).

Exemplification of Reaction Scheme 17

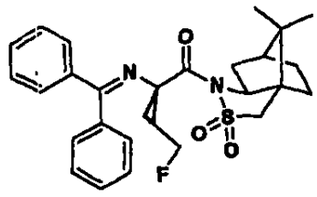


(2*R*)-2-{N-(4-Chlorobenzenesulfonyl)-N-[4-(3-piperidin-1-yl-propionylamino)-benzyl]-amino}-4-methyl-pentanoic acid amide (**Example 274**):

To a solution of N-(4-{[N-((1*S*)-1-carbamoyl-3-methyl-butyl)-N-(4-chlorobenzenesulfonyl)amino]-methyl}-phenyl)-acrylamide (0.10 g, 0.22 mmol) in toluene (5 mL) was added piperidine (20 mg, 0.24 mmol). The mixture was heated at a gentle reflux for 1 h and then the solvent was removed *in vacuo*. Purification by flash chromatography (SiO_2, 10% MeOH/CH_2Cl_2) afforded the title compound (105 mg) in 86% yield. MS (ESI), $(M+H)^+$ 449.16, ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, 2H, *J* = 8.0), 7.63 (d, 2H, *J* = 8.0), 7.38 (d, 2H, *J* = 8.0), 7.23 (d, 2H, *J* = 8.0), 6.25 (br s, 1H), 5.35 (br s, 1H), 4.75 (d, 1H, J_{ab} = 16),

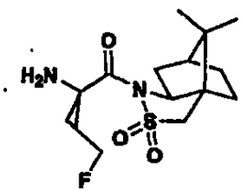
4.38 (d, 1H, J_{ab} = 16), 3.25 (t, 1H, J = 6.0), 2.65 (t, 2H, J = 6.0), 2.56-2.44 (m, 6H), 1.95 (m, 1H), 1.68-1.45 (m, 8H), 0.98 (d, 3H, J = 7.0), 0.94 (d, 3H, J = 7.0)

Exemplification of Reaction Scheme 18



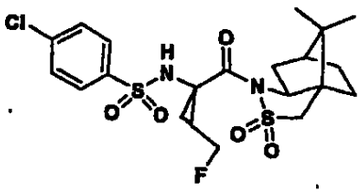
(2*R*)-2-(Benzhydrylidene-amino)-1-{(1'*S*),(5'*S*)-10',10'-dimethyl-3',3'-dioxo-3'λ^6-thia-4'-aza-tricyclo-[5.2.1.0^{1,5}]dec-4'-yl}-4-fluorobutan-1-one:

To a –78 °C solution of N-2-(benzhydrylidene-amino)-1-{(1'*S*),(5'*S*)-10',10'-dimethyl-3',3'-dioxo-3'λ^6-thia-4'-aza-tricyclo-[5.2.1.0^{1,5}]dec-4'-yl}ethanone (ref: Josien, H.; Martin, A.; Chassaing, G. Tetrahedron Lett. 1991, 32, 6547; 30.0g, 68 mmol) in HMPA (60 mL) and THF (300 mL) was added n-BuLi (1.6 M in hexane, 42.4 mL, 68 mmol) dropwise, maintaining the temperature below –65 °C. The reaction was allowed to come to rt, at which time a solution of 1-bromo-3-fluoroethane (17.4 g, 137 mmol) in THF (30 mL) was added dropwise at rt. After 18 h the reaction was poured over H_2O/ HOAc (200 mL/2 mL), diluted with EtOAc, and the organic layers were washed with saturated NH_4Cl, brine, dried over $MgSO_4$, and concentrated. The resulting orange oil was then further purified by silica gel chromatography (25% EtOAc/hexanes) to afford a white solid which was recrystallized from 15% EtOAc/hexanes to give the desired material (24.3 g, 70%). MS (ESI) (M +H$^+$) 483.27; ^{1}H NMR ($CDCl_3$) δ 7.66 (d, 2H, J = 7.2), 7.13-7.44 (m, 8H), 4.82-4.83 (m, 2H), 4.39-4.81 (m, 2H), 3.84-3.87 (m, 1H), 3.28 (ABq, 2H, J = 18, 10) 2.33-2.41 (m, 2H), 2.02-2.04 (m, 2H), 1.84-1.87 (m, 2H), 1.32-1.39 (m, 2H), 1.10 (s, 3H), 0.91 (s, 3H).



(2*R*)-2-Amino-1-{(1'*S*),(5'*S*)-10',10'-dimethyl-3',3'-dioxo-3'λ^6-thia-4'-aza-tricyclo-[5.2.1.0^{1,5}]dec-4'-yl}-4-fluorobutan-1-one:

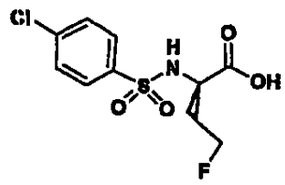
A solution of (2*R*)-2-(benzhydrylidene-amino)-1-{(1'*S*),(5'*S*)-10',10'-dimethyl-3',3'-dioxo-3'λ^6-thia-4'-aza-tricyclo-[5.2.1.0^{1,5}]dec-4'-yl}-4-fluorobutan-1-one (20.0 g, 41.0 mmol) in THF (400 mL) was treated with 1 N HCl (200 mL). After 3 h, the reaction was diluted with H_2O and extracted with Et_2O. The aqueous phase was then neutralized by the addition of 0.5 N NaOH. The basic phase was then extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated to give a white solid (11.9 g, 90%). ^{1}H NMR ($CDCl_3$) δ 4.56-4.71 (m, 2H), 4.23-4.31 (m, 1H), 3.40-3.49 (m, 3H), 3.11 (d, 2H, J = 4.4), 1.17-2.23 (m, 8H), 1.13 (s, 3H), 0.93-1.12 (m, 3H).



(2*R*)-2-(4-Chlorobenzensulfonylamino)-1-{(1'*S*),(5'*S*)-10',10'-dimethyl-3',3'-dioxo-3'λ^6-thia-4'-aza-tricyclo-[5.2.1.0^{1,5}]dec-4'-yl}-4-fluorobutan-1-one:

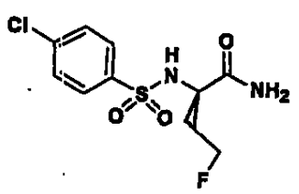
To a solution of (2*R*)-2-amino-1-{(1'*S*),(5'*S*)-10',10'-dimethyl-3',3'-dioxo-3'λ^6-thia-4'-aza-tricyclo-[5.2.1.0^{1,5}]dec-4'-yl}-4-fluorobutan-1-one: (12 g, 36 mmol) and Et_3N (10.4 mL, 72.0 mmol) in CH_2Cl_2 (350 mL) was added 4-chlorobenzenesulfonyl chloride (9.1 g, 43 mmol) in one portion. After 18 h the reaction was concentrated and the resulting residue was taken into EtOAc and washed with H_2O, brine, dried over $MgSO_4$, and concentrated. The material was

then further purified by silica gel chromatography (30% EtOAc/hexanes) to afford the titled compound (16.0 g, 92%) as a white wax. ^{1}H NMR ($CDCl_3$) δ 7.79 (d, 2H, J = 8.0), 7.43 (d, 2H, J = 8.0), 5.69 (br d, 8.0), 4.42-4.77 (m, 4H), 3.71-3.72 (m, 1H), 3.10 (ABq, 2H, J = 9, 4.4) 2.11-2.29 (m, 2H), 1.33-1.99 (m, 6H), 1.04 (s, 3H), 0.91 (s, 3H).



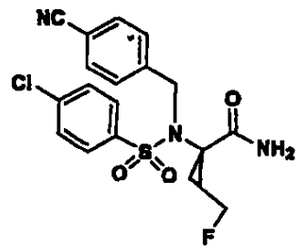
(2*R*)-2-(4-Chlorobenzenesulfonylamino)-4-fluorobutanoic acid:

To a rapidly stirred solution of (2*R*)-2-(4-chlorobenzensulfononylamino)-1-{(1'*S*),(5'*S*)-10',10'-dimethyl-3',3'-dioxo-3'λ^6-thia-4'-aza-tricyclo-[5.2.1.0^{1,5}]dec-4'-yl}-4-fluorobutan-1-one: (16 g, 32 mmol) in acetonitrile (200 mL) was added LiBr (13.9 g, 15 mmol), tetrabutylammonium bromide (4.13g, 12.8 mmol), and LiOH (5.45 g, 0.130 mol). After 4.5 h the reaction was concentrated to half volume then diluted with H_2O and extracted with CH_2Cl_2. The aqueous layer was acidified with 1 N HCl and extracted with EtOAc. The EtOAc extracts were combined, dried over $MgSO_4$, and concentrated to give a white solid of which 9.4 g was taken directly towards the next step. ^{1}H NMR (DMSO-d_6) δ 8.39 (d, 1H, J = 9.0), 7.76 (d, 2H, J = 6.8), 7.64 (d, 2H, J = 6.8), 7.00 (br s, 1H), 4.29-4.48 (m, 2H), 3.80-3.88 (m, 1H), 1.66-1.96 (m, 2H).



(2*R*)-2-(4-Chlorobenzenesulfonylamino)-4-fluorobutanoic acid amide:

To a solution of (2*R*)-2-(4-chlorobenzenesulfonylamino)-4-fluorobutanoic acid (9.0 g, 31 mmol) in DMF (250 mL) was added consecutively 1-hydroxybenzotriazole hydrate (6.2 g, 46 mmol), N, N-diisopropylethylamine (23 mL, 124 mmol), ammonium chloride (3.34 g, 62 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (8.8 g, 46 mmol) under N_2. The resulting solution was stirred at rt for 18 h. The solution was poured over ice water (500 mL) and the solid was filtered off and dried. The material was then precipitated from 10% EtOAc/hexanes to afford a clean white solid (4.5g) in 50% yield. $[\alpha]_D$ = -21.0 (c 1.00, DMF); MS (ESI) (M – H$^-$) 293.01; ^{1}H NMR (DMSO-d_6) δ 8.12 (d, 1H, *J* = 8.8), 7.77 (d, 2H, *J* = 7.0), 7.62 (d, 2H, *J* = 7.0), 7.38 (br s, 1H), 7.03 (br s, 1H), 4.22-4.47 (m, 2H), 3.71-3.85 (m, 1H), 1.65-1.92 (m, 2H).

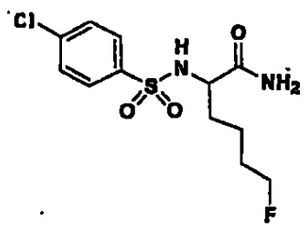


(2*R*)-2-[(4-Chlorobenzenesulfonyl)-(4-cyanobenzyl)-amino]-4-fluorobutyramide (**Example 360**):

(2*R*)-2-(4-Chlorobenzenesulfonylamino)-4-fluorobutyramide (20 mg, 0.7 mmol) was converted to the title compound as in Reaction Scheme 1, method A to afford the titled compound (208 mg) in 73% yield. MS (ESI) (M - H)$^-$ 407.99; $[\alpha]_D$ = +39.13 (c 1.00, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2H, *J* = 8.4) 7.58 (d, 2H, *J* = 8.4), 7.50 (d, 2H, *J* = 8.4), 7.45 (d, 2H, *J* = 8.4), 6.29 (br s, 1H), 5.21 (br s, 1H), 4.19-4.67 (m, 5H), 2.17-2.28 (m, 1H), 1.49-1.61 (m, 1H).

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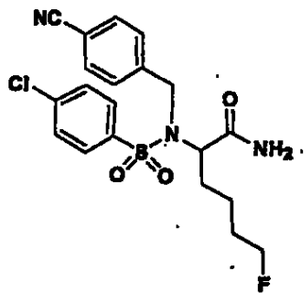
Exemplification of Reaction Scheme 19



2-(4-Chlorobenzenesulfonylamino)-6-fluoro-hexanoic acid amide (III):

A mixture of (benzhydrylidene-amino)acetic acid ethyl ester (8.6 g, 32 mmol), 4-bromo-1-fluorobutane (10.0 g, 64.5 mmol), K_2CO_3 (13.4 g, 96.9 mmol), tetrabutylammonium bromide (2.1 g, 6.5 mmol), and acetonitrile (300 mL) was heated at reflux for 72 h. The reaction was cooled to rt and filtered through a sintered glass funnel. The filtrate was concentrated *in vacuo*. The residue was dissolved in diethyl ether (250 mL) and a white solid precipitated. The solid was removed by vacuum filtration. A solution of 1 N HCl (100 mL) was added to the filtrate, which contained the crude product (2-(benzhydrylideneamino)-6-fluoro-hexanoic acid ethyl ester). The resulting biphasic mixture was stirred vigorously for 3 h. The mixture was transferred to a separatory funnel. The aqueous layer was collected. The organic layer was extracted with 1 N HCl (30 mL). The combined aqueous layers were washed with 200 mL of diethyl ether. Concentrated HCl (10.8 mL) was added to the aqueous portion and the resulting solution was heated at reflux for 6 h. The reaction mixture was cooled to rt and concentrated *in vacuo*. Toluene was added to the residue and the mixture was reconcentrated *in vacuo* to afford 2-amino-6-fluoro-hexanoic acid hydrochloride as a white solid. The crude amino acid salt was used without purification or characterization. 2-Amino-6-fluorohexanoic acid hydrochloride (32.3 mmol, theoretically) was suspended in anhydrous methanol (300 mL) and cooled to 0 °C. Thionyl chloride (10.3 mL, 129 mmol) was slowly was over 5 min. The resulting solution was allowed to warm to rt and stir for 18 h. The reaction mixture was concentrated *in vacuo* to afford methyl 2-amino-6-fluoro-hexanoic

acid hydrochloride. Toluene (100 mL) and 28% ammonia in water (75 mL) were added to the crude amino ester. The resulting biphasic mixture was stirred vigorously at rt for 24 h. The reaction mixture was concentrated *in vacuo*. The residual solid was suspended in toluene (200 mL) and reconcentrated *in vacuo* to afford 6-fluorohexanoic acid amide (II) as a white solid. The crude amino acid amide was dissolved in anhydrous DMF (50 mL) and CH_2Cl_2 (350 mL) and reacted with 4-chlorobenzenesulfonylchloride (82 g, 32.3 mmol) and Et_3N (13.5 mL, 96.9 mmol). After 2 h, a second portion of 4-chlorobenzenesulfonylchloride (1.70 g, 8.1 mmol) was added. After an additional 18 h, the resulting mixture was poured into 1 N HCl (500 mL). The organic layer was collected and washed with water (2 x 500 mL). Hexane (600 mL) was added to the organic layer. A white precipitate formed. The solid was collected by vacuum filtration, rinsed with cold ethanol (50 mL), and dried *in vacuo* to afford 4.95 g (48% yield, 6 steps) of 2-(4-chlorobenzenesulfonylamino)-6-fluoro-hexanoic acid amide (III): LCMS $(M+Na)^+$ 345.2; ^1H NMR (400 MHz, DMSO-d_6) 7.99 (d, 1H, $J = 8.8$), 7.77 (d, 2H, $J = 8.8$), 7.62 (d, 2H, $J = 8.8$), 7.29 (s, 1H), 6.95 (s, 1H), 4.34 (dt, 2H, $J_d = 47.5$, $J_t = 6.1$), 3.65 (dt, 1H, $J_d = 5.6$, $J_t = 8.6$), 1.60-1.39 (m, 4H), 1.36-1.15 (m, 2H); Anal. Calcd for $C_{12}H_{16}ClFN_2O_3S$: C, 44.65; H, 4.99; N, 8.67. Found: C, 44.61; H, 5.08; N, 8.75.

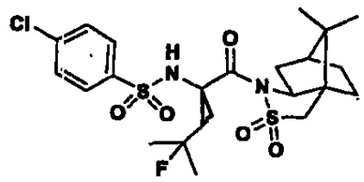


2-[(4-Chlorobenzenesulfonyl)-(4-cyanobenzyl)-amino]-6-fluoro-hexanoic acid amide (Example 333):

2-(4-Chlorobenzenesulfonylamino)-6-fluoro-hexanoic acid amide (0.500 g, 1.55 mmol) was converted to the title compound (360 mg, 50% yield) as in

Reaction Scheme 1, method A. LCMS $(M+Na)^+$ 459.9; ^1H NMR (400 MHz, DMSO-d_6) δ 7.82 (d, 2H, J = 8.8), 7.79 (d, 2H, J = 8.5), 7.63 (d, 2H, J = 8.8), 7.58 (d, 2H, J = 8.3), 7.52 (s, 1H), 7.09 (s, 1H). 4.82 (ABq, 2H, Δν = 37.2, J_{ab} = 17.6), 4.34 (dd, 1H, J = 8.0, 6.6), 4.25 (dt, 2H, J_d = 47.2, J_t = 5.7), 1.58 (m, 1H), 1.49-1.12 (m, 5H); Anal. Calcd for $C_{20}H_{21}ClFN_3O_5S$: C, 54.85; H, 4.83; N, 9.59. Found: C, 54.92; H, 4.76; N, 9.54.

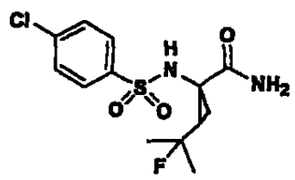
Exemplification of Reaction Scheme 20



(2*R*)-2-(4-Chlorobenzensulfonylamino)-1-{(1'*S*),(5'*S*)-10',10'-dimethyl-3',3'-dioxo-3'λ^6-thia-4'-aza-tricyclo-[5.2.1.0^{1,5}]dec-4'-yl}-4-fluoro-4-methyl-pentan-1-one:

To a solution of (2*R*)-2-(4-chlorobenzensulfonylamino)-1-{(1'*S*),(5'*S*)-10',10'-dimethyl-3',3'-dioxo-3'λ^6-thia-4'-aza-tricyclo-[5.2.1.0^{1,5}]dec-4'-yl}-4-methyl-4-penten-1-one [500 mg, 1 mmol, prepared as in Reaction Scheme 18 from N-2-(benzhydrylidene-amino)-1-{(1'*S*),(5'*S*)-10',10'-dimethyl-3',3'-dioxo-3'λ^6-thia-4'-aza-tricyclo-[5.2.1.0^{1,5}]dec-4'-yl}ethanone (ref: Josien, H.; Martin, A.; Chassaing, G. Tetrahedron Lett. 1991, 32, 6547) and 1-bromo-2-methyl-2-propene] in THF (5 mL) at 0 °C was added hydrofluoric acid•pyridine (10 mL). The reaction mixture was allowed to warm to rt and stir for 18 h. The reaction contents were carefully added to a saturated aqueous solution of $NaHCO_3$ (300 mL). The aqueous mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were sequentially washed with 1 N HCl (200 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford 490 mg (94%) of the title compound as a white

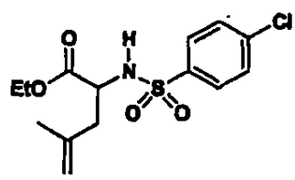
solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (d, 2H, J = 8.8), 7.45 (d, 2H, J = 8.8), 5.37 (d, 1H, J = 8.1), 4.65 (m, 1 H), 3.64 (t, 1H, J = 6.4), 3.43 (ABq, 2H, Δν = 5.4, J_{ab} = 13.7), 2.19-1.83 (m, 7H), 1.41-1.31 (m, 8H), 1.04 (s, 3H), 0.94 (s, 3H).



(2*R*)-2-(4-Chlorobenzenesulfonylamino)-4-fluoro-4-methyl-pentanoic acid amide:

(2*R*)-2-(4-Chlorobenzensulfonylamino)-1-{(1'*S*),(5'*S*)-10',10'-dimethyl-3',3'-dioxo-3'λ^6-thia-4'-aza-tricyclo-[5.2.1.0^{1,5}]dec-4'-yl}-4-fluoro-4-methyl-pentan-1-one was converted to the title compound in two steps as in Reaction Scheme 18 (165 mg, 55% yield): LCMS (M+Na)$^+$ 345.1; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.10 (d, 1H, J = 9.2), 7.77 (d, 2H, J = 8.5), 7.62 (d, 2H, J = 8.9), 7.34 (s, 1H), 6.92 (s, 1H). 3.85 (m, 1H), 1.89 (m, 1H), 1.74 (m, 1H), 1.31 (d, 3H, J = 21.7), 1.29 (d, 3H, J = 21.9).

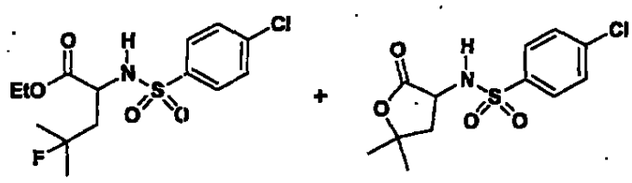
Exemplification of Reaction Scheme 21



Ethyl 2-(4-chlorobenzenesulfonylamino)-4-methyl-4-pentenoate:

A solution of ethyl 2-amino-4-methyl-4-pentenoate (2.84 g, 18.1 mmol, prepared as in Reaction Scheme 19 from (benzhydrylideneamino)acetic acid ethyl ester and 1-bromo-2-methyl-2-propene) in CH_2Cl_2 (250 mL) was reacted with 4-chlorobenzenesulfonyl chloride (4.20 g, 19.9 mmol) and Et_3N (3.78 mL, 27.2

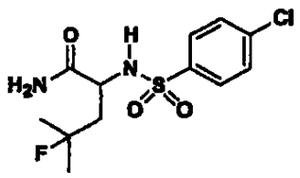
mmol). After 4 h, the resulting mixture was poured into 1 N aqueous HCl (500 mL) and extracted with EtOAc (3 x 150 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude concentrate was purified using silica gel column chromatography (10:1 to 5:1 gradient, hexanes/EtOAc) to afford 3.04 g (25% yield over 3 steps) of ethyl 2-(4-chlorobenzenesulfonylamino)-4-methyl-4-pentenoate: LCMS $(M+Na)^+$ 354.2; ^1H NMR (400 MHz, $CDCl_3$) 7.77 (d, 2H, $J = 9.1$), 7.46 (d, 2H, $J = 8.8$), 5.07 (d, 1H, $J = 9.0$), 4.84 (s, 1H), 4.73 (s, 1H), 4.05 (m, 1H), 3.95 (q, 2H, $J = 7.1$), 2.40 (m, 2 H), 1.66 (s, 3H), 1.13 (t, 3H, $J = 7.1$).



2-(4-Chlorobenzenesulfonylamino)-4-fluoro-4-methyl-pentanoic acid ethyl ester and 4-Chloro-N-(5, 5-dimethyl-2-oxo-tetrahydro-furan-3-yl)-benzenesulfonamide:

Hydrogen fluoride•pyridine (10 mL) was added to a 0 °C solution of ethyl 2-(4-chloro-benzenesulfonylamino)-4-methyl-4-pentenoate (1.0 g, 3.0 mmol) in THF (15 mL). The reaction mixture was allowed to warm to rt. After 5 h, an additional portion (10 mL) of hydrogen fluoride•pyridine was added. The mixture was stirred for 24 h, then a third portion of hydrogen fluoride•pyridine (10 mL) was added. After a total of 53 h, the reaction was quenched with ice chips (20 mL). The crude mixture was poured into ice water (500 mL) and extracted with CH_2Cl_2 (2 x 200 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (100 mL) and concentrated *in vacuo*. The crude concentrate was purified using silica gel column chromatography (10:1 to 5:1 gradient, hexanes/EtOAc) to afford 0.395 g (37% yield) of ethyl 2-(4-chlorobenzenesulfonylamino)-4-fluoro-4-methyl-pentanoate and 0.425 g (46% yield) of 4-chloro-*N*-(5, 5-dimethyl-2-oxo-tetrahydro-furan-3-y)-

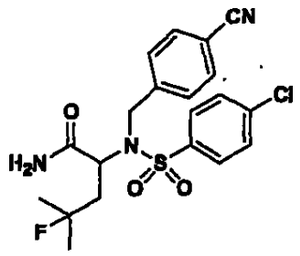
benzenesulfonamide. Data for ethyl 2-(4-chlorobenzenesulfonylamino)-4-fluoro-4-methyl-pentanoate: LCMS $(M+Na)^+$ 374.1; ^1H NMR (500 MHz, $CDCl_3$) 7.78 (d, 2H, J = 8.9), 7.47 (d, 2H, J = 8.5), 5.19 (d, 1H, J = 7.9), 4.08 (m, 1H), 3.93 (m, 2H), 2.09-1.94 (m, 2H), 1.42 (d, 3H, J = 21.6), 1.37 (d, 3H, J = 21.6), 1.12 (t, 3H, J = 7.0). Data for 4-chloro-*N*-(5, 5-dimethyl-2-oxo-tetrahydro-furan-3-y)-benzenesulfonamide: LCMS $(M+Na)^+$ 326.0; ^1H NMR (400 MHz, DMSO-d_6) 8.41 (d, 1H, J = 9.1), 7.86 (d, 2H, J = 8.6), 7.67 (d, 2H, J = 8.8), 4.57 (m, 1H), 2.22 (dd, 1H, J = 12.4, 9.0), 1.72 (t, 1H, J = 12.0), 1.33 (s, 3H), 1.31 (s, 3H).



2-(4-Chlorobenzenesulfonylamino)-4-fluoro-4-methyl-pentanoic acid amide:

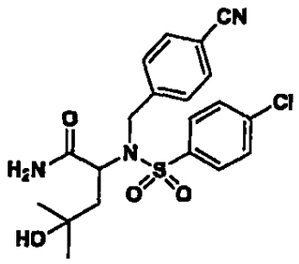
A solution of 2-(4-chlorobenzenesulfonylamino)-4-fluoro-4-methyl-pentanoic acid ethyl ester (457 mg, 1.30 mmol) in MeOH (20 mL) was treated with 10 N NaOH (780 µL, 7.8 mmol) at rt for 18 h. The crude reaction mixture was concentrated *in vacuo*. The residue was treated with water (50 mL) and 1 N HCl (20 mL). The aqueous solution was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a white solid containing 2-(4-chlorobenzenesulfonylamino)-4-fluoro-4-methyl-pentanoic acid. A mixture of the crude solid, 1-hydroxybenzotriazole (263 mg, 1.95 mmol), diisopropylethylamine (670 mg, 5.2 mmol), ammonium chloride (140 mg, 2.6 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (373 mg, 1.95 mmol), and DMF (20 mL) was stirred at rt for 24 h. The crude mixture was poured into water (500 mL). The aqueous solution was extracted with EtOAc/hexane (90:10, 3 x 150 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude concentrate was purified using silica gel column chromatography (95:5, chloroform/MeOH) to

afford 0.426 g (100% yield) of the title compound: LCMS $(M+Na)^+$ 345.3; ^1H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, 1H, J = 9.2), 7.77 (d, 2H, J = 8.5), 7.62 (d, 2H, J = 8.9), 7.34 (s, 1H), 6.92 (s, 1H). 3.85 (m, 1H), 1.89 (m, 1H), 1.74 (m, 1H), 1.31 (d, 3H, J = 21.7), 1.29 (d, 3H, J = 21.9).



2-[(4-Chlorobenzenesulfonyl)-(4-cyanobenzyl)-amino]-4-fluoro-4-methyl-pentanoic acid amide (**Example 357**):

2-(4-Chlorobenzenesulfonylamino)-4-fluoro-4-methyl-pentanoic acid amide was converted to the title compound as in Reaction Scheme 1, method A. LCMS $(M+Na)^+$ 460.2; ^1H NMR (400 MHz, DMSO-d_6) δ 7.83 (d, 2H, J = 8.5), 7.75 (d, 2H, J = 8.3), 7.68 (s, 1H), 7.64 (d, 2H, J = 8.6), 7.49 (d, 2H, J = 8.1), 7.20 (s, 1H), 4.67 (ABq, 2H, $\Delta\nu$ = 28.3, J_{ab} = 17.3), 4.54 (dd, 1H, J = 9.3, 3.2), 2.23 (m, 1H), 1.42 (m, 1H), 1.25 (d, 3H, J = 21.6), 1.21 (d, 3H, J = 21.7).

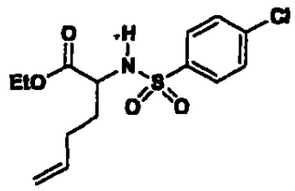


2-[(4-Chlorobenzenesulfonyl)-(4-cyanobenzyl)-amino]-4-hydroxy-4-methyl-pentanoic acid amide (**Example 443**):

A sealed vial containing a mixture of 4-chloro-*N*-(5, 5-dimethyl-2-oxo-tetrahydro-furan-3-yl)-benzenesulfonamide (0.20 g, 0.66 mmol) and 28%

ammonia in water (3 mL) was heated in a microwave reactor at 80 °C for 40 min. The reaction mixture was cooled to rt and concentrated to dryness in vacuo to afford a white solid containing 2-(4-chlorobenzenesulfonylamino)-4-hydroxy-4-methyl-pentanoic acid amide. The crude solid was converted to the title compound (98 mg, 34% yield) as in Reaction Scheme 1, method A: LCMS $(M+Na)^+$ 458.2; ^1H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, 2H, J = 8.6), 7.76 (d, 2H, J = 8.3), 7.62 (d, 2H, J = 8.8), 7.51 (d, 2H, J = 8.3), 7.40 (s, 1H), 7.11 (s, 1H), 4.63 (ABq, 2H, $\Delta\nu$ = 5.9, J_{ab} = 17.6), 4.56 (dd, 1H, J = 8.3, 2.5), 4.54 (s, 1H), 1.95 (dd, 1H, J = 13.7, 8.6), 1.26 (dd, 1H, J = 13.6, 2.4), 1.04 (s, 3H), 0.99 (s, 3H). Anal. Calcd for $C_{20}H_{22}ClN_3O_4S$: C, 55.10; H, 5.08; N, 9.64. Found: C, 54.96; H, 5.14; N, 9.58.

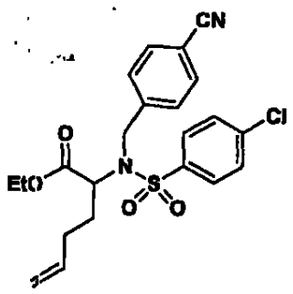
Exemplification of Reaction Scheme 22



2-(4-Chlorobenzenesulfonylamino)-5-hexenoic acid ethyl ester:

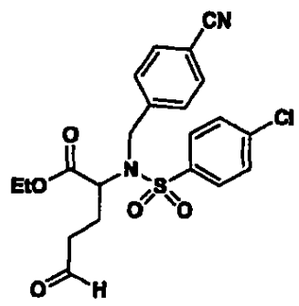
A mixture of (benzhydrylidene-amino)acetic acid ethyl ester (20 g, 74.8 mmol), 4-bromo-1-butene (10.1 g, 74.8 mmol), K_2CO_3 (31.0 g, 224 mmol), tetrabutylammonium bromide (2.41 g, 7.48 mmol), and acetonitrile (150 mL) was heated at reflux for 6 h. The reaction was cooled to rt and filtered through a sintered glass funnel. The filtrate was concentrated *in vacuo*. The residue was dissolved in diethyl ether (250 mL) and a white solid precipitated. The solid was removed by vacuum filtration. A solution of 1 N HCl (150 mL) was added to the filtrate, which contained the crude product (2-(benzhydrylidene-amino)-hex-5-enoic acid ethyl ester). The resulting biphasic mixture was stirred vigorously for 18 h. The mixture was transferred to a separatory funnel. The aqueous layer was

collected and concentrated *in vacuo*. The residue was dissolved in toluene (2 x 200 mL) and reconcentrated. The crude amino ester was dissolved in CH_2Cl_2 and reacted with 4-chlorobenzenesulfonyl chloride (15.8 g, 74.8 mmol) and Et_3N (31.2 mL, 224 mmol). After 18 h, the resulting mixture was poured into 1 N HCl (500 mL). The organic layer was collected and washed sequentially with 1 N HCl (500 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude concentrate was purified using silica gel column chromatography (5:1, hexanes/EtOAc) to afford 5.57 g (23% yield over 3 steps) of the title compound: LCMS $(M+Na)^+$ 354.0; ^1H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, 1H, J = 8.8), 7.76 (d, 2H, J = 8.8), 7.66 (d, 2H, J = 8.8), 5.69 (m, 1H), 4.95-4.88 (m, 2H). 3.86 (q, 2H, J = 7.1), 3.76 (m, 1H), 1.98 (m, 2H), 1.71-1.54 (m, 2H), 1.03 (t, 3H, J = 7.1).



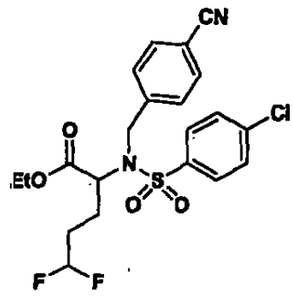
2-[(4-Chlorobenzenesulfonyl)-(4-cyanobenzyl)-amino]-hex-5-enoic acid ethyl ester:

2-[(4-Chlorobenzenesulfonyl)-(4-cyanobenzyl)-amino]-hex-5-enoic acid ethyl ester was made in a similar manner to Reaction Scheme 1 starting from 2-(4-chloro-benzenesulfonylamino)-hex-5-enoic acid ethyl ester. 2-[(4-Chlorobenzenesulfonyl)-(4-cyanobenzyl)-amino]-hex-5-enoic acid ethyl ester was isolated as a crude yellow solid (1.14 g) and used in the next step without further purification. ^1H NMR ($CDCl_3$) δ 7.71 (d, 2H, J = 8.0), 7.61 (d, 2H, J = 8.0), 7.53 (d, 2H, J = 8.0), 7.46 (d, 2H, J = 8.0), 5.54 (m, 2H), 4.90 (m, 2H), 4.74 (d, 1H, J = 16.0), 4.48 (m, 2H), 3.90 (m, 1H), 1.95 (m, 2H), 1.81 (m, 1H), 1.48 (m, 1H), 1.11 (t, 3H, J = 8.0).



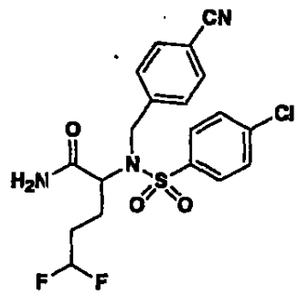
2-[(4-Chlorobenzenesulfonyl)-(4-cyanobenzyl)-amino]-5-oxo-pentanoic acid ethyl ester

A mixture of (4-chlorobenzenesulfonyl)-(4-cyanobenzyl)-amino]-hex-5-enoic acid ethyl ester (1.14 g, 2.56 mmol), osmium tetraoxide (0.030 g, 0.13 mmol), and trimethylamine N-oxide (0.41 g, 5.5 mmol) was dissolved in acetone (50 mL) and stirred for 4 h at rt. Upon completion, the solution was concentrated *in vacuo* and redissolved in 1.5:1 dioxane:H_2O (50 mL). To this solution, sodium periodate (0.66 g, 3.07 mmol) was added and stirred at rt for 18 h. The reaction was then diluted with EtOAc (500 mL) and washed with H_2O, brine, dried over Na_2SO_4 and concentrated to give a crude colorless oil. Further purification by flash chromatography (SiO_2, 5 to 75 % EtOAc/hexanes) afforded 2-[(4-chlorobenzenesulfonyl)-(4-cyanobenzyl)-amino]-5-oxo-pentanoic acid ethyl ester (0.26 g) as a colorless oil in 23 % yield. ^1H NMR ($CDCl_3$) δ 9.57 (s, 1H), 7.69 (d, 2H, J = 8.0), 7.51 (m, 6H), 5.99 ABq, 2H, Δν = 16, J_{ab} = 168), 4.47 (m, 1H), 3.89 (m, 2H), 2.53 (m, 1H), 2.32 (m, 1H), 2.11 (m, 1H), 1.61 (m, 1H), 1.06 (t, 3H, J = 8.0).



2-[(4-Chlorobenzenesulfonyl)-(4-cyanobenzyl)-amino]-5, 5-difluoro-pentanoic acid ethyl ester:

2-[(4-Chlorobenzenesulfonyl)-(4-cyanobenzyl)-amino]-5-oxo-pentanoic acid ethyl ester (0.05 g, 0.11 mmol) was slowly added to a solution of DAST (0.020 mL, 0.11 mmol) in CH_2Cl_2 (2 mL) at rt and stirred for 16 h. The reaction was diluted with CH_2Cl_2 (20 mL) and extracted with H_2O (2 x 25 mL). The combined organic layers were washed with H_2O, brine, dried over Na_2SO_4 and concentrated to give 2-[(4-Chloro-benzenesulfonyl)-(4-cyanobenzyl)-amino]-5, 5-difluoro-pentanoic acid ethyl ester as a crude yellow residue (61 mg). This crude residue was taken onto the next step without further purification.

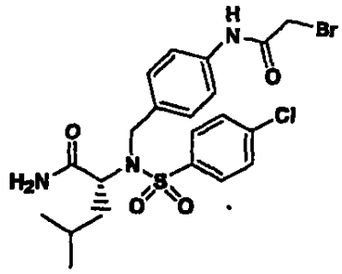


2-[(4-Chlorobenzenesulfonyl)-(4-cyanobenzyl)-amino]-5, 5-difluoro-pentanoic acid amide (Example 377):

The crude 2-[(4-chlorobenzenesulfonyl)-(4-cyanobenzyl)-amino]-5, 5-difluoro-pentanoic acid ethyl ester (0.061 g, 0.13 mmol) was dissolved in MeOH (2 mL). To this mixture was added 10 N NaOH (0.052 mL, 0.52 mmol) and the

resulting solution was stirred at rt for 16 h. The reaction was diluted with H_2O (25 mL), acidified with 1 N HCl, and extracted with CH_2Cl_2 (4 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the carboxylic acid moiety as a crude colorless oil. The carboxylic acid intermediate was then dissolved in DMF (10 mL) and mixed with 1-hydroxybenzotriazole (0.030 g, 0.20 mmol), *i*Pr_2NEt (0.090 mL, 0.52 mmol), NH_4Cl (0.01 g, 0.26 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.04 g, 0.20 mmol) and stirred at rt for 72 h. The reaction was diluted with EtOAc (150 mL) and washed with H_2O (4 x 50 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give a crude off-white solid. Further purification by flash chromatography (SiO_2, 5 to 85 % EtOAc/hexanes) afforded the titled compound (10.7 mg) as a white solid in 19 % yield. LCMS $(M+Na)^+$ 464.01; ^1H NMR ($CDCl_3$) δ 7.69 (d, 2H, J = 8.3), 7.60 (d, 2H, J = 8.3), 7.49 (m, 4H), 6.18 (br s, 1H), 5.67 (tt, 1H, J = 56, 4.0), 5.22 (br s, 1H), 4.52 (ABq, 2H, $\Delta\nu$ = 16, J_{ab} = 100), 4.34(m, 1H), 2.03 (m, 1H), 1.68 (m, 1H), 1.38 (m, 1H), 0.86 (m, 1H).

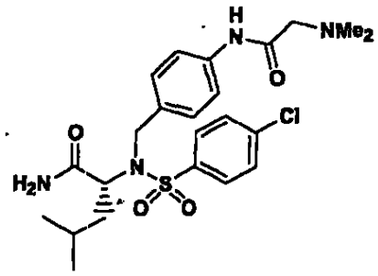
Exemplification of Reaction Scheme 23



(2*R*)-2-[[4-(2-Bromo-acetylamino)-benzyl]-(4-chlorobenzenesulfonyl)-amino]-4-methyl-pentanoic acid amide:

To a solution of (2*R*)-2-[(4-aminobenzyl)-(4-chloro-benzenesulfonyl)amino]-4-methyl-pentanoic acid amide (248 mg, 0.56 mmol) and Et_3N (176 mg, 1.74 mmol) in CH_2Cl_2 (3 mL) was added bromoacetylchloride

(105 mg, 0.67 mmol). The reaction mixture was stirred overnight at rt. The reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with 1 N HCl, brine, and dried through a cotton plug. The solvent was removed *in vacuo*. Purification by flash chromatography (SiO_2, 10% acetone/CH_2Cl_2) afforded the title compound (124 mg) in 42 % yield. MS (ESI), $(M+H)^+$ 531.86, ^1H NMR ($CDCl_3$, 400 MHz) δ 8.78 (br s, NH), 7.95 (d, 2H, J = 8.0), 7.82 (d, 2H, J = 8.0), 7.42 (d, 2H, J = 8.0), 7.33 (d, 2H, J = 8.0), 6.20 (br s, 1H), 5.20 (br s, 1H), 4.30 (s, 2H), 4.22 (d, 1H, J_{ab} = 16), 4.14 (d, 1H, J_{ab} = 16), 3.25 (t, 1H, J = 6.0), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J = 7.0), 0.94 (d, 3H, J = 7.0)

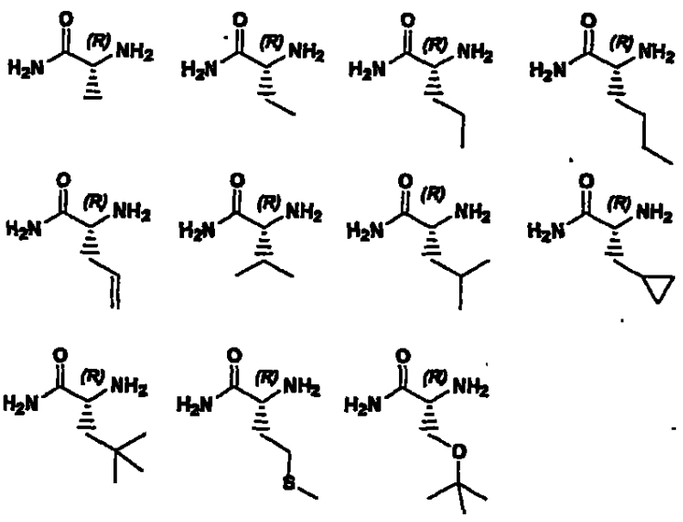


(2*R*)-2-{(4-Chlorobenzenesulfonyl)-[4-(2-dimethylamino-acetylamino)-benzyl]-amino}-4-methyl-pentanoic acid amide (**Example 308**):

To a solution of (2*R*)-2-[[4-(2-bromo-acetylamino)-benzyl]-(4-chlorobenzenesulfonyl)-amino]-4-methyl-pentanoic acid amide (41 mg, 0.77 mmol) in CH_2Cl_2 (2 mL) was added excess 2.0 M dimethylamine in THF. The reaction mixture was stirred overnight. The solvent was removed *in vacuo*. Purification by flash chromatography (SiO_2, 10% MeOH/CH_2Cl_2) afforded the title compound (24 mg) in 63% yield. MS (ESI), $(M+H)^+$ 495.14, ^1H NMR ($CDCl_3$, 400 MHz) δ 8.85 (s, 1H), 8.02 (d, 2H, J = 8.0), 7.75 (d, 2H, J = 8.0), 7.38 (d, 2H, J = 8.0), 7.29 (d, 2H, J = 8.0), 6.23 (br s, 1H), 5.39 (br s, 1H), 4.62 (m, 4H), 3.25 (t, 1H, J = 6.0), 2.95 (s, 6H), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J = 7.0), 0.94 (d, 3H, J = 7.0)

Starting Materials

The following α-amino amides were commercially available or obtained by standard methods from commercially available amino acids:



5,5,5-Trifluoro-2-aminopentanoic acid amide and 6,6,6-trfluoro-2-aminohexanoic acid were prepared according to: Ojima, I.; Kato, K.; Nakahashi, K. *J. Org. Chem.* 1989, *54*, 4511.

The benzyl bromide used in the synthesis of the compounds of **Examples 100 and 155** was prepared according to: Ishihara, Y.; Fujisawa, Y.; Furuyama, N. PCT Int. Appl. WO 9846590; Senanayake, C.H.; Fang, Q.K.; Wilkinson, S.H. PCT Int. Appl. WO 9833789.

The aldehydes required for the synthesis of the compounds of **Examples 91, 248, 249, 289, 290, and 300** (see Reaction Scheme 2) were prepared as exemplified for 4-(piperidin-1-yl)benzaldehyde. A suspension of 4-fluorobenzaldehye (0.48mL, 4 mmol), K_2CO_3 (522 mg, 4 mmol), piperidine (340 mg, 4 mmol) in DMSO (5 mL) was heated in a sealed tube at 150°C for 18h. after which time, the reaction was concentrated and purified by silica gel chromatography (CH_2Cl_2, then 2% MeOH/CH_2Cl_2) to afford 4-(piperidin-1-yl)benzaldehyde , 748 mg, 98% yield.

The aldehydes used in the synthesis of the compounds of **Examples 317, 318, and 320** were prepared as exemplified for 4-(piperidin-1-yl)-3-fluorobenzaldehyde. A suspension of 4,3-difluorobenzaldehye (500 mg, 3.5 mmol), K_2CO_3 (483 mg, 3.5 mmol), piperidine (298 mg, 3.5 mmol) in DMSO (5 mL) was heated in a sealed tube at 130 °C for 18h. The reaction mixture was allowed to cool to rt, concentrated and purified by silica gel chromatography (CH_2Cl_2, then 2% MeOH/CH_2Cl_2) to afford 4-(piperidin-1-yl)3-fluorobenzaldehyde , 740 mg, 99% yield.

The benzyl chloride used in the preparation of the compounds of **Examples 433, 474, 480, and 500** was prepared by the following method. To a solution of 2-[(4-chloromethyl)phenyl]propan-2-ol (769 mg, 4.16 mmol) (ref: Creary, X.; Mehrsheikh-Mohammadi, M.E.; McDonald, S. *J. Org. Chem.* **1987**, *52,* 3254.) in CH_2Cl_2 (14 mL) at -78 °C was added DAST (0.72 mL, 5.4 mmol). After 1.5 h, the solution was quenched with water and warmed to rt. The mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash column chromatography (SiO_2, 0 to 5% EtOAc/hexanes) provided the chloride as a pale yellow liquid (512 mg, 66%). ^1H NMR ($CDCl_3$, 300MHz) δ 7.30-7.48 (m, 4H), 4.58 (s, 2H), 1.70 (s, 3H), 1.63 (s, 3H).

The preparation of the 2-trimethylsilanyl ethyl ester of 4-bromomethyl benzoic acid, which is used in the synthesis of the compound of **Example 470** is described by Graffner-Nordberg, M.; Sjoedin, K.; Tunek, A.; Hallberg, A. *Chem. Pharm. Bull.* **1998**, *46,* 591.

Conditions for Chromatographic Separation of Enantiomeric Mixtures

Condition 1: Example 345 was separated using the following method. 4.6 X 250 mm, 10 μM, Chiracel OJ column, 1.0 mL/min, 85 % Hexane/EtOH 0.1 % DEA, over 20 min.

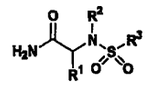
Condition 2: Example 346 was separated using the following method. 4.6 X 250 mm, 10 μM, Chiralpak AD column, 1.0 mL/min, 80 % Hexane/EtOH 0.15 % DEA, over 20 min.

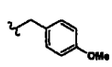
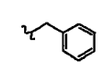
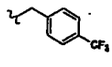
Condition 3: Example 347 was separated using the following method. 4.6 X 250 mm, 10 μM, Chiralpak AD column, 1.0 mL/min, 65 % Hexane/IPA 0.1 % DEA, over 18 min.

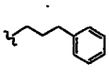
Condition 4: Examples 365 and 366 were separated using the following method. 4.6 X 250 mm, 10 μM, Chiralpak AD column, 1.0 mL/min, 75 % Hexane/EtOH 0.15 % DEA, over 25 min.

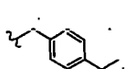
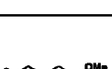
Condition 5: Examples 408 and 409 were separated using the following method. 4.6 X 250 mm, 10 μM, Chiracel OD column, 1.0 mL/min, 90 % Hexane/EtOH 0.15 % DEA, over 36 min.

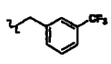
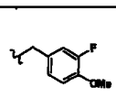
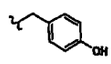
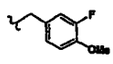
TABLE 4

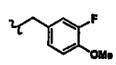
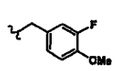
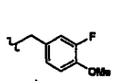
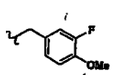


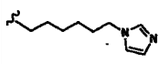
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
1				1, 2	white solid	424.95	1.76 Method B	425.1	^{1}H NMR ($CDCl_3$) δ 7.63 (d,2H,J=7.0Hz),7.42 (d,2H,J=7.0Hz), 7.25 (d,2H,J=8.0Hz), 6.79 (d,2H,J=8.0Hz), 6.25 (s, br,1H), 5.35 (s, br,1H), 4.36 (dd,2H, J=50Hz,15Hz), 4.26 (t,1H, J=7.2Hz), 3.78 (s,3H), 1.83 (m, 1H), 1.18-1.34 (m,3H), 0.75 (d,3H,J=7.0Hz), 0.67 (d,3H,J=7.0Hz).
2				1	white solid	394.92	1.71 - Method B	395.2	^{1}H NMR (d_6DMSO) δ 7.81 (d,2H,J=7.0Hz), 7.60 (d,2H,J=7.0Hz), 7.50 (s, br,1H), 7.41,(d,2H,J=8.0Hz), 7.32 (m,2H), 7.24 (m,1H), 7.18 (s, br,1H), 4.76 (dd,2H, J=50Hz,15Hz), 4.36 (t,1H, J=7.0Hz), 3.33 (s,3H), 1.20-1.34 (m,3H), 0.79 (d,3H,J=6.0Hz), 0.46 (d,3H,J=6.0Hz).
3				1	white solid	462.92	1.71 Method A	463.1	^{1}H NMR (d_6DMSO) δ 7.83 (d,2H,J=7.0Hz), 7.67 (d,2H,J=7.0Hz), 7.57-7.62 (m, 4H), 7.06 (s, br, 1H), 4.79 (dd, 2H, J=70Hz,17Hz), 4.38 (t,1H, J=6.0Hz), 3.32 (s,3H), 1.23-1.35 (m,3H), 0.81 (d,3H,J=6.0Hz), 0.50 (d,3H,J=6.0Hz)

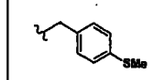
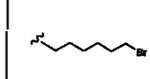
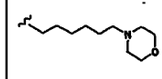
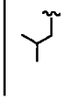
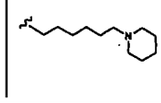
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
4				1	white solid	429.37	1.69 Method A	429.1	^{1}H NMR (d_6DMSO) δ 7.83 (d,2H,J=7.0Hz), 7.61 (d,2H,J=7.0Hz), 7.52 (s, br,1H), 7.41 (d,2H,J=8.2Hz), 7.37 (d,2H,J=8.2Hz), 7.03 (s, br,1H), 4.70 (dd,2H, J=50Hz,15Hz), 4.35 (t,1H, J=7.0Hz), 1.28-1.30 (m,3H), 0.80 (d,3H,J=6.0Hz), 0.51 (d,3H,J=6.0Hz).
5				1	white solid	422.98	1.71 Method A	423.2	^{1}H NMR (d_6DMSO) δ 7.76 (d,2H,J=7.0Hz), 7.61 (d,2H,J=7.0Hz), 7.42 (s, br,1H), 7.16-7.20 (m,5H), 6.99 (s, br,1H), 4.24 (m,1H), 3.45-3.51 (m,1H), 3.10-3.18 (m,1H), 2.52-2.59 (m,2H), 1.95-2.05 (m, 1H), 1.69-1.80 (m,1H), 1.55-1.74 (m,3H), 0.84 (m,6H).
6				1	white solid	419.93	1.45 Method A	420.13	^{1}H NMR (d_6DMSO) δ 7.84 (d,2H,J=8.0Hz), 7.79 (d,2H,J=8.0Hz), 7.63 (d,2H,J=8.0Hz), 7.58 (m,3H), 7.03 (s, br,1H), 4.87 (dd,2H, J=50Hz,15Hz), 4.32 (t,1H, J=7.0Hz), 1.28-1.30 (m,3H), 0.81 (d,3H,J=6.0Hz), 0.53 (d,3H,J=6.0Hz).
7				1	white solid	412.91	1.58 Method A	413.4	^{1}H NMR (d_6DMSO) δ 7.81 (d,2H,J=7.0Hz), 7.61 (d,2H,J=7.0Hz), 7.51 (s, br,1H) 7.43 (m,1H), 7.11-7.14 (m,2H), 7.03 (s, br,1H), 4.77 (dd,2H, J=50Hz,15Hz), 4.33 (t,1H, J=6.0Hz), 1.21-1.31 (m,3H), 0.80 (d,3H,J=6.0Hz), 0.50 (d,3H,J=6.0Hz).

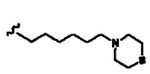
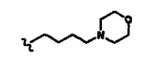
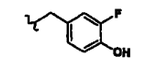
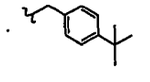
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
8				1	white solid	412.91	1.58 Method A	413..2	^{1}H NMR (d_6DMSO) δ 7.82 (d,2H,J=8.0Hz), 7.61 (d,2H,J=8.0Hz), 7.55 (s, br,1H) 7.39 (m,1H), 7.05-7.32 (m,4H), 7.03 (s, br,1H), 4.78 (dd,2H, J=50Hz,15Hz), 4.38 (t,1H, J=6.0Hz), 1.26-1.32 (m,3H), 0.81 (d,3H,J=6.0Hz), 0.54 (d,3H,J=6.0Hz)
9				1	white solid	451.03	2.99 Method C	451.2	^{1}H NMR (d_6DMSO) δ 7.75 (d,2H,J=8.5Hz), 7.55 (d,2H,J=8.5Hz), 7.51 (s, br,1H), 7.25-7.29 (m,4H), 7.03 (s, br,1H), 4.69 (dd,2H, J=25Hz,14Hz), 4.35 (m,1H), 1.21-1.31 (m,3H),1.25 (s, 9H) 0.81 (d,3H,J=6.0Hz), 0.46 (d,3H,J=6.0Hz)
10				1	white solid	424.95	1.56 Method A	425.2	^{1}H NMR (d_6DMSO) δ 7.80 (d,2H,J=8.0Hz),.7.58 (d,2H,J=8.0Hz), 7.50 (s, br,1H) 7.21 (m,1H), 7.04 (m, 1H), 6.80-6.95 (m,3H), 4.70 (dd,2H, J=50Hz,15Hz), 4.37 (m,1H), 3.70 (s,3H), 1.30-1.39 (m,3H), 0.81 (d,3H,J=6.0Hz), 0.52 (d,3H,J=6.0Hz)
11				1	white olid	463.81	1.76 Method A	463	^{1}H NMR (d_6DMSO) δ 7.80 (d,2H,J=8.0Hz), 7.61 (d,2H,J=8.0Hz), 7.55-7.60 (m, 2H) 7.40 (m,1H), 7.10 (s, br,1H), 4.72 (dd,2H, J=50Hz,15Hz), 4.40 (m,1H), 1.26-1.40 (m,3H), 0.83 (d,3H,J=6.0Hz), 0.60 (d,3H,J=6.0Hz)

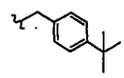
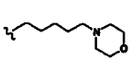
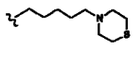
Ex. No.	R¹	R²	R³	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H⁺	NMR Data
12				1	white solid	462.92	1.68 Method A	463.1	^{1}H NMR (d_6DMSO) δ 7.80 (d,2H,J=8.0Hz), 7.68-7.80 (m,2H), 7.54-7.61 (m,4H) , 7.08 (s, br,1H), 4.80 (dd,2H, J=50Hz,15Hz), 4.38 (t,1H, J=6.0Hz), 1.26-1.33 (m,3H), 0.82 (d,3H,J=6.0Hz), 0.52 (d,3H,J=6.0Hz)
13				1	white solid	442.94	1.55 Method A	443.2	^{1}H NMR (d_6DMSO) δ 7.78 (d,2H,J=8.0Hz), 7.61 (d,2H,J=8.0Hz), 7.56 (s, br,1H), 7.05-7.24 (m,4H), 4.65 (dd,2H, J=50Hz,15Hz), 4.40 (t,1H, J=6.0Hz), 3.81 (s,3H) 1.28-1.35 (m,3H), 0.81 (d,3H,J=6.0Hz), 0.56 (d,3H,J=6.0Hz)
14				1	white solid	410.92	1.51 Method B	411.2	^{1}H NMR ($CDCl_3$) δ 7.69 (d,2H,J=8.0Hz),7.45 (d,2H,J=8.5Hz), 7.26 (d,2H,J=8.5Hz), 6.73 (d,2H,J=8.0Hz), 6.33 (s, br,1H), 5.24 (s, br,1H), 4.28 (dd,2H, J=70Hz,20Hz), 4.23 (m,1H), 1.67-1.93 (m, 2H), 1.12-1.32 (m,2H), 0.77 (d,3H,J=7.0Hz), 0.68 (d,3H,J=7.0Hz)
15				1	sticky pale yellow foam	408.5	1.58 Method B	409.3	^{1}H NMR ($CDCl_3$) δ 7.77 (d,2H,J=8.0Hz), 7.74-7.59 (m,3H), 7.02-7.13 (m, 2H), 6.84 (t,1H,J=8.4Hz), 6.32 (s, br,1H), 5.31 (s, br,1H), 4.48 (dd,2H, J=50Hz,17Hz), 4.26 (m,1H), 3.85 (s,3H), 1.79-1.84 (m, 1H), 1.25-1.30 (m,1H), 1.04-1.11 (m,1H), 0.72 (d,3H,J=7.0Hz), 0.63 (d,3H,J=7.0Hz)

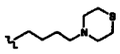
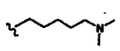
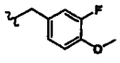
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
16				1	white film	426.49	1.63 Method B	427.3	^{1}H NMR ($CDCl_3$) δ 7.73-7.77 (m,2H), 6.81-7.18 (m,5H), 6.29 (s, br,1H), 5.37 (s, br,1H), 4.45 (dd,2H, J=50Hz,17Hz), 4.26 (m,1H), 3.89 (s,3H), 1.76-1.84 (m, 1H), 1.26-1.33 (m,1H), 1.08-1.17 (m,1H), 0.74 (d,3H,J=7.0Hz), 0.65 (d,3H,J=7.0Hz)
17				1	pale yellow solid	476.49	1.79 Method B	477.2	^{1}H NMR ($CDCl_3$) δ 7.84 (d,2H,J=8.0Hz),7.72 (d,1H,J=8.0Hz), 7.10 (d,1H,J=9.5Hz), 6.99 (d,2H,J=8.5Hz), 6.82 (t,1H,J=8.5Hz), 6.21 (s, br,1H), 5.35 (s, br,1H), 4.46 (dd,2H, J=50Hz,15Hz), 4.31 (t,1H, J=7.5Hz), 3.87 (s,3H), 1.78-1.85 (m, 1H), 1.30-1.35 (m,1H), 1.12-1.21 (m,1H), 0.77 (d,3H,J=7.0Hz), 0.68 (d,3H,J=7.0Hz)
18				1	pale yellow solid	476.49	1.76 Method B	477.2	^{1}H NMR ($CDCl_3$) δ 7.79-7.89 (m,3H), 7.59-7.64 (m,1H), 7.01-7.08 (m,1H), 6.83 (t,1H,J=8.8Hz), 6.25 (s, br,1H), 5.42 (s, br,1H), 4.45 (dd,2H, J=50Hz,17Hz), 4.33 (m,1H), 3.88 (s,3H), 1.78-1.85 (m, 1H), 1.31-1.35 (m,1H), 1.17-1.23 (m,1H), 0.77 (d,3H,J=7.0Hz), 0.70 (d,3H,J=7.0Hz)
19				1	white solid	442.94	1.73 Method B	443.2	^{1}H NMR ($CDCl_3$) δ 7.42-7.63 (m,4H), 7.02-7.10 (m,2H), 6.86 (t,1H,J=8.5Hz), 6.24 (s, br,1H), 5.42 (s, br,1H), 4.45 (dd,2H, J=50Hz,17Hz), 4.27 (m,1H), 3.87 (s,3H), 1.79-1.87 (m, 1H), 1.27-1.33 (m,1H), 1.14-1.22 (m,1H), 0.78 (d,3H,J=7.0Hz), 0.71 (d,3H,J=7.0Hz)

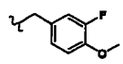
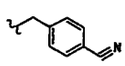
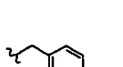
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
20				1	pale yellow oil	422.52	1.68 Method B	423.2	^{1}H NMR ($CDCl_3$) δ 7.52-7.57 (m,2H), 7.37-7.39 (m,2H), 7.02-7.12 (m,2H), 6.84 (t,1H,J=8.5Hz), 6.34 (s, br,1H), 5.35 (s, br,1H), 4.45 (dd,2H, J=50Hz,17Hz), 4.25 (m,1H), 3.86 (s,3H), 2.38 (s,3H), 1.78-1.87 (m, 1H), 1.25-1.31 (m,1H), 1.04-1.11 (m,1H), 0.72 (d,3H,J=7.0Hz), 0.65 (d,3H,J=7.0Hz)
21				1	pale yellow oil	422.52	1.67 Method B	423.2	^{1}H NMR ($CDCl_3$) δ 7.64 (d,2H,J=8.0Hz), 7.25-7.30 (m,2H), 7.02-7.12 (m,2H), 6.84 (t,1H,J=8.5Hz), 6.34 (s, br,1H), 5.32 (s, br,1H), 4.45 (dd,2H, J=50Hz,17Hz), 4.26 (t,1H,J=10Hz), 3.86 (s,3H), 2.42 (s,3H), 1.76-1.85 (m, 1H), 1.25-1.31 (m,1H), 1.05-1.12 (m,1H), 0.72 (d,3H,J=7.0Hz), 0.62 (d,3H,J=7.0Hz)
22				3	clear oil	455.02	1.94 Method B	455.2	^{1}H NMR (d_6DMSO) δ 7.82 (d,2H,J=8.0Hz), 7.68 (d,2H,J=8.0Hz), 7.56 (s, br,1H), 7.45 (m,1H), 7.16 (m,1H), 7.04 (s,1H), 6.86 (m,1H), 4.25 (m, 1H), 3.94 (m,1H), 3.40-3.55 (m,2H), 3.02-3.14 (m,1H), 1.18-1.69 (m,10H), 0.76 (s,br,6H)

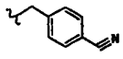
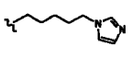
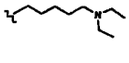
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
23				1	white solid	441.01	1.67 Method A	441.2	^{1}H NMR (d_6DMSO) δ 7.79 (d,2H,J=8.0Hz), 7.59 7.51 (s,br,1H), 7.31 (d,2H,J=8.0Hz), 7.19 (d,2H,J=8.0Hz), 7.03 (s, br,1H), 4.68 (dd,2H, J=50Hz,15Hz), 4.35 (t,1H, J=7.0Hz), 3.32 (s,3H), 1.24-1.35 (m,3H), 0.81 (d,3H,J=6.0Hz), 0.51 (d,3H,J=6.0Hz)
24				1	white solid	467.86	1.75 Method A	469.1	^{1}H NMR (d_6DMSO) δ 7.83 (d,2H,J=8.0Hz), 7.64 (d,2H,J=8.0Hz), 7.42 (s, br,1H), 7.01 (s,1H), 4.25 (m, 1H), 3.35-3.51 (m,3H), 3.08-3.14 (m,1H), 1.19-1.82 (m,11H), 0.86 (d,6H,J=6.0Hz)
25				3	clear oil	474.07	1.34 Method A	474.4	^{1}H NMR (d_6DMSO) δ 7.82 (d,2H,J=8.0Hz), 7.64 (d,2H,J=8.0Hz), 7.42 (s, br,1H), 6.99 (s,1H), 4.25 (m, 1H), 3.51-3.60 (s,br,4H), 3.18-3.41 (m,2H), 2.25-2.35 (s,br,4H), 2.27 (m,2H)1.15-1.62 (m,9H), 0.90 (d,6H,J=6.0Hz)
26				3	clear oil	472.09	1.27 Method A	472	^{1}H NMR (d_6DMSO) δ 7.83 (d,2H,J=8.0Hz), 7.64 (d,2H,J=8.0Hz), 7.42 (s, br,1H), 7.00 (s,1H), 4.23-4.26 (m, 1H), 3.22-3.45 (m,1H), 3.11-3.14 (m,1H), 2.16-2.28 (m,5H), 1.19-1.52 (m,18H), 0.86 (m,6H).

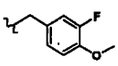
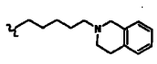
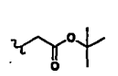
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
27				3	clear oil	490.13	1.21 Method A	490	^{1}H NMR (d_6DMSO) δ 7.83 (d,2H,J=8.0Hz), 7.64 (d,2H,J=8.0Hz), 7.44 (s, br,1H) 7.06 (s,1H), 4.21-4.25 (m, 1H), 3.55(s,br,4H), 3.19-3.40 (m,4H), 2.43-2.57 (m,8H), 2.23-2.30 (m,2H), 1.18-1.69 (m,9H), 0.82 (m,6H).
28				3	clear oil	446.01	1.08 Method A	446.2	^{1}H NMR (d_6DMSO) δ 7.84 (d,2H,J=8.0Hz), 7.66 (d,2H,J=8.0Hz), 7.49 (s, br,1H) 7.02 (s,1H), 4.23-4.26 (m, 1H), 3.94 (s,br,2H), 3.71 (s,br,2H), 3.52-3.57 (m,1H), 3.14-3.17(m,1H), 3.06 (s,br,4H), 1.17-1.65 (m,7H), 0.86 (m,6H).
29				1	white solid	428.91	1.51 Method A	429.1	^{1}H NMR ($CDCl_3$) δ 7.69 (d,2H,J=9.0Hz),7.47 (d,2H,J=9.0Hz), 7.13 (d,1H,J=11.2Hz), 7.00 (d,1H,J=8.0Hz), 6.88 (m, 1H), 6.27 (s, br,1H), 5.49 (s,br,1H), 5.24 (s, br,1H), 4.40 (dd, 2H, J=90Hz,18Hz), 3.20 (m,1H), 1.09-1.82 (m,3H), 0.77 (d,3H,J=7.0Hz), 0.68 (d,3H,J=7.0Hz).
30				1	white solid	484.59	1.89 Method A	485.0	^{1}H NMR ($CDCl_3$) δ 7.73 (d,2H,J=8.0Hz), 7.65 (d,2H,J=8.0Hz), 7.18-7.27 (m,4H), 5.25 (s, br,1H), 5.29 (s, br,1H), 4.40-4.69(m, 3H), 1.80-1.88 (m, 1H), 1.29 (s,9H), 1.25-1.33 (m,2H), 0.80 (d,3H,J=7.0Hz), 0.69 (d,3H,J=7.0Hz).

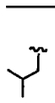
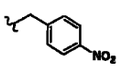
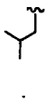
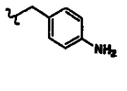
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
31				1	white solid	430.61	1.82 Method A	431.2	^{1}H NMR ($CDCl_3$) δ 7.60 (d,2H,J=8.2Hz), 7.24- 7.39(m,6H), 6.34 (s, br,1H), 5.19 (s,br,1H), 4.42-4.44(m, 2H), 4.30 (t,1H,J=8Hz), 2.41 (s,3H), 1.74-1.83 (m, 1H), 1.28 (s,9H), 1.25-1.33 (m,1H), 0.93-1.01 (m,1H), 0.72 (d,3H,J=7.0Hz), 0.60 (d,3H,J=7.0Hz)
32				3	brown oil	460.04	1.15 Method A	460.2	^{1}H NMR (d_6DMSO) δ 7.83 (d,2H,J=8.0Hz), 7.64 (d,2H,J=8.0Hz), 7.42 (s, br,1H) 7.00 (s,1H), 4.22-4.26 (m, 1H), 3.55(s,br,4H), 3.11-3.32 (m,2H), 2.13-2.37 (m,6H), 1.12-1.51 (m,9H), 0.86 (m,6H)
33				1	white solid	400.97	1.85 Method A	401	^{1}H NMR (d_6DMSO) δ 7.85 (d,2H,J=8.0Hz), 7.65 (d,2H,J=8.0Hz), 7.32 (s,br,1H) 7.05 (s,br,1H), 4.19 (t,1H,J=7.5Hz), 2.99-3.02 (m,1H), 1.07-1.65 (m,14H), 0.78-0.84(m,7H)
34				3	clear Oil	476.1	1.28 Method A	476.1	^{1}H NMR ($CDCl_3$) δ 7.76 (d,2H,J=8.0Hz), 7.51 (d,2H,J=8.0Hz), 6.55 (s, br,1H), 5.41(s,1H), 4.17-4.20 (m, 1H), 3.26-3.38 (m, 1H), 3.13-3.17 (m,1H), 2.62-2.92 (m,8H), 2.32-2.36 (m,2H), 1.85-1.87 (m,1H), 1.25-1.47 (m,7H), 0.96-0.99 (m,1H), 0.75 (d,3H,J=6.6Hz), 0.72 (d,3H,J=6.6Hz)

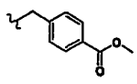
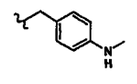
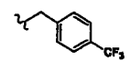
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
35				3	clear oil	462.08	1.31 Method A	462.2	^{1}H NMR ($CDCl_3$) δ 7.75 (d,2H,J=8.0Hz), 7.52 (d,2H,J=8.0Hz), 6.51 (s, br,1H), 6.05 (s,1H), 4.15-4.18 (m, 1H), 3.56-3.78 (m, 4H), 3.45-3.47 (m,1H), 3.09-3.14 (m,1H), 2.90-3.08 (m,4H), 2.61-2.69 (m,2H), 1.62-2.05 (m,5H), 1.21-1.29(m, 1H), 0.80-0.83 (m,1H), 0.78 (d,3H,J=6.6Hz), 0.71 (d,3H,J=6.6Hz).
36				3	clear oil	418.0	1.25 Method A	418.2	^{1}H NMR ($CDCl_3$) δ 7.77 (d,2H,J=8.5Hz), 7.51 (d,2H,J=8.5Hz), 6.56 (s, br,1H), 5.41 (s,1H), 4.18-4.21 (m, 1H), 3.15-3.32 (m,2H), 2.25-2.28 (m,2H), 2.24 (s,6H), 1.84-1.88 (m,1H), 1.25-1.49 (m, 7H), 0.97-1.00 (m,1H), 0.71-0.74 (m,6H).
37				1	tan solid	428.91	1.5 Method A	429.1	^{1}H NMR ($CDCl_3$) δ 7.57 (d,2H,J=8.0Hz),7.38 (d,2H,J=9.0Hz), 7.03-7.13 (m,2H), 6.80 (t,1H,J=8.8Hz), 6.17 (s,br,1H), 5.39 (s,br,1H), 4.48 (dd,2H, J=55Hz,16Hz), 3.84 (s,3H), 3.75-3.84 (m,1H), 1.11-1.30 (m,1H), 0.91 (d,3H,J=7.0Hz), 0.54 (d,3H,J=7.0Hz).

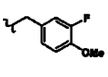
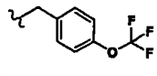
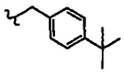
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
38				1	white solid	412.46	1.46 Method A	413.2	^{1}H NMR ($CDCl_3$) δ 7.65-7.70 (m,2H), 7.04-7.12 (m,4H), 6.79 (t,1H,J=8.5Hz), 6.21 (s, br,1H), 5.27 (s,br,1H), 4.48 (dd,2H, J=50Hz,15Hz), 3.86 (s,3H), 3.79-3.85 (m,1H), 2.16-2.22 (m,1H), 0.90 (d,3H,J=7.0Hz), 0.51 (d,3H,J=7.0Hz).
39				1	white solid	403.48	1.47 Method A	404.2	^{1}H NMR ($CDCl_3$) δ 7.77-7.80 (m,2H), 7.59 (d,2H,J=8.0Hz), 7.49 (d,2H,J=8.0Hz), 7.17-7.22(m,2H), 6.17 (s, br,1H), 5.20 (s, br,1H), 4.50(dd,2H, J=60Hz,17Hz), 4.28 (t,1H,J=10Hz), 1.74-1.83 (m, 1H), 1.25-1.33 (m,1H), 0.99-1.10 (m,1H), 0.77 (d,3H,J=7.0Hz), 0.66 (d,3H,J=7.0Hz)
40				1	white solid	453..49	1.65 Method A	454.1	^{1}H NMR ($CDCl_3$) δ 7.88 (d,2H,J=8.2Hz), 7.78 (d,2H,J=8.5Hz), 7.59 (d,2H,J=8.5Hz), 7.49 (d,2H,J=8.5Hz), 6.10 (s, br,1H), 5.19 (s, br,1H), 4.59(dd,2H, J=50Hz,16Hz), 4.33 (t,1H,J=10Hz), 1.76-1.81 (m, 1H), 1.25-1.35 (m,1H), 1.02-1.07 (m,1H), 0.78 (d,3H,J=7.0Hz), 0.65 (d,3H,J=7.0Hz).

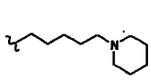
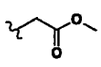
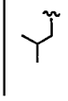
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
41				1	white solid	399.52	1.53 Method A	400.2	^{1}H NMR ($CDCl_3$) δ 7.65 (d,2H,J=8.0Hz), 7.58 (d,2H,J=8.2Hz), 7.47 (d,2H,J=8.0Hz), 7.31 (d,2H,J=8.5Hz), 6.24 (s,br,1H), 5.16 (s, br,1H), 4.50(dd,2H,J=50Hz,17Hz), 4.27 (t,1H,J=10Hz), 2.44 (s,3H), 1.74-1.83 (m, 1H), 1.25-1.33 (m,1H), 0.93-1.01 (m,1H), 0.74 (d,3H,J=7.0Hz), 0.63 (d,3H,J=7.0Hz)
42				3	clear oil	441.0	1.27 Method A	441.2	^{1}H NMR ($CDCl_3$) δ 7.74 (d,2H,J=8.2Hz),7.67 (s,1H), 7.50 (d,2H,J=8.2Hz), 7.10 (s, 1H)). 6.93 (s,1H), 6.51 (s,br,1H) 5.55 (s,br,1H), 4.14-4.17 (m, 1H), 3.97 (t, 2H,J=6.0Hz), 3.29-3.35 (m,1H), 3.09-3.14 (m,1H), 1.62-1.66 (m,3H),1.55-1.62 (m,2H), 1.25-1.29(m, 3H), 0.80-0.83 (m,1H), 0.74 (d,3H,J=6.6Hz), 0.71 (d,3H,J=6.6Hz).
43				3	clear oil	446.06	1.29 Method A	446.3	^{1}H NMR ($CDCl_3$) δ 7.76 (d,2H,J=8.0Hz), 7.52 (d,2H,J=8.0Hz), 6.61 (s, br,1H) 5.45 (s,1H), 4.15-4.18 (m, 1H), 3.09-3.24 (m,2H), 2.50-2.58 (m,4H), 2.31-2.39 (m,2H), 1.92-1.99 (m,1H),1.15-1.59(m, 8H), 1.00-1.04 (m,7H), 0.71-0.74 (m,6H).

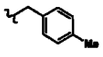
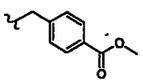
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
44				1	tan wax	428.91	1.58 Method A	429.1	^{1}H NMR ($CDCl_3$) δ 7.67 (d,2H,J=8.0Hz),7.45 (d,2H,J=9.0Hz), 7.03-7.15 (m,2H), 6.84 (t,1H,J=8.0Hz), 6.25 (s,br,1H), 5.19 (s,br,1H), 4.45 (dd,2H, J=80Hz,18Hz), 4.19-4.22 (m,1H), 3.87 (s,3H), 1.82-1.95 (m,1H), 0.96-1.30 (m,3H), 0.77-0.77(e,2H).
45				3	clear oil	506.11	1.39 Method A	506.2	^{1}H NMR ($CDCl_3$) δ 7.75 (d,2H,J=8.0Hz),7.50 (d,2H,J=8.5Hz), 7.01-7.13 (m,4H), 6.55 (s, br,1H), 5.39 (s, br,1H), 4.18 (t,1H, J=6.0Hz), 3.32- 3.60 (m,1H), 3.16-19 (m,1H), 2.91 (s,br,2H), 2.76 (s,br,2H), 2.52 (s,br,2H), 1.27-1.86 (m, 8H), 0.97-1.00 (m,1H), 0.73 (e,6H).
46				1	white solid	418.94	2.7 Method A	441 ($M+Na^+$)	^{1}H NMR (d_6DMSO) δ 7.89 (d,2H,J=8.2Hz), 7.65 (d,2H,J=8.4Hz), 7.52 (s,br,1H) 7.00 (s,br,1H), 4.25 (dd,2H,J=80Hz,18Hz), 4.10-4.13 (m,1H), 2.59-2.60 (m,1H), 1.35 (s,9H), 1.32-1.35 (m,2H), 0.860(d,3H,J=6.0Hz), 0.75 (d,3H,J=6.0Hz).

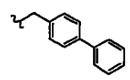
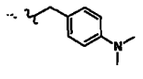
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
47				1	yellow solid	439.92	1.69 Method A	440.2	^{1}H NMR ($CDCl_3$) δ 8.17 (d,2H,J=7.0Hz),7.72 (d,2H,J=7.0Hz), 7.54 (d,1H,J=8.8Hz), 7.49 (d,1H,J=8.8Hz), 6.14 (s,br,1H), 5.18 (s,br,1H), 4.60 (dd,2H, J=70Hz,18Hz), 4.29-4.34 (m,1H), 1.74-1.83 (m,1H), 1.00-1.34 (m,2H), 0.78 (d,3H,J=7.0Hz), 0.67 (d,3H,J=7.0Hz).
48				4	tan solid	409.94	1.26 Method A	410.1	^{1}H NMR ($CDCl_3$) δ 7.80 (d,2H,J=8.5Hz),7.63 (d,2H,J=8.5Hz), 7.52 (s,br,1H), 7.46 (d,1H,J=8.0Hz), 7.26 (d,1H,J=8.0Hz), 7.02 (s,br,1H), 4.70 (dd,2H,J=50Hz,18Hz), 4.30-4.41 (m,1H), 3.67 (s,br,2H), 1.28-1.33 (m,3H), 0.86 (d,3H,J=7.0Hz), 0.57 (d,3H,J=7.0Hz).
49				3	Tan foam	431.99	1.19 Method A	432	^{1}H NMR (d_6DMSO) δ 7.81 (d,2H,J=8.0Hz), 7.66 (d,2H,J=8.0Hz), 7.45 (s, br,1H) 7.02 (s,1H), 4.27 (m, 1H), 3.56 (s,br,4H), 3.55-3.57 (m,1H), 3.08-3.14 (m,1H), 2.22-2.32 (m, 6H), 1.79-1.82 m,11H),1.17-1.62(m, 4H), 0.86 (d,6H,J=6.0Hz).

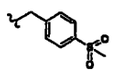
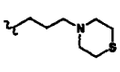
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
50				1	white solid	436.51	1.58 Method A	437.1	^{1}H NMR ($CDCl_3$) δ 7.95 (d,2H,J=8.0Hz), 7.74-7.79 (m,2H), 7.42 (d,2H,J=8.0Hz), 7.14-7.19(m,2H) 6.24 (s,br,1H), 5.20 (s, br,1H), 4.50 (dd, 2H, J=50Hz,17Hz), 4.12 (m,1H), 3.91 (s,3H), 1.75-1.82 (m, 1H), 1.25-1.31 (m,1H), 1.05-1.12 (m,1H), 0.75 (d,3H,J=7.0Hz), 0.64 (t,3H,J=7.0Hz)
51				4	tan solid	423.97	1.21 Method A	424.1	^{1}H NMR ($CDCl_3$) δ 7.65 (d,2H,J=8.0Hz), 7.58 (d,2H,J=8.2Hz), 7.47 (d,2H,J=8.0Hz), 7.31 (d,2H,J=8.5Hz), 6.24 (s,br,1H), 5.16 (s, br,1H), 4.50(dd,2H, J=50Hz,17Hz), 4.27 (t,1H,J=10Hz), 2.44 (s,3H), 1.74-1.83 (m, 1H), 1.25-1.33 (m,1H), 0.93-1.01 (m,1H), 0.74 (d,3H,J=7.0Hz), 0.63 (d,3H,J=7.0Hz).
52				1	white solid	448.90	1.79 Method A	449.0	^{1}H NMR ($CDCl_3$) δ 7.66 (d,2H,J=8.5Hz),7.43 (d,2H,J=8.5Hz), 7.12 (d,1H,J=8.0Hz), 6.49 (d,1H,J=8.0Hz), 6.24 (s,br,1H), 5.22 (s,br,1H), 4.35 (dd,2H, J=50Hz,15Hz), 4.22--4.27 (m,1H), 2.04 (s,3H), 1.27-1.89 (m,3H), 0.74 (d,3H,J=7.0Hz), 0.68 (d,3H,J=7.0Hz).

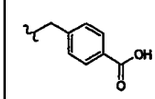
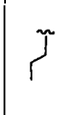
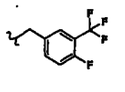
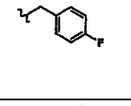
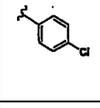
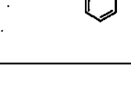
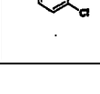
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
53				1-Method A	white solid	424.95	1.58 Method A	425.2	^{1}H NMR (DMSO-d_6, 500MHz) δ 7.82 (d, 2H, J = 8.2), 7.62 (d, 2H, J = 8.3), 7.44 (d, 2H, J = 7.1), 7.21 (t, 1H, J = 6.7), 6.97 (s, 1H), 6.92 (d, 2H, J = 6.9), 4.99 (d, 1H, J = 17), 4.40 (d, 1H, J = 17), 4.33 (br s, 1H), 3.76 (s, 3H), 1.20-1.40 (m, 3H), 0.79 (d, 3H, 5.2), 0.54 (d, 3H, J = 3.2).
54				1-Method A	white solid	400.86	1.81 min Method B	398.94 (M-H$^-$)	^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2H, J=6.8Hz), 7.48 (d, 2H, J=6.8Hz), 7.15 (d, 2H, J=10Hz), 7.02 (d, 2H, J=8.0Hz), 6.85(t, 1H, J=7.5Hz), 6.19 (s, br, 1H), 5.13 (s, br, 1H), 4.31 (dd, 2H, J=50Hz, 15Hz), 4.43-4.45 (m, 1H), 3.87 (s, 3H), 1.17 (d, 3H, J=6.8Hz).
55				1-Method A	white solid	478.92	1.76 Method A	479.1	^{1}H NMR (DMSO-d_6, 500MHz) δ 7.81 (d, 2H, J = 8.5), 7.60 (d, 2H, J = 8.2), 7.54 (s, 1H), 7.51 (d, 2H, J = 8.5), 7.30 (d, 2H, J = 8.2), 7.04 (s, 1H), 4.83 (d, 1H, J = 17), 4.71 (d, 1H, J = 17), 1.20-1.35 (m, 3H), 0.80 (d, 3H, J = 6.1), 0.47 (d, 3H, J = 6.2).
56				1-Method A	white solid	434.58	1.95 min Method A	435.24	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.67 (dd, 2H, J = 5.0, 8.9), 7.20-7.30 (m, 4H), 7.09 (dd, 2H, J = 8.6, 8.6), 6.28 (br s, 1H), 5.24 (br s, 1H), 4.44 (s, 2H), 4.34 (t, 1H, J = 7.8), 1.75-1.90 (m, 1H), 1.22-1.38 (m, 2H), 1.30 (s, 9H), 0.77 (d, 3H, J = 6.4), 0.67 (d, 3H, J = 6.4).

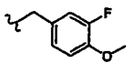
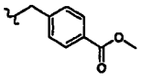
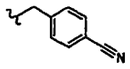
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
57				3	brown oil	458.07	2.16 Method C	458.2	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.77 (dd, 2H, J = 1.6, 6.8), 7.53 (dd, 2H, J = 2.0, 6.7), 6.55 (s, 1H), 5.64 (s, 1H), 4.15 (dd, 1H, J = 5.6, 9.2), 3.57 (t, 2H, J = 12), 3.35-3.45 (m, 1H), 3.10-3.17 (m, 1H), 2.87-3.00 (m, 2H), 2.57-2.70 (m, 2H), 2.27-2.40 (m, 2H), 1.80-2.00 (m, 6H), 1.63-1.73 (m, 2H), 1.20-1.50 (m, 4H), 0.85-0.90 (m, 1H), 0.73 (d, 3H, J = 6.4), 0.70 (t, 3H, J = 6.8).
58				5	colorless oil	390.89	1.51 Method A	391.2	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.91 (dd, 2H, J = 2.0, 6.8), 7.51 (dd, 2H, J = 2.2, 6.9), 7.06 (s, 1H), 5.33 (s, 1H), 4.13-4.25 (m, 2H), 4.03-4.15 (m, 3H), 1.77-1.85 (m, 1H), 1.35-1.45 (m, 1H), 1.30 (t, 3H, J = 7.1), 1.15-1.22 (m, 1H), 0.74 (d, 3H, J = 6.6), 0.71 (d, 3H, J = 6.5).
59				5	white solid	362.83	1.28 Method A	363.1	^{1}H NMR (DMSO-d_6, 500MHz) δ7.90 (dd, 2H, J = 2.0, 6.8), 7.65 (dd, 2H, J = 2.0, 6.8), 7.60 (s, 1H), 7.06 (s, 1H), 4.32 (d, 1H, J = 18), 4.12 (t, 1H, J = 8.0), 4.02 (d, 1H, J = 18), 1.55-1.65 (m, 1H), 1.35-1.45 (m, 2H), 0.78 (d, 3H, J = 6.1), 0.73 (d, 3H, J = 6.1).

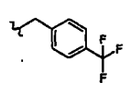
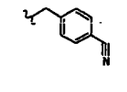
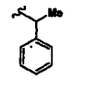
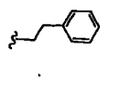
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
60				1-solid support	white solid	408.95	1.82 min Method B	409.1	^{1}H NMR ($CDCl_3$) δ 7.64 (d, 2H, J=8.0Hz), 7.44 (d, 2H, J=8.0Hz), 7.22 (d, 2H, J=8.0Hz), 7.08 (d, 2H, J=8.0Hz), 6.29 (s, br, 1H), 5.34 (s, br, 1H), 4.53 (d, 1H, J=15.20Hz), 4.34 (d, 1H, J=15.20Hz), 4.27 (t, 1H, J=7.2Hz), 2.32 (s, 3H), 1.84 (m, 1H), 1.30 (m, 1H), 1.21 (m, 1H), 0.75 (d, 3H, J=6.8Hz), 0.67 (d, 3H, J=6.8Hz)
61				1-Method A	white solid	452.96	1.85 min Method A	453.08	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.97 (dd, 2H, *J* =1.7, 8.4), 7.68 (dd, 2H, *J* = 2.0, 8.7), 7.41-7.48 (m, 4H), 6.23 (br s, 1H), 5.16 (br s, 1H), 4.64 (d, 1H, *J* = 15.8), 4.47 (d, 1H, *J* = 15.9), 4.31 (t, 1H, *J* = 7.8), 3.92 (s, 3H), 1.76-1.83 (m, 1H), 1.26-1.35 (m, 1H), 1.08-1.13 (m, 1H), 0.76 (d, 3H, *J* = 6.0), 0.65 (d, 3H, *J* = 6.7)
62				1-solid support	white solid	430.95	1.81 min Method B	431.06	^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.49 (d, 2H, J=8.0Hz), 7.24 (m, 1H), 6.95 (m, 2H), 6.25 (s, br, 1H), 5.27 (s, br, 1H), 4.62 (d, 1H, J=16.0Hz), 4.45 (d, 1H, J=16.0Hz), 4.33 (t, 1H, J=6.8Hz), 1.84 (m, 1H), 1.30 (m, 1H), 1.21 (m, 1H), 0.78 (d, 3H, J=6.8Hz), 0.70 (d, 3H, J=6.8Hz)

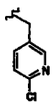
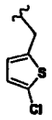
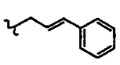
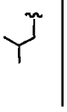
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
63				1-solid support	pale yellow solid	471.02	2.04 min Method B	471.09	^{1}H NMR ($CDCl_3$) δ 7.65 (d, 2H, J=8.0Hz), 7.58 (d, 2H, J=8.0Hz), 7.47 (d, 2H, J=8.0Hz), 7.37-7.44 (m, 6H), 6.27 (s, br, 1H), 5.33 (s, br, 1H), 4.58 (d, 1H, J=15.2Hz), 4.45 (d, 1H, J=15.2Hz), 4.36 (t, 1H, J=7.2Hz), 1.84 (m, 1H), 1.30 (m, 1H), 1.21 (m, 1H), 0.78 (d, 3H, J=6.8Hz), 0.70 (d, 3H, J=6.8Hz)
64				1-solid support	pale pink solid	372.92	1.82 min Method B	395.11 M+Na	^{1}H NMR ($CDCl_3$) δ 7.65 (d, 2H, J=8.0Hz), 7.50 (d, 2H, J=8.0Hz), 6.75 (s, br, 1H), 6.70 (s, br, 1H), 5.04 (m, 1H), 4.32 (t , 1H, J=7.2Hz), 3.91 (d br, 2H, J=7.0Hz), 1.81 (m, 1H), 1.66 (s br, 6H), 1.30 (m, 1H), 1.21 (m, 1H), 0.77 (d, 3H, J=6.5Hz), 0.76 (d, 3H, J=6.5Hz)
65				4	white solid	437.99	1.39 Method A	438.1	^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.74 (dd, 2H, J = 1.9, 6.7), 7.5 (dd, 2H, J = 1.9, 6.8), 7.43 (s, 1H), 7.16 (d, 2H, J = 8.6), 7.01 (s, 1H), 6.61 (d, 2H, J = 8.8), 4.59 (q, 2H, J = 16, 25), 4.34 (dd, 1H, J = 5.0, 9.3), 2.85 (s, 6H), 1.27-1.47 (m, 3H), 0.80 (d, 3H, J = 5.9), 0.52 (d, 3H, J = 6.1)

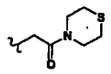
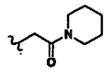
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
66				1-Method A	white solid	473.01	1.58 Method A	437.0	^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.87 (d, 2H, J = 8.2), 7.83 (d, 2H, J = 8.3), 7.64 (d, 2H, J = 8.5), 7.63 (d, 2H, J = 8.5), 7.59 (s, 1H), 7.08 (s, 1H), 4.92 (d, 1H, J = 17), 4.76 (d, 1H, J = 17), 4.39 (t, 1H, J = 6.9), 3.35 (br s, 1H), 1.20-1.40 (m, 3H), 0.81 (d, 3H, J = 6.2), 0.54 (d, 3H, J = 6.2)
67				1-Method A	colorless oil	346.88	1.79 Method A	347.1	^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.83 (d, 2H, J = 8.8), 7.63 (d, 2H, J = 8.6), 7.41 (s, 1H), 7.0 (s, 1H), 4.25 (dd, 1H, J = 4.8, 8.9), 3.38-3.47 (m, 1H), 3.0-3.13 (m, 1H), 1.55-1.70 (m, 1H), 1.40-1.55 (m, 1H), 1.30-1.40 (m, 1H), 0.87 (t, 3H, J = 7.6), 0.73 (d, 3H, J = 6.4), 0.72 (d, 3H, J = 6.7)
68				3	white oil	448.05	1.25 min Method C	448.19	^{1}H NMR ($CDCl_3$, 500MHz), δ 7.76 (dd, 2H, J = 2.0, 6.7), 7.50 (dd, 2H, J = 2.0, 6.7), 6.51 (s, 1H), 5.45 (s, 1H), 4.20 (dd, 1H, J = 6.4, 8.2), 3.35-3.45 (m, 1H), 3.20-3.30 (m, 1H), 2.68 (br s, 8H), 2.35 (br s, 2H), 1.70-1.90 (m, 3H), 1.20-1.40 (m, 1H), 0.95-1.05 (m, 1H), 0.75 (d, 3H, J = 4.3), 0.73 (d, 3H, J = 4.4)

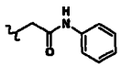
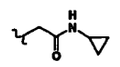
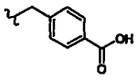
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
69				6	white solid	422.48	1.56 min Method A	423.14	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.89-7.93 (m, 4H), 7.84 (br s, 1H), 7.49 (d, 2H, *J* =8.2), 7.24-7.29 (m, 2H), 6.58 (br s, 1H), 5.12 (d, 1H, *J* = 15.3), 4.23 (dd, 1H, *J* = 4.6, 9.7), 4.05 (d, 1H, *J* = 15.4), 2.04-2.14 (m, 1H), 1.23-1.32 (m, 1H), 0.79-0.88 (m, 1H), 0.72 (d, 3H, *J* = 6.6), 0.67 (d, 3H, *J* = 6.6).
70				1-Method A	white solid	466.89	1.77min Method B	467.03	^{1}H NMR ($CDCl_3$) δ 7.65 (d, 2H, J=6.8Hz), 7.52-7.56 (m, 2H), 7.47 (d, 2H, J=6.8Hz), 7.11 (t, 1H, J=8.5Hz), 6.22 (s, br, 1H), 5.24 (s, br, 1H), 4.41 (dd, 2H, J=50Hz, 15Hz), 4.28 (t, 1H, 7.5Hz), 1.80-1.92 (m, 1H), 1.21-1.30 (m, 1H), 0.95-1.19 (m, 2H), 0.76 (t, 3H, J=7.0Hz).
71				1-Method A	white wax	398.89	1.80min Method B	388.0	^{1}H NMR ($CDCl_3$) δ 7.67 (d, 2H, J=8.0Hz) 7.54 (d, 2H, J=8.0Hz) , 7.42-7.49 (m, 4H), 6.20 (s, br, 1H), 5.21 (s, br, 1H), 4.54 (dd, 2H, J=50Hz, 15Hz), 4.25-4.29 (m, 1H), 1.82-1.95 (m, 1H), 1.26-1.33 (m, 1H), 0.98-1.12 (m, 2H), 0.75 (t, 3H, J=7.0Hz).
72				1-Method A	white solid	482.01	1.79min Method B	482.06	^{1}H NMR ($CDCl_3$) δ 7.76 (d, 1H, J=7.5Hz) , 7.63-7.67 (m, 4H), 7.43-7.50 (m, 8H), 6.24 (s, br, 1H), 5.28 (s, br, 1H), 4.53 (dd, 2H, J=50Hz, 15Hz), 4.27 (t, 1H, J=7.3Hz), 1.87-1.99 (m, 1H), 1.30-1.39 (m, 1H), 1.03-1.11 (m, 2H), 0.76 (t, 3H, J=8.0Hz).

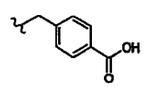
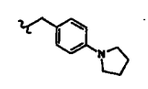
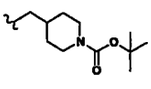
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
73				1-Method A	pale yellow solid	426.90	1.86 min Method A	427.09	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.69 (ddd, 2H, J=2.0, 2.7, 8.7), 7.47 (dd, 2H, J = 2.0, 8.7), 7.15 (dd, 1H, J = 2.1, 12.0), 7.03 (d, 1H, J = 8.4), 6.84 (t, 1H, J = 8.5), 6.30 (br s, 1H), 5.25-5.30 (m, 2H), 4.96 (d, 1H, J = 1.4), 4.87 (td, 1H, J = 1.4, 9.9), 4.57 (d, 1H, J = 15.4), 4.23-4.32 (m, 2H), 3.87 (s, 3H), 2.60-2.67 (m, 1H), 2.15-2.24 (m, 1H)
74				1-Method A	colorless oil	436.92	1.88 min Method A	437.09	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.97 (dd 2H, J=1.7, 8.3), 7.71 (dd, 2H, J = 2.0, 8.7), 7.43-7.50 (m, 4H), 6.26 (br s, 1H), 5.22-5.35 (m, 1H), 5.18 (br s, 1H), 4.84-4.96 (m, 2H), 4.69 (d, 1H, J = 15.8), 4.41 (d, 1H, J = 15.8), 4.31 (t, 1H, J = 7.5), 3.91 (s, 3H), 2.60-2.67 (m, 1H), 2.11-2.24 (m, 1H)
75				1-Method A	white solid	403.89	1.63 min Method A	404.03	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.71 (ddd, 2H, J = 2.0, 2.6, 8.7), 7.60 (dd, 2H, J = 1.9, 8.3), 7.49-7.52 (m, 4H), 6.21 (br s, 1H), 5.22-5.33 (m, 1H), 5.17 (br s, 1H), 4.88-4.98 (m, 2H), 4.71 (d, 1H, J = 16.2), 4.40 (d, 1H, J = 16.1), 4.32 (t, 1H, J = 7.6), 2.54-2.63 (m, 1H), 2.09-2.19 (m, 1H)

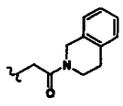
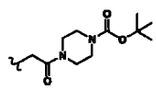
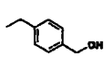
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
76				1-Method A	white solid	446.88	2.04 min Method A	447.05	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.67 (d, 2H, J = 8.6), 7.45-7.56 (m, 6H), 6.24 (br s, 1H), 5.25-5.39 (m, 1H), 5.19 (br s, 1H), 4.88-4.98 (m, 2H), 4.68 (d, 1H, J = 15.8), 4.42 (d, 1H, J = 15.81), 4.34 (t, 1H, J = 7.5), 2.58-2.68 (m, 1H), 2.13-2.32 (m, 1H).
77				1-Method A	white solid	405.91	1.51min Method B	406.2	^{1}H NMR ($CDCl_3$) δ 7.70 (d, 2H, J=8.0Hz) 7.68 (d, 2H, J=8.0Hz) , 7.47-7.51 (m, 4H), 6.15 (s, br, 1H), 5.16 (s, br, 1H), 4.53 (dd, 2H, J=50Hz, 15Hz), 4.21-4.26 (m, 1H), 1.82-1.87 (m, 1H), 1.20-1.25 (m, 1H), 0.97-1.09 (m, 2H), 0.74 (t, 3H, J=7.0Hz)
78				1-solid support	white foam	408.95	1.84min Method B	431.04 M+Na	^{1}H NMR ($CDCl_3$) δ 7.83 (d, 2H, J=8.0Hz), 7.52 (d, 2H, J=8.0Hz), 7.34 - 7.45 (m, 5H), 5.85(s, br, 2H), 5.17 (q, 1H, 7.2Hz), 3.78 (dd 1H, J=8.4Hz, 4Hz), 2.36 (m, 1H), 1.62 (m, 1H), 1.50 (d, 3H, J=7.2Hz), 1.23 (m, 1H), 0.91 (d, 3H, J=6.6Hz), 0.84 (d, 3H, J=6.6Hz)
79				1-solid support	colorless syrup	408.95	1.89 Method B	431.04 M+Na	^{1}H NMR ($CDCl_3$) δ 7.77 (d, 2H, J=8.0Hz), 7.50 (d, 2H, J=8.0Hz), 7.17 - 7.32 (m, 5H), 6.67 (s, br, 1H), 6.15 (s, br, 1H), 5.17 (q, 1H, 7.2Hz), 4.26 (dd 1H, J=6.6Hz), 3.48 (m, 1H), 3.37 (m, 1H), 2.97 (m, 1H), 2.90 (m, 1H), 1.92(m, 1H), 1.33(m, 1H), 1.10(m, 1H), 0.76 (d, 3H, J=6.6Hz), 0.75 (d, 3H, J=6.6Hz)

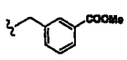
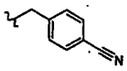
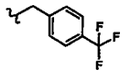
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
80				1-solid support	yellow solid	430.36	1.64min Method B	430.02	^{1}H NMR ($CDCl_3$) δ 8.34 (s, 1H), 7.67 (d, 1H, J=6.8Hz), 7.48 (d, 1H, 6.8Hz), 7.25 (d, 1H, J=6.8Hz), 6.1 (br. S, 1H), 5.29 (br. s, 1H), 4.59 (d, 1H, J=16Hz), 4.39 (d, 1H, J=16Hz), 1.8 (m, 1H), 1.32(m, 1H), 1.06(m, 1H), 0.78 (d, 3H, J=64.Hz), 0.68 (d, 3H, J=6.4Hz)
81				1-solid support	white solid	435.39	1.87 Method B	456.92 M+Na	^{1}H NMR ($CDCl_3$) δ 7.64 (d, 2H, J=8.0Hz), 7.50 (d, 2H, J=8.0Hz), 6.79 (d, 1H, J=3.7Hz), 6.72 (d, 1H, J=3.7Hz), 4.60 (d, 1H, J=21.9), 4.56(d, 1H, J=21.9Hz), 4.28(t, 1H, J=7.4Hz), 1.86(m, 1H), 1.33(m, 1H), 1.25(m, 1H), 0.76(d, 3H, J=6.5Hz), 0.73(d, 3H, J=6.5Hz)
82				1-Method A	white solid	420.96	1.97 Method A	421.2	^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77 (d, 2H, J = 8.6), 7.45 (d, 2H, J = 9.10), 7.26-7.35 (m, 5H), 6.54 (d, 1H, J = 16), 6.38 (br s, 1H), 6.00-6.07 (m, 1H), 5.34 (br s, 1H), 4.36 (t, 1H, J = 7.2), 4.02-4.15 (m, 2H), 1.83-1.92 (m, 1H), 1.35-1.43 (m, 1 H), 1.25-1.32 (m, 1 H), 0.79 (d, 3H, J = 6.7), 0.77 (d, 3H, J = 6.7)
83				5	white solid	389.90	1.91 Method D	390.2	^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.08 (br s, 1H), 7.97 (d, 2H, J = 8.7), 7.65 (d, 2H, J = 8.5), 7.01 (br s, 1H), 4.46 (d, 1H, J = 18), 4.22 (d, 1H, J = 18), 3.91 (t, 1H, J = 6.3), 3.00 (s, 3H), 2.85 (s, 3H), 1.40-1.50 (m, 2H), 1.30-1.40 (m, 1 H), 0.85 (d, 3H, J = 5.1), 0.64 (d, 3H, J = 6.0)

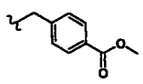
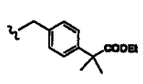
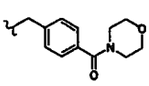
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
84				5	white solid	375.88	1.38 Method A	376.0	^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (dd, 2H, J = 1.8, 6.8), 7.50 (dd, 2H, J = 2.0, 6.8), 7.40 (br s, 1H), 6.37 (br s, 1H), 5.25 (br s1H), 4.26 (dd, 1H, J = 6.2, 8.6), 3.97 (d, 1H, J = 17), 3.85 (d, 1H, J = 17), 2.85 (d, 3H, J = 4.8), 1.75-1.85 (m, 1H), 1.40-1.48 (m, 1H), 0.88 (d, 3H, J = 6.4), 0.87(d, 3H, J = 6.6)
85				5	white solid	448.01	2.18 Method C	448.1	^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10 (br s, 1H), 7.92 (d, 2H, J = 8.5), 7.50 (d, 2H, J = 8.5), 5.18 (br s, 1H), 4.35 (d, 1H, J = 17), 4.15 (t, 1H, J = 7.4), 3.97-4.05 (m, 1H), 3.95 (d, 1H, J = 17), 3.70-3.89 (m, 3H), 2.55-2.85 (m, 4H), 1.85-1.91 (m, 1H), 1.55-1.85 (m, 1H), 1.30-1.40 (m, 1H), 0.85 (d, 3H, J=6.4), 0.83 (d, 3H, J=6.4)
86				5	white solid	429.97	2.26 Method C	430.2	^{1}H NMR ($CDCl_3$, 500MHz) δ 8.59 (br s, 1H), 7.92 (d, 2H, J = 9.1), 7.47 (d, 2H, J = 8.6), 5.16 (br s, 1H), 4.42 (d, 1H, J = 17), 4.23 (dd, 1H, J = 5.6, 8.6), 3.87 (d, 1H, J = 17), 3.55-3.65 (m, 1H), 3.40-3.52 (m, 3H), 1.80-2.00 (m, 1H), 1.45-1.80 (m, 7H), 1.35-1.45 (m, 1H), 0.89 (d, 3H, J = 6.7), 0.86 (d, 3H, J = 6.5)

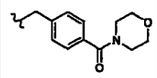
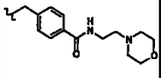
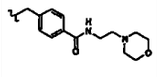
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
87				5	white solid	437.95	2.37 Method C	438.2	^{1}H NMR ($CDCl_3$, 500MHz) δ 8.95 (br s, 1H), 7.83 (d, 2H, J = 8.6), 7.47 (d, 2H, J = 8.1), 7.43 (d, 2H, J = 8.6), 7.33 (t, 2H, J = 8.1), 7.13 (t, 1H, J = 7.6), 6.65 (br s, 1H), 5.45 (br s, 1H), 4.40 (dd, 1H, J = 6.1, 8.6), 4.07 (d, 1H, J = 17), 4.03 (d, 1H, J = 17), 1.70-1.80 (m, 1H), 1.55-1.65 (m, 2H), 0.93 (d, 3H, J = 7.0), 0.90 (d, 3H, 6.4).
88				5	white solid	401.92	1.94 Method C	402.2	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.85 (dd, 2H, J = 1.9, 8.9), 7.50 (dd, 2H, J = 2.0, 8.7), 7.40 (br s, 1H), 6.55 (br s, 1H), 6.30 (br s, 1H), 4.23 (dd, 1H, J = 2.9, 8.9), 3.92 (d, 1H, J = 17), 3.83 (d, 1H, J = 17), 2.68-2.73 (m, 1H), 1.75-1.83 (m, 1H), 1.50-1.57 (m, 1H), 1.40-1.49 (m, 1H), 0.88 (d, 3H, J = 6.4), 0.87 (d, 3H, J = 6.7), 0.80 (d, 2H, J = 7.0), 0.51 (t, 3H, J = 4.0).
89				6	white solid	438.93	1.67 min Method A	439.17	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.91 (d, 2H, J = 8.2), 7.81-7.84 (m, 3H), 7.56 (d, 2H, J = 8.6), 7.49 (d, 2H, J = 8.2), 6.55 (br s, 1H), 5.10 (d, 1H, J = 15.4), 4.23 (dd, 1H, J = 4.6, 9.7), 4.05 (d, 1H, J = 15.4), 2.04-2.14 (m, 1H), 1.20-1.31 (m, 1H), 0.80-0.89 (m, 1H), 0.74 (d, 3H, J = 6.6), 0.68 (d, 3H, J = 6.6).

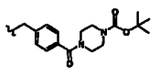
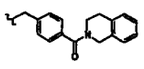
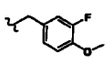
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
90				6	white solid	422.89	1.41 min Method A	423.05	^{1}H NMR (dmso-d_6, 300MHz) δ 7.86 (d, 2H, J = 8.2), 7.85 (br s, 1H), 7.81 (d, 2H, J = 8.6), 7.61 (d, 2H, J = 8.6), 7.47 (d, 2H, J = 8.0), 7.10 (br s, 1H), 5.45-5.55 (m, 1H), 4.83-4.95 (m, 3H), 4.71 (d, 1H, J = 17.0), 4.47 (t, 1H, J = 7.4), 2.29-2.37 (m, 1H), 2.13-2.22 (m, 1H)
91				2	tan solid	450.0	1.62min Method B	450.2	^{1}H NMR ($CDCl_3$) δ 7.67 (d, 2H, J=7.0Hz) 7.42 (d, 2H, J=7.0Hz) , 7.17-7.26 (m, 2H), 6.49-6.58 (m, 2H), 6.18 (s, br, 1H), 5.11 (s, br, 1H), 4.33 (dd, 2H, J=50Hz, 15Hz), 4.12-4.20 (m, 1H), 3.21-3.30 (m, 4H), 1.91-2.04 (m, 5H), 1.32-1.38 (m, 1H), 0.94-1.09 (m, 2H), 0.75 (t, 3H, J=8.0Hz)
92				7	white solid	502.08	1.72 Method A	502.1	^{1}H NMR (DMSO-d_6, 500MHz) δ 7.86 (dd, 2H, J = 2.0, 6.8), 7.65 (dd, 2H, J = 2.0, 6.8) 7.37 (br s, 1H), 7.07 (br s, 1H), 4.19 (t, 1H, J = 7.6), 3.92 (br s, 2H), 3.35 (dd, 1H, J = 15, 6.8), 3.05 (dd, 1H, J = 15, 8.1), 1.85 (br s, 1H), 1.50-1.70 (m, 4H), 1.38 (s, 9H), 1.10-1.20 (m, 1H), 0.80-1.00 (m, 3H), 0.82 (d, 6H, J = 7.6)

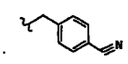
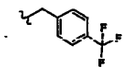
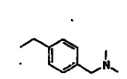
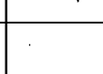
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
93				5	white solid	478.01	1.60 Method A	478.1	^{1}H NMR (DMSO-d_6, 500MHz) δ 8.05 (s, 1H), 7.98 (d, 2H, J = 7.8), 7.65 (d, 2H, J = 7.8), 7.05 (s, 1H), 4.73 (s, 1H), 4.55-4.65 (m, 2H), 4.37 (t, 1H, J = 16), 3.95 (br s, 1H), 3.70 (br s, 2H), 2.90 (br s, 1H), 2.77 (br s, 1H), 1.00-1.55 (m, 4H), 0.70 (d, 6H, J = 6.1)
94				5	white solid	530.20	1.59 Method A	531.2	^{1}H NMR (DMSO-d_6, 500MHz) δ 7.96 (d, 2H, J = 8.7), 7.65 (d, 2H, 8.6), 7.02 (s, 1H), 4.5 (d, 1H, J = 18), 4.27 (d, 2H, J = 18), 3.95 (br s, 1H). 3.35-3.50 (m, 8H), 1.30-1.55 (m, 3H), 1.41 (s, 9H), 0.74 (d, 3H, J = 6.5) 0.66 (d, 3H, J = 6.0).
95				8	white solid	424.95	1.49 min Method A	425.17	^{1}H NMR , 500Hz, ($CDCl_3$) δ 7.68 (d, 2H, J=8.0Hz), 7.46 (d, 2H, J=8.0Hz), 7.33 (d, 2H, J=8.0Hz), 7.28 (d, 2H, J=8.0Hz), 6.26 (s, br, 1H), 5.35 (s, br, 1H), 4.67 (s, br, 2H), 4.56 (d, 1H, J_{ab}=16Hz), 4.36 (d, 1H, J_{ab}=16Hz), 4.26 (t, 1H, J=7.6Hz), 1.86-1.80 (m, 2H), 1.34-1.28 (m, 1H), 1.16-1.10 (m, 1H), 0.96 (d, 3H, J=7.0Hz), 0.93 (t, 3H, J=7.0Hz)

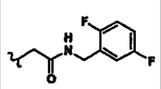
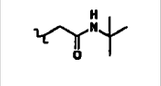
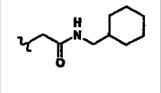
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
96				1-Method A	white solid	452.96	1.75 min Method A	453.1	^{1}H NMR ($CDCl_3$) δ 7.96-7.90 (m, 2H), 7.64 (A of ABq, 2H, J=8.8Hz), 7.56 (d, 1H, J=7.5Hz), 7.43 (B of ABq, 2H, J=8.8Hz), 7.37 (t, 1H, J=7.5Hz), 6.28 (bs, 1H), 5.25 (bs, 1H), 4.61 (A of ABq, 1H, J=15.7Hz,), 4.48 (B of ABq, 1H, J=15.7Hz), 4.36 (t, 1H, J=7.3Hz), 3.91 (s, 3H), 1.86-1.76 (m, 1H), 1.39-1.30 (m, 1H), 1.23-1.13 (m, 1H), 0.78 (d, 3H, J=6.6Hz), 0.68 (d, 3H, J=6.6Hz)
97				1-Method A	white solid	417.92	1.53 min Method A	418.11	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.71 (d, 2H, J = 8.7), 7.60 (d, 2H, J = 8.4), 7.47-7.51 (m, 4H), 6.28 (br s, 1H), 5.17 (br s, 1H), 4.73 (d, 1H, J = 16.2), 4.41 (d, 1H, J = 15.9), 4.32 (dd, 1H, J = 1.5, 8.1), 1.65-1.82 (m, 1H), 1.14-1.30 (m, 1H), 0.27-0.40 (m, 2H), 0.12-0.22 (m, 1H), -0.18-0.05 (m, 2H)
98				1-Method A	white solid	460.91	1.76 min Method A	461.05	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.67 (d, 2H, J = 8.4), 7.44-7.56 (m, 6H), 6.32 (br s, 1H), 5.20 (br s, 1H), 4.70 (d, 1H, J = 15.6), 4.43 (d, 1H, J = 15.6), 4.35 (t, 1H, J = 7.8), 1.70-1.84 (m, 1H), 1.26-1.32 (m, 1H), 0.32-0.40 (m, 2H), 0.16-0.24 (m, 1H), -0.14-0.00 (m, 2H)

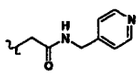
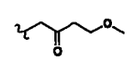
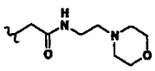
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
99				1-Method A	white solid	450.94	1.63 min Method A	451.06	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.97 (d, 2H, J = 8.3), 7.70 (d, 2H, J = 8.7), 7.43-7.48 (m, 4H), 6.32 (br s, 1H), 5.15 (br s, 1H), 4.70 (d, 1H, J = 15.8), 4.43 (d, 1H, J = 15.8), 4.35 (t, 1H, J = 7.8), 3.91 (s, 3H), 1.70-1.82 (m, 1H), 1.23-1.35 (m, 1H), 0.32-0.40 (m, 2H), 0.10-0.21 (m, 1H), -0.25- -0.05 (m, 2H).
100				1-Method A	white solid	509.06	1.94 min Method A	509.2	^{1}H NMR ($CDCl_3$) δ 7.58 (A of ABq, 2H, J=8.8Hz), 7.40 (B of ABq, 2H, J=8.8Hz), 7.24 (bs, 4H), 6.20 (bs, 1H), 5.23 (bs, 1H), 4.45 (s, 2H), 4.36 (t, 1H, J=7.3Hz), 4.12 (q, 2H, J=7.2Hz), 1.83-1.74 (m, 1H), 1.55 (s, 3H), 1.55 (s, 3H), 1.39-1.20 (m, 2H), 1.19 (t, 3H, J=7.2Hz), 0.78 (d, 3H, J=6.6Hz), 0.66 (d, 3H, J=6.6Hz).
101				6	white solid	508.04	1.48 min Method A	508.22	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.68 (d, 2H, J = 8.6), 7.29-7.47 (m, 6H), 6.38 (br s, 1H), 5.75 (br s, 1H), 4.65 (d, 1H, J = 16.0), 4.42 (d, 1H, J = 16.0), 4.32 (t, 1H, J = 7.5), 3.30-3.85 (br m, 8H), 1.69-1.78 (m, 1H), 1.28-1.37 (m, 1H), 1.08-1.14 (m, 1H), 0.76 (d, 3H, J = 6.5), 0.63 (d, 3H, J = 6.6).

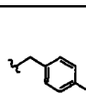
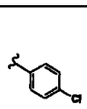
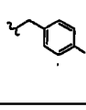
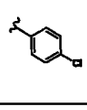
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
102				6	white solid	491.59	1.39 min Method A	492.23	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.75-7.80 (m, 2H), 7.42 (d, 2H, J = 8.2), 7.33 (d, 2H, J = 8.2), 7.14-7.20 (m, 2H), 6.37 (br s, 1H), 5.64 (br s, 1H), 4.64 (d, 1H, J = 16.0), 4.44 (d, 1H, J = 16.0), 4.31 (t, 1H, J = 7.1), 3.20-3.85 (br m, 8H), 1.70-1.78 (m, 1H), 1.28-1.35 (m, 1H), 1.05-1.14 (m, 1H), 0.76 (d, 3H, J = 6.5), 0.63 (d, 3H, J = 6.6).
103				6	colorless oil	551.11	1.32 min Method A	551.24	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.67-7.72 (m, 4H), 7.42-7.48 (m, 4H), 6.82 (br s, 1H), 6.25 (br s, 1H), 5.31 (br s, 1H), 4.65 (d, 1H, J = 15.9), 4.43 (d, 1H, J = 15.9), 4.30 (t, 1H, J = 7.9), 3.70-3.79 (m, 4H), 3.53-3.59 (m, 2H), 2.53-2.65 (m, 6H), 1.79-1.86 (m, 1H), 1.29-1.38 (m, 1H), 1.08-1.14 (m, 1H), 0.76 (d, 3H, J = 6.5), 0.65 (d, 3H, J = 6.6).
104				6	white solid	534.66	1.22 min Method A	535.28	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.75-7.80 (m, 2H), 7.71 (d, 2H, J = 8.2), 7.43 (d, 2H, J = 8.1), 7.14-7.20 (m, 2H), 6.81 (br s, 1H), 6.28 (br s, 1H), 5.31 (br s, 1H), 4.64 (d, 1H, J = 15.9), 4.44 (d, 1H, J = 15.9), 4.29 (t, 1H, J = 7.6), 3.70-3.79 (m, 4H), 3.53-3.59 (m, 2H), 2.52-2.63 (m, 6H), 1.77-1.85 (m, 1H), 1.29-1.38 (m, 1H), 1.06-1.13 (m, 1H), 0.75 (d, 3H, J = 6.5), 0.65 (d, 3H, J = 6.6).

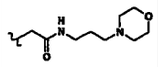
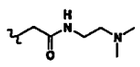
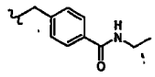
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
105				6	white solid	607.17	1.70 min Method A	607.29	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.69 (d, 2H, *J* = 8.6), 7.30-7.47 (m, 6H), 6.38 (br s, 1H), 5.75 (br s, 1H), 4.65 (d, 1H, *J* = 16.0), 4.43 (d, 1H, *J* = 16.0), 4.33 (t, 1H, *J* = 7.5), 3.30-3.85 (br m, 8H), 1.72-1.79 (m, 1H), 1.45 (s, 9H), 1.24-1.39 (m, 1H), 1.05-1.18 (m, 1H), 0.76 (d, 3H, *J* = 6.5), 0.62 (d, 3H, *J* = 6.6).
106				6	white solid	554.11	1.75 min Method A	554.19	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.70 (ddd, 2H, *J* = 1.9, 2.4, 8.6), 7.47 (ddd, 2H, *J* = 2.0, 2.3, 8.7), 7.37-7.42 (m, 4H), 7.15-7.20 (m, 4H), 6.31 (br s, 1H), 5.60 (br s, 1H), 4.87 (br s, 1H), 4.65 (d, 1H, *J* = 15.9), 4.52 (br s, 1H), 4.47 (d, 1H, *J* = 15.9), 4.33 (t, 1H, *J* = 7.2), 4.05 (br s, 1H), 3.61 (br s, 1H), 2.85-3.01 (br m, 2H), 1.72-1.85 (m, 1H), 1.30-1.42 (m, 1H), 1.08-1.18 (m, 1H), 0.79 (d, 3H, *J* = 6.5), 0.65 (d, 3H, *J* = 6.6).
107				1-Method A	clear wax	456.97	1.60min Method B	455.1 (M-H$^-$)	^{1}H NMR ($CDCl_3$) δ 7.61 (d, 2H, J=8.0Hz) 7.43 (d, 2H, J=8.0Hz) , 6.82-7.10 (m, 3H), 6.21 (s, br, 1H), 5.15 (s, br, 1H), 4.35 (dd, 2H, J=50Hz, 15Hz), 4.15-4.22 (m, 1H), 3.89(s, br, 3H), 2.30-2.33 (m, 1H), 1.85-1.98 (m, 1H), 0.74 (s, 9H)

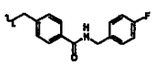
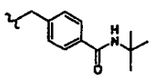
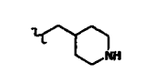
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
108				1-Method A	white solid	433.96	1.58min Method B	432.14 (M-H)	^{1}H NMR ($CDCl_3$) δ 7.67 (d, 2H, J=8.0Hz) 7.58 (d, 2H, J=8.0Hz) , 7.45-7.49 (m, 4H), 6.19 (s, br, 1H), 5.15 (s, br, 1H), 4.55 (dd, 2H, J=50Hz, 15Hz), 4.20-4.24 (m, 1H), 2.25-2.31 (m, 1H), 0.84-0.88 (m, 1H), 0.74 (s, 9H).
109				1-Method A	white solid	476.95	1.62min Method B	475.12 (M-H)	^{1}H NMR ($CDCl_3$) δ 7.61 (d, 2H, J=8.0Hz) 7.51 (d, 2H, J=8.0Hz) , 7.40-7.44 (m, 4H), 6.20 (s, br, 1H), 5.21 (s, br, 1H), 4.51 (dd, 2H, J=50Hz, 15Hz), 4.24-4.28 (m, 1H), 2.28-2.32 (m, 1H), 0.91-0.96 (m, 1H), 0.76 (s, 9H).
110				8	tan solid	452.02	1.25min Method A	452.23	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.94 (d, 2H, J=8.0Hz), 7.74 (d, 2H, J=8.0Hz), 7.63 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.27 (s, br, 1H), 5.40 (s, br, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.44 (d, 1H, J_{ab}=16Hz), 3.28-3.23 (m, 3H), 2.17 (s, br, 6H), 1.95 (m, 1H), 1.55 (m, 2H), 0.96 (d, 3H, J=7.0Hz), 0.93 (d, 3H, J=7.0Hz)
111				5	white solid	535.97	2.65 min Method C	536.04	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.80 (dd, 2H, *J* = 2.0, 9.0), 7.45 (dd, 2H, *J* = 2.0, 9.0), 7.32 (dd, 2H, *J* = 1.8, 9.0), 7.24 (br s, 1H), 7.17 (d, 2H, *J* = 9.0), 5.50 (br s, 1H), 4.43 (qd, 2H, *J* = 6.0, 15), 4.22 (t, 1H, *J* = 7.0), 4.05 (d, 1H, *J* = 17), 3.90 (d, 1H, *J* = 17), 1.70-1.80 (m, 1H), 1.42-1.55 (m, 1H), 1.32-1.41 (m, 1H), 0.83 (d, 6H, *J* = 7.9).

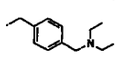
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
112				5	white foam	487.93	1.52 min Method A	488.20	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.77 (d, 2H, J = 8.3), 7.45 (d, 2H, J = 9.0), 7.30 (br s, 1H), 7.05-7.10 (m, 1H), 6.90-7.05 (m, 2H), 5.53 (br s, 1H), 4.39-4.50 (m, 2H), 4.24 (t, 1H, J = 7.1), 4.02 (d, 1H, J = 17), 3.90 (d, 2H, J = 17), 1.70-1.80 (m, 1H), 1.42-1.55 (m, 1 H), 1.35-1.42 (m, 1H), 0.83 (d, 6H, J = 7.7).
113				5	white oily solid	417.96	1.52 min Method A	418.23	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.92 (br s, 1H), 7.82 (d, 2H, J = 8.2), 7.47 (d, 2H, J = 8.2), 7.25 (br s, 1H), 6.23 (br s, 1H), 5.47 (br s, 1H), 4.25 (t, 1H, J = 7.2), 3.91 (d, 1H, J = 17), 3.75 (d, 1H, J = 17), 1.75-1.82 (m, 1H), 1.50-1.62 (m, 1H), 1.38-1.50 (m, 1H), 1.35 (s, 9H), 0.89 (d, 3H, J = 5.4), 0.87 (d, 3H, J = 5.6).
114				5	white solid	458.02	1.62 min Method A	458.26	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.84 (dd, 2H, J = 2.0, 8.8), 7.68 (br s, 1H), 7.47 (dd, 2H, 2.0, 8.3), 6.62 (br t, 1H, J = 5.3), 5.45 (br s, 1H), 4.25 (dd, 1H, J = 2.3, 6.1), 3.98 (d, 1H, J = 17), 3.85 (d, 1H, J = 17), 303-3.15 (m, 2H), 1.86-1.92 (m, 1H), 1.40-1.85 (m, 7H), 1.05-1.35 (m, 4H), 0.90-0.99 (m, 2H), 0.88 (d, 3H, J = 6.6), 0.87 (d, 3H, J = 6.4).

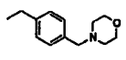
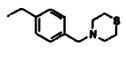
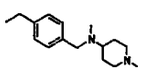
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
115				5	white solid	452.96	1.14 min Method A	453.22	^{1}H NMR ($CDCl_3$, 400MHz) δ 8.53 (d, 2H, J = 5.2), 8.04 (t, 1H, J = 5.2), 7.80 (dd, 2H, J = 1.8, 8.5), 7.46 (dd, 2H, J = 1.8, 8.7), 7.33 (br s, 1H), 7.29 (d, 2H, J = 5.4), 5.78 (br s, 1H), 4.47 (qd, 2H, J = 6.0, 16,), 4.21 (t, 1H, J = 7.4), 4.07 (d, 1H, J = 17), 3.92 (d, 1H, J = 17), 1.67-1.77 (m, 1H), 1.30-1.47 (m, 2H), 0.81 (d, 3H, J = 6.5), 0.77 (d, 3H, J = 7.0).
116				5	white foam	419.93	1.29 Min Method A	420.23	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.87 (dd, 2H, J = 2.0, 8.5), 7.85 (br s, 1H), 7.49 (dd, 2H, J = 2.1, 9.0), 6.73 (br s, 1H), 5.55 (br s, 1H), 4.22 (dd, 1H, J = 6.1, 8.3), 4.02 (d, 1H, J = 17), 3.87 (d, 1H, J = 17), 3.40-3.50 (m, 4H), 3.36 (s, 3H), 1.77-1.86 (m, 1H), 1.46-1.57 (m, 1H), 1.30-1.41 (m, 1H), 0.84 (d, 3H, J = 6.7), 0.83 (d, 3H, J = 6.5).
117				5	white foam	475.01	1.16 min Method A	475.26	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.85 (dd, 2H, J = 2.0, 8.5), 7.64 (br s, 1H), 7.47 (dd, 2H, J = 1.5, 7.1), 6.87 (br s, 1H), 5.55 (br s, 1H), 4.22 (dd, 1H, J = 6.2, 7.9), 4.00 (d, 1H, J = 17), 3.87 (d, 1H, J = 17), 3.72 (t, 1H, J = 4.2), 3.30-3.45 (m, 2H), 2.45-2.55 (m, 5H), 1.75-1.85 (m, 1H), 1.50-1.63 (m, 1H), 1.30-1.41 (m, 1H), 0.86 (d, 3H, J = 9.0).

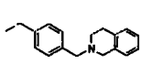
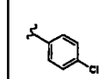
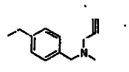
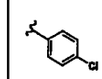
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
118				1-Method A	white solid	459.79	1.62min Method B	461.1	^{1}H NMR ($CDCl_3$) δ 7.67 (d, 2H, J=7.0Hz) 7.48 (d, 2H, J=7.0Hz) , 7.41 (d, 2H, J=6.5Hz), 7.21 (d, 2H, J-6.5Hz), 6.21 (s, br, 1H), 5.20 (s, br, 1H), 4.43 (dd, 2H, J=50Hz, 15Hz), 4.12-4.24 (m, 1H), 1.88-1.90 (m, 1H), 1.24-1.29 (m, 1H), 0.98-1.08 (m, 2H), 0.74 (t, 3H, J=7.0Hz)
119				1-Method A	yellow solid	437.06	1.84 min Method F	$(M+Na)^+$ 459.9	^{1}H NMR (400 MHz, DMSO) δ 7.83 (d, 2H, J=8.8), 7.80 (d, 2H, J=8.3), 7.64 (d, 2H, J=8.5), 7.59 (d, 2H, J=8.6), 7.48 (s, 1H), 7.15 (s, 1H), 4.79 (ABq, 2H, Δυ=22.2, J_{ab}=17.4), 4.44 (dd, 1H, J=8.0, 6.3), 2.21 (m, 2H), 1.84 (m, 1H), 1.81 (s, 3H), 1.53 (m, 1H).
120				1-Method A	white solid	480.06	2.08 min Method F	$(M+Na)^+$ 503.0	^{1}H NMR (400 MHz, DMSO) δ 7.82 (d, 2H, J=8.8), 7.68 (d, 2H, J=8.6), 7.61 (m, 4H), 7.48 (s, 1H), 7.16 (s, 1H), 4.80 (ABq, 2H, , Δυ=16.7, J_{ab}=17.0), 4.45 (dd, 1H, J=8.2, 6.2), 2.22 (m, 2H), 1.82 (m, 1H), 1.78 (s, 3H), 1.61 (m, 1H)

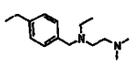
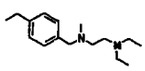
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
121				5	white solid	488.19	1.20 min Method A	489.26	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.95 (br s, 1H), 7.85 (dd, 2H, J = 2.5, 9.2), 7.70 (br s, 1H), 7.47 (dd, 2H, 2.0, 8.8), 5.42 (br s, 1H), 4.23 (dd, 1H, J = 6.3, 8.3), 3.94 (d, 1H, J = 17), 3.83 (d, 1H, J = 17), 3.73 (t, 4H, J = 4.7), 3.39-3.48 (m, 1H), 3.22-3.33 (m, 1H), 2.42-2.55 (m, 4H), 1.79-1.88 (m, 2H), 1.63-1.75 (m, 2H), 1.49-1.61 (m, 1H), 1.31-1.45 (m, 1H), 1.05-1.11 (m, 1H), 0.88 (d, 6H, J = 6.6).
122				5	white solid	432.16	1.59 min Method C	433.12	^{1}H NMR ($CDCl_3$, 400MHz) δ 8.04 (br s, 1H), 7.88 (dd, 2H, J = 1.9, 6.9), 7.46 (dd, 2H, J = 1.8, 6.8), 6.93 (br s, 1H), 5.55 (br s, 1H), 4.20 (dd, 1H, J = 6.2, 8.3), 4.01 (d, 1H, J = 17), 3.80 (d, 1 H, J = 17), 3.25-3.40 (m, 2H), 2.40-2.50 (m, 2H), 2.25 (s, 6H), 1.75-1.90 (m, 1 H), 1.45-1.60 (m, 1H), 1.30-1.45 (m, 1H), 0.84 (d, 3H, J = 6.1), 0.82 (d, 3H, J = 6.4)
123				6	white solid	466.00	1.49 min Method A	466.17	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.68 (d, 4H, J = 8.6), 7.47 (ddd, 2H, J = 1.6, 2.4, 8.6), 7.41 (d, 2H, J = 8.2), 6.25 (br s, 1H), 6.12 (br s, 1H), 5.30 (br s, 1H), 4.63 (d, 1H, J = 15.8), 4.44 (d, 1H, J = 15.8), 4.30 (t, 1H, J = 6.8), 3.47-3.52 (m, 2H), 1.78-1.84 (m, 1H), 1.30-1.34 (m, 1H), 1.25 (t, 3H), J = 7.2), 1.08-1.13 (m, 1H), 0.76 (d, 3H, J = 6.6), 0.65 (d, 3H, J = 6.6).

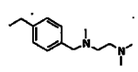
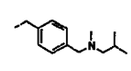
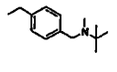
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
124				6	colorless oil	546.05	1.65 min Method A	546.19	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.71 (d, 2H, J = 8.2), 7.67 (d, 2H, J = 8.6), 7.46 (d, 2H, J = 8.6), 7.41 (d, 2H, J = 8.0), 6.52 (br s, 1H), 6.24 (br s, 1H), 5.40 (br s, 1H), 4.63 (d, 1H, J = 15.9), 4.59 (d, 2H, J = 5.6), 4.42 (d, 1H, J = 15.9), 4.29 (t, 1H, J = 6.6), 1.78-1.84 (m, 1H), 1.29-1.34 (m, 1H), 1.25 (t, 3H), J = 7.2), 1.06-1.11 (m, 1H), 0.76 (d, 3H, J = 6.6), 0.66 (d, 3H, J = 6.6).
125				6	colorless oil	494.06	1.67 min Method A	494.24	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.68 (dd, 2H, J = 1.7, 8.6), 7.63 (d, 2H, J = 8.2), 7.46 (d, 2H, J = 8.6), 7.39 (d, 2H, J = 8.2), 6.28 (br s, 1H), 5.94 (br s, 1H), 5.35 (br s, 1H), 4.63 (d, 1H, J = 15.8), 4.41 (d, 1H, J = 15.8), 4.29 (t, 1H, J = 6.6), 1.78-1.84 (m, 1H), 1.46 (s, 9H), 1.29-1.34 (m, 1H), 1.25 (t, 3H), J = 7.2), 1.06-1.11 (m, 1H), 0.76 (d, 3H, J = 6.6), 0.66 (d, 3H, J = 6.6).
126				7	white solid	401.15	1.34 min Method A	402.15	^{1}H NMR (DMSO-d_6, 500MHz), δ 7.87 (d, 2H, J = 8.5), 7.66 (d, 2H, J = 8.6), 7.41 (s, 1H), 7.04 (s, 1H), 4.17 (t, 1H, J = 7.3), 3.40-3.50 (m, 1H), 3.20-3.25 (m, 1H), 3.03-3.10 (m, 1H), 2.65-2.80 (m, 2H), 1.85-2.00 (m, 1H), 1.20-1.85 (m, 2H), 1.45-1.60 (m, 1H), 1.30-1.40 (m, 1H), 1.10-1.30 (m, 4H), 0.75-0.90 (m, 1H), 0.82 (d, 3H, J = 7.3), 0.80 (d, 1H, J = 7.0).

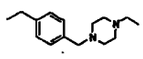
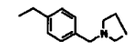
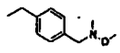
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
127				8	white solid	480.07	1.34 min Method A	480.25	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.60 (d, 2H, J=8.0Hz), 7.39-7.33 (m, 4H), 6.26 (s, br, 1H), 5.40 (s, br, 1H), 4.53 (d, 1H, J_{ab}=16Hz), 4.42 (d, 1H, J_{ab}=16Hz), 2.58 (q, 4H, J=8.0Hz), 1.94 (m, 1H), 1.59 (m, 2H), 1.06 (t, 6H, J=8.0Hz), 0.97 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)
128				8	white solid	504.1	1.32 min Method A	504.25	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.73 (d, 2H, J=8.0Hz), 7.48 (d, 2H, J=8.0Hz), 7.35 (d, 2H, J=8.0Hz), 6.25 (s, br, 1H), 5.35 (s, br, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.44 (d, 1H, J_{ab}=16Hz), 3.35 (s, 2H), 3.47-3.42 (m, 1H), 3.01 (s, br, 1H), 1.90 (m, 1H), 1.63 (m, 2H) 0.97 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)
129				8	white solid	583.2	1.26 min Method A	583.40	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.37 (m, 4H), 7.21 (m, 5H), 6.35 (s, br, 1H), 5.87 (s, br, 1H), 4.72 (d, 1H, J_{ab}=16Hz), 4.48 (d, 1H, J_{ab}=16Hz), 3.55 (s, 3H), 3.52 (s, 3H), 3.74-3.43 (m, 1H), 2.45 (m, 8H), 1.59 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz)

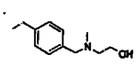
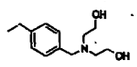
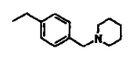
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
130				8	amber glass	496.06	1.32 min Method A	496.25	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.68 (d, 2H, J=8.0Hz), 7.72 (d, 2H, J=8.0Hz), 7.40-7.36 (m, 4H), 6.35 (s, br, 1H), 5.37 (s, br, 1H), 4.59 (d, 1H, J_{ab}=16Hz), 4.37 (d, 1H, J_{ab}=16Hz), 3.7-3.5 (m, 4H), 3.48 (s, 3H), 3.46 (m, 1H), 2.23-2.1 (m, 4H), 1.85 (m, 1H), 1.55 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz)
131				8	amber oil.	510.12	1.33 min Method A	510.23	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.65 (s, b, 4H), 7.37 (d, 2H, J=8.0Hz), 6.25 (s, b, 1H), 5.36 (s, b, 1H), 4.60 (d, 1H, J_{ab}=16Hz), 4.38 (d, 1H, J_{ab}=16Hz), 3.47-3.43 (m, 3H), 2.61 (m, 4H), 2.30 (m, 4H), 1.90 (m, 1H), 1.59 (m, 2H), 0.96 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)
132				8	amber glass	535.15	1.24 min Method A	535.32	^{1}H NMR, 400Hz, ($CDCl_3$) δ 8.02 (d, 2H, J=8.0Hz), 7.71 (d, 2H, J=8.0Hz), 7.40 (d, 2H, J=8.0Hz), 7.36 (d, 2H, J=8.0Hz), 6..27 (s, b, 1H), 5.40 (s, b, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.44 (d, 1H, J_{ab}=16Hz), 3.61 (s, 2H), 3.45 (m, 1H), 2.72-2.63 (m, 3H), 2.41 (s, 3H), 2.32 (s, 3H), 2.05 (t, 4H, J=12.0Hz), 1.90 (m, 3H), 1.74-1.55 (m, 3H), 0.96 (d, 3H, J=7.0Hz), 0.93 (d, 3H, J=7.0Hz)

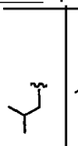
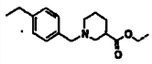
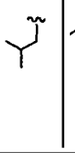
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
133				8	amber glass	540.13	1.28 min Method A	540.34	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.70 (d, 2H, J=8.0Hz), 7.52 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.24-7.14 (m, 3H), 6.88 (m, 1H), 6.25 (s, br, 1H), 5.39 (s, br, 1H), 4.62 (d, 1H, J_{ab}=16Hz), 4.40 (d, 1H, J_{ab}=16Hz), 3.45 (s, 2H), 3.46 (m, 1H), 3.35-3.19 (m, 2H), 3.93 (m, 1H), 2.71 (m, 1H), 2.61 (m, 1H), 2.49-2.43 (m, 2H), 1.89 (m, 1H), 1.67-1.54 (m, 2H), 0.97 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)
134				8	white solid	476.04	1.31 min Method A	476.17	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.79 (d, 2H, J=8.0Hz), 7.65 (d, 2H, J=8.0Hz), 7.47 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.35 (s, br, 1H), 5.85 (s, br, 1H), 4.60 (s, 2H), 4.76 (d, 1H, J_{ab}=16Hz), 4.30 (d, 1H, J_{ab}=16Hz), 3.72 (s, br, 2H), 3.46 (m, 1H), 2.40 (s, br, 3H), 2.20 (s, 1H), 1.90 (m, 1H), 1.63 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz)

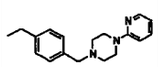
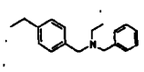
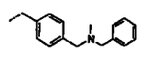
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
135				8	white solid	532.14	1.34 min Method A	532.32	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.62 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 7.33 (d, 2H, J=8.0Hz), 6.27 (s, br, 1H), 5.40 (s, br, 1H), 4.59 (d, 1H, J_{ab}=16Hz), 4.37 (d, 1H, J_{ab}=16Hz), 3.53 (s, 3H), 3.44 (m, 1H), 2.79 (t, 2H, J=8.0Hz), 2.62 (q, 2H, J=8.0Hz), 2.41 (t, 2H, J=8.0Hz), 2.25 (s, 6H), 1.95-1.85 (m, 1H), 1.67-1.54 (m, 2H), 1.07 (t, 3H, J=8.0Hz), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz)
136				8	white solid	537.17	1.24 min Method A	537.34	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.41-7.36 (m, 4H), 6.57 (s, br, 1H), 5.40 (s, br, 1H), 4.59 (d, 1H, J_{ab}=16Hz), 4.37 (d, 1H, J_{ab}=16Hz), 3.51 (s, 2H), 3.45 (m, 1H), 2.69 (t, 2H, J=8.0Hz), 2.62 (t, 2H, J=8.0Hz), 2.55 (q, 4H, J=8.0Hz), 2.35 (s, 3H), 1.89 (m, 1H), 1.60 (m, 2H), 1.00 (t, 6H, J=8.0Hz), 0.96 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)

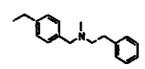
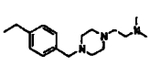
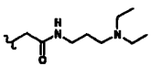
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
137				8	white solid	509.12	1.32 min Method A	509.33	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 8.01 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.40 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.27 (s, br, 1H), 5.39 (s, br, 1H), 4.58 (d, 1H, J_{ab}=16Hz), 4.36 (d, 1H, J_{ab}=16Hz), 3.51 (s, 2H), 3.45 (m, 1H), 2.66 (t, 2H, J=8.0Hz), 2.39 (t, 2H, J=8.0Hz), 2.35 (s, 3H), 2.25 (s, 6H), 1.90 (m, 1H), 1.59 (m, 2H), 0.97 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)
138				8	clear glass	494.1	1.37 min Method A	494.27	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.72 d, 2H, J=8.0Hz), 7.74 (d, 2H, J=8.0Hz), 7.52 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.26 (s, br, 1H), 5.39 (s, br, 1H), 4.55 (d, 1H, J_{ab}=16Hz), 4.42 (d, 1H, J_{ab}=16Hz), 3.70 (s, 3H), 3.46 (m, 1H), 2.38-2.35 (m, 5H), 1.91 (m, 2H), 1.60 (m, 2H), 0.96 (d, 3H, J=7.0Hz), 0.90 (d, 3H, J=7.0Hz)
139				8	white solid	494.1	1.33 min Method A	494.26	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.63 (d, 2H, J=8.0Hz), 7.73 (d, 2H, J=8.0Hz), 7.48 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.35 (s, br, 1H), 5.38 (s, br, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.44 (d, 1H, J_{ab}=16Hz), 3.47-3.40 (m, 3H), 2.12 (s, 3H), 1.88 (m, 1H), 1.60 (m, 2H), 1.03 (s, 9H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz)

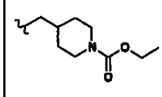
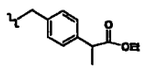
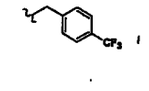
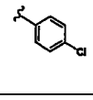
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
140				8	amber glass	521.13	1.27 min Method A	521.31	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.65 (d, 2H, J=8.0Hz), 7.39-7.36 (m, 4H), 6.30 (s, br, 1H), 5.35 (s, br, 1H), 4.59(d, 1H, J_{ab}=16Hz), 4.37 (d, 1H, J_{ab}=16Hz), 3.55 (s, 2H), 3.45 (m, 1H), 2.84 (m, 4H), 2.48 (q, 2H, J=7.0Hz), 2.28 (m, 4H), 1.88 (m, 1H), 1.60 (m, 2H), 1.20 (t, 3H, J=7.0Hz), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)
141				8	white solid	478.06	1.31 min Method A	478.22	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.71 (d, 2H, J=8.0Hz), 7.48 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.27 (s, br, 1H), 5.40 (s, br, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.43 (d, 1H, J_{ab}=16Hz), 3.58 (s, br, 2H), 3.45 (m, 1H), 2.66 (m, 4H), 1.86 (m, 5H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz)
142				8	white foam	468.02	1.58 min Method A	468.25	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.76 (d, 2H, J=8.0Hz), 7.75 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.25 (s, br, 1H), 5.38 (s, br, 1H), 4.76 (d, 1H, J_{ab}=16Hz), 4.30 (d, 1H, J_{ab}=16Hz), 3.75 (s, 2H), 3.45 (m, 1H), 3.36 (s, 3H), 2.61 (s, 3H), 1.88 (m, 1H), 1.59 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz)

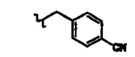
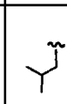
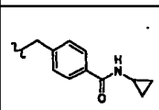
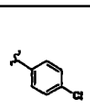
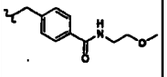
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
143				8	white solid	482.05	1.28 min Method A	482.24	^{1}H NMR, 400Hz, ($CDCl_3$) 7.69 (d, 2H, J=8.0Hz), 7.72 (d, 2H, J=8.0Hz), 7.42-7.36 (m, 4H), 6.35 (s, br, 1H), 5.83 (s, br, 1H), 4.58 (d, 1H, J_{ab}=16Hz), 4.39 (d, 1H, J_{ab}=16Hz), 3.52 (s, 1H), 3.50 (s, 2H), 3.48 (s, 1H), 3.45 (m, 1H), 2.55 (t, 2H, J=8.0Hz), 2.20 (s, 3H), 1.90 (m, 1H), 1.59 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz)
144				8	clear glass	512.07	1.22 min Method A	512.25	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.71 (d, 2H, J=8.0Hz), 7.74 (d, 2H, J=8.0Hz), 7.39 (d, 2H, J=8.0Hz), 7.31 (d, 2H, J=8.0Hz), 6.27 (s, br, 1H), 5.40 (s, br, 1H), 4.72 (d, 1H, J_{ab}=16Hz), 4.39 (d, 1H, J_{ab}=16Hz), 3.76 (t, 4H, J=8.0Hz), 3.45 (m, 1H), 3.38 (s, br, 2H), 3.15 (s, br, 2H), 3.76 (t, 4H, J=8.0Hz), 1.89 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz)
145				8	white solid	492.09	1.31 min Method A	492.21	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.63 (d, 2H, J=8.0Hz), 7.71 (d, 2H, J=8.0Hz), 7.47 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.26 (s, br, 1H), 5.39 (s, br, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.43 (d, 1H, J_{ab}=16Hz), 3.47-3.43 (m, 3H), 2.26 (m, 4H), 1.89 (m, 2H), 1.60 (m, 2H), 1.46-1.29 (m, 4H), 0.97 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)

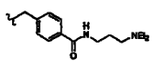
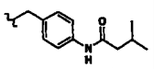
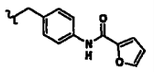
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
146				8	white solid	564.15	1.33 min Method A	564.24	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.71 (d, 2H, J=8.0Hz), 7.48 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.35 (s, br, 1H), 5.40 (s, br, 1H), 4.72 (d, 1H, J_{ab}=16Hz), 4.48 (d, 1H, J_{ab}=16Hz), 4.03 (q, 2H, J=8.0Hz), 3.47-3.42 (m, 3H), 3.21 (m, 1H), 2.62 (m, 1H), 2.63-2.36 (m, 3H), 2.06-1.95 (m, 1H), 1.93-1.80 (m, 3H), 1.67-1.50 (m, 3H), 1.13 (t, 3H, J=8.0Hz), 0.98 (d, 3H, J=.07Hz), 0.95 (d, 3H, J=7.01Hz)
147				8	white solid	582.21	1.46 min Method A	582.41	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.71 (d, 2H, J=8.0Hz), 7.47 (d, 2H, J=8.0Hz), 7.38(d, 2H, J=8.0Hz), 7.24 (t, 1H, J=8.0Hz), 7.03 (t, 2H, J=8.0Hz), 6.95 (d, 2H, J=8.0Hz), 6.27 (s, br, 1H), 5.40 (s, br, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.44 (d, 1H, J_{ab}=16Hz), 3.48-3.43 (m, 3H), 2.76 (m, 2H), 2.61 (m, 2H), 1.88 (m, 3H), 1.69-1.54 (m, 6H), 1.26 (m, 1H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.01Hz)

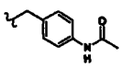
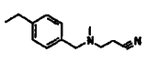
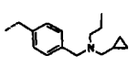
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
148				8	white foam	570.16	1.41 min Method A	570.34	^{1}H NMR, 400Hz, ($CDCl_3$) δ 8.09 (d, 1H, J=4.0Hz), 8.02 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.41-7.36 (m, 5H), 6.72 (d, 1H, J=12.0Hz), 6.49 (t, 1H, J=8.0Hz), 6.35 (s, br, 1H), 5.87 (s, br, 1H), 4.80 (d, 1H, J_{ab}=16Hz), 4.30 (d, 1H, J_{ab}=16Hz), 3.84 (m, 4H), 3.55 (s, 2H), 3.46 (m, 1H), 2.57 (m, 4H), 1.89 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 2H, J=7.0Hz)
149				8	white solid	542.15	1.45 min Method A	542.24	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.70 (d, 2H, J=8.0Hz), 7.68 (d, 2H, J=8.0Hz), 7.47 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.29-7.16 (m, 5H), 6.28 (s, br, 1H), 5.38 (s, br, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.42 (d, 1H, J_{ab}=16Hz), 3.54 (s, 2H), 3.45 (m, 1H), 2.62 (q, 2H, J=7.0Hz), 1.89 (m, 1H), 1.60 (m, 2H), 1.08 (t, 3H, J=7.0Hz), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 2H, J=7.0Hz)
150				8	amber film	528.12	1.45 min Method A	528.33	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.68 (d, 2H, J=8.0Hz), 7.54 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 7.35-7.29 (m, 5H), 6.27 (s, br, 1H), 5.37 (s, br, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.43 (d, 1H, J_{ab}=16Hz), 3.55 (s, 2H), 3.45 (m, 1H), 2.17 (s, 3H), 1.89 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz)

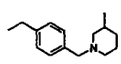
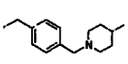
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
151				8	clear glass	542.15	1.46 min Method A	542.29	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.68 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.45 (d, 2H, J=8.0Hz), 7.39-7.26 (m, 4H), 6.97 (d, 1H, J=8.0Hz), 6.27 (s, br, 1H), 5.38 (s, br, 1H), 4.54 (d, 1H, J_{ab}=16Hz), 4.44 (d, 1H, J_{ab}=16Hz), 3.43 (s, 2H), 3.25 (t, 1H, J=4.0Hz), 2.77-2.69 (m, 4H), 2.40 (s, 3H), 1.94 (m, 1H), 1.60 (m, 2H), 0.97 (d, 2H, J=7.0Hz), 0.94 (d, 2H, J=7.0Hz)
152				8	amber glass	564.2	1.22 min Method A	564.32	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.59 (d, 2H, J=8.0Hz), 7.39-7.33 (m, 4H), 6.21 (s, br, 1H), 5.34 (s, br, 1H), 4.76 (d, 1H, J_{ab}=16Hz), 4.31 (d, 1H, J_{ab}=16Hz), 3.57 (s, 2H), 2.69-2.55 (m, 6H), 2.36-2.18 (m, 12H), 1.95 (m, 1H), 1.66-1.50 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)
153				5	white solid	474.21	1.78 min Method C	476.17	^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 (br s, 2H), 7.85 (dd, 2H, J = 2.0, 6.8), 7.46 (dd, 2H, J = 2.0, 6.8), 5.46 (s, 1H), 4.21 (dd, 1H, J = 5.9, 8.8), 3.92 (d, 1H, J = 17), 3.77 (d, 1H, J = 17), 3.27-3.41 (m, 2H), 2.48-2.62 (m, 6H), 1.80-1.90 (m, 1H), 1.50-1.72 (m, 3H), 1.35-1.49 (m, 1H), 1.05 (t, 6H, J = 7.1), 0.87 (d, 3H, J =6.4), 0.85 (d, 3H, J = 6.7)

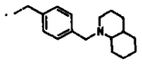
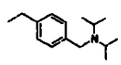
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
154				5	white solid	516.18	1.53 min Method A	517.30	^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 (dd, 2H, J = 1.9, 6.8), 7.47 (dd, 2H, J = 2.0, 6.8), 7.31 (br s, 1H), 7.11 (br s, 1H), 5.57 (br s, 1H), 4.23 (dd, 1H, J = 6.8, 8.4), 4.00-4.15 (m, 2H), 3.95 (d, 1H, J = 17), 3.83 (d, 1H, J = 17), 2.93 (br s, 2H), 1.75-1.95 (m, 4H), 1.60-1.75 (1H, 1.25-1.55 (m, 1H), 1.25 (t, 5H, J = 7.7), 0.85 (d, 3H, J = 6.3), 0.83 (d, 3H, J = 6.3).
155				1-Method A	white solid	495.04	1.88 min Method A	495.1	^{1}H NMR ($CDCl_3$) δ 7.62-7.59 (m, 2H), 7.43-7.39 (m, 2H), 7.28-7.25 (m, 2H), 7.22-7.19 (m, 2H), 6.22 (bs, 1H), 5.29 (bs, 1H), 4.53-4.43 (m, 2H), 4.42-4.37 (m, 1H), 4.16-4.07 (m, 2H), 1.82-1.73 (m, 1H), 1.48 (d, 3H, J=7.3Hz, isomer A), 1.47(d, 3H, J=7.3Hz, isomer B), 1.36-1.22 (m, 2H), 1.21 (t, 3H, J=7.1Hz), 0.77 (d, 3H, J=6.4Hz, isomerA), 0.77 (d, 3H, J=6.4Hz, isomerB), 0.65 (d, 3H, J=6.7Hz, isomerA), 0.65 (d, 3H, J=6.7Hz, isomerB)
156				1-Method A	white solid	434.07	1.57 min Method B	$(M+H)^+$ 435.1	^{1}H NMR (400 MHz, DMSO) δ 7.80 (d, 2H, J=8.7), 7.66 (d, 2H, J=8.3), 7.60 (m, 4H), 7.53 (s, 1H), 7.10 (s, 1H), 4.80 (ABq, 2H, Δυ=39.8, J_{ab}=17.2), 4.30 (t, 1H, J=7.5), 1.60 (m, 1H), 1.39 (m, 1H), 0.71 (t, 3H, J=7.3).

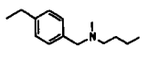
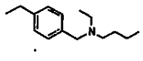
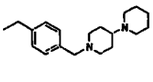
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
157				1-Method A	white solid	391.08	1.32 min Method B	$(M+H)^+$ 392.1	^{1}H NMR (400 MHz, DMSO) δ 7.81 (d, 2H, J=8.7), 7.78 (d, 2H, J=8.4), 7.62 (d, 2H, J=8.7), 7.57 (d, 2H, J=8.3,), 7.52 (s, 1H), 7.09 (s, 1H), 4.80 (ABq, 2H, Δυ=45.0, J_{ab}=17.6), 4.28 (t, 1H, J=7.5,), 1.58 (m, 1H), 1.36 (m, 1H), 0.70 (t, 3H, J=7.3).
158				6	white solid	478.01	1.53 min Method A	478.17	^{1}H NMR (CD_3OD, 300MHz) δ 7.80 (ddd, 2H, *J* = 1.9, 2.4, 8.7), 7.73 (d, 2H, *J* = 8.3), 7.48-7.54 (m, 4H), 4.87 (m, 1H), 4.79 (d, 1H, *J* = 16.0), 4.49 (t, 1H, *J* = 6.2), 2.81-2.87 (m, 1H), 1.25-1.43 (m, 3H), 0.83 (d, 3H, *J* = 6.2), 0.77-0.83 (m, 2H), 0.63-0.66 (m, 2H), 0.57 (d, 3H, *J* = 6.1).
159				6	white solid	496.03	1.50 min Method A	496.21	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.70 (d, 2H, *J* = 8.0), 7.68 (d, 2H, *J* = 8.6), 7.46 (d, 2H, *J* = 8.6), 7.41 (d, 2H, *J* = 8.1), 4.64 (d, 1H, *J* = 15.9), 4.43 (d, 1H, *J* = 15.9), 4.30 (t, 1H, *J* = 6.8), 3.63-3.66 (m, 2H), 3.55-3.58 (m, 2H), 3.39 (s, 3H), 1.76-1.84 (m, 1H), 1.28-1.34 (m, 1H), 1.05-1.11 (m, 1H), 0.75 (d, 3H, *J* = 6.5), 0.66 (d, 3H, *J* = 6.7).

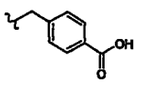
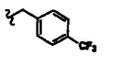
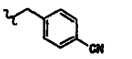
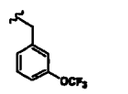
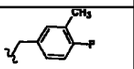
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
160				6	white solid	551.15	1.33 min Method A	551.28	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, *J* = 8.2), 7.67 (dd, 2H, *J* = 2.0, 8.7), 7.44 (dd, 2H, *J* = 1.8, 8.6), 7.39 (d, 2H, *J* = 8.2), 6.35 (br s, 1H), 5.46 (br s, 1H), 4.60 (d, 1H, *J* = 15.9), 4.50 (d, 1H, *J* = 15.9), 4.31 (t, 1H, *J* = 7.3), 3.54-3.57 (m, 2H), 2.56-2.64 (m, 6H), 1.72-1.80 (m, 3H), 1.28-1.34 (m, 1H), 1.13-1.16 (m, 1H), 1.03 (t, 6H, *J* = 7.2), 0.74 (d, 3H, *J* = 6.6), 0.61 (d, 3H, *J* = 6.6).
161				9	white solid	494.06	1.51min Method B	494.2	^{1}H NMR ($CDCl_3$) δ 7.69 (d, 2H, J=7.0Hz), 7.45-7.47 (m, 4H), 7.30 (d, 2H, J=8.0Hz), 7.12 (s, br, 1H), 6.25 (s, br, 1H), 5.22 (s, br, 1H), 4.40 (dd, 2H, J=50Hz, 15Hz), 4.25 (t, 1H, J=7.4Hz), 2.48-2.51 (m, 1H), 1.54-1.86 (m, 1H), 1.17-1.34 (m, 10H), 0.75 (d, 3H, J=7.0Hz), 0.67 (d, 3H, J=7.0Hz).
162				9	tan solid	504.01	1.52min Method B	504.1	^{1}H NMR ($CDCl_3$) δ8.10 (s, br, 1H), 7.67 (d, 2H, J=7.0Hz), 7.58 (d, 2H, J=7.0Hz), 7.23-7.49 (m, 6H), 6.54-6.57 (m, 1H), 6.27 (s, br, 1H), 5.50 (s, br, 1H), 4.51 (dd, 2H, J=50Hz, 15Hz), 4.28 (t, 1H, J=7.4Hz), 1.78-1.85 (m, 1H), 1.12-1.32 (m, 2H), 0.75 (d, 3H, J=7.0Hz), 0.67 (d, 3H, J=7.0Hz).

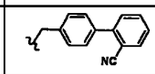
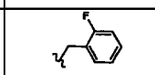
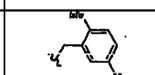
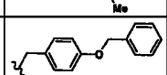
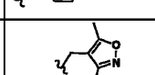
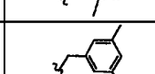
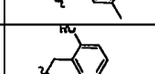
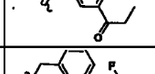
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
163				9	white solid	451.98	1.50min Method B	450.18 (M-H$^-$)	^{1}H NMR ($CDCl_3$) δ 7.67 (d, 2H, J=8.0Hz), 7.28-7.46 (m, 6H), 7.12 (s, br, 1H), 6.24 (s, br, 1H), 5.19 (s, br, 1H), 4.48 (dd, 2H, J=50Hz, 15Hz), 4.27 (t, 1H, J=7.0Hz), 2.18 (s, 3H), 1.80-2.01 (m, 1H), 1.12-1.32 (m, 2H), 0.75 (d, 3H, J=7.0Hz), 0.67 (d, 3H, J=7.0Hz).
164				8	white solid	491.06	1.31 min Method A	491.24	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.51 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.25 (s, br, 1H), 5.35 (s, br, 1H), 4.59 (d, 1H, J_{ab}=16Hz), 4.36 (d, 1H, J_{ab}=16Hz), 3.62 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 2.55-2.48 (m, 7H), 1.94 (m, 1H), 1.60 (m, 2H), 0.97 (d, 3H, J=7.0Hz), 0.84 (d, 3H, J=7.0Hz).
165				8	white solid	520.14	1.40 min Method A	520.32	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.66 (d, 2H, J=8.0Hz), 7.51 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.28 (s, br, 1H), 5.39 (s, br, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.43 (d, 1H, J_{ab}=16Hz), 3.57 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 2.59 (t, 2H, J=8.0Hz), 2.30 (d, 2H, J=6.0Hz), 2.01-1.90 (m, 1H), 1.68-1.49 (m, 4H), 1.02 (m, 1H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz), 0.89 (t, 3H, J=8.0Hz), 0.44-0.31 (m, 4H)

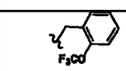
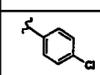
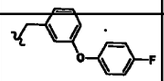
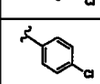
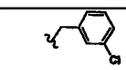
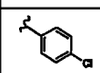
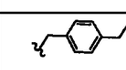
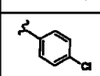
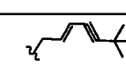
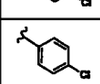
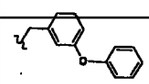
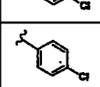
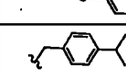
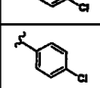
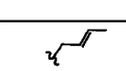
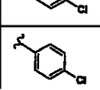
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
166				8	clear glass	506.11	1.41 min Method A	506.31	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.73 (d, 2H, J=8.0Hz), 7.65 (d, 2H, J=8.0Hz), 7.44 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.27 (s, br, 1H), 5.39 (s, br, 1H), 4.56 (d, 1H, J_{ab}=16Hz), 4.42 (d, 1H, J_{ab}=16Hz), 3.45 (d, 1H, J_{ab}=12Hz), 3.28 (d, 1H, J_{ab}=12Hz), 3.25 (t, 1H, J=6.0Hz), 2.75 (m, 4H), 2.0-1.53 (m, 7H), 1.35 (m, 1H), 1.17 (m, 1H), 0.97 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz), 0.87 (m, 3H)
167				8	clear glass	506.11	1.42 min Method A	506.30	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.71 (d, 2H, J=8.0Hz), 7.65 (d, 2H, J=8.0Hz), 7.43 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.26 (s, br, 1H), 5.40 (s, br, 1H), 4.56 (d, 1H, J_{ab}=16Hz), 4.42 (d, 1H, J_{ab}=16Hz), 3.48 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 2.56-2.42 (m, 4H), 1.93 (m, 1H), 1.89-1.48 (m, 6H), 1.34 (m, 1H), 0.98-0.93 (m, 9H)

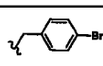
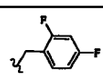
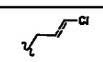
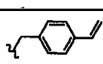
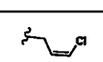
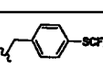
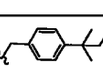
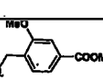
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
168				8	clear glass	546.18	1.46 min Method A	546 35	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.65 (d, 2H, J=8.0Hz), 7.42 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.27 (s, br, 1H), 5.40 (s, br, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.43 (d, 1H, J_{ab}=16Hz), 3.45 (d, 1H, J_{ab}=12Hz), 3.28 (d, 1H, J_{ab}=12Hz), 3, 25 (t, 1H, J=6.0Hz), 2.87 (m, 1H), 2.70-2.56 (m, 3H), 2.39 (m, 1H), 2.31-2.19 (m, 4H), 1.95 (m, 1H), 1.77 (m, 1H), 1.68-1.59 (m, 2H), 1.54-1.44 (m, 4H), 1.28 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 2H, J=7.0Hz)
169				8	clear glass	508.13	1.39 min Method A	502.28	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.70 (d, 2H, J=8.0Hz), 7.68 (d, 2H, J=8.0Hz), 7.55 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.28 (s, br, 1H), 5.37 (s, br, 1H), 4.57 (d, 1H, J_{ab}=16Hz), 4.36 (d, 1H, J_{ab}=16Hz), 3.38 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 2.83 (m, 2H), 1.92 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz), 0.84 (s, 6H), 0.82 (s, 6H)

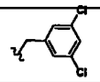
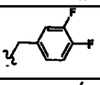
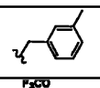
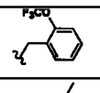
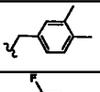
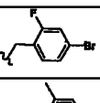
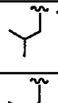
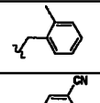
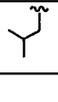
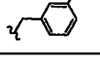
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
170				8	clear glass	494.1	1.34 min Method A	494.26	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.67 (d, 2H, J=8.0Hz), 7.44 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.27 (s, br, 1H), 5.39 (s, br, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.44 (d, 1H, J_{ab}=16Hz), 3.40 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 2.39 (s, 3H), 1.94 (m, 1H), 1.68-1.50 (m, 2H), 1.43 (m, 2H), 1.30 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz), 0.86 (t, 3H, J=7.0Hz)
171				8	clear glass	508.13	1.40 min Method A	508.27	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.4-7.33 (m, 4H), 6.25 (s, br, 1H), 5.35 (s, br, 1H), 4.52(d, 1H, J_{ab}=16Hz), 4.43 (d, 1H, J_{ab}=16Hz), 3.46 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 2.62 (t, 2H, J=6.0Hz), 2.52 (q, 2H, J=7.0Hz), 1.94 (m, 1H), 1.68-1.45 (m, 4H), 1.29 (m, 2H), 1.02 (t, 3H, J=7.0Hz), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz), 0.88 (t, 3H, J=7.0Hz)
172				8	amber glass	575.22	1.34 min Method A	575.32	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.59 (d, 2H, J=8.0Hz), 7.39-7.33 (m, 4H), 6.25 (s, br, 1H), 5.36 (s, br, 1H), 4.53 (d, 1H, J_{ab}=16Hz), 4.39 (d, 1H, J_{ab}=16Hz), 3.57 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 2.62-2.32 (m, 9H), 1.94 (m, 1H), 1.68-1.50 (m, 2H), 1.48-1.20 (m, 12H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)

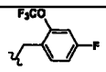
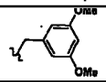
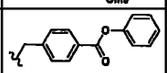
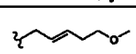
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
173				6	white solid	436.92	1.52 min Method A	437.16	^{1}H NMR (dmso-d_6, 300MHz) δ 7.85 (d, 2H, J = 8.4), 7.82 (dd, 2H, J = 1.8, 8.7), 7.61 (dd, 2H, J = 1.8, 8.7), 7.54 (br s, 1H), 7.47 (d, 2H, J = 8.4), 7.09 (br s, 1H), 4.85 (d, 1H, J = 17.4), 4.69 (d, 1H, J = 17.1), 4.42 (t, 1H, J = 7.2), 1.40-1.48 (m, 1H), 1.27-1.34 (m, 1H), 0.42-0.47 (m, 1H), 0.25-0.30 (m, 2H), 0.00-0.03 (m, 1H), 0.10 - 0.07 (m, 1H).
174				1-Method A	off-white solid	492.11	2.13 min Method D	M+Na 514.95	^{1}H NMR (DMSO) δ 7.76 (d, 2H, J=6.8Hz), 7.61 (m, 6H), 7.44(s, br, 1H), 7.13 (s, br, 1H), 4.78 (dd, 2H, J=52Hz, 16Hz), 4.58 (t, 1H, J=8.0Hz), 3.47 (d, 2H, J=6.0Hz), 0.88 (s, 9H)
175				1-Method A	white solid	449.12	1.94 min Method D	M+Na 471.97	^{1}H NMR (DMSO) δ 7.77 (m, 4H), 7.60 (m, 4H), 7.45 (s, br, 1H), 7.12 (s, br, 1H), 4.78 (dd, 2H, J=56Hz, 20Hz), 4.57 (t, 1H, J=8.0Hz), 3.47 (d, 2H, J=6.0Hz), 0.88 (s, 9H)
176				1-solid support		478.90	1.86 Method B	479.02	
177				1-solid support		426.90	1.82 Method B	449.02 M+Na	

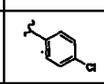
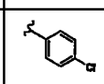
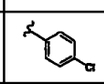
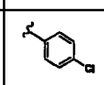
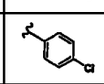
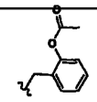
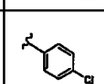
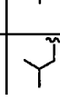
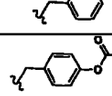
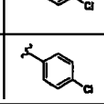
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
178				1-solid support		496.00	1.81 Method B	496.06	
179				1-solid support		412.90	1.72 Method B	413.04	
180				1-solid support		423.00	1.86 Method B	445.02 M+Na	
181				1-solid support		501.10	1.94 Method B	523.04 M+Na	
182				1-solid support		413.90	1.53 Method B	414.05	
183				1-solid support		423.00	1.88 Method B	423.08	
184				1-solid support		467.00	1.60 Method B	467.06	
185				1-solid support		505.00	1.89 Method B	505.07	

Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
186				1-solid support		478.90	1.84 Method B	479.02	
187				1-solid support		505.00	1.93 Method B	505.06	
188				1-solid support		429.40	1.80 Method B	450.90 M+Na	
189				1-solid support		423.00	1.89 Method B	423.09	
190				1-solid support		425.00	1.92 Method B	425.11	
191				1-solid support		487.00	1.91 Method B	487.04	
192				1-solid support		437.00	1.95 Method B	459.05 M+Na	
193				1-solid support		358.90	1.67 Method B	381.07 M+Na	

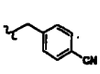
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
194				1-solid support		473.80	1.86 Method B	472.9	
195				1-solid support		430.9	1.75 Method B	431.04	
196				1-solid support		379.30	1.65 Method B	400.98	
197				1-solid support		421.00	1.82 Method B	443.06 M+Na	
198				1-solid support		379.30	1.64 Method B	400.99	
199				1-solid support		495.00	1.95 Method B	494.98	
200				1-solid support		465.10	2.05 Method B	487.10 M+Na	
201				1-solid support		483.00	1.72 Method B	483.04	

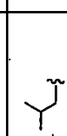
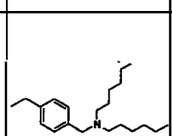
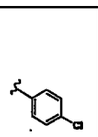
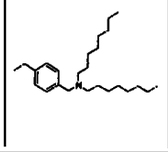
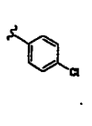
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
202				1-solid support		463.80	1.91 Method B	486.96 M+Na	
203				1-solid support		430.90	1.77 Method B	431.04	
204				1-solid support		409.00	1.79 Method B	409.07	
205				1-solid support		462.90	1.81 Method B	463.04	
206				1-solid support		423.00	1.86 Method B	423.10	
207				1-solid support		491.80	1.88 Method B	492.91	
208				1-solid support		409.00	1,78 Method B	431.04 M+Na	
209				1-solid support		419.9	1.58 Method B	442.04 M+Na	

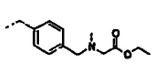
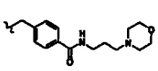
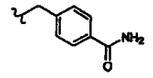
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210				1-solid support		344.90	1.56 Method B	367.05 M+Na	
211				1-solid support		480.90	1.87. Method B	481.02	
212				1-solid support		430.90	1.76 Method B	453.02	
213				1-solid support		455.00	1.71 Method B	455.07	
214				1-solid support		515.00	1.91 Method B	515.09	
215				1-solid support		447.40	1.82 Method B	468.99 M+Na	
216				1-solid support		480.90	1.80 Method B	481.00	
217				1-solid support		402.90	1.600 Method B	403.12	

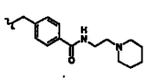
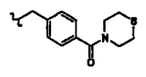
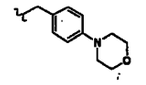
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
218				1-solid support		429.40	1.78 Method B	429.04	
219				1-solid support		448.90	1.78 Method B	471.00	
220				1-solid support		430.90	1.75 Method B	453.03	
221				1-solid support		480.90	1.85 Method B	503.00 M+Na	
222				1-solid support		445.00	1.87 Method B	467.06 M+Na	
223				1-solid support		453.00	1.62 Method B	453.03	
224				1-solid support		453.00	1.63 Method B	453.05	

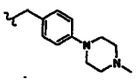
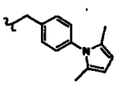
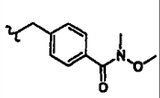
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
225				1-solid support		416.00	1.53 Method B	416.04	
226				1-solid support		401.90	1.45 Method B	401.96	
227				1-solid support		395.90	1.12 Method B	396.01	
228				1-solid support		358.90	1.62 Method B	381.01 M+Na	
229				1-solid support		439.00	1.80 Method B	460.97 M+Na	
230				1-solid support		424.90	1.72 Method B	425.03	
231				1-solid support		463.80	1.85 Method B	464.90	
232				1-solid support		456.90	1.64 Method B	456.02	

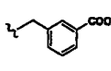
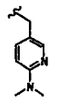
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
233				1-solid support		447.40	1.78 Method B	468.92 M+Na	
234				1-Method A	white solid	419.11	1.91 min Method F	$(M+Na)^+$ 442.0	^{1}H NMR (400 MHz, DMSO) δ 7.82 (d, 2H, J=8.7), 7.80 (d, 2H, J=8.4), 7.62 (d, 2H, J=8.7), 7.59 (d, 2H, J=8.3,), 7.51 (s, 1H), 7.07 (s, 1H), 4.81 (ABq, 2H, Δυ=38.0, J_{ab}=17.5), 4.31 (t, 1H, J=6.7), 1.54 (m, 1H), 1.29 (m, 1H), 1.03 (m, 3H), 0.85 (m, 1H), 0.66 (t, 3H, J=5.9)
235				1-Method A	white solid	462.10	2.13 min Method F	$(M+Na)^+$ 485.0	^{1}H NMR (400 MHz, DMSO) δ 7.81 (d, 2H, J=8.7), 7.69 (d, 2H, J=8.3), 7.61 (m, 4H), 7.51 (s, 1H), 7.07 (s, 1H), 4.82 (ABq, 2H, Δυ=31.9, J_{ab}=17.1), 4.32 (t, 1H, J=8.3), 1.53 (m, 1H), 1.31 (m, 1H), 1.05 (m, 3H), 0.88 (m, 1H), 0.63 (t, 3H, J=5.0)
236				1-solid support	white solid	530.92	1.92 Method B	530.99	
237				1-solid support	white solid	416.93	1.61 Method B	417.07	
238				1-solid support	white solid	466.99	1.62 Method B	467.06	

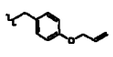
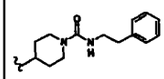
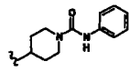
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
239				1-solid support	white solid	379.13	1.62	400.98 M+Na	
240				1-solid support	white solid	395.91	1.13	396.01	
241				8	amber glass	592.29	1.69 min Method A	592.39	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.65(d, 2H, J=8.0Hz), 7.43(d, 2H, J=8.0Hz), 7.37(d, 2H, J=8.0Hz), 6.27 (s, br, 1H), 5.40 (s, br, 1H), 4.56 (d, 1H, J_{ab}=16Hz), 4.40 (d, 1H, J_{ab}=16Hz), 3.56 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 2.40 (t, 4H, J=6.0Hz), 1.95 (m, 1H), 1.68-1.52 (m, 2H), 1.42 (q, 4H, J=6.0Hz), 1.28-1.22 (m, 12H), 0.98 (d, 3H, J=7.0Hz), 0.88 (t, 6H, J=6.0Hz)
242				8	amber glass	648.4	1.88 min Method A	648.43	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.71 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.43 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.27 (s br, 1H), 5.40 (s, br, 1H), 4.56 (d, 1H, J_{ab}=16Hz), 4.40 (d, 1H, J_{ab}=16Hz), 3.56 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 2.47 (t, 4H, J=6.0Hz), 1.95 (m, 1H), 1.68-1.50 (m, 2H), 1.43-1.14 (m, 14H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz), 0.88 (t, 6H, J=6.0Hz)

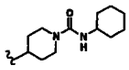
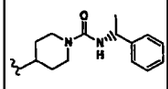
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
243				9	clear glass	524.08	1.35 min Method A	542 25	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.50 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.25 (s, br, 1H), 5.34 (s, br, 1H), 4.70 (d, 1H, J_{ab}=16Hz), 4.48 (d, 1H, J_{ab}=16Hz), 4.24-4.08 (m, 4H), 3.42 (s, 2H), 3.25 (t, 1H, J=6Hz), 2.51 (s, 3H), 1.94 (M, 1H), 1.68-1.54 (m, 2H), 1.22 (t, 3H, J=6.0Hz), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)
244				6	white solid	565.14	1.29 min Method B	564.99	^{1}H NMR ($CDCl_3$, 300MHz) δ 8.12 (br s, 1H), 7.77 (d, 2H, *J* = 8.8), 7.70 (d, 2H, *J* = 8.6), 7.47 (d, 2H, *J* = 8.4), 7.45 (d, 2H, *J* = 8.0), 6.25 (br s, 1H), 5.31 (br s, 1H), 4.66 (d, 1H, *J* = 15.7), 4.38 (d, 1H, *J* = 15.8), 4.27 (t, 1H, *J* = 7.1), 3.51-3.89 (m, 4H), 2.35-2.74 (m, 4H), 1.78-1.88 (m, 2H), 1.40-1.65 (m, 4H), 1.24-1.32 (m, 2H), 1.03-1.10 (m, 1H), 0.74 (d, 3H, *J* = 6.5), 0.65 (d, 3H, *J* = 6.6).
245				6	white solid	437.95	1.36 min Method B	438.20	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.72 (dd, 2H, *J* = 8.3), 7.69 (dd, 2H, *J* = 1.9, 8.7), 7.46 (dd, 2H, *J* = 1.8, 8.7), 7.44 (d, 2H, *J* = 8.6), 6.21 (br s, 1H), 5.98 (br s, 1H), 5.88 (br s, 1H), 5.39 (br s, 1H), 4.66 (d, 1H, *J* = 15.7), 4.41 (d, 1H, *J* = 15.9), 4.29 (t, 1H, *J* = 6.5), 1.77-1.87 (m, 1H), 1.25-1.36 (m, 1H), 1.03-1.11 (m, 1H), 0.75 (d, 3H, *J* = 6.6), 0.65 (d, 3H, *J* = 6.6).

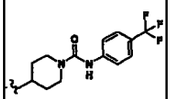
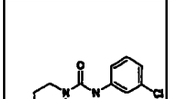
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
246				6	white solid	549.14	1.34 min Method B	549.00	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.82 (d, 2H, J = 7.8), 7.67 (dd, 2H, J = 2.0, 8.7), 7.40-7.46 (m, 5H), 6.22 (br s, 1H), 5.23 (br s, 1H), 4.61 (d, 1H, J = 15.9), 4.42 (d, 1H, J = 15.7), 4.28 (t, 1H, J = 7.2), 3.60-3.69 (m, 2H), 2.45-2.83 (m, 6H), 1.40-1.85 (m, 7H), 1.24-1.35 (m, 1H), 1.05-1.14 (m, 1H), 0.75 (d, 3H, J = 6.5), 0.66 (d, 3H, J = 6.6)
247				6	white solid	524.11	1.61 min Method B	523.94	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.68 (d, 2H, J = 8.4), 7.46 (d, 2H, J = 8.4), 7.39 (d, 2H, J = 8.1), 7.29 (d, 2H, J = 8.1), 6.20 (br s, 1H), 5.24 (br s, 1H), 4.60 (d, 1H, J = 15.8), 4.44 (d, 1H, J = 15.9), 4.30 (t, 1H, J = 6.9), 3.70-4.05 (br m, 4H), 2.45-2.60 (m, 4H), 1.73-1.80 (m, 1H), 1.28-1.35 (m, 1H), 1.05-1.14 (m, 1H), 0.76 (d, 3H, J = 6.5), 0.66 (d, 3H, J = 6.6)
248				2	red solid	466.00	1.48 min Method B	466.2	^{1}H NMR ($CDCl_3$) δ 7.65 (d, 2H, J=7.0Hz), 7.41 (d, 2H, J=7.0Hz), 7.20 (d, 2H, J=8.8Hz), 6.79 (d, 2H, J=8.8Hz), 6.23 (s, br, 1H), 5.20 (s, br, 1H), 4.32 (dd, 2H, J=50Hz, 15Hz), 4.19-4.27 (m, 1H), 3.84-3.87 (m, 4H), 3.12-3.16 (m, 4H), 1.91-1.95 (m, 1H), 1.35-1.39 (m, 1H), 0.92-1.06 (m, 2H), 0.74 (t, 3H, J=8.0Hz)

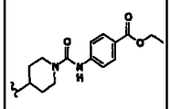
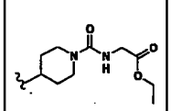
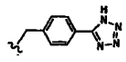
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
249				2	yellow solid	479.05	1.18min Method B	479.02	^{1}H NMR ($CDCl_3$) δ 7.63 (d, 2H, J=8.0Hz), 7.40 (d, 2H, J=8.0Hz), 7.19 (d, 2H, J=8.8Hz), 6.78 (d, 2H, J=8.8Hz), 6.25 (s, br, 1H), 5.21 (s, br, 1H), 4.36 (dd, 2H, J=50Hz, 15Hz), 4.20-4.27 (m, 1H), 3.28-3.35 (m, 4H), 2.69-2.76 (m, 4H), 2.48 (s, 3H), 1.93-1.97 (m, 1H), 1.35-1.39 (m, 1H), 0.90-1.07 (m, 2H), 0.72 (t, 3H, J=8.0Hz).
250				2	tan solid	474.03	1.92min Method B	474.2	^{1}H NMR ($CDCl_3$) δ 7.68 (d, 2H, J=8.8Hz), 7.43-7.45 (m, 4H), 7.12 (d, 2H, J=8.8Hz), 6.78 (d, 2H, J=8.8Hz), 6.19 (s, br, 1H), 5.18 (s, br, 1H), 4.56 (dd, 2H, J=50Hz, 15Hz), 4.21-4.30 (m, 1H), 2.01 (s, 6H), 1.93-1.97 (m, 1H), 1.35-1.39 (m, 1H), 0.90-1.07 (m, 2H), 0.72 (t, 3H, J=8.0Hz).
251				6	white solid	482.00	2.01 min Method B	479.07	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.67 (ddd, 2H, J = 1.9, 2.4, 8.7), 7.58 (d, 2H, J = 8.1), 7.43 (ddd, 2H, J = 1.5, 2.4, 8.7), 7.37 (d, 2H, J = 8.2), 6.30 (br s, 1H), 5.70 (br s, 1H), 4.62 (d, 1H, J = 15.9), 4.46 (d, 1H, J = 15.9), 4.32 (t, 1H, J = 7.3), 3.51 (s, 3H), 3.32 (s, 3H), 1.73-1.80 (m, 1H), 1.28-1.35 (m, 1H), 1.05-1.14 (m, 1H), 0.74 (d, 3H, J = 6.5), 0.61 (d, 3H, J = 6.5).

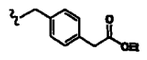
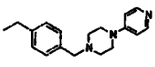
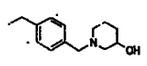
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
252				1-Method A	white solid	466.98	1.92 min Method A	467.2	^{1}H NMR ($CDCl_3$) δ 7.92 (d, 1H, J=8.0Hz), 7.79 (A of ABq, 2H, J=8.8Hz), 7.72 (d, 1H, J=7.7Hz), 7.50 (B of ABq, 2H, J=8.8Hz), 7.31 (t, 1H, J=7.7Hz), 6.29 (bs, 1H), 5.21 (bs, 1H), 5.02 (s, 2H), 4.35 (q, 2H, J=7.0Hz), 4.27 (dd, 1H, J=8.6, 5.5Hz), 1.88-1.78 (m, 1H), 1.39 (t, 3H, J=7.0Hz), 1.37-1.29 (m, 1H), 1.02-0.93 (m, 1H), 0.75 (d, 3H, J=6.6Hz), 0.66 (d, 3H, J=6.6Hz).
253				1-Method A	white solid	481.01	1.81 min Method A	481.2	^{1}H NMR ($CDCl_3$) δ 7.67(A of ABq, 2H, J=8.8Hz), 7.44 (B of ABq, 2H, J=8.8Hz), 7.27-7.15 (m, 3H), 6.24 (bs, 1H), 5.26 (bs, 1H), 4.55 (A of ABq, 1H, J=15.4Hz), 4.39 (B of ABq, 1H, J=15.4Hz), 4.29 (t, 1H, J=7.0Hz), 4.15 (q, 2H, J=7.2Hz), 1.87-1.78 (m, 1H), 1.37-1.29 (m, 1H), 1.26 (t, 3H, =7.2Hz), 1.24-1.13 (m; 1H), 0.76 (d, 3H, J=6.2Hz), 0.67 (d, 3H, J=6.6Hz).
254				10	white solid	438.98	1.20 Method B	439.05	^{1}H NMR ($CDCl_3$) TFA salt: δ 8.04 (s, 1H), 8.03 (d, 1H, J= 9.80Hz), 7.76 (d, 2H, J=7.6 Hz), 7.54 (d, 2H, J=7.6 Hz), 6.83 (d, 1H, J=9.8 Hz), 6.62 (br s. 1H), 6.40 (br s, 1H), 4.64 (d, 1H, J=15.9 Hz), 4.29 (m, 1H), 4.18 (d, 1H, J=15.9 Hz), 3.30 (s, 6H), 1.84 (m, 1H), 1.29 (m, 1H), 0.93 (m, 1H), 0.77 (d, 3H, J=6.5Hz), 0.72 (d, 3H, J=6.5Hz)

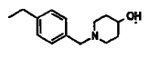
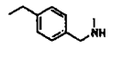
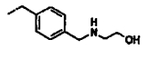
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
255				1-Method A	light orange residue	450.14	2.02 min Method B	450.98	^{1}H NMR (DMSO) δ 7.78 (d, 2H, J =8.4Hz), 7.58 (d, 2H, J =8.8Hz), 7.47 (s, br, 1H), 7.29 (d, 2H, J =8.8Hz), 7.00 (s br, 1H), 6.87 (d, 2H, J =8.8Hz), 6.03 (m, 1H), 5.32 (dd, 2H, J=12Hz, 56Hz), 4.63 (m, 4H), 5.32 (dd, 2H, J=12Hz, 56Hz), 4.35 (m, 1H), 1.33 (m, 3H), 0.80 (d, 3H, J=6.0Hz), 0.50 (d, 3H, J=6.0Hz).
256				7	white solid	548.22	1.87 min Method A	549.00	^{1}H NMR ($CDCl_3$, 500MHz), δ 7.71 (d, 2H, J = 8.6), 7.71 (d, 2H, J = 8.9), 7.15-7.35 (m, 5H), 6.64 (s, 1H), 5.86 (s, 1H), 4.15 (dd, 1H, J = 5.2, 9.5), 3.88 (d, 1H, J = 13), 3.76 (d, 1H, J = 13), 3.46 (t, 2H, J = 6.7), 3.21-3.29 (m, 1H), 2.97 (dd, 1H, J = 4.6, 14), 2.65-2.85 (m, 4H), 1.75-1.95 (m, 3H), 1.00-1.30 (m, 5H), 0.75-0.80 (m, 1H), 0.72 (d, 3H, J = 6.7), 0.67 (d, 3H, J = 6.7).
257				7	white solid	520.19	1.74 min Method A	521.31	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, J = 8.8), 7.51 (d, 2H, J = 8.8), 7.33 (d, 2H, J = 7.6), 7.28 (d, 2H, J = 7.6), 7.03 (t, 1H, J = 7.3), 6.67 (s, 1H), 5.42 (s, 1H), 3.97-4.22 (m, 3H), 3.27-3.35 (m, 1H), 2.78-3.02 (m, 3H), 1.83-1.99 (m, 3H), 1.09-1.42 (m, 4H), 0.75-0.82 (m, 1H), 0.74 (d, 3H, J = 6.4), 0.67 (d, 3H, J = 6.7).

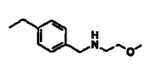
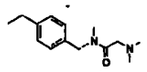
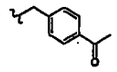
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
258				7	white solid	526.24	1.81 min Method A	527.34	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.73 (d, 2H, J = 8.9), 7.51 (d, 2H, 8.9), 6.65 (s, 1H), 5.37 (s, 1H), 4.15 (dd, 1H, J = 5.1, 6.5), 3.92 (d, 1H, J = 12), 3.82 (d, 1H, J = 14), 3.57-3.67 (m, 1H), 3.26 (dd, 1H, J = 10, 14), 2.98 (dd, 1H, J = 4.5, 14), 2.74 (q, 2H, J = 12, 24), 1.80-1.97 (m, 5H), 1.64-1.72 (m, 3H), 1.00-1.43 (m, 10H), 0.75-0.82 (m, 1H), 0.73 (d, 3H, J = 6.4), 0.67 (d, 3H, J = 6.7)
259				7	white solid	548.22	1.78 min Method A	549.32	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.71 (d, 2H, J = 8.2), 7.50 (d, 2H, J = 8.5), 7.30 (d, 4H, J = 4.3), 7.20-7.25 (m, 1H), 6.65 (s, 1H), 5.74 (s, 1H), 4.99 (t, 1H, J = 7.02), 4.70-4.77 (m, 1H), 4.10-4.25 (m, 1H), 4.00 (d, 1H, J = 13), 3.90 (d, 1H, J = 13), 3.15-3.35 (m, 1H), 2.90-3.00 (m, 1H), 2.60-2.75 (m, 2H), 1.50-1.95 (m, 5H), 1.46 (d, 3H, J = 6.7), 1.00-1.30 (m, 2H), 0.75-0.83 (m, 1H), 0.73 (d, 3H, J = 6.4), 0.67 (d, 3H, J = 6.4)

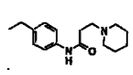
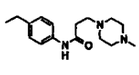
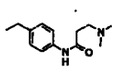
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
260				7	white solid	588.18	1.90 min Method A	589.25	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.73 (d, 2H, J = 8.9), 7.62 (d, 4H, J = 8.6), 7.45 (d, 2H, J = 8.5), 6.67 (s, 1H), 6.52 (s, 1H), 4.45 (s, 1H), 4.16 (dd, 1H, J = 5.2, 9.8), 4.12 (d, 1H, J = 12), 4.03 (d, 1H, J = 14), 3.80 (dd, 1H, J = 10, 14), 3.00 (dd, 1H, J = 4.5, 14), 2.84-2.92 (m, 2H), 1.85-2.00 (m, 3H), 1.69 (d, 1H, J = 12), 1.10-1.35 (m, 3H), 0.75-0.82 (m, 1H), 0.74 (d, 3H, J = 6.7), 0.68 (d, 3H, J = 6.7).
261				7	white solid	554.14	1.86 min Method A	555.24	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.73 (d, 2H, J = 8.6), 7.52 (d, 2H, J = 8.9), 7.45 (s, 1H), 7.18 (d, 2H, J = 6.7), 6.95-7.02 (m, 1H), 6.65 (s, 1H), 6.50 (s, 1H), 5.50 (s, 1H), 4.16 (dd, 1H, J = 5.2, 9.5), 4.08 (d, 1H, J = 15), 3.99 (d, 1H, J = 14), 3.30 (dd, 1H, J = 10, 15), 2.99 (dd, 1H, J = 4.5, 15), 2.80-2.92 (m, 2H), 1.80-2.00 (m, 3H), 1.67 (d, 1H, J = 13), 1.05-1.40 (m, 4H), 0.75-0.80 (m, 1H), 0.74 (d, 3H, J = 6.7), 0.68 (d, 3H, J = 6.7).

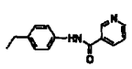
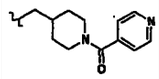
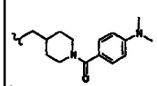
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
262				7	white solid	592.21	1.86 min Method A	593.30	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.96 (d, 2H, J = 8.9), 7.73 (d, 2H, J = 8.9), 7.51 (d, J = 8.6), 7.42 (d, 2H, J = 8.6), 6.65 (s, 2H), 5.45 (s, 1H), 4.83 (q, 2H, J = 7.0), 4.16 (dd, 1H, J = 5.2, 9.8), 4.11 (d, 1H, J = 13), 4.03 (d, 1H, J = 13), 3.30 (dd, 1H, J = 10, 14), 3.00 (dd, 1H, J = 4.2, 14), 2.81-2.95 (m, 2H), 1.84-2.01 (m, 3H), 1.68 (d, 1H, J = 13), 1.37 (t, 3H, J = 7.3), 1.08-1.34 (m, 4H), 0.76-0.82 (m, 1H), 0.74 (d, 3H, J = 6.7), 0.68 (d, 3H, J = 6.7)
263				7	white solid	530.20	2.18 min Method C	531.11	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.73 (d, 2H, J = 8.5), 7.51 (d, 2H, J = 8.6), 6.67 (s, 1H), 5.41 (s, 1H), 4.97 (s, 1H), 4.20 (q, 2H, J = 7.0), 4.15 (dd, 1H, J = 5.1, 9.5), 3.90-4.04 (m, 4H), 3.26 (dd, 1H, J = 10, 14), 2.99 (dd, 1H, J = 4.5, 14), 2.70-2.82 (m, 2H), 1.80-1.95 (m, 3H), 1.28 (t, 3H, J = 7.3), 1.05-1.25 (m, 3H), 0.75-0.80 (m, 1H), 0.72 (d, 3H, J = 6.7), 0.67 (d, 3H, J = 6.4)
264				1-Method A	white solid	462.96	1.47 Method B	462.98	^{1}H NMR ($CDCl_3$) δ 7.81 (d, 2H, J=8.4Hz), 7.75 (d, 2H, J=8.0Hz), 7.55 (d, 2H, J=8.4Hz), 7.5 (d, 2H, J=8.0Hz), 6.86 (s, 1H), 6.44 (s, 1H), 4.96 (d, 1H, J=15.6Hz), 4.36 (dd, 1H, J=5.6Hz, 6.0Hz), 1.99 (m, 1H), 1.29 (m, 1H), 1.06 (m, 1H), 0.77(d, 3H, J=6.8Hz), 0.74 (d, 3H, J=6.8Hz)

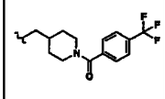
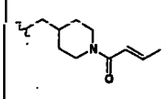
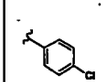
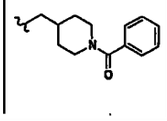
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
265				1-Method A	white solid	481.01	1.81 min Method A	481.3	^{1}H NMR ($CDCl_3$) δ 7.61 (A of ABq, 2H, J=8.8Hz), 7.42 (B of ABq, 2H, J=8.8Hz), 7.27 (A of ABq, 2H, J=8.4Hz), 7.19 (B of ABq, 2H, J=8.4Hz), 6.21 (bs, 1H), 5.19 (bs, 1H), 4.52 (A of ABq, 1H, J=15.5Hz, 1H), 4.39 (B of ABq, 1H, J=15.5Hz, 1H), 4.30 (t, 1H, J=7.3Hz), 4.14 (q, 2H, J=7.1Hz), 3.58 (s, 2H), 1.86-1.76 (m, 1H), 1.36-1.27 (m, 1H), 1.14 (t, 3H, J=7.1Hz), 1.23-1.13 (m, 1H), 0.76 (d, 3H, J=6.2Hz), 0.66 (d, 3H, J=6.6Hz)
266				8	white foam	570.16	1.17 min Method A	570.39	^{1}H NMR, 400Hz, ($CDCl_3$) δ 8.21 (d, 2H, J=4.0Hz), 8.02 (d, 2H, J=8.0Hz), 7.59 (d, 2H, J=8.0Hz), 7.39-7.33 (m, 4H), 6.83 (d, 2H, J=4.0Hz), 6.23 (s, br, 1H), 5.34 (s, br, 1H), 4.60 (d, 1H, J_{ab}=16Hz), 4.39 (d, 1H, J_{ab}=16Hz), 3.57 (s, 2H), 3.27-3.15 (m, 5H), 2.58-2.45 (m, 4H), 1.94 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)
267				8	white foam	508.08	1.28 min Method A	508.21	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.63 (d, 2H, J=8.0Hz), 7.43-7.36 (m, 4H), 6.27 (s, br, 1H), 5.39 (s, br, 1H), 4.59 (d, 1H, J_{ab}=16Hz), 4.36 (d, 1H, J_{ab}=16Hz), 2.83 (m, 1H), 2.41 (m, 2H), 2.18 (m, 1H), 1.95 (m, 1H), 1.85 (m, 1H), 1.76-1.52 (m, 5H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)

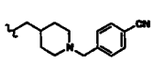
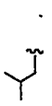
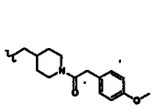
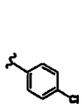
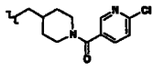
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
268				8	white foam	508.08	1.26 min Method A	508.18	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.65 (d, 2H, J=8.0Hz), 7.45 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.27 (s, br, 1H), 5.39 (s, br, 1H), 4.59 (d, 1H, J_{ab}=16Hz), 4.36 (d, 1H, J_{ab}=16Hz), 3.77 (m, 1H), 3.47 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 2.80 (m, 4H), 1.95 (m, 1H), 1.77-1.50 (m, 6H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)
269				8	white foam	437.99	1.28 min Method A	438.16	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.71 (d, 2H, J=8.0Hz), 7.66 (d, 2H, J=8.0Hz), 7.43 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.35 (s, br, 1H), 5.87 (s, br, 1H), 4.76 (d, 1H, J_{ab}=16Hz), 4.30 (d, 1H, J_{ab}=16Hz), 3.54 (s, 5H), 3.25 (t, 1H, J=6.0Hz), 1.94 (m, 1H), 1.60 (m, 2H), 1.18 (s, br, NH), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)
270				8	white solid	468.02	1.28 min Method A	468.16	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.67 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7. 33 (d, 2H, J=8.0Hz), 6.35 (s, br, 1H), 5.85 (s, br, 1H), 4.24-4.12 (m, 4H), 3.67 (s, 2H), 3.24 (t, 1H, J=6.0Hz), 3.06 (t, 2H, J=6.0Hz), 2.60 (s, br, NH), 1.95 (m, 1H), 1.68-1.52 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)

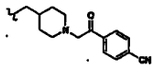
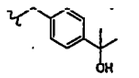
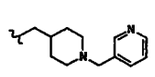
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
271				8	clear glass	482.05	1.31 min Method A	482.18	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.79 (d, 2H, J=8.0Hz), 7.69 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.33 (d, 2H, J=8.0Hz), 6.35 (s, br, 1H), 5.85 (s, br, 1H), 4.60 (d, 1H, J_{ab}=16Hz), 4.43 (d, 1H, J_{ab}=16Hz), 3.67 (s, 2H), 3.61 (t, 2H, J=6.0Hz), 3.35 (s, 3H), 3.29-3.24 (m, 3H), 1.94 (m, 1H), 1.62 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)
272				9	white solid	523.1	1.30 min Method A	523.40	^{1}H NMR, 400Hz, ($CDCl_3$) δ 8.02 (d, 2H, J=8.0Hz), 7.71 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 7.28 (d, 2H, J=8.0Hz), 6.23 (s, br, 1H), 5.51 (s, br, 1H), 4.46 (s, 2H), 4.70 (d, 1H, J_{ab}=16Hz), 4.33 (d, 1H, J_{ab}=16Hz), 3.25 (t, 1H, J=6.0Hz), 2.69 (s, 3H), 2.63 (s, 2H), 2.20 (s, 6H), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)
273				16	white solid	436.96	1.43 min Method B	437.13	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.87 (d, 2H, *J* = 8.4), 7.67 (dd, 2H, *J* = 1.8, 8.7), 7.42-7.46 (m, 4H), 6.21 (br s, 1H), 5.28 (br s, 1H), 4.64 (d, 1H, *J* = 15.9), 4.45 (d, 1H, *J* = 15.9), 4.31 (t, 1H, *J* = 6.6), 2.58 (s, 3H), 1.73-1.80 (m, 1H), 1.25-1.35 (m, 1H), 1.05-1.14 (m, 1H), 0.74 (d, 3H, *J* = 6.5), 0.65 (d, 3H, *J* = 6.6)

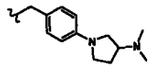
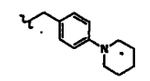
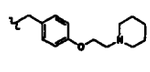
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
274				17	yellow foam	549.14	1.38 min Method A	549.16	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.63 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.23 (d, 2H, J=8.0Hz), 6.25 (s, br, 1H), 5.35 (s, br, 1H), 4.75 (d, 1H, J_{ab}=16Hz), 4.38 (d, 1H, J_{ab}=16Hz), 3.25 (t, 1H, J=6.0Hz), 2.65 (t, 2H, J=6.0Hz), 2.56-2.44 (m, 6H), 1.95 (m, 1H), 1.68-1.45 (m, 8H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)
275				17	clear glass	564.15	1.21 min Method A	564.32	^{1}H NMR, 400Hz, ($CDCl_3$) δ 9.30 (s, 1H, NH), 8.02 (d, 2H, J=8.0Hz), 7.61 (d, 2H, J=8.0Hz), 7.36 (d, 2H, J=8.0Hz), 7.23 (d, 2H, J=8.0Hz), 6.25 (s, br, 1H), 5.33 (s, br, 1H), 4.72 (d, 1H, J_{ab}=16Hz), 4.48 (d, 1H, J_{ab}=16Hz), 3.25 (t, 1H, J=6.0Hz), 2.65-2.38 (m, 12H), 2.28 (s, 2H), 1.95 (m, 1H), 1.59 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)
276				17	tan foam	509.07	1.33 min Method A	509.17	^{1}H NMR, 400Hz, ($CDCl_3$) δ 9.31 (s, 1H, NH), 8.02 (d, 2H, J=8.0Hz), 7.63 (d, 2H, J=8.0Hz), 7.36 (d, 2H, J=8.0Hz), 7.23 (d, 2H, J=8.0Hz), 6.25 (s, br, 1H), 5.34 (s, br, 1H), 4.71 (d, 1H, J_{ab}=16Hz), 4.48 (d, 1H, J_{ab}=16Hz), 3.25 (t, 1H, J=6.0Hz), 2.66 (t, 2H, J=8.0Hz), 2.56 (t, 2H, J=8.0Hz), 2.38 (s, 6H), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)

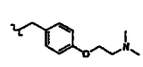
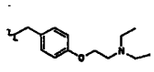
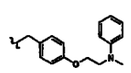
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
277				9	tan foam	515.04	1.47 min Method A	515.13	^{1}H NMR, 400Hz, ($CDCl_3$) δ 8.95 (s, br, NH), 8.67 (d, 1H, J=8.0Hz), 8.17 (d, 1H, J=8.0Hz), 8.02 (d, 2H, J=8.0Hz), 7.77 (d, 2H, J=8.0Hz), 7.57 (m, 4H), 7.38 (d, 2H, J=8.0Hz), 6.27 (s, br, 1H), 5.39 (s, br, 1H), 4.72 (d, 1H, J_{ab}=16Hz), 4.30 (d, 1H, J_{ab}=16Hz), 3.25 (t, 1H, J=6.0Hz), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
278				7	white solid	507.06	2.44 min Method C	509.20	^{1}H NMR ($CDCl_3$, 500MHz) δ 8.66 (br s, 2H), 7.80 (d, 1H, *J* = 8.6), 7.73 (d, 2H, *J* = 8.5), 7.51 (d, 2H, *J* = 7.6), 7.41 (br s, 1H), 6.64 (br s, 1H), 5.35 (br s, 1H), 4.70 (br s, 1H), 4.10 (br s, 1H), 3.71 (br s, 1H), 3.33 (br s, 1H), 3.02 (dd, 2H, *J* = 4.8, 16), 2.70-2.85 (br s, 1H), 1.50-2.09 (m, 5H), 1.18-1.33 (m, 4H), 0.73 (d, 3H, *J* = 6.7), 0.68 (d, 3H, *J* = 6.5).
279				7	white solid	549.14	2.76 min Method C	549.07	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.74 (dd, 2H, *J* = 1.7, 6.7), 7.51 (dd, 2H, *J* = 2.2, 6.9), 7.34 (d, 2H, *J* = 8.0), 6.70 (br s, 1H), 6.60 (br s, 1H), 5.30 (br s, 1H), 4.13 (dd, 1H, *J* = 5.5, 10), 3.35 (dd, 1H, *J* = 11, 14), 3.00 (s, 6H), 2.85 (s, 2H), 1.80-2.00 (m, 3H), 1.50-1.70 (m, 1H), 1.10-1.30 (m, 4H), 0.80-0.90 (m, 1H), 0.745 (d, 3H, *J* = 6.7), 0.67 (d, 3H, *J* = 6.5).

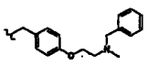
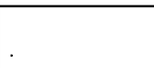
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
280				7	white solid	574.07	3.03 Method C	574.03	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.73 (d, 2H, J = 8.2), 7.65 (d, 2H, J = 7.9), 7.51 (d, 2H, J = 8.9), 7.48 (d, 2H, J = 7.6), 6.65 (br s, 1H), 5.45 (br s, 1H), 4.71 (br s, 1H), 4.13 (br s, 1H), 3.65 (br s, 1H), 3.30 (br s, 1H), 2.97 (d, 2H J = 12), 2.65-2.86 (m, 1H), 1.45-2.07 (m, 6H), 0.98-1.85 (m, 3H), 0.73(br, s, 3H), 0.67(br, s, 3H)
281				7	white solid	470.04	2.78 min Method C	470.03	H NMR ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, J = 8.5), 7.50 (d, 2H, J = 8.6), 6.78-6.90 (m, 1H), 6.55-6.65 (m, 1H), 6.23 (dd, 1H, J = 1.5, 15), 5.33-5.60 (m, 1H), 4.50-4.75 (m, 1H), 4.09-4.20 (m, 1H), 3.90-4.05 (m, 1H), 2.80-3.25 (m, 3H), 2.40-2.75 (m, 1H), 1.50-2.00 (m, 8H), 1.00-1.40 (m, 3H), 0.73 (br, s, 3H), 0.67(br, s, 3H)
282				7	white solid	506.07	2.86 min Method C	508.03	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.73 (d, 2H, J = 8.5), 7.51 (d, 2H, J = 8.5), 7.38 (br s, 4H), 6.65 (br s, 1H), 5.35 (br s, 1H), 4.71 (br s, 1H), 4.14 (br s, 1H), 3.76 (br s, 1H, 3.30 (br s, 1H), 2.60-3.05 (m, 3H), 0.99-2.05 (m, 10H), 0.73 (d, 3H, J = 7.8), 0.67 (d, 3H, J = 7.8)

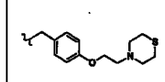
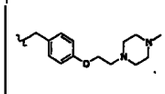
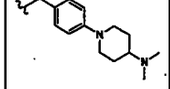
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Rst. Time/ Method	M+H$^+$	NMR Data
283				7	white solid	517.09	1.34 min Method A	517.19	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, *J* = 8.5), 7.50-7.65 (m, 2H), 7.50 (d, 2E, *J* = 7.0), 7.35-7.45 (m, 2H), 6.67 (s, 1H), 5.32 (s, 1H), 4.14 (dd, 1H, *J* = 5.0, 9.0), 3.52 (br s, 1H), 3.28 (t, 1H, *J* = 14), 2.97 (dd, 1H, *J* = 3.5, 14), 2.82 (br s, 1H), 1.00-2.00 (m, 10H), 0.71 (d, 3H, *J* = 6.5), 0.66 (d, 3H, *J* = 6.5).
284				7	white solid	550.12	2.87 min Method C	550.06	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, *J* = 8.6), 7.50 (d, 2H, *J* = 8.5), 7.13 (d, 2H, *J* = 8.5), 6.85 (br s, 2H), 6.63 (d, 1H, *J* = 33), 5.41 (br s, 1H), 4.62 (t, 1H, *J* = 14), 4.10-4.17 (m, 1H), 3.75-3.90 (m, 4H), 3.65 (s, 3H), 3.14-3.30 (m, 1H), 2.80-2.95 (m, 2H), 2.43-2.60 (m, 1H), 1.45-2.00 (m, 4H), 1.15-1.30 (m, 2H), 0.71 (dd, 3H, *J* = 7.6, 8.4), 0.65 (dd, 3H, *J* = 6.0, 8.0).
285				7	white solid	541.50	2.76 min Method C	540.98	^{1}H NMR ($CDCl_3$, 500MHz) δ 8.43 (s, 1H), 7.73 (d, 2H, *J* = 8.5), 7.70 (d, 1H, *J* = 2.4, 8.4), 7.51 (d, 2H, *J* = 8.6), 7.87 (d, 1H, *J* = 8.2), 6.63 (br s, 1H), 5.35 (br s, 1H), 4.68 (br s, 1H), 4.15 (dd, 1H, *J* = 4.9, 9.8), 3.71 (br s, 1H), 3.31 (br s, 1H), 3.00 (dd, 2H, *J* = 4.8, 14), 2.65-2.86 (m, 1H), 1.77-2.07 (m, 3H), 1.6-1.76 (m, 1H), 1.00-1.86 (m, 3H), 0.85-0.93 (m, 1H), 0.73 (d, 3H, *J* = 6.7), 0.67 (d, 3H, *J* = 6.7).

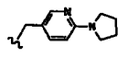
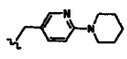
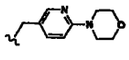
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
286				7	white solid	545.11	1.36 min Method A	545.16	^{1}H NMR ($CDCl_3$, 500MHz) δ 8.11 (d, 2H, J = 8.6), 7.75 (d, 2H, J = 8.6), 7.73 (d, 2H, J = 8.9), 7.50 (d, 2H, J = 8.9), 6.65 (br s, 1H), 5.38 (br s, 1H), 4.14 (dd, 1H, J = 5.5, 9.5), 3.80 (br s, 1H), 3.27 (dd, 1H, J = 10, 14), 2.97 (dd, 2H, J = 4.6, 14), 1.17-2.00 (m, 11H), 0.75-0.81 (m, 1H), 0.73 (d, 3H, J = 6.4), 0.67 (d, 3H, J = 6.7)
287				12	white solid	453.01	1.81 min Method A	453.16	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.61 (d, 2H, J = 8.7), 7.40 (d, 2H, J = 8.7), 7.37 (d, 2H, J = 8.4), 7.26 (d, 2H, J = 8.4), 6.28 (br s, 1H), 5.25 (br s, 1H), 4.49 (d, 1H, J = 15.9), 4.41 (d, 1H, J = 15.9), 4.33 (t, 1H, J = 6.6), 1.73-1.80 (m, 1H), 1.55 (s, 6H), 1.28-1.35 (m, 1H), 1.20-1.25 (m, 1H), 0.77 (d, 3H, J = 6.5), 0.66 (d, 3H, J = 6.6)
288				7	white solid	493.07	1.25 min Method A	493.23	^{1}H NMR ($CDCl_3$, 500MHz) δ 8.51 (s, 2H), 7.73 (d, 2H, J = 8.5), 7.50 (d, 2H, J = 8.5), 6.67 (s, 1H), 5.83 (s, 1H), 4.15 (dd, 1H, J = 5.2, 8.9), 3.50 (br s, 2H), 3.25 (dd, 1H, J = 8.5, 14), 2.75-3.05 (m, 3H), 1.60-2.10 (m, 6H), 1.10-1.40 (m, 4H), 0.75-0.85 (m, 1H), 0.72 (d, 3H, J = 6.4), 0.67 (d, 3H, J = 6.7)

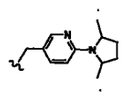
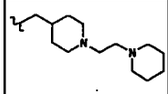
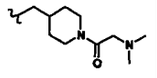
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
289				2	yellow solid	493.07	0.93min Method B	493.2	^{1}H NMR ($CDCl_3$) δ 7.67 (d, 2H, J=7.0Hz), 7.44 (d, 2H, J=7.0Hz), 7.19 (d, 2H, J=8.0Hz), 6.46 (d, 2H, J=8.0Hz), 6.21 (s, br, 1H), 5.17 (s, br, 1H), 4.31 (dd, 2H, J=50Hz, 15Hz), 4.15-4.22 (m, 1H), 3.84-3.87 (m, 4H), 3.91-3.99 (m, 1H), 3.51-3.54 (m, 3H), 3.22-3.26 (m, 1H), 2.75 (s, 3H), 2.72 (s, 3H), 2.23-2.36 (m, 2H), 1.91-1.98 (m, 1H), 1.32-1.40 (m, 1H), 0.81-1.04 (m, 2H), 0.73 (t, 3H, 7.2Hz)
290				2	tan solid	464.03	1.16min Method B	464.2	^{1}H NMR ($CDCl_3$) δ 7.62 (d, 2H, J=8.8Hz), 7.40 (d, 2H, J=8.0Hz), 7.11-7.20 (m, 2H), 6.79-6.88 (m, 2H), 6.20 (s, br, 1H), 5.13 (s, br, 1H), 4.30 (dd, 2H, J=50Hz, 15Hz), 4.13-4.21 (m, 1H), 3.10-3.19 (m, 4H), 1.92-1.95 (m, 1H), 1.39-1.90 (m, 8H), 1.22-1.26 (m, 1H), 0.97-1.05 (m, 2H), 0.73 (t, 3H, J=8.0Hz)
291				11	orange solid	522.11	1.52 min Method E	522.1	^{1}H NMR (DMSO) δ 7.78 (d, 2H, J =8.4Hz), 7.58 (d, 2H, J =8.8Hz), 7.47 (s, br, 1H), 7.27 (d, 2H, J =8.4Hz), 7.00 (s br, 1H), 6.85 (d, 2H, J =8.8Hz), 4.63 (dd, 2H, J=16Hz, 38Hz), 4.34 (m, 1H), 4.03 (s, 2H), 2.63 (m, 2H), 2.42 (m, 3H), 1.39 (m, 10H), 0.80 (d, 3H, J=6.0Hz), 0.50 (d, 3H, J=6.0Hz)

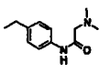
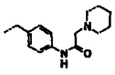
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
292				11	white solid	481.18	1.46 min Method E	482.06	^{1}H NMR (DMSO) δ 7.79 (d, 2H, J =8.8Hz), 7.60 (d, 2H, J =8.8Hz), 7.49 (s, br, 1H), 7.35 (d, 2H, J =8.4Hz), 7.01(s br, 1H), 6.94 (d, 2H, J =8.8Hz), 4.68 (dd, 2H, J=16Hz, 53Hz), 4.35 (m, 1H), 4.28 (t, 2H, J=4.8Hz), 3.34 (m, 2H), 2.86 (s, 6H), 1.33 (m, 3H), 0.80 (d, 3H, J=6.0Hz), 0.50 (d, 3H, J=6.0Hz)
293				11	white residue	509.21	1.52 min Method E	M+Na 532.03	^{1}H NMR (DMSO) δ 7.79 (d, 2H, J =8.4Hz), 7.60 (d, 2H, J=8.4Hz), 7.48 (s, br, 1H), 7.35 (d, 2H, J =8.8Hz), 7.01(s br, 1H), 6.94 (d, 2H, J =8.8Hz), 4.68 (dd, 2H, J=17Hz, 54Hz), 4.35 (m, 1H), 4.28 (t, 2H, J=4.8Hz), 3.51 (m, 3H), 3.21 (m, 3H), 1.29 (m, 9H), 0.80 (d, 3H, J=6.0Hz), 0.50 (d, 3H, J=6.0Hz)
294				11	light brown solid	544.12	1.78 min Method E	544.13	^{1}H NMR (DMSO) δ 7.78(d, 2H, J =8.9Hz), 7.57 (d, 2H, J=8.0Hz), 7.45 (s, br, 1H), 7.27 (d, 2H, J =8.0Hz), 7.17 (t, 2H, J=8.9Hz) 7.00 (s br, 1H), 6.84 (d, 2H, J =8.0Hz), 6.75 (d, 2H, J=8.0Hz), 6.62 (t, 1H, J=8.0Hz), 4.65 (dd, 2H, J=17Hz, 41Hz), 4.34 (m, 1H), 4.10 (t, 2H, J=5.5Hz), 3.71 (t, 2H, J=7.9Hz), 2.96 (m, 3H), 1.32 (m, 3H), 0.79 (d, 3H, J=6.0Hz), 0.49 (d, 3H, J=6.0Hz)

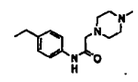
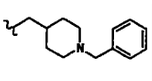
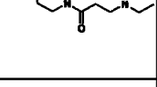
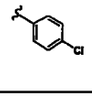
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
295				11	white powder	558.14	1.62 min Method E	558.10	^{1}H NMR (DMSO) δ 7.80 (d, 2H, J =8.6Hz), 7.60 (d, 2H, J=8.6Hz), 7.54 (m, 2H), 7.49 (m, 4H), 7.34 (d, 2H, J=8.6Hz) 7.01 (s br, 1H), 6.93 (d, 2H, J=8.6Hz), 4.68 (dd, 2H, J=17.0Hz, 54Hz), 4.47 (m, 1H), 4.36 (m, 4Hz), 3.50 (m, 2H), 2.80 (s, 3H), 1.34 (m, 3H), 0.80 (d, 3H, J=6.0Hz), 0.51 (d, 3H, J=6.0Hz)
296				11	white powder	508.08	1.49 min Method E	508.07	^{1}H NMR (DMSO) δ 7.79(d, 2H, J =8.6Hz), 7.61 (d, 2H, J=8.6Hz), 7.49 (s, br, 1H), 7.35 (d, 2H, J =8.6Hz), 7.00 (s br, 1H), 6.94 (d, 2H, J=8.6Hz), 4.68 (dd, 2H, J =17.0Hz, 53Hz), 4.35 (m, 1H), 4.27 (m, 2H), 3.59 (m, 4H), 3.13 (m, 2H), 2.03 (m, 2H), 1.89 (m, 2H), 1.34 (m, 3H), 0.80 (d, 3H, J=6.0Hz), 0.52 (d, 3H, J=6.0Hz)
297				11	off white solid	524.08	1.46 min Method E	524.09	^{1}H NMR (DMSO) δ 7.78(d, 2H, J =8.9Hz), 7.57 (d, 2H, J=8.0Hz), 7.45 (s, br, 1H), 7.27 (d, 2H, J =8.0Hz), 7.17 (t, 2H, J=8.9Hz) 7.00 (s br, 1H), 5.84 (d, 2H, J =8.0Hz), 6.75 (d, 2H, J=8.0Hz), 6.62 (t, 1H, J=8.0Hz), 4.65 (dd, 2H, J=17Hz, 41Hz), 4.34 (m, 1H), 4.10 (t, 2H, J=5.5Hz), 3.71 (t, 2H, J=7.9Hz), 2.96 (m, 3H), 1.32 (m, 2H), 0.79 (d, 3H, J=6.0Hz), 0.49 (d, 3H, J=6.0Hz)

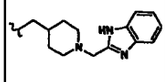
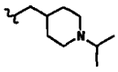
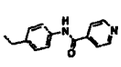
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
298				11	white solid	540.15	1.52 min Method E	540.06	^{1}H NMR (DMSO) δ 7.80(d, 2H, J =8.8Hz), 7.60 (d, 2H, J=8.0Hz), 7.48 (s br, 1H), 7.35 (d, 2H, J =8.8Hz), 7.01 (s br, 1H) 6.95 (d, 2H, J=8.8Hz), 4.68(dd, 2H, J=16.4Hz, 55Hz), 4.34 (m, 3H), 3.79 (m, 2H), 3.58 (m, 2H), 3.27 (m, 2H), 3.02 (m, 2H), 2.89 (m, 2H), 1.34 (m, 3H), 0.80 (d, 3H, J=6.0Hz), 0.52 (d, 3H, J=6.0Hz)
299				11	light orange solid	537.13	1.43 min Method E	537.13	^{1}H NMR (DMSO) δ 7.79(d, 2H, J =8.8Hz), 7.59 (d, 2H, J=8.0Hz), 7.48 (s br, 1H), 7.31 (d, 2H, J =8.8Hz), 7.00 (s br, 1H) 6.88 (d, 2H, J=8.8Hz), 4.66 (dd, 2H, J=16.4Hz, 49Hz), 4.35 (m, 1H), 4.11 (m, 2H), 3.18 (m, 9H), 2.78 (m, 3H), 2.63 (m, 1H), 1.34 (m, 3H), 0.80 (d, 3H, J=6.0Hz), 0.51 (d, 3H, J=6.0Hz)
300				2	tan solid	507.10	1.19min Method B	507.2	^{1}H NMR ($CDCl_3$) δ 7.63 (d, 2H, J=8.0Hz), 7.41 (d, 2H, J=8.0Hz), 7.13-7.24 (m, 2H), 6.74-6.80 (m, 2H), 6.23 (s, br, 1H), 5.13 (s, br, 1H), 4.37 (dd, 2H, J=50Hz, 15Hz), 4.11-4.19 (m, 1H), 3.77-3.81 (m, 1H), 3.44 (s, 6H), 3.06-3.13 (m, 8H), 1.93-1.96 (m, 1H), 1.25-1.29 (m, 1H), 0.95-1.09 (m, 2H), 0.71 (t, 3H, J=8.0Hz)

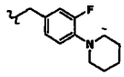
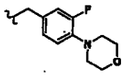
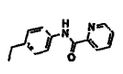
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
301				10	yellow foam	465.02	1.22 Method B	465.25	^{1}H NMR ($CDCl_3$) TFA salt: δ 8.07 (s, 1H), 7.91 (d, 1H, J= 9.6Hz), 7.74 (d, 2H, J=6.8Hz), 7.52(d, 2H, J=6.8Hz), 6.64 (d, 1H, J=9.6Hz), 6.36 (s, 1H), 5.77 (s, 1H), 4.52 (d, 1H, J=16.0Hz), 4.28 (dd, 1H, J=5.6Hz, 6.0Hz), 4.21 (d, 1H, J=16.0Hz), 3.62 (m, 4H), 2.13 (m, 4H), 1.84 (m, 1H), 1.32 (m, 1H), 0.96 (m, 1H), 0.79 (d, 3H, J=6.8Hz), 0.71 (d, 3H, J=6.8Hz)
302				10	yellow foam	479.05	1.28 Method B	479.06	^{1}H NMR ($CDCl_3$) TFA salt: δ 8.01 (s, 1H), 7.95 (d, 1H, J= 9.6Hz), 7.75 (d, 2H, J=8.0Hz), 7.50 (d, 2H, J=8.4Hz), 6.88 (d, 1H, J=9.6Hz), 6.43 (s, 1H), 6.04 (s, 1H), 4.53 (d, 1H, J=16.0Hz), 4.28 (dd, 1H, J=5.6Hz, 6.0Hz), 4.20 (d, 1H, J=16.0Hz), 3.65 (m, 4H), 1.82(m, 1H), 1.74 (m, 6H), 1.31 (m, 1H), 0.95 (m, 1H), 0.78 (d, 3H, J=6.4Hz), 0.71 (d, 3H, J=6.4Hz).
303				10	white solid	481.02	1.16 Method B	481.05	^{1}H NMR ($CDCl_3$) TFA salt: δ 8.25 (s, 1H), 8.06 (d, 1H, J= 9.6Hz), 7.74(d, 2H, J=8.0Hz), 7.54 (d, 2H, J=8.0Hz), 6.91(d, 1H, J=9.6Hz), 6.55 (s, 1H), 6.28 (s, 1H), 4.61 (d, 1H, J=16.0Hz), 4.28 (dd, 1H, J=5.2Hz, 5.2Hz), 4.21 (d, 1H, J=16.0Hz), 3.87 (m, 4H), 3.67 (m, 4H), 1.84 (m, 1H), 1.27 (m, 1H), 0.93 (m, 1H), 0.76 (d, 3H, J=6.4Hz), 0.73 (d, 3H, J=6.4Hz.)

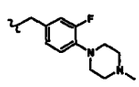
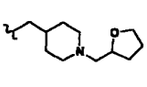
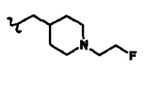
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
304				10	brown solid	493.07	1.357 Method B	493.04	^{1}H NMR ($CDCl_3$) TFA salt δ 8.04 (s, 1H), 7.93 (d, 1H, J= 9.2Hz), 7.73 (d, 2H, J=8.0Hz), 7.50 (d, 2H, J=8.0Hz), 6.69 (d, 1H, J=9.2Hz), 6.38 (s, 1H), 5.98 (s, 1H), 4.50 (d, 1H, J=16.0Hz), 4.30 (dd, 1H, J=5.6Hz, 6.0Hz), 4.22 (d, 1H, J=16.0Hz), 4.20 (m, 2H), 3.87 (m, 4H), 2.24 (m, 2H), 1.90 (m, 2H), 1.84 (m, 1H), 1.36 (d, 3H, J=2.0Hz), 1.34 (d, 3H, J=2.0Hz), 1.32 (m, 1H), 0.98 (m, 1H), 0.79 (d, 3H, J=6.4Hz), 0.72 (d, 3H, J=6.4Hz).
305				7	white solid	513	1.03 min Method A	513.36	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, *J* = 8.5), 7.50 (d, 2H, *J* = 7.0), 6.65 (s, 1H), 6.35 (s, 1H), 4.14 (dd, 1H, *J* = 5.5, 9.0), 3.25 (dd, 1H, *J* = 10, 14), 1.35-2.95 (m, 24H), 1.15-1.30 (m, 3H), 0.72 (d, 3H, *J* = 6.5), 0.67 (d, 3H, *J* = 6.7).
306				7	white solid	487	1.43 min Method A	487.019	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.72 (d, 2H, *J* = 8.4), 7.51 (d, 2H, *J* = 8.7), 6.67 (d, 1H, *J* = 24.3), 5.40 (d, 1H, *J* = 12, 6), 4.54 (br s, 1H), 3.90-4.20 (m, 4H), 3.40-3.55 (m, 2H), 3.05-3.35 (m, 2H), 2.85-3.05 (m, 2H), 2.40-2.60 (m, 1H), 2.35 (d, 6H, *J* = 8.1), 0.60-1.95 (m, 11H).

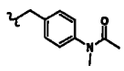
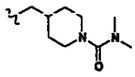
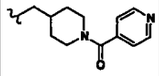
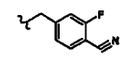
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
307				1-Method A	clear oil	444.03	1.28 min Method B	444.04	^{1}H NMR ($CDCl_3$) δ 7.72 (d, J=6.8Hz, 2H), 7.52 (d, J= 6.8Hz, 2H), 6.75 (s, br, 1H), 5.79 (s, br, 1H), 4.14 (dd, J=9.6Hz, 4.8Hz, 1H), 3.23 (dd, J=14.4Hz, 10.0Hz , 1H), 3.12 (m, 1H), 2.92 (dd, J=14.4Hz, 4.8Hz, 1H), 2.77 (m, 6H), 2.09 (m, 2H), 1.83 (m, 1H), 1.71 (m, 1H), 0.75-1.52 (m, 8H), 0.73 (d, J=6.8Hz, 3H), 0.67 (d, J=6.8Hz, 3H).
308				23	tan foam	495.04	1.31 min Method A	495.14	^{1}H NMR, 400Hz, ($CDCl_3$) δ 8.85 (s, 1H, NH), 8.02 (d, 2H, J=8.0Hz), 7.75 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.29 (d, 2H, J=8.0Hz), 6.23 (s, br, 1H), 5.39 (s, br, 1H), 4.62 (m, 4H), 3.25 (t, 1H, J=6.0Hz), 2.95 (s, 6H), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)
309				23	tan foam	535.11	1.34 min Method A	535.29	^{1}H NMR, 400Hz, ($CDCl_3$) δ 8.85 (s, 1H, NH), 8.02 (d, 2H, J=8.0Hz), 7.78 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.30 (d, 2H, J=8.0Hz), 5.25 (s, br, 1H), 5.36 (s, br, 1H), 4.62 (m, 4H), 3.25 (t, 1H, J=6.0Hz), 2.42 (m, 4H), 1.95 (m, 1H), 1.68-1.38 (m, 8H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)

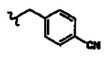
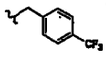
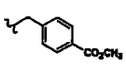
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
310				23	tan foam	550.12	1.24 min Method A	550.25	^{1}H NMR, 400Hz, ($CDCl_3$) δ 8.83 (s, 1H, NH), 8.02 (d, 2H, J=8.0Hz), 7.78 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.30 (d, 2H, J=8.0Hz), 6.20 (s, br, 1H), 5.39 (s, br, 1H), 4.71 (d, 1H, J_{ab}=16Hz), 4.48 (d, 1H, J_{ab}=16Hz), 4.26 (s, 2H), 3.25 (m, 1H), 2.67 (m, 8H), 2.40 (s, 3H), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)
311				7	white solid	492.09	2.30 min Method C	492.16	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.73 (d, 2H, J = 8.4), 7.48 (d, 2H, J = 8.4), 7.15-7.38 (m, 5H), 6.67 (s, 1H), 5.37 (s, 1H), 4.14 (dd, 1H, J = 5.4, 9.0), 3.47 (s, 2H), 3.24 (dd, 1H, J = 10, 14), 2.75-3.05 (m, 3H), 1.45-2.05 (m, 10H), 0.75-0.90 (m, 1H), 0.71 (d, 3H, J = 6.6), 0.65 (d, 3H, J = 6.6)
312				7	white solid	529.15	2.27 min Method C	529.16	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.73 (d, 2H, J = 8.7), 7.50 (d, 2H, J = 8.7), 6.65 (d, 1H, J = 5.1), 4.55 (br s, 1H), 4.05-4.30 (m, 1), 3.57-3.95 (m, 1H), 3.10-3.40 (m, 1H), 2.40-3.00 (m, 12H), 1.70-2.00 (m, 3H), 0.90-1.30 (m, 10H), 0.60-0.75 (m, 6H)
313				7	white solid	573.16	1.78 min Method A	573.18	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.72 (d, 2H, J = 7.8), 7.50 (d, 2H, J = 8.7), 6.65 (d, 1H, J = 14), 5.35 (s, 1H), 4.45-4.65 (m, 1H), 3.67-4.25 (m, 3H), 3.35-3.60 (m, 3H), 3.10-3.25 (m, 1H), 2.80-3.10 (m, 2H), 2.90 (s, 3H), 0.95-2.00 (m, 7H), 1.46 (s, 9H), 0.73 (br s, 3H), 0.67 (br, s, 3H)

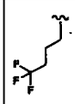
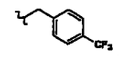
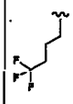
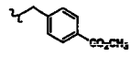
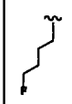
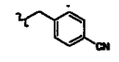
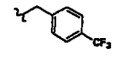
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
314				7	white solid	532.11	1.47 min Method A	532.19	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.74 (d, 2H, J = 8.8), 7.50 (d, 3H, 8.8), 7.17-7.27 (m, 3H), 6.63 (s, 1H), 5.60 (s, 1H), 4.13 (dd, 1H, J = 5.5, 9.2), 3.80 (s, 2H), 3.28 (dd, 1H, J = 9.5, 15), 2.80-305 (m, 3H), 1.50-2.25 (m, 6H), 1.15-1.45 (m, 5H), 0.72 (d, 3H, J = 6.6), 0.66 (d, 3H, J = 6.6).
315				7	white solid	444.04	2.11 min Method C	444.13	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.73 (d, 2H, J = 8.7), 7.48 (d, 2H, J = 8.4), 6.69 (br s, 1H), 5.45 (br s, 1H), 4.14 (dd, 1H, J = 10, 15), 3.15-3.35 (m, 1H), 2.90-3.05 (m, 1H), 2.75-2.90 (m, 1H), 2.60-2.75 (m, 1H), 1.50-2.25 (m, 6H), 1.05-1.40 (m, 3H), 1.00 (d, 6H, J = 11), 0.75-0.90 (m, 1H), 0.71 (d, 3H, J = 10), 0.66 (d, 3H, J = 10).
316				9	yellow foam	515.04	1.50 min Method A	515.08	^{1}H NMR, 400Hz, ($CDCl_3$) δ 9.97 (s, 1H, NH), 8.82 (d, 2H, J=4.0Hz), 8.02 (d, 2H, J=8.0Hz), 7.76 (d, 2H, J=8.0Hz), 7.73 (d, 2H, J=4.0Hz), 7.46 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.27 (s, br, 1H), 5.39 (s, br, 1H), 4.72 (d, 1H, J_{ab}=16Hz), 4.30 (d, 1H, J_{ab}=16Hz), 4.26 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)

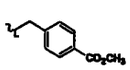
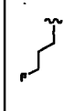
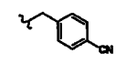
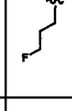
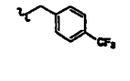
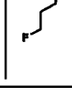
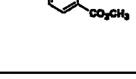
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
317				2	dark wax	482.02	1.42min Method B	482.01	^{1}H NMR ($CDCl_3$) δ 7.63 (d, 2H, J=8.2Hz), 7.42 (d, 2H, J=8.2Hz), 6.71-7.08 (m, 3H), 6.20 (s, br, 1H), 5.15 (s, br, 1H), 4.27 (dd, 2H, J=50Hz, 15Hz), 4.23- (t, 1H, J=7.0Hz), 2.99-3.10 (m, 4H), 1.92-1.95 (m, 1H), 1.53-1.59 (m, 2H), 1.41-1.90 (m, 4H), 1.21-1.24 (m, 1H), 0.98-1.08 (m, 2H), 0.74 (t, 3H, J=8.0Hz)
318				2	dark solid	498.02	1.68min Method B	498.2	^{1}H NMR ($CDCl_3$) δ 7.66 (d, 2H, J=8.0Hz), 7.42 (d, 2H, J=8.0Hz), 6.84-7.02 (m, 3H), 6.20 (s, br, 1H), 5.22 (s, br, 1H), 4.34 (dd, 2H, J=50Hz, 15Hz), 4.19-4.25 (m, 1H), 3.84-3.86 (m, 4H), 3.15-3.17 (m, 1H), 3.03-3.06 (m, 4H), 1.31-1.77 (m, 2H) , 0.95 (d, 3H, J=7.0Hz), 0.83 (t, 3H, J=7.0Hz)
319				9	tan foam	515.04	1.77 min Method A	515.15	^{1}H NMR, 400Hz, ($CDCl_3$) δ 9.90 (s, 1H, NH), 8.51 (d, 1H, J=4.0Hz), 8.11 (d, 2H, J=8.0Hz), 8.01 (d, 2H, J=8.0Hz), 7.78 (m, 3H), 7.59 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.32 (t, 1H, J=4.0Hz), 6.27 (s, br, 1H), 5.38 (s, br, 1H), 4.71 (d, 1H, J_{ab}=16Hz), 4.31 (d, 1H, J_{ab}=16Hz), 3.25 (t, 1H, J=6.0Hz), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz)

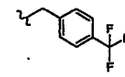
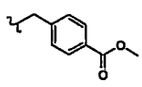
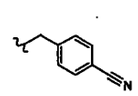
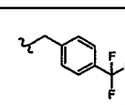
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
320				2	tan solid	511.06	1.12min Method B	511.2	^{1}H NMR (d_6DMSO) δ 7.78 (d, 2H, J=8.2Hz), 7.55 (d, 2H, J=8.2Hz), 7.02-7.14 (m, 3H), 6.80 (s, br, 1H), 4.82 (s, br, 1H), 3.58-4.63 (m, 2H), 4.32-4.38 (m, 1H), 3.42-3.56 (m, 4H), 3.16-3.21 (m, 1H), 2.84 (s, 3H), 2.49-2.51 (m, 4H), 1.85 (s, 3H), 1.76-1.82 (m, 1H) , 1.21-1.33 (m, 2H), 0.82 (d, 3H, J=7.0Hz), 0.56 (d, 3H, J=7.0Hz).
321				7	white solid	486.08	2.22 min Method C	486.12	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.73 (d, 2H, J = 8.5), 7.49 (d, 2H, J = 8.6), 6.67 (s, 1H), 5.35 (s, 1H), 4.15 (dd, 1H, J = 5.8, 9.2), 4.05 (br s, 1H), 3.85 (dd, 1H, J = 7.0, 15), 3.73 (dd, 1H, J = 7.3, 15), 3.20-3.29 (m, 1H, 2.95-3.05 (m, 3H), 2.43-2.51 (br s, 2H), 1.20-2.10 (m, 14H), 0.80-0.90 (m, 1H), 0.72 (d, 3H, J = 6.7), 0.67 (d, 3H, J = 6.7).
322				7	white solid	448.00	1.34 min Method A	448.24	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.73 (d, 2H, J = 8.7), 7.48 (d, 2H, J = 8.7), 5.67 (s, 1H), 5.43 (s, 1H), 4.60 (d, 1H, J = 5.1), 4.45 (d, 1H, J = 4.8), 4.15 (dd, 1H, J = 5.6, 9.0), 3.25 (dd, 1H, J = 10, 15), 2.85-3.05 (m, 3H), 2.70 (t, 1H, J = 5.0), 2.67 (t, 1H, J = 4.7), 1.50-2.15 (m, 6H), 1.10-1.40 (3H), 0.75-0.90 (m, 1H), 0.71 (d, 3H, J = 6.3), 0.66 (d, 3H, J = 6.7).

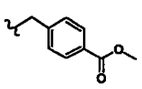
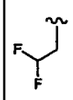
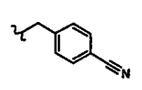
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
323				9	tan solid	465.14	1.52min Method B	466.1	^{1}H NMR ($CDCl_3$) δ 7.68 (d, 2H, J=8.4Hz), 7.46 (d, 2H, J=8.4Hz), 7.43 (d, 2H, J=8.0Hz), 7.10 (d, 2H, J=8.0Hz), 6.19 (s, br, 1H), 5.16 (s, br, 1H), 4.44 (dd, 2H, J=50Hz, 15Hz), 4.31-4.35 (m, 1H), 3.23(s, 3H), 1.85 (s, 3H), 1.76-1.82 (m, 1H), 1.14-1.35 (m, 2H), 0.78 (d, 3H, J=7.0Hz), 0.65 (d, 3H, J=7.0Hz)
324				7	white powder	473.04	1.54 mins Method A	473.17	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.73 (d, 2H, J = 8.1), 7.50 (d, 2H, J = 8.1), 6.67 (s, 1H), 5.85 (s, 1H), 4.15 (dd, 1H, J = 5.1, 9.2), 3.65 (d, 2H, J = 10), 3.26 (dd, 1H, J = 9.9, 15), 2.97 (dd, 1H, J = 4.4, 14), 2.60-2.85 (m, 3H), 2.80 (s, 6H), 1.75-1.95 (m, 3H), 1.05-1.30 (m, 3H), 0.72 (d, 3H, J = 6.2), 0.65 (d, 3H, J = 6.6)
325				7	white solid	507.06	1.41 min Method A	507.20	^{1}H NMR ($CDCl_3$, 300MHz), δ 8.64 (s, 2H), 7.72 (d, 3H, J = 8.4), 7.50 (d, 2H, J = 8.8), 7.35 (dd, 1H, J = 4.8, 7.7), 6.63 (s, 1H), 5.39 (br s, 1H), 4.69 (br s, 1H), 4.05-4.20 (m, 1H), 3.72 (br s, 1H), 3..25 (m, 1H), 2.50-3.200 (m, 3H), 1.50-2.10 (m, 5H), 1.00-1.40 (m, 3H), 0.72 (d, 3H, J = 6.6), 0.66 (d, 3H, J = 6.6)
326				1-Method A	white solid	423.90	1.55min Method B	424.11	^{1}H NMR ($CDCl_3$) δ 7.69-7.71 (m, 3H), 7.48-7.56 (m, 4H), 6.11 (s, br, 1H), 5.22 (s, br, 1H), 4.57 (dd, 2H, J=50Hz, 15Hz), 4.22-4.26 (m, 1H), 1.80-1.83 (m, 1H), 0.99-1.23 (m, 3H), 0.74 (t, 3H, J=8.0Hz)

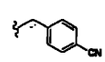
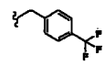
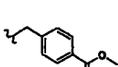
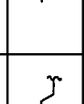
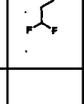
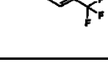
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
327				1-Method A	white solid	459.06	1.57 min Method G	$(M+Na)^+$ 481.9	^{1}H NMR (400 MHz, DMSO) δ 7.84 (d, 2H, J=8.8), 7.80 (d, 2H, J=8.6), 7.65 (d, 2H, J=8.7), 7.59 (d, 2H, J=8.3,), 7.47 (s, 1H), 7.25 (s, 1H). 4.79 (ABq, 2H, Δυ=5.1, J_{ab}=17.4), 4.43 (dd, 1H, J=8.5, 6.6), 2.05 (m, 2H), 1.87 (m, 1H), 1.40 (m, 1H).
328				1-Method A	white solid	502.06	1.83 min Method G	$(M+H)^+$ 502.9	^{1}H NMR (400 MHz, DMSO) δ 7.84 (d, 2H, J=8.8), 7.68 (d, 2H, J=8.0), 7.65-7.60 (m, 4H), 7.47 (s, 1H), 7.26 (s, 1H). 4.79 (s, 2H), 4.45 (dd, 1H, J=8.8, 6.1), 2.03 (m, 2H), 1.82 (m, 1H), 1.57 (m, 1H).
329				1-Method A	white solid	492.07	2.39 min Method G	$(M+H)^+$ 492.9	^{1}H NMR (400 MHz, DMSO) δ 7.91 (d, 2H, J=8.3), 7.85 (d, 2H, J=8.8), 7.64 (d, 2H, J=8.6), 7.54 (d, 2H, J=8.3), 7.43 (s, 1H), 7.23 (s, 1H). 4.79 (ABq, 2H, Δυ=3.4, J_{ab}=17.2), 4.42 (dd, 1H, J=8.5, 6.1), 3.85 (s, 3H), 2.02 (m, 2H), 1.80 (m, 1H), 1.57 (m, 1H).
330				1-Method A	white solid	473.08	1.60 Method G	$(M+Na)^+$ 495.9	^{1}H NMR (400 MHz, DMSO) δ 7.83 (d, 2H, J=8.8), 7.80 (d, 2H, J=8.3), 7.63 (d, 2H, J=8.6), 7.59 (d, 2H, J=8.3), 7.50 (s, 1H), 7.13 (s, 1H). 4.83 (ABq, 2H, Δυ=36.2, J_{ab}=17.6), 4.37 (dd, 1H, J=8.5, 6.3), 2.09 (m, 1H), 1.88 (m, 1H), 1.64 (m, 1H), 1.45 (m, 1H), 1.37 (m, 3H).

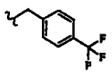
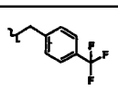
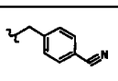
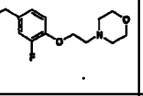
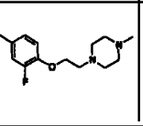
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
331				1-Method A	white solid	516.07	1.84 Method G	$(M+H)^+$ 516.9	^{1}H NMR (400 MHz, DMSO) δ 7.82 (d, 2H, J=8.8), 7.69-7.60 (m, 6H), 7.49 (s, 1H), 7.13 (s, 1H). 4.85 (ABq, 2H, Δυ=27.9, J_{ab}=17.1), 4.38 (dd, 1H, J=9.0, 5.9), 2.05 (m, 1H), 1.75 (m, 1H), 1.65 (m, 1H), 1.46 (m, 1H), 1.27 (m, 2H).
332				1-Method A	white solid	506.09	1.67 Method G	$(M+H)^+$ 506.9	^{1}H NMR (400 MHz, DMSO) δ 7.90 (d, 2H, J=8.6), 7.83 (d, 2H, J=8.8), 7.62 (d, 2H, J=8.8), 7.54 (d, 2H, J=8.3), 7.47 (s, 1H), 7.11 (s, 1H). 4.84 (ABq, 2H, Δυ=36.3, J_{ab}=17.4), 4.36 (dd, 1H, J=8.6, 6.1), 3.85 (s, 3H), 2.04 (m, 1H), 1.82 (m, 1H), 1.62 (m, 1H), 1.45 (m, 1H), 1.26 (m, 2H).
333				19	white solid	437.10	1.48 Method G	$(M+Na)^+$ 459.9	^{1}H NMR (400 MHz, DMSO) δ 7.82 (d, 2H, J=8.8), 7.79 (d, 2H, J=8.5), 7.63 (d, 2H, J=8.8), 7.58 (d, 2H, J=8.3), 7.52 (s, 1H), 7.09 (s, 1H). 4.82 (ABq, 2H, Δυ=37.2, J_{ab}=17.6), 4.34 (dd, 1H, J=8.0, 6.6), 4.25 (dt, 2H, J_d=47.2, J_t=5.7), 1.58 (m, 1H), 1.49-1.12 (m, 5H).
334				19	white solid	480.09	1.76 Method G	$(M+Na)^+$ 502.9	^{1}H NMR (400 MHz, DMSO) δ 7.80 (d, 2H, J=8.6), 7.67 (d, 2H, J=8.6), 7.60 (m, 4H), 7.52 (s, 1H), 7.09 (s, 1H), 4.83 (ABq, 2H, Δυ=30.1, J_{ab}=17.4), 4.36 (dd, 1H, J=8.6, 6.2), 4.22 (dt, 2H, J_d=47.5, J_t=6.4), 1.61 (m, 1H), 1.48-1.11 (m, 5H).

Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
335				19	white solid	470.11	1.58 Method G	$(M+H)^+$ 471.0	^{1}H NMR (400 MHz, DMSO) δ 7.90 (d, 2H, J=8.3), 7.82 (d, 2H, J=8.8), 7.62 (d, 2H, J=8.8), 7.53 (d, 2H, J=8.4), 7.50 (s, 1H), 7.07 (s, 1H). 4.82 (ABq, 2H, Δυ=39.4, J_{ab}=17.4), 4.34 (dd, 1H, J=8.3, 6.6), 4.22 (dt, 2H, J_d=41.6, J_t=6.1), 3.85 (s, 3H), 1.58 (m, 1H), 1.46-1.12 (m, 5H).
336				19	white solid	423.08	1.43 Method G	$(M+H)^+$ 423.9	^{1}H NMR (400 MHz, DMSO) δ 7.82 (d, 2H, J=8.8), 7.78 (d, 2H, J=8.3), 7.63 (d, 2H, J=6.8), 7.57 (d, 2H, J=8.6), 7.53 (s, 1H), 7.14 (s, 1H), 4.81 (ABq, 2H, Δυ=36.2, J_{ab}=17.6), 4.38 (t, 1H, J=7.6), 4.27 (m, 1H), 4.15 (m, 1H), 1.64 (m, 1H), 1.54-1.36 (m, 3H).
337				19	white solid	466.07	1.72 Method G	$(M+Na)^+$ 489.0	^{1}H NMR (400 MHz, DMSO) δ 7.80 (d, 2H, J=8.8), 7.66 (d, 2H, J=8.1), 7.62-7.57 (m, 4H), 7.54 (s, 1H), 7.15 (s, 1H), 4.81 (ABq, 2H, Δυ=29.1, J_{ab}=17.1), 4.40 (t, 1H, J=6.9), 4.25 (m, 1H), 4.13 (m, 1H), 1.67 (m, 1H), 1.55-1.39 (m, 3H).
338				19	yellow solid	456.09	1.54 Method G	$(M+H)^+$ 457.0	^{1}H NMR (400 MHz, DMSO) δ 7.90 (d, 2H, J=8.3), 7.83 (d, 2H, J=8.8), 7.62 (d, 2H, J=8.8), 7.52 (d, 2H, J=8.3), 7.50 (s, 1H), 7.11 (s, 1H), 4.82 (ABq, 2H, Δυ=54.5, J_{ab}=17.3), 4.37 (t, 1H, J=8.0), 4.28-4.03 (m, 2H), 3.85 (s, 3H), 1.64 (m, 1H), 1.53-1.36 (m, 3H).

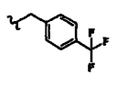
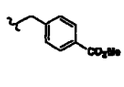
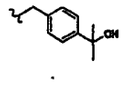
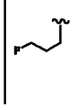
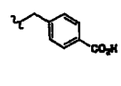
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
339				19	white solid	452.86	1.85 min Method A	452.91	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.70 (d, 2H, J = 8.7), 7.54 (d, 2H, J = 8.4), 7.42-7.49 (m, 4H), 6.31 (br s, 1H), 5.23 (br s, 1H), 4.58-4.63 (m, 2H), 4.33-4.41 (m, 2H), 4.19 (t, 1H, J = 4.5), 2.18-2.37 (m, 1H), 1.54-1.66 (m, 1H).
340				19	white solid	442.89	1.68 min Method A	442.90	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.96 (d, 2H, J = 8.4), 7.72 (d, 2H, J = 8.7), 7.48 (d, 2H, J = 8.7), 7.39 (d, 2H, J = 8.4), 6.32 (br s, 1H), 5.18 (br s, 1H), 4.54-4.63 (m, 2H), 4.30-4.42 (m, 2H), 4.16 (t, 1H, J = 4.5), 3.90 (s, 3H), 2.18-2.37 (m, 1H), 1.54-1.66 (m, 1H).
341				19	white solid	409.87	1.57 min Method A	410.07	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.72 (dd, 2H, J = 1.8, 8.7), 7.59 (d, 2H, J = 8.1), 7.50 (dd, 2H, J = 2.1, 8.7), 7.46 (d, 2H, J = 8.1), 6.30 (br s, 1H), 5.21 (br s, 1H), 4.56-4.68 (m, 2H), 4.31-4.37 (m, 2H), 4.18 (t, 1H, J = 4.8), 2.17-2.37 (m, 1H), 1.48-1.64 (m, 1H).
342				19	white solid	470.85	1.88 min Method A	470.89	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.70 (d, 2H, J = 8.7), 7.56 (d, 2H, J = 8.4), 7.51 (d, 2H, J = 8.4), 7.43 (d, 2H, J = 8.1), 6.32 (br s, 1H), 5.75 (tm, 1H, J_{H-F} = 57), 5.34 (br s, 1H), 4.52-4.63 (m, 2H), 4.32 (d, 1H, J = 15.6), 2.51-2.66 (m, 1H), 1.54-1.69 (m, 1H)

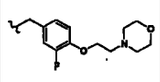
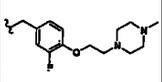
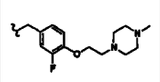
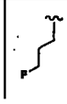
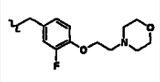
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
343				19	white solid	460.88	1.74 min Method A	461.07	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.97 (dd, 2H, J = 2.0, 8.4), 7.72 (d, 2H, J = 8.7), 7.51 (d, 2H, J = 8.7), 7.38 (d, 2H, J = 8.4), 6.32 (br s, 1H), 5.75 (tm, 1H, J_{H-F} = 57), 5.18 (br s, 1H), 4.60 (d, 1H, J = 15.6), 4.50-4.55 (m, 1H), 4.32 (d, 1H, J = 15.6), 3.91 (s, 3H), 2.51-2.66 (m, 1H), 1.54-1.69 (m, 1H)
344				19	white solid	427.85	1.62 min Method A	428.06	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.70 (d, 2H, J = 8.7), 7.61 (d, 2H, J = 8.1), 7.53 (d, 2H, J = 8.7), 7.45 (d, 2H, J = 7.8), 6.32 (br s, 1H), 5.71 (tm, 1H, J_{H-F} = 57), 5.21 (br s, 1H), 4.64 (d, 1H, J = 15.6), 4.51-4.55 (m, 1H), 4.28 (d, 1H, J = 15.6), 2.48-2.60 (m, 1H), 1.54-1.69 (m, 1H)
345				1-Method A, sep cond 1	white solid	502.87	1.99 min Method E	503.02	^{1}H NMR (DMSO) δ 7.83 (d, 2H, J =8.8Hz), 7.64 (m, 6H), 7.46 (s br, 1H), 7.25 (s br, 1H) 4.79 (s, 2H), 4.44 (m, 1H), 2.03 (m, 2H), 1.83 (m, 1H), 1.50 (m, 1H)
346				1-Method A, sep cond 2	white solid	459.88	1.76 min Method E	460.13	^{1}H NMR (DMSO) δ 7.84 (d, 2H, J=8.0Hz), 7.80 (d, 2H, J=7.7Hz), 7.65 (d, 2H, J=8.2Hz), 7.59 (d, 2H, J=7.7Hz), 7.47 (s br, 1H), 7.25 (s br, 1H), 4.78 (AB_2, 2H, Δν=5Hz, J_{ab}=17Hz), 4.43 (m, 1H), 2.05 (m, 2H), 1.83 (m, 1H), 1.48 (m, 1H)

Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
347				1-Method A, scp cond 3	yellow waxy solid	437.92	1.67 min Method B	438.22	^{1}H NMR (DMSO) δ 7.81 (m, 4H), 7.61 (m, 4H), 7.53 (s br, 1H), 7.09 (s br, 1H), 4.81 (AB_2, 2H, Δv=5Hz, J_{ab}=17Hz), 4.33 (m, 2H), 4.19 (t, 1H, J=6.0Hz), 1.44 (m, 6H)
348				1-Method A, scp cond 3	white powder	480.91	1.94 min Method B	M+Na 503.14	^{1}H NMR (DMSO) δ 7.99 (d, 2H, J=8.8Hz), 7.82 (m, 6H), 7.70 (s br, 1H), 7.27 (s br, 1H), 5.00 (m, 2H), 4.51 (m, 2H), 4.33 (m, 1H), 1.77 (m, 1H), 1.47 (m, 6H)
349				1-Method A	white powder	470.94	1.59 min Method B	493.17 M+Na+	^{1}H NMR ($CDCl_3$) δ 7.94 (d, J=8.0Hz, 2H), 7.72 (d, J=6.8Hz, 2H), 7.46 (d, J=6.8Hz, 2H), 7.38 (d, J=8.0Hz, 2H), 6.25 (s, br, 1H), 5.26 (s, br, 1H), 4.37-4.62 (m, 3H), 3.90 (s, 3H), 2.45 (m, 1H), 1.45 (m, 1H), 1.27 (d, J=21.2Hz, 3H), 1.17 (d, J=21.6Hz, 3H)
350				22	white solid	484.88	1.93 min Method B	485.09	^{1}H NMR (DMSO) δ 7.81 (d, 2H, J=8.8Hz), 7.63 (m, 6H), 7.51 (s br, 1H), 7.21 (s br, 1H), 5.85 (t, 1H, 56Hz), 4.81(AB_2, 2H, Δv=5Hz, J_{ab}=15Hz), 4.42 (t, 1H, J=8.0Hz), 1.49 (m, 4H)
351				1-Method A	white solid	437.92	1.49 min Method B	460.13 M+Na+	^{1}H NMR ($CDCl_3$) δ 7.72 (d, J=6.8Hz, 2H), 7.58 (d, J=8.4Hz, 2H), 7.48 (d, J=8.4Hz, 2H), 7.45 (d, J=6.8Hz, 2H), 6.25 (s, br, 1H), 5.28 (s, br, 1H), 4.32-4.64 (m, 3H), 2.45 (m, 1H), 1.38 (m, 1H), 1.24 (d, J=21.2Hz, 3H), 1.21 (d, J=22Hz, 3H),

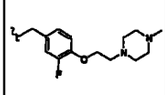
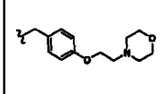
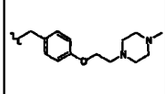
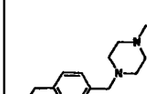
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
352				1-Method A	white solid	480.91	1.76 min Method B	503.12 M+Na+	^{1}H NMR ($CDCl_3$) δ 7.69 (d, J=8.4Hz, 2H), 7.52 (d, J=8.0Hz, 2H), 7.45 (d, J=8.4Hz, 2H), 7.43 (d, J=8.0Hz, 2H), 6.30 (s, br, 1H), 5.44 (s, br, 1H), 4.34-4.66 (m, 3H), 2.49 (m, 1H), 1.46 (m, 1H), 1.26 (d, J=21.6Hz, 3H), 1.22 (d, J=21.6Hz, 3H).
353				18	white solid	466.89	1.41min Method B	466.16	^{1}H NMR ($CDCl_3$) δ 7.66 (d, 2H, J=8.4Hz) 7.45-7.55 (m, 6H), 6.17 (s, br, 1H), 5.19 (s, br, 1H), 4.53 (dd, 2H, J=50Hz, 15Hz), 4.34-4.37 (m, 2H), 4.22-4.25 (m, 1H), 2.00-2.05 (m, 1H), 1.43-1.49 (m, 3H).
354				18	white solid	423.90	1.54min Method B	424.1	^{1}H NMR (d_6DMSO) δ 7.86 (d, 2H, J=8.0Hz) 7.48-7.75 (m, 6H), 6.56 (s, br, 1H), 5.69 (s, br, 1H), 4.72 (dd, 2H, J=42Hz, 16Hz), 4.51-4.55 (m, 3H), 1.42-2.07 (m, 4H).
355				11	yellow solid	582.02	1.47 min Method E	582.22	^{1}H NMR (DMSO) δ 7.81 (d, 2H, J=8.8Hz), 7.63 (d, 2H, J=8.5Hz), 7.43 (s br, 1H), 7.24 (m, 4H), 4.64 (s, 2H), 4.42 (m, 3H), 3.99 (m, 2H), 3.62 (m, 6H), 3.23 (m, 2H), 1.85 (m, 4H)
356				11	brown solid	595.06	1.42 min Method E	595.23	^{1}H NMR (DMSO) δ 7.80 (d, 2H, J=8.8Hz), 7.63 (d, 2H, J=8.5Hz), 7.42 (s br, 1H), 7.17 (m, 4H), 4.62 (s, 2H), 4.41 (m, 1H), 4.18 (m, 2H), 3.96 (s, 1H), 3.39 (m, 2H), 3.05 (m, 7H), 2.78 (s, 3H), 1.97 (m, 3H), 1.58 (m, 1H)

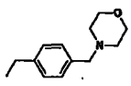
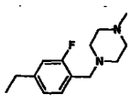
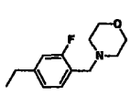
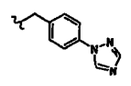
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
357				21	white solid	437.10	1.50 Method G	$(M+Na)^+$ 460.2	^{1}H NMR (400 MHz, DMSO) δ 7.83 (d, 2H, J=8.5), 7.75 (d, 2H, J=8.3), 7.68 (s, 1H), 7.64 (d, 2H, J=8.6), 7.49 (d, 2H, J=8.1), 7.20 (s, 1H), 4.67 (ABq, 2H, Δυ=28.3, J_{ab}=17.3), 4.54 (dd, 1H, J=9.3, 3.2), 2.23 (m, 1H), 1.42 (m, 1H), 1.25 (d, 3H, J=21.6), 1.21 (d, 3H, J=21.7).
358				21	white solid	480.09	1.76 Method G	$(M+Na)^+$ 503.2	^{1}H NMR (400 MHz, DMSO) δ 7.80 (d, 2H, J=8.6), 7.69 (s, 1H), 7.61 (m, 4H), 7.50 (d, 2H, J=8.1), 7.22 (s, 1H), 4.68 (ABq, 2H, Δυ=2.7, J_{ab}=17.1), 4.57 (dd, 1H, J=9.1, 3.0), 2.26 (m, 1H), 1.47 (m, 1H), 1.24 (d, 3H, J=21.5), 1.22 (d, 3H, J=21.5).
359				21	white solid	470.11	1.62 Method G	$(M+Na)^+$ 493.2	^{1}H NMR (400 MHz, DMSO) δ 7.86 (d, 2H, J=8.3), 7.83 (d, 2H, J=8.8), 7.63 (m, 3H), 7.44 (d, 2H, J=8.3), 7.18 (s, 1H), 4.67 (ABq, 2H, □□=10.3, J_{ab}=17.1), 4.53 (dd, 1H, J=9.3, 2.9), 3.85 (s, 3H), 2.22 (m, 1H), 1.46 (m, 1H), 1.22 (d, 3H, J=21.5), 1.19 (d, 3H, J=21.6).
360				18	white solid	409.87	1.53min Method B	407.99 (M-H)	^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2H, J=8.4Hz) 7.58 (d, 2H, J=8.4Hz), 7.50 (d, 2H, J=8.4Hz), 7.45 (d, 2H, J=8.4Hz), 6.29 (s, br, 1H), 5.21 (s, br, 1H), 4.19-4.67 (m, 5H), 2.17-2.28 (m, 1H), 1.49-1.61 (m, 1H).

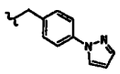
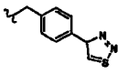
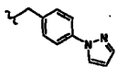
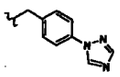
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
361				18	white solid	452.86	1.56min Method B	452.85	^{1}H NMR ($CDCl_3$) δ 7.69 (d, 2H, J=8.4Hz) 7.56 (d, 2H, J=8.4Hz), 7.49 (d, 2H, J=8.4Hz), 7.43 (d, 2H, J=8.4Hz), 6.31 (s, br, 1H), 5.24 (s, br, 1H), 4.19-4.62 (m, 5H), 2.16-2.30 (m, 1H), 1.56-1.63 (m, 1H),
362				18	white solid	456.93	1.86 min Method B	457.16	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.96 (d, 2H, J = 8.4), 7.69 (dd, 2H, J = 1.8, 8.4), 7.47 (ddd, 2H, J = 1.5, 2.1, 8.7), 7.42 (d, 2H, J = 8.4), 6.19 (br s, 1H), 5.18 (br s, 1H), 4.64 (d, 1H, J = 15.6), 4.42 (d, 1H, J = 15.9), 4.30-4.35 (m, 2H), 4.18 (t, 1H, J = 3.6), 3.90 (s, 3H), 1.89-2.08 (m, 1H), 1.38-1.50 (m, 3H)
363				18	white solid	456.97	1.80 min Method B	454.98 (neg. ion)	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.64 (d, 2H, J = 8.7), 7.42 (d, 2H, J = 8.7), 7.38 (d, 2H, J = 8.4), 7.26 (d, 2H, J = 8.4), 6.19 (br, 1H), 5.28 (br s, 1H), 4.51 (d, 1H, J = 15.6), 4.39 (d, 1H, J = 15.3), 4.30-4.35 (m, 2H), 4.18 (t, 1H, J = 3.6), 1.92-2.08 (m, 1H), 1.55 (s, 6H), 1.35-1.50 (m, 3H)
364				18	white solid	442.90	1.73 min Method B	443.12	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.81 (d, 2H, J = 8.4), 7.59 (dd, 2H, J = 1.8, 8.4), 7.29-7.33 (m, 4H), 6.76 (br, 1H), 5.80 (br s, 1H), 4.62 (d, 1H, J = 16.2), 4.44 (d, 1H, J = 16.2), 4.31 (t, 1H, J = 6.9), 3.85-4.10 (m, 2H), 1.70-1.85 (m, 1H), 1.30-1.48 (m, 3H)

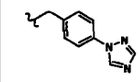
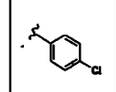
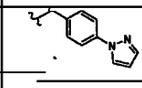
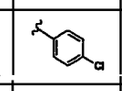
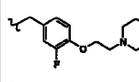
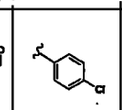
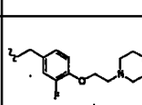
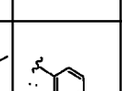
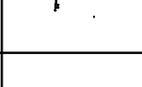
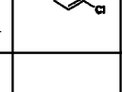
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
365				11, sep cond 4	off-white solid	585.02	1.47 min Method E	582.18	^{1}H NMR (DMSO) δ 7.80 (m, 2H), 7.62 (m, 2H), 7.42 (m, 1H), 7.18 (m, 4H), 4.62 (m, 3H), 4.42 (m, 1H), 4.14 (m, 1H), 4.00 (m, 3H), 3.58 (m, 4H), 2.93 (m, 1H), 2.70 (m, 2H), 2.01 (m, 2H), 1.85 (m, 1H), 1.59 (m, 1H)
366				11, sep cond 4	yellow solid	595.06	1.43 min Method E	595.19	^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2H, J=8.7Hz), 7.52 (d, 2H, J=8.8Hz), 7.14 (m, 1H), 7.01 (m, 1H), 6.87 (m, 1H), 6.24 (s br, 1H), 5.36 (m, 1H), 4.51 (m, 1H), 4.28 (m, 4H), 3.23 (m, 9H), 2.77 (m, 3H), 1.94 (m, 3H), 1.40 (m, 1H)
367				11, sep cond 4	white solid	595.06	1.42 min Method E	595.20	^{1}H NMR (DMSO) δ 7.80 (m, 2H), 7.62 (m, 2H), 7.42 (s br, 1H), 7.18 (m, 4H), 4.61 (m, 2H), 4.42 (m, 1H), 4.14 (m, 2H), 3.72 (m, 1H), 3.57 (m, 1H), 3.32 (s, 3H), 2.75 (m, 6H), 2.27 (m, 2H), 1.97 (m, 3H), 1.60 (m, 1H)
368				11, sep cond 4	dark yellow solid	546.04	1.55 min Method E	546.20	^{1}H NMR ($CDCl_3$) δ 7.77 (d, 2H, J=8.5Hz), 7.61 (d, 2H, J=8.5Hz), 7.53 (m, 1H), 7.19 (m, 4H), 4.67 (ABq, 2H, Δν=35, J_{ab}=16Hz), 4.30 (m, 6H), 4.01 (m, 4H), 3.48 (m, 4H), 1.68 (m, 1H), 1.49 (m, 4H)

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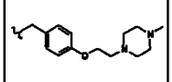
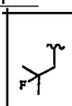
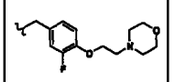
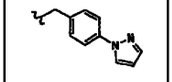
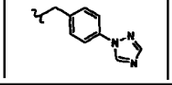
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
369				11, sep cond 4	orange-yellow solid	559.08	1.29 min Method E	559.22	^{1}H NMR (DMSO) δ 7.77 (d, 2H, J=8.3Hz), 7.60 (d, 2H, J=8.3Hz), 7.50 (s br, 1H), 7.16 (m, 4H), 4.65 (ABq, 2H, Δν□20, J_{AB}=16Hz), 4.33 (m, 2H), 4.18 (m, 4H), 3.17 (m, 7H), 2.78 (s, 3H), 1.67 (m, 1H), 1.59 (m, 5H)
370				11, sep cond 4	yellow solid	528.05	1.32 min Method E	528.17	^{1}H NMR (DMSO) δ 7.74 (d, 2H, J=8.3Hz), 7.60 (d, 2H, J=8.3Hz), 7.44 (s br, 1H), 7.35 (d, 2H, J=8.5Hz), 7.08 (s br, 1H), 6.95 (d, 2H, J=8.5Hz), 4.68 (ABq, 2H, Δν=24, J_{AB}=16Hz), 3.77 (m, 13H), 1.66 (m, 1H), 1.45 (m, 5H)
371				11, sep cond 4	light-orange solid	541.09	1.26 min Method E	541.24	^{1}H NMR (DMSO) δ 7.77 (d, 2H, J=8.3Hz), 7.59 (d, 2H, J=8.3Hz), 7.43 (s br, 1H), 7.31 (d, 2H, J=8.5Hz), 7.08 (s br, 1H), 6.87 (d, 2H, J=8.8Hz), 4.66 (ABq, 2H, Δν=16, J_{AB}=16Hz), 4.22 (m, 5H), 3.17 (m, 8H), 2.77 (m, 3H), 1.65 (m, 1H), 1.46 (m, 5H)
372				18, 8	amber glass	511.05	1.09 min Method A	511.21	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.66 (d, 2H, J=8.0Hz), 7.43 (d, 2H, J=8.0Hz), 7.26 (d, 2H, J=8.0Hz), 7.21 (d, 2H, J=8.0Hz), 6.25 (s, br, 1H), 5.45 (s, br, 1H), 4.52 (d, 1H, J_{AB}=12.0Hz), 4.38 (d, 1H, J_{AB}=12.0Hz), 4.29 (m, 2H), 4.18 (t, 1H, J=6.0Hz), 3.72 (m, 1H), 3.47 (s, 2H), 2.29 (s, 3H), 2.0 (m, 2H), 1.83 (m, 2H)

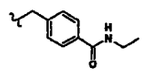
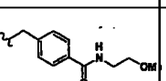
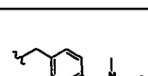
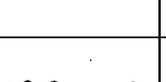
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
373				18, 8	amber glass	498.01	1.40 min Method A	498.20	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.66 (d, 2H, J=8.0Hz), 7.44 (d, 2H, J=8.0Hz), 7.27 (d, 2H, J=8.0Hz), 7.22 (d, 2H, J=8.0Hz), 6.24 (s, br, 1H), 5.42 (s, br, 1H), 4.52 (d, 1H, J_{ab}=12.0Hz), 4.38 (d, 1H, J_{ab}=12.0Hz), 4.29 (m, 2H), 4.18 (m, 1H), 3.68 (t, 4H, J=4.0Hz), 3.45 (s, 2H), 2.40 (s, br, 4H), 1.90 (m, 1H), 1.45 (m, 2H)
374				18, 8	amber glass	529.08	1.17 min Method A	529.22	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.68 (d, 2H, J=8.0Hz), 7.46 (d, 2H, J=8.0Hz), 7.25 (t, 1H, J=6.0Hz), 7.05 (t, 1H, J=6.0Hz), 6.28 (s, br, 1H), 5.49 (s, br, 1H), 4.54 (d, 1H, J_{ab}=12.0Hz), 4.33 (m, 2H), 4.22 (m, 1H), 3.57 (s, 2H), 2.32 (s, 3H), 2.01 (m, 1H), 1.44 (m, 2H)
375				18, 8	amber glass	516.00	1.10 min Method A	516.17	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.68 (d, 2H, J=8.0Hz), 7.45 (d, 2H, J=8.0Hz), 7.28 (t, 1H, J=6.0Hz), 7.06 (t, 2H, J=6.0Hz), 6.24 (s, br, 1H), 5.40 (s, br, 1H), 4.53 (d, 1H, J_{ab}=12.0Hz), 4.36 (d, 1H, J_{ab}=12.0Hz), 4.34 (m, 2H), 4.21 (m, 1H), 3.69 (t, 4H, J=4.0Hz), 3.53 (s, 2H), 2.44 (s, br, 3H), 2.0 (m, 1H), 1.45 (m, 2H)
376				18	white solid	451.91	1.39min Method B	451.90	^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1H), 8.09 (s, 1H), 7.75 (d, 2H, J=8.0Hz) 7.62 (d, 2H, J=8.4Hz), 7.47-7.51 (m, 4H), 6.36 (s, br, 1H), 5.28 (s, br, 1H), 4.31-4.62 (m, 5H), 2.16-2.30 (m, 1H) 1.56-1.66 (m, 1H),

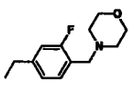
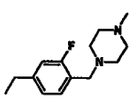
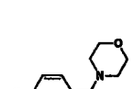
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
377				22	white solid	441.89	1.65 min Method E	M+Na 464.01	^{1}H NMR ($CDCl_3$) δ 7.69 (d, 2H, J=8.3Hz), 7.60 (d, 2H, J=8.3Hz), 7.49 (m, 4H), 6.18 (s br, 1H), 5.67 (tt, 1H, J=56Hz, 4.0Hz), 5.22 (s br, 1H), 4.52 (AB_2, 2H, Δν=16, J_{AB}=100Hz), 4.34(m, 1H), 2.03 (m, 1H), 1.68 (m, 1H), 1.38 (m, 1H), 0.86 (m, 1H)
378				18	white solid	450.92	1.52min Method B	450.91	^{1}H NMR ($CDCl_3$) δ 7.91 (s, 1H), 7.71 (m, 3H) 7.63 (d, 2H, J=8.4Hz), 7.50 (d, 2H, J=8.4Hz), 7.41 (d, 2H, J=8.4Hz), 6.47 (s, 1H), 6.34 (s, br, 1H), 5.18 (s, br, 1H), 4.30-4.60 (m, 5H), 2.14-2.29 (m, 1H), 1.56-1.66 (m, 1H)
379				18	white solid	468.96	1.53min Method B	469.04	^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1H), 7.98 (d, 2H, J=8.4Hz), 7.75 (d, 2H, J=8.4Hz), 7.45-7.50 (m, 4H), 6.35 (s, br, 1H), 5.20 (s, br, 1H), 4.22-4.64 (m, 5H), 2.20-2.35 (m, 1H), 1.54-1.63 (m, 1H)
380				18	white solid	464.95	1.54min Method B	464.99	^{1}H NMR ($CDCl_3$) δ 8.54 (s, 1H), 8.10 (s, 1H), 7.73 (d, 2H, J=8.4Hz), 7.62 (d, 2H, J=8.4Hz), 7.48-7.52 (m, 5H), 6.22 (s, br, 1H), 5.18 (s, br, 1H), 4.32-4.69 (m, 5H), 2.09-2.19 (m, 1H), 1.44-1.61 (m, 3H)
381				18	white solid	465.94	1.49min Method B	465.96	^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1H), 8.09 (s, 1H), 7.73 (d, 2H, J=8.4Hz), 7.62 (d, 2H, J=8.4Hz), 7.47-7.51 (m, 3H), 6.36 (s, br, 1H), 5.28 (s, br, 1H), 4.31-4.66 (m, 5H), 2.10-2.39 (m, 1H), 1.56-1.66 (m, 3H)

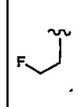
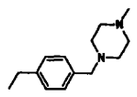
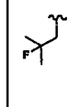
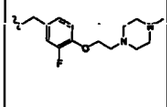
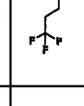
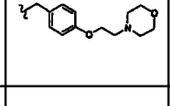
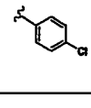
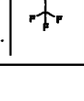
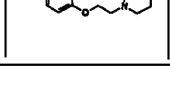
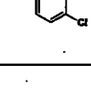
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
382				1-Method A	white solid	501.92	1.53min Method B	502.1	^{1}H NMR ($CDCl_3$) δ 8.56 (s, 1H), 8.10 (s, 1H), 7.72 (d, 2H, J=8.4Hz), 7.64 (d, 2H, J=8.4Hz), 7.49-7.52 (m, 4H), 6.23 (s, br, 1H), 5.22 (s, br, 1H), 4.32-4.64 (m, 3H), 1.44-2.20 (m, 4H)
383				1-Method A	white solid	500.93	1.66min. Method B	501.13	^{1}H NMR ($CDCl_3$) δ 7.91 (s, 1H), 7.41-7.78 (m, 9H), 6.47 (s, 1H), 6.23 (s, br, 1H), 5.27 (s, br, 1H), 4.30-4.59 (m, 3H), 1.47-2.21 (m, 4H)
384				18, 11	beige solid	532.01	1.36 min Method E	532.18	^{1}H NMR (DMSO) δ 7.80 (d, 2H, J=8.3Hz), 7.61 (d, 2H, J=8.3Hz), 7.56 (s br, 1H), 7.23 (s br, 1H), 7.19 (m, 3H), 4.64 (ABq, 2H, Δv=16, J_{ab}=16Hz), 4.51 (t, 1H, J=8.0Hz), 4.42 (m, 2H), 4.03 (m, 12H), 2.02 (m, 1H), 1.82 (m, 1H)
385				18, 11	pale orange solid	545.05	1.32 min Method B	545.25	^{1}H NMR (DMSO) δ 7.79 (d, 2H, J=8.3Hz), 7.60 (d, 2H, J=8.3Hz), 7.54 (s br, 1H), 7.14 (m, 5H), 4.62 (ABq, 2H, Δv=8.0Hz, J_{ab}=16Hz), 4.51 (t, 1H, J=8.0Hz), 4.24 (m, 5H), 3.17 (m, 8H), 2.78 (m, 3H), 2.02 (m, 1H), 1.81 (m, 1H)
386				18, 11	yellow residue	514.02	1.33 min Method E	514.20	^{1}H NMR (DMSO) δ 7.80 (d, 2H, J=8.3Hz), 7.61 (d, 2H, J=8.3Hz), 7.48 (s br, 1H), 7.33 (d, 2H, J=8.3Hz), 7.15 (s br, 1H), 6.95 (d, 2H, J=8.3Hz), 4.65 (ABq, 2H, Δv=8.0Hz, J_{ab}=16Hz), 3.86 (m, 15H), 2.03 (m, 1H), 1.79 (m, 1H)

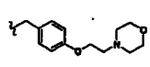
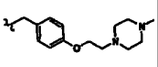
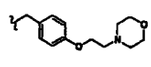
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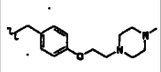
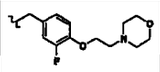
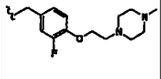
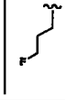
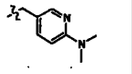
Ex. No.	R¹	R²	R³	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H⁺	NMR Data
387				18, 11	orange solid	527.06	1.28 min Method E	527.20	^{1}H NMR (DMSO) δ 7.79 (d, 2H, J=8.3Hz), 7.60 (d, 2H, J=8.3Hz), 7.47 (s br, 1H), 7.30 (d, 2H, J=8.3Hz), 7.15 (s br, 1H), 6.89 (d, 2H, J=8.3Hz), 4.63 (ABq, 2H, Δν=8.0Hz, J_{AB}=16Hz), 4.48 (t, 1H, J=8.0Hz), 4.15 (m, 4H), 3.24 (m, 10H), 2.79 (m, 3H), 2.03 (m, 1H), 1.80 (br, 1H)
388				18, 11	tan solid	560.06	1.65 min Method E	559.14	^{1}H NMR (DMSO) δ 7.76 (d, 2H, J=8.3Hz), 7.59 (m, 3H), 7.21 (s br, 1H), 7.08 (s br, 1H), 7.04 (m, 2H), 4.53 (m, 5H), 3.92 (m, 4H), 3.45 (m, 6H), 2.25 (m, 1H), 1.54 (m, 1H), 1.25 (d, 3H, J=20Hz), 1.22 (d, 3H, J=20Hz)
389				18	yellow solid	478.91	1.55min Method B	491.04 (M^+Na)	^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1H), 7.72-7.76 (m, 3H), 7.65 (d, 2H, J=8.4Hz) 7.52 (d, 2H, J=8.4Hz), 7.40 (d, 2H, J=8.4Hz) 6.47 (s, 1H), 6.30 (s, br, 1H), 5.21 (s, br, 1H), 4.27-4.57 (m, 3H), 2.51-2.60 (m, 1H), 1.53-1.65 (m, 3H).
390				18	white solid	469.90	1.48min Method B	470.1	^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1H), 7.40-7.76 (m, 9H), 6.50 (s, 1H), 6.27 (s, br, 1H), 5.22 (s, br, 1H), 4.25-4.55 m, 3H), 2.49-2.58 (m, 1H), 1.51-1.63 (m, 3H).

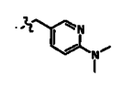
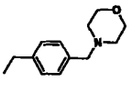
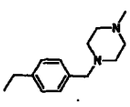
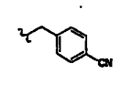
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
391				18, 6	white solid	469.97	1.59 min Method A	470.09	^{1}H NMR (MeOD, 400MHz) δ 7.77 (ddd, 2H, J = 2.0, 2.4, 8.8), 7.71 (d, 2H, J = 8.4), 7.51 (ddd, 2H, J = 2.0, 2.4, 8.8), 7.48 (d, 2H, J = 8.0), 4.80 (d, 1H, J = 16.4), 4.72 (d, 1H, J = 16.4), 4.47 (t, 1H, J = 7.2), 4.05-4.28 (m, 2H), 3.38 (q, 2H, J = 7.2), 1.70-1.85 (m, 1H), 1.30-1.48 (m, 3H), 1.20 (t, 3H, J = 7.2).
392				18, 6	white solid	500.00	1.57 min Method A	500.10	^{1}H NMR (MeOD, 400MHz) δ 7.72-7.81 (m, 4H), 7.48-7.52 (m, 4H), 4.80 (d, 1H, J = 16.4), 4.72 (d, 1H, J = 16.4), 4.47 (t, 1H, J = 7.2), 4.05-4.28 (m, 2H), 3.54 (s, 3H), 3.25-2.36 (m, 4H), 1.70-1.85 (m, 1H), 1.30-1.48 (m, 3H).
393				18, 6	white solid	484.00	1.65 min Method A	484.12	^{1}H NMR (MeOD, 400MHz) δ 7.79 (d, 2H, J = 8.8), 7.50-7.54 (m, 4H), 7.29-7.33 (m, 2H), 4.79 (d, 1H, J = 16.4), 4.72 (d, 1H, J = 16.4), 4.47 (t, 1H, J = 7.2), 4.05-4.28 (m, 2H), 3.52-.356 (m, 2H), 3.03 and 2.94 (2 s, 3H), 1.70-1.85 (m, 1H), 1.30-1.48 (m, 3H), 1.15-1.25 (m, 3H).
394				18, 6	white solid	533.03	1.36 min Method A	533.15	^{1}H NMR (MeOD, 400MHz) δ 8.48 (d, 1H, J = 4.8), 7.76-7.82 (m, 5H), 7.50-7.53 (m, 4H), 7.41 (d, 1H, J = 8.0), 7.28-7.30 (m, 1H), 4.82 (d, 1H, J = 16.0), 4.72 (d, 1H, J = 16.4), 4.67 (s, 2H), 4.48 (t, 1H, J = 7.2), 4.05-4.28 (m, 2H), 1.70-1.85 (m, 1H), 1.30-1.48 (m, 3H).

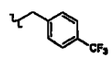
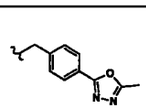
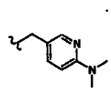
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
395				18, 8	amber glass	501.98	1.17 min Method A	502.25	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.77 (d, 2H, J=8.0Hz), 7.51 (d, 2H, J=8.0Hz), 7.42 (t, 1H, J=6.0Hz), 7.26 (d, 1H, J=6.0Hz), 7.14 (d, 1H, J=6.0Hz), 6.35 (s, br, 1H), 6.07 (s, br, 1H), 4.82 (d, 1H, J_{ab}=12.0Hz), 4.35 (m, 1H), 4.19 (m, 5H), 3.59 (s, br, 4H), 3.48 (d, br, 1H), 2.90 (d, br, 1H), 2.20 (m, 1H), 1.50 (m, 1H)
396				18, 8	amber glass	515.02	1.21min Method A	515.27	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.76 (d, 2H, J=8.0Hz), 7.50 (d, 2H, J=8.0Hz), 7.32 (m, 1H), 7.19 (d, 1H, J=8.0Hz), 7.07 (d, 1H, J=8.0Hz), 6.35 (s, br, 1H), 5.67 (s, br, 1H), 4.86 (d, 1H, J_{ab}=12.0Hz), 4.70 (s, 2H), 4.56 (m, 2H), 4.17 (m, 6H), 2.80 (s, 3H), 2.22 (m, 1H), 1.54 (m, 1H)
397				18, 8	amber glass	483.98	1.21 min Method A	483.98	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.77 (d, 2H, J=8.0Hz), 7.51 (d, 2H, J=8.0Hz), 7.41 (d, 2H, J=8.0Hz), 7.31 (d, 2H, J=8.0Hz), 6.34 (s, br, 1H), 6.05 (s, br, 1H), 4.83 (d, 1H, J_{ab}=12.0Hz), 4.51 (m, 1H), 4.20 (m, 4H), 3.94 (m, 5H), 3.51 (d, 1H, J=12.0Hz), 3.40 (d, 1H, J=12.0Hz), 2.89 (t, 1H, J=6.0Hz), 2.76 (t, 1H, J=6.0Hz), 2.20 (m, 1H), 1.51 (m, 1H)

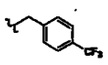
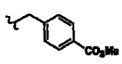
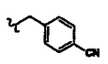
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
398				18, 8	amber glass	497.03	1.16 min Method A	498.74	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.76 (d, 2H, J=8.0Hz), 7.51 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 7.27 (d, 2H, J=8.0Hz), 6.31 (s, br, 1H), 5.80 (s, br, 1H), 4.82 (d, 1H, J_{ab}=12.0Hz), 4.55 (m, 2H), 4.16 (m, 5H), 3.82 (d, 1H), 2.78 (s, 3H), 2.21 (m, 1H), 1.52 (m, 1H)
399				20, 11	colorless residue	573.11	1.63 min Method E		^{1}H NMR (DMSO) δ 7.76 (d, 2H, J=8.3Hz), 7.59 (m, 3H), 7.20 (s br, 1H), 7.08 (s br, 1H), 7.03 (m, 2H), 4.53 (m, 11H), 3.92 (m, 4H), 3.45 (m, 3H), 2.24 (m, 1H), 1.54 (m, 1H), 1.25 (d, 3H, J=20Hz), 1.22 (d, 3H, J=20Hz)
400				11	light yellow solid	564.03	1.51min Method E	564.19	^{1}H NMR (DMSO) δ 7.81 (d, 2H, J=8.3Hz), 7.63 (d, 2H, J=8.3Hz), 7.36 (m, 3H), 7.20 (s br, 1H), 6.96 (d, 2H, J=8.0Hz), 4.64 (s, 2H), 4.37 (m, 3H), 4.00 (m, 2H), 3.61 (m, 6H), 3.21 (m, 2H), 1.97 (m, 2H), 1.82 (m, 1H), 1.60 (m, 1H)
401				11	pale orange solid	577.07	1.47min Method E	577.20	^{1}H NMR (DMSO) δ 7.80 (d, 2H, J=8.0Hz), 7.62 (d, 2H, J=8.0Hz), 7.33 (m, 3H), 7.20 (s br, 1H), 6.89 (d, 2H, J=8.0Hz), 4.63 (s, 2H), 4.39 (m, 1H), 4.10 (m, 2H), 3.25 (m, 10H), 2.77 (s, 3H), 1.89 (m, 2H), 1.81 (m, 1H), 1.60 (m, 1H)

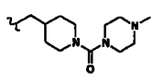
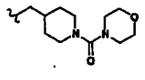
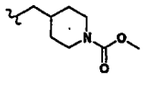
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
402				20, 11	pale yellow residue	542.07	1.51min Method E	542.21	^{1}H NMR (DMSO) δ 7.77 (d, 2H, J=8.0Hz), 7.59 (d, 2H, J=8.0Hz), 7.55 (s br, 1H), 7.26 (d, 2H, J=8.0Hz), 7.15 (s br, 1H), 6.90 (d, 2H, J=8.0Hz), 4.52 (m, 2H), 4.32 (m, 2H), 4.00 (m, 2H), 3.71 (m, 2H), 3.38 (m, 7H), 2.23(m, 1H), 1.55 (m, 1H), 1.23 (d, 3H, J=20Hz), 1.21 (d, 3H, J=20Hz)
403				20, 11	light orange solid	555.12	1.45min Method E	555.27	^{1}H NMR (DMSO) δ 7.76 (d, 2H, J=8.0Hz), 7.58 (d, 2H, J=8.0Hz), 7.54 (s br, 1H), 7.22 (d, 2H, J=8.0Hz), 7.16 (s br, 1H), 6.84 (d, 2H, J=8.0Hz), 4.52 (m, 2H), 4.13 (m, 2H), 3.25 (m, 11H), 2.79 (m, 3H), 2.20 (m, 1H), 1.56 (m, 1H), 1.23 (d, 3H, J=20Hz), 1.20 (d, 3H, J=20Hz)
404				18, 11	pale yellow residue	532.01	1.43min Method E	532.18	^{1}H NMR (DMSO) δ 7.81 (d, 2H, J=8.0Hz), 7.62 (d, 2H, J=8.0Hz), 7.48 (s br, 1H), 7.34 (d, 2H, J=8.0Hz), 7.25 (s br, 1H), 6.96 (d, 2H, J=8.0Hz), 5.72 (tt, 1H, J=8.0Hz, 56Hz), 4.61 (s, 2H), 4.52 (t, 1H, J=8.0Hz), 4.33 (t, 2H, J=8.0Hz), 3.96 (m, 2H), 3.56 (m, 2H), 3.22 (m, 2H), 3.24 (m, 1H), 1.91 (m, 1H)

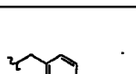
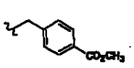
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
405				18, 11	pale yellow solid	545.05	1.37min Method E	545.19	^{1}H NMR (DMSO) δ 7.81 (d, 2H, J=8.0Hz), 7.61 (d, 2H, J=8.0Hz), 7.46 (s br, 1H), 7.30 (d, 2H, J=8.0Hz), 7.25 (s br, 1H), 6.89 (d, 2H, J=8.0Hz), 5.64 (m, 1H), 4.60 (s, 2H), 4.52 (t, 1H, J=8.0Hz), 4.11 (m, 2H), 3.17 (m, 10H), 2.77 (m, 3H), 2.24 (m, 1H), 1.96 (m, 1H)
406				18, 11	yellow residue	550.00	1.43min Method E	550.16	^{1}H NMR (DMSO) δ 7.80 (d, 2H, J=8.0Hz), 7.62 (d, 2H, J=8.0Hz), 7.56 (s br, 1H), 7.23 (m, 4H), 5.80 (tt, 1H, J=4.0Hz, 56Hz), 3.93 (m, 15H), 2.29 (m, 1H), 1.99 (m, 1H)
407				18, 11	orange solid	563.04	1.37min Method E	563.21	^{1}H NMR (DMSO) δ 7.80 (d, 2H, J=8.0Hz), 7.62 (d, 2H, J=8.0Hz), 7.55 (s br, 1H), 7.29 (s br, 1H), 7.15 (m, 3H), 5.78 (tt, 1H, J=4.0Hz, 56Hz), 4.56 (m, 3H), 4.21 (m, 2H), 3.22 (m, 10H), 2.79 (m, 3H), 2.30 (m, 1H), 1.97 (m, 1H)
408				18, 10, sep cond 5	clear oil	442.94	0.993 min Method B	443.19	^{1}H NMR ($CDCl_3$) δ 8.07 (s, 1H), 7.67 (d, J=6.8Hz, 2H), 7.55 (d, J=8.8Hz, 1H), 7.44 (d, J=6.8Hz, 2H), 6.47 (d, J=8.8Hz, 1H), 6.30 (s, br, 1H), 5.45 (s, br, 1H), 4.20-4.46 (m, 5H), 3.12 (s, 6H), 1.22-1.85 (m, 4H)

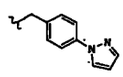
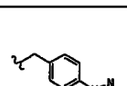
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
409				18, 10, second 5	clear oil	442.94	0.993 min Method B	443.19	^{1}H NMR ($CDCl_3$) δ 8.07 (s, 1H), 7.67 (d, J=6.8Hz, 2H), 7.55 (d, J=8.8Hz, 1H), 7.44 (d, J=6.8Hz, 2H), 6.47 (d, J=8.8Hz, 1H), 6.30 (s, br, 1H), 5.45 (s, br, 1H), 4.20-4.46 (m, 5H), 3.12 (s, 6H), 1.22-1.85 (m, 4H).
410				20, 8	amber glass	512.04	1.44 min Method B	512.20	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.42 (d, 2H, J=8.0Hz), 7.22 (dd, 4H, J=8.0Hz), 6.27 (s, br, 1H), 5.26 (s, br, 1H), 4.58 (d, 1H), 4.43 (d, 1H, J_{ab}=16.0Hz), 4.36 (d, 1H, J_{ab}=16.0Hz), 3.68 (m, 6H), 3.46 (s, 2H), 2.45 (m, 6H), 1.53 (m, 1H), 1.26 (d, 3H, J=20.0Hz), 1.17 (d, 3H, J=20.0Hz)
411				20, 8	amber glass	525.08	1.38 min Method B	525.24	^{1}H NMR, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.42 (d, 2H, J=8.0Hz), 7.22 (dd, 4H, J=8.0Hz), 6.26 (s, br, 1H), 5.24 (s, br, 1H), 4.57 (m, 1H), 4.43 (d, 1H, J_{ab}=16.0Hz), 4.35 (d, 1H, J_{ab}=16.0Hz), 3.48 (s, 2H), 2.47 (m, 7H), 2.30 (s, 3H), 1.26 (d, 3H, J=20.0Hz), 1.18 (d, 3H, J=20.0Hz)
412				18	white solid	427.87	1.39 min Method B	428.13	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.72 (dd, 2H, *J* = 2.0, 8.8), 7.61 (d, 2H, *J* =8.4), 7.53 (dd, 2H, *J* =2.0, 8.4), 7.45 (d, 2H, *J* =8.0), 6.32 (br s, 1H), 5.73 (tm, 1H, J_{H-F} =57), 5.22 (br s, 1H), 4.64 (d, 1H, *J* = 16.4), 4.50-4.60 (m, 1H), 4.28 (d, 1H, *J* = 16.4), 2.42-2.60 (m, 1H), 1.50-1.63 (m, 1H)

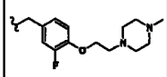
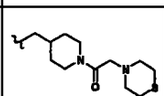
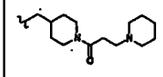
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
413				18	white solid	470.86	1.69 min Method B	471.13	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.69 (dd, 2H, J = 1.6, 8.8), 7.56 (d, 2H, J =8.4), 7.51 (ddd, 2H, J =2.0, 2.4, 8.4), 7.43 (d, 2H, J =8.4), 6.32 (br s, 1H), 5.75 (tm, 1H, J_{H-F} =57), 5.25 (br s, 1H), 4.60 (d, 1H, J = 15.6), 4.50-4.60 (m, 1H), 4.32 (d, 1H, J = 15.6), 2.50-2.60 (m, 1H), 1.55-1.70 (m, 1H).
414				18, 13	white solid	480.95	1.41 min Method B	481.22	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.96 (d, 2H, J = 8.4), 7.70 (d, 2H, J = 8.4), 7.47-7.50 (m, 4H), 6.22 (br s, 1H), 5.18 (br s, 1H), 4.66 (d, 1H, J = 15.6), 4.43 (d, 1H, J = 15.6), 4.30-4.35 (m, 2H), 4.19-4.21 (m, 1H), 2.61 (s, 3H), 1.93-2.08 (m, 1H), 1.38-1.50 (m, 3H).
415				18, 10	white foam	428.92	1.34 Method B	429.18	^{1}H NMR ($CDCl_3$) TFA salt δ 8.10 (s, 1H), 8.04 (d, 1H, J=9.2Hz), 7.76 (d, 2H, J=6.8Hz), 7.52 (d, 2H, J=6.8Hz), 6.80 (d, 2H, J=9.2Hz), 6.46 (s, 1H), 6.00 (s, 1H), 4.60 (d, 1H, J=15.6Hz), 4.54 (dd, 1H, J=5.2Hz, 6.2Hz), 4.30 (m, 1H), 4.18 (m, 1H), 4.07 (d, 1H, J=15.6Hz), 3.29 (s, 6H), 2.25 (m, 1H), 1.55 (m, 1H).

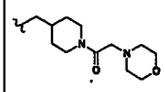
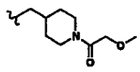
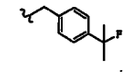
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
416				1-Method A	off-whits solid	463.91	1.50 min Method B	464.11	^{1}H NMR ($CDCl_3$, 300MHz) δ 8.72 (d, 1H, J = 2.4), 7.82 (dd, 1H, J = 2.7, 8.4), 7.55 (d, 2H, J = 8.1), 7.47 (d, 2H, J = 8.1), 7.37 (d, 1H, J = 8.4), 5.97 (br s, 1H), 5.26 (br s, 1H), 4.62 (d, 1H, J = 16.2), 4.54 (d, 1H, J = 15.9), 4.44 (t, 1H, J = 7.5), 1.70-1.77 (m, 1H), 1.35-1.43 (m, 1H), 1.21-1.31 (m, 1H), 0.85 (d, 3H, J = 6.3), 0.67 (d, 3H, J = 6.6).
417				1-Method A	white solid	453.95	1.37 min Method B	454.14	^{1}H NMR ($CDCl_3$, 300MHz) δ 8.71 (d, 1H, J = 3.0), 7.96 (d, 2H, J = 8.1), 7.85 (dd, 1H, J = 2.4, 8.4), 7.37-7.43 (m, 3H), 5.99 (br s, 1H), 5.24 (br s, 1H), 4.61 (d, 1H, J = 15.9), 4.53 (d, 1H, J = 15.9), 4.41 (t, 1H, J = 7.2), 3.91 (s, 3H), 1.70-1.76 (m, 1H), 1.35-1.43 (m, 1H), 1.21-1.31 (m, 1H), 0.82 (d, 3H, J = 6.6), 0.66 (d, 3H, J = 6.6).
418				1-Method A	white solid	420.92	1.64 min Method A	421.15	^{1}H NMR ($CDCl_3$, 300MHz) δ 8.74 (d, 1H, J = 2.4), 7.90 (dd, 1H, J = 2.4, 8.4), 7.61 (d, 2H, J = 8.4), 7.50 (d, 2H, J = 8.4), 7.44 (d, 1H, J = 8.4), 5.92 (br s, 1H), 5.22 (br s, 1H), 4.65 (d, 1H, J = 16.5), 4.52 (d, 1H, J = 16.5), 4.40 (t, 1H, J = 7.5), 1.65-1.74 (m, 1H), 1.33-1.40 (m, 1H), 1.18-1.25 (m, 1H), 0.83 (d, 3H, J = 6.6), 0.66 (d, 3H, J = 6.6).

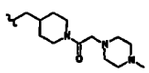
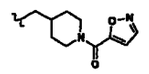
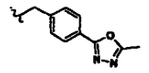
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
419				7	white solid	528.12	1.35 min Method A	528.26	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, J = 8.6), 7.51 (d, 2H, J = 8.8), 6.65 (s, 1H), 5.35 (s, 1H), 4.14 (dd, 1H, J = 5.1, 9.5), 3.63-3.75 (m, 2H), 3.35-3.55 (m, 3H), 3.25 (dd, 1H, J = 9.8, 14), 2.98 (dd, 1H, J = 4.5, 14), 2.35-2.87 (m, 8H), 1.77-1.92 (m, 3H), 1.59 (d, 2H, J =13), 1.05-1.30 (m, 3H), 0.75-0.80 (m, 1H), 0.72 (d, 3H, J = 6.4), 0.67 (d, 3H, J = 6.7).
420				7	white solid	515.08	1.56 min Method A	515.33	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.71 (d, 2H, J = 8.5), 7.50 (d, 2H, J = 8.5), 6.65 (s, 1H), 5.47 (s, 1H), 4.13 (dd, 1H, J = 5.2, 9.2), 3.60-3.75 (m, 6H), 3.15-3.30 (m, 6H), 2.97 (dd, 1H, J = 4.6, 14), 2.71 (dd, 2H, J = 14, 25), 1.75-1.92 (m, 3H), 1.67 (d, 1H, J = 12), 1.05-1.30 (m, 3H), 0.75-0.81 (m, 1H), 0.71 (d, 3H, J = 6.7), 0.65 (d, 3H, J = 6.7).
421				7	white solid	460.00	1.68 min Method A	460.17	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.73 (d, 2H, J = 8.5), 7.50 (d, 2H, J = 8.6), 6.65 (s, 1H), 5.35 (s, 1H), 4.15 (dd, 3H, J = 5.2, 9.5), 3.67 (s, 3H), 3.25 (t, 1H, J = 10), 3.97 (dd, 1H, J = 4.8, 14), 2.61-2.80 (m, 2H), 1.74-1.94 (m, 3H), 0.89-1.40 (m, 4H), 0.75-0.80 (m, 1H), 0.72 (d, 3H, J = 6.4), 0.67 (m, 3H, J = 6.7).

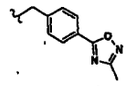
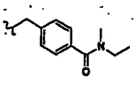
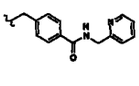
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
422				1-Method A	tan solid	491.81	1.84min Method B	491.04	^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2H, J=8.0Hz), 7.50-7.58 (m, 2H), 7.41 (d, 2H, J=8.0Hz), 7.17-7.22 (m, 1H), 6.23 (s, br, 1H), 5.25 (s, br, 1H), 4.41 (dd, 2H, J=50Hz, 15Hz), 4.31-4.35 (m, 1H), 1.80-1.86 (m, 1H), 1.41-1.44 (m, 1H), 1.11-1.15 (m, 1H), 0.81 (d, 3H, J=7.0Hz), 0.71 (d, 3H, J=7.0Hz)
423				1-Method A	white solid	424.09	1.54 min Method F	$(M+H)^+$ 425.1	^{1}H NMR (400 MHz, DMSO) δ 7.90 (d, 2H, J=8.1), 7.82 (d, 2H, J=8.5), 7.61 (d, 2H, J=8.5), 7.52 (d, 2H, J=8.1), 7.49 (s, 1H), 7.07 (s, 1H), 4.81 (ABq, 2H, $\Delta\upsilon$=45.3, J_{AB}=17.3), 4.27 (t, 1H, J=7.3), 3.85 (s, 3H), 1.55 (m, 1H), 1.38 (m, 1H), 0.68 (t, 3H, J=7.3)
424				1-Method A	white solid	452.12	1.69 min Method F	$(M+H)^+$ 453.1	^{1}H NMR (400 MHz, DMSO) δ 7.90 (d, 2H, J=8.3), 7.83 (d, 2H, J=8.8), 7.62 (d, 2H, J=8.8), 7.54 (d, 2H, J=8.3), 7.48 (s, 1H), 7.04 (s, 1H), 4.82 (ABq, 2H, $\Delta\upsilon$=41.3, J_{AB}=17.3), 4.31 (t, 1H, J=8.1), 3.85 (s, 3H), 1.52 (m, 1H), 1.29 (m, 1H), 1.04 (m, 3H), 0.90 (m, 1H), 0.67 (t, 3H, J=7.3)

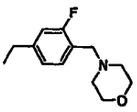
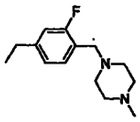
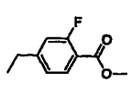
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
425				1-Method A	pale yellow solid	460.99	1.48 min Method B	460.13	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.91 (d, 1H, J = 1.5), 7.67-7.72 (m, 3H), 7.62 (d, 2H, J = 8.7), 7.42-7.48 (m, 4H), 6.46 (t, 1H, J = 2.1), 6.24 (br s, 1H), 5.21 (br s, 1H), 4.62 (d, 1H, J = 15.3), 4.42 (d, 1H, J = 15.6), 4.29 (t, 1H, J = 6.9), 1.80-1.88 (m, 1H), 1.28-1.40 (m, 1H), 1.12-1.21 (m, 1H), 0.75 (d, 3H, J = 6.6), 0.66 (d, 3H, J = 6.6)
426				1-Method A	white solid	461.97	1.39 min Method B	462.18	^{1}H NMR ($CDCl_3$, 300MHz) δ 8.54 (s, 1H), 8.10 (s, 1H), 7.71 (d, 2H, J = 8.4), 7.61 (d, 2H, J = 8.4), 7.46-7.52 (m, 4H), 6.23 (br s, 1H), 5.19 (br s, 1H), 4.66 (d, 1H, J = 15.9), 4.42 (d, 1H, J = 15.9), 4.30 (t, 1H, J = 6.9), 1.79-1.89 (m, 1H), 1.30-1.38 (m, 1H), 1.07-1.14 (m, 1H), 0.76 (d, 3H, J = 6.6), 0.66 (d, 3H, J = 6.6)
427				11	pale yellow solid	542.07	1.48 min Method B	542.25	^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2H, J=8.00Hz), 7.49 (d, 2H, J=8.0Hz), 7.16 (d, 1H, J=12.0Hz), 7.05 (d, 1H, J=8.0Hz), 6.86 (t, 1H, J=8.0Hz), 6.40 (s, br, 1H), 5.87 (s br, 1H), 4.42 (ABq, 2H, Δv=16, J_{AB}=164Hz), 4.49 (d, 2H, J=4.0Hz), 4.27 (t, 1H, J=8.0Hz), 4.04 (m, 4H), 3.69 (m, 2H), 3.51 (m, 2H), 3.10 (m, 2H), 1.83 (m, 1H), 1.29 (m, 1H), 1.07 (m, 1H), 0.75 (d, 3H, J=8.0Hz), 0.68 (d, 3H, J=8.0Hz)

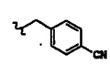
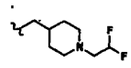
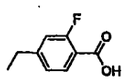
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
428				11	yellow solid	555.12	1.41 min Method E	555.28	^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2H, J=8.00Hz), 7.50 (d, 2H, J=8.0Hz), 7.16 (d, 1H, J=12.0Hz), 7.05 (d, 1H, J=8.0Hz), 6.87 (t, 1H, J=6.0Hz), 6.38 (s, br, 1H), 5.91 (s br, 1H), 4.41 (AB_2, 2H, $\Delta\nu$=16, J_{ab}=176Hz), 4.45 (m, 2H), 4.27 (t, 1H, J=8.0Hz), 3.81 (m, 4H), 3.67 (m, 4H), 3.48 (m, 1H), 2.89 (s, 3H), 1.83 (m, 1H), 1.29 (m, 1H), 1.05 (m, 1H), 0.75 (d, 3H, J=8.0Hz), 0.68 (d, 3H, J=8.0Hz).
429				7	white solid	545.17	1.84min Method C	545.36	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.73 (d, 2H, *J* = 9.0), 7.51 (d, 2H, *J* = 8.0), 6.65 (2 s, 1H), 5.40 (s, 1H), 4.54 (t, 1H, *J* = 13), 3.85-4.20 (m, 2H), 2.40-3.50 (m, 12H), 1.75-2.00 (m, 3H), 0.92-1.20 (m, 1H), 0.73 (d, 3H, *J* = 5.8, 6.1), 0.67 (d, 3H, *J* = 6.1, 6.4)
430				7	white solid	541.16	1.43 min Method A	541.24	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.71 (d, 2H, *J* = 6.4), 7.50 (d, 2H, *J* = 8.2), 6.65 (d, 1H, *J* = 41), 5.44 (s, 1H), 4.55 (t, 1H, *J* = 13), 4.15 (br s, 1H), 3.95 (br s, 1H), 3.15-3.35 (m, 1H), 2.90-3.00 (m, 2H), 2.60-2.70 (m, 2H), 2.50-2.57 (m, 2H), 2.35-2.50 (m, 6H), 1.85-2.00 (m, 3H), 1.35-1.75 (m, 3H), 1.00-1.30 (m, 5H), 0.90-1.00 (m, 1H), 0.72 (dd, 3H, *J* = 7.0, 7.3), 0.66 (dd, 3H, *J* = 6.1, 6.4)

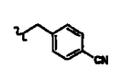
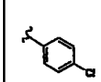
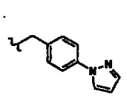
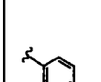
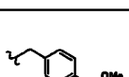
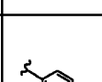
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
431				7	white solid	529.10	1.38 min Method A	529.27	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, 8.5), 7.51 (d, 2H, J = 8.9), 6.65 (d, 1H, J = 32), 5.43 (s, 1H), 4.55 (t, 1H, J = 13) 4.14 (dd, 1H, J = 4.8, 9.5), 3.88 (br s, 4H), 3.21-3.84 (m, 2H), 2.90-3.05 (m, 3H), 2.47-2.67 (m, 1H), 1.80-2.05 (m, 3H), 1.40-1.75 (m, 6H), 1.00-1.35 (m, 4H), 0.73 (dd, 3H, J = 3.4, 6.4), 0.67 (dd, 3H, J = 2.7, 6.7)
432				7	white solid	474.02	1.55 min Method A	474.28	^{1}H NMR ($CDCl_3$, 500MHz) δ7.72 (d, 2H, J = 7.6), 7.50 (d, 2H, J = 8.6), 6.65 (d, 1H, J = 40), 5.46 (s, 1H), 4.56 (t, 1H, J = 13), 4.00-4.20 (m, 2H), 3.80-3.90 (m, 1H), 3.40 (s, 3H), 3.20-3.35 (m, 1H), 2.85-3.05 (m, 2H), 2.40-2.65 (m, 1H), 1.50-2.00 (m, 5H), 1.00-1.45 (m, 2H), 0.83-0.90 (m, 1H), 0.72 (dd, 3H, J = 6.7, 8.2), 0.67 (dd, 3H, J = 5.8, 6.4)
433				1-Method A	white solid	455.00	1.83 min Method B	454.15	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.61 (dd, 2H, J = 1.8, 8.7), 7.40 (ddd, 2H, J = 2.1, 2.4, 8.7), 7.26 (d, 4H, J = 7.2), 6.25 (br s, 1H), 5.19 (br s, 1H), 4.51 (d, 1H, J = 15.6), 4.43 (d, 1H, J = 15.6), 4.34 (t, 1H, J = 7.2), 1.75-1.85 (m, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 1.22-1.35 (m, 2H), 0.78 (d, 3H, J = 6.3), 0.66 (d, 3H, J = 6.3)

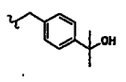
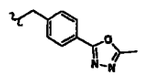
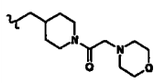
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
434				7	white solid	542.15	1.73 min Method C	542.46	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, J = 8.5), 7.51 (d, 2H, J = 8.5), 6.65 (d, 1H, J = 39), 5.42 (s, 1H), 4.55 (t, 1H, J = 14), 4.00-4.17 (m, 2H), 3.05-3.33 (m, 3H), 2.85-3.05 (m, 2H), 2.40-2.70 (m, 8H), 2.32 (s, 3H), 1.55-2.10 (m, 6H), 1.00-1.30 (m, 6H), 0.72 (t, 3H, J = 6.7, 6.7), 0.67 (t, 3H, J = 6.1, 6.4).
435				7	white solid	497.02	1.70 min Method A	479.19	^{1}H NMR ($CDCl_3$, 500MHz) δ 8.31 (s, 1H), 7.76 (d, 2H, J = 8.9), 7.56 (d, 2H, J = 8.5), 6.74 (s, 1H), 4.81 (t, 1H, J = 7.6), 4.71 (br s, 1H), 4.20 (br s, 1H), 3.13 (t, 2H, J = 8.6), 2.70-2.95 (m, 2H), 2.05-2.20 (m, 1H), 1.85-2.00 (m, 2H), 1.55-1.85 (m, 4H), 1.10-1.35 (m, 3H), 1.00 (d, 3H, J = 6.4), 0.97 (d, 3H, J = 6.7), 0.87 (t, 1H, J = 7.0).
436				13	white solid	476.99	1.76 min Method B	477.22	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.94 (dd, 2H, J = 1.8, 8.4), 7.69 (dd, 2H, J = 1.8, 8.7), 7.45-7.50 (m, 4H), 6.23 (br s, 1H), 5.19 (br s, 1H), 4.65 (d, 1H, J = 15.9), 4.46 (d, 1H, J = 15.9), 4.31 (dd, 1H, J = 6.6, 7.8), 2.61 (s, 3H), 1.75-1.85 (m, 1H), 1.28-1.35 (m, 1H), 1.08-1.15 (m, 1H), 0.76 (d, 3H, J = 6.6), 0.64 (d, 3H, J = 6.6).

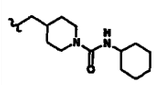
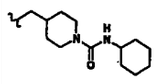
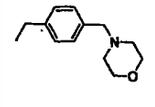
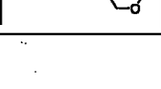
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
437				14	pale yellow solid	476.99	1.92 min Method B	477.18	^{1}H NMR ($CDCl_3$, 300MHz) δ 8.04 (d, 2H, J = 8.4), 7.70 (dd, 2H, J = 1.8, 8.4), 7.45-7.52 (m, 4H), 6.23 (br s, 1H), 5.19 (br s, 1H), 4.67 (d, 1H, J = 16.2), 4.47 (d, 1H, J = 15.9), 4.31 (t, 1H, J = 7.2), 2.47 (s, 3H), 1.75-1.85 (m, 1H), 1.28-1.35 (m, 1H), 1.08-1.15 (m, 1H), 0.76 (d, 3H, J = 6.6), 0.61 (d, 3H, J = 6.6)
438				6	white solid	480.03	1.81 min Method B	480.26	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.67 (d, 2H, J = 8.7), 7.45 (d, 2H, J = 8.7), 7.38 (d, 2H, J = 8.1), 7.32 (d, 2H, J = 7.5), 6.23 (br s, 1H), 5.19 (br s, 1H), 4.59 (d, 1H, J = 16.2), 4.45 (d, 1H, J = 15.9), 4.30 (t, 1H, J = 6.9), 3.47-3.56 (br m, 1H), 3.15-3.35 (br m, 1H), 2.81-3.09 (br m, 3H), 1.75-1.85 (m, 1H), 1.05-1.40 (m, 5H), 0.76 (d, 3H, J = 6.6), 0.65 (d, 3H, J = 6.6)
439				6	white solid	529.06	1.60 min Method B	529.25	^{1}H NMR ($CDCl_3$, 300MHz) δ 8.57 (d, 1H, J = 4.8), 7.80 (d, 2H, J = 8.4), 7.70-7.73 (m, 2H), 7.67 (d, 2H, J = 8.4), 7.45 (d, 2H, J = 8.4), 7.42 (d, 2H, J = 7.8), 7.36 (d, 1H, J = 7.8), 7.28 (br s, 1H), 6.23 (br s, 1H), 5.22 (br s, 1H), 4.77 (d, 2H, J = 4.8), 4.63 (d, 1H, J = 15.9), 4.44 (d, 1H, J = 15.9), 4.29 (t, 1H, J = 7.2), 1.73-1.85 (m, 1H), 1.25-1.38 (m, 1H), 1.06-1.14 (m, 1H), 0.75 (d, 3H, J = 6.3), 0.65 (d, 3H, J = 6.6)

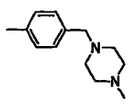
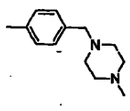
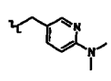
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
440				8	amber glass	512.04	1.36 min Method A	512.24	^{1}H NMR 400Hz ($CDCl_3$) δ 7.70 (d, 2H, J=8.0Hz), 7.74 (d, 2H, J=8.0Hz), 7.31 (d, 2H, J=6Hz), 7.08 (d, 2H, J=8.0Hz), 6.25 (s, br, 1H), 5.41 (s, br, 1H), 4.56 (d, 1H, J_{ab}=12Hz), 4.43 (d, 1H, J_{ab}=12Hz), 4.35 (t, 1H, J=6.0Hz), 3.72 (t, 4H, J=4.0Hz), 3.56 (s, 2H), 2.48 (t, 4H, J=4.0Hz), 1.79 (m, 1H), 1.36 (m, 1H), 1.18 (m, 1H), 0.79 (d, 3H, J=6.0Hz), 0.69 (d, 3H, J=6.0Hz)
441				8	amber glass	525.08	1.35 min Method A	525.23	^{1}H NMR 400Hz ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.47 (d, 2H, J=8.0Hz), 7.28 (t, 1H, J=6.0Hz), 7.07 (dd, 2H, J=8.0Hz), 6.29 (s, br, 1H), 5.55 (s, br, 1H), 4.46 (d, 1H, J_{ab}=14.0Hz), 4.41 (d, 1H, J_{ab}=14.0Hz), 4.34 (t, 1H, J=6.0Hz), 3.58 (s, 2H), 2.33 (s, 3H), 1.78 (m, 1H), 1.18 (m, 1H), 0.79 (d, 3H, J=6.0Hz), 0.68 (d, 3H, J=6.0Hz)
442				1-Method A	amber glass	470.94	1.74 min Method A	471.12	^{1}H NMR 400Hz ($CDCl_3$) δ 7.78 (t, 1H, J=6.0Hz), 7.72 (d, 2H, J=8.0Hz), 7.51 (d, 2H, J=8.0Hz), 7.19 (m, 2H), 6.21 (s, br, 1H), 5.37 (s, br, 1H), 4.64 (d, 1H, J_{ab}=14.0Hz), 4.47 (d, 1H, J_{ab}=14.0Hz), 4.34 (t, 1H, J=6.0Hz), 3.95 (s, 3H), 1.80 (m, 1H), 1.37 (m, 1H), 1.01 (m, 1H), 0.80 (d, 3H, J=6.0Hz), 0.69 (d, 3H, J=6.0Hz)

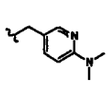
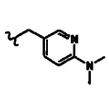
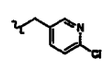
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
443				21	white solid	435.10	1.40 min Method D	$(M+Na)^+$ 458.2	^{1}H NMR (400 MHz, DMSO) δ 7.84 (d, 2H, J=8.6), 7.76 (d, 2H, J=8.3), 7.62 (d, 2H, J=8.8), 7.51 (d, 2H, J=8.3), 7.40 (s, 1H), 7.11 (s, 1H), 4.63 (ABq, 2H, $\Delta\upsilon$=5.9, J_{ab}=17.6), 4.56 (dd, 1H, J=8.3, 2.5), 4.54 (s, 1H), 1.95 (dd, 1H, J=13.7; 8.6), 1.26 (dd, 1H, J=13.6, 2.4), 1.04 (s, 3H), 0.99 (s, 3H).
444				7	clear oil	465.17	1.38 min Method A	466.20	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.73 (d, 2H, *J* = 8.8), 7.50 (d, 2H, *J* = 8.9), 6.67 (s, 1H), 5.37 (s, 1H), 4.14 (dd, 1H, *J* = 5.5, 9.5), 3.25 (dd, 1H, *J* = 10, 14), 2.97 (dd, 1H, *J* = 4.5, 14), 2.87-2.95 (m, 2H), 2.65-2.75 (m, 2H), 2.07-2.23 (m, 2H), 1.83-1.90 (m, 1H), 1.50-1.82 (m, 4H), 1.15-1.40 (m, 3H), 0.77-0.85 (m, 1H), 0.72 (d, 3H, *J* = 6.7), 0.66 (d, 3H, *J* = 6.4).
445				6	amber glass	456.92	1.62 min Method A	457.32	^{1}H NMR 400Hz ($CDCl_3$) δ 7.77 (d, 2H, J=6.0Hz), 7.68 (t, 1H, J=6.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.39 (m, 3H), 6.21 (s, br, 1H), 5.35 (s, br, 1H), 4.67 (d, 1H, J_{ab}=14.0Hz), 4.38 (d, 1H, J_{ab}=14.0Hz), 3.44 (m, 1H), 1.88 (m, 1H), 1.59 (m, 2H), 0.79 (d, 3H, J=6.0Hz), 0.69 (d, 3H, J=6.0Hz)

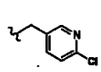
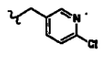
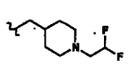
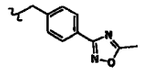
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Rot. Time/ Method	M+H$^+$	NMR Data
446				18	off-white solid	417.09	1.53 min Method F	(M+Na)$^+$ 418.2	^{1}H NMR (400 MHz, DMSO) δ 7.82 (d, 2H, J=8.8), 7.74 (d, 2H, J=8.5), 7.63 (d, 2H, J=8.8), 7.62 (s, 1H), 7.53 (d, 2H, J=8.5), 7.09 (s, 1H), 4.80 (ABq, 2H, Δυ=17.9, J_{AB}=17.8), 4.70 (s, 1H), 4.62 (t, 1H, J=7.6), 4.60 (s, 1H), 2.34 (dd, 1H, J=14.4, 7.1), 2.02 (dd, 1H, J=14.6, 7.3), 1.57 (s, 3H).
447				18	off-white solid	458.12	1.59 min Method G	(M+Na)$^+$ 459.2	^{1}H NMR (400 MHz, DMSO) δ 8.45 (d, 1H, J=2.2), .82 (d, 2H, J=8.6), 7.72 (m, 3H), 7.60 (d, 2H, J=8.8), 7.57 (s, 1H), 7.44 (d, 2H, J=8.5), 7.09 (s, 1H), 6.54 (t, 1H, J=2.0), 4.74 (ABq, 2H, Δυ=25.5, J_{AB}=16.8), 4.71 (s, 1H), 4.61 (m, 2H), 2.37 (dd, 1H, J=14.2, 7.1), 2.08 (dd, 1H, J=14.7, 7.6), 1.57 (s, 3H).
448				18	off-white solid	442.90	1.74 min Method A	443.05	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.96 (d, 2H, *J* = 8.2), 7.72 (d, 2H, *J* = 8.0), 7.48 (d, 2H, *J* = 8.0), 7.39 (d, 2H, *J* = 8.0), 6.33 (br s, 1H), 5.20 (br s, 1H), 4.55-4.62 (m, 2H), 4.39 (d, 1H, *J* = 15.4), 4.28-4.32 (m, 1H), 4.17-4.21 (m, 1H), 3.90 (s, 3H), 2.17-2.35 (m, 1H), 1.56-1.65 (m, 1H).

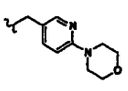
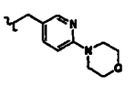
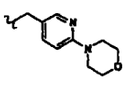
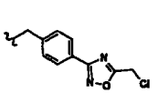
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
449				18, 12	yellow foam	442.94	1.65 min Method A	442.11	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.67 (ddd, 2H, J = 2.0, 2.6, 8.8), 7.42 (ddd, 2H, J = 2.0, 2.3, 8.8), 7.39 (d, 2H, J = 8.2), 7.24 (d, 2H, J = 8.2), 6.34 (br s, 1H), 5.35 (br s, 1H), 4.56 (dd, 1H, J = 5.8, 8.5), 4.48 (d, 1H, J = 15.5), 4.35 (d, 1H, J = 15.5), 4.30-4.33 (m, 1H), 4.18-4.22 (m, 1H), 2.23-2.39 (m, 1H), 1.56-1.670 (m, 2H), 1.57 (s, 6H)
450				18, 13	white solid	466.92	1.61 min Method A	467.18	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.96 (ddd, 2H, J = 1.7, 2.0, 8.4), 7.73 (ddd, 2H, J = 1.9, 2.5, 8.7), 7.49 (ddd, 2H, J = 2.0, 2.3, 8.7), 7.46 (d, 2H, J = 8.6), 6.34 (br s, 1H), 5.21 (br s, 1H), 4.64 (d, 1H, J = 15.4), 4.57-4.60 (m, 1H), 4.39 (d, 1H, J = 16.1), 4.30-4.32 (m, 1H), 4.18-4.21 (m, 1H), 2.61 (s, 3H), 2.18-2.36 (m, 1H), 1.55-1.66 (m, 1H)
451				18, 7	clear oil	533.07	1.71 min Method A	533.22	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.73 (d, 2H, J = 8.6), 7.51 (d, 2H, J = 8.8), 6.67 (s, 1H), 5.51 (s, 1H), 4.14-4.52 (m, 4H), 3.76-3.95 (m, 2H), 3.50-3.72 (m, 1H), 3.19-3.27 (m, 1H), 2.86-3.07 (m, 1H), 2.56-2.80 (m, 2H), 1.70-1.99 (m, 7H), 1.36-1.63 (m, 10H)

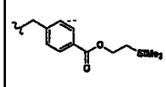
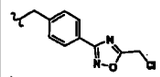
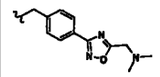
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
452				18, 7	clear oil	517.07	2.53 min Method A	517.32	^{1}H NMR ($CDCl_3$, 400MHz) δ7.74 (d, 2H, J = 8.6), 7.50 (d, 2H, J = 8.5), 6.70 (s, 1H), 5.60 (s, 1H), 4.50 (dd, 1H, J = 4.9, 9.8), 4.22-4.31 (m, 2H), 3.81-4.00 (m, 5H), 3.53-3.66 (m, 2H), 3.40-3.50 (m, 1H), 3.13-3.25 (m, 3H), 2.89 (dd, 1H, J = 4.6, 14), 2.62-2.77 (m, 3H), 1.50-1.95 (m, 6H), 1.01-1.16 (m, 3H)
453				18, 7	clear oil	531.09	2.27 min Method A	531.36	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.73 (d, 2H, J = 8.6), 7.51 (d, 2H, J = 8.6), 6.65 (d, 1H, J = 28), 5.47 (s, 1H), 4.50-4.63 (m, 1H), 4.20-4.45 (m, 1H), 4.05-4.15 (m, 2H), 3.55-3.65 (m, 2H), 3.05-3.35 (m, 6H), 2.85-3.00 (m, 3H), 2.55-2.35 (m, 2H), 1.50-2.00 (m, 6H), 1.00-1.45 (m, 7H).
454				8	amber glass	533.99	1.40 min Method A	534.27	^{1}H NMR 400Hz ($CDCl_3$) δ 7.78 (d, 2H, J=8.0Hz), 7.39 (m, 6H), 6.34 (s, br, 1H), 5.80 (s, br, 1H), 4.72 (d, 1H, J_{ab}=14.0Hz), 4.16 (m, 1H), 4.34 (d, 1H, J_{ab}= 14.0Hz), 3.60 (m, 4H), 3.84 (s, 2H), 2.62 (m, 2H), 2.25 (m, 4H)
455				18, 8	amber glass	501.98	1.27 min Method A	502.24	^{1}H NMR 400Hz ($CDCl_3$) δ 7.79 (d, 2H, J=8.0Hz), 7.39 (m, 6H), 6.33 (s, br, 1H), 5.80 (s, br, 1H), 4.68 (d, 1H, J_{ab}=14.0Hz), 4.22 (d, 1H, J_{ab}=14.0Hz), 3.55 (s, 2H), 2.62 (m, 2H), 2.43 (m, 8H), 2.30 (s, 3H)

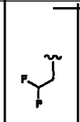
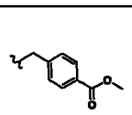
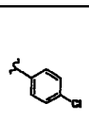
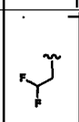
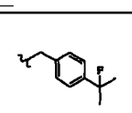
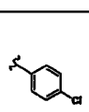
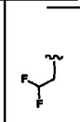
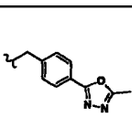
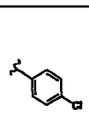
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
456				18, 8	amber glass	515.02	1.22 min Method A	515.31	^{1}H NMR 400Hz ($CDCl_3$) δ 7.79 (d, 2H, J=8.0Hz), 7.52 (d, 2H, J=8.0Hz), 7.39 (m, 4H), 6.34 (s, br, 1H), 5.78 (s, br, 1H), 5.72 (t, 1H, J=54.0Hz), 4.68 (d, 1H, J_{ab}=14.0Hz), 4.34 (d, 1H, J_{ab}=14.0Hz), 3.88 (m, 1H), 3.56 (m, 4H), 2.49 (m, 2H), 2.26 (m, 4H)
457				8	amber glass	547.03	1.26 min Method A	547.20	^{1}H NMR 400Hz ($CDCl_3$) δ 7.78 (d, 2H, J=8.0Hz), 7.50 (d, 2H, J=8.0Hz), 7.41 (m, 4H), 6.35 (s, br, 1H), 5.80 (s, br, 1H), 5.72 (t, 1H, J=54.0Hz), 4.68 (d, 1H, J_{ab}=14.0Hz), 4.35 (d, 1H, J_{ab}= 14.0Hz), 3.87 (m, 1H), 3.55 (s, 2H), 2.44 (m, 10H), 2.30 (s, 3H)
458				18, 1-Method B	white foam	446.91	1.01 Method B	447.13	^{1}H NMR ($CDCl_3$) TFA salt δ 8.14 (s, 1H), 7.98 (d, 1H, J=9.6Hz), 7.76 (d, 2H, J=6.8Hz), 7.55 (d, 2H, J=6.8Hz), 6.81 (d, 2H, J=9.6Hz), 6.45 (s, 1H), 6.10 (s, 1H), 5.70 (t, 1H, J=110.0Hz), 4.60 (d, 1H, J=16.0Hz), 4.51 (m, 1H), 4.06 (d, 1H, J=16Hz), 3.30 (s, 6H), 2.55 (m, 1H), 1.60 (m, 1H).

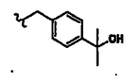
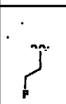
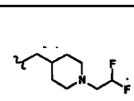
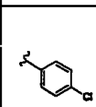
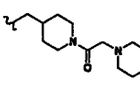
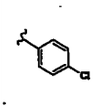
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
459				18, 1-Method B	white foam	456.97	1.14 Method B	457.23	^{1}H NMR ($CDCl_3$) TFA salt δ 8.11 (s, 1H), 7.95 (d, 1H, J=9.6Hz), 7.77 (d, 2H, J=6.8Hz), 7.51 (d, 2H, J=6.8Hz), 6.76 (d, 2H, J=9.6Hz), 6.34 (s, 1H), 6.02 (s, 1H), 4.58 (d br., 1H, J=8.4Hz), 4.46 (d, 1H, J=16.0Hz), 4.06 (d, 1H, J=16Hz), 3.29 (s, 6H), 2.50 (m, 1H), 1.39 (m, 1H), 1.25 (d, 3H, J=22.0Hz), 1.17 (d, 3H, J=22.0Hz).
460				1-Method B	light yellow gummy solid	478.92	1.89 min 3 X 50 mm ODS-A C-18 column, 4mL/min, 0-100% MeOH/H2O 0.1 %TFA 4min gradient	479.21	^{1}H NMR ($CDCl_3$) δ 8.09(s, 1H), 8.01 (d, 1H, J=9.2Hz), 7.75 (d, 2H, J=8.4Hz), 7.53 (d, 2H, J=8.4Hz), 6.82 (d, 1H, J=9.2Hz), 6.62 (s, br, 1H), 6.12 (s, br, 1H), 4.18-4.58 (m, 3H), 3.30 (s, 6H), 2.15 (m, 1H), 2.05(m, 1H), 1.85 (m, 1H), 1.40 (m, 1H)
461				18	clear oil	438.28	1.41 min Method B	438.01	^{1}H NMR ($CDCl_3$) δ 8.33(s, 1H), 7.73 (d, 1H, J=8.4Hz), 7.71 (d, 2H, J=8.8Hz), 7.51 (d, 2H, J=8.8Hz), 7.27 (d, 1H, J=8.4Hz), 6.56 (s, br, 1H), 6.11 (s, br, 1H), 5.69 (m, 1H), 4.21-4.62 (m, 3H), 2.52 (m, 1H), 1.63 (m, 1H)

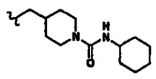
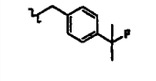
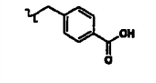
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
462				1	white solid	470.30	1.53 min Method B	470.02	^{1}H NMR ($CDCl_3$) δ 8.38 (s, 1H), 7.79 (d, 1H, J=8.0Hz), 7.68 (d, 2H, J=8.4Hz), 7.50 (d, 2H, J=8.4Hz), 7.31 (d, 1H, J=8.0Hz), 6.57 (s, br, 1H), 6.25 (s, br, 1H), 4.29-4.64 (m, 3H), 2.12 (m, 1H), 1.98 (m, 1H), 1.81 (m, 1H), 1.43 (m, 1H)
463				18	clear oil	434.32	1.43 min Method B	434.13	^{1}H NMR ($CDCl_3$) δ 8.37 (s, 1H), 7.70 (d, 1H, J=8.8Hz), 7.68 (d, 1H, J=8.8Hz), 7.67 (d, 2H, J=6.8Hz), 7.48 (d, 2H, J=6.8Hz), 6.25 (s, br, 1H), 5.31 (s, br, 1H), 4.34-4.62 (m, 5H), 1.35-2.05 (m, 4H)
464				18, 7	clear oil	469.14	1.14 min Method A	470.17	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.73 (d, 2H, J = 8.8), 7.51 (d, 2H, J = 8.8), 6.65 (s, 1H), 5.39 (s, 1H), 4.05-4.35 (m, 2H), 3.25 (dd, 1H, J = 10, 14), 2.85-3.04 (m, 3H), 2.65-2.85 (m, 2H), 2.09-2.29 (m, 2H), 1.93-2.10 (m, 1H), 1.83-1.91 (m, 10H)
465				15	white solid	476.99	1.91 min Method A	477.13	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.98 (d, 2H, J = 8.2), 7.68 (d, 2H, J = 8.9), 7.45 (d, 4H, J = 8.5), 6.21 (s, 1H), 5.19 (s, 1H), 4.62 (d, 1H, J = 15), 4.48 (d, 1H, J = 16), 4.31 (t, 1H, J = 7.0), 2.65 (s, 3H), 1.75-1.85 (m, 1H), 1.20-1.35 (m, 4H), 1.10-1.17 (m, 1H), 0.85-0.90 (m, 1H), 0.75 (d, 3H, J = 6.7), 0.64 (d, 3H, J = 6.4)

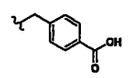
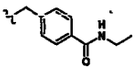
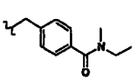
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
466				1-Method B	clear gummy solid	520.96	1.17 min Method B	521.19	^{1}H NMR ($CDCl_3$) δ 8.16 (s, 1H), 8.06 (d, 1H, J=9.2Hz), 7.75 (d, 2H, J=8.4Hz), 7.50 (d, 2H, J=8.4Hz), 7.31 (d, 1H, J=9.2Hz), 6.67 (s, br, 1H), 6.20 (s, br, 1H), 4.19-4.60(m, 3H), 3.87 (m, 4H), 3.69(m, 4H), 2.14 (m, 1H), 1.98 (m, 1H), 1.83(m, 1H), 1.38 (m, 1H)
467				18, 1-Method B	clear gummy solid	470.95	0.983 min Method B	471.19	^{1}H NMR ($CDCl_3$) δ 8.15 (s, 1H), 8.10 (d, 1H, J=9.2Hz), 7.77 (d, 2H, J=8.4Hz), 7.53 (d, 2H, J=8.4Hz), 6.93 (d, 1H, J=9.2Hz), 6.65 (s, br, 1H), 6.22 (s, br, 1H), 4.09-4.67 (m, 5H), 3.87 (m, 4H), 3.68 (m, 4H), 2.25 (m, 1H), 1.63(m, 1H)
468				1-Method B	clear gummy solid	499.01	1.153 min Method B	499.23	^{1}H NMR ($CDCl_3$) δ 8.12 (s, 1H), 8.07 (d, 1H, J=9.2Hz), 7.78 (d, 2H, J=8.4Hz), 7.52 (d, 2H, J=8.4Hz), 6.91 (d, 1H, J=9.2Hz), 6.63 (s, br, 1H), 6.19 (s, br, 1H), 4.07-4.62 (m, 3H), 3.86 (m, 4H), 3.68 (m, 4H), 2.46 (m, 1H), 1.31 (m, 1H), 1.25 (d, 3H, J=21.6), 1.17(d, 3H, J=21.6)
469				15	white solid	511.43	1.90 min Method C	511.13	^{1}H NMR ($CDCl_3$, 400MHz) δ 8.01 (d, 2H, *J* = 8.3), 7.69 (d, 2H, *J* = 8.8), 7.43-7.51 (m, 4H), 6.20 (s, 1H), 5.15 (s, 1H), 4.74 (s, 2H), 4.63 (d, 1H, *J* = 15), 4.47 (d, 1H, *J* = 16), 4.31 (t, 1H, *J* = 6.8), 1.74-1.87 (m, 1H), 1.04-1.88 (m, 4H), 0.82-0.94 (m, 1H), 0.76 (d, 3H, *J* = 6.6), 0.65 (d, 3H, *J* = 6.6).

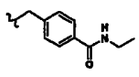
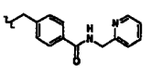
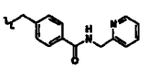
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
470				1	white solid	529.11	2.17 min Method D	529.11	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.95 (d, 2H, J = 8.4), 7.71 (dd, 2H, J = 1.6, 8.4), 7.48 (dd, 2H, J = 2.4, 8.8), 7.38 (dd, 2H, J = 2.4, 8.8), 6.31 (br s, 1H), 5.22 (br s, 1H), 4.60 (d, 1H, J = 15.6), 4.55-4.58 (m, 1H), 4.38-4.42 (m, 3H), 4.29-4.32 (m, 1H), 4.17-4.21 (m, 1H), 2.18-2.32 (m, 2H), 1.12 (dd, 2H, J = 6.8, 8.4), 0.08 (s, 9H).
471				15, 23	white solid	510.14	1.86 min Method A	511.13	^{1}H NMR ($CDCl_3$, 400MHz) δ 8.01 (d, 2H, J = 8.4), 7.69 (d, 2H, J = 8.8), 7.47 (d, 2H, J = 8.0), 7.46 (d, 2H, J = 8.8), 6.20 (br s, 1H), 5.20 (br s, 1H), 4.74 (s, 2H), 4.64 (d, 1H, J = 15), 4.49 (d, 1H, J = 15), 4.31 (t, 1H, J = 7.0), 1.73-1.87 (m, 1H), 1.20-1.37 (m, 1H), 1.07-1.17 (m, 1H), 0.76 (d, 3H, J = 6.6), 0.65 (d, 3H, J = 6.6)
472				15, 8	white solid	519.17	1.42 min Method A	520.18	^{1}H NMR ($CDCl_3$, 400MHz) δ 8.02 (d, 2H, J = 7.6), 7.71 (d, 2H, J = 8.4), 7.52 (d, 2H, J = 8.0), 7.48 (d, 2H, J = 8.4), 6.23 (br s, 1H), 5.17 (br s, 1H), 4.70 (d, 1H, J = 16), 4.44 (d, 1H, J = 16), 4.31 (t, 1H, J = 6.4), 3.70 (s, 2H), 3.02 (s, 6H), 1.75-1.90 (m, 1H), 1.00-1.40 (m, 2H), 0.76 (d, 3H, J = 6.8), 0.66 (d, 3H, J = 6.4)

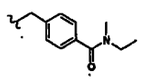
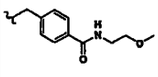
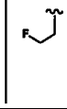
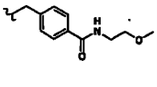
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
473				1	off-white foam	460.89	2.11 min Method A	461.08	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.97 (d, 2H, J = 8.4), 7.72 (d, 2H, J = 8.4), 7.51 (dd, 2H, J = 2.0, 8.4), 7.38 (d, 2H, J = 8.0), 6.32 (br s, 1H), 5.71 (tm, 1H, J_{H-F} = 55), 5.19 (br s, 1H), 4.60 (d, 1H, J = 15.6), 4.49-4.53 (m, 1H), 4.33 (d, 1H, J = 15.6), 3.91 (s, 3H), 2.42-2.68 (m, 1H), 1.54-1.65 (m, 1H).
474				1	pale yellow foam	462.92	2.24 min Method A	485.07 ($M + Na^+$)	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.67 (d, 2H, J = 8.4), 7.47 (d, 2H, J = 8.8), 7.25-7.29 (m, 4H), 6.33 (br s, 1H), 5.72 (tm, 1H, J_{H-F} = 57), 5.23 (br s, 1H), 4.49-4.53 (m, 1H), 4.46 (d, 1H, J = 15.6), 4.34 (d, 1H, J = 15.0), 2.52-2.60 (m, 1H), 1.55-1.65 (m, 1H), 1.48 (s, 3H), 1.43 (s, 3H).
475				1, 13	white foam	484.91	1.67 min Method D	485.07	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.97 (d, 2H, J = 8.0), 7.73 (dd, 2H, J = 2.0, 8.8), 7.52 (dd, 2H, J = 2.0, 8.8), 7.45 (d, 2H, J = 8.4), 6.34 (br s, 1H), 5.73 (tm, 1H, J_{H-F} = 57), 5.20 (br s, 1H), 4.63 (d, 1H, J = 15.6), 4.52-4.55 (m, 1H), 4.32 (d, 1H, J = 15.6), 2.61 (s, 3H), 2.55-2.60 (m, 1H), 1.61-1.65 (m, 1H).

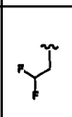
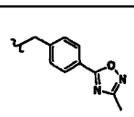
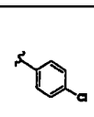
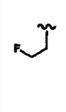
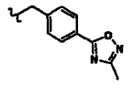
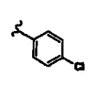
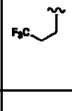
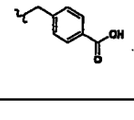
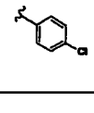
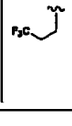
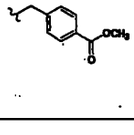
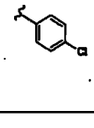
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
476				1, 12	white foam	460.93	1.72 min Method D	483.07 (M + Na$^+$)	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.68 (dd, 2H, J = 2.0, 8.8), 7.48 (dd, 2H, J = 8.4), 7.41 (d, 2H, J = 8.4), 7.23 (d, 2H, J = 8.8), 6.30 (br s, 1H), 5.73 (tm, 1H, $J_{H,F}$ = 57), 5.18 (br s, 1H), 4.48-4.52 (m, 1H), 4.44 (d, 1H, J = 15.2), 4.34 (d, 1H, J = 15.2), 2.50-2.65 (m, 1H), 1.61-1.70 (m, 1H), 1.56 (s, 6H).
477				7	clear oil	455.93	0.99 min Method A	456.20	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.72-7.86 (m, 2H), 7.45-7.52 (m, 2H), 6.70 (br s, 1H), 5.44 (br s, 1H), 4.46-4.57 (m, 2H), 4.00-4.37 (m, 2H), 3.24 (dd, 1H, J = 4.4, 9.8), 2.70-3.15 (m, 6H), 2.15-2.34 (m, 2H), 1.80-1.93 (m, 2H), 1.54-1.63 (m, 2H), 1.25-1.35 (m, 2H).
478				7	clear oil	519.04	1.12 min Method A	519.23	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.71-7.84 (m, 2H), 7.39-7.55 (m, 2H), 6.70 (br m, 1H), 5.87 (br m, 1H), 4.88 (m, 1H), 4.50 (d, 1H, J = 9.5), 4.21-4.31 (m, 2H), 4.11-4.20 (m, 2H), 3.80-3.87 (m, 2H), 3.69-3.77 (m, 2H), 3.31-3.50 (m, 2H), 3.00-3.21 (m, 2H), 2.80-3.95 (m, 2H), 2.10-2.50 (m, 4H), 1.85-1.95 (m, 2H), 1.73 (d, 2H, J = 8.5), 1.40-1.50 (m, 2H)

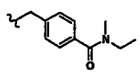
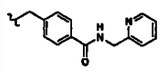
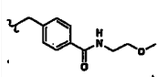
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
479				7	clear oil	535.06	1.72 min Method A	535.18	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.73 (d, 2H, J = 8.6), 7.53 (d, 2H, J = 8.6), 6.70 (br s, 1H), 5.70 (tm, 1H, J_{HF} = 50), 5.55 (br s, 1H), 4.46 (dd, 1H, J = 3.8, 10), 3.80-4.00 (m, 3H), 3.50-3.70 (m, 1H), 3.15-3.30 (m, 1H), 2.80-3.95 (m, 1H), 2.60-2.80 (m, 2H), 2.40-2.60 (m, 1H), 1.05-2.00 (m, 16H)
480				1	off-white foam	444.93	1.89 min Method D	467.09 ($M+Na^+$)	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.66 (ddd, 2H, J = 2.0, 2.4, 8.8), 7.44 (ddd, 2H, J = 2.0, 2.4, 8.8), 7.25-7.31 (m, 4H), 6.30 (br s, 1H), 5.22 (br s, 1H), 4.56-4.60 (m, 1H), 4.47 (d, 1H, J = 15.6), 4.39 (d, 1H, J = 16.0), 4.32-4.36 (m, 1H), 4.20-4.24 (m, 1H), 2.23-2.39 (m, 1H), 1.70-1.85 (m, 1H), 1.65-1.68 (m, 3H), 1.53 (s, 3H).
481				6	white solid	428.87	1.58 min Method D	429.04	^{1}H NMR (CD_3OD, 400MHz) δ 7.92 (d, 2H, J = 8.4), 7.79 (ddd, 2H, J = 2.0, 2.4, 8.8), 7.52 (ddd, 2H, J = 2.0, 2.8, 8.8), 7.47 (d, 2H, J = 8.0), 4.80 (d, 1H, J = 16), 4.66 (d, 1H, J = 14.5), 4.64 (t, 1H, J = 7.6), 4.10-4.33 (m, 2H), 2.05-2.12 (m, 1H), 1.72-1.80 (m, 1H)

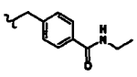
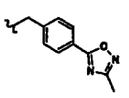
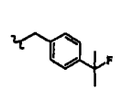
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
482				6	yellow solid	446.86	1.39 min Method B	447.06	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.89 (d, 2H, J = 8.0), 7.66 (dd, 2H, J = 2.0, 8.0), 7.41 (dd, 2H, J = 2.0, 8.4), 7.31 (d, 2H, J = 8.0), 6.61 (br s, 1H), 5.90 (br s, 1H), 5.76 (tm, 1H, $J_{H,F}$ = 57), 4.56 (d, 1H, J = 16.0), 4.49-4.52 (m, 1H), 4.36 (d, 1H, J = 12.0), 2.50-2.65 (m, 1H), 1.61-1.70 (m, 1H).
483				6	white solid	455.94	1.34 min Method B	488.11 ($M+Na^+$)	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.72 (d, 2H, J = 8.0), 7.68 (d, 2H, J = 8.0), 7.49 (ddd, 2H, J = 2.0, 2.4, 8.4), 7.38 (d, 2H, J = 8.0), 6.32 (br s, 1H), 6.06 (br s, 1H), 5.19 (br s, 1H), 4.59 (d, 1H, J = 15.0), 4.56-4.60 (m, 1H), 4.37 (d, 1H, J = 15.0), 4.29-4.32 (m, 1H), 4.16-4.19 (m, 1H), 3.45-3.49 (m, 2H), 2.15-2.30 (m, 1H), 1.50-1.65 (m, 1H), 1.25 (t, 3H, J = 8.0).
484				6	white solid	469.97	1.40 min Method B	470.15	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.72 (d, 2H, J = 8.0), 7.48 (d, 2H, J = 8.0), 7.30-7.36 (m, 4H), 6.30 (br s, 1H), 5.26 (br s, 1H), 4.54-4.58 (m, 2H), 4.38 (d, 1H, J = 15.2), 4.29-4.32 (m, 1H), 4.18-4.22 (m, 1H), 3.55-3.59 (m, 1H), 3.22-3.27 (m, 1H), 2.90 and 3.05 (2 s, 3H), 2.20-2.33 (m, 1H), 1.50-1.65 (m, 1H), 1.08-1.30 (m, 3H).

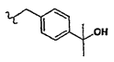
Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
485				6	white solid	473.93	1.33 min Method B	474.11	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.72 (d, 2H, J = 8.8), 7.70 (d, 2H, J = 8.4), 7.51 (d, 2H, J = 8.8), 7.38 (d, 2H, J = 8.0), 6.31 (br s, 1H), 6.05 (br s, 1H), 5.72 (tm, 1H, J_{H-F} = 57), 5.20 (br s, 1H), 4.59 (d, 1H, J = 15.6), 4.49-4.52 (m, 1H), 4.31 (d, 1H, J = 15.6), 3.46-3.53 (m, 2H), 2.45-2.65 (m, 1H), 1.57-1.65 (m, 1H), 1.25 (t, 3H, J = 7.2)
486				6	white solid	536.99	1.13 min Method B	537.17	^{1}H NMR ($CDCl_3$, 400MHz) δ 8.57 (d, 1H, J = 4.8), 7.83 (d, 2H, J = 8.4), 7.71-7.78 (m, 3H), 7.71 (br s, 1H), 7.52 (dd, 2H, J = 1.6, 8.8), 7.40 (d, 2H, J = 8.0), 7.30-7.35 (m, 1H), 7.23-7.28 (m, 1H), 6.32 (br s, 1H), 5.72 (tm, 1H, J_{H-F} = 57), 5.25 (br s, 1H), 4.75 (d, 2H, J = 4.8), 4.59 (d, 1H, J = 15.6), 4.49-4.53 (m, 1H), 4.33 (d, 1H, J = 15.6), 2.48-2.65 (m, 1H), 1.58-1.65 (m, 1H).
487				6	white solid	519.00	1.10 min Method B	519.35	^{1}H NMR ($CDCl_3$, 400MHz) δ 8.58 (d, 1H, J = 4.4), 7.92 (d, 2H, J = 8.4), 7.71-7.78 (m, 4H), 7.48 (dd, 2H, J = 2.0, 8.8), 7.39-7.44 (m, 3H), 7.24-7.30 (m, 1H), 6.28 (br s, 1H), 5.20 (br s, 1H), 4.78 (d, 2H, J = 4.8), 4.55-4.61 (m, 2H), 4.39 (d, 1H, J = 15.6), 4.29-4.32 (m, 1H), 4.17-4.21 (m, 1H), 2.20-2.33 (m, 1H), 1.50-1.65 (m, 1H)

Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
488				6	white solid	487.96	1.63 min Method D	488.34	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.72 (dd, 2H, J = 2.0, 8.8), 7.51 (dd, 2H, J = 2.0, 8.4), 7.50 (s, 4H), 6.30 (br s, 1H), 5.72 (tm, 1H, J_{H-F} = 57), 5.24 (br s, 1H), 4.55 (d, 1H, J = 15.5), 4.49-4.52 (m, 1H), 4.33 (d, 1H, J = 15.5), 3.57 (br s, 1H), 3.23 (br s, 1H), 2.90 and 3.05 (2 s, 3H), 2.48-2.62 (m, 1H), 1.57-1.72 (m, 1H), 1.08-1.30 (m, 3H).
489				6	off-white solid	503.96	1.40 min Method A	504.41	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.72 (d, 4H, J = 8.4), 7.52 (d, 2H, J = 8.8), 7.38 (d, 2H, J = 8.4), 6.49 (br s, 1H), 6.31 (br s, 1H), 5.72 (tm, 1H, J_{H-F} = 57), 5.19 (br s, 1H), 4.59 (d, 1H, J = 15.0), 4.48-4.52 (m, 1H), 4.31 (d, 1H, J = 15.6), 3.62-3.68 (m, 2H), 3.53-3.59 (m, 2H), 3.39 (s, 3H), 2.48-2.62 (m, 1H), 1.57-1.72 (m, 1H).
490				6	white solid	485.97	1.27 min Method B	486.14	^{1}H NMR ($CDCl_3$, 300MHz) δ 7.69-7.74 (m, 4H), 7.51 (dd, 2H, J = 1.8, 8.4), 7.38 (d, 2H, J = 8.1), 6.48 (br s, 1H), 6.32 (br s, 1H), 5.19 (br s, 1H), 4.54-4.62 (m, 2H), 4.30-4.41 (m, 2H), 4.13-4.19 (m, 1H), 3.61-3.67 (m, 2H), 3.53-3.59 (m, 2H), 3.39 (s, 3H), 2.48-2.62 (m, 1H), 1.57-1.72 (m, 1H).

Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
491				14	off-white solid	484.91	1.54 min Method B	485.12	^{1}H NMR ($CDCl_3$, 400MHz) δ 8.06 (d, 2H, J = 8.4), 7.74 (d, 2H, J = 8.8) 7.53 (d, 2H, J = 8.8), 7.48 (d, 2H, J = 8.4), 6.34 (br s, 1H), 5.72 (tm, 1H, J_{H-F} = 57), 5.20 (br s, 1H), 4.65 (d, 1H, J = 15.4), 4.51-4.56 (m, 1H), 4.33 (d, 1H, J = 15.8), 2.48-2.65 (m, 1H), 2.47 (s, 3H), 1.57-1.65 (m, 1H).
492				14	off-white solid	466.92	1.65 min Method A	467.19	^{1}H NMR ($CDCl_3$, 400MHz) δ 8.04 (d, 2H, J = 8.0), 7.74 (dd, 2H, J = 1.6, 8.4), 7.48-7.51 (m, 4H), 6.32 (br s, 1H), 5.17 (br s, 1H), 4.65 (d, 1H, J = 16.0), 4.56-4.60 (m, 1H), 4.40 (d, 1H, J = 16.0), 4.29-4.32 (m, 1H), 4.18-4.21 (m, 1H), 2.47 (s, 3H), 2.18-2.38 (m, 1H), 1.50-1.65 (m, 1H).
493				6	white solid	478.88	1.59 min Method A	479.15	^{1}H NMR (dmso-d_6, 400MHz) δ 7.88 (d, 2H, J = 8.0); 7.85 (d, 2H, J = 8.8), 7.63 (d, 2H, J = 8.8), 7.51 (d, 2H, J = 8.0), 7.42 (br s, 1H), 7.24 (br s, 1H), 4.77 (d, 2H, J = 2.0), 4.40-4.44 (m, 1H), 1.97-2.05 (m, 2H), 1.75-1.84 (m, 1H), 1.43-1.50 (m, 1H).
494				1	white solid	492.91	1.66 min Method A	493.11	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.97 (d, 2H, J = 8.4), 7.69 (dd, 2H, J = 1.6, 8.4), 7.50 (dd, 2H, J = 2.0, 8.4), 7.40 (d, 2H, J = 8.4), 6.22 (br s, 1H), 5.19 (br s, 1H), 4.58 (d, 1H, J = 16.0), 4.43 (d, 1H, J = 15.6), 4.31-4.35 (m, 1H), 3.91 (s, 3H), 2.08-2.20 (m, 1H), 1.88-2.03 (m, 1H), 1.69-1.82 (m, 1H), 1.38-1.47 (m, 1H).

Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
495				6	off-white solid	519.97	1.48 min Method B	520.21	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.70 (d, 2H, J = 8.4), 7.50 (d, 2H, J = 8.8), 7.37 (d, 2H, J = 8.4), 7.33 (d, 2H, J = 8.0), 6.20 (br s, 1H), 5.26 (br s, 1H), 4.45-4.52 (m, 2H), 4.33 (t, 1H, J = 7.2), 3.61-3.70 (m, 1H), 3.22-3.27 (m, 1H), 2.90 and 3.06 (2 s, 3H), 2.05-2.18 (m, 1H), 1.90-2.03 (m, 1H), 1.69-1.82 (m, 1H), 1.38-1.47 (m, 1H), 1.11-1.28 (m, 3H).
496				6	off-white solid	569.01	1.21 min Method B	569.16	^{1}H NMR ($CDCl_3$, 400MHz) δ 8.57 (d, 1H, J = 4.8), 7.82 (d, 2H, J = 8.4), 7.68-7.72 (m, 4H), 7.50 (d, 2H, J = 8.8), 7.42 (d, 2H, J = 8.4), 7.35 (d, 1H, J = 8.0), 7.24 (br s, 1H), 6.24 (br s, 1H), 5.26 (br s, 1H), 4.76 (d, 2H, J = 4.8), 4.58 (d, 1H, J = 15.6), 4.41 (d, 1H, J = 15.6), 4.31-4.35 (m, 1H), 2.10-2.19 (m, 1H), 1.90-2.03 (m, 1H), 1.69-1.82 (m, 1H), 1.38-1.47 (m, 1H).
497				6	white solid	535.97	1.53 min Method A	536.16	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.72 (d, 2H, J = 8.0), 7.69 (d, 2H, J = 8.4), 7.50 (d, 2H, J = 8.4), 7.40 (d, 2H, J = 8.4), 6.48 (br s, 1H), 6.22 (br s, 1H), 5.20 (br s, 1H), 4.57 (d, 1H, J = 15.6), 4.41 (d, 1H, J = 15.6), 4.30-4.34 (m, 1H), 3.63-3.67 (m, 2H), 3.55-3.57 (m, 2H), 3.39 (s, 3H), 2.10-2.20 (m, 1H), 1.88-2.03 (m, 1H), 1.69-1.82 (m, 1H), 1.38-1.47 (m, 1H).

Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	M+H$^+$	NMR Data
498				6	white solid	505.95	1.55 min Method A	506.10	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.69 (dd, 2H, J = 1.6, 8.4), 7.50 (d, 2H, J = 8.4), 7.39 (d, 2H, J = 8.0), 7.25-7.28 (m, 2H), 6.22 (br s, 1H), 6.03 (br s, 1H), 5.19 (br s, 1H), 4.57 (d, 1H, J = 15.6), 4.41 (d, 1H, J = 15.6), 4.30-4.33 (m, 1H), 3.48-3.53 (m, 2H), 2.10-2.20 (m, 1H), 1.88-2.03 (m, 1H), 1.69-1.82 (m, 1H), 1.38-1.47 (m, 1H), 1.25 (t, 3H, J = 7.2).
499				14	Beige solid	516.93	1.65 min Method B	517.15	^{1}H NMR ($CDCl_3$, 400MHz) δ 8.06 (dd, 2H, J = 1.6, 8.4), 7.71 (dd, 2H, J = 2.0, 8.4), 7.49-7.52 (m, 4H), 6.22 (br s, 1H), 5.20 (br s, 1H), 4.63 (d, 1H, J = 15.6), 4.44 (d, 1H, J = 15.6), 4.33-4.37 (m, 1H), 2.47 (s, 3H), 2.10-2.20 (m, 1H), 1.91-2.03 (m, 1H), 1.73-1.86 (m, 1H), 1.40-1.51 (m, 1H).
500				1	off-white foam	494.94	1.74 min Method B	475.27 (M–HF+H+)	^{1}H NMR ($CDCl_3$, 500MHz) δ 7.65 (dd, 2H, J = 2.0, 8.5), 7.46 (ddd, 2H, J = 2.0, 2.5, 7.5), 7.25-7.31 (m, 4H), 6.18 (br s, 1H), 5.24 (br s, 1H), 4.47 (d, 1H, J = 15.5), 4.41 (d, 1H, J = 15.0), 4.35 (t, 1H, J = 7.7), 2.08-2.20 (m, 1H), 1.88-2.03 (m, 1H), 1.69-1.82 (m, 1H), 1.68 (s, 3H), 1.63 (s, 3H), 1.38-1.47 (m, 1H).

Ex. No.	R^1	R^2	R^3	Reaction Scheme	Appearance	Calc. MW	Ret. Time/ Method	$M+H^+$	NMR Data
501				12	off-white solid	492.95	2.20 min Method A	475.96 (- H_2O) 492.01 (neg ion)	^{1}H NMR ($CDCl_3$, 400MHz) δ 7.65 (d, 2H, J = 8.8), 7.46 (d, 2H, J = 8.4), 7.40 (d, 2H, J = 8.4), 7.25-7.27 (m, 2H), 6.19 (br s, 1H), 5.23 (br s, 1H), 4.46 (d, 1H, J = 15.4), 4.41 (d, 1H, J = 15.4), 4.34 (t, 1H, J = 7.6), 2.08-2.20 (m, 1H), 1.88-2.03 (m, 1H), 1.69-1.82 (m, 1H), 1.56 (s, 3H), 1.54 (s, 3H), 1.38-1.47 (m, 1H).

Method A = 4.6 X 33 mm ODS-A C-18 column, 5mL/min, 10:90:0.1 (MeOH/H_2O/TFA) to 90:10:0.1 (MeOH/H_2O/TFA), 2min gradient

Method B = 3 X 50 mm ODS-A C-18 column, 5mL/min, 10:90:0.1 (MeOH/H_2O/TFA) to 90:10:0.1 (MeOH/H_2O/TFA), 2min gradient

Method C = 3 X 50 mm ODS-A C-18 column, 5mL/min, 10:90:0.1 (MeOH/H_2O/TFA) to 90:10:0.1 (MeOH/H_2O/TFA), 3min gradient

Method D = 4.6 X 50 mm Phenomenex Luna C-18 S5 column, 5mL/min, 0-100% MeOH/H_2O, 0.1%TFA, 2min gradient

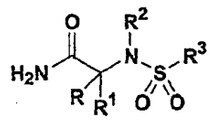
Method E = 4.6 X 50 mm Xterra C18 S5 column, 5mL/min, 0-100% MeOH/H_2O, 0.1 % TFA, 2min gradient

Method F = 4.6 X 50 mm Phenomenex Luna C-18 S5 column, 5mL/min, 10:90:0.1 (MeOH/H_2O/TFA) to 90:10:0.1 (MeOH/H_2O/TFA), 2min gradient

Method G= 3.0 X 50 mm Xterra C18 S7 column, 5mL/min, 10:90:0.1 (MeOH/H_2O/TFA) to 90:10:0.1 (MeOH/H_2O/TFA), 2min gradient

What is claimed is:

1. A compound of formula I; or an optical isomer thereof



I

wherein:

R^1 is selected from the group consisting of

(a) a straight or branched-chain C_{1-6} alkyl or C_{2-6}alkenyl optionally substituted with substituents selected from the group consisting of hydroxy, C_{3-7} cycloalkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, and halogen;

(b) C_{3-7} cycloalkyl optionally substituted with hydroxy or halogen;

R is hydrogen or R^1 and R taken together is C_{2-5}alkylene;

R^2 is selected from the group consisting of

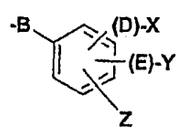
(a) a straight or branched-chain C_{1-6}alkyl or C_{3-6}alkenyl optionally substituted with substituents selected from the group consisting of halogen, C_{1-4}alkoxy, and NR^4R^5;

(b) C_{3-7} cycloalkylmethyl optionally substituted with substituents selected from the group consisting of amino, $(C_{1-4}alkyl)NH$-, $di(C_{1-4}alkyl)N$-, C_{1-4}alkylC(=O)NH-, and C_{1-4}alkylOC(=O)NH-;

(c) a straight or branched-chain C_{1-6}alkyl-C(=O)-A;

(d) -B-naphthyl;

(e)



D and E are each independently a direct bond, a straight or branched-chain C_{1-6}alkyl, C_{2-6} alkenyl, or C_{3-7} cycloalkyl;

Z is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halogen, cyano, hydroxy, $-OCHF_2$, $-OCF_3$, $-CF_3$, and $-CHF_2$;

X and Y are each independently selected from the group consisting of hydrogen, hydroxy, halogen, (halogen)$_3$C-, (halogen)$_2$CH-, C_{1-4}alkylS-, C_{1-4}alkylS(O)-, C_{1-4}alkylSO$_2$-, nitro, F_3S-, and cyano;

$-OR^6$;

$-NR^4R^5$;

$-NR^7C(=O)R^8$;

$-NR^7C(=O)OR^8$;

$-NHSO_2C_{1-4}$alkyl;

$-N(SO_2C_{1-4}alkyl)_2$;

-C(=O)W wherein W is selected from the group consisting of hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, phenoxy, and $-NR^4R^5$;

$-OC(=O)C_{1-4}$alkyl;

-phenyl in which said phenyl is optionally substituted with cyano, halogen, C_{1-4}alkoxy, C_{1-4}alkylS-, $CH_3C(=O)$, C_{1-4}alkylS(O)-, or C_{1-4}alkylSO$_2$-; and

heterocyclic group, in which said heterocyclic group is selected from the group consisting of furanyl, thiofuranyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, oxadiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, and thiazolyl, wherein said heterocyclic group is optionally substituted with substituents selected from the group consisting of cyano, halogen, C_{1-4}alkyl, (halogen)C_{1-4}alkyl, and CO_2C_{1-4}alkyl;

(f) -B-(heterocycle), in which said heterocycle is selected from the group consisting of furanyl, thiofuranyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, oxadiazolyl, oxazolyl, isoxazolyl, thiadiazolyl and thiazolyl wherein said heterocycle is optionally substituted with substituents selected from the group consisting of cyano, halogen, C_{1-4}alkyl, CO_2C_{1-4}alkyl, amino,

(C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and 4-(C_{1-6}alkyl)piperazin-1-yl;

(g) -B-(piperidin-4-yl), in which said piperidin-4-yl is optionally substituted with substituents selected from the group consisting of a straight or branched-chain C_{1-6}alkyl, $CH_2C(=O)$phenyl, phenyl and phenylmethyl in which said C_{1-6}alkyl and said phenyl are optionally substituted with substituents selected from the group consisting of cyano, halogen, benzimidazol-2-yl, pyridyl and tetrahydrofuran-2-yl; and -C(=O)W' wherein W' is selected from the group consisting of C_{1-4}alkoxy, R^9, and $-NR^4R^5$;

A is hydroxy, C_{1-4}alkoxy or NR^4R^5;

B is a straight or branched-chain C_{1-6}alkyl or C_{3-6}alkenyl;

R^3 is phenyl or pyridyl optionally substituted with substituents selected from the group consisting of halogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkyl, $(halogen)_3C$-, $(halogen)_2CH$-, and $halogenCH_2$-;

R^4 and R^5 each are independently hydrogen, a straight or branched-chain C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylmethyl, C_{1-4}alkoxy, phenyl, benzyl, pyridyl, piperidin-4-yl, indan-1-yl, indan-2-yl, tetrahydrofuran-3-yl, or pyrrolidin-3-yl; in which each is optionally substituted with substituents selected from the group consisting of hydroxy, cyano, halogen, $(halogen)_3C$-, $(halogen)_2CH$-, $halogenCH_2$-, hydroxymethyl, benzyloxymethyl, phenyl, pyridyl, C_{1-4}alkyl, C_{1-4}alkoxy, $(halogen)_3C$-O-, $(halogen)_2CH$-O-, C_{1-4}alkylthio, amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, 4-(C_{1-6}alkyl)piperazin-1-yl, 4-phenylpiperazin-1-yl, 4-benzylpiperazin-1-yl, 4-pyridylpiperazin-1-yl, CO_2H, CO_2C_{1-4}alkyl, $C(=O)NHC_{1-4}$alkyl, and $C(=O)N(C_{1-4}alkyl)_2$;

R^4 and R^5 taken together may be morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, decahydroquinolin-1-yl, piperidin-1-yl, piperazin-1-yl, [1,4]-oxazepan-4-yl, azetidin-1-yl, 2,3-

dihydro-1*H*-isoindol-2-yl, or 2,3-dihydro-1*H*-indol-1-yl; in which each is optionally substituted with substituents selected from the group consisting of hydroxy, cyano, halogen, (halogen)$_3$C-, (halogen)$_2$CH-, halogenCH$_2$-, phenyl, pyridyl, benzyl, C_{1-6}alkyl, C_{3-7} cycloalkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, CO_2H, CO_2C_{1-4}alkyl, C(=O)NHC_{1-4}alkyl, and C(=O)N(C_{1-4}alkyl)$_2$;

R^6 is a straight or branched-chain C_{1-6}alkyl, C_{3-6} alkenyl, benzyl, or phenyl in which each is optionally substituted with substituents selected from the group consisting of halogen, C_{1-4}alkyl, C_{1-4}alkoxy, amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, (C_{1-4}alkyl)(phenyl)N-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and 4-(C_{1-6}alkyl)piperazin-1-yl;

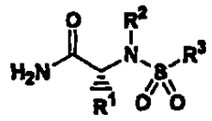
R^7 is hydrogen, a straight or branched-chain C_{1-6} alkyl;

R^8 is a straight or branched-chain C_{1-6}alkyl, C_{3-7} cycloalkyl, phenyl, pyridyl, or furanyl; in which each is optionally substituted with substituents selected from the group consisting of halogen, C_{1-4}alkyl, C_{1-4}alkoxy, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and 4-(C_{1-6}alkyl)piperazin-1-yl;

R^9 is a straight or branched-chain C_{1-6}alkyl, C_{3-6} alkenyl, benzyl, phenyl, oxazolyl or pyridyl; in which each is optionally substituted with substituents selected from the group consisting of halogen, (halogen)$_3$C-, (halogen)$_2$CH-, halogenCH$_2$-, C_{1-4}alkyl, C_{1-4}alkoxy, amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and 4-(C_{1-6}alkyl)piperazin-1-yl;

or a non-toxic pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 having the formula



Ia

wherein:

R^1 is selected from the group consisting of

(a) a straight or branched-chain C_{1-6} alkyl or C_{2-6}alkenyl optionally substituted with substituents selected from the group consisting of hydroxy, C_{3-7} cycloalkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, and halogen;

(b) C_{3-7} cycloalkyl optionally substituted with hydroxy or halogen;

R^2 is selected from the group consisting of

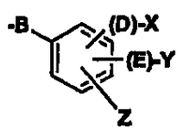
(a) a straight or branched-chain C_{1-6}alkyl or C_{3-6}alkenyl optionally substituted with substituents selected from the group consisting of halogen, C_{1-4}alkoxy, and NR^4R^5;

(b) C_{3-7} cycloalkylmethyl optionally substituted with substituents selected from the group consisting of amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, C_{1-4}alkylC(=O)NH-, and C_{1-4}alkylOC(=O)NH-;

(c) a straight or branched-chain C_{1-6}alkyl-C(=O)-A;

(d) -B-naphthyl;

(e)



D and E are each independently a direct bond, a straight or branched-chain C_{1-6}alkyl, C_{2-6} alkenyl, or C_{3-7} cycloalkyl;

Z is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halogen, cyano, hydroxy, $-OCHF_2$, $-OCF_3$, $-CF_3$, and $-CHF_2$;

X and Y are each independently selected from the group consisting of hydrogen, hydroxy, halogen, (halogen)$_3$C-, (halogen)$_2$CH-, C_{1-4}alkylS-, C_{1-4}alkylS(O)-, C_{1-4}alkylSO$_2$-, nitro, F$_3$S-, and cyano;

-OR^6;

-NR^{4}R^5;

-NR^{7}C(=O)R^8;

-NR^{7}C(=O)OR^8;

-NHSO$_2$C$_{1-4}$alkyl;

-N(SO$_2$C$_{1-4}$alkyl)$_2$;

-C(=O)W wherein W is selected from the group consisting of hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, phenoxy, and -NR^{4}R^5;

-OC(=O)C_{1-4}alkyl;

-phenyl in which said phenyl is optionally substituted with cyano, halogen, C_{1-4}alkoxy, C_{1-4}alkylS-, CH$_3$C(=O), C_{1-4}alkylS(O)-, or C_{1-4}alkylSO$_2$-; and

heterocyclic group, in which said heterocyclic group is selected from the group consisting of furanyl, thiofuranyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, oxadiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, and thiazolyl, wherein said heterocyclic group is optionally substituted with substituents selected from the group consisting of cyano, halogen, C_{1-4}alkyl, (halogen)C_{1-4}alkyl, and CO$_2$C$_{1-4}$alkyl;

(f) -B-(heterocycle), in which said heterocycle is selected from the group consisting of furanyl, thiofuranyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, oxadiazolyl, oxazolyl, isoxazolyl, thiadiazolyl and thiazolyl wherein said heterocycle is optionally substituted with substituents selected from the group consisting of cyano, halogen, C_{1-4}alkyl, CO$_2$C$_{1-4}$alkyl, amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and 4-(C_{1-6}alkyl)piperazin-1-yl;

(g) -B-(piperidin-4-yl), in which said piperidin-4-yl is optionally substituted with substituents selected from the group consisting of a straight or branched-chain C_{1-6}alkyl, $CH_2C(=O)$phenyl, phenyl and phenylmethyl in which said C_{1-6}alkyl and said phenyl are optionally substituted with substituents selected from the group consisting of cyano, halogen, benzimidazol-2-yl, pyridyl and tetrahydrofuran-2-yl; and -C(=O)W' wherein W' is selected from the group consisting of C_{1-4}alkoxy, R^9, and $-NR^4R^5$;

A is hydroxy, C_{1-4}alkoxy or NR^4R^5;

B is a straight or branched-chain C_{1-6}alkyl or C_{3-6}alkenyl;

R^3 is phenyl or pyridyl optionally substituted with substituents selected from the group consisting of halogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkyl, $(halogen)_3C$-, $(halogen)_2CH$-, and $halogenCH_2$-;

R^4 and R^5 each are independently hydrogen, a straight or branched-chain C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylmethyl, C_{1-4}alkoxy, phenyl, benzyl, pyridyl, piperidin-4-yl, indan-1-yl, indan-2-yl, tetrahydrofuran-3-yl, or pyrrolidin-3-yl; in which each is optionally substituted with substituents selected from the group consisting of hydroxy, cyano, halogen, $(halogen)_3C$-, $(halogen)_2CH$-, $halogenCH_2$-, hydroxymethyl, benzyloxymethyl, phenyl, pyridyl, C_{1-4}alkyl, C_{1-4}alkoxy, $(halogen)_3C$-O-, $(halogen)_2CH$-O-, C_{1-4}alkylthio, amino, $(C_{1-4}alkyl)NH$-, $di(C_{1-4}alkyl)N$-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, 4-$(C_{1-6}$alkyl)piperazin-1-yl, 4-phenylpiperazin-1-yl, 4-benzylpiperazin-1-yl, 4-pyridylpiperazin-1-yl, CO_2H, CO_2C_{1-4}alkyl, $C(=O)NHC_{1-4}$alkyl, and $C(=O)N(C_{1-4}alkyl)_2$;

R^4 and R^5 taken together may be morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, decahydroquinolin-1-yl, piperidin-1-yl, piperazin-1-yl, [1,4]-oxazepan-4-yl, azetidin-1-yl, 2,3-dihydro-1*H*-isoindol-2-yl, or 2,3-dihydro-1*H*-indol-1-yl; in which each is optionally substituted with substituents selected from the group consisting of hydroxy, cyano, halogen, $(halogen)_3C$-, $(halogen)_2CH$-, $halogenCH_2$-,

phenyl, pyridyl, benzyl, C_{1-6}alkyl, C_{3-7} cycloalkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, CO_2H, CO_2C_{1-4}alkyl, C(=O)NHC_{1-4}alkyl, and C(=O)N(C_{1-4}alkyl)$_2$;

R^6 is a straight or branched-chain C_{1-6}alkyl, C_{3-6} alkenyl, benzyl, or phenyl in which each is optionally substituted with substituents selected from the group consisting of halogen, C_{1-4}alkyl, C_{1-4}alkoxy, amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, (C_{1-4}alkyl)(phenyl)N-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and 4-(C_{1-6}alkyl)piperazin-1-yl;

R^7 is hydrogen, a straight or branched-chain C_{1-6} alkyl;

R^8 is a straight or branched-chain C_{1-6}alkyl, C_{3-7} cycloalkyl, phenyl, pyridyl, or furanyl; in which each is optionally substituted with substituents selected from the group consisting of halogen, C_{1-4}alkyl, C_{1-4}alkoxy, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and 4-(C_{1-6}alkyl)piperazin-1-yl;

R^9 is a straight or branched-chain C_{1-6}alkyl, C_{3-6} alkenyl, benzyl, phenyl, oxazolyl or pyridyl; in which each is optionally substituted with substituents selected from the group consisting of halogen, (halogen)$_3$C-, (halogen)$_2$CH-, halogenCH$_2$-, C_{1-4}alkyl, C_{1-4}alkoxy, amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and 4-(C_{1-6}alkyl)piperazin-1-yl;

or a non-toxic pharmaceutically acceptable salt thereof.

3. The compound of Claim 2 in which R^1 is a straight or branched-chain C_{1-6} alkyl or C_{2-6}alkenyl optionally substituted with substituents selected from the group consisting of hydroxy, C_{3-7}cycloalkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, and halogen.

4. The compound of Claim 2 in which R^1 is C_{3-7}cycloalkyl optionally substituted with hydroxy or halogen.

5. The compound of Claim 3 in which R^1 is a straight or branched-chain C_{1-6} alkyl optionally substituted with C_{3-7} cycloalkyl.

6. The compound of Claim 3 in which R^1 is a straight or branched-chain C_{1-6} alkyl optionally substituted with halogen.

7. The compound of Claim 2 in which R^3 is phenyl optionally substituted with substituents selected from the group consisting of halogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkyl, (halogen)$_3$C-, (halogen)$_2$CH-, and halogenCH_2-.

8. The compound of Claim 2 in which R^3 is pyridyl optionally substituted with substituents selected from the group consisting of halogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkyl, (halogen)$_3$C-, (halogen)$_2$CH-, and halogenCH_2-.

9. The compound of Claim 7 in which R^3 is phenyl optionally substituted with halogen.

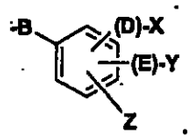
10. The compound of Claim 2 in which R^2 is a straight or branched-chain C_{1-6}alkyl or C_{3-6}alkenyl optionally substituted with substituents selected from the group consisting of halogen, C_{1-4}alkoxy, and NR^4R^5.

11. The compound of Claim 2 in which R^2 is C_{3-7} cycloalkylmethyl optionally substituted with substituents selected from the group consisting of amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, C_{1-4}alkylC(=O)NH-, and C_{1-4}alkylOC(=O)NH-.

12. The compound of Claim 2 in which R^2 is a straight or branched-chain C_{1-6}alkyl-C(=O)-A.

13. The compound of Claim 2 in which R^2 is -B-naphthyl.

14. The compound of Claim 2 in which R^2 is



15. The compound of Claim 2 in which R^2 is-B-(heterocycle), in which said heterocycle is selected from the group consisting of furanyl, thiofuranyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, oxadiazolyl, oxazolyl, isoxazolyl, thiadiazolyl and thiazolyl wherein said heterocycle is optionally substituted with substituents selected from the group consisting of cyano, halogen, C_{1-4}alkyl, CO_2C_{1-4}alkyl, amino, (C_{1-4}alkyl)NH-, di(C_{1-4}alkyl)N-, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, and 4-(C_{1-6}alkyl)piperazin-1-yl.

16. The compound of Claim 2 in which R^2 is -B-(piperidin-4-yl), in which said piperidin-4-yl is optionally substituted with substituents selected from the group consisting of a straight or branched-chain C_{1-6}alkyl, $CH_2C(=O)$phenyl, phenyl or phenylmethyl in which said C_{1-6}alkyl and said phenyl are optionally substituted with substituents selected from a group consisting of cyano, halogen, benzimidazol-2-yl, pyridyl and tetrahydrofuran-2-yl; and -C(=O)W' wherein W' is selected from the group consisting of C_{1-4}alkoxy, R^9, and $-NR^4R^5$.

17. The compound of Claim 14 in which B is straight-chain C_{1-4}alkyl.

18. The compound of Claim 17 wherein Z is hydrogen.

19. The compound of Claim 17 wherein X is C(=O)W, E is a direct bond and Y is hydrogen.

20. The compound of Claim 17 wherein X is $-NR^4R^5$, E is a direct bond and Y is hydrogen.

21. The compound of Claim 17 wherein X is $-OR^6$, E is a direct bond and Y is hydrogen.

22. The compound of Claim 17 wherein X is $-NR^7C(=O)R^8$, E is a direct bond and Y is hydrogen.

23. A pharmaceutical composition for the treatment of disorders responsive to the inhibition of β-amyloid peptide production comprising a therapeutically effective amount of a compound of claim 1 in association with a pharmaceutically acceptable carrier or diluent.

24. A method for the treatment of disorders responsive to the inhibition of β-amyloid peptide production in a mammal in need thereof, which comprises administering to said mammal a therapeutically effective amount of a compound of claim 1.

25. A method of claim 24 wherein said disorder is Alzheimer's Disease and Down's Syndrome.

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(71) Solicitante: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; Apartado de Correos 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000 (US).

(72) Inventores: **PARKER, Michael F**; 45 Brainard Hill Road, Higganum, CT 06441 (US). **MCELHONE, Katharine, E.**; 25 Midway Drive, Cromwell, CT 06416 (US). **MATE, Robert, A.**; 380-91 Hitchcock Road, Waterbury, CT 06705 (US). **BRONSON, Joanne, J.**; 230 Parmelee Hill Road, Durham, CT 06422 (US). **GAI, Yonghua**; 12 Linnea Lane, Killingworth, CT 06419 (US). **BERGSTROM, Carl, P.**; 22 Paper Mill Drive, Madison, CT 06443 (US). **MARCIN, Lawrence, R.**; 40 Ridgewood Drive, Bethany, CT 06437 (US). **MACOR, John, E.**; 644 Moose Hill Road, Guilford, CT 06437 (US).

(74) Agentes: **BABAJKO, Suzanne** y colaboradores; Bristol-Myers Squibb Company, Apartado de Correos 4000, Princeton, NJ 08543-4000 (US).

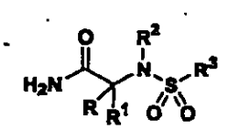
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Para códigos de dos letras y otras abreviaciones, referirse a las "Notas de Guía sobre Códigos y Abreviaciones" que aparecen al principio de cada ejemplar regular de la gaceta del PCT.

(54) Título: DERIVADOS DE α-(N-SULFONAMIDO)ACETAMIDA COMO INHIBIDORES DEL PÉPTIDO β-AMILOIDEO



I

(57) Resumen: Se proporciona una serie de compuestos novedosos de α-(N-sulfonamido)acetamida de la fórmula (I), en donde R, R^1, R^2 y R^3 son como se definiera en la presente, los cuales son inhibidores de la producción del péptido β-amiloideo (β-AP) y son útiles en el tratamiento de la enfermedad Alzheimer y otras condiciones afectadas por la actividad anti-amiloidea.

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DERIVADOS DE ALFA-(N-SULFONAMIDO)ACETAMIDA COMO INHIBIDORES DEL PÉPTIDO BETA-AMILOIDEO

CAMPO DE LA INVENCIÓN

Esta invención proporciona compuestos novedosos de α-(N-sulfonamido)acetamida que tienen propiedades de fármaco y bio-afectación, sus composiciones farmacéuticas y un método de uso. En particular, la invención está relacionada con las α-(N-arilsulfonamido)acetamidas. Estos compuestos poseen la inhibición única de la producción del péptido β-amiloideo (β-AP, por sus siglas en inglés), con lo cual actúan para prevenir la acumulación de depósitos de proteína amiloidea en el cerebro. Más particularmente, la presente invención se refiere al tratamiento de la Enfermedad de Alzheimer (AD, por sus siglas en inglés).

ANTECEDENTES DE LA INVENCIÓN

La Enfermedad de Alzheimer es un trastorno neurodegenerativo, progresivo que está caracterizado por el deterioro de la memoria y la disfunción cognoscitiva. La AD está caracterizada patológicamente por la acumulación de placas seniles (neuríticas), marañas neurofibrilares, deposición amiloidea en tejidos y bazos neurales, pérdida sináptica y muerte neuronal. Es la forma más común de demencia y ahora representa la tercera causa principal de

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muerte después de los trastornos cardiovasculares y el cáncer. El costo de la enfermedad de Alzheimer es enorme (en los Estados Unidos, más de $100 mil millones al año) e incluye el sufrimiento de los pacientes, el sufrimiento de las familias y la pérdida de productividad de los pacientes y proveedores de cuidados. A medida que incrementa la longevidad de la sociedad, la ocurrencia de la AD incrementará marcadamente. Se estima que más de 10 millones de estadounidenses sufrirán de AD en el año 2020, si no se encuentran métodos para la prevención y el tratamiento. Actualmente, se estima la AD afecta a 10% de la población mayor de 65 años de edad y hasta 50% de aquellas personas mayores de 85 años de edad. No está disponible actualmente un tratamiento que prevenga de manera efectiva la AD o invierta los síntomas clínicos y la patofisiología implícita (para una revisión véase Selkoe, D.J. *Ann. Rev. Cell Biol.*, 1994, 10: 373-403).

Ha habido muchas teorías con relación a la etiología y patogénesis de la AD. Estas teorías estuvieron basadas ya sea en analogías con otras enfermedades y condiciones (por ejemplo, teorías de virus lentos y aluminio), o estuvieron basadas en observaciones patológicas (por ejemplo, teorías colinérgicas, amiloideas o de marañas). Los análisis genéticos pueden diferenciar potencialmente entre las teorías competentes. La identificación de las

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mutaciones en la proteína precursora β-amiloidea (β-APP, por sus siglas en inglés) de individuos propensos a formas de comienzo temprano de AD y trastornos relacionados soporta fuertemente las teorías amiloidogénicas.

El examen histopatológico del tejido cerebral derivado de la autopsia o de especimenes neuroquirúrgicos en individuos afectados revela la ocurrencia de placas amiloideas y marañas neurofibrilares en la corteza cerebral de estos pacientes. Las alteraciones similares se observan en pacientes con Trisomy 21 (síndrome de Down). Los estudios bioquímicos e inmunológicos revelan que el componente proteínico, dominante de la placa amiloidea es una proteína de aproximadamente 4.2 kilodaltons (kD) de aproximadamente 39 a 43 aminoácidos. Esta proteína es designada Aβ, péptido β-amiloïdeo, y algunas veces β/A4; referida en este texto como Aβ. Además de su deposición en las placas amiloideas, Aβ también se encuentra en las paredes de arteriolas meníngeas y parenquimatosas, arterias pequeñas, capilares y, algunas veces, vénulas. La evidencia apremiante, acumulada durante al menos una década, revela que Aβ es un polipéptido interno derivado de una proteína de membrana integral tipo 1, denominada proteína precursora β-amiloidea (APP, por sus siglas en inglés) (Selkoe, D. *Physiol. Rev.* 2001, **81**, 741-766; Wolfe, M. *J. Med. Chem.* 2001, **44**, 2039-2060). La β-APP es producida normalmente por muchas células tanto *in vivo*

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como en células cultivadas, derivadas de varios animales y humanos. Varios fragmentos proteolíticos de APP son generados por proteinasas referidas como secretasas. Un subconjunto de estos fragmentos proteolíticos, designado péptido β-amiloideo (Aβ), contiene de 39 a 43 aminoácidos y es generado por la acción combinada de β-secretasa y γ-secretasa. La β-secretasa es una aspartil-proteasa unida a la membrana que forma la terminación N del péptido Aβ. La terminación C del péptido Aβ está formada por γ-secretasa, un complejo aparentemente oligómérico que incluye presenilina-1 y/o presenilina-2. La presenilina-1 y la presenilina-2 son proteínas proteolíticas que cubren la membrana que pueden contener los componentes catalíticos de γ-secretasa (Seiffert, D.; Bradley, J. y colaboradores, *J. Biol. Chem.* 2000, **275**, 34086-34091).

Múltiples de líneas de evidencia juntas sugieren fuertemente que una reducción en los niveles de Aβ en el cerebro impedirá el comienzo y progreso de AD. Primero, Aβ es un constituyente principal de las placas parenquimatosas observadas en todos los pacientes con AD y los depósitos amiloideos, vasculares, cerebrales observados en 90% de pacientes con AD (revisado en Selkoe, D. *Physiol. Rev.* 2001, **81**, 741-766; Wolfe, M. *J. Med. Chem.* 2001, **44**, 2039-2060). Estas placas están formadas de la agregación de Aβ soluble, cuyos niveles en el cerebro están correlacionados altamente con la gravedad de la neurodegeneración de AD (McLean, C.,

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Cherny, R. y colaboradores, *Ann. Neurol.* 1999, **46**, 860-866). Segundo, las mutaciones en tres genes (APP, PS-1 o PS-2) que incrementan la Aβ causan la AD familiar (FAD, por sus siglas en inglés), donde el comienzo de AD es acelerado por al menos una década. Entre las mutaciones que incrementan la Aβ está incluido el cromosoma de Trisomy 21 que causa el síndrome de Down. Tercero, los ratones transgénicos que expresan uno o más de los genes FAD mutantes han incrementado los niveles de Aβ, forman placas parenquimatosas y depósitos vasculares, cerebrales que contienen Aβ, exhiben déficits de memoria (Chapman, P.; White, G. y colaboradores, *Nature Neurosci.* 1999, **2**, 271-276) y aumentan la degeneración neurofibrilar en ratones que también scbreexpresan la proteína mutante tau (Lewis, J.; Dickson, D. y colaboradores, *Science* 2001, **293**, 1487-1491). Cuarto, la Aβ es tóxica para las células cultivadas (Dahlgren, K.; Manelli, A. y colaboradores, *J. Biol. Chem.* 2002 **277**, 32046-32053), induce marañas neurofibrilares en ratones con la proteína mutante tau (Gotz, J., Chen, F. y colaboradores, *Science* 2001, **293**, 1491-1495) e interfiere con la potencialización a largo plazo, probablemente un componente de la memoria (Walsh, D., Klyubin, I. y colaboradores, *Nature* 2002, **416**, 535-539 y referencias en la misma. Tomados conjuntamente, estos datos conducen a una persona experta en el campo a concluir que el exceso de la producción de Aβ y/o aclaramiento reducido de Aβ

causan la AD. Después de esto sigue que la reducción de los niveles de Aβ en el cerebro por medio de la inhibición de γ-secretasa impedirá el comienzo y progreso de la AD.

Además de la AD, la producción en exceso y/o el aclaramiento reducido de Aβ causa la angiopatía amiloidea, cerebral (CAA, por sus siglas en inglés) (revisado en Thal, D., Gherbremedhin, E. y colaboradores, *J. Neuropath. Exp. Neuro.* 2002, **61**, 282-293). En estos pacientes, los depósitos amiloideos, vasculares causan la degeneración de las paredes de los bazos y aneurismas que pueden ser responsables de 10-15% de apoplejías hemorrágicas en pacientes de edad avanzada. Como en la AD, las mutaciones en el gen que codifica la Aβ conducen a una forma de comienzo temprano de CAA, referida como hemorragia cerebral con amiloidosis del tipo Dutch y los ratones que expresan esta proteína mutante desarrollan CAA que es similar para los pacientes.

Existe la hipótesis que la inhibición de la producción de Aβ impedirá y reducirá la degeneración neurológica, reduciendo la neurotoxicidad y, generalmente, mediando la patología asociada con la producción de Aβ. Los métodos de tratamiento podrían centrarse en la formación de Aβ a través de las enzimas involucradas en el procesamiento proteolítico de la proteína precursora β-amiloidea. Los compuestos que inhiben la actividad de la β- o γ-secretasa, ya sea directa o indirectamente, podrían controlar la

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producción de Aβ. De manera ventajosa, los compuestos que se centran específicamente en las γ-secretasas, podrían controlar la producción de Aβ. Esta inhibición de las β- o γ-secretasas podría reducir con lo cual la producción de Aβ, lo cual podría reducir o prevenir los trastornos neurológicos asociados con la proteína Aβ.

Smith y colaboradores, en la solicitud de internacional WO 00/50391, publicada el 31 de agosto de 2000, describen una serie de compuestos de sulfonamida que pueden actuar para modular la producción de la proteína amiloidea β como un medio para tratar una variedad de enfermedades, especialmente la Enfermedad de Alzheimer y otras enfermedades que se relacionan con la deposición del péptido amiloideo. La patente japonesa No. 11343279, publicada el 14 de diciembre de 1999, describe una serie de derivados de sulfonamida, los cuales son inhibidores de TNF-alfa útiles para tratar enfermedades autoinmunes.

Ninguna de estas referencias se puede considerar que describe o sugiere los compuestos novedosos de esta invención y su uso para inhibir la producción de β-AP.

BREVE DESCRIPCIÓN DE LA INVENCIÓN

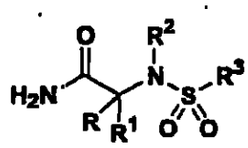
Una serie de derivados de α-(N-sulfonamido)acetamida han sido sintetizados. Estos compuestos inhiben específicamente la producción del péptido β-amiloideo

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(β-AP) a partir de la proteína precursara β-amiloidea (β-APP). La acción farmacológica de estos compuestos los hace útiles para el tratamiento de condiciones responsables de la inhibición de β-AP en un paciente, por ejemplo, Enfermedad de Alzheimer (AD) y síndrome de Down. La terapia que utiliza la administración de estos compuestos a pacientes que sufren de, o son susceptibles a, estas condiciones involucra la reducción de β-AP disponible para la acumulación y deposición en los cerebros de estos pacientes.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La presente invención comprende los compuestos de la fórmula I, sus formulaciones farmacéuticas y su uso en la inhibición de la producción β-AP en paciente que sufren de, o son susceptibles a, AD u otros trastornos resultantes de la acumulación de β-AP en el tejido cerebral. Los compuestos de la fórmula I, que incluyen sales y/o hidratos farmacéuticamente aceptables, no tóxicos de los mismos, tienen la siguiente fórmula y significados:



I

en donde:

R^1 se selecciona del grupo que consiste de

(a) un grupo alquilo de 1 a 6 átomos de carbono o

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alquenilo de 2 a 6 átomos de carbono de cadena recta o ramificada sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de hidroxi, cicloalquilo de 3 a 7 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, alquiltio de 1 a 4 átomos de carbono y halógeno;

(b) cicloalquilo de 3 a 7 átomos de carbono sustituido opcionalmente por hidroxi o halógeno;

R es hidrógeno o R^1 y R tomados conjuntamente son alquileno de 2 a 5 átomos de carbono;

R^2 se selecciona del grupo que consiste de

(a) un grupo alquilo de 1 a 6 átomos de carbono o alquenilo de 3 a 6 átomos de carbono de cadena recta o ramificada sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, alcoxi de 1 a 4 átomos de carbono y NR^4R^5;

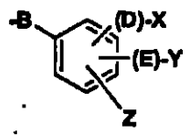
(b) cicloalquilmetilo de 3 a 7 átomos de carbono sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de amino, (alquil-C_1-C_4)NH-, di(alquil-C_1-C_4)N-, alquil-C_1-C_4-C(=O)NH- y alquil-C_1-C_4-OC(=O)NH-;

(c) un grupo alquil-C_1-C_6-C(=O)-A de cadena recta o

ramificada;

(d) -B-naftilo;

(e)



D y E son cada uno, independientemente, un enlace directo, un grupo alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono o cicloalquilo de 3 a 7 átomos de carbono de cadena recta o ramificada;

Z se selecciona del grupo que consiste de hidrógeno, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, halógeno, ciano, hidroxi, $-OCHF_2$, $-OCF_3$, $-CF_3$ y $-CHF_2$;

X e Y se seleccionan cada uno, independientemente, del grupo que consiste de hidrógeno, hidroxi, halógeno, $(halógeno)_3C-$, $(halógeno)_2CH-$, alquil-C_1-C_4-S-, alquil-C_1-C_4-S(O)-, alquil-C_1-C_4-SO_2-, nitro, F_3S- y ciano; $-OR^6$; $-NR^4R^5$; $-NR^7C(=O)R^8$; $-NR^7C(=O)OR^8$; $-NHSO_2$-alquilo de 1 a 4 átomos de carbono; $-N(SO_2$-alquil-C_1-$C_4)_2$; $-C(=O)W$, en donde W se selecciona del grupo que consiste de hidroxi, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, fenoxi y $-NR^4R^5$; -

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OC(=O)alquilo de 1 a 4 átomos de carbono; -fenilo en el cual el grupo fenilo es sustituido opcionalmente por ciano, halógeno, alcoxi de 1 a 4 átomos de carbono, alquil-C_1-C_4-S-, $CH_3C(=O)$, alquil-C_1-C_4-S(O)- o alquil-C_1-C_4-SO_2; y un grupo heterocíclico, en el cual el grupo heterocíclico se selecciona del grupo que consiste de furanilo, tiofuranilo, pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, oxadiazolilo, oxazolilo, isoxazolilo, tiadiazolilo y tiazolilo, en donde el grupo heterocíclico es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de ciano, halógeno, alquilo de 1 a 4 átomos de carbono, (halógeno)alquilo de 1 a 4 átomos de carbono y CO_2-alquilo de 1 a 4 átomos de carbono;

(f) -B-(heterociclo), en el cual el heterociclo se selecciona del grupo que consiste de furanilo, tiofuranilo, pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, oxadiazolilo, oxazolilo, isoxazolilo, tiadiazolilo y tiazolilo, en donde el heterociclo es

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sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de ciano, halógeno, alquilo de 1 a 4 átomos de carbono, CO_2-alquilo de 1 a 4 átomos de carbono, amino, (alquilo C_1-C_4)NH-, di(alquil-C_1-C_4)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo y 4-(alquil-C_1-C_6)-piperazin-1-ilo;

(g) -B-(piperidin-4-ilo), en el cual el grupo piperidin-4-ilo es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de un grupo alquilo de 1 a 6 átomos de carbono, de cadena recta o ramificada, $CH_2C(=O)$fenilo, fenilo y fenilmetilo en el cual el grupo alquilo de 1 a 6 átomos de carbono y el grupo fenilo son sustituidos opcionalmente por sustituyentes seleccionados del grupo que consiste de ciano, halógeno, bencimidazol-2-ilo, piridilo y tetrahidrofuran-2-ilo; y -C(=O)W', en donde W' se selecciona del grupo que consiste de alcoxi de 1 a 4 átomos de carbono, R^3 y $-NR^4R^5$;

A es hidroxi, alcoxi de 1 a 4 átomos de carbono o NR^4R^5;

B es alquilo de 1 a 6 átomos de carbono o alquenilo de

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3 a 6 átomos de carbono de cadena recta o ramificada;

R^3 es fenilo o piridilo sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, hidroxi, alcoxi de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono, $(halógeno)_3C-$, $(halógeno)_2CH-$ y $halógeno-CH_2-$;

R^4 y R^5 son cada uno, independientemente, hidrógeno, un grupo alquilo de 1 a 6 átomos de carbono, alquenilo de 3 a 6 átomos de carbono, alquinilo de 3 a 6 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, cicloalquilmetilo de 3 a 7 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, fenilo, bencilo, piridilo, piperidin-4-ilo, indan-1-ilo, indan-2-ilo, tetrahidrofuran-3-ilo o pirrolidin-3-ilo de cadena recta o ramificada; en el cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de hidroxi, ciano, halógeno, $(halógeno)_3C-$, $(halógeno)_2CH-$, $halógeno-CH_2-$, hidroximetilo, benciloximetilo, fenilo, piridilo, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, $(halógeno)_3C-O-$, $(halógeno)_2CH-O-$, alquiltio de 1 a 4 átomos de carbono, amino, $(alquil-C_1-C_4)NH-$, $di-(alquil-C_1-C_4)N-$, morfolin-4-ilo, tiomorfolin-4-ilo,

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pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo, 4-(alquil-C_1-C_6)piperazin-1-ilo, 4-fenilpiperazin-1-ilo, 4-bencilpiperazin-1-ilo, 4-piridilpiperazin-1-ilo, CO_2H, CO_2-alquilo de 1 a 4 átomos de carbono, C(=O)NH-alquilo de 1 a 4 átomos de carbono y $C(=O)N(alquil\text{-}C_1\text{-}C_4)_2$;

R^4 y R^5 tomados conjuntamente pueden ser morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, 1,2,3,4-tetrahidroisoquinolin-2-ilo, decahidroquinolin-1-ilo, piperidin-1-ilo, piperazin-1-ilo, [1,4]-oxazepan-4-ilo, azetidin-1-ilo, 2,3-dihidro-1*H*-isoindol-2-ilo o 2,3-dihidro-1*H*-indol-1-ilo; en el cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de hidroxi, ciano, halógeno, $(halógeno)_3C$-, $(halógeno)_2CH$-, halógeno-CH_2-, fenilo, piridilo, bencilo, alquilo de 1 a 6 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, alquiltio de 1 a 4 átomos de carbono, amino, (alquil-C_1-C_4)NH-, di-(alquil-C_1-C_4)N-, CO_2H, CO_2-alquilo de 1 a 4 átomos de carbono, C(=O)NH-alquilo de 1 a 4 átomos de carbono y $C(=O)N(alquil\text{-}C_1\text{-}C_4)_2$;

R^6 es un grupo alquilo de 1 a 6 átomos de carbono, alquenilo de 3 a 6 átomos de carbono, bencilo o

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fenilo de cadena recta o ramificada, en el cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, amino, (alquil-C_1-C_4)NH-, di-(alquil-C_1-C_4)N-, (alquil-C_1-C_4)(fenil)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo y 4-(alquil-C_1-C_6)piperazin-1-ilo;

R^7 es hidrógeno, un grupo alquilo de 1 a 6 átomos de carbono de cadena recta o ramificada;

R^8 es un grupo alquilo de 1 a 6 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, fenilo, piridilo o furanilo de cadena recta o ramificada; en el cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, (alquil-C_1-C_4)NH-, di(alquil-C_1-C_4)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo y 4-(alquil-C_1-C_6)piperazin-1-ilo;

R^9 es un grupo alquilo de 1 a 6 átomos de carbono, alquenilo de 3 a 6 átomos de carbono, bencilo, fenilo, oxazolilo o piridilo de cadena recta o

ramificada; en el cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, (halógeno)$_3$C-, (halógeno)$_2$CH-, halógeno-CH$_2$-, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, amino, (alquil-C$_1$-C$_4$)NH-, di(alquil-C$_1$-C$_4$)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo y 4-(alquil-C$_1$-C$_6$)piperazin-1-ilo;

o una sal farmacéuticamente aceptable, no tóxica de los mismos.

La presente invención también proporciona un método para el tratamiento o alivio de trastornos asociados con el péptido β-amiloideo, especialmente la Enfermedad de Alzheimer, el cual comprende administrar junto con un adyuvante, portador o diluyente convencional, una cantidad terapéuticamente efectiva de un compuesto de la fórmula I o una sal, solvato o hidrato farmacéuticamente aceptable, no tóxico del mismo.

El término "alquilo de 1 a 6 átomos de carbono", como se utiliza en este texto y en las reivindicaciones (a menos que el contexto indique lo contrario), significa grupos alquilo de cadena recta o ramificada tales como metilo, etilo, propilo, isoprcpilo, butilo, isobutilo, t-butilo, pentilo, 3-metilbutilo, hexilo y similares. El término

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"alquenilo de 2 a 6 átomos de carbono", como se utiliza en este texto y en las reivindicaciones (a menos que el contexto indique lo contrario), significa grupos alquenilo de cadena recta o ramificada tales como etenilo (es decir vinilo), propenilo, alilo, butenilo, 3-metilbutenilo, pentenilo, hexenilo y similares. A menos que se especifique de otra manera, el término "halógeno", como se utiliza en este texto y en las reivindicaciones, se propone que incluya bromo, cloro, yodo y flúor, mientras que el término "haluro" se propone que incluya un anión de bromuro, cloruro y yoduro.

El término "cicloalquilo de 3 a 7 átomos de carbono" significa un sistema de anillos cíclicos de carbono, tal como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo.

El término "haloalquilo de 1 a 4 átomos de carbono" significa un grupo alquilo de 1 a 4 átomos de carbono de cadena recta o ramificada que contiene de 1 a 3 átomos de halógeno, tal como trifluorometilo, fluoroetilo, 1,2-dicloroetilo, tricloroetilo y similares.

El término "alquileno de 2 a 5 átomos de carbono" significa un grupo alquileno de cadena recta o ramificada, tal como metileno, etileno, propileno, metiletileno, butileno, metilpropileno, pentileno, metilbutileno y etilpropileno.

Como los compuestos de la presente invención poseen

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un átomo de carbono asimétrico, la presente invención incluye el racemato así como también las formas enantioméricas, individuales de los compuestos de la fórmula I, como se describe en este texto y en las reivindicaciones. El uso de una designación individual tal como (R) o (S) se propone que incluya principalmente un estereoisómero. Las mezclas de isómeros se pueden separar en isómeros individuales de acuerdo con métodos que son conocidos per se, por ejemplo, la cristalización fraccional, cromatografía de adsorción u otros procesos de separación adecuados. Los racematos resultantes se pueden separar en antípodos de manera usual después de la introducción de agrupaciones formadoras de sales adecuadas, por ejemplo, al formar una mezcla de sales diastereoisoméricas con agentes formadores de sales ópticamente activos, separar la mezcla en sales diastereoméricas y convertir las sales separadas en los compuestos libres. Las posibles formas enantiómericas también se pueden separar por medio del fraccionamiento a través de columnas de cromatografía líquida de alta presión, quirales.

El término "sal farmacéuticamente aceptable, no tóxica", como se utiliza en este texto y en las reivindicaciones, se propone que incluya sales de adición de bases no tóxicas. Las sales adecuadas incluyen aquellas derivadas de ácidos orgánicos e inorgánicos tales como, sin limitación, ácido clorhídrico, ácido bromhídrico, ácido

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fosfórico, sulfúrico, ácido metanosulfónico, ácido acético, ácido tartárico, ácido láctico, ácido sulfínico, ácido cítrico, ácido maleico, ácido fumárico, ácido sórbico, ácido aconítico, ácido salicílico, ácido ftálico y similares.

En el método de la presente invención, el término "cantidad terapéuticamente efectiva" significa la cantidad total de cada componente activo del método que es suficiente para mostrar un beneficio significante para el paciente, es decir, la curación de condiciones agudas que están caracterizadas por la inhibición de la producción del péptido β-amiloideo. Cuando se aplica a un ingrediente activo individual, administrado solo, el término se refiere a ese ingrediente solo. Cuando se aplica a una combinación, el término se refiere a cantidades combinadas de los ingredientes activos que dan por resultado el efecto terapéutico, ya sea administrados en combinación, en serie o simultáneamente. Los términos "tratar, trato, tratamiento", como se utilizan en este texto y en las reivindicaciones, significan prevenir o aliviar las enfermedades asociadas con el péptido β-amiloideo.

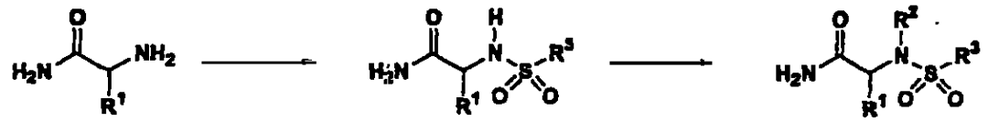
Esquemas de Reacción Generales

Los procedimientos generales utilizados para sintetizar los compuestos de la fórmula I se describen en los esquemas de reacción 1-23. Las variaciones razonables de los

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procedimientos descritos, las cuales serían evidentes para una persona experta en el campo, se propone que estén dentro del alcance de la presente invención.

Esquema de Reacción 1



II III I

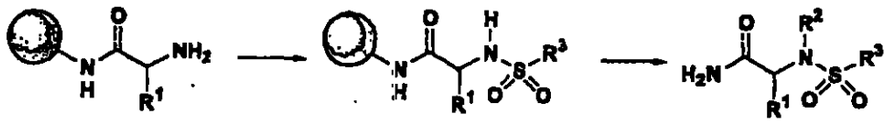
Las (α-amino)acetamidas de inicio de la fórmula II se utilizan en forma racémica o en forma enantioméricamente pura y son comercialmente disponibles o se preparan por medio de procedimientos bibliográficos bien conocidos a partir de (α-amino)ácidos comercialmente disponibles (referencia general para la preparación de amida: R.C. Larock "Comprehensive Organic Transformations, VCH Publishers, Nueva York, 1989, páginas 972-976; véase también el Esquema de Reacción 18 para la conversión del ácido de la fórmula XLVIII a la amida de fórmula XLIX). El compuesto de la fórmula II es tratado con una base adecuada y un reactivo de sulfonilación tal como cloruro de sulfonilo en un solvente aprótico tal como CH_2Cl_2 a temperatura ambiente para generar la (α-sulfonamido)acetamida de la fórmula III. Las bases adecuadas incluyen trietilamina y piridina.

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En una modalidad para la conversión del compuesto de la fórmula III a la sulfonamida de la fórmula I, el compuesto de la fórmula III es tratado con una base adecuado y un agente de alquilación en un solvente aprótico con o sin calentamiento. Las bases adecuadas para esta reacción incluyen carbonato de potasio y carbonato de cesio. Los agentes de alquilación incluyen haluros de alquilo (por ejemplo, cloruro de alquilo, bromuro de alquilo o yoduro de alquilo) y sulfonatos de alquilo (tosilatos, mesilatos, trifluorometanosulfonatos). Los solventes preferidos incluyen DMF y acetonitrilo. El rango de temperatura para la reacción es típicamente de 20°C a 100°C.

Un método alternativo para conversión del compuesto de la fórmula III al compuesto de la fórmula I involucra el tratamiento del compuesto de la fórmula III con trifenilfosfina, un azodicarboxilato de dialquilo y un alcohol en un solvente inerte con o sin calentamiento.

Esquema de Reacción 1-soporte sólido



IV V I

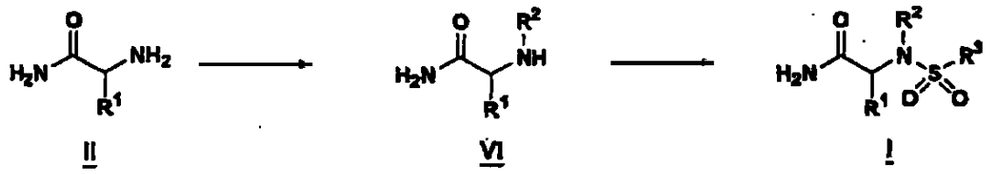
Los compuestos de la fórmula I también se pueden

preparar utilizando la metodología de fase sólida. Por ejemplo, la resina de amida Rink protegida con FMOC es tratada con piperidina en DMF para efectuar la remoción del grupo FMOC. La resina entonces es acoplada con un (α-amino)ácido protegido con amino en presencia de un agente de acoplamiento tal como 1-hidroxibenzotriazol y una carbodiimida de dialquilo en un solvente inerte tal como DMF con o sin calentamiento. La desprotección del grupo α-amino proporciona la amida unida al polímero de la fórmula IV. En el caso de un aminoácido protegido con FMOC, la desprotección se puede realizar por medio del tratamiento con piperidina en DMF.

La reacción del compuesto de la fórmula IV con una base apropiada, tal como piridina, y un agente de sulfonación, tal como cloruro de sulfonilo, en un solvente inerte proporciona la sulfonamida enlazada a resina de la fórmula V. La alquilación del compuesto de la fórmula V con un haluro de alquilo (por ejemplo, cloruro de alquilo, bromuro de alquilo o yoduro de alquilo) o sulfonato de alquilo (por ejemplo, mesilato, tosilato o trifluorometanosulfonato) se lleva a cabo en presencia de una base en un solvente inerte a temperatura ambiente. Una base preferida es 2-t-butilimino-2-dietilamino-1,3-dimetilperhidro-1,3,2-diasafosforina. La escisión de la resina proporciona la sulfonamida de la fórmula I. En el caso

de la resina de amida Rink, la escisión se lleva a cabo preferiblemente utilizando ácido trifluoroacético en un solvente inerte tal como CH_2Cl_2.

Esquema de Reacción 2

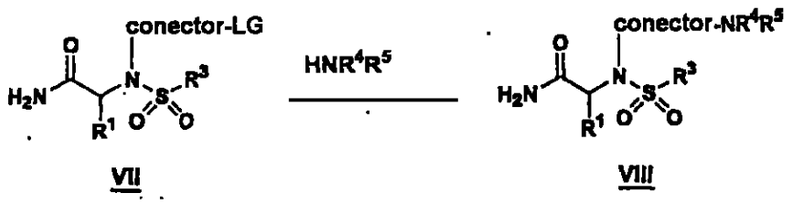


II VI I

Los compuestos de la fórmula I también se pueden preparar como se muestra en el esquema de reacción 2. La alquilación reductiva de la amina de la fórmula I para proporcionar la amina de la fórmula IV se efectúa por medio del tratamiento con un aldehído y un agente de reducción de hidruro en presencia de un catalizador ácido con o sin calentamiento. Un agente de reducción preferido es cianoborohidruro de sodio. Un catalizador de ácido preferido es un ácido Lewis tal como $ZnCl_2$. El solvente de reacción es preferiblemente metanol. La amina de la fórmula VI entonces es tratada con un agente de sulfonilación tal como cloruro de sulfonilo en presencia de una amina tal como trietilamina. Esta reacción se lleva a cabo en un solvente inerte tal como CH_2Cl_2 con o sin calentamiento para proporcionar el producto de la fórmula I. La reacción se lleva a cabo típicamente a temperatura ambiente.

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Esquema de Reacción 3



VII VIII

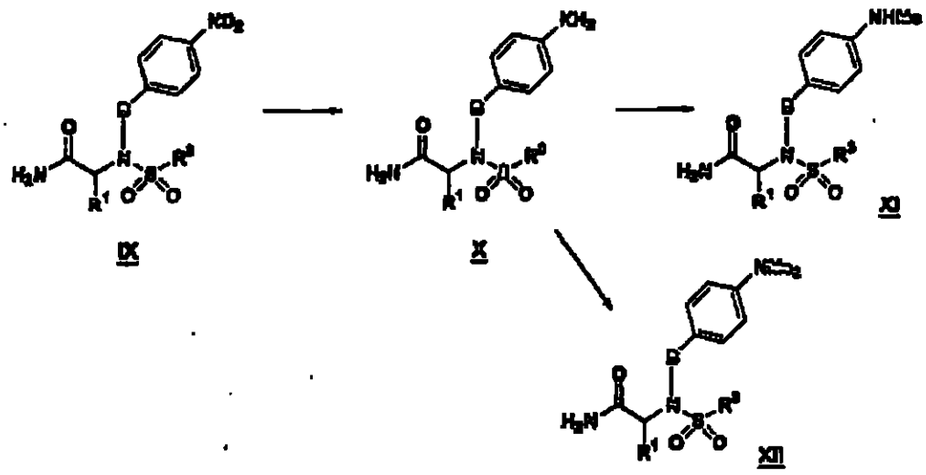
en donde conector = alquilo C_1-C_6 o alquenilo C_3-C_6 de cadena recta o ramificada;

LG = grupo saliente

La preparación de los compuestos de la fórmula VIII se realiza como se muestra en el esquema de reacción 3 por medio de la reacción del compuesto de la fórmula VII con una amina en presencia de un eliminador de ácido tal como trietilamina en un solvente inerte tal como CH_2Cl_2 con o sin calentamiento. El compuesto de la fórmula VII se prepara por medio de la secuencia mostrada en el esquema de reacción 1 o el esquema de reacción 2.

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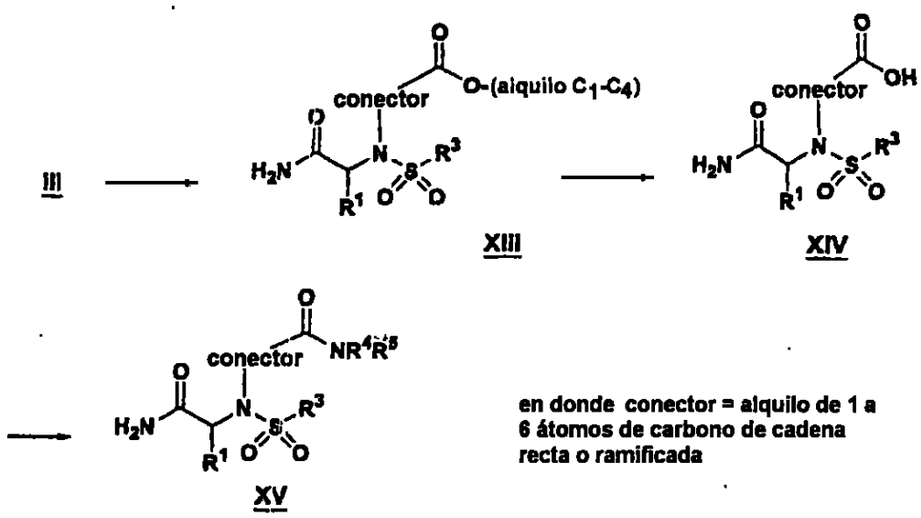
Esquema de Reacción 4



Los compuestos de la fórmula XI y XII se preparan como se muestra en el esquema de reacción 4. La reducción del grupo nitro del compuesto de la fórmula IX (preparado por medio de la secuencia mostrada en el esquema de reacción 1 o 2) con gas de hidrógeno bajo presión en presencia de un catalizador de paladio, ácido y en un solvente, tal como metanol, proporcionó el derivado de anilina de la fórmula X. La monometilación del compuesto de la fórmula X para proporcionar el compuesto de la fórmula XI se realiza por medio de la reacción con equivalentes 1.1 de un haluro de metilo o un sulfonato de metilo, por ejemplo, sulfonato de dimetilo, en presencia de una base tal como trietilamina y en un solvente inerte tal como DMF. La reacción de monometilación se lleva a cabo típicamente entre 20°C y 40°C. La preparación de la dimetilanilina de la fórmula XII se

efectúa por medio del tratamiento de la anilina de la fórmula X con un exceso de un haluro de metilo tal como yoduro de metilo o un sulfonato de metilo en presencia de una base, por ejemplo carbonato de cesio, en un solvente tal como DMF, con o sin calentamiento.

Esquema de Reacción 5

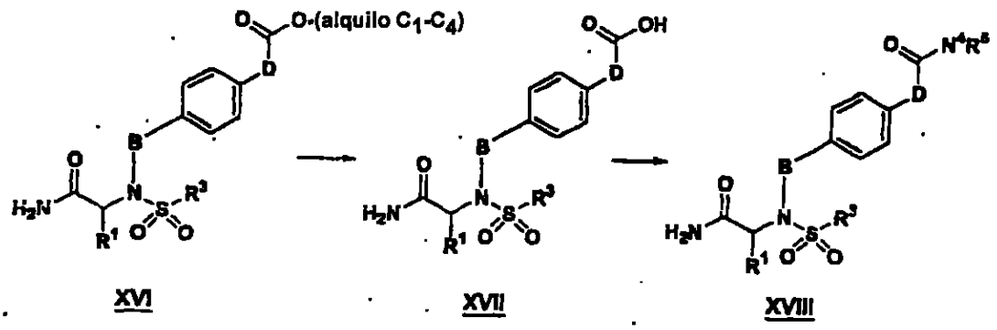


El esquema de reacción 5 resume la síntesis de los ésteres de la fórmula XIII, los ácidos de la fórmula XIV y las amidas de la fórmula XV. La reacción de un compuesto de la fórmula III con un éster de haloalquilcarboxilato, por ejemplo bromoacetato de *t*-butilo, en presencia de una base tal como carbonato de potasio y en un solvente inerte tal como DMF proporciona el éster de la fórmula XIII. La desprotección del éster se efectúa por medio de métodos conocidos para aquellas personas expertas en el campo

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(referencia: T.W. Greene y P. G. M. Wuts, "Protecting Groups in Organic Synthesis", Wiley Interscience, Nueva York, 1999, páginas 373-442). Por ejemplo, para los ésteres de t-butilo, la escisión para el ácido de la fórmula XVI se realiza por medio del tratamiento con ácido trifluoroacético en un solvente tal como CH_2Cl_2. La conversión del ácido a la amida de la fórmula XV se lleva a cabo utilizando procedimientos de acoplamiento de amida comunes que son bien conocidos para aquellas personas expertas en el campo (referencia: R.C. Larock "Comprehensive Organic Transformations, VCH Publishers, Nueva York, 1989, páginas 972-976). En un procedimiento preferido, el ácido de la fórmula XIV es tratado con una amina primaria o secundaria en presencia de 1-hidroxibenzotriazol y 1,3-diciclohexilcarbodiimida en un solvente aprótico tal como CH_2Cl_2 o DMF.

Esquema de Reacción 6



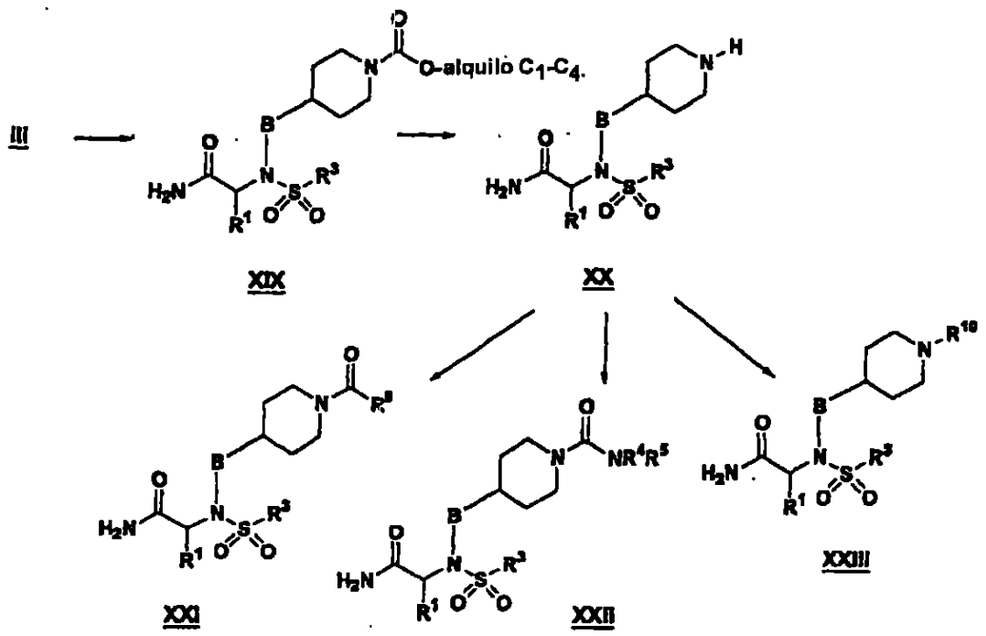
La preparación de los ácidos de la fórmula XVII y

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las amidas de la fórmula XVIII se muestra en el esquema de reacción 6. La conversión de un éster de la fórmula XVI (preparado como se muestra en los esquemas de reacción 1 o 2) a un ácido de la fórmula XVII se realiza utilizando condiciones de escisión de éster estándar que son bien conocidas para aquellas personas expertas en el campo (referencia: T.W. Greene y P. G. M. Wuts, "Protecting Groups in Organic Synthesis", Wiley Interscience, Nueva York, 1999, páginas 373-442). En el caso de un éster metílico de la fórmula XVI, el tratamiento con hidróxido de sodio acuoso en un solvente tal como metanol o una mezcla de metanol/THF de 20°C a 40°C proporciona el ácido de la fórmula XVII. La conversión del ácido de la fórmula XVII a la amida de la fórmula XVIII se logra utilizando los procedimientos de acoplamiento de amida comunes que son bien conocidos para aquellas personas expertas en el campo (referencia: R.C. Larock "Comprehensive Organic Transformations, VCH Publishers, Nueva York, 1989, páginas 972-976). En un procedimiento preferido, el ácido de la fórmula XVII es tratado con una amina primaria o secundaria en presencia de 1-hidroxibenzotriazol y una carbodiimida, por ejemplo 1-(3-dimetilaminopropil)-3-etilcarbodiimida, en un solvente tal como DMF o CH_2Cl_2. Se puede adicionar una base tal como diisopropiletilamina como un eliminador de ácido.

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Esquema de Reacción 7



La síntesis de los derivados de piperidina de las fórmulas XIX, XX, XXI, XXII y XXIII se describe en el esquema de reacción 7. La reacción de un compuesto de la fórmula III con una piperidina N-protegida sustituida por un grupo 4-haloalquilo o 4-sulfoniloxialquilo, tal como 4-(toluenosulfoniloximetil)-1-(t-butoxicarbonil)piperidina, en presencia de una base tal como carbonato de cesio en un solvente tal como DMF, con o sin calentamiento, proporciona el carbamato de la fórmula XIX. La escisión del grupo carbamato en el compuesto de la fórmula XIX se lleva a cabo bajo condiciones estándar que son bien conocidas para aquellas personas expertas en el campo (referencia: T.W.

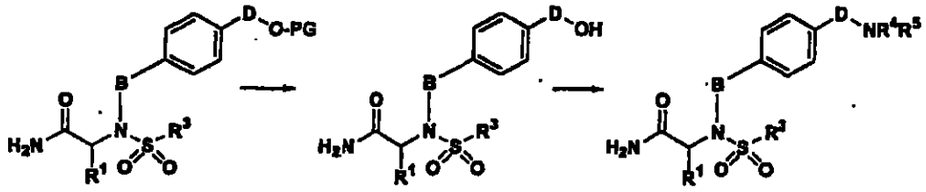
Greene y P. G. M. Wuts, "Protecting Groups in Organic Synthesis", Wiley Interscience, Nueva York, 1999, páginas 503-550) para proporcionar la piperidina de la fórmula XX. En el caso de un derivado de (t-butoxicarbonil)piperidina, la escisión se efectúa por medio del tratamiento con ácido trifluoroacético en CH_2Cl_2.

La conversión de la piperidina de la fórmula XX a una amida de la fórmula XXI se lleva a cabo utilizando los procedimientos de acoplamiento de amida bien conocidos para aquellas personas expertas en el campo (referencia: R.C. Larock "Comprehensive Organic Transformations, VCH Publishers, Nueva York, 1989, páginas 972-976). En un método preferido, la piperidina of fórmula XX es tratada con un cloruro de acilo en presencia de una amina tal como trietilamina y en un solvente inerte tal como CH_2Cl_2 con o sin calentamiento. Alternativamente, la piperidina de la fórmula XX se puede acoplar con un ácido en presencia de agentes de acoplamiento tales como hidroxibenzotriazol y una carbodiimida para proporcionar una amida de la fórmula XXI. La preparación de la urea de la fórmula XXII se logra por medio del tratamiento de la amina de la fórmula XX con un isocianato y una base tal como trietilamina en un solvente tal como CH_2Cl_2 con o sin calentamiento. La alquilación de la piperidina de la fórmula XX proporciona las piperidinas N-sustituidas de la fórmula XXIII. En un procedimiento típico,

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la piperidina es tratada con un haluro de alquilo o un sulfonato de alquilo en presencia de una base tal como trietilamina y en un solvente tal como CH_2Cl_2.

Esquema de Reacción 8



PG = un grupo protector de alcohol

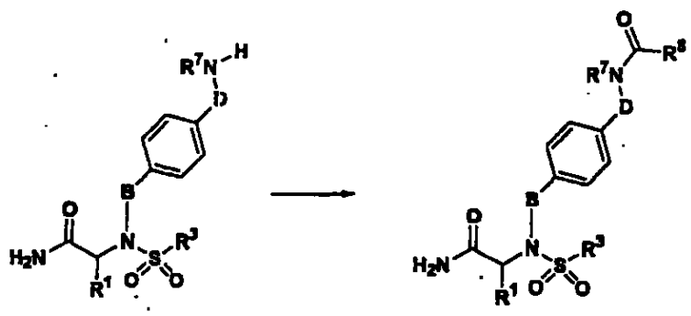
D es diferente de un enlace

Los alcoholes de la fórmula XXV y las aminas de la fórmula XXVI son sintetizados por medio de la secuencia mostrada en el esquema de reacción 8.Un alcohol protegido de la fórmula XXIV se prepara por medio del procedimiento mostrado en los esquemas de reacción 1 o 2. La desprotección del alcohol bajo las condiciones apropiadas para el grupo protector seleccionado (referencia: T.W. Greene y P. G. M. Wuts, "Protecting Groups in Organic Synthesis", capítulo 2) proporciona el alcohol de la fórmula XXV. Por ejemplo, cuando el grupo protector es un radical tetrahidropiranilo, el alcohol es liberado por medio del tratamiento del compuesto de la fórmula XXIV con ácido *p*-toluenosulfónico en un

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solvente tal como metanol. El alcohol de la fórmula XXV se convierte a un grupo saliente (por ejemplo, haluro o sulfonato) y luego es tratado con una amina primaria o secundaria para proporcionar una amina de la fórmula XXVI. Por ejemplo, el alcohol puede ser convertido a un derivado de mesilato por medio de la reacción con cloruro de metanosulfonilo y una base tal como trietilamina en CH_2Cl_2. La reacción subsecuente del mesilato con una amina primaria o secundaria en presencia de una base tal como trietilamina en un solvente tal como CH_2Cl_2 proporciona la amina de la fórmula XXVI.

Esquema de Reacción 9



XXVII XXVIII

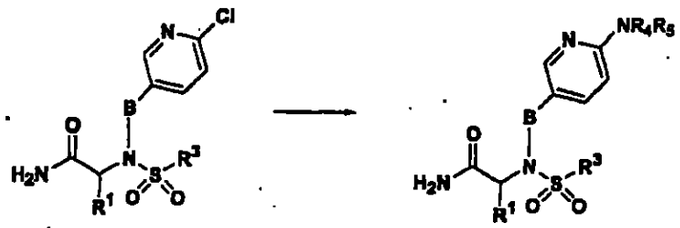
Las amidas de la fórmula XXVIII se preparan a partir de las aminas de la fórmula XXVII como se muestra en el esquema de reacción 9. Las aminas de la fórmula XXVII, en donde D es un enlace directo, se preparan como se describe en el esquema de reacción 1 o 4. Las aminas de

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la fórmula XXVII, en donde D es diferente de un enlace directo, se preparan como se describe en el esquema de reacción 8. La conversión de las aminas de la fórmula XXVII a las amidas de la fórmula XXVIII se lleva a cabo utilizando condiciones de acoplamiento de amida bien conocidas para aquellas personas expertas en el campo (referencia: R. C. Larock "Comprehensive Organic Transformations, VCH Publishers, Nueva York, 1989, páginas 972-976). Por ejemplo, la reacción de la amina de la fórmula XXVII con un cloruro ácido en presencia de una base tal como trietilamina en un solvente tal como CH_2Cl_2 proporciona la amida de la fórmula XXVIII. La conversión de las aminas de la fórmula XXVII a derivados de carbamato se puede llevar a cabo utilizando condiciones bien conocidas para aquellas personas expertas en el campo (referencia: T. W. Greene y P. G. M. Wuts, "Protecting Groups in Organic Synthesis", páginas 503-550). La preparación de los derivados de sulfonamida a partir de una amina de la fórmula XXVII también se puede lograr utilizando métodos tales como aquellos descritos para conversión del compuesto intermedio de la fórmula II a la sulfonamida de la fórmula III.

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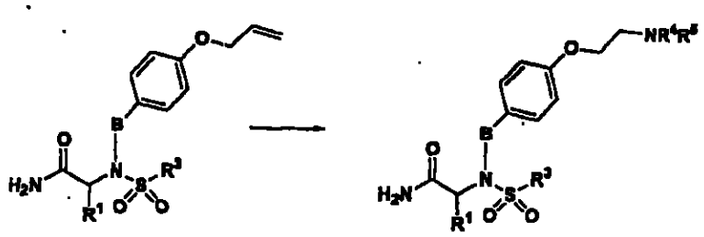
Esquema de Reacción 10



XXIX XXX

La síntesis de los derivados de piridina de la fórmula XXX se realiza como se muestra en el esquema de reacción 10. El derivado de choropiridina de la fórmula XXIX se prepara utilizando la química descrita en los esquemas de reacción 1 o 2. El tratamiento del compuesto de la fórmula XXIX con una amina primaria o secundaria en un solvente tal como THF a temperaturas de 20°C a 100°C, utilizando un recipiente presurizado, sellado, como sea apropiado, proporciona la aminopiridina de la fórmula XXX.

Esquema de Reacción 11



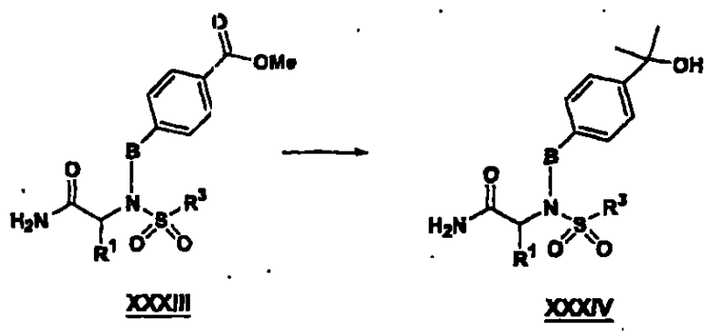
XXXI XXXII

Los éteres fenólicos sustituidos por amina de la

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fórmula XXXII se preparan a partir de (O-alil)fenoles como se indica en el esquema de reacción 11. Los éteres alílicos de inicio de la fórmula XXXI se preparan como se muestra en los esquemas de reacción 1 o 2. El tratamiento del compuesto de la fórmula XXXI con tetróxido de osmio y N-óxido de trimetilamina en un solvente tal como acetona seguido por el tratamiento con peryodato de sodio proporciona un aldehído intermedio que se utiliza típicamente sin purificación. La reacción del aldehído no purificado con una amina primaria o secundaria y un agente de reducción tal como triacetoxiborohidruro de sodio en un solvente tal como etanol con o sin calentamiento proporciona la amina de la fórmula XXXII.

Esquema de Reacción 12

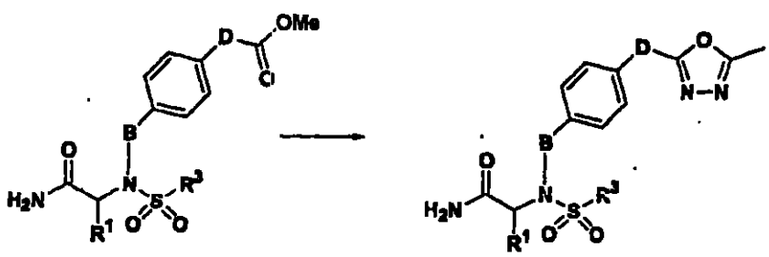


XXXIII XXXIV

La conversión del éster de la fórmula XXXIII al alcohol terciario de la fórmula XXXIV se lleva a cabo como se muestra en el esquema de reacción 12. La reacción del éster

de la fórmula XXXIII con un exceso de un reactivo organometálico de metilo tal como bromuro de metil-magnesio en un solvente tal como THF a una temperatura que varía de 0°C a 25°C produce el alcohol de la fórmula XXXIV.

Esquema de Reacción 13

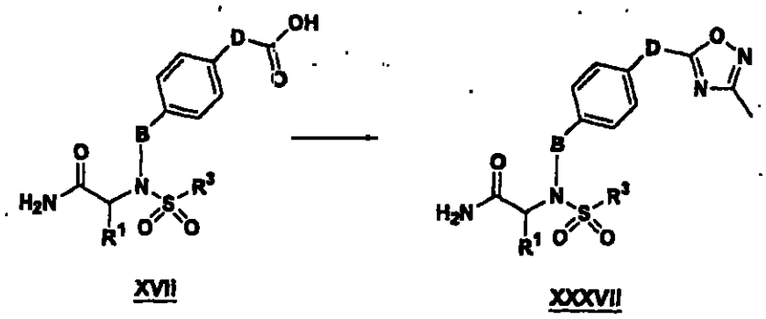


XXXV XXXVI

La preparación del 1,3,4-oxadiazol de la fórmula XXXVI se lleva a cabo como se muestra en el esquema de reacción 13 utilizando métodos bien conocidos para aquellas personas expertas en el campo (referencia: Joule, J. A.; Mills, K.; Smith, G. F. Heterocyclic Chemistry, 3ª edición, Chapman & Hall: Londres, 1995; 452-456 y referencias citadas en la misma). Por ejemplo, el éster de la fórmula XXXV es tratado con hidrazina en metanol con calentamiento hasta el punto de reflujo. El compuesto intermedio de hidrazida de acilo resultante se utiliza sin purificación en una reacción subsecuente con un acetimidato de alquilo en piridina con calentamiento a reflujo para proporcionar el oxadiazol de la

fórmula XXXVI.

Esquema de Reacción 14

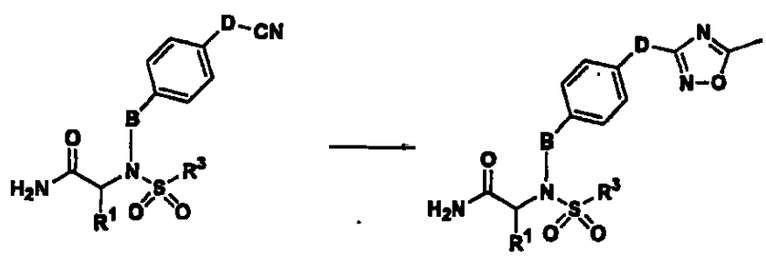


XVII XXXVII

La síntesis del 1,2,4-oxadiazol de la fórmula XXXVII se logra como se muestra en el esquema de reacción 14 utilizando métodos bien conocidos para aquellas personas expertas en el campo (referencia: Joule, J. A.; Mills, K.; Smith, G. F. Heterocyclic Chemistry, 3ª edición, Chapman & Hall: Londres, 1995; 452-456 y referencias citadas en la misma). Por ejemplo, el tratamiento del ácido de la fórmula XVII con hidroxibenzotriazol, una carbodiimida y (N-hidroxietanimidamida) de acetamidoxima en presencia de una base tal como trietilamina proporciona un compuesto intermedio que se calienta en piridina a reflujo para proporcionar el oxadiazol de la fórmula XXXVII.

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Esquema de Reacción 15

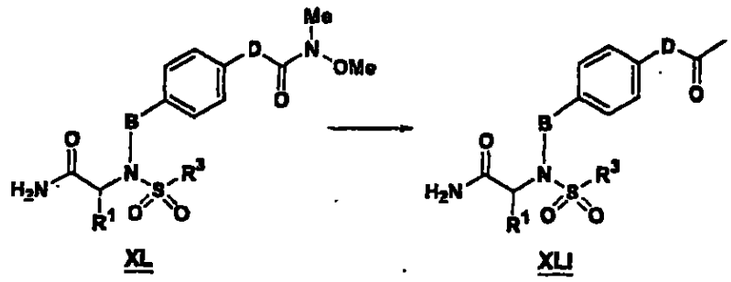


XXXVIII XXXIX

El 1,2,4-oxadiazol de la fórmula XXXIX se prepara a partir del nitrilo de la fórmula XXXVIII (esquema de reacción 15) utilizando métodos bien conocidos para aquellas personas expertas en el campo (referencia: Joule, J. A.; Mills, K.; Smith, G. F. Heterocyclic Chemistry, 3ª edición, Chapman & Hall: Londres, 1995; 452-456 y referencias citadas en la misma). Por ejemplo, la reacción del nitrilo de la fórmula XXXVIII con hidroxilamina en un solvente tal como etanol a temperaturas de hasta la temperatura de reflujo proporciona un compuesto intermedio de N-hidroxiamidina que es tratado subsecuentemente con cloruro de acetilo en presencia de una base tal como trietilamina en un solvente tal como CH_2Cl_2 para proporcionar el 1,2,4-oxadiazol de la fórmula XXXIX.

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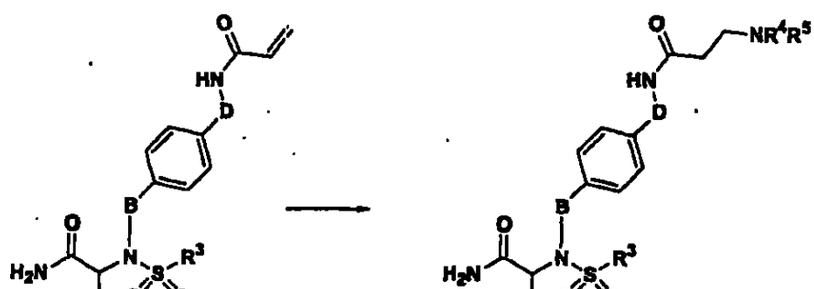
Esquema de Reacción 16



XL XLI

El esquema de reacción 16 muestra la transformación de la amida de la fórmula XL a la cetona de la fórmula XLI. La amida de la fórmula XL, la cual se prepara como se describe en el esquema de reacción 6, es tratada con un reactivo organometálico de metilo tal como bromuro de metil-magnesio en un solvente tal como THF para proporcionar la cetona de la fórmula XLI. El rango de la temperatura de reacción es de -20°C a 25°C.

Esquema de Reacción 17

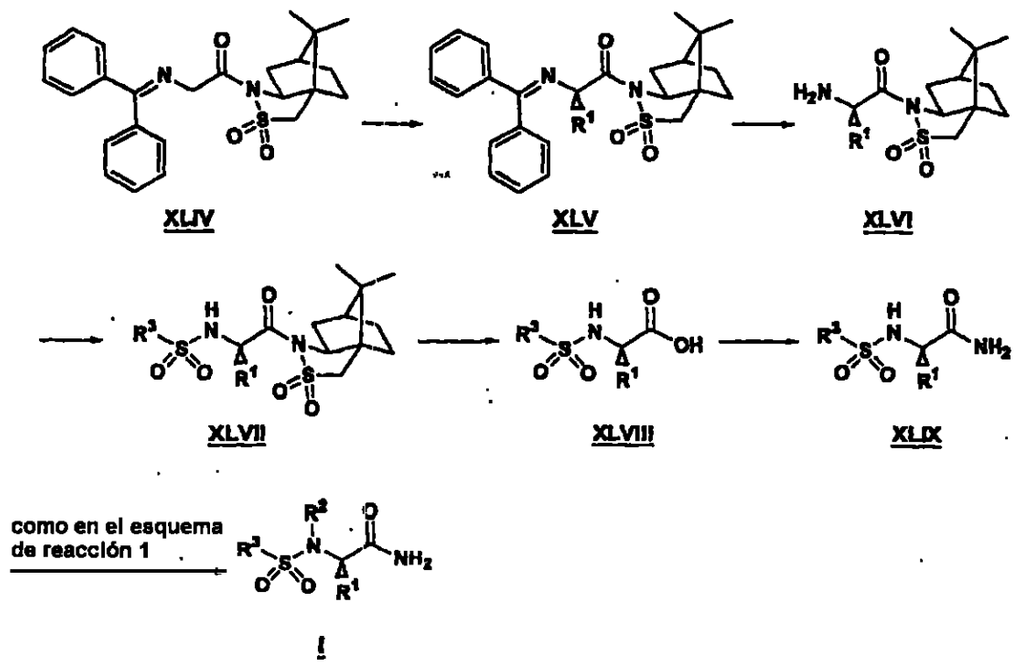


XLII XLIII

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Las β-amino-amidas de la fórmula XLIII se preparan a partir de las acrilamidas de la fórmula XLII como se muestra en el esquema de reacción 17.Por ejemplo, una acrilamida de la fórmula XLII, la cual se prepara como se describe en el esquema de reacción 9, es tratada con una amina primaria o secundaria en un solvente tal como tolueno para proporcionar la β-amino-amida de la fórmula XLIII.

Esquema de Reacción 18



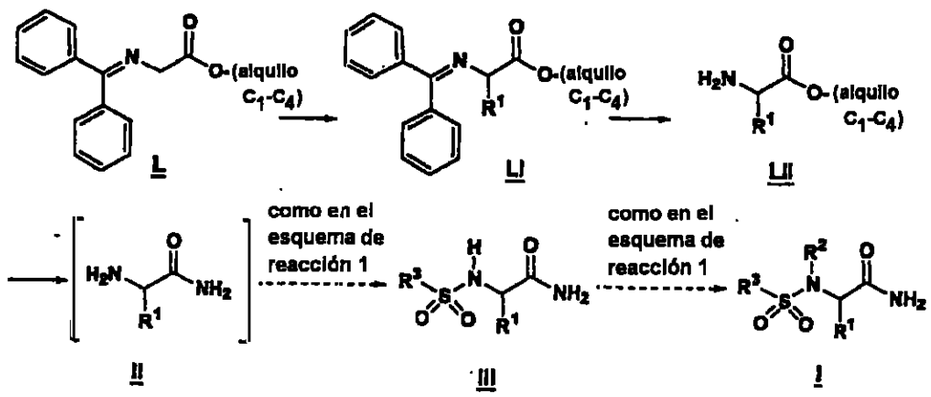
La preparación del compuesto intermedio de sulfonamida de la fórmula XLIX (un enantiómero individual del compuesto de la fórmula III) se resume en el esquema de reacción 18. La reacción del α-anión del compuesto

intermedio de la fórmula XLIV (referencia: Josien, H.; Martin, A.; Chassaing, G. Tetrahedron Lett. **1991**, 32, 6547) con un agente alquilante tal como haluro de alquilo (por ejemplo, un cloruro de alquilo, bromuro de alquilo o yoduro de alquilo) o un sulfonato de alquilo (por ejemplo, un mesilato de alquilo, tosilato de alquilo o trifluorometanosulfonato de alquilo) proporciona el compuesto intermedio de la fórmula XLV. El α-anión del compuesto de la fórmula XLIV se forma por medio del tratamiento con una base fuerte tal como alquil-litio (por ejemplo, n-BuLi) o una dialquilamida (por ejemplo, diisopropilamida de litio) en un solvente tal como THF con o sin un co-solvente, tal como HMPA. La temperatura de reacción es típicamente entre -78°C y 25°C. La remoción del grupo protector de benzhidrilideno del compuesto de la fórmula XLV se lleva a cabo bajo condiciones bien conocidas para aquellas personas expertas en el campo (referencia: T. W. Greene y P. G. M. Wuts, "Protecting Groups in Organic Synthesis", Wiley Interscience, Nueva York, 1999, páginas 587-588). Por ejemplo el compuesto de la fórmula XLV es tratado con un ácido tal como HCl en agua en un solvente tal como THF para efectuar la hidrólisis del grupo protector de benzhidrilideno. La amina resultante de la fórmula XLVI es tratada con un agente de sulfonilación tal como se describe para el

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esquema de reacción 1 para proporcionar la sulfonamida de la fórmula XLVII. La hidrólisis de la acilsulfonamida de la fórmula XLVII para proporcionar el ácido de la fórmula XLVIII se lleva a cabo por medio del tratamiento con un ión de hidróxido, por ejemplo en la forma de hidróxido de litio, en presencia de aditivos tales como bromuro de litio y bromuro de tetrabutilamonio. El ácido de la fórmula XLVIII se convierte a la amida de la fórmula XLIX bajo condiciones que son bien conocidas para aquellas personas expertas en el campo (referencia general para la preparación de amida: R. C. Larock "Comprehensive Organic Transformations, VCH Publishers, Nueva York, 1989, páginas 972-976). Por ejemplo, la reacción del compuesto de la fórmula XLVIII con cloruro de amonio en presencia de 1-hidroxibenzotriazol, un reactivo de carbodiimida y una base de amina tal como diisopropiletilamina proporciona la amida de la fórmula XLIX. Esta reacción se lleva a cabo típicamente en un solvente polar tal como DMF y a una temperatura de reacción de 0°C a 40°C. La amida de la fórmula XLIX se convierte a los compuestos de la fórmula I por medio del método descrito en el esquema de reacción 1.

Esquema de Reacción 19



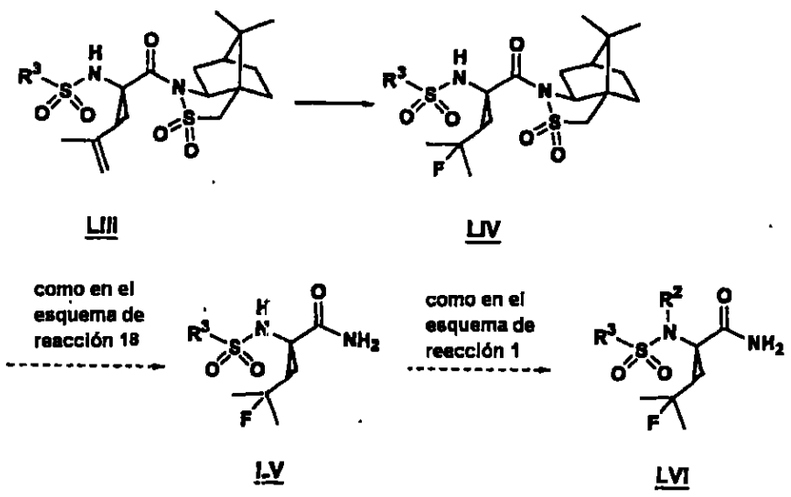
El esquema de reacción 19 ilustra un método para la síntesis de un compuesto intermedio de (N-sulfonamido)acetamida α-sustituida de la fórmula III iniciando con un derivado de glicina activada de la fórmula L. La reacción del compuesto de la fórmula L (referencia: Haufe, G.; Laue, K. W.; Triller, M. U.; Takeuchi, Y.; Shibata, N. *Tetrahedron* **1998**, 54, páginas 5929-5938; Kroger, S.; Haufe, G. *Amino Acids* **1997**, 12, páginas 363-372) con un agente de alquilación tal como haluro de alquilo (por ejemplo, un cloruro de alquilo, bromuro de alquilo o yoduro de alquilo) o un sulfonato de alquilo (por ejemplo, un mesilato de alquilo, tosilato de alquilo o trifluorometanosulfonato de alquilo) en presencia de una base tal como carbonato de potasio y en un aditivo, tal como bromuro de tetrabutilamonio, y un solvente inerte, tal como acetonitrilo, a una temperatura de reacción de entre 25°C y

70°C proporciona el compuesto de la fórmula LI. La remoción del grupo protector benzhidrilideno se lleva a cabo bajo condiciones bien conocidas para aquellas personas expertas en el campo (referencia: T. W. Greene y P. G. M. Wuts, "Protecting Groups in Organic Synthesis", Wiley Interscience, Nueva York, 1999, páginas 587-588). Por ejemplo, una solución del compuesto de la fórmula LI en un solvente tal como éter dietílico es tratada con un ácido acuoso (por ejemplo, HCl acuoso), típicamente a una temperatura de reacción de entre 0°C y 30°C, para proporcionar el éster de amina de la fórmula LII. La conversión del éster de la fórmula LII a la amida de la fórmula II se lleva a cabo utilizando procedimientos bien conocidos para aquellas personas expertas en el campo. Por ejemplo, cuando el compuesto de la fórmula LII es un éster etílico, la hidrólisis del éster se logra por medio del tratamiento de una solución etérea de un ácido tal como HCl, típicamente con el calentamiento de la mezcla de reacción en un solvente a reflujo. El compuesto intermedio, ácido, resultante entonces se convierte a un éster metílico de la fórmula LII por medio de la transformación al cloruro ácido bajo condiciones estándar (por ejemplo, tratamiento con cloruro de tionilo y metanol), seguido por la reacción con amoniaco acuoso en un solvente tal como tolueno (referencia: R. C. Larock "Comprehensive Organic Transformations, VCH Publishers, Nueva York, 1989, páginas 972-976). La amina de

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la fórmula II se convierte al compuesto de la fórmula I como se describiera en el esquema de reacción 1.

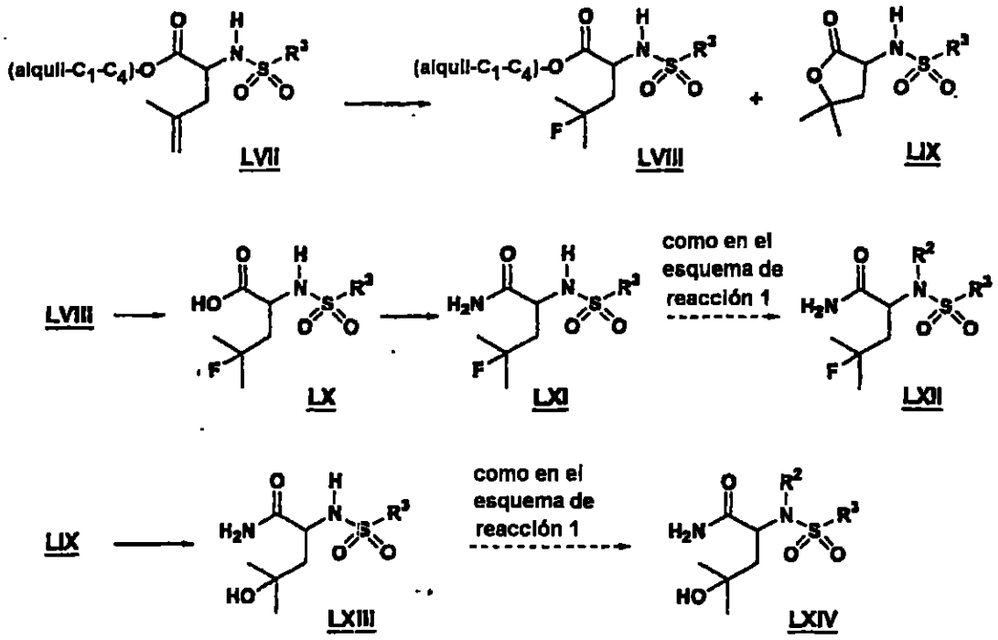
Esquema de Reacción 20



La preparación del compuesto de la fórmula LVII se muestra en el esquema de reacción 20. El alqueno LIII se prepara como se describe en el esquema de reacción 18 a partir de un compuesto intermedio de la fórmula XLIV y 1-bromo-2-metil-2-propeno). El tratamiento del alqueno de la fórmula LIII con HF•piridina en un solvente tal como THF a una temperatura de reacción entre 0°C y 25°C proporciona el compuesto de fluoroalquilo de la fórmula LIV. La conversión del compuesto de la fórmula LIV a la amida de la fórmula LV se realiza como se describe en el esquema de reacción 18. La transformación de la amida de la fórmula LV al compuesto de la fórmula LVI se lleva a cabo como se describe en el esquema

de reacción I.

Esquema de Reacción 21



Las síntesis de los compuestos de la fórmula LXII y la fórmula LXIV se resumen en el esquema de reacción 21. El 2-amino-4-metil-4-pentenoato de etilo (preparado como en el esquema de reacción 19 a partir de éster etílico del ácido (benzhidrilidenamino)acético y 1-bromo-2-metil-2-propeno) se trata con un agente de sulfonilación tal como un cloruro de sulfonilo en presencia de una base tal como trietilamina en un solvente inerte tal como CH_2Cl_2 para proporcionar el éster de la fórmula LVII. La reacción del éster de la fórmula LVII con HF•piridina en un solvente tal como THF y a una temperatura de reacción de entre 0°C y 25°C proporciona una

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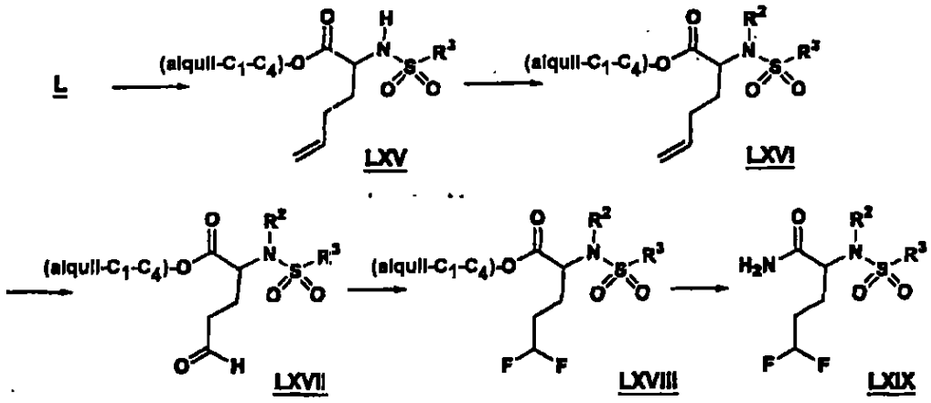
mezcla del derivado de fluoroalquilo de la fórmula LVIII y la lactona de la fórmula LIX. Estos productos se separan y se llevan individualmente en reacciones subsecuentes.

El éster de la fórmula LVIII es hidrolizado al ácido de la fórmula LX utilizando métodos bien conocidos para aquellas personas expertas en el campo (referencia: T. W. Greene y P. G. M. Wuts, "Protecting Groups in Organic Synthesis", Wiley Interscience, Nueva York, 1999, páginas 373-442). Por ejemplo, el tratamiento del éster de la fórmula LVIII con hidróxido de sodio acuoso tal como metanol proporciona el ácido de la fórmula LX. El ácido de la fórmula LX se convierte a la amida de la fórmula LXI utilizando el procedimiento descrito en el esquema de reacción 18 para la preparación de la amida de la fórmula XLIX. La preparación de la amida de la fórmula LXII a partir del compuesto de la fórmula LXI se logra como se describe en el esquema de reacción 1.

Para la lactona de la fórmula LIX, el tratamiento con amoniaco acuoso proporciona la amida de la fórmula LXIII. Esta reacción se lleva a cabo típicamente con el calentamiento en un tubo sellado. La temperatura de reacción es entre 40°C y 80°C. La conversión adicional del compuesto intermedio de la fórmula LXIII a la sulfonamida de la fórmula LXIV procedió como se describe en el esquema de reacción 1.

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Esquema de Reacción 22

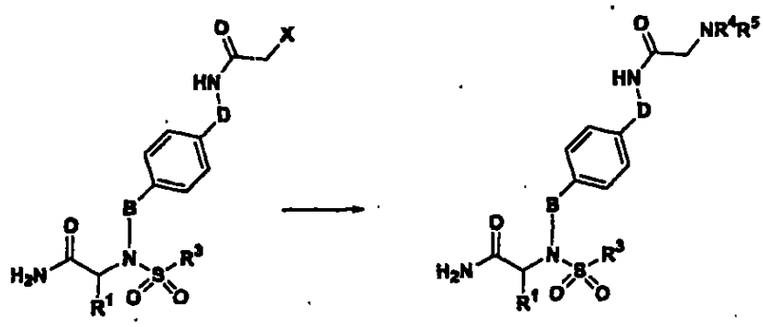


La secuencia sintética para la preparación de una difluoroalquilamida de la fórmula LXIX se muestra en el esquema de reacción 22. El compuesto de la fórmula L es tratado con 4-bromo-1-buteno en presencia de una base tal como carbonato de potasio en presencia de una sal de haluro de tetraalquilamonio tal como bromuro de tetrabutilamonio en un solvente tal como CH_3CN a una temperatura de 20°C a 70°C. La remoción del grupo protector de benzhidrilideno como se describe en el esquema de reacción 19 proporciona una amina intermedia que luego es tratada con un reactivo de sulfonilación tal como cloruro de sulfonilo para proporcionar el éster de la fórmula LXV. La alquilación del nitrógeno de sulfonamida se realiza utilizando el procedimiento descrito en el esquema de reacción 1 para proporcionar el compuesto de la fórmula LXVI. La conversión del alqueno de la fórmula LXVI

al aldehído de la fórmula LXVII se logra por medio de la reacción del alqueno con tetróxido de osmio y N-óxido de trimetilamina en un solvente tal como acetona, seguido por el tratamiento con peryodato de sodio. La temperatura de reacción es típicamente de 20°C a 40°C. La reacción del aldehído de la fórmula LXVII con un agente de fluoración tal como DAST en un solvente tal como CH_2Cl_2 produce el derivado difluoroalquilo de la fórmula LXVIII. El compuesto de la fórmula LXVIII se convierte a la amida de la fórmula LXIX por medio de la hidrólisis del éster a un ácido utilizando una base tal como hidróxido de sodio en un solvente tal como metanol. El ácido intermedio se convierte a la amida utilizando condiciones bien conocidas para aquellas personas expertas en el campo (referencia: R. C. Larock "Comprehensive Organic Transformations, VCH Publishers, Nueva York, 1989, páginas 972-976). Por ejemplo, la reacción del ácido con cloruro de amonio en presencia de hidroxibenzotriazol y un reactivo de carbodiimida y una base de amina tal como diisopropiletilamina proporciona la amida de la fórmula LXIX. Esta reacción se lleva a cabo típicamente en un solvente polar tal como DMF y a una temperatura de reacción de 0°C a 40°C.

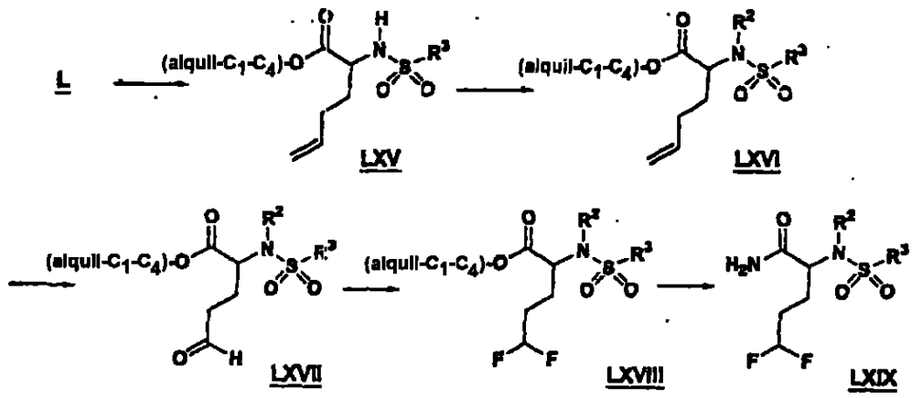
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Esquema de Reacción 23



LXX LXXI

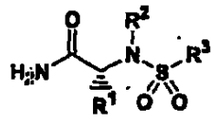
La α-amino-amida de fórmula LXXI se prepara utilizando la reacción mostrada en el esquema de reacción 23. La amida de la fórmula LXX se prepara como se describe en el esquema de reacción 9. El tratamiento del compuesto de la fórmula LXX con una amina secundaria o terciaria en un solvente tal como THF a una temperatura de reacción entre 20°C y 40°C proporciona la amina de la fórmula LXXI.



L LXV LXVI LXVII LXVIII LXIX

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En una modalidad preferida, la presente invención incluye compuestos de la fórmula Ia o una sal farmacéuticamente aceptable de los mismos



Ia

en donde:

R^1 se selecciona del grupo que consiste de

(a) un grupo alquilo de 1 a 6 átomos de carbono o alquenilo de 2 a 6 átomos de carbono de cadena recta o ramificada sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de hidroxi, cicloalquilo de 3 a 7 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, alquiltio de 1 a 4 átomos de carbono y halógeno;

(b) cicloalquilo de 3 a 7 átomos de carbono sustituido opcionalmente por hidroxi o halógeno;

R^2 se selecciona del grupo que consiste de

(a) un grupo alquilo de 1 a 6 átomos de carbono o alquenilo de 3 a 6 átomos de carbono de cadena recta o ramificada sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, alcoxi de 1 a 4 átomos

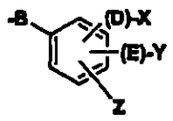
de carbono y NR^4R^5;

(b) cicloalquilmetilo de 3 a 7 átomos de carbono sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de amino, (alquil-C_1-C_4)NH-, di(alquil-C_1-C_4)N-, alquil-C_1-C_4-C(=O)NH- y alquil-C_1-C_4-OC(=O)NH-;

(c) un grupo alquil-C_1-C_6-C(=O)-A de cadena recta o ramificada;

(d) -B-naftilo;

(e)



D y E son cada uno, independientemente, un enlace directo, un grupo alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono o cicloalquilo de 3 a 7 átomos de carbono de cadena recta o ramificada;

Z se selecciona del grupo que consiste de hidrógeno, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, halógeno, ciano, hidroxi, $-OCHF_2$, $-OCF_3$, $-CF_3$ y $-CHF_2$;

X e Y se seleccionan cada uno, independientemente, del grupo que consiste de hidrógeno, hidroxi, halógeno, (halógeno)$_3$C-,

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(halógeno)$_2$CH-, alquil-C_1-C_4-S-, alquil-C_1-C_4-S(O)-, alquil-C_1-C_4-SO_2-, nitro, F_3S- y ciano;

$-OR^6$;

$-NR^4R^5$;

$-NR^7C(=O)R^8$;

$-NR^7C(=O)OR^8$;

$-NHSO_2$-alquilo de 1 a 4 átomos de carbono;

$-N(SO_2$-alquil-C_1-$C_4)_2$;

-C(=O)W, en donde W se selecciona del grupo que consiste de hidroxi, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, fenoxi y $-NR^4R^5$;

-OC(=O)alquilo de 1 a 4 átomos de carbono;

-fenilo, en el cual el grupo fenilo es sustituido opcionalmente por ciano, halógeno, alcoxi de 1 a 4 átomos de carbono, alquil-C_1-C_4-S-, $CH_3C(=O)$, alquil-C_1-C_4-S(O)- o alquil-C_1-C_4-SO_2; y

un grupo heterocíclico, en el cual el grupo heterocíclico se selecciona del grupo que consiste de furanilo, tiofuranilo, pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, oxadiazolilo, oxazolilo, isoxazolilo, tiadiazolilo y tiazolilo, en donde el grupo

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heterocíclico es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de ciano, halógeno, alquilo de 1 a 4 átomos de carbono, (halógeno)alquilo de 1 a 4 átomos de carbono y CO_2-alquilo de 1 a 4 átomos de carbono;

(f) -B-(heterociclo), en el cual el heterociclo se selecciona del grupo que consiste de furanilo, tiofuranilo, pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, oxadiazolilo, oxazolilo, isoxazolilo, tiadiazolilo y tiazolilo, en donde el heterociclo es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de ciano, halógeno, alquilo de 1 a 4 átomos de carbono, CO_2-alquilo de 1 a 4 átomos de carbono, amino, (alquil-C_1-C_4)NH-, di(alquil-C_1-C_4)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo y 4-(alquil-C_1-C_6)-piperazin-1-ilo;

(g) -B-(piperidin-4-ilo), en el cual el grupo piperidin-4-ilo es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de alquilo de 1 a 6 átomos de carbono

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de cadena recta o ramificada, $CH_2C(=O)$fenilo, fenilo y fenilmetilo en el cual el grupo alquilo de 1 a 6 átomos de carbono y el grupo fenilo son sustituidos opcionalmente por sustituyentes seleccionados del grupo que consiste de ciano, halógeno, bencimidazol-2-ilo, piridilo y tetrahidrofuran-2-ilo; y $-C(=O)W'$, en donde W' se selecciona del grupo que consiste de alcoxi de 1 a 4 átomos de carbono, R^9 y $-NR^4R^5$;

A es hidroxi, alcoxi de 1 a 4 átomos de carbono o NR^4R^5;

B es un grupo alquilo de 1 a 6 átomos de carbono o alquenilo de 3 a 6 átomos de carbono de cadena recta o ramificada;

R^3 es fenilo o piridilo sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, hidroxi, alcoxi de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono, $(halógeno)_3C-$, $(halógeno)_2CH-$ y $halógeno-CH_2-$;

R^4 y R^5 son cada uno, independientemente, hidrógeno, un grupo alquilo de 1 a 6 átomos de carbono, alquenilo de 3 a 6 átomos de carbono, alquinilo de 3 a 6 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, cicloalquilmetilo de 3 a 7 átomos de

carbono, alcoxi de 1 a 4 átomos de carbono, fenilo, bencilo, piridilo, piperidin-4-ilo, indan-1-ilo, indan-2-ilo, tetrahidrofuran-3-ilo o pirrolidin-3-ilo de cadena recta o ramificada; en el cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de hidroxi, ciano, halógeno, (halógeno)$_3$C-, (halógeno)$_2$CH-, halógeno-CH$_2$-, hidroximetilo, benciloximetilo, fenilo, piridilo, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, (halógeno)$_3$C-O-, (halógeno)$_2$CH-O-, alquiltio de 1 a 4 átomos de carbono, amino, (alquil-C$_1$-C$_4$)NH-, di(alquil-C$_1$-C$_4$)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo, 4-(alquil-C$_1$-C$_6$)piperazin-1-ilo, 4-fenilpiperazin-1-ilo, 4-bencilpiperazin-1-ilo, 4-piridilpiperazin-1-ilo, CO$_2$H, CO$_2$-alquilo de 1 a 4 átomos de carbono, C(=O)NH-alquilo de 1 a 4 átomos de carbono y C(=O)N(alquil-C$_1$-C$_4$)$_2$;

R^4 y R^5 tomados conjuntamente pueden ser morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, 1,2,3,4-tetrahidroisoquinolin-2-ilo, decahidroquinolin-1-ilo, piperidin-1-ilo, piperazin-1-ilo, [1,4]-oxazepan-4-ilo, azetidin-1-ilo, 2,3-dihidro-1*H*-isoindol-2-ilo o 2,3-dihidro-1*H*-indol-1-ilo; en el

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cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de hidroxi, ciano, halógeno, (halógeno)$_3$C-, (halógeno)$_2$CH-, halógeno-CH$_2$-, fenilo, piridilo, bencilo, alquilo de 1 a 6 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, alquiltio de 1 a 4 átomos de carbono, amino, (alquil-C$_1$-C$_4$)NH-, di(alquil-C$_1$-C$_4$)N-, CO$_2$H, CO$_2$-alquilo de 1 a 4 átomos de carbono, C(=O)NH-alquilo de 1 a 4 átomos de carbono y C(=O)N(alquil-C$_1$-C$_4$)$_2$;

R^6 es un grupo alquilo de 1 a 6 átomos de carbono, alquenilo de 3 a 6 átomos de carbono, bencilo o fenilo de cadena recta o ramificada, en el cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, amino, (alquil-C$_1$-C$_4$)NH-, di(alquil-C$_1$-C$_4$)N-, (alquil-C$_1$-C$_4$)(fenil)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo y 4-(alquil-C$_1$-C$_6$)piperazin-1-ilo;

R^7 es hidrógeno, un grupo alquilo de 1 a 6 átomos de carbono de cadena recta o ramificada;

R^8 es un grupo alquilo de 1 a 6 átomos de carbono,

cicloalquilo de 3 a 7 átomos de carbono, fenilo, piridilo o furanilo de cadena recta o ramificada; en el cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, (alquil-C_1-C_4)NH-, di(alquil-C_1-C_4)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo y 4-(alquil-C_1-C_6)piperazin-1-ilo;

R^9 es un grupo alquilo de 1 a 6 átomos de carbono, alquenilo de 3 a 6 átomos de carbono, bencilo, fenilo, oxazolilo o piridilo de cadena recta o ramificada; en el cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, (halógeno)$_3$C-, (halógeno)$_2$CH-, halógeno-CH_2-, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, amino, (alquil-C_1-C_4)NH-, di(alquil-C_1-C_4)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo y 4-(alquil-C_1-C_6)piperazin-1-ilo;

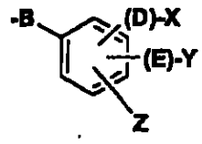
o una sal farmacéuticamente aceptable, no tóxica de los mismos.

En otra modalidad preferida, la invención incluye

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los compuestos de la fórmula Ia o una sal farmacéuticamente aceptable de los mismos, en donde R^3 es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, hidroxi, alcoxi de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono, $(halógeno)_3C$-, $(halógeno)_2CH$- y halógeno-CH_2-.

En aún otra modalidad preferida, la invención incluye compuestos de la fórmula Ia o una sal farmacéuticamente aceptable de los mismos, en donde R^2 es



MÉTODOS DE PRUEBA BIOLÓGICA

Se espera que los compuestos de la fórmula (I) posean actividad inhibidora de γ-secretasa. La detección de la actividad de γ-secretasa requiere ensayos capaces de la detección confiable, precisa y conveniente de los productos de escisión de γ-secretasa, particularmente Aβ. La actividad inhibidora de γ-secretasa de los compuestos de la presente invención se demuestra utilizando ensayos para esta actividad, por ejemplo, utilizando los ensayos descritos posteriormente. Se ha mostrado que los compuestos dentro del alcance de la presente invención inhiben la actividad de γ-secretasa, como se determina utilizando los ensayos para esta

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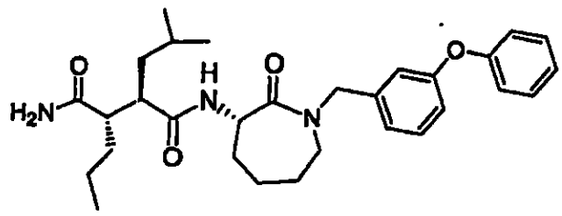
actividad.

Los compuestos proporcionados por esta invención también deben ser útiles como estándares y reactivos en la determinación de la capacidad de un producto farmacéutico potencial para inhibir la producción de Aβ. Estos se proporcionarían en equipos comerciales que comprenden un compuesto de esta invención.

Ensayo de unión in vitro para identificar los inhibidores de γ-secretasa.

Los ensayos de unión competitiva se pueden utilizar para identificar moléculas que inhiben la unión de un inhibidor de γ-secretasa radioetiquetado y por lo tanto inhiben la capacidad de γ-secretasa. Por ejemplo, el [^{3}H]-compuesto A se puede utilizar para ensayos de unión con membranas de células THP-1 (Seiffert, D.; Bradley, J. y colaboradores, *J. Biol. Chem.* 2000, 275, 34086-34091). El compuesto A es (2R,3S)N1-[(3S)-hexahidro-1-(3-fenoxibencil)-2-oxo-1H-azepin-3-il]-2-(2-metilpropil)-3-(propil)-butanodiamida, la síntesis del cual se describe en la patente norteamericana No. US6331408 (12/18/2001); publicación del PCT WO 00/28331; publicación del PCT WO 00/07995; y Seiffert, D., Bradley, J. y colaboradores, *J. Biol. Chem.* 2000, **275**.34086-34091.

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Compuesto A

Para estos ensayos, las células THP-1 se desarrollaron en cultivos giratorios en RPMI 1640 que contenía L-glutamina y β-mercaptoetanol 10 μM a una densidad de 5 x 10^5 células/ml. Las células se recolectaron por medio de la centrifugación y las pelotillas de células se congelaron rápidamente en hielo seco/etanol y se almacenaron a -70°C antes del uso. Las pelotillas de aproximadamente 2 x 10^4 células THP-1 fueron homogenizadas utilizando un disposivo Brinkman Polytron en un ajuste de 6 durante 10 segundos. El producto homogeneizado se centrífugo a 48,000 x g durante 12 minutos, y la pelotilla resultante se lavó al repetir la homogenización y centrifugación. La pelotilla de célula final se resuspendió en amortiguador para producir una concentración de proteína de aproximadamente 0.5 mg/ml. Los ensayos se iniciaron por la adición de 150 μl de suspensión de membrana a 150 μl de amortiguador de ensayo que contenía 0.064 μCi de radioligando y varias concentraciones de compuestos no etiquetados. Los ensayos de unión se realizaron por duplicado en placas de 96 pocillos

de polipropileno en un volumen final de 0.3 ml que contenía Hepes 50 mM, pH 7.0 y sulfóxido de dimetilo al 5%. La unión no específica se definió utilizando incubaciones con el compuesto A 300 nM (Seiffert, D., Bradley, J. y colaboradores, *J. Biol. Chem.* 2000, **275**, 34086-34091). Después de la incubación a 23°C durante 1.3 horas, el ligando unido se separó del radioligando libre por medio de la filtración sobre filtros de fibra de vidrio GFF previamente remojados en solución polimérica de etilenimina al 0.3%. Los filtros se lavaron tres veces con 0.3 ml de solución salina amortiguada con fosfato enfriada con hielo, pH 7.0, que contenía Triton X-100 al 0.1%. La radioactividad unida al filtro se midió por medio del conteo de centelleo. Entonces se determinaron los valores IC_{50} y se utilizaron para calcular los valores K_i utilizando la corrección Cheng-Prusoft para los valores IC_{50}. Los compuestos se almacenaron como inhibidores activos de γ-secretasa si los valores K_i fueron menores de 10 μM.

Los ejemplcs de los resultados obtenidos cuando los compuestos de la invención se sujetaron al ensayo descrito anteriormente se muestran en la tabla 1. En la tabla, una concentración inhibidora (IC_{50}) menor que o igual que 50 nM es representada por +++; entre 50 nM y 500 nM por ++; entre 500 nM y 10000 nM por +.

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TABLA 1: Ejemplos de actividad en el ensayo de unión *in vitro*

EJEMPLO	CLASIFICACIÓN DE LA ACTIVIDAD[a]
96	+++
123	+++
159	+++
315	++
341	++
357	++
362	+++
365	+++
366	+++
367	+
376	++
379	+++
385	+++
389	+++
394	+++
403	++
405	+++
408	+
409	++
437	+++
441	+++

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443	++
445	+++
447	+++
450	++
451	+
452	++
457	++
464	+
474	+++
476	+++
479	++
486	+++

[a] Actividad basada en los valores IC_{50}

+++ = <50 nM

++ = 50-500 nM

+ = >500 nM y <10,000 nM

Ensayo *in vitro* para identificar un inhibidor de γ-secretasa basado en la inhibición de la formación de Aβ a partir de preparaciones de membrana

Una fracción de membrana aislada que contiene la γ-secretasa funcionalmente activa y substratos de β-APP puede generar productos de escisión de γ-secretasa que incluyen Aβ (Roberts, S. B.; Hendrick, J. P.; Vinitsky, A.; Lewis, M.; Smith, D. W.; Pak, R. publicación del PCT WO 01/0175435;

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Fechteler, K.; Kostka, M.; Fuchs, M. solicitud de patente No. DE 99-19941039; Shearman, M.; Beher, D. y colaboradores, *Biochemistry*, 2000, 39, 8698-8704; Zhang, L. Song, L. y colaboradores, *Biochemistry* 2001, 40, 5049-5055). Una fracción de membrana aislada se puede preparar a partir de líneas de células derivadas de humano tales como HeLa y H4, las cuales han sido transfectadas con formas de origen natural o mutantes de β-APP o una a construcción de fusión de β-APP y fosfatasa alcalina de humano y expresan de manera estable altos niveles de substratos de γ-secretasa. La γ-secretasa endógena que está presente en las membranas aisladas preparadas a 0-4°C escinde los substratos de β-APP cuando las membranas son cambiadas de 0-4 a 37°C. La detección de los productos de escisión que incluyen Aβ se pueden supervisar por medio de técnicas estándar tales como la inmunoprecipitación (Citron, M.; Diehl, T. S. y colaboradores, *Proc. Natl. Acad. Sci.* EUA, 1996, 93, 13170-13175), técnica de inmunotransferencia western (Klafki, H. -W.; Ambramowski, D. y colaboradores. *J. Biol. Chem.* 1996, 271, 28655-28659), ensayo inmunoabsorbente enlazado a enzimas (ELISA) como se demuestra por Seubert, P.; Vigo-Pelfrey, C. y colaboradores, *Nature*, 1992, 359, 325-327, o por un método preferido que utiliza fluorescencia resuelta en función del tiempo de la muestra homogénea que contiene membranas y Aβ (Roberts, S. B.; Hendrick, J. P.; Vinitsky, A.; Lewis, M.;

Smith, D. W.; Pak, R. publicación del PCT WO 01/0175435; Shearman, M.; Beher, D. y colaboradores, *Biochemistry*, 2000, 39, 8698-8704). La Aβ presente en una muestra homogénea que contiene membranas se puede detectar por medio de la fluorescencia resuelta en función del tiempo con dos anticuerpos que reconocen diferentes epítopos de Aβ. Uno de los anticuerpos reconoce un epítopo que está presente en Aβ pero no está presente en los fragmentos precursores; preferiblemente, el anticuerpo se une a la terminación carboxilo de Aβ generada por la escisión de γ-secretasa. El segundo anticuerpo se une a cualquier otro epítopo presente en Aβ. Por ejemplo, se conocen los anticuerpos que se unen la región N-terminal (por ejemplo, 26D6-B2-B3^{MR} SIBIA Neurosciences, La Jolla, CA) o que se unen al extremo C-terminal (por ejemplo, el anticuerpo 9S3.2^{MR}, Biosolutions, Newark, DE) del péptido Aβ. Los anticuerpos son etiquetados con un par de aductos fluorescentes que transfieren energía fluorescente cuando los aductos son llevados en proximidad estrecha como resultado de la unión de los extremos N- y C-terminales o regiones de Aβ. Una falta de fluorescencia es indicativa de la ausencia de productos de escisión, lo que da por resultado la inhibición de γ-secretasa. El ensayo de membrana aislada se puede utilizar para identificar agentes candidatos que inhiben la actividad de la escisión de γ-secretasa y la producción de Aβ.

Un ensayo típico basado en membranas requiere 45 µg de proteína de membrana por pocillo en un formato de 96 o 384 posillos. Las membranas en un amortiguador neutro se combinan con el compuesto de prueba y se cambian de 0-4 a 37°C. Los agentes de prueba pueden consistir típicamente de compuestos sintéticos, metabolitos secundarios de extractos de fermentación bacterianos o fungales o extractos de muestras vegetales o marinas. Todos los agentes sintéticos son examinados inicialmente en dosis que varían de 10-100 µM o en el caso de extractos a una dilución suficiente para minimizar la citotoxicidad. La incubación de las membranas con el agente de prueba continuará durante aproximadamente 90 minutos, tiempo en el cual se adicionan los anticuerpos etiquetados con fluorescencia a cada pocillo para la cuantificación de Aβ. La detección y cuantificación de fluorescencia resuelta en función del tiempo de Aβ se describe en otra parte (Roberts, S. B.; Hendrick, J. P.; Vinitsky, A.; Lewis, M.; Smith, D. W.; Pak, R. publicación del PCT WO 01/0175435; Shearman, M.; Beher, D. y colaboradores, *Biochemistry*, 2000. 39, 8698-8704). Los resultados se obtienen por medio del análisis de la placa en un lector de placas de fluorescencia y la comparación de las membranas tratadas con un compuesto falso y las muestras en las cuales se adicionaron cantidades conocidas de Aβ para construir una curva de concentración estándar. Un compuesto

de acción positiva es uno que inhibe la Aβ con relación a la muestra de control por al menos 50% en la concentración sometida a prueba inicial. Si se encuentra que un compuesto es activo, entonces se realiza un experimento de respuesta a la dosis para determinar la dosis más baja del compuesto que es necesaria para producir la inhibición de la producción de Aβ. Los compuestos se registraron como inhibidores activos de γ-secretasa si los valores K_i fueron menores de 10 μM.

Los ejemplos de los resultados obtenidos cuando los compuestos de la invención se sujetaron al ensayo descrito anteriormente se muestran en la tabla 2. En la tabla, una concentración inhibidora (IC_{50}) menor que o igual que 50 nM es representada por +++; entre 50 nM y 500 nM por ++; entre 500 nM y 10000 nM por +.

TABLA 2: Ejemplos de actividad en el ensayo *in vitro* basado en la inhibición de la formación de Aβ a partir de las preparaciones de membrana

EJEMPLO	CLASIFICACIÓN DE LA ACTIVIDAD[a]
1	+++
2	+++
3	+++
4	+++
5	+++

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6	+++
7	+++
8	+++
9	+++
10	+++
11	+++
12	+++
13	+++
14	+++
15	+++
16	+++
17	+++
18	++
19	++
20	++
21	+++
22	+++
23	+++
24	+++
25	+++
26	+++
27	++
28	++
29	+++

203

30	++
31	++
32	+++
33	+++
34	+++
35	++
36	++
37	+++
38	+++
39	+++
40	+++
41	+++
42	+++
43	+++
44	+++
45	+++
46	+++
47	+++
48	+++
49	++
50	+++
51	+++
52	+++
59	++

61	+++
83	+
85	+
87	+++
89	+++
95	+++
103	+++
113	++
122	+
133	+++
153	++

[a] Actividad basada en los valores IC_{50}

+++ = <50 nM

++ = 50-500 nM

+ = >500 nM y <10,000 nM

Ensayos *in vitro* para identificar un inhibidor de γ-secretasa basado en la inhibición de la formación de Aβ en células cultivadas .

Las líneas de células humanas cultivadas, tales como las células HEK293 y H4, las cuales expresan la APP y actividad de γ-secretasa o la líneas de células derivadas, transfectadas que sobreexpresan la APP de tipo no cultivado, APP mutante o proteínas de fusión de APP secretarán los péptidos Aβ en los medios de cultivo que pueden ser

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cuantificados como se resume previamente (Dovey, H., John, V. y colaboradores, *J. Neurochem.* 2001, **76**, 173-181). La incubación de estas células cultivadas con inhibidores de γ-secretasa disminuye la producción de péptidos Aβ. Por ejemplo, las células H4 transfectadas de manera estable para sobreexpresar la proteína de fusión HPLAP-APP descrita anteriormente se desarrollaron como se describiera anteriormente, se separaron y se ajustaron a 2 x 10^5 células/ml. Entonces se adicionaron 100 µl de la suspensión resultante a cada pocillo de una placa de 96 pocillos. Después de 4 horas, los medios se removieron y se reemplazaron con 100 µl de medios libres de suero que contenían varias diluciones del compuesto de prueba. Las placas entonces se incubaron durante 18 horas a 37°C y se removió una alícuota de 100 µl del sobrenadante de cultivo de tejido para la determinación de los niveles de Aβ utilizando la fluorescencia resuelta en función del tiempo de la muestra homogénea como se resume anteriormente. Alternativamente, se podrían utilizar los otros métodos descritos anteriormente para la determinación de Aβ. El grado de inhibición de Aβ se utilizó para calcular el valor IC_{50} para el compuesto de prueba. Los compuestos de la presente invención se consideran activos cuando se sometieron a prueba en el ensayo anterior si el valor IC_{50} para el compuesto de prueba es menor que 50 µM.

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Los ejemplos de los resultados obtenidos cuando los compuestos de la invención se sujetaron al ensayo descrito anteriormente se muestran en la tabla 3. En la tabla, una concentración inhibidora (IC_{50}) menor que o igual que 50 nM es representada por +++; entre 50 nM y 500 nM por ++; entre 500 nM y 50000 nM por +.

TABLA 3: Ejemplos de actividad en el ensayo *in vitro* basado en la inhibición de la formación de Aβ en células cultivadas

EJEMPLO	CLASIFICACIÓN DE LA ACTIVIDAD[a]
1	+++
5	+++
19	++
26	+++
38	+++
41	+++
51	+++
55	+++
61	+++
72	+++
80	+++
89	+++
96	+++
101	+++

207

123	+++
127	++
143	+++
147	++
158	+++
171	++
193	+++
203	+++
205	++
207	+++
245	+++
246	+++
249	++
254	+++
256	+++
260	+++
272	+++
280	++
282	+++
288	++
301	++
302	+++
321	++
322	+++

329	+++
330	++
331	+
340	+++
341	++
342	+++
349	+++
352	++
358	++
359	+++
366	+++
367	+
378	+++
383	+++
394	+++
403	++
416	+++
418	+++
424	+++
433	+++
434	+++
439	+++
442	+++
472	+++

481	+
492	++
495	+++
497	+++

[a] Actividad basada en los valores IC_{50}

+++ = <50 nM

++ = 50-500 nM

+ = >500 nM y <10,000 nM

Se ha demostrado que los compuestos de la presente invención tienen un valor IC_{50} menor que 10 μM en uno o todos los ensayos anteriores. Por lo tanto, los compuestos de la fórmula I o composiciones farmacéuticas de los mismos son útiles en el tratamiento, alivio o eliminación de trastornos u otros trastornos asociados con la inhibición del péptido β-amiloideo.

Además de la escisión de APP, la γ-secretasa escinde otros substratos que incluyen: la familia Notch de los receptores transmembrana (revisado en: Selkoe, D. *Physiol. Rev.* 2001, **81**, 741-766; Wolfe, M. *J. Med. Chem.* 2001 **44**, 2039-2060); proteína relacionada con el receptor LDL (May, P., Reddy, Y. K., Herz, J. *J. Biol. Chem.* 2002, **277**, 18736-18743); ErbB-4 (Ni, C. Y., Murphy, M. P., Golde, T. E., Carpenter, G. *Science* 2001, **294**, 2179-2181); E-cadherin (Marambaud, P., Shioi, J. y colaboradores, *EMBO J.* 2002, **21**,

1948-1956); y CD44 (Okamoto, I., Kawano, Y. y colaboradores, *J. Cell Biol.* 2001, **155**, 755-762). Si la inhibición de la escisión de substratos diferentes de APP causa efectos indeseables en humanos, entonces los inhibidores deseados de γ-secretasa inhibirían preferiblemente la escisión de APP con relación a los substratos indeseados. La escisión de Notch se puede supervisar directamente al medir la cantidad de producto de escisión o indirectamente al medir el efecto del producto de escisión sobre la transcripción (Mizutani, T., Taniguchi, Y. y colaboradores, *Proc. Natl. Acad. Sci.* EUA 2001, **98**, 9026-9031).

Ensayos *in vivo* para la determinación de la reducción de Aβ por los inhibidores de γ-secretasa.

Los ensayos *in vivo* son disponibles para demostrar la inhibición de la actividad de γ-secretasa. En estos ensayos, los animales, tales como ratones, que expresan niveles normales de APP o γ-secretasa o están diseñados para expresar niveles más altos de APP y por lo tanto Aβ se pueden utilizar para demostrar la utilidad capacidad de los inhibidores de γ-secretasa (Dovey, H., John, V. y colaboradores, *J. Neurochem.* 2001, **76**, 173-181). En estos ensayos, los inhibidores de γ-secretasa se administraron a animales y los niveles de Aβ en múltiples compartimientos, tales como extractos de plasma, fluido cerebroespinal y

cerebro, se supervisaron por los niveles de Aβ utilizando los métodos resumidos previamente. Por ejemplo, a los ratones Tg2576, los cuales sobreexpresan la APP de humano, se les administró inhibidores de γ-secretasa por cebadura oral en dosis que causarán la disminución mesurable de Aβ, típicamente menores que 100 mg/kg. Tres horas después de la dosificación, se colectaron el plasma, el cerebro y el CSF, se congelaron en nitrógeno líquido y se almacenaron a -80°C hasta el análisis. Para detección de Aβ, el plasma se diluyó 15 veces en PBS con Chaps al 0.1% mientras que el CSF se diluyó 15 veces en Chaps al 1% con inhibidores de proteasa (5 µg/ml de leupeptina, 30 µl/ml de aprotinina, fenilmetilsulfonilfluoruro, 1 mM, pepstatina 1 µM). Los cerebros fueron homogenizados en Chaps al 1% con inhibidores de proteasa utilizando 24 ml de solución/g de tejido cerebral. Los productos homogeneizados entonces se centrifugaron a 100,000 x g durante 1 hora a 4°C. Los sobrenadantes resultantes entonces se diluyeron 10 veces en Chaps al 1% con inhibidores de proteasa. Los niveles de Aβ en el lisado de plasma, CSF y cerebro se midieron utilizando la fluorescencia resuelta en función del tiempo de la muestra homogénea o uno de los otros métodos descritos previamente.

Un inhibidor de γ-secretasa se considera activo en uno de los ensayos *in vivo* descritos anteriormente si este reduce el péptido Aβ por al menos 50% en una dosis de 100

mg/kg.

Por lo tanto, los compuestos de la fórmula I o composiciones farmacéuticas de los mismos son útiles en el tratamiento, alivio o eliminación de trastornos u otros trastornos asociados con la inhibición del péptido β-amiloideo.

En otra modalidad, esta invención incluye composiciones farmacéuticas que comprenden al menos un compuesto de la fórmula I en combinación con un adyuvante, portador o diluyente farmacéutico.

En aún otra modalidad, esta invención se refiere a un método para el tratamiento o prevención de trastornos responsables de la inhibición del péptido β-amiloideo en un mamífero en necesidad del mismo, el cual comprende administrar al mamífero una cantidad terapéuticamente efectiva de un compuesto de la fórmula I o una sal, solvato o hidrato farmacéuticamente aceptable, no tóxico del mismo.

En todavía otra modalidad, esta invención se refiere a un método para tratar la enfermedad de Alzheimer y el síndrome de Down en un mamífero en necesidad del mismo, el cual comprende administrar al mamífero una cantidad terapéuticamente efectiva de un compuesto de la fórmula I o una sal, solvato o hidrato farmacéuticamente aceptable, no tóxico del mismo.

Para el uso terapéutico, los compuestos

farmacológicamente activos de la fórmula I se administrarán normalmente como una composición farmacéutica que comprende, como el (o un) ingrediente activo, esencial al menos un compuesto de este tipo en asociación con un portador farmacéuticamente aceptable, sólido o líquido y, opcionalmente, con adyuvantes y excipientes farmacéuticamente aceptables empleando técnicas estándar y convencionales.

Las composiciones farmacéuticas incluyen formas de dosificación adecuadas para la administración oral, parenteral (inclusive subcutánea, intramuscular, intradérmica e intravenosa), bronquial o nasal. De esta manera, si se utiliza un portador sólido, la preparación puede ser para fabricar tabletas, se puede colocar en una cápsula de gelatina dura en forma de polvo o pelotillas o en la forma de un trocisco o pastilla. El portador sólido puede contener excipientes convencionales, tales como agentes aglutinantes, materiales de relleno, lubricantes para la fabricación de tabletas, desintegrantes, agentes humectantes y similares. Si se desea, la tableta puede ser revestida con película por medio de técnicas convencionales. Si se emplea un portador líquido, la preparación puede estar en la forma de un jarabe, emulsión, cápsula de gelatina suave, vehículo estéril para inyección, una suspensión líquida ya sea acuosa o no acuosa o puede ser un polvo seco para la reconstrucción con agua u otro vehículo adecuado antes del uso. Las preparaciones

líquidas pueden contener aditivos convencionales tales como agentes de suspensión, agentes emulsionantes, agentes humectantes, vehículos no acuosos (que incluyen aceites comestibles), conservadores, así como también agentes saborizantes y/o colorantes. Para la administración parenteral, un vehículo comprenderá normalmente agua estéril, al menos en gran parte, aunque se pueden utilizar soluciones salinas, soluciones de glucosa y similares. Las suspensiones inyectables también se pueden utilizar, caso en el cual se pueden emplear agentes de suspensión convencionales. Los conservadores convencionales, agentes amortiguadores y similares también se pueden adicionar a las formas de dosificación parenterales. Las composiciones farmacéuticas se preparan por medio de técnicas convencionales que son apropiadas para la preparación deseada que contiene cantidades apropiadas del ingrediente activo, esto es, el compuesto de la fórmula I de acuerdo con la invención. Véase, por ejemplo, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, 17ª edición, 1985.

La dosificación de los compuestos de la fórmula I para lograr un efecto terapéutico dependerá no únicamente de factores tales como la edad, peso y sexo del paciente y el modo de administración, sino también del grado deseado de inhibición de β-AP y la potencia del compuesto particular que se utiliza para el trastorno particular de la enfermedad

relacionada. También se contempla que el tratamiento y la dosificación del compuesto particular se pueden administrar en una forma de dosificación unitaria y que la forma de dosificación unitaria sería ajustada por consiguiente por una persona experta en el campo para reflejar el nivel relativo de actividad. La decisión en cuanto a la dosificación particular que se emplea (y el número de veces que es administrada al día) está dentro de la discreción del médico y puede ser variada por la titulación de la dosificación para las circunstancias particulares de esta invención para producir el efecto terapéutico deseado.

Una dosis adecuada de un compuesto de la fórmula I o una composición farmacéutica del mismo para un mamífero, inclusive el hombre, que sufre de, o probablemente sufre de cualquier condición relacionada con la producción de β-AP descrita en este texto, generalmente la dosis diaria será de aproximadamente 0.05 mg/kg a aproximadamente 10 mg/kg y, preferiblemente, de aproximadamente 0.1 a 2 mg/kg cuando se administra por la ruta parenteral. Para la administración oral, la dosis puede estar en el rango de aproximadamente 1 a aproximadamente 75 mg/kg y preferiblemente de 0.1 a 10 mg/kg de peso corporal. El ingrediente activo será administrado preferiblemente en dosis iguales de una a cuatro veces al día. Sin embargo, usualmente se administra una dosificación pequeña y la dosificación es incrementada gradualmente hasta

que se determina la dosificación óptima para el hospedante bajo tratamiento. De acuerdo con la buena práctica clínica, se prefiere administrar los presentes compuestos en un nivel de concentración que producirá un efecto antiamiloideo, efectivo sin causar ningún efecto colateral dañino o indeseado. Sin embargo, se entenderá que la cantidad del compuesto administrado realmente será determinada por un médico, en vista de las circunstancias relevantes que incluyen la condición a ser tratada, la selección del compuesto a administrarse, la ruta de administración seleccionada, la edad, peso y respuesta del paciente individual y la gravedad de los síntomas del paciente.

Los siguientes ejemplos se proporcionan a manera de ilustración y de ninguna manera se deben considerar como limitantes de la invención puesto que son posibles muchas variaciones de la invención dentro del espíritu de la misma.

DESCRIPCIÓN DE LAS MODALIDADES ESPECÍFICAS

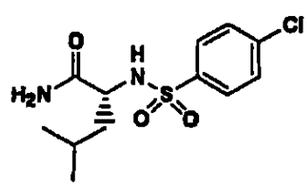
En los siguientes ejemplos, todas las temperaturas se proporcionan en grados centígrados. Los puntos de fusión se registraron en un aparato de punto de fusión capilar Thomas Scientific Unimelt y no están corregidos. Los espectros de resonancia magnética de protones (RMN ^{1}H) se registraron en un espectrómetro Bruker Avance 300, Bruker Avance 400, o Bruker Avance 500. Todos los espectros se

determinaron en los solventes indicados y los cambios químicos se reportan en unidades δ campo abajo del tetrametilsilano estándar, interno (TMS) y las constantes de acoplamiento entre protones se reportan en Hertz (Hz). Los patrones de corte se designan como sigue:: s, singulete; d, doblete; t, triplete; q, cuarteto; m, multiplete; br, pico amplio; dd, doblete de doblete; br d, doblete amplio; dt, doblete de triplete; br s, singulete amplio; dq, doblete de cuarteto. Los espectros infrarrojos (IR) utilizando una película de bromuro de potasio (KBr) o cloruro de sodio se determinaron en un espectrómetro Jasco FT/IR-410 o Perkin Elmer 2000 FT-IR de 4000 cm^{-1} a 400 cm^{-1}, calibrado a una absorción de 1601 cm^{-1} de una película de poliestireno y se reportaron en centímetros recíprocos (cm^{-1}). Las rotaciones ópticas ($[\alpha]_D$ se determinaron en un polarímetro Rudolph Scientific Autopol IV en los solventes indicados; las concentraciones se proporcionan en mg/mL. Los espectros de masas de baja resolución (EM) y el peso molecular aparente (MH^+) o $(M-H)^+$ se determinaron en un dispositivo Finnegan SSQ7000. Los espectros de masas de alta resolución se determinaron en un dispositivo Finnegan MAT900. La cromatografía líquida (CL)/espectro de masas se llevaron a cabo en un dispositivo Shimadzu LC acoplado a un dispositivo Water Micromass ZQ.

Se utilizan las siguientes abreviaciones: DMF

(dimetilformamida); THF (tetrahidrofurano); DMSO (sulfóxido de dimetilo), Leu (leucina); TFA (ácido trifluoroacético); DAST [trifluoruro de (dietilamino)azufre], CLAP (cromatografía líquida de alta presión); ta (temperatura ambiente); ac. (acuoso).

Ejemplificación del Esquema de Reacción 1

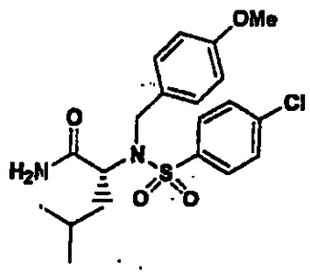


Amida del ácido (2*R*)-2-(4-clorobencensulfonilamino)-4-metilpentanoico:

A una solución de clorhidrato de (*D*)-leucinamida (0.25 g, 1.5 mmol), y Et_3N (0.43 mL, 3.0 mmol) en CH_2Cl_2 (150 mL) se adicionó cloruro de 4-clorobencensulfonilo (380 mg, 1.8 mmol). La solución resultante se agitó a temperatura ambiente durante 18 horas. La reacción entonces se diluyó con CH_2Cl_2 (200 mL) y se lavó con H_2O, HCl 0.5 N, salmuera y se secó sobre $MgSO_4$, para proporcionar el compuesto del título (410 mg) como un sólido de color blanco en un rendimiento de 90%. EM (ESI), $(M+H)^+$ 305.2; RMN ^1H (DMSO-d_6) δ 7.77 (d, 2H, J=8.7), 7.62 (d, 2H, J=8.7), 6.90 (s amplio, 1H), 3.67 (m, 1H), 1.54 (m, 1H), 1.31 (m, 2H), 0.81 (d, 3H, J=7.0), 0.71

(d, 3H, J=7.0).

Método A para la conversión de III a I

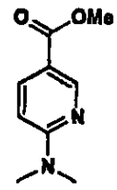


Amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(4-metoxibencil)amino]-4-metilpentanoico **(Ejemplo 1)**:

La amida del ácido (2*R*)-2-(4-clorobencensulfonilamino)-4-metilpentanoico (300 mg, 1 mmol), K_2CO_3 (170 mg, 1.2 mmol) y cloruro de 4-metoxibencilo (170 mg, 1.1 mmol) en DMF (25 mL) se calentó a 60°C durante 18 horas. La reacción entonces se diluyó con EtOAc (150 mL) y se lavó con H_2O, salmuera, se secó sobre $MgSO_4$ y se concentró para dar una cera cruda de color blanco. La purificación adicional mediante la cromatografía con evaporación instantánea (SiO_2, EtOAc al 25%/hexanos) proporcionó el compuesto del título (297 mg) como un sólido de color blanco en un rendimiento del 70%. $[\alpha]_D$ = +44.2 (c 1.00, MeOH); ES (ESI), $(M-H)^-$ 422.9; RMN ^1H ($CDCl_3$) δ 7.63 (d, 2H, J=7.0), 7.42 (d, 2H, J=7.0), 7.25 (d, 2H, J=8.0), 6.79 (d, 2H, J=8.0), 6.25 (s amplio, 1H), 5.35 (s amplio, 1H), 4.36 (dd,

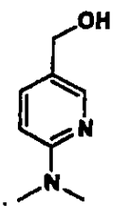
2H, J=50, 15), 4.26 (t, 1H, J=7.2), 3.78 (s, 3H), 1.83 (m, 1H), 1.18-1.34 (m, 2H), 0.75 (d, 3H, J=7.0), 0.67 (d, 3H, J=7.0); IR (KBr) 3480, 2959, 1693, 1674, 1514, 1333, 1158 cm^{-1}.

Método B para la conversión de III a I



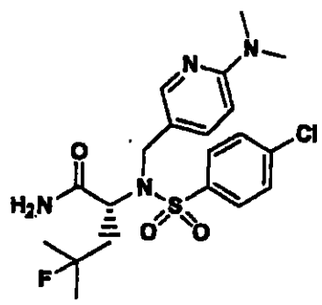
6-Dimetilaminonicotinato de metilo:

Una solución de 6-cloronicotinato de metilo (4.0 g, 23 mmol) en dimetilamina/MeOH (2 M, 80 mL, 160 mmol) en un recipiente de presión se agitó a 95°C durante 2 horas, se enfrió a temperatura ambiente y se concentró. El residuo se disolvió en EtOAc (250 mL), se lavó con agua (2 x 150 mL), se secó sobre Na_2SO_4 y se concentró para proporcionar el compuesto del título como un sólido de color de canela (4.1 g, 98%). EM (ESI), $(M+H)^+$ 181.24; RMN ^1H ($CDCl_3$) δ 8.79 (s, 1H), 7.99 (d, 1H, J=9.2), 6.45 (d, 1H, J=9.2), 3.85 (s, 3H), 3.15 (s, 6H).



2-Dimetilamino-5-hidroximetilpiridina:

Una solución de 6-dimetilamino-nicotinato de metilo (4.14 g, 23.0 mmol) en éter anhidro (80 mL) a 0°C se trató con hidruro de litio-aluminio (1 M en éter, 20 mL, 20 mmol). La mezcla se agitó a temperatura ambiente durante 0.5 horas, se enfrió nuevamente a 0°C y se enfrió lentamente con $NaHCO_3$ acuoso, saturado (10 mL). La mezcla resultante se agitó a temperatura ambiente durante 0.5 horas, se filtró y se lavó con éter. Los productos filtrados, combinados se secaron sobre Na_2SO_4 y se concentraron para dar el compuesto del título como un sólido ceroso de color beige (3.5 g, 100%). EM (ESI), $(M+H)^+$ 153.4; RMN ^1H ($CDCl_3$) δ 8.06 (d, 1H, J=2.4), 7.47 (dd, 1H, J=2.4, 8.8), 6.45 (d, 1H, J=8.8), 4.50 (s, 2H), 3.06 (s, 6H), 1.98 (s amplio, 1H).

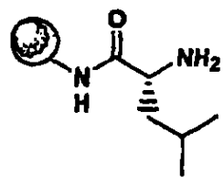


Sal de TFA de amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(2-dimetilaminopiridin-5-il)amino]-4-fluoro-4-metilpentanoico **(Ejemplo 459)**:

A una solución turbia de amida del ácido (2*R*)-2-[(4-clorobencensulfonilamino)-4-fluoro-4-metilpentanoico

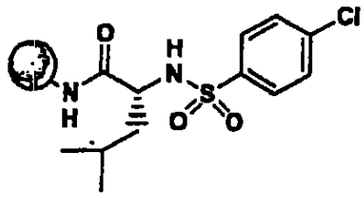
(preparada como en el esquema de reacción 20 o a partir del éster metílico de γ-fluoro-D-Leu-OH, Papageorgiou y colaboradores, Bioorg. & Med. Chem. Lett. 1994, volumen 4, páginas 267-272; 0.060 g, 0.18 mmol), 2-dimetilamino-5-hidroximetilpiridina (71 mg, 0.46 mmol), trifenilfosfina (122 mg, 0.464 mmol) en CH_2Cl_2 (9.5 mL) a temperatura ambiente se adicionó gota a gota azodicarboxilato de diisopropilo (75 µL, 0.46 mmol). La solución resultante de color amarillo pálido se agitó a temperatura ambiente durante 2 horas y se concentró bajo vacío. El residuo se disolvió en metanol y se purificó por medio de la CLAP preparativa de fase inversa (YMC S5, ODS, MeOH-agua-TFA) para proporcionar el compuesto del título como una espuma de color blanco (90 mg, 85%). EM (ESI), $(M+H)^+$ 457.2; RMN ^1H ($CDCl_3$) δ 8.11 (s, 1H), 7.95 (d, 1H, J=9.6), 7.77 (d, 2H, J=6.8), 7.51 (d, 2H, J=6.8), 6.76 (d, 2H, J=9.6), 6.34 (s, 1H), 6.02 (s, 1H), 4.58 (d amplio, 1H, J=8.4), 4.46 (d, 1H, J=16.0), 4.06 (d, 1H, J=16), 3.29 (s, 6H), 2.50 (m, 1H), 1.39 (m, 1H), 1.25 (d, 3H, J=22.0), 1.17 (d, 3H, J=22.0).

Ejemplificación del Esquema de Reacción 1 - Soporte Sólido



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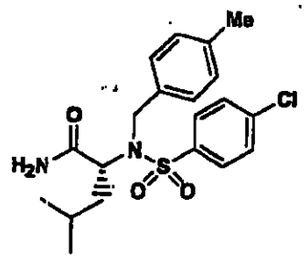
D-Leu-NH_2 unida a un polímero: La resina de amida Rink protegida con FMOC (30 g, 0.61 mmol/g, 18 mmol) se trató con una solución de piperidina/DMF (250 mL). La mezcla se agitó a temperatura ambiente durante 24 horas, se drenó, se lavó con DMF (5 x 200 mL), CH_2Cl_2 (5 x 200 mL) y se secó bajo vacío. La resina entonces se trató con FMOC-D-Leu-OH (22 g, 62 mmol), hidrato de 1-hidroxibenzotriazol (2.5 g, 18 mmol), 1,3-diisopropilcarbodiimida (9.8 mL, 62 mmol) y DMF (250 mL). La mezcla se agitó durante 20 horas, se drenó, se lavó con DMF (4 x 200 mL), DMF-agua (1:1, 3 x 200 mL), DMF (3 x 200 mL), MeOH (3 x 200 mL), CH_2Cl_2 (3 x 200 mL) y se secó. El complemento de la reacción y la carga de FMOC-D-Leu-NH_2 unida a la resina v(0.56 mmol/g) se determinaron por medio del tratamiento de 52 mg de la resina con TFA al 10%/CH_2Cl_2 (v/v) (2 mL) para dar 11 mg de FMOC-D-Leu-NH_2. La FMOC-D-Leu-NH_2 unida a la resina se desprotegió con una solución de piperidina al 20%/DMF (v/v) (250 mL) para dar la D-Leu-NH_2 unida a un polímero (20 g).



Amida del ácido (R)-2-(4-clorobencensulfonilamino)-4-metilpentanoico unida a un polímero:

La D-Leu-NH_2 unida a un polímero, anterior (20 g)

se trató con CH_2Cl_2 (150 mL), piridina (100 mL) y cloruro de 4-clorofenilsulfonilo (20.0 g, 94.8 mmol). La mezcla se agitó durante 24 horas, se drenó, se lavó con DMF (4 x 200 mL), CH_2Cl_2 (4 x 200 mL) y se concentró para dar la amida del ácido (R)-2-(4-clorobencensulfonilamino)-4-metilpentanoico unida a un polímero como una resina de color amarillo (22 g). El complemento de la reacción y la carga de la resina (0.57 mmol/g) se determinaron por medio del tratamiento de 50 mg de la resina con TFA al 10%/CH_2Cl_2 (v/v) (2 mL) para dar 8.7 mg de la amida del ácido (R)-2-(4-clorobencensulfonilamino)-4-metilpentanoico.



Amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(4-metilbencil)amino]-4-metilpentanoico **(Ejemplo 60)**:

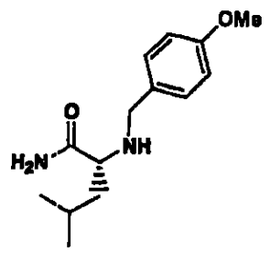
A una mezcla de la amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)amino]-4-metilpentanoico unida a un polímero (carga de 0.45 mmol/g, 50.0 mg, 0.0225 mmol), bromuro de 4-metilbencilo (44 mg, 0.24 mmol) y DMF (1.5 mL) se adicionó 2-ter-butilimino-2-dietilamino-1,3-dimetilperhidro-1,3,2-diaza-fosforina (0.10 mL, 0.34 mmol). La mezcla resultante se agitó a temperatura ambiente durante

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2 días, entonces se drenó y se lavó con DMF (4 x 2 mL), MeOH (4 x 2 mL) y CH_2Cl_2 (4 X 2 mL).

La resina entonces se trató con TFA al 10%/CH_2Cl_2 (v/v). La mezcla se agitó durante 1 hora, se filtró y se lavó con CH_2Cl_2 (2 x 0.5 mL). Los productos filtrados, combinados se concentraron bajo vacío para dar el compuesto del título como un sólido de color beige (7.7 mg, 100%, pureza de CLAP >95%). EMAR (ESI), $(M-H)^-$ para $C_{20}H_{24}SClN_2O_3$ calculado: 407.1206, encontrado: 407.1201; RMN ^1H ($CDCl_3$) δ 7.64 (d, 2H, J=8.0), 7.44 (d, 2H, J=8.0), 7.22 (d, 2H, J=8.0), 7.08 (d, 2H, J=8.0), 6.29 (s amplio, 1H), 5.34 (s amplio, 1H), 4.53 (d, 1H, J=15.2), 4.34 (d, 1H, J=15.2), 4.27 (t, 1H, J=7.2), 2.32 (s, 3H), 1.84 (m, 1H), 1.30 (m, 1H), 1.21 (m, 1H), 0.75 (d, 3H, J=6.8), 0.67 (d, 3H, J=6.8); IR (KBr) 3467, 3367, 2956, 2869, 1694, 1670, 1340, 1160 cm^{-1}.

Ejemplificación del Esquema de Reacción 2

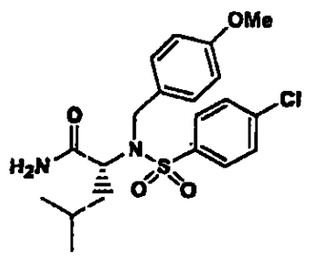


Amida del ácido (2*R*)-2-(4-metoxibencilamino)-4-metilpentanoico:

Una solución de clorhidrato de D-leucinamida (2.8

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g, 16.8 mmol), y p-anisaldehído (2.29 g, 16.8 mmol) en metanol (150 mL) se trató con $ZnCl_2$ anhidro (538 mg, 5 mmol). La suspensión resultante entonces se trató con $NaCNBH_3$ (1.05 g, 16.8 mmol) porción a porción y se calentó a reflujo durante 3 horas. La reacción se enfrió a temperatura ambiente, se enfrió rápidamente con $NaHCO_3$ saturado (3 mL), se diluyó con EtOAc (500 mL) y se lavó con salmuera. la concentración dio la amina de bencilo cruda como una cera de color blanco, la cual se llevó sin purificación adicional (3.57 g, 84%). EM (ESI), $(M+H)^+$251.4; RMN ^1H ($CDCl_3$) δ 7.20 (d, 2H, J=6.6), 7.10 (s amplio, 2H), 6.88 (d, 2H, J=8.4), 5.30 (s amplio, 1H), 3.80 (s, 3H), 3.63 (dd, 2H, J=4.5, 12), 1.44-1.65 (m, 3H), 0.95 (d, 3H, J=6.3), 0.80 (d, 3H, J=6.3).

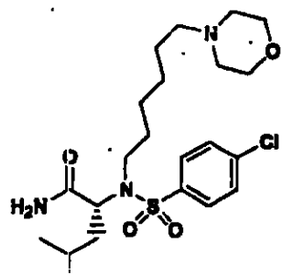


Amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(4-metoxibencil)amino]-4-metilpentanoico **(Ejemplo 1)**:

La amida del ácido (2*R*)-2-[N-(4-metoxibencilamino]-4-metilpentanoico (3.57 g, 14.3 mmol) se disolvió en CH_2Cl_2 (100 mL) y se trató con Et_3N (4.2 mL, 29 mmol) y cloruro de 4-clorobencensulfonilo (3.6 g, 17 mmol) a temperatura

ambiente durante 18 horas. Los solventes se removieron y el residuo se tomó en EtOAc (500 mL). La solución orgánica se lavó con H_2O, salmuera, se secó sobre $MgSO_4$ y se concentró. El material resultante entonces se purificó adicionalmente por medio de la cromatografía con evaporación instantánea (SiO_2, MeOH al 1%/CH_2Cl_2) para proporcionar el compuesto del título (2.4 g) como un sólido ligeramente coloreado en un rendimiento de 40%. EM (ESI), $(M-H)^-$422.9; RMN ^1H ($CDCl_3$) δ 7.63 (d, 2H, J=7.0), 7.42 (d, 2H, J=7.0), 7.25 (d, 2H, J=8.0), 6.79 (d, 2H, J=8.0), 6.25 (s amplio, 1H), 5.35 (s amplio, 1H), 4.36 (dd, 2H, J=5.0, 15), 4.26 (t, 1H, J=7.2), 3.78 (s, 3H), 1.83 (m, 1H), 1.18-1.34 (m, 2H), 0.75 (d, 3H, J=7.0), 0.67 (d, 3H, J=7.0); IR (KBr) 3480, 2959, 1693, 1674, 1514, 1333, 1158 cm^{-1}.

Ejemplificación del Esquema de Reacción 3

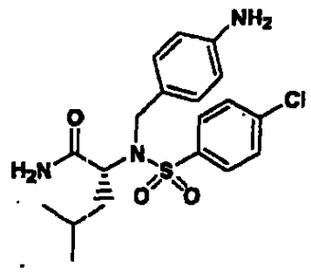


Amida del ácido (2*R*)-2-[N-(4-morfolinohexil)-N-(4-clorobencensulfonil)amino]-4-metilpentanoico **(Ejemplo 25)**:

Una solución de la amida del ácido (2*R*)-2-[N-(4-

bromohexil)-N-(4-clorobencensulfonil)amino]-4-metilpentanoico (ejemplo 24; preparada como se describe en el esquema de reacción 1; 0.20 g, 0.44 mmol), Et_3N (0.25 mL, 1.7 mmol), y morfolina (150 mg, 1.7 mmol) en CH_2Cl_2 (2 mL) se agitó a temperatura ambiente durante 18 horas. La reacción entonces se concentró para dar una cera cruda de color blanco, la cual se purificó mediante la cromatografía con evaporación instantánea (SiO_2, EtOAc al 85%/hexanos al 5%/MeOH al 10%) para proporcionar el compuesto del título (112 mg) como un sólido de color blanco en un rendimiento del 54%. EM (ESI), $(M+H)^+$474.4; RMN ^1H (DEMO-d_6) δ 7.82 (d, 2H, J=8.0), 7.64 (d, 2H, J=8.0), 7.42 (s amplio, 1H) 6.99 (s, 1H), 4.25 (m, 1H), 3.51-3.60 (s amplio, 4H), 3.18-3.41 (m, 2H), 2.25-2.35 (s amplio, 4H), 2.27 (m, 2H) 1.15-1.62 (m, 9H), 0.80 (d, 6H, J=6.0).

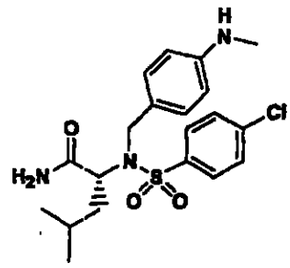
Ejemplificación del Esquema de Reacción 4



Amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(4-aminobencil)amino]-4-metilpentanoico **(Ejemplo 48)**:

La amida del ácido (2*R*)-(2-[N-(4-

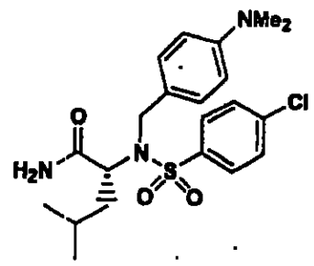
clorobencensulfonil)-N-(4-nitrobencil)amino]-4-metilpentanoico (compuesto del ejemplo 24; preparada como se describe en el esquema de reacción 1; 2.8 g, 6.6 mmol) se suspendió con Pd al 10%/C (1 g) y HCl concentrado (1 mL) en MeOH (100 mL) y se colocó bajo una atmósfera de hidrógeno a 2.809 kg/cm^2 (40 psi) durante 1 hora. La suspensión se filtró a través de Celite^{MR} y luego se concentró para dar el compuesto del título como un sólido de color canela (2.4 g, rendimiento del 88%). EM (ESI), $(M+H)^+$ 410.1; RMN ^{1}H ($CDCl_3$) δ 7.80 (d, 2H, J=8.5), 7.63 (d, 2H, J=8.5), 7.52 (s amplio, 1H), 7.46 (d, 1H, J=8.0), 7.26 (d, 1H, J=8.0), 7.02 (s amplio, 1H), 4.70 (dd, 2H, J=50, 18), 4.30-4.41 (m, 1H), 3.67 (s amplio, 2H), 1.28-1.33 (m, 3H), 0.86 (d, 3H, J=7.0), 0.57 (d, 3H, J=7.0).



Amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(4-metilaminobencil)amino]-4-metilpentanoico **(Ejemplo 51)**:

Una solución de la amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(4-aminobencil)amino]-4-metil-pentanoico (ejemplo 48, 400 mg, 1 mmol), Et_3N (0.16 mL, 1.1 mmol), sulfato de dimetilo (139 mg, 1.1 mmol) en 25 mL de

tolueno se agitó a temperatura ambiente durante 18 horas. La reacción se concentró, luego se tomó en EtOAc y se lavó con H_2O, salmuera, se secó sobre K_2CO_3 y se concentró para dar una mezcla cruda del material de inicio y el producto. El material se purificó adicionalmente por medio de la cromatografía con evaporación instantánea (SiO_2, EtOAc al 35%/hexanos) para proporcionar el compuesto del título, 195 mg, en un rendimiento del 46%. EM (ESI), $(M+H)^+$424.1; RMN ^1H ($CDCl_3$): δ 7.65 (d, 2H, J=8.0), 7.58 (dd, 2H, J=8.2), 7.47 (d, 2H, J=8.0), 7.31 (d, 2H, J=8.5), 6.24 (s amplio, 1H), 5.16 (s amplio, 1H), 4.50 (dd, 2H, J=50, 17), 4.27 (t, 1H, J=10), 2.44 (s, 3H), 1.74-1.83 (m, 1H), 1.25-1.33 (m, 1H), 0.93-1.01 (m, 1H), 0.74 (d, 3H, J=7.0), 0.63 (d, 3H, J=7.0).

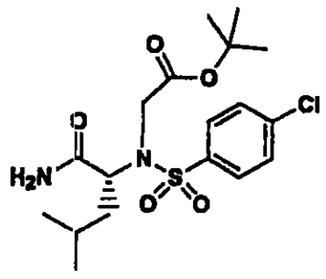


Amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(4-dimetilaminobencil)amino]-4-metilpentanoico **(Ejemplo 65)**:

La amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(4-aminobencil)amino]-4-metilpentanoico (ejemplo 48, 0.10 g, 0.22 mmol) se disolvió

en DMF (5 mL). A esta solución se adicionó yodometano (62 mg, 0.44 mmol) y carbonato de cesio (220 mg, 0.66 mmol). La reacción entonces se agitó a 40°C durante 18 horas. La reacción se vertió sobre EtOAc y agua. Los extractos orgánicos se colectaron, se secaron sobre $MgSO_4$ y se concentraron a un residuo oleoso. El residuo se purificó adicionalmente (Biotage 40 M, cargado en CH_2Cl_2, eluido en EtOAc al 25%/hexanos) para producir un polvo de color amarillo (15 mg, 16%). EM (ESI), $(M+H)^+$ 438.1; RMN ^1H (DMSO-d_6, 500 MHz) δ 7.74 (dd, 2H, J=1.9, 6.7), 7.54 (dd, 2H, J=1.9, 6.8), 7.43 (s, 1H), 7.16 (d, 2H, J=8.6), 7.01 (s, 1H), 6.61 (d, 2H, J=8.8), 4.59 (q, 2H, J=16, 25), 4.34 (dd, 1H, J=5.0, 9.3), 2.85 (s, 6H), 1.27-1.47 (m, 3H), 0.80 (d, 3H, J=5.9), 0.52 (d, 3H, J=6.1).

Ejemplificación del Esquema de Reacción 5

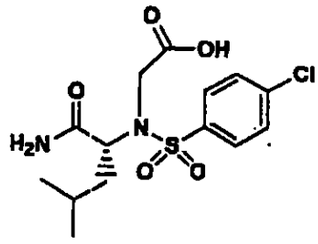


Éster ter-butílico del ácido {N-[(1*R*)-1-carbamoil-3-metil-butil]-N-(4-clorobencensulfonil)amino}acético **(Ejemplo 46)**:

La amida del ácido (2*R*)-2-(4-

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clorobencensulfonilamino)-4-metilpentanoico (3.00 g, 9.87 mmol) se disolvió en DMF (50 mL). A la solución se adicionó carbonato de potasio (6.0 g, 39 mmol) y éster ter-butílico de ácido bromoacético (6.0 mL, 39 mmol). La solución se calentó a 70°C durante 3 horas. La reacción se enfrió rápidamente con EtOAc y $NaHCO_3$ saturado. La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró. El aceite crudo se purificó adicionalmente en un sistema Biotage 40M (cargado en CH_2Cl_2, eluido en EtOAc al 30%/hexanos) para proporcionar un polvo de color blanco (1.2 g, 35%). EM (ESI), $(M+H)^+$ 446.3; RMN ^1H ($CDCl_3$) δ 7.76 (d, 2H, J=8.0), 7.52 (d, 2H, J=8.0), 6.61 (s amplio, 1H) 5.45 (s, 1H), 4.15-4.18 (m, 1H), 3.09-3.24 (m, 2H), 2.50-2.58 (m, 4H), 2.31-2.39 (m, 2H), 1.92-1.99 (m, 1H), 1.15-1.59 (m, 8H), 1.00-1.04 (m, 7H), 0.71-0.74 (m, 6H).

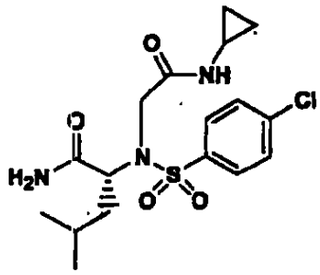


Ácido {N-[(1*R*)-1-carbamoil-3-metil-butil]-N-(4-clorobencensulfonil)amino}acético **(Ejemplo 59):**

El ácido trifluoroacético (15 mL) se adicionó a una solución de éster ter-butílico del ácido {N-[(1*R*)-1-carbamoil-3-metil-butil]-N-(4-clorobencensulfonil)amino}-

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acético (0.50 g, 1.2 mmol) en CH_2Cl_2 (15 mL). La reacción se agitó a temperatura ambiente durante 4 horas. La reacción luego se concentró a un sólido de color blanco (0.40 g, 92%), el cual se utilizó sin purificación adicional. EM (ESI), $(M+H)^+$ 363.1; RMN ^1H (DMSO-d_6, 500MHZ) δ 7.90 (dd, 2H, J=2.0, 6.8), 7.65 (dd, 2H, J=2.0, 6.8), 7.60 (s, 1H), 7.06 (s, 1H), 4.32 (d, 1H, J=18), 4.12 (t, 1H, J=8.0), 4.02 (d, 1H, J=18), 1.55-1.65 (m, 1H), 1.35-1.45 (m, 2H), 0.78 (d, 3H, J=6.1), 0.73 (d, 3H, J=6.1).

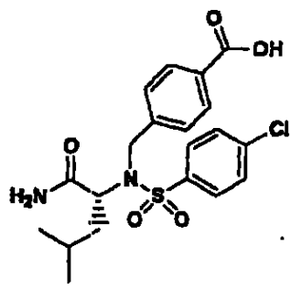


Amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(ciclopropilcarbamoilmetil)amino]-4-metil-pentanoico **(Ejemplo 88):**

A una solución del ácido {N-[(1*R*)-1-carbamoil-3-metil-butil]-N-(4-clorobencensulfonil)amino}acético (ejemplo 59, 175 mg, 0.480 mmol), ciclopropilamina (41 µL, 0.58 mmol) en CH_2Cl_2 (3 mL) se adicionó 1-hidroxibenzotriazol (47 mg, 0.72 mmol) y 1,3-diciclohexilcarbodiimida (144 mg, 0.720 mmol). La reacción se agitó durante 18 horas a temperatura ambiente y luego se vertió en una mezcla de EtOAc/agua. La capa orgánica se separó, se seco sobre $MgSO_4$ y se concentró a

un residuo de aceite claro. El residuo se purificó adicionalmente por medio de un sistema Biotage 40S (eluido en EtOAc al 40% en hexanos) para proporcionar un sólido de color blanco (54 mg, 29%). EM (ESI), $(M+H)^+$ 402.2; RMN ^1H ($CDCl_3$, 500MHz) δ 7.85 (dd, 2H, J=1.9, 8.9), 7.50 (dd, 2H, J=2.0, 8.7), 7.40 (s amplio, 1H), 6.55 (s amplio, 1H), 6.30 (s amplio, 1H), 4.23 (dd, 1H, J=2.9, 8.9), 3.92 (d, 1H, J=17), 3.83 (d, 1H, J=17), 2.68-2.73 (m, 1H), 1.75-1.83 (m, 1H), 1.50-1.57 (m, 1H), 1.40-1.49 (m, 1H), 0.88 (d, 3H, J=6.4), 0.87 (d, 3H, J=6.7), 0.80 (d, 2H, J=7.0), 0.51 (t, 2H, J=4.0).

Ejemplificación del Esquema de Reacción 6

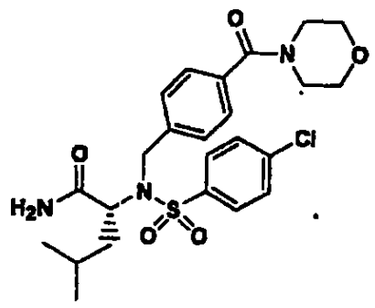


Ácido 4-{[N-((1*R*)-1-carbamoil-3-metil-butil)-N-(4-cloro-bencensulfonil)amino]-metil}-benzoico **(Ejemplo 89)**:

Una solución del compuesto del ejemplo 61 [éster metílico del ácido 4-{[N-((1*R*)-1-carbamoil-3-metil-butil)-N-(4-clorobencensulfonil)amino]-metil}-benzoico, 354 mg, 0.782 mmol] se disolvió en metanol (4 mL). Una solución de NaOH 5N

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(1 mL) se adicionó, seguido por suficiente THF (1 mL) para lograr la homogeneidad. Después de 1 hora, se agregó una alícuota adicional de NaOH 5 N (1 mL) y la agitación continuó durante 2.5 horas. La sclución se acidificó a pH 2 con HCl 1 N y se extrajo con $CHCl_3$ (2x). Las capas orgánicas, combinas se secaron (Na_2SO_3) y se concentraron para dar un sólido de color blanco (343 mg, 100%). EM (ESI), $(M+H)^+$ 439.17; RMN ^1H ($CDCl_3$, 300MHz) δ 7.91 (d, 2H, J=8.2), 7.81-7.84 (m, 3H), 7.56 (d, 2H, J=8.6), 7.49 (d, 2H, J=8.2), 6.55 (s amplio, 1H), 5.10 (d, 1H, J=15.4), 4.23 (dd, 1H, J=4.6, 9.7), 4.05 (d, 1H, J=15.4), 2.04-2.14 (m, 1H), 1.20-1.31 (m, 1H), 0.80-0.89 (m, 1H), 0.74 (d, 3H, J=6.6), 0.68 (d, 3H, J=6.6).



Amida del ácido (2*R*)-2-{N-(4-clorobencensulfonil)-N-[4-(morfolin-4-carbonil)-bencil]amino}-4-metil-pentanoico

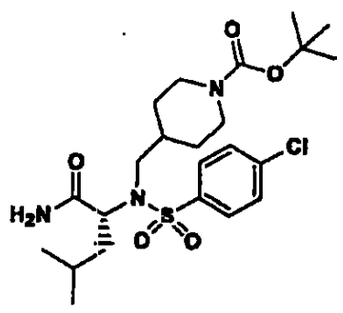
(Ejemplo 101):

A un solución a 0°C de ácido 4-{[N-((1*R*)-1-carbamoil-3-metil-butil)-N-(4-clorobencensulfonil)amino]-metil}benzoico (50.0 mg, 0.114 mmol) en DMF (0.3 mL) se adicionó morfolina (12.9 mg, 0.148 mmol), seguido por 1-

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hidroxibenzotriazol (18.5 mg, 0.137 mmol), clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (26.2 mg, 0.137 mmol) e iPr_2NEt (26 µL, 0.15 mmol). Después de 2 horas, la solución se calentó a temperatura ambiente. Después de 4 horas, la solución se vertió en ácido cítrico acuoso al 10% y se extrajo con EtOAc (2x). Las capas orgánicas, combinadas se lavaron secuencialmente con agua y $NaHCO_3$ acuoso, saturado, luego se secaron ($MgSO_4$) y se concentraron. La cromatografía en columna con evaporación instantánea (SiO_2, EtOAc al 40-100%/hexanos) dio el compuesto del título como un sólido de color blanco (46.0 mg, 79%). EM (ESI), $(M+H)^+$ 508.22; RMN ^1H ($CDCl_3$, 300MHz) δ 7.68 (d, 2H, J = 8.6), 7.29-7.47 (m, 6H), 6.38 (s amplio, 1H), 5.75 (s amplio, 1H), 4.65 (d, 1H, J = 16.0), 4.42 (d, 1H, J = 16.0), 4.32 (t, 1H, J = 7.5), 3.30-3.85 (m amplio, 8H), 1.69-1.78 (m, 1H), 1.28-1.37 (m, 1H), 1.08-1.14 (m, 1H), 0.76 (d, 3H, J = 6.5), 0.63 (d, 3H, J = 6.6).

Ejemplificación del Esquema de Reacción 7

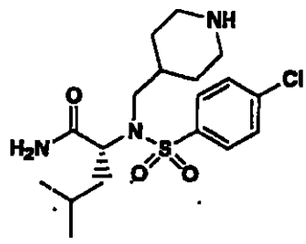


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Éster ter-butílico del ácido 4-{[N-((1R)-1-carbamoil-3-metil-butil)-N-(4-clorobencensulfonil)amino]-metil}-piperidin-1-carboxílico **(Ejemplo 92)**:

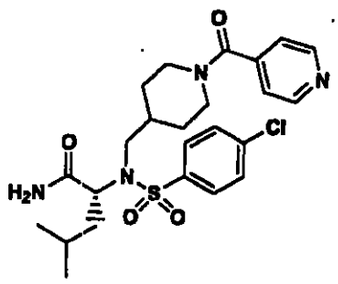
A una solución de amida del ácido (2*R*)-2-(4-clorobencensulfonilamino)-4-metilpentanoico (4.2 gramos, 14 mmol) en DMF (50 mL) se adicionó carbonato de cesio (13.6 gramos, 417 mmol). A esta reacción se adicionó éster *ter*-butílico del ácido 4-(toluen-4-sulfoniloximetil)-piperidin-1-carboxílico (referencia: Gilissen, C.; Bormans, G.; De Groot, T.; Verbruggen, A. *J. Labeled Cmpd. Radiopharm.* **1999**, *42*, 1289; 10.4 g, 282 mmol). La reacción se agitó a 70°C durante 18 horas. La reacción luego se enfrió rápidamente con $NaHCO_3$ acuoso, saturado y se extrajo con EtOAc. La capa orgánica se colectó, se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró a un aceite claro. El aceite luego se purificó en un sistema Biotage 40S (eluido con EtOAc al 30% en hexanos) para proporcionar un sólido de color blanco (3.0 g, 44%). EM (ESI), $(M+H)^+$ 502.1; RMN ^1H (DMSO-d_6, 500MHz) δ 7.86 (dd, 2H, J = 2.0, 6.8), 7.65 (dd, 2H, J = 2.0, 6.8) 7.37 (s amplio, 1H), 7.07 (s amplio, 1H), 4.19 (t, 1H, J = 7.6), 3.92 (s amplio, 2H), 3.35 (dd, 1H, J = 15, 6.8), 3.05 (dd, 1H, J = 15, 8.1), 1.85 (s amplio, 1H), 1.50-1.70 (m, 4H), 1.38 (s, 9H), 1.10-1.20 (m, 1H), 0.80-1.00 (m, 3H), 0.82 (d, 6H, J = 7.6).

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Amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(piperidin-4-ilmetil)amino]-4-metil-pentanoico **(Ejemplo 126)**:

A una solución del éster ter-butílico del ácido 4-{[N-((1R)-1-carbamoil-3-metil-butil)-N-(4-clorobencensulfonil)amino]-metil}-piperidin-1-carboxílico (ejemplo 92, 2.6 gramos, 5.2 mmol) en CH_2Cl_2 (25 mL) se adicionó ácido trifluoroacético (10 mL). La reacción se agitó a temperatura ambiente durante 1 hora y luego se concentró para dar un sólido de color blanco (1.6 gramos, 84%). EM (ESI), $(M+H)^+$ 402.15; RMN ^1H (DMSO-d_6, 500MHz), δ 7.87 (d, 2H, J = 8.5), 7.66 (d, 2H, J = 8.6), 7.41 (s, 1H), 7.04 (s, 1H), 4.17 (t, 1H, J = 7.3), 3.40-3.50 (m, 1H), 3.20-3.25 (m, 1H), 3.03-3.10 (m, 1H), 2.65-2.80 (m, 2H), 1.85-2.00 (m, 1H), 1.20-1.85 (m, 2H), 1.45-1.60 (m, 1H), 1.30-1.40 (m, 1H), 1.10-1.30 (m, 4H), 0.75-0.90 (m, 1H), 0.82 (d, 3H, J = 7.3), 0.80 (d, 3H, J = 7.0).

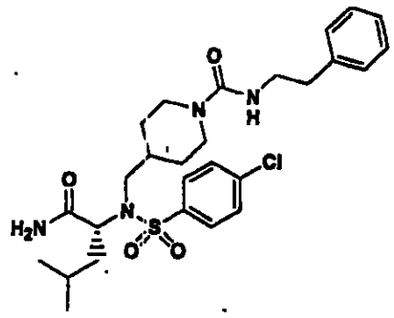




Amida del ácido (2*R*)-2-{N-(4-clorobencensulfonil)-N-[1-(piridin-4-carbonil)-piperidin-4-ilmetil]-amino}-4-metil-pentanoico **(Ejemplo 278)**:

A una solución de amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(piperidin-4-ilmetil)amino]-4-metil-pentanoico (ejemplo 126, 0.10 g, 0.22 mmol) y Et_3N (0.06 mL, 0.5 mmol) en CH_2Cl_2 (3.0 mL) se adicionó clorhidrato de cloruro de isonicotinoilo (56 mg, 0.32 mmol). La reacción se agitó a temperatura ambiente durante 18 horas y luego se vertió en una mezcla de EtOAc y $NaHCO_3$ acuoso, saturado. La solución orgánica se separó y se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró a un residuo oleoso. El residuo se purificó en un sistema Biotage 10M (eluido con EtOAc al 80%/hexanos) para dar un sólido de color blanco (36 mg, 30%). EM (ESI), $(M+H)^+$ 509.20; RMN ^1H ($CDCl_3$, 500MHz) δ 8.66 (s amplio, 2H), 7.80 (d, 1H, J = 8.6), 7.73 (d, 2H, J = 8.5), 7.51 (d, 2H, J = 7.6), 7.41 (s amplio, 1H), 6.64 (s amplio, 1H), 5.35 (s amplio, 1H), 4.70 (s amplio, 1H), 4.10 (s amplio, 1H), 3.71 (s amplio, 1H), 3.33 (s amplio, 1H), 3.02 (dd, 2H, J = 4.8, 16), 2.70-2.85 (s amplio, 1H), 1.50-2.09 (m, 5H), 1.18-1.33 (m, 4H), 0.73 (d, 3H, J = 6.7), 0.68 (d, 3H, J = 6.5).

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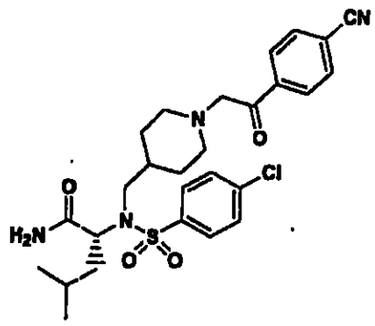


Fenetilamida del ácido 4-{[N-((1R)-1-carbamoil-3-metil-butil)-N-(4-clorobencensulfonil)amino]-metil}-piperidin-1-carboxílico **(Ejemplo 256)**:

A una solución de la amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(piperidin-4-ilmetil)amino]-4-metil-pentanoico (ejemplo 126, 0.10 g, 0.22 mmol) y Et_3N (32 µL, 0.25 mmol) en CH_2Cl_2 (3.0 mL) se adicionó (2-isocianato-etil)-benceno (0.040 mL, 0.30 mmol). La reacción se agitó a temperatura ambiente durante 18 horas y luego se vertió en $NaHCO_3$ acuoso, saturado y se extrajo con EtOAc. La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró a un residuo oleoso. El residuo se purificó adicionalmente en un sistema Biotage (eluido con EtOAc al 75%/hexanos) para proporcionar el producto deseado como un sólido de color blanco (67 mg, 52%). EM (ESI), $(M+H)^+$ 549.00; RMN ^1H ($CDCl_3$, 500MHz) δ 7.71 (d, 2H, J = 8.6), 7.71 (d, 2H, J = 8.9), 7.15-7.35 (m, 5H), 6.64 (s, 1H), 5.86 (s, 1H), 4.15 (dd, 1H, J = 5.2, 9.5), 3.88 (d, 1H, J = 13), 3.76 (d, 1H, J = 13), 3.46 (t, 2H, J = 6.7), 3.21-3.29 (m, 1H), 2.97 (dd, 1H, J = 4.6, 14), 2.65-2.85 (m, 4H), 1.75-1.95 (m, 3H), 1.00-

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1.30 (m, 5H), 0.75-0.80 (m, 1H), 0.72 (d, 3H, J = 6.7), 0.67 (d, 3H, J = 6.7).



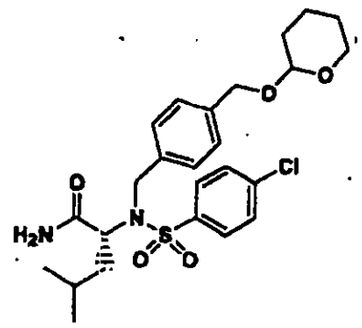
Amida del ácido (2*R*)-2-(N-(4-clorobencensulfonil)-N-{1-[2-(4-cianofenil)-2-oxo-etil]-piperidin-4-ilmetil}-amino)-4-metil-pentanoico **(Ejemplo 286)**:

A una solución de la amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(piperidin-4-ilmetil)amino]-4-metil-pentanoico (ejemplo 126, 0.050 g, 0.12 mmol) y Et_3N (0.040 mL, 0.30 mmol) en CH_2Cl_2 (2.0 mL) se adicionó 4-(2-cloro-acetil)-benzonitrilo (55 mg, 0.30 mmol). La reacción se agitó a temperatura ambiente durante 18 horas y luego se concentró a un residuo. El residuo se purificó en un sistema Biotage (eluido con EtOAc al 80%/hexanos) para producir 29 mg (48%) del producto deseado como un sólido de color blanco. EM (ESI), $(M+H)^+$ 545.16; RMN ^1H ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, J = 8.5), 7.50-7.65 (m, 2H), 7.50 (d, 2H, J = 7.0), 7.35-7.45 (m, 2H), 6.67 (s, 1H), 5.32 (s, 1H), 4.14 (dd, 1H, J = 5.0, 9.0), 3.52 (s amplio, 1H), 3.28 (t, 1H, J =14), 2.97 (dd, 1H,

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J = 3.5, 14), 2.82 (s amplio, 1H), 1.00-2.00 (m, 10H), 0.71 (d, 3H, J = 6.5), 0.66 (d, 3H, J = 6.5).

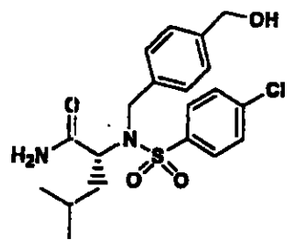
Ejemplificación del Esquema de Reacción 8



Amida del ácido (2*R*)-2-{N-(4-clorobencensulfonil)-N-[4-(tetrahidro-piran-2-iloximetil)-bencil]-amino}-4-metil-pentanoico:

La amida del ácido (2*R*)-2-(4-clorobencensulfonilamino)-4-metilpentanoico (6.35 g, 196 mmol), Cs_2CO_3 (5.62 g, 196 mmol) y 2-[(4-bromometil)bencil]oxi)tetrahidropirano (5.62 g, 196 mmol) en acetonitrilo (200 mL) se calentó a reflujo durante 1 hora. La reacción se filtró en caliente con succión a través Celite. El producto filtrado se redujo *in vacuo* a una espuma de color blanco (9.5 g, 96%). La espuma se utilizó como estaba en la siguiente reacción. EM (ESI), $(M+H)^+$ 510.9, RMN ^1H ($CDCl_3$) δ 7.83 (d, 2H, J = 8.0), 7.75 (d, 2H, J = 8.0), 7.39 (d, 2H, J = 8.0), 7.24 (d, 2H, J = 8.0), 6.25 (s amplio, 1H), 5.35 (s amplio, 1H), 4.82 (d, 1H, J_{ab} = 12), 4.65 (m, 1H), 4.52 (d,

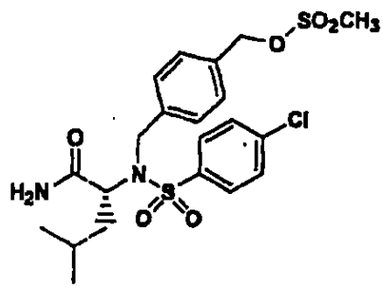
1H, $J_{ab=}$ 12), 4.30 (d, 1H, J_{ab} = 16), 4.20 (d, 1H, J_{ab} = 16), 3.74 (m, 2H), 3.46 (m, 1H), 1.89 (m, 1H), 1.66 (m, 6H), 0.97 (d, 3H, J = 7.0), 0.94 (d, 3H, J = 7.0).



Amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(4-hidroximetil)bencilamino]-4-metil-pentanoico **(Ejemplo 95)**:

Una solución de amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-[4-(tetrahidropiran-2-iloximetil)bencilamino]-4-metil-pentanoico (9.5 g, 186 mmol) en metanol (200 mL) se adicionó una cantidad catalítica de ácido P-toluensulfónico. La mezcla se agitó durante toda la noche a temperatura ambiente. El solvente se removió *in vacuo*. La espuma resultante se disolvió en CH_2Cl_2 (100 mL), se lavó con NaOH 1 N, H_2O, salmuera y se secó sobre $MgSO_4$. El solvente del filtrado se removió *in vacuo*. La espuma resultante se cristalizó a partir de hexano caliente para proporcionar el producto como un sólido de color blanco (7.7 g) en un rendimiento del 92%. EM (ESI), $(M+H)^+$ 425.17, RMN ^1H ($CDCl_3$) δ 7.68 (d, 2H, J = 7.0), 7.46 (d, 2H, J = 7.0), 7.33 (d, 2H, J = 8.0), 7.28 (d, 2H, J = 8.0), 6.26 (s amplio, 1H), 5.35 (s amplio, 1H), 4.67 (s amplio, 2H), 4.59 (d, 1H, J_{ab} =

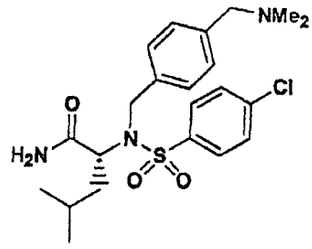
16), 4.37 (d, 1H, J_{ab} = 16), 4.26 (t, 1H, 7.0), 1.86-1.80 (m, 2H), 1.34-1.28 (m, 1H), 1.16-1.10 (m, 1H), 0.96 (d, 3H, J = 7.0), 0.93 (d, 3H, J = 7.0).



Éster 4-{[N-((1*R*)-1-carbamoil-3-metil-butil)-N-(4-clorobencen-sulfonil)-amino]metil}bencílico del ácido metanosulfónico:

A una solución agitada de la amida del ácido (2*R*)-2-[N-(4-cloro-bencensulfonil)-N-(4-hidroximetil-bencil)amino]-4-metil-pentanoico (1.5 g, 3.5 mmol) en CH_2Cl_2 (15 mL) enfriada a 0°C se adicionó Et_3N (0.74 mL, 5.3 mmol). Una solución de clorurc de metanosulfonilo (0.29 mL, 3.5 mmol) en 5 mL de CH_2Cl_2 se adicionó gota a gota y la reacción se dejó agitar a 0°C durante 1 hora. La mezcla de reacción se diluyó con 25 mL de CH_2Cl_2, se lavó rápidamente con HCl 1 N, salmuera y se secó al pasar la fase orgánica a través un tapón de algodón. El solvente se removió *in vacuo* para proporcionar el compuesto del título en un rendimiento cuantitativo. La espuma resultante se utilizó como estaba en las reacciones subsecuentes. EM (ESI), $(M-95)^+$, 409.15, RMN ^1H ($CDCl_3$) δ 7.70 (d, 2H, J = 8.0), 7.48 (d, 2H, J = 8.0),

7.41 (d, 2H, J = 8.0), 7.38 (d, 2H, J = 8.0), 6.27 (s amplio, 1H), 5.32 (s amplio, 1H), 5.24 (s, 2H), 4.64 (d, 1H, J_{ab} = 16), 4.43 (d, 1H, J_{ab} = 16), 4.33 (t, 1H, J = 6), 2.90 (s, 3H), 1.90 (m, 1H), 1.60 (m, 2H), 0.96 (d, 3H, J = 7.0), 0.91 (d, 3H, J = 7.0)

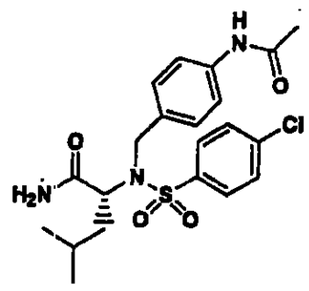


Amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(4-dimetilaminometil-bencil)amino]-4-metil-pentanoico **(Ejemplo 110):**

A una solución agitada de éster 4-{[N-((1*R*)-1-carbamoil-3-metil-butil)-N-(4-clorobencensulfonil)amino]-metil}-bencílico del ácido metanosulfónico (150 mg, 0.298 mmol) en (3 mL) CH_2Cl_2 a 0°C se adicionó 1 equivalente de Et_3N, seguido por dimetilamina (0.3 mL, 2 M en THF). La reacción se agitó durante toda la noche a temperatura ambiente. La mezcla se diluyó con CH_2Cl_2, se lavó con H_2O, salmuera, se secó sobre $MgSO_4$ y se concentró para dar un vidrio de color ámbar. La purificación por medio de la cromatografía con evaporación instantánea (SiO_2, MeOH al 10%/CH_2Cl_2) proporcionó el compuesto del título (95 mg) en un rendimiento del 71%. EM (ESI), $(M+H)^+$ 452.23, RMN ^1H ($CDCl_3$) δ

7.94 (d, 2H, J = 8.0), 7.74 (d, 2H, J = 8.0), 7.63 (d, 2H, J = 8.0) 7.38 (d, 2H, J = 8.0), 6.23 (s amplio, 1H), 5.35 (s amplio, 1H), 4.22 (d, 1H, J_{ab} = 16), 4.14 (d, 1H, J_{ab} = 16), 3.28-3.23 (m, 3H), 2.17 (s amplio, 6H), 1.95 (m, 1H), 1.55 (m, 2H), 0.96 (d, 3H, J = 7.0), 0.93 (d, 3H, J = 7.0).

Ejemplificación del Esquema de Reacción 9

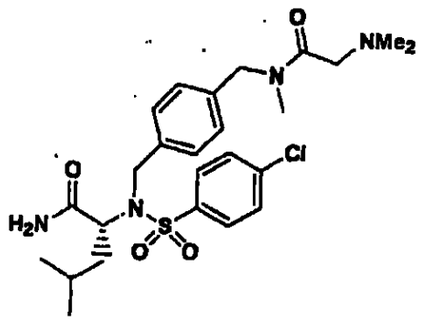


Amida del ácido (2*R*)-2-[N-(4-acetilaminobencil)-N-(4-clorobencensulfonil)amino]-4-metil-pentanoico **(Ejemplo 163)**:

Una solución del compuesto del ejemplo 48 [amida del ácido [(2*R*)-2-[N-(4-clorobencensulfonil)-N-(4-aminobencil)amino]-4-metil-pentanoico (250 mg, 0.60 mmol) y Et_3N (120 mg, 1.2 mmol) en CH_2Cl_2 (20 mL) se trató con cloruro de acetilo (56 mg, 0.72 mmol). Después de agitar durante 18 horas, la reacción se concentró, se sometió a la cromatografía utilizando la cromatografía en gel de sílice con evaporación instantánea (metanol al 1%/CH_2Cl_2) para proporcionar el compuesto del título (110 mg, 41%). EM (ESI), $(M-H)^-$ 422.9; RMN ^1H ($CDCl_3$) δ 7.67 (d, 2H, J = 8.0), 7.28-

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7.46 (m, 6H), 7.12 (s amplio, 1H), 6.24 (s amplio, 1H), 5.19 (s amplio, 1H), 4.48 (dd, 2H, J = 50, 15), 4.27 (t, 1H, J = 7.0), 2.18 (s, 3H), 1.80-2.01 (m, 1H), 1.12-1.32 (m, 2H), 0.75 (d, 3H, J = 7.0), 0.67 (d, 3H, J = 7.0).



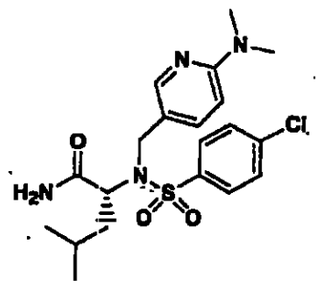
Amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(4-{[(2-dimetilamino-acetil)-metil-amino]-metil}-bencil)-amino]-4-metil-pentanoico **(Ejemplo 272)**:

La amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(4-metilaminometil-bencil)-amino]-4-metil-pentanoico (75 mg, 0.17 mmol), ácido (α-dimetilamino)acético (18 mg, 0.17 mmol), 1-hidroxibenzotriazol (24 mg, 0.17 mmol) y clorhidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (33 mg, 0.17 mmol) se combinaron en 3 mL de CH_2Cl_2 y se agitaron durante toda la noche. La mezcla de reacción se diluyó con 5 mL de CH_2Cl_2 y se lavó con NaOH 1 N y salmuera. La fase orgánica se secó mediante la filtración a través de algodón y el solvente se removió *in vacuo*. La purificación por medio de la CLAR preparativa proporcionó el compuesto del título (61 mg) en un

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rendimiento del 68%. EM (ESI), 523.4 $(M+H)^+$ RMN ^1H ($CDCl_3$) δ 8.02 (d, 2H, J = 8.0), 7.71 (d, 2H, J = 8.0), 7.37 (d, 2H, J = 8.0), 7.28 (d, 2H, J = 8.0), 6.23 (s amplio, 1H), 5.51 (s amplio, 1H), 4.46 (s, 2H), 4.70 (d, 1H, J_{ab} = 16), 4.33 (d, 1H, J_{ab} = 16), 3.25 (t, 1H, J = 6.0), 2.69 (s, 3H), 2.63 (s, 2H), 2.20 (s, 6H), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J = 7.0), 0.94 (d, 3H, J = 7.0).

Ejemplificación del Esquema de Reacción 10

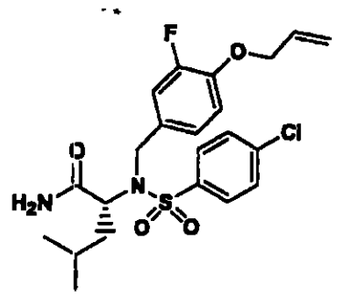


Sal de TFA de amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(2-dimetilaminopiridin-5-ilmetil)amino]-4-metilpentanoico **(Ejemplo 254)**:

Una solución de amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(2-cloropiridin-5-ilmetil)amino]-4-metilpentanoico (preparada por medio del esquema de reacción 1, 18 mg, 41 mmol) en dimetilamina/THF (2 M, 20 mL, 40 mmol) se agitó a 95°C durante 30 horas en un recipiente de presión. Se purificaron cinco mL de la mezcla de reacción (25% del volumen de reacción total) por medio de la CLAP preparativa

de fase inversa (YMC S5, ODS, MeOH-agua-TFA) para proporcionar el compuestc del título como una espuma de color blanco (17 mg, rendimiento del 30%). EMAR (ESI), $(M-H)^-$ para $C_{20}H_{26}SClN_4O_3$ calculado: 437.1426, encontrado: 437.1420; RMN ^1H ($CDCl_3$): δ 8.04 (s, 1H), 8.03 (d, 1H, J = 9.8), 7.76 (d, 2H, J = 7.6), 7.54 (d, 2H, J = 7.6), 6.83 (d, 1H, J = 9.8), 6.62 (s amplio, 1H), 6.40 (s amplio, 1H), 4.64 (d, 1H, J = 15.9), 4.29 (m, 1H), 4.18 (d, 1H, J = 15.9), 3.30 (s, 6H), 1.84 (m, 1H), 1.29 (m, 1H), 0.93 (m, 1H), 0.77 (d, 3H, J = 6.5), 0.72 (d, 3H, J = 6.5).

Ejemplificación del Esquema de Reacción 11

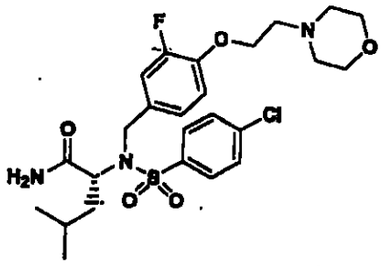


Amida del ácido (2*R*)-2-[N-(4-aliloxi-3-fluorobencil)-N-(4-clorobencensulfonil)amino]-4-metil-pentanoico:

Una solución de la amida del ácido (2*R*)-2-(4-clorobencensulfonilamino)-4-metil-pentanoico (1.00 g, 3.29 mmol) y Cs_2CO_3 (1.29 g, 3.95 mmol) en DMF (25 mL) se adicionó 1-aliloxi-4-bromometil-2-fluorobenceno (referencia: Graham, Samuel L; y colaboradores, Eur. Pat. Appl. (1992): EP 487270;

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0.88 g, 3.67 mmol). La solución resultante se agitó a temperatura ambiente durante 18 horas. La reacción luego se diluyó con EtOAc:hexanos 9:1 (350 mL) y se lavó con H_2O (4 x 200 mL), salmuera y se secó sobre Na_2SO_4 para proporcionar el compuesto del título (393 mg) como un sólido de color blanco en un rendimiento del 26%. EM (ESI), $(M+H)^+$ 469.1; RMN ^1H ($CDCl_3$) δ 7.66 (d, 2H, J = 8.1), 7.45 (d, 2H, J = 8.1), 7.11 (d, 1H, J = 12.0), 6.98 (m, 1H), 6.84 (t, 1H, J = 8.0), 6.22 (s amplio, 1H), 6.04 (m, 2H), 5.42 (m, 1H), 5.16 (s amplio, 1H), 4.59 (m, 2H), 4.40 (m, 3H), 1.83 (m, 1H), 1.32 (m, 1H), 1.14 (m, 1H), 0.76 (d, 3H, J = 7.0), 0.68 (d, 3H, J = 7.0).



Amida del ácido (2*R*)-2-{N-(4-clorobencensulfonil)-N-[3-fluoro-4-(2-morfolin-4-il-etoxi)-bencil]-amino}-4-metil-pentanoico **(Ejemplo 427)**:

Una mezcla del compuesto intermedio de aliloxi anterior (0.39 g, 0.84 mmol), tetraóxido de osmio (0.01 g, 0.04 mmol), y N-óxido de trimetilamina (0.140 g, 1.81 mmol) se disolvió en acetona (10 mL) y se agitó durante 4 horas a temperatura ambiente. La solución se concentró *in vacuo* y se

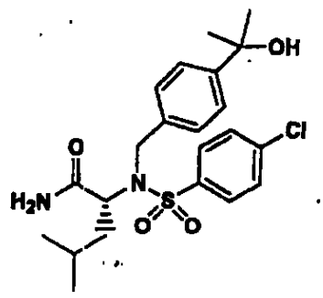
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redisolvió en dioxano:H_2O 1.5:1 (15 mL). Se adicionó peryodato de sodio (0.22 g, 1.0 mmol) y la solución se agitó a temperatura ambiente durante 18 horas. La reacción luego se diluyó con EtOAc (200 mL) y se lavó con H_2O, salmuera, se secó sobre Na_2SO_4 y se concentró para dar la amida del ácido (2R)-{N-(4-cloro-bencensulfonil)-N-[3-fluoro-4-(2-oxo-etoxi)-bencil]-amino}-4-metil-pentanoico como un sólido crudo de color beige. Este material crudo se tomó en el siguiente paso sin purificación adicional. La amida del ácido (2*R*)-2-{N-(4-clorobencensulfonil)-N-[3-fluoro-4-(2-oxo-etoxi)-bencil]-amino}-4-metil-pentanoico (0.16 g, 0.34 mmol) y morfolina (0.090 g, 1.0 mmol) se disolvieron en EtOH (5 mL) y se calentaron a 80°C durante aproximadamente 15 minutos. El baño de aceite se removió y se adicionó triacetoxiborohidruro de sodio (0.290 g, 1.36 mmol) y la suspensión espesa se agitó a temperatura ambiente durante 16 horas. La solución se concentró a sequedad, se tomó en salmuera, se extrajo con EtOAc (2 x 100 mL), se secó sobre Na_2SO_4 y se concentró *in vacuo* para dar un residuo crudo de color anaranjado. La purificación adicional por medio de la CLAP preparativa (columna YMC S5 ODS C-18 20 x 100 mm, 25 mL/minuto, MeOH al 0-100%/H_2O TFA al 0.1%, 15 minutos) proporcionó como una sal de TFA el compuesto del título (69.5 mg) como un sólido de color amarillo pálido en un rendimiento del 31%. $[\alpha]_D$+23 (c 6.4, CH_2Cl_2); CL-EM $(M+H)^+$ 542.25; RMN ^1H ($CDCl_3$) δ 7.71 (d,

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2H, J = 8.0), 7.50 (d, 2H, J = 8.0), 7.16 (d, 1H, J = 12.0), 7.05 (d, 1H, J = 8.0), 6.37 (t, 1H, J = 8.0), 6.38 (s amplio, 1H), 5.91 (s amplio, 1H), 4.41 (ABq, 2H, J = 16, J_{ab} = 176), 4.45 (m, 2H), 4.27 (t, 1H, J = 8.0), 4.03 (m, 4H), 3.70 (m, 2H), 3.51 (m, 2H), 3.10 (m, 2H), 1.83 (m, 1H), 1.29 (m, 1H), 1.05 (m, 1H), 0.75 (d, 3H, J = 8.0), 0.68 (d, 3H, J = 8.0).

Ejemplificación del Esquema de Reacción 12



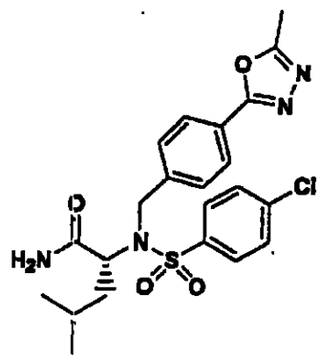
Amida del ácido (2*R*)-2-{N-(4-clorobencensulfonil)-*N*-[4-(1-hidroxi-1-metil-etil)-bencil]-amino}-4-metil-pentanoico

(Ejemplo 287):

Una solución del compuesto del ejemplo 61 [éster metílico del ácido [4-{[*N*-((1*R*)-1-carbamoil-3-metil-butil)-*N*-(4-clorobencensulfonil)amino]-metil}-benzoico, 101 mg, 0.221 mmol] se enfrió a 0°C en THF (2 mL). Una solución de bromuro de metil-magnesio (1.4 M en tolueno/THF, 0.50 mL, 0.71 mmol) se adicionó gota a gota. La solución de color amarillo oscuro se agitó a 0°C y después de 30 minutos, se agregó una solución adicional de bromuro de metil-magnesio (0.25 mL,

0.353 mmol). Después de 1 hora, la solución se dejó calentar a temperatura ambiente. Después de 3.5 horas, la reacción se enfrió rápidamente por la adición de NH_4Cl acuoso, saturado y la mezcla se extrajo con EtOAc (2x). Las capas orgánicas, combinadas se secaron (Na_2SO_4) y se concentraron. La cromatografía en columna con evaporación instantánea (SiO_2, EtOAc al 20-100%/hexanos) proporcionó el compuesto del título como una espuma de color blanco (62 mg, 62%). EM (ESI), $(M+H)^+$ 453.16; RMN ^1H ($CDCl_3$, 300MHz) δ 7.61 (d, 2H, J = 8.7), 7.40 (d, 2H, J = 8.7), 7.37 (d, 2H, J = 8.4), 7.26 (d, 2H, J = 8.4), 6.28 (s amplio, 1H), 5.25 (s amplio, 1H), 4.49 (d, 1H, J = 15.9), 4.41 (d, 1H, J = 15.9), 4.33 (t, 1H, J = 6.6), 1.73-1.80 (m, 1H), 1.55 (s, 6H), 1.28-1.35 (m, 1H), 1.20-1.25 (m, 1H), 0.77 (d, 3H, J = 6.5), 0.66 (d, 3H, J = 6.6).

Ejemplificación del Esquema de Reacción 13



Amida del ácido (2*R*)-2-{N-(4-clorobencensulfonil)-[4-(5-metil-[1,3,4]oxadiazol-2-il)-bencil]-amino}-4-metil-

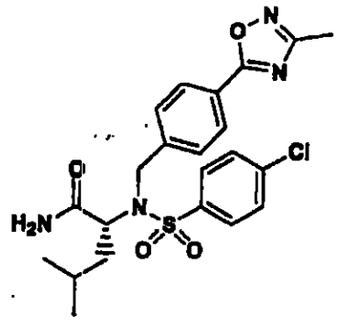
pentanoico **(Ejemplo 436)**:

Paso 1: Una solución del compuesto del ejemplo 61 [éster metílico del ácido [4-{[N-((1*R*)-1-carbamoil-3-metil-butil)-N-(4-clorobencensulfonil)amino]-metil}-benzoico, 0.500 g, 1.10 mmol] se diluyó con metanol (10 mL) y se adicionó hidrazina (2 mL). El material de inicio se disolvió lentamente durante 5 minutos. Después de 30 minutos, la solución se calentó a reflujo. Después de 22 horas, la solución se enfrió a temperatura ambiente. Se adicionó agua (15 mL) y se formó un producto precipitado de color blanco. La mezcla se extrajo con EtOAc (2x). Las capas orgánicas, combinadas se lavaron con salmuera, se secaron (Na_2SO_4) y se concentraron para dar la hidrazina de acilo correspondiente como una espuma de color blanco, la cual se llevó directamente al paso de ciclización sin purificación.

Paso 2: La hidrazina de acilo cruda (0.150 g, 0.331 mmol) se disolvió en piridina (2.2 mL) y se adicionó clorhidrato de acetimidato de etilo (60.0 mg, 0.364 mmol). La mezcla se calentó a reflujo durante 1.25 horas. La solución se enfrió a temperatura ambiente y se concentró para remover la piridina. El residuo se tomó en EtOAc y se lavó secuencialmente con agua, HCl 1 N (2x), $NaHCO_3$ acuoso, saturado y salmuera. La solución se secó ($MgSO_4$) y se concentró. La cromatografía en columna con evaporación instantánea (SiO_2, EtOAc al 50-100%/hexanos) proporcionó el

compuesto listado como un sólido de color blanco (138 mg, 88% para los 2 pasos). $[\alpha]_D$+11.1 (c 7.0 mg/ml, $CHCl_3$); EM (ESI), $(M+H)^+$ 477.22, RMN ^1H ($CDCl_3$, 300MHz) δ 7.94 (dd, 2H, J = 1.8, 8.4), 7.69 (dd, 2H, J = 1.8, 8.7), 7.45-7.50 (m, 4H), 6.23 (s amplio, 1H), 5.19 (s amplio, 1H), 4.65 (d, 1H, J = 15.9), 4.46 (d, 1H, J = 15.9), 4.31 (dd, 1H, J = 6.6, 7.8), 2.61 (s, 3H), 1.75-1.85 (m, 1H), 1.28-1.35 (m, 1H), 1.08-1.15 (m, 1H), 0.76 (d, 3H, J = 6.6), 0.64 (d, 3H, J = 6.6).

Ejemplificación del Esquema de Reacción 14



Amida del ácido (2*R*)-2-{N-(4-clorobencensulfonil)-N-[4-(3-metil-[1,2,4]oxadiazol-5-il)-bencil]-amino}-4-metil-pentanoico (**Ejemplo 437**):

Paso 1: A una solución a temperatura ambiente del compuesto del ejemplo 89 [ácido [4-{[N-((1*R*)-1-carbamoil-3-metil-butil)-N-(4-clorobencen-sulfonil)-amino]-metil}-benzoico, 520 mg, 1.2 mmol] en DMF (2.4 mL) y CH_2Cl_2 (7.1 mL) se adicionó 1-hidroxibenzotriazol (192 mg, 1.42 mmol), clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida

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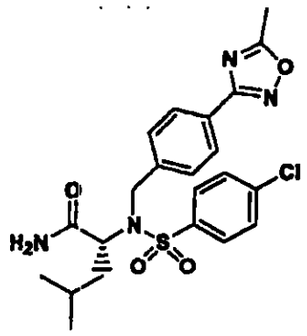
(272 mg, 1.42 mmol), y iPr_2NEt (0.31 mL, 1.8 mmol). También se adicionó N-hidroxiacetamida (105 mg, 1.42 mmol). Después de 21 horas, el material de inicio fue evidente, de manera que se agregaron periódicamente porciones adicionales de todos los reactivos para adelantar la reacción. Después de 3 días, la mezcla se concentró y se dividió entre $NaHCO_3$ acuoso, saturado y EtOAc (2x). Las capas orgánicas; combinadas se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron a un aceite de color amarillo, el cual se llevó al siguiente paso sin purificación adicional.

Paso 2: La acetamidoxima cruda se disolvió en tolueno (10 mL) y la solución se calentó a reflujo. Después de 1 hora, se adicionó piridina (2 mL) y el calentamiento continuó durante otras 15 horas. La mezcla se concentró y se diluyó con EtOAc. La fase orgánica se lavó secuencialmente con agua, HCl 1 N (2x), $NaHCO_3$ acuoso, saturado y salmuera, luego se secó ($MgSO_4$) y se concentró. La cromatografía en columna con evaporación instantánea (SiO_2, EtOAc al 10-40%/hexanos) dio el compuesto del título como un sólido de color amarillo pálido (238 mg, 42% para los dos pasos). $[\alpha]^{23}_D$+9.30 (c 5.93, $CHCl_3$); EM (ESI), $(M+H)^+$ 477.18; RMN ^1H ($CDCl_3$, 300MHz) δ 8.04 (d, 2H, J = 8.4), 7.70 (dd, 2H, J = 1.8, 8.4), 7.45-7.52 (m, 4H), 6.23 (s amplio, 1H), 5.19 (s amplio, 1H), 4.67 (d, 1H, J = 16.2), 4.47 (d, 1H, J = 15.9), 4.31 (t, 1H, J = 7.2), 2.47 (s, 3H), 1.75-1.85 (m, 1H), 1.28-

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1.35 (m, 1H), 1.08-1.15 (m, 1H), 0.76 (d, 3H, J = 6.6), 0.64 (d, 3H, J = 6.6).

Ejemplificación del Esquema de Reacción 15



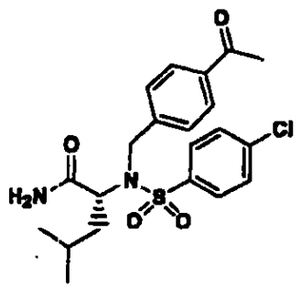
Amida del ácido (2*R*)-2-{N-(4-clorobencensulfonil)-N-[4-(5-metil-[1,2,4]oxadiazol-3-il)-bencil]-amino}-4-metil-pentanoico **(Ejemplo 465):**

Una solución del compuesto del ejemplo 6 [amida del ácido (2*R*)-2-[N-(4-clorobencensulfonil)-N-(4-cianobencil)amino]-4-metil-pentanoico (0.20 g, 0.47 mmol) en etanol (6 mL) se trató con hidroxilamina (solución al 50% en agua, 0.050 mL, 0.71 mmol). La reacción se calentó a 80°C durante 18 horas. La reacción se concentró a un residuo y se recristalizó a partir de EtOAc/hexanos para producir un sólido de color blanco (136 mg, 51%). Este sólido (0.18 mmol) entonces se disolvió en cloroformo y se trató con Et_3N (0.030 mL, 0.24 mmol) y cloruro de acetilo (0.020 mL, 0.18 mmol). La reacción se agitó temperatura ambiente durante 2 horas y

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luego se vertió en EtOAc y salmuera. La capa orgánica se separó, se secó sobre $MgSO_4$ y se concentró a un residuo. El residuo se tomó en tolueno y se calentó a reflujo durante 24 horas. La reacción se concentró a un residuo y se purificó en un sistema Biotage (eluido en EtOAc/hexanos 1:1) para proporcionar el producto deseado como un sólido de color blanco (35 mg, rendimiento del 39%). EM (ESI), $(M+H)^+$ 477.13; RMN ^1H ($CDCl_3$, 500MHz) δ 7.98 (d, 2H, J = 8.2), 7.68 (d, 2H, J = 8.9), 7.45 (d, 4H, J = 8.5), 6.21 (s, 1H), 5.19 (s, 1H), 4.62 (d, 1H, J = 15), 4.48 (d, 1H, J = 16), 4.31 (t, 1H, J = 7.0), 2.65 (s, 3H), 1.75-1.85 (m, 1H), 1.20-1.35 (m, 4H), 1.10-1.17 (m, 1H), 0.85-0.90 (m, 1H), 0.75 (d, 3H, J = 6.7), 0.64 (d, 3H, J = 6.4).

Ejemplificación del Esquema de Reacción 16



Amida del ácido (2*R*)-2-[N-(4-acetilbencil)-N-(4-clorobencensulfonil)amino]-4-metil-pentanoico **(Ejemplo 273)**:

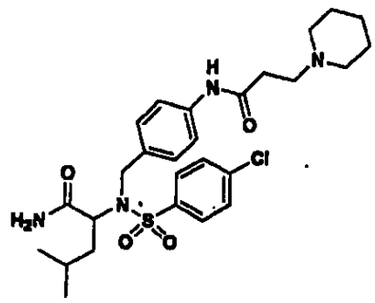
Una solución del compuesto del ejemplo 251 [4-{[N-((1*S*)-1-carbamoil-3-metil-butil)-N-(4-clorobencensulfonil)-

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amino]-metil]-N-metoxi-N-metil-benzamida, 0.100 g, 0.207 mmol] se enfrió a 0°C en THF (2.1 mL). Una solución de bromuro de metil-magnesio (1.4 M en tolueno/THF, 0.178 mL, 0.249 mmol) se adicionó gota a gota. La solución resultante se agitó a 0°C durante 3 horas, tiempo en el cual se agregó una solución adicional de bromuro de metil-magnesio (0.178 mL, 0.249 mmol). Después de otros 30 minutos, se adicionó una porción final de una solución de MeMgBr (0.3 mL). Después de 15 minutos finales, la reacción se enfrió rápidamente por la adición de NH_4Cl acuoso, saturado y HCl 1 N y la mezcla se extrajo con EtOAc (2x). Las capas orgánicas, combinadas se lavaron con $NaHCO_3$ acuoso, saturado y salmuera, se secaron (Na_2SO_4) y se concentraron. La cromatografía en columna con evaporación instantánea (SiO_2 EtOAc al 20-60%/hexanos) dio el compuesto deseado como una espuma de color blanquecino (79 mg, 87%). $[\alpha]^{23}_D$+20.4 (c 7.57, $CHCl_3$); EM (ESI), $(M+H)^+$ 437.13; RMN ^1H ($CDCl_3$, 300MHz) δ 7.87 (d, 2H, J = 8.4), 7.67 (dd, 2H, J = 1.8, 8.7), 7.42-7.46 (m, 4H), 6.21 (s amplio, 1H), 5.28 (s amplio, 1H), 4.64 (d, 1H, J = 15.9), 4.45 (d, 1H, J = 15.9), 4.31 (t, 1H, J = 6.6), 2.58 (s, 3H), 1.73-1.80 (m, 1H), 1.25-1.35 (m, 1H), 1.05-1.14 (m, 1H), 0.74 (d, 3H, J = 6.5), 0.65 (d, 3H, J = 6.6).

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Ejemplificación del Esquema de Reacción 17

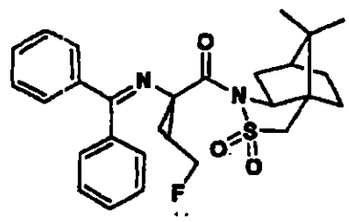


Amida del ácido (2*R*)-2-{N-(4-clorobencensulfonil)-N-[4-(3-piperidin-1-il-propionilamino)-bencil]-amino}-4-metil-pentanoico **(Ejemplo 274)**:

A una solución de N-(4-{[N-((1*S*)-1-carbamoil-3-metil-butil)-N-(4-clorobencensulfonil)amino]-metil}-fenil)-acrilamida (0.10 g, 0.22 mmol) en tolueno (5 mL) se adicionó piperidina (20 mg, 0.24 mmol). La mezcla se calentó a reflujo suave durante 1 hora y luego se removió el solvente *in vacuo*. La purificación mediante la cromatografía con evaporación instantánea (SiO_2, MeOH al 10%/CH_2Cl_2) proporcionó el compuesto de título (105 mg) en un rendimiento del 86%. EM (ESI), $(M+H)^+$ 449.16, RMN ^1H ($CDCl_3$, 400 MHz) δ 7.69 (d, 2H, J = 8.0), 7.63 (d, 2H, J = 8.0), 7.38 (d, 2H, J = 8.0), 7.23 (d, 2H, J = 8.0), 6.25 (s amplio, 1H), 5.35 (s amplio, 1H), 4.75 (d, 1H, J_{ab} = 16), 4.38 (d, 1H, J_{ab} = 16), 3.25 (t, 1H, J = 6.0), 2.65 (t, 2H, J = 6.0), 2.56-2.44 (m, 6H), 1.95 (m, 1H), 1.68-1.45 (m, 8H), 0.98 (d, 3H, J = 7.0), 0.94 (d, 3H, J = 7.0).

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Ejemplificación del Esquema de Reacción 18

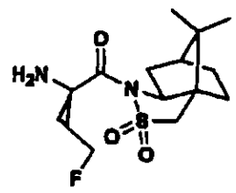


(2*R*)-2-(benzhidriliden-amino)-1-{(1'*S*),(5'*S*)-10'10'-dimetil-3',3'-dioxo-3'λ^6-tia-4'-aza-triciclo-[5.2.1.$0^{1,5}$]dec-4'-il}-4-fluorobutan-1-ona:

A una solución de a -78°C de N-2-(benzhidriliden-amino)-1-{(1'*S*),(5'*S*)-10'10'-dimetil-3',3'-dioxo-3'λ^6-tia-4'-aza-triciclo-[5.2.1.$0^{1,5}$]dec-4'-il}-4-etanona (referencia: Josien, H.; Martin, A.; Chassaing, G. Tetrahedron Lett. **1991**, 32, 6547; 30.0 g, 68 mmol) en HMPA (60 mL) y THF (300 mL) se adicionó n-BuLi (1.6 M en hexano, 42.4 mL, 68 mmol) gota a gota, manteniendo la temperatura abajo de -65°C. La reacción se dejó llegar a la temperatura ambiente, momento en el cual se adicionó gota a gota a temperatura ambiente una solución de 1-bromo-3-fluoroetano (17.4 g, 137 mmol) en THF (30 mL). Después de 18 horas, la reacción se vertió sobre H_2O/HOAc (200 mL/2 mL), se diluyó con EtOAc y las capas orgánicas se lavaron con NH_4Cl saturado, salmuera, se secaron sobre $MgSO_4$ y se concentraron. El aceite de color anaranjado, resultante entonces se purificó adicionalmente por medio de la cromatografía en gel de sílice (EtOAc al 25%/hexanos) para

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dar un sólido de color blanco, el cual se recristalizó a partir de EtOAc al 15%/hexanos para dar el material deseado (24.3 g, 70%). EM (ESI) ($M+H^+$) 483.27; RMN ^1H ($CDCl_3$) δ 7.66 (d, 2H, J = 7.2), 7.13-7.44 (m, 8H), 4.82-4.83 (m, 2H), 4.39-4.81 (m, 2H), 3.84-3.87 (m, 1H), 3.28 (ABq, 2H, J = 18, 10) 2.33-2.41 (m, 2H), 2.02-2.04 (m, 2H), 1.84-1.87 (m, 2H), 1.32-1.39 (m, 2H), 1.10 (s, 3H), 0.91 (s, 3H).

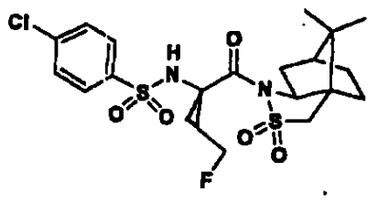


(2*R*)-2-amino-1-{(1'*S*),(5'*S*)-10'10'-dimetil-3',3'-dioxo-3'λ^6-tia-4'-aza-triciclo-[5.2.1.$0^{1,5}$]dec-4'-il}-4-fluorobutan-1-ona:

Una solución de (2*R*)-2-(benzhidriliden-amino)-1-{(1'*S*),(5'*S*)-10'10'-dimetil-3',3'-dioxo-3'λ^6-tia-4'-aza-triciclo-[5.2.1.$0^{1,5}$]dec-4'-il}-4-fluorobutan-1-ona (20.0 g, 41.0 mmol) en THF (400 mL) se trató con HCl 1 N (200 mL). Después de 3 horas, la reacción se diluyó con H_2O y se extrajo con Et_2O. La fase acuosa entonces se neutralizó por medio de la adición de NaOH 0.5 N. La fase básica entonces se extrajo con CH_2Cl_2, se secó sobre $MgSO_4$ y se concentró para dar un sólido de color blanco (11.9 g, 90%). RMN ^1H ($CDCl_3$) δ 4.56-4.71 (m, 2H), 4.23-4.31 (m, 1H), 3.40-3.49 (m, 3H), 3.11 (d, 2H, J = 4.4), 1.17-2.23 (m, 8H), 1.13 (s, 3H), 0.93-1.12

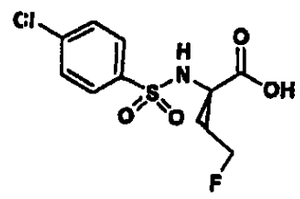
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(m, 3H).



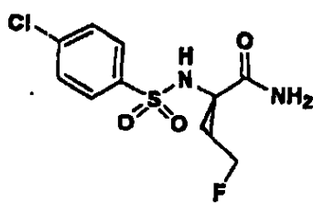
(2*R*)-2-(4-clorobencensulfonilamino)-1-{(1'*S*),(5'*S*)-10'10'-dimetil-3',3'-dioxo-3'λ^6-tia-4'-aza-triciclo-[5.2.1.$0^{1,5}$]dec-4'-il}-4-fluorobutan-1-ona:

A una solución de (2*R*)-2-amino-1-{(1'*S*),(5'*S*)-10'10'-dimetil-3',3'-dioxo-3'λ^6-tia-4'-aza-triciclo-[5.2.1.$0^{1,5}$]dec-4'-il}-4-fluorobutan-1-ona (12 g, 36 mmol) y Et_3N (10.4 mL, 72.0 mmol) en CH_2Cl_2 (350 mL) se adicionó cloruro de 4-clorobencensulfonilo (9.1 g, 43 mmol) en una porción. Después de 18 horas, la reacción se concentró y el residuo resultante se tomó en EtOAc y se lavó con H_2O, salmuera, se secó sobre $MgSO_4$ y se concentró. El material entonces se purificó adicionalmente por medio de la cromatografía en gel de sílice (EtOAc al 30%/hexanos) para proporcionar el compuesto del título (16.0 g, 92%) como una cera de color blanco. RMN ^1H ($CDCl_3$) δ 7.79 (d, 2H, J = 8.0), 7.43 (d, 2H, J = 8.0), 5.69 (d amplio, 8.0), 4.42-4.77 (m, 4H), 3.71-3.72 (m, 1H), 3.10 (ABq, 2H, J = 9, 4.4) 2.11-2.29 (m, 2H), 1.33-1.99 (m, 6H), 1.04 (s, 3H), 0.91 (s, 3H).



Ácido (2*R*)-2-(4-clorobencensulfonilamino)-4-fluorobutanoico:

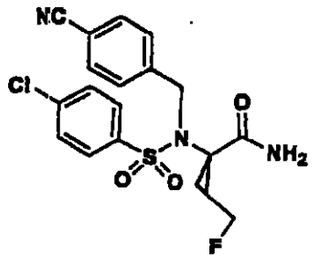
A una solución agitada rápidamente de (2*R*)-2-(4-clorobencensulfononilamino)-1-{(1'*S*),(5'*S*)-10'10'-dimetil-3',3'-dioxo-3'λ^6-tia-4'-aza-triciclo-[5.2.1.$0^{1,5}$]dec-4'-il}-4-fluorobutan-1-ona: (16 g, 32 mmol) en acetonitrilo (200 mL) se adiciono LiBr (13.9 g, 16 mmol), bromuro de tetrabutilamonio (4.13 g, 12.8 mmol), y LiOH (5.45 g, 0.130 mol). Después de 4.5 horas, la reacción se concentró a la mitad del volumen, luego se diluyó con H_2O y se extrajo con CH_2Cl_2. La capa acuosa se acidificó con HCl 1 N y se extrajo con EtOAc. Los extractos de EtOAc se combinaron, se secaron sobre $MgSO_4$ y se concentraron para dar un sólido de color blanco del cual se tomaron 9.4 g directamente hacia el siguiente paso. RMN ^{1}H (DMSO-d_6) δ 8.39 (d, 1H, J = 9.0), 7.76 (d, 2H, J = 6.8), 7.64 (d, 2H, J = 6.8), 7.00 (s amplio, 1H), 4.29-4.48 (m, 2H), 3.80-3.88 (m, 1H), 1.66-1.96 (m, 2H).



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Amida del ácido (2*R*)-2-(4-clorobencensulfonilamino)-4-fluorobutanoico:

A una solución del ácido (2*R*)-2-(4-clorobencensulfonilamino)-4-fluorobutanoico (9.0 g, 31 mmol) en DMF (250 mL) se adicionó consecutivamente hidrato de 1-hidroxibenzotriazol (6.2 g, 46 mmol), N,N-diisopropiletilamina (23 mL, 124 mmol), cloruro de amonio (3.34 g, 62 mmcl) y clorhidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (8.8 g, 46 mmol) bajo N_2. La solución resultante se agitó a temperatura ambiente durante 18 horas. La solución se vertió sobre agua helada (500 mL) y el sólido se filtró y se secó. El material entonces se precipitó a partir de EtOAc al 10%/hexanos para dar un sólido limpio de color blanco (4.5 g) en un rendimiento del 50%. $[\alpha]_D$=-21.0 (c 1.00, DMF); EM (ESI) ($M-H^-$) 293.01; RMN ^1H (DMSO-d_6) δ 8.12 (d, 1H, J = 8.8), 7.77 (d, 2H, J = 7.0), 7.62 (d, 2H, J = 7.0), 7.38 (s amplio, 1H), 7.03 (s amplio, 1H), 4.22-4.47 (m, 2H), 3.71-3.85 (m, 1H), 1.65-1.92 (m, 2H).

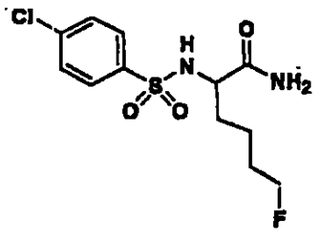


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(2*R*)-2-[(4-clorobencensulfonil)-(4-cianobencil)-amino]-4-fluorobutiramida **(Ejemplo 360)**:

La (2*R*)-2-(4-clorobencensulfonilamino)-4-fluorobutiramida (20 mg, 0.7 mmol) se convirtió al compuesto del compuesto de título como en el esquema de reacción 1, método A para dar el compuesto del título (208 mg) en un rendimiento del 73%. EM (ESI) $(M-H)^-$ 407.99; $[\alpha]_D$=+39.13 (c 1.00, MeOH); RMN ^1H ($CDCl_3$) δ 7.72 (d, 2H, J = 8.4) 7.58 (d, 2H, J = 8.4), 7.50 (d, 2H, J = 8.4), 7.45 (d, 2H, J = 8.4), 6.29 (s amplio, 1H), 5.21 (s amplio, 1H), 4.19-4.67 (m, 5H), 2.17-2.28 (m, 1H), 1.49-1.61 (m, 1H).

Ejemplificación del Esquema de Reacción 19



Amida del ácido 2-(4-clorobencensulfonilamino)-6-fluoro-hexanoico (III):

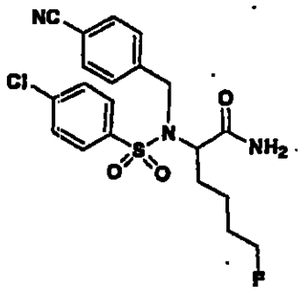
Una mezcla de éster etílico del ácido (benzhidriliden-amino)acético (8.6 g, 32 mmol), 4-bromo-1-fluorobutano (10.0 g, 64.5 mmol), K_2CO_3 (13.4 g, 96.9 mmol), bromuro de tetrabutilamonio (2.1 g, 6.5 mmol) y acetonitrilo (300 mL) se calentó a reflujo durante 72

horas. La reacción se enfrió a temperatura ambiente y se filtró a través de un embudo de vidrio sinterizado. El producto filtrado se concentró *in vacuo*. El residuo se disolvió en éter dietílico (250 mL) y se precipitó un sólido de color blanco. El sólido se removió por medio de la filtración al vacío. Se adicionó una solución de HCl 1 N (100 mL) al producto filtrado, el cual contuvo el producto crudo (éster etílico del ácido (2-(benzhidrilidenamino)-6-fluoro-hexanoico). La mezcla bifásica, resultante se agitó vigorosamente durante 3 horas. La mezcla se transfirió a un embudo separatorio. La capa acuosa se colectó. La capa orgánica se extrajo con HCl 1 N (30 mL). Las capas acuosas, combinadas se lavaron con 200 mL de éter dietílico. Se adicionó HCl concentrado (10.8 mL) a la porción acuosa y la solución resultante se calentó a reflujo durante 6 horas. La mezcla de reacción se enfrió a temperatura ambiente y se concentró *in vacuo*. Se adicionó tolueno al residuo y la mezcla se reconcentró *in vacuo* para dar clorhídrico de ácido 2-amino-6-fluoro-hexanoico como un sólido de color blanco. La sal de aminoácido crudo se utilizó sin purificación o caracterización. El clorhidrato de ácido 2-amino-6-fluorohexanoico (32.3 mmol, teóriçamente) se suspendió en metanol anhidro (300 mL) y se enfrió a 0°C. Se adicionó lentamente cloruro de tionilo (10.3 mL, 129 mmol) durante

5 minutos. La solución resultante se dejó calentar a temperatura ambiente y se agitó durante 18 horas. La mezcla de reacción se concentró *in vacuo* para proporcionar el clorhidrato del ácido 2-amino-6-fluoro-hexanoico de metilo. Se adicionó tolueno (100 mL) y amoniaco al 28% en agua (75 mL) al éster de amino crudo. La mezcla bifásica, resultante se agitó vigorosamente a temperatura ambiente durante 24 horas. La mezcla de reacción se concentró *in vacuo*. El sólido residual se suspendió en tolueno (200 mL) y se concentró *in vacuo* para proporcionar la amida de ácido 6-fluorohexanoicc (II) como un sólido de color blanco. La amida de aminoácido cruda se disolvió en DMF anhidro (50 mL) y CH_2Cl_2 (350 mL) y se hizo reaccionar con 4-clorobencensulfonil-cloruro (82 g, 32.3 mmol) y Et_3N (13.5 mL, 96.9 mmol). Después de 2 horas, se adicionó una segunda porción de 4-clorobencensulfonil-cloruro (1.70 g, 8.1 mmol). Después de 18 horas adicionales, la mezcla resultante se vertió en HCl 1 N (500 mL). La capa orgánica se colectó y se lavó con agua (2 x 500 mL). Se adicionó hexano (600 mL) a la capa orgánica. Se formó un producto precipitado de color blanco. El sólido se colectó por filtración al vacío, se enjuagó con etanol frío (50 mL) y se secó *in vacuo* para dar 4.95 g (rendimiento del 48%, 6 pasos) de amida del ácido 2-(4-clorobencensulfonilamino)-6-fluoro-hexanoico (III): CL-EM $(M+Na)^+$ 345.2; RMN ^1H (400

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MHz, DMSO-d_6) 7.99 (d, 1H, J = 8.8), 7.77 (d, 2H, J = 8.8), 7.62 (d, 2H, J = 8.8), 7.29 (s, 1H), 6.95 (s, 1H), 4.34 (dt, 2H, J_d = 47.5, J_t = 6.1), 3.65 (dt, 1H, J_d = 5.6, J_t = 8.6), 1.60-1.39 (m, 4H), 1.36-1.15 (m, 2H); Análisis Calculado para $C_{12}H_{16}ClFN_2O_3S$: C, 44.65; H, 4.99; N, 8.67. Encontrado: C, 44.61; H, 5.08; N, 8.75.

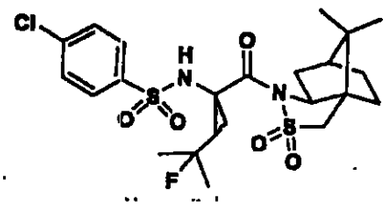


Amida del ácido 2-[(4-clorobencensulfonil)-(4-cianobencil)-amino]-6-fluoro-hexanoico (**Ejemplo 333**):

La amida del ácido 2-(4-clorobencensulfonilamino)-6-fluoro-hexanoico (0.500 g, 1.55 mmol) se convirtió al compuesto del título (360 mg, rendimiento del 50%) como en el esquema de reacción 1, método A. CL-EM $(M+Na)^+$ 459.9; RMN ^1H (400 MHz, DMSO-d_6) δ 7.82 (d, 2H, J = 8.8), 7.79 (d, 2H, J = 8.5), 7.63 (d, 2H, J = 8.8), 7.58 (d, 2H, J = 8.3), 7.52 (s, 1H), 7.09 (s, 1H), 4.82 (ABq, 2H, Δν = 37.2, J_{ab} = 17.6), 4.34 (dd, 1H, J = 8.0, 6.6), 4.25 (dt, 2H, J_d = 47.2, J_t = 5.7), 1.58 (m, 1H), 1.49-1.12 (m, 5H); Análisis Calculado para $C_{20}H_{21}ClFN_3O_3S$: C, 54.85; H, 4.83; N, 9.59. Encontrado: C, 54.92; H, 4.76; N, 9.54.

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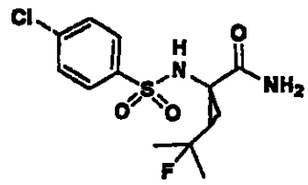
Ejemplificación del Esquema de Reacción 20



(2*R*)-2-(4-clorobencensulfonilamino)-1-{(1'*S*),(5'*S*)-10'10'-dimetil-3',3'-dioxo-3'λ^6-tia-4'-aza-triciclo-[5.2.1.$0^{1,5}$]dec-4'-il}-4-fluoro-4-metil-pentan-1-ona:

A una solución de (2*R*)-2-(4-clorobencensulfonilamino)-1-{(1'*S*),(5'*S*)-10'10'-dimetil-3',3'-dioxo-3'λ^6-tia-4'-aza-triciclo-[5.2.1.$0^{1,5}$]dec-4'-il}-4-metil-4-penten-1-ona [500 mg, 1 mmol, preparada como en el esquema de reacción 18 a partir de N-2-(benzhidriliden-amino)-1-{(1'*S*),(5'*S*)-10'10'-dimetil-3',3'-dioxo-3'λ^6-tia-4'-aza-triciclo-[5.2.1.$0^{1,5}$]dec-4'-il}-etanona (referencia: Josien, H.; Martin, A.; Chassaing, G. Tetrahedron Lett. **1991**, 32, 6547) y 1-bromo-2-metil-2-propeno] en THF (5 mL) a 0°C se adicionó ácido clorhídrico•piridina (10 mL). La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 18 horas. Los contenidos de la reacción se adicionaron cuidadosamente a una solución acuosa, saturada de $NaHCO_3$ (300 mL). La mezcla acuosa se extrajo con EtOAc (3 x 100 mL). Las capas orgánicas, combinadas se lavaron secuencialmente con HCl 1 N (200 mL) y salmuera (100 mL). La

capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró *in vacuo* para proporcionar 490 mg (94%) del compuesto del título como un sólido de color blanco: RMN ^1H (400 MHz, DMSO-d_6) δ 7.83 (d, 2H, J = 8.8), 7.45 (d, 2H, J = 8.8), 5.37 (d, 1H, J = 8.1), 4.65 (m, 1H), 3.64 (t, 1H, J = 6.4), 3.43 (ABq, 2H, $\Delta\nu$ = 5.4, J_{ab} = 13.7), 2.19-1.83 (m, 7H), 1.41-1.31 (m, 8H), 1.04 (s, 3H), 0.94 (s, 3H).

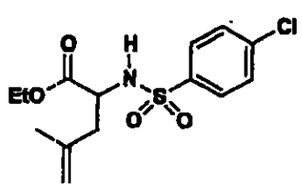


Amida del ácido (2*R*)-2-(4-clorobencensulfonilamino)-4-fluoro-4-metil-pentanoico:

La (2*R*)-2-(4-clorobencensulfonilamino)-1-{(1'*S*),(5'*S*)-10'10'-dimetil-3',3'-dioxo-3'λ^6-tia-4'-aza-triciclo-[5.2.1.$0^{1,5}$]dec-4'-il}-4-fluoro-4-metil-pentan-1-ona se convirtió al compuesto del título en dos pasos como en el esquema de reacción 18 (165 mg, rendimiento del 55%): CL-EM $(M+Na)^+$ 345.1; RMN ^1H (500 MHz, DMSO-d_6) δ 8.10 (d, 1H, J = 9.2), 7.77 (d, 2H, J = 8.5), 7.62 (d, 2H, J = 8.9), 7.34 (s, 1H), 6.92 (s, 1H), 3.85 (m, 1H), 1.89 (m, 1H), 1.74 (m, 1H), 1.31 (d, 3H, J = 21.7), 1.29 (d, 3H, J = 21.9).

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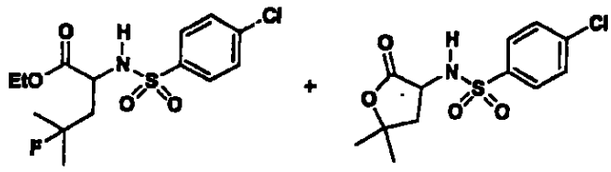
Ejemplificación del Esquema de Reacción 21



2-(4-clorobencensulfonilamino)-4-metil-4-pentenoato de etilo:

Una solución de 2-amino-4-metil-4-pentenoato de etilo (2.84 g, 18.1 mmol, preparado como en el esquema de reacción 19 a partir de éster etílico del ácido (benzhidrilidenamino)acético y 1-bromo-2-metil-2-propeno) en CH_2Cl_2 (250 mL) se hizo reaccionar con cloruro de 4-clorobencensulfonilo (4.20 g, 19.9 mmol) y Et_3N (3.78 mL, 27.2 mmol). Después de 4 horas, la mezcla resultante se vertió en HCl acuoso 1 N (500 mL) y se extrajo con EtOAc (3 x 150 mL). La capa orgánica se lavó con salmuera (50 mL), se secó ($MgSO_4$), se filtró y se concentró *in vacuo*. El producto concentrado, crudo se purificó utilizando la cromatografía en columna de gel de sílice (gradiente de 10:1 a 5:1, hexanos/EtOAc) para proporcionar 3.04 g (rendimiento del 25% sobre 3 pasos) de 2-(4-clorobencensulfonilamino)-4-metil-4-pentenoato de etilo CL-EM $(M+Na)^+$ 354.2; RMN ^1H (400 MHz, $CDCl_3$) 7.77 (d, 2H, J = 9.1), 7.46 (d, 2H, J = 8.8), 5.07 (d, 1H, J = 9.0), 4.84 (s, 1H), 4.73 (s, 1H), 4.05 (m, 1H), 3.95 (q, 2H, J = 7.1), 2.40 (m, 2H), 1.66 (s, 3H), 1.13 (t, 3H, J

= 7.1).

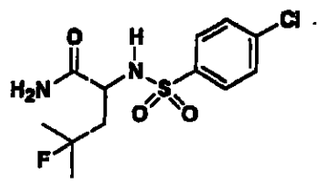


Éster etílico del ácido 2-(4-clorobencensulfonilamino)-4-fluoro-4-metil-pentanoico y 4-cloro-N-(5,5-dimetil-2-oxo-tetrahidro-furan-3-il)-bencensulfonamida:

Se adicionó fluoruro de hidrógeno•piridina (10 mL) a una solución a 0°C de 2-(4-cloro-bencensulfonilamino)-4-metil-4-pentenoato de etilo (1.0 g, 3.0 mmol) en THF (15 mL). La mezcla de reacción se dejó calentar a temperatura ambiente. Después de 5 horas, se agregó una porción adicional (10 mL) de fluoruro de hidrógeno•piridina. La mezcla se agitó durante 24 horas, luego se adicionó una tercera porción de fluoruro de hidrógeno•piridina (10 mL). Después de un total de 53 horas, la reacción se enfrió rápidamente con briznas de hielo (20 mL). La mezcla cruda se vertió sobre agua helada (500 mL) y se extrajo con CH_2Cl_2 (2 x 200 mL). Las capas orgánicas, combinadas se lavaron con $NaHCO_3$ acuoso, saturado (100 mL) y se concentraron *in vacuo*. El producto crudo se purificó utilizando la cromatografía en columna de gel de sílice (gradiente de 10:1 a 5:1, hexanos/EtOAc) para proporcionar 0.395 g (rendimiento del 37%) de 2-(4-clorobencensulfonilamino)-4-fluoro-4-metil-pentanoato de

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etilo y 0.425 g (rendimiento del 46%) de 4-cloro-*N*-(5,5-dimetil-2-oxo-tetrahidro-furan-3-i)-bencensulfonamida. Los datos para el 2-(4-clorobencensulfonilamino)-4-fluoro-4-metil-pentanoato de etilo: CL-EM $(M+Na)^+$ 374.1; RMN ^1H (500 MHz, $CDCl_3$) 7.78 (d, 2H, J = 8.9), 7.47 (d, 2H, J = 8.5), 5.19 (d, 1H, J = 7.9), 4.08 (m, 1H), 3.93 (m, 2H), 2.09-1.94 (m, 2H), 1.42 (d, 3H, J = 21.6), 1.37 (d, 3H, J = 21.6), 1.12 (t, 3H, J = 7.0). Datos para la 4-cloro-*N*-(5,5-dimetil-2-oxo-tetrahidro-furan-3-il)-bencensulfonamida: CL-EM $(M+Na)^+$ 326.0; RMN ^1H (400 MHz, DMSO-d_6) 8.41 (d, 1H, J = 9.1), 7.86 (d, 2H, J = 8.6), 7.67 (d, 2H, J = 8.8), 4.57 (m, 1H), 2.22 (dd, 1H, J = 12.4, 9.0), 1.72 (t, 1H, J = 12.0), 1.33 (s, 3H), 1.31 (s, 3H).

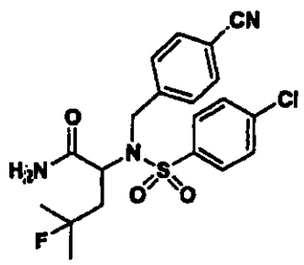


Amida del ácido 2-(4-clorobencensulfonilamino)-4-fluoro-4-metil-pentanoico:

Una solución del éster etílico del ácido 2-(4-clorobencensulfonilamino)-4-fluoro-4-metil-pentanoico (457 mg, 1.30 mmol) en MeOH (20 mL) se trató con NaOH 10 N (780 µL, 7.8 mmol) a temperatura ambiente durante 18 horas. La mezcla de reacción cruda se concentró *in vacuo*. El residuo se trató con agua (50 mL) y HCl 1 N (20 mL). La solución acuosa

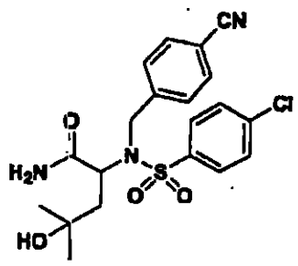
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se extrajo con EtOAc (3 x 100 mL). Las capas orgánicas, combinadas se lavaron con salmuera (50 mL), se secaron sobre $MgSO_4$, se filtraron y se concentraron *in vacuo* para dar un sólido de color blanco que contenía ácido 2-(4-clorobencensulfonilamino)-4-fluoro-4-metil-pentanoico. Una mezcla del sólido crudo, 1-hidroxibenzotriazol (263 mg, 1.95 mmol), diisopropiletilamina (670 mg, 5.2 mmol), cloruro de amonio (140 mg, 2.6 mmol), clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (373 mg, 1.95 mmol), y DMF (20 mL) se agitó temperatura ambiente durante 24 horas. La mezcla cruda se vertió en agua (500 mL). La solución acuosa se extrajo con EtOAC/hexano (90:10, 3 x 150 mL). Las capas orgánicas, combinadas se lavaron con salmuera (50 mL), se secaron sobre $MgSO_4$, se filtraron y se concentraron in vacuo. El producto concentrado, crudo se purificó utilizando la cromatografía en columna de gel de sílice (95:5, cloroformo/MeOH) para proporcionar 0.426 g (rendimiento del 100%) del compuesto del título: CL-EM $(M+Na)^+$ 345.3; RMN ^1H (400 MHz, DMSO-d_6) δ 8.10 (d, 1H, J = 9.2), 7.77 (d, 2H, J = 8.5), 7.62 (d, 2H, J = 8.9), 7.34 (s, 1H), 6.92 (s, 1H), 3.85 (m, 1H), 1.89 (m, 1H), 1.74 (m, 1H), 1.31 (d, 3H, J = 21.7), 1.29 (d, 3H, J = 21.9).



Amida del ácido 2-[(4-clorobencensulfonil)-(4-cianobencil)-amino]-4-fluoro-4-metil-pentanoico **(Ejemplo 357)**:

La amida del ácido 2-(4-clorobencensulfonilamino)-4-fluoro-4-metil-pentanoico se convirtió al compuesto del título como en el esquema de reacción 1, método A. CL-EM $(M+NA)^+$ 460.2; RMN ^1H (400 MHz, DMSO-d_6) δ 7.83 (d, 2H, J = 8.5), 7.75 (d, 2H, J = 8.3), 7.68 (s, 1H), 7.64 (d, 2H, J = 8.6), 7.49 (d, 2H, J = 8.1), 7.20 (s, 1H), 4.67 (ABq, 2H, Δν = 28.3, J_{ab} = 17.3), 4.54 (dd, 1H, J = 9.3, 3.2), 2.23 (m, 1H), 1.42 (m, 1H), 1.25 (d, 3H, J = 21.6), 1.21 (d, 3H, J = 21.7).



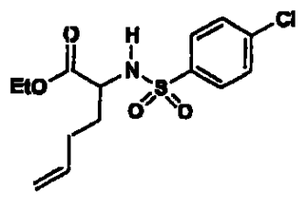
Amida del ácido 2-[(4-clorobencensulfonil)-(4-cianobencil)-amino]-4-hidroxi-4-metil-pentanoico **(Ejemplo 443)**:

Un frasquito sellado que contenía una mezcla de 4-cloro-N-(5,5-dimetil-2-oxo-tetrahidro-furan-3-il)-

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bencensulfonamida (0.20 g, 0.66 mmol) y amoniaco al 28% en agua (3 mL) se calentó en reactor de microondas a 80°C durante 40 minutos. La mezcla de reacción se enfrió a temperatura ambiente y se concentró a sequedad *in vacuo* para proporcionar un sólido de color blanco que contenía amida del ácido 2-(4-clorobencensulfonilamino)-4-hidroxi-4-metil-pentanoico. El sólido crudo se convirtió al compuesto del título (98 mg, rendimiento del 34%) como en el esquema de reacción 1, método A: CL-EM $(M+Na)^+$ 458.2; RMN ^1H (400 MHz, DMSO-d_6) δ 7.84 (d, 2H, J = 8.6), 7.76 (d, 2H, J = 8.3), 7.62 (d, 2H, J = 8.8), 7.51 (d, 2H, J = 8.3), 7.40 (s, 1H), 7.11 (s, 1H), 4.63 (ABq, 2H, Δν = 5.9, J_{ab} = 17.6), 4.56 (dd, 1H, J = 8.3, 2.5), 4.54 (s, 1H), 1.95 (dd, 1H, J = 13.7, 8.6), 1.26 (dd, 1H, J = 13.6, 2.4), 1.04 (s, 3H), 0.99 (s, 3H). Análisis Calculado para $C_{22}H_{22}ClN_3O_4S$: C, 55.10; H, 5.08; N, 9.64. Encontrado: C, 54.96; H, 5.14; N, 9.58.

Ejemplificación del Esquema de Reacción 22

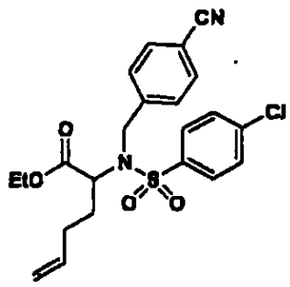


Éster etílico del ácido 2-(4-clorobencensulfonilamino)-5-hexenoico:

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Una mezcla del éster etílico del ácido (benzhidriliden-amino)acético (20 g, 74.8 mmol), 4-bromo-1-buteno (10.1 g, 74.8 mmol), K_2CO_3 (31.0 g, 224 mmol), bromuro de tetrabutilamonio (2.41 g, 7.48 mmol) y acetonitrilo (150 mL) se calentó a reflujo durante 6 horas. La reacción se enfrió a temperatura ambiente y se filtró a través de un embudo de vidrio sinterizado. El producto filtrado se concentró *in vacuo*. El residuo se disolvió en éter dietílico (250 mL) y se precipitó un sólido color blanco. El sólido se removió por medio de la filtración al vacío. Una solución de HCl 1 N (150 mL) se adicionó al producto filtrado, el cual contuvo el producto crudo (éster etílico del ácido 2-(benzhidriliden-amino)-hex-5-enoico). LA mezcla bifásica, resultante se agitó vigorosamente durante 18 horas. La mezcla se transfirió a un embudo separatorio. La capa acuosa se colectó y se concentró *in vacuo*. El residuo se disolvió en tolueno (2 x 200 mL) y se reconcentró. El éster de amino crudo se disolvió en CH_2Cl_2 y se hizo reaccionar con cloruro de 4-clorobencensulfonilo (15.8 g, 74.8 mmol) y Et_3N (31.2 mL, 224 mmol). Después de 18 horas, la mezcla resultante se vertió en HCl 1 N (500 mL). La capa orgánica se colectó y se lavó secuencialmente con HCl 1 N (500 mL) y salmuera (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró *in vacuo*. El producto concentrado, crudo se purificó utilizando la cromatografía en columna de gel de

sílice (hexanos/EtOAc, 5:1) para proporcionar 5.57 g (rendimiento del 23% sobre 3 pasos) del compuesto del título: CL-EM $(M+Na)^+$ 354.0; RMN ^1H (400 MHz, DMSO-d_6) δ 8.47 (d, 1H, J = 8.8), 7.76 (d, 2H, J = 8.8), 7.66 (d, 2H, J = 8.8), 5.69 (m, 1H), 4.95-4.88 (m, 2H), 3.86 (q, 2H, J = 7.1), 3.76 (m, 1H), 1.98 (m, 2H), 1.71-1.54 (m, 2H), 1.03 (t, 3H, J = 7.1).

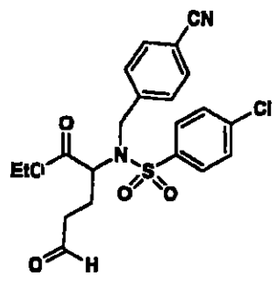


Éster etílico del ácido 2-[(4-clorobencensulfonil)-(4-cianobencil)-amino]-hex-5-enoico:

El éster etílico del ácido 2-[(4-clorobencensulfonil)-(4-cianobencil)-amino]-hex-5-enoico se hizo de manera similar al esquema de reacción 1 iniciando a partir de éster etílico del ácido 2-(4-clorobencensulfonilamino)-hex-5-enoico. El éster etílico del ácido 2-[(4-clorobencensulfonil)-(4-cianobencil)-amino]-hex-5-enoico se aisló como un sólido crudo de color amarillo (1.14 g) y se utilizó en el siguiente paso sin purificación adicional. RMN ^1H ($CDCl_3$) δ 7.71 (d, 2H, J = 8.0), 7.61 (d, 2H, J = 8.0), 7.53 (d, 2H, J = 8.0), 7.46 (d, 2H, J = 8.0), 5.54 (m, 2H), 4.90 (m, 2H), 4.74 (d, 1H, J = 16.0), 4.48 (m, 2H), 3.90 (m, 1H), 1.95 (m, 2H), 1.81 (m, 1H), 1.48 (m, 1H),

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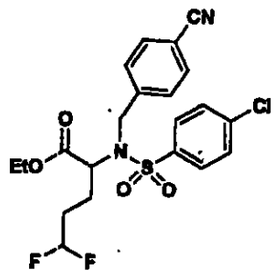
1.11 (t, 3H, J = 8.0).



Éster etílico del ácido 2-[(4-clorobencensulfonil)-(4-cianobencil)-amino]-5-oxo-pentanoico:

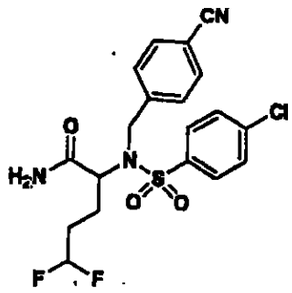
Una mezcla del éster etílico del ácido (4-clorobencensulfonil)-(4-cianobencil)-amino]-hex-5-enoico (1.14 g, 2.56 mmol), tetraóxido de osmio (0.030 g, 0.13 mmol) y N-óxido de trimetilamina (0.41 g, 5.5 mmol) se disolvió en acetona (50 mL) y se agitó durante 4 horas a temperatura ambiente. Con el complemento, la solución se concentró *in vacuo* y se redisolvió en dioxano:H_2O 1.5:1 (50 mL). A esta solución, se adicionó peryodato de sodio (0.66 g, 3.07 mmol) y se agitó temperatura ambiente durante 18 horas. La reacción entonces se diluyó con EtOAc (500 mL) y se lavó con H_2O, salmuera, se secó sobre Na_2SO_4 y se concentró para dar un aceite incoloro, crudo. La purificación adicional por medio de la cromatografía con evaporación instantánea (SiO_2, EtOAc al 5-75%/hexanos) proporcionó el éster etílico del ácido 2-[(4-clorobencensulfonil)-(4-cianobencil)-amino]-5-oxo-pentanoico (0.26 g) como un aceite incoloro en un rendimiento del 23%. RMN ^1H ($CDCl_3$) δ 9.57 (s, 1H), 7.69 (d, 2H, J =

8.0), 7.51 (m, 6H), 5.99 ABq, 2H, $\Delta\nu$ = 16, J_{ab} = 168), 4.47 (m, 1H), 3.89 (m, 2H), 2.53 (m, 1H), 2.32 (m, 1H), 2.11 (m, 1H), 1.61 (m, 1H), 1.06 (t, 3H, J = 8.0).



Éster etílico del ácido 2-[(4-clorobencensulfonil)-(4-cianobencil)-amino]-5,5-difluoro-pentanoico:

El éster etílico del ácido 2-[(4-clorobencensulfonil)-(4-cianobencil)-amino]-5-oxo-pentanoico (0.05 g, 0.11 mmol) se adicionó lentamente a una solución de DAST (0.020 mL, 0.11 mmol) en CH_2Cl_2 (2 mL) a temperatura ambiente y se agitó durante 16 horas. La reacción se diluyó con CH_2Cl_2 (20 mL) y se extrajo con H_2O (2 x 25 mL). Las capas orgánicas, combinadas se lavaron con H_2O, salmuera, se secaron sobre Na_2SO_4 y se concentraron para dar el éster etílico del ácido 2-[(4-cloro-bencensulfonil)-(4-cianobencil)-amino]-5,5-difluoro-pentanoico como un residuo crudo de color amarillo (61 mg). Este residuo crudo se tomó sobre el siguiente paso sin purificación adicional.

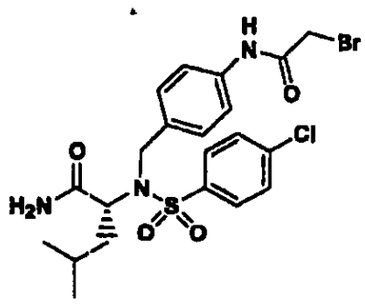


Amida del ácido 2-[(4-clorobencensulfonil)-(4-cianobencil)-amino]-5,5-difluoro-pentanoico **(Ejemplo 377)**:

El éster etílico del ácido 2-[(4-clorobencensulfonil)-(4-cianobencil)-amino]-5,5-difluoro-pentanoico crudo (0.061 g, 0.13 mmol) se disolvió en MeOH (2 mL). A esta mezcla se adicionó NaOH 10 N (0.052 mL, 0.52 mmol) y la solución resultante se agitó temperatura ambiente durante 16 horas. La reacción se diluyó con H_2O (25 mL), se acidificó con HCl 1 N y se extrajo con CH_2Cl_2 (4 x 100 mL). Las capas orgánicas, combinadas se secaron sobre Na_2SO_4 y se concentraron *in vacuo* para dar la porción de ácido carboxílico como un aceite crudo incoloro. El producto intermedio de ácido carboxílico entonces se disolvió en DMF (10 mL) y se mezcló con 1-hidroxibenzotriazol (0.030 g, 0.20 mmol), iPr_2NEt (0.090 mL, 0.52 mmol), NH_4Cl (0.01 g, 0.26 mmol), clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (0.04 g, 0.20 mmol) y se agitó a temperatura ambiente durante 72 horas. La reacción se diluyó con EtOAc (150 mL) y se lavó con H_2O (4 x 50 mL). La capa orgánica secó

sobre Na_2SO_4 y se concentró *in vacuo* para dar un sólido crudo de color blanquecino. La purificación adicional mediante la cromatografía con evaporación instantánea (SiO_2, EtOAc al 5-85%/hexanos) proporcionó el compuesto del título (10.7 mg) como un sólido de color blanco en un rendimiento del 19%. CL-EM $(M+NA)^+$ 464.01; RMN ^1H ($CDCl_3$) δ 7.69 (d, 2H, J = 8.3), 7.60 (d, 2H, J = 8.3), 7.49 (m, 4H), 6.18 (s amplio, 1H), 5.67 (tt, 1H, J = 56, 4.0), 5.22 (s amplio, 1H), 4.52 (ABq, 2H, $\Delta\nu$ = 16, J_{ab} = 100), 4.34 (m, 1H), 2.03 (m, 1H), 1.68 (m, 1H), 1.38 (m, 1H), 0.86 (m, 1H).

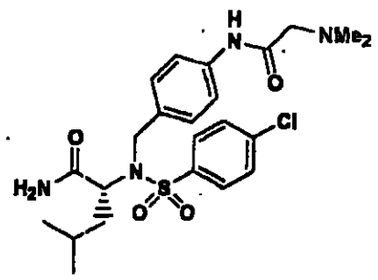
Ejemplificación del Esquema de Reacción 23



Amida del ácido (2*R*)-2-[[4-(2-bromo-acetilamino)-bencil]-(4-clorobencensulfonil)-amino]-4-metil-pentanoico:

A una solución de la amida del ácido (2*R*)-2-[(4-aminobencil)-(4-cloro-bencensulfonil)amino]-4-metil-pentanoico (248 mg, 0.56 mmol) y Et_3N (176 mg, 1.74 mmol) en CH_2Cl_2 (3 mL) se adicionó cloruro de bromoacetilo (105 mg, 0.67 mmol). La mezcla de reacción se agitó durante toda la

noche a temperatura ambiente. La mezcla de reacción se diluyó con CH_2Cl_2 (5 mL), se lavó con HCl 1 N, salmuera y se secó a través de un tapón de algodón. El solvente se removió *in vacuo*. La purificación por medio de la cromatografía con evaporación instantánea (SiO_2, acetona al 10%/CH_2Cl_2) proporcionó el compuesto del título (124 mg) en un rendimiento del 42%. EM (ESI), $(M+H)^+$ 531.86, RMN ^1H ($CDCl_3$, 400 MHz) δ 8.78 (s amplio, NH), 7.95 (d, 2H, J = 8.0), 7.82 (d, 2H, J = 8.0), 7.42 (d, 2H, J = 8.0), 7.33 (d, 2H, J = 8.0), 6.20 (s amplio, 1H), 5.20 (s amplio, 1H), 4.30 (s, 2H), 4.22 (d, 1H, J_{ab} = 16), 4.14 (d, 1H, J_{ab} = 16), 3.25 (t, 1H, J = 6.0), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J = 7.0), 0.94 (d, 3H, J = 7.0).



Amida del ácido (2*R*)-2-{(4-clorobencensulfonil)-[4-(2-dimetilamino-acetilamino)-bencil]-amino}-4-metil-pentanoico

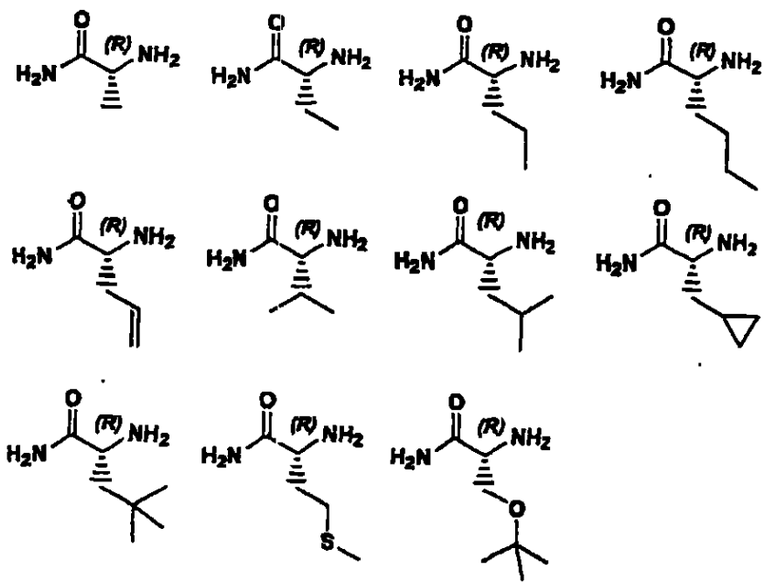
(Ejemplo 308):

A una solución de la amida del ácido (2*R*)-2-[[4-(2-bromo-acetilamino)-bencil]-(4-clorobencensulfonil)-amino]-4-metil-pentanoico (41 mg, 0.77 mmol) en CH_2Cl_2 (2 mL) se adicionó un exceso de dimetilamina 2.0 M en THF. La mezcla de

reacción se agitó durante toda la noche. El solvente se removió *in vacuo*. La purificación por medio de la cromatografía con evaporación instantánea (SiO_2, MeOH 10%/CH_2Cl_2) proporcionó el compuesto del título (24 mg) en un rendimiento del 63%. EM (ESI), $(M+H)^+$ 495.14, RMN ^1H ($CDCl_3$, 400 MHz) δ 8.85 (s, 1H), 8.02 (d, 2H, J = 8.0), 7.75 (d, 2H, J = 8.0), 7.38 (d, 2H, J = 8.0), 7.29 (d, 2H, J = 8.0), 6.23 (s amplio, 1H), 5.39 (s amplio, 1H), 4.62 (m, 4H), 3.25 (t, 1H, J = 6.0), 2.95 (s, 6H), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J = 7.0), 0.94 (d, 3H, J = 7.0).

Materiales de Inicio

Las siguientes α-amino-amidas fueron comercialmente disponibles o se obtuvieron por medio de métodos estándar a partir de aminoácidos comercialmente disponibles:



La amida del ácido 5,5,5-trifluoro-2-aminopentanoico y ácido 6,6,6-trifluoro-2-aminohexanoico se prepararon de acuerdo con: Ojima, I.; Kato, K.; Nakahashi, K. *J. Org. Chem.* 1989, *54*, 4511.

El brómuro de bencilo utilizado en la síntesis de los compuestos de los **Ejemplos 100** y **155** se preparó de acuerdo con: Ishihara, Y.; Fujisawa, Y.; Furuyama, N. solicitud internacional del PCT WO 9846590; Senanayake, C. H.; Fang, Q. K.; Wilkinson, S. H. solicitud internacional del PCT WO 9833789.

Los aldehídos requeridos para la síntesis de los compuestos de los **Ejemplos 91, 248, 249, 289, 290** y **300** (véase esquema de reacción 2) se prepararon como se ejemplifica para 4-(piperidin-1-il)benzaldehído. Una suspensión de 4-fluorobenzaldehído (0.48 mL, 4 mmol), K_2CO_3 (522 mg, 4 mmol), piperidina (340 mg, 4 mmol) en DMSO (5 mL) se calentó en un tubo sellado a 150°C durante 18 horas. Después de ese tiempo, la reacción se concentró y se purificó por medio de la cromatografía en gel de sílice (CH_2Cl_2, luego MeOH al 2%/CH_2Cl_2) para proporcionar el 4-(piperidin-1-il) benzaldehído, 748 mg, rendimiento del 98%.

Los aldehídos utilizados en la síntesis de los compuestos de los **Ejemplos 317, 318** y **320** se prepararon como se ejemplifica para el 4-(piperidin-1-il)-3-fluorobenzaldehído. Una suspensión de 4,3-

difluorobenzaldehído (500 mg, 3.5 mmol), K_2CO_3 (483 mg, 3.5 mmol), piperidina (298 mg, 3.5 mmol) en DMSO (5 mL) se calentó en un tubo sellado a 130°C durante 18 horas. La mezcla de reacción se dejó enfriar a temperatura ambiente, se concentró y se purificó por medio de la cromatografía en gel de sílice (CH_2Cl_2, luego MeOH al 2%/CH_2Cl_2) para proporcionar el 4-(piperidin-1-il)3-fluorobenzaldehído, 740 mg, rendimiento del 99%.

El cloruro de bencilo utilizado en la preparación de los compuestos de los **Ejemplos 433,. 474, 480** y **500** se preparó por medio del siguiente método. A una solución de 2-([4-clorometil)fenil]propan-2-ol (769 mg, 4.16 mmol) (referencia: Creary, X.; Mehrsheikh-Mohammadi, M. E.; McDonald, S. *J. Org. Chem.* **1987**, *52*, 3254.) en CH_2Cl_2 (14 mL) a -78°C se adicionó DAST (0.72 mL, 5.4 mmol). Después de 1.5 horas, la solución se enfrió rápidamente con agua y se calentó a temperatura ambiente. La mezcla se extrajo con CH_2Cl_2 (3x). Las capas orgánicas, combinadas se secaron (Na_2SO_4) y se concentraron. La cromatografía en columna con evaporación instantánea (SiO_2, EtOAc al 0-5%/hexanos) proporcionó el cloruro como un líquido de color amarillo pálido (512 mg, 66%). RMN ^1H ($CDCl_3$, 300MHz) δ 7.30-7.48 (m, 4H), 4.58 (s, 2H), 1.70 (s, 3H), 1.63 (s, 3H).

La preparación del éster etílico de 2-trimetilsilanilo de ácido 4-bromometil-benzoico, el cual se

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utiliza en la síntesis del compuesto del **Ejemplo 470**, es descrita por Graffner-Nordberg, M.; Sjoedin, K.; Tunek, A.; Hallberg, A. *Chem. Pharm. Bull.* **1998**, *46*, 591.

Condiciones para la Separación Cromatográfica de las Mezclas Enantioméricas

Condición 1: El ejemplo 345 se separó utilizando el siguiente método. Columna Chiracel *OJ*, 10 µL, 4.6 X 250 mm, 1.0 mL/minuto, Hexano al 85%/EtOH DEA al 0.1%, durante 20 minutos.

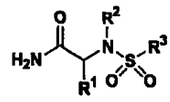
Condición 2: El ejemplo 346 se separó utilizando el siguiente método. Columna Chiralpak AD, 10 µM, 4.6 X 250 mm, 1.0 mL/minuto, Hexano al 80%/EtOH DEA al 0.15%, durante 20 minutos.

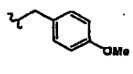
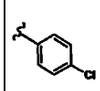
Condición 3: El ejemplo 347 se separó utilizando el siguiente método. Columna Chiralpak AD, 10 µL, 4.6 X 250 mm, 1.0 mL/minuto, Hexano al 65%/IPA DEA al 0.1%, durante 18 minutos.

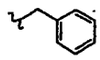
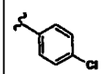
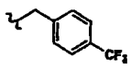
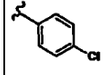
Condición 4: Los ejemplos 365 y 366 se separaron utilizando el siguiente método. Columna Chiralpak AD, 10 µL, 4.6 X 250 mm, 1.0 mL/minuto, Hexano al 75%/EtOH DEA al 0.15 %, durante 25 minutos.

Condición 5: Los ejemplos 408 y 409 se separaron utilizando el siguiente método. Columna Chiracel OD, 10 µL, 4.6 X 250 mm, 1.0 mL/minuto, Hexano al 90%/EtOH DEA al 0.15%, durante 36 minutos.

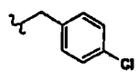
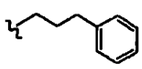
TABLA 4



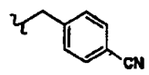
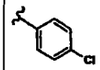
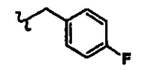
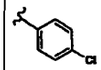
Ej. No.	R^1	R^2	R^3	Esquema de Reacción	Apariencia	PM Calc.	Tiempo de Ret./Método	M+H+	Datos de RMN
1				1.2	sólido blanco	424.95	1.76 Método B	425.1	RMN ^1H ($CDCl_3$) δ 7.63 (d, 2H, J=7.0Hz), 7.42 (d, 2H, J=7.0Hz), 7.25 (d, 2H, J=8.0Hz), 6.79 (d, 2H, J=0.8Hz), 6.25 (s, amplio, 1H), 5.35 (s, amplio, 1H), 4.36 (dd, 2H, J=50Hz, 15Hz), 4.26 (t, 1H, J=7.2Hz), 7.38 (s, 3H), 1.83 (m, 1H), 1.18-1.34 (m, 3H), 0.75 (d, 3H, J=7.0Hz), 0.67 (d, 3H, J=7.0Hz).

2				1	sólido blanco	394.92	1.71 Método B	395.2	RMN ^1H (d_6DMSO) δ 7.81 (d, 2H, J=7.0Hz), 7.60 (d, 2H, J=7.0Hz), 7.50 (s, amplio, 1H), 7.41, (d, 2H, J=8.0Hz), 7.32 (m, 2H), 7.24 (m, 1H), 7.18 (s, amplio, 1H), 4.76 (dd, 2H, J=50Hz, 15Hz), 4.36 (t, 1H, J=7.0Hz), 3.33 (s, 3H), 1.20-1.34 (m, 3H), 0.79 (d, 3H, J=6.0Hz), 0.46 (d, 3H, J=6.0Hz).
3				1	sólido blanco	462.92	1.71 Método A	463.1	RMN ^1H (d_6DMSO) δ 7.83 (d, 2H, J=7.0Hz), 7.67 (d, 2H, J=7.0Hz), 7.57-7.62 (m, 4H), 7.06 (s, amplio, 1H), 4.79 (dd, 2H, J=70Hz, 17Hz), 4.38 (t, 1H, J=6.0Hz), 3.32 (s, 3H), 1.23-1.35 (m, 3H), 0.81 (d, 3H, J=6.0Hz), 0.50 (d, 3H, J=6.0Hz).

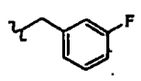
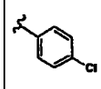
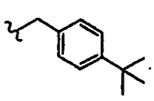
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4				1	sólido blanco	429.37	1.69 Método A	429.1	RMN ^{1}H (d_6DMSO) δ 7.83 (d, 2H, J=7.0Hz), 7.61 (d, 2H, J=7.0Hz), 7.52 (s, amplio, 1H), 7.41 (d, 2H, J=8.2Hz), 7.37 (d, 2H, J=8.2Hz), 7.03 (s, amplio, 1H), 4.70 (dd, 2H, J=50Hz, 15Hz), 4.35 (t, 1H, J=7.0Hz), 1.28-1.30 (m, 3H), 0.60 (d, 3H, J=6.0Hz), 0.51 (d, 3H, J=6.0Hz).
5				1	sólido blanco	422.98	1.71 Método A	423.2	RMN ^{1}H (d_6DMSO) δ 7.76 (d, 2H, J=7.0Hz), 7.61 (d, 2H, J=7.0Hz), 7.42 (s, amplio, 1H), 7.16-7.20 (m, 5H), 6.99 (s, amplio, 1H), 4.24 (m, 1H), 3.45-3.51 (m, 1H), 3.10-3.18 (m, 1H), 2.52-2.59 (m, 2H), 1.95-2.05 (m, 1H), 1.69-1.80 (m, 1H), 1.55-1.34 (m, 3H), 0.84 (m, 6H).

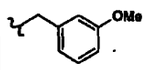
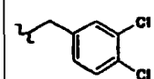
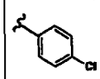
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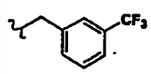
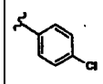
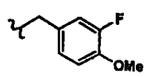
6				1	solido blanco	419 93	1 45 Metodo A	420 13	RMN ^{1}H (d_6DMSO) δ 7 84 (d 2H, J=8 0Hz) 7 79 (d 2H J=8 0Hz) 7 63 (d, 2H J=8 0Hz), 7 58 (m, 3H) 7 03 (s, amplio 1H) 4 87 (dd 2H J=50Hz 15Hz), 4 32 (t 1H J=7 0Hz) 1 28 1 30 (m 3H), 0 81 (d 3H J=6 0Hz) 0 53 (d 3H J=6 0Hz)
7				1	solido blanco	412 91	1 58 Método A	413 4	RMN ^{1}H (d_6DMSO) δ 7 81 (d 2H J=7 0Hz) 7 61 (d 2H J=7 0Hz) 7 51 (s amplio 1H), 7 43 (m 1H) 7 11 7 14 (m 2H) 7 03 (s amplio 1H) 4 77 (dd 2H J=50Hz 15Hz) 4 33 (t 1H J=6 0Hz) 1 21 1 31 (m 3H) 0 80 (d 3H J=6 0Hz) 0 50 (d 3H J=6 0Hz)

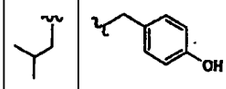
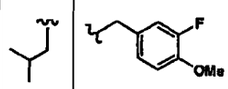
293

8				1	sólido blanco	412.91	1.58 Método A	413.2	RMN ^1H (d_6DMSO) δ 7.82 (d, 2H, J=8.0Hz), 7.61 (d, 2H, J=8.0Hz), 7.55 (s, amplio, 1H) 7.39 m, 1H), 7.05-7.32 (m, 4H), 7.03 (s, amplio, 1H), 4.78 (dd, 2H, J=50Hz, 15Hz), 4.38 (t, 1H, J=6.0Hz), 1.26-1.32 (m, 3H), 0.81 (d, 3H, J=6.0Hz), 0.54 (d, 3H, J=6.0Hz).
9				1	sólido blanco	451.03	2.99 Método C	451.2	RMN ^1H (d_6DMSO) δ 7.75 (d, 2H, J=8.5Hz), 7.55 (d, 2H, J=8.5Hz), 7.51 (s, amplio, 1H), 7.25-7.29 (m, 4H), 7.03 (s, amplio, 1H), 4.69 (dd, 2H, J=25Hz, 14Hz), 4.35 (m, 1H), 1.21-1.31 (m, 3H), 1.25 (s, 9H) 0.81 (d, 3H, J=6.0Hz), 0.46 (d, 3H, J=6.0Hz).

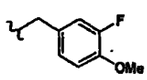
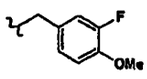
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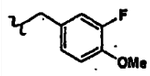
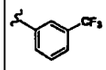
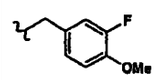
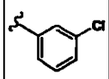
10				1	sólido blanco	424.95	1.56 Método A	425.2	RMN ^{1}H (d_6DMSO) δ 7.80 (d, 2H, J=8.0Hz), 7.58 (d, 2H, J=8.0Hz), 7.50 (s, amplio, 1H) 7.21 (m, 1H), 7.04 (m, 1H), 6.80-6.95 (m, 3H), 4.70 (dd, 2H, J=50Hz, 15Hz), 4.37 (m, 1H), 3.70 (s, 3H), 1.30-1.39 (m, 3H), 0.81 (d, 3H, J=6.0Hz), 0.52 (d, 3H, J=6.0Hz).
11				1	sólido blanco	463.81	1.76 Método A	463	RMN ^{1}H (d_6DMSO) δ 7.80 (d, 2H, J=8.0Hz), 7.61 (d, 2H, J=8.0Hz), 7.55-7.60 (m, 2H), 7.40 (m, 1H), 7.10 (s, amplio, 1H), 4.72 (dd, 2H, J=50Hz, 15Hz), 4.40 (m, 1H), 1.26-1.40 (m, 3H), 0.83 (d, 3H, J=6.0Hz), 0.60 (d, 3H, J=6.0Hz).

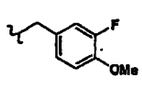
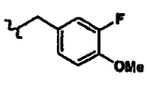
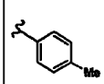
12				1	sólido blanco	462.92	1.68 Método A	463.1	RMN ^{1}H (d_6DMSO) δ 7.80 (d, 2H, J=8.0Hz), 7.68-7.80 (m, 2H), 7.54-7.61 (m, 4H), 7.08 (s, amplio, 1H), 4.80 (dd, 2H, J=50Hz, 15Hz), 4.38 (t, 1H, J=6.0Hz), 1.26-1.33 (m, 3H), 0.82 (d, 3H, J=6.0Hz), 0.52 (d, 3H, J=6.0Hz).
13				1	sólido blanco	442.94	1.55 Método A	443.2	RMN ^{1}H (d_6DMSO) δ 7.78 (d, 2H, J=8.0Hz), 7.61 (d, 2H, J=8.0Hz), 7.56 (s, amplio, 1H), 7.05-7.24 (m, 4H), 4.65 (dd, 2H, J=50Hz, 15Hz), 4.40 (t, 1H, J=6.0Hz), 3.81 (s, 3H) 1.28-1.35 (m, 3H), 0.81 (d, 3H, J=6.0Hz), 0.56 (d, 3H, J=6.0Hz).

14				1	sólido blanco	410.92	1.51 Método B	411.2	RMN ^1H ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.45 (d, 2H, J=8.5Hz), 7.26 (d, 2H, J=8.5Hz), 6.73 (d, 2H, J=8.0Hz), 6.33 (s, amplio, 1H), 5.24 (s, amplio, 1H), 4.28 (dd, 2H, J=70Hz, 20Hz), 4.23 (m, 1H), 1.67-1.93 (m, 2H), 1.12-1.32 (m, 2H), 0.77 (d, 3H, J=7.0Hz), 0.68 (d, 3H, J=7.0Hz).
15				1	espuma pegajosa amarillo pálido	408.5	1.58 Método B	409.3	RMN ^1H ($CDCl_3$) δ 7.77 (d, 2H, J=8.0Hz), 7.74-7.59 (m, 3H), 7.02-7.13 (m, 2H), 6.84 (t, 1H, J=8.4Hz), 6.32 (s, amplio, 1H), 5.31 (s, amplio, 1H), 4.48 (dd, 2H, J=50Hz, 17Hz), 4.26 (m, 1H), 3.85 (s, 3H), 1.79-1.84 (m, 1H), 1.25-1.30 (m, 1H), 1.04-1.11 (m, 1H), 0.72 (d, 3H, J=7.0Hz), 0.63 (d, 3H, J=7.0Hz).

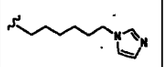
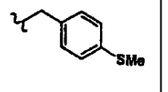
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16				1	película blanca	426.49	1.63 Método B	427.3	RMN ^{1}H ($CDCl_3$) δ 7.73-7.77 (m, 2H), 6.81-7.18 (m, 5H), 6.29 (s, 1.63 amplio, 1H), 5.37 (s, amplio, 1H), 4.45 (dd, 2H, J=50Hz, 17Hz), 4.26 (m, 1H), 3.89 (s, 3H), 1.76-1.84 (m, 1H), 1.26-1.33 (m, 1H), 1.08-1.17 (m, 1H), 0.74 (d, 3H, J=7.0Hz), 0.66 (d, 3H, J=7.0Hz).
17				1	sólido amarillo pálido	476.49	1.79 Método B	477.2	RMN ^{1}H ($CDCl_3$) δ 7.84 (d, 2H, J=8.0Hz), 7.72 (d, 1H, J=8.0Hz), 7.10 (d, 1H, J=9.5Hz), 6.99 (d, 2H, J=8.5Hz), 6.82 (t, 1H, J=8.5Hz), 6.21 (s, amplio, 1H), 5.35 (s, amplio, 1H), 4.46 (dd, 2H, J=50Hz, 15Hz), 4.31 (t, 1H, J=7.5Hz), 3.87 (s, 3H), 1.78-1.85 (m, 1H), 1.30-1.35 (m, 1H), 1.12-1.21 (m, 1H), 0.77 (d, 3H, J=7.0Hz), 0.68 (d, 3H, J=7.0Hz).

18				1	sólido amarillo pálido	476.49	1.76 Método B	477.2	RMN ^1H ($CDCl_3$) δ 7.79-7.89 (m, 3H), 7.59-7.64 (m, 1H), 7.01-7.08 (m, 1H), 6.83 (t, 1H, J=8.8Hz), 6.25 (s, amplio, 1H), 5.42 (s, amplio, 1H), 4.45 (dd, 2H, J=50Hz, 17Hz), 4.33 (m, 1H), 3.88 (s, 3H), 1.78-1.85 (m, 1H), 1.31-1.35 (m, 1H), 1.17-1.23 (m, 1H), 0.77 (d, 3H, J=7.0Hz), 0.70 (d, 3H, J=7.0Hz).
19				1	sólido blanco	442.94	1.73 Método B	443.2	RMN ^1H ($CDCl_3$) δ 7.42-7.63 (m, 4H), 7.02-7.10 (m, 2H), 6.86 (t, 1H, J=8.5Hz), 6.24 (s, amplio, 1H), 5.42 (s, amplio, 1H), 4.45 (dd, 2H, J=50Hz, 17Hz), 4.27 (m, 1H), 3.87 (s, 3H), 1.79-1.87 (m, 1H), 1.27-1.33 (m, 1H), 1.14-1.22 (m, 1H), 0.78 (d, 3H, J=7.0Hz), 0.71 (d, 3H, J=7.0Hz).

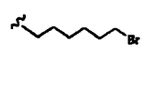
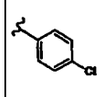
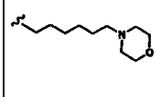
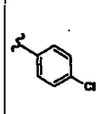
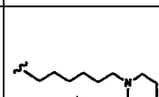
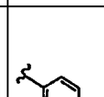
20				1	aceite amarillo pálido	422.52	1.68 Método B	423.2	RMN ^1H ($CDCl_3$) δ 7.52-7.57 (m, 2H), 7.37-7.39 (m, 2H), 7.02-7.12 (m, 2H), 6.84 (t, 1H, J=8.5Hz), 6.34 (s, amplio, 1H), 5.35 (s, amplio, 1H), 4.45 (dd, 2H, J=50Hz, 17Hz), 4.25 (m, 1H), 3.86 (s, 3H), 2.38 (s. 3H), 1.78-1.87 (m, 1H), 1.25-1.31 (m, 1H), 1.04-1.11 (m, 1H), 0.72 (d, 3H, J=7.0Hz), 0.65 (d, 3H, J=7.0Hz).
21				1	aceite amarillo pálido	422.52	1.67 Método B	423.2	RMN ^1H ($CDCl_3$) δ 7.64 (d, 2H, J=8.0Hz), 7.25-7.30 (m, 2H), 7.02-7.12 (m, 2H), 6.84 (t, 1H, J=8.5Hz), 6.34 (s, amplio, 1H), 5.32 (s, amplio, 1H), 4.45 (dd, 2H, J=50Hz, 17Hz), 4.26 (t, 1H, J=10Hz), 3.86 (s, 3H), 2.42 (s, 3H), 1.76-1.85 (m, 1H), 1.25-1.31 (m, 1H), 1.05-1.12 (m, 1H), 0.72 (d, 3H,

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									J=7.0Hz), 0.62 (d, 3H, J=7.0Hz).
22				3	aceite claro	455.02	1.94 Método B	455.2	RMN ^{1}H (d6DMSO) δ 7.82 (d, 2H, J=8.0Hz), 7.68 (d, 2H, J=8.0Hz), 7.56 (s, amplio, 1H), 7.45 (m, 1H), 7.16 (m, 1H), 7.04 (s, 1H), 6.86 (m, 1H), 4.25 (m, 1H), 3.94 (m, 1H), 3.40-3.55 (m, 2H), 3.02-3.14 (m, 1H), 1.18-1.69 (m, 10H), 0.76 (s, amplio, 6H).
23				1	sólido blanco	441.01	1.67 Método A	411.2	RMN ^{1}H (d_8DMSO) δ 7.79 (d, 2H, J=8.0Hz), 7.59 7.51 (s, amplio, 1H), 7.31 (d, 2H, J=8.0Hz), 7.19 (d, 2H, J=8.0Hz), 7.03 (s, amplio, 1H), 4.68 (dd, 2H, J=50Hz, 15Hz), 4.35 (t, 1H, J=7.0Hz), 3.32 (s, 3H), 1.24-1.35 (m, 3H), 0.81 (d, 3H, J=6.0Hz), 0.51 (d, 3H, J=6.0Hz).

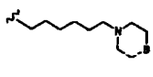
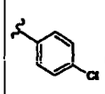
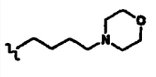
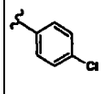
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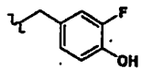
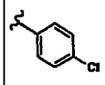
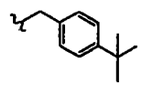
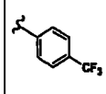
24				1	sólido blanco	467.86	1.75 Método A	469.1	RMN ^1H (d_6DMSO) δ 7.83 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.42 (s, amplio, 1H), 7.01 (s, 1H), 4.25 (m, 1H), 3.35-3.51 (m, 3H), 3.08-3.14 (m, 1H), 1.19-1.82 (m, 11H), 0.86 (d, 6H, J=6.0Hz).
25				3	aceite claro	474.07	1.34 Método A	474.4	RMN ^1H (d_6DMSO) δ 7.82 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.42 (s, amplio, 1H), 6.99 (s, 1H), 4.25 (m, 1H), 3.51-3.60 (s, amplio, 4H), 3.18-3.41 (m, 2H), 2.25-2.35 (s, amplio, 4H), 2.27 (m, 2H) 1.15-1.62 (m, 9H), 0.80 (d, 6H, J=6.0Hz).
26				3	aceite claro	472.09	1.27 Método A	472	RMN ^1H (d_6DMSO) δ 7.83 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.42 (s, amplio, 1H), 7.00 (s, 1H), 4.23-4.26 (m, 1H), 3.22-3.45 (m,

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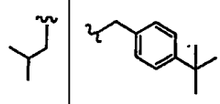
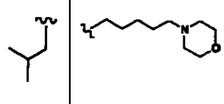
									1H), 3.11-3.14 (m, 1H), 2.16-2.28 (m, 5H), 1.19-1.52 (m, 18H), 0.86 (m, 6H).
27				3	aceite claro	490.13	1.21 Método A	490	RMN ^{1}H (d_6DMSO) δ 7.83 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.44 (s, amplio, 1H) 7.06 (s, 1H), 4.21-4.25 (m, 1H), 3.55 (s, amplio, 4H), 3.19-3.40 (m, 4H), 2.43-2.57 (m, 8H), 2.23-2.30 (m, 2H), 1.18-1.59 (m, 9H), 0.82 (m, 6H).
28				3	aceite claro	446.01	1.08 Método A	446.2	RMN ^{1}H (d_6DMSO) δ 7.84 (d, 2H, J=8.0Hz), 7.66 (d, 2H, J=8.0Hz), 7.49 (s, amplio, 1H) 7.02 (s, 1H), 4.23-4.26 (m, 1H), 3.94 (s, amplio, 2H), 3.71 (s, amplio, 2H), 3.52-3.57 (m, 1H), 3.14-3.17 (m, 1H), 3.06 (s, amplio, 4H), 1.17-1.65 (m, 7H), 0.86 (m, 6H).

303

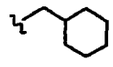
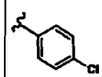
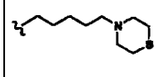
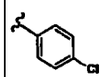
29				1	sólido blanco	428.91	1.51 Método A	429.1	RMN ^1H ($CDCl_3$) δ 7.69 (d, 2H, J=9.0Hz), 7.47 (d, 2H, J=9.0Hz), 7.13 (d, 1H, J=11.2Hz), 7.00 (d, 1H, J=8.0Hz), 6.88 (m, 1H), 6.27 (s, amplio, 1H), 5.49 (s, amplio, 1H), 5.24 (s, amplio, 1H), 4.40 (dd, 2H, J=90Hz, 18Hz), 3.20 (m, 1H), 1.09 1.82 (m, 3H), 0.77 (d, 3H, J=7.0Hz), 0.68 (d, 3H, J=7.0Hz).
30				1	sólido blanco	484.59	1.89 Método A	485.0	RMN ^1H ($CDCl_3$) δ 7.73 (d, 2H, J=8.0Hz), 7.65 (d, 2H, J=8.0Hz), 7.18-7.27 (m, 4H), 6.25 (s, amplio, 1H), 5.29 (s, amplio, 1H), 4.40-4.69 (m, 3H), 1.80-1.88 (m, 1H), 1.29 (s, 9H), 1.25-1.33 (m, 2H), 0.80 (d, 3H, J=7.0Hz), 0.69 (d, 3H, J=7.0Hz).

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304

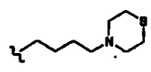
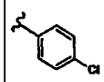
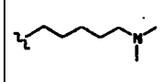
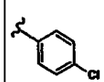
31				1	sólido blanco	430.61	1.82 Método A	431.2	RMN ^1H ($CDCl_3$) δ 7.60 (d, 2H, J=8.2Hz), 7.24-7.39 (m, 6H), 6.34 (s, amplio, 1H), 5.19 (s, amplio, 1H), 4.42-4.44 (m, 2H), 4.30 (t, 1H, J=8Hz), 2.41 (s, 3H), 1.74-1.83 (m, 1H), 1.28 (s, 9H), 1.25-1.33 (m, 1H), 0.93-1.01 (m, 1H), 0.72 (d, 3H, J=7.0Hz), 0.60 (d, 3H, J=7.0Hz).
32				3	aceite café	460.04	1.15 Método A	460.2	RMN ^1H (d_6DMSO) δ 7.83 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.42 (s, amplio, 1H) 7.00 (s, 1H), 4.22-4.26 (m, 1H), 3.55 (s, amplio, 4H), 3.11-3.32 (m, 2H), 2.13-2.37 (m, 6H), 1.12-1.51 (m, 9H), 0.86 (m, 6H).

305

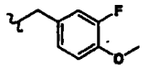
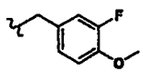
33				1	sólido blanco	400.97	1.85 Método A	401	RMN ^1H (d_6DMSO) δ 7.85 (d, 2H, J=8.0Hz), 7.65 (d, 2H, J=8.0Hz), 7.32 (s, amplio, 1H), 7.05 (s, amplio, 1H), 4.19 (t, 1H, J=7.5Hz), 2.99-3.02 (m, 1H), 1.07-1.65 (m, 14H), 0.78-0.84 (m, 7H).
34				3	aceite claro	476.1	1.28 Método A	476.1	RMN ^1H ($CDCl_3$) δ 7.76 (d, 2H, J=8.0Hz), 7.51 (d, 2H, J=8.0Hz), 6.55 (s, amplio, 1H), 5.41 (s, 1H), 4.17-4.20 (m, 1H), 3.26-3.38 (m, 1H), 3.13-3.17 (m, 1H), 2.62-2.92 (m, 8H), 2.32-2.36 (m, 2H), 1.85-1.87 (m, 1H), 1.25-1.47 (m, 7H), 0.96-0.99 (m, 1H), 0.75 (d, 3H, J=6.6Hz), 0.72 (d, 2H, J=6.6Hz).

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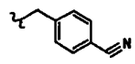
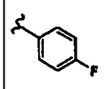
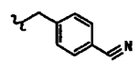
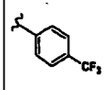
306

35				3	aceite claro	462.08	1.31 Método A	462.2	RMN ^1H ($CDCl_3$) δ 7.75 (d, 2H, J=8.0Hz), 7.52 (d, 2H, J=8.0Hz), 6.51 (s, amplio, 1H), 6.05 (s, 1H), 4.15-4.18 (m, 1H), 3.56-3.78 (m, 4H), 3.45-3.47 (m, 1H), 3.09-3.14 (m, 1H), 2.90-3.08 (m, 4H), 2.61-2.69 (m, 2H), 1.62-2.05 (m, 5H), 1.21-1.29 (m, 1H), 0.80-0.83 (m, 1H), 0.78 (d, 3H, J=6.6Hz), 0.71 (d, 2H, J=6.6Hz).
36				3	aceite claro	418.0	1.25 Método A	418.2	RMN ^1H ($CDCl_3$) δ 7.77 (d, 2H, J=8.5Hz), 7.51 (d, 2H, J=8.5Hz), 6.56 (s, amplio, 1H), 5.41 (s, 1H), 4.18-4.21 (m, 1H), 3.15-3.32 (m, 2H), 2.25-2.28 (m, 2H), 2.24 (s, 6H), 1.84-1.88 (m, 1H), 1.25-1.49 (m, 7H), 0.97-1.00 (m, 1H), 0.71-0.74 (m, 6H).

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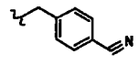
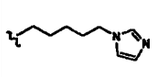
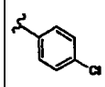
37				1	sólido color canela	428.91	1.5 Método A	429.1	RMN ^1H ($CDCl_3$) δ 7.57 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=9.0Hz), 7.03-7.13 (m, 2H), 6.80 (t, 1H, J=8.8Hz), 6.17 (s, amplio, 1H), 5.39 (s, amplio, 1H), 4.48 (dd, 2H, J=55Hz, 16Hz), 3.84 (s, 3H), 3.75-3.84 (m, 1H), 1.11-1.30 (m, 1H), 0.91 (d, 3H, J=7.0Hz), 0.54 (d, 3H, J=7.0Hz).
38				1	sólido blanco	412.46	1.46 Método A	413.2	RMN ^1H ($CDCl_3$) δ 7.65-7.70 (m, 2H), 7.04-7.12 (m, 4H), 6.79 (t, 1H, J=8.5Hz), 6.21 (s, amplio, 1H), 5.27 (s, amplio, 1H), 4.48 (dd, 2H, J=50Hz, 15Hz), 3.86 (s, 3H), 3.79-3.85 (m, 1H), 2.16-2.22 (m, 1H), 0.90 (d, 3H, J=7.0Hz), 0.51 (d, 3H, J=7.0Hz).

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39				1	sólido blanco	403.48	1.47 Método A	404.2	RMN ^1H ($CDCl_3$) δ 7.77-7.80 (m, 2H), 7.59 (d, 2H, J=8.0Hz), 7.49 (d, 2H, J=8.0Hz), 7.17-7.22 (m, 2H), 6.17 (s, amplio, 1H), 5.20 (s, amplio, 1H), 4.50 (dd, 2H, J=60Hz, 17Hz), 4.28 (t, 1H, J=10Hz), 1.74-1.83 (m, 1H), 1.25-1.33 (m, 1H), 0.99-1.10 (m, 1H), 0.77 (d, 3H, J=7.0Hz), 0.66 (d, 3H, J=7.0Hz).
40				1	sólido blanco	453.49	1.65 Método A	454.1	RMN ^1H ($CDCl_3$) δ 7.88 (d, 2H, J=8.2Hz), 7.78 (d, 2H, J=8.5Hz), 7.59 (d, 2H, J=8.5Hz), 7.49 (d, 2H, J=8.5Hz), 6.10 (s, amplio, 1H), 5.19 (s, amplio, 1H), 4.59 (dd, 2H, J=50Hz, 16Hz), 4.33 (t, 1H, J=10Hz), 1.76-1.81 (m, 1H), 1.25-1.35 (m, 1H), 1.02-1.07 (m, 1H), 0.78 (d, 3H, J=7.0Hz), 0.65 (d, 3H, J=7.0Hz).

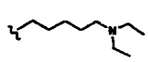
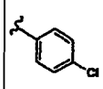
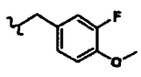
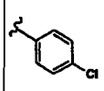
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41				1	sólido blanco	399.52	1.53 Método A	400.2	RMN ^1H ($CDCl_3$) δ 7.65 (d, 2H, J=8.0Hz), 7.58 (d, 2H, J=8.2Hz), 7.47 (d, 2H, J=8.0Hz), 7.31 (d, 2H, J=8.5Hz), 6.24 (s, amplio, 1H), 5.16 (2, amplio, 1H), 4.50 (dd, 2H, J=50Hz, 17Hz), 4.27 (t, 1H, J=10Hz), 2.44 (s, 3H), 1.74-1.83 (m, 1H), 1.25-1.33 (m, 1H), 0.93-1.01 (m, 1H), 0.74 (d, 3H, J=7.0Hz), 0.63 (d, 3H, J=7.0Hz).
42				3	aceite claro	441.0	1.27 Método A	441.2	RMN ^1H ($CDCl_3$) δ 7.74 (d, 2H, J=8.2Hz), 7.67 (s, 1H), 7.50 (d, 2H, J=8.2Hz), 7.10 (s, 1H)).6.93 (s, 1H), 6.51 (s, amplio, 1H) 5.55 (s, amplio, 1H), 4.14-4.17 (m, 1H), 3.97 (t, 2H, J=6.0Hz), 3.29-3.35 (m, 1H), 3.09-3.14 (m, 1H), 1.62-1.66 (m, 3H),

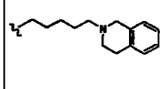
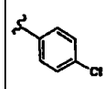
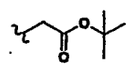
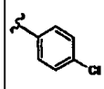
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									1.55-1.62 (m, 2H), 1.25-1.29 (m, 3H), 0.80-0.83 (m, 1H), 0.74 (d, 3H, J=6.6Hz), 0.71 (d, 2H, J=6.6Hz).
43				3	aceite claro	446.06	1.29 Método A	446.3	RMN ^1H ($CDCl_3$) δ 7.76 (d, 2H, J=8.0Hz), 7.52 (d, 2H, J=8.0Hz), 6.61 (s, amplio, 1H) 5.45 (s, 1H), 4.15-4.18 (m, 1H), 3.09-3.24 (m, 2H), 2.50-2.58 (m, 4H), 2.31-2.39 (m, 2H), 1.92-1.99 (m, 1H), 1.15-1.59 (m, 8H), 1.00-1.04 (m, 7H), 0.71-0.74 (m, 6H).
44				1	cera color canela	428.91	1.58 Método A	429.1	RMN ^1H ($CDCl_3$) δ 7.67 (d, 2H, J=8.0Hz), 7.45 (d, 2H, J=9.0Hz), 7.03-7.15 (m, 2H), 6.84 (t, 1H, J=8.0Hz), 6.25 (s, amplio, 1H), 5.19 (s, amplio, 1H), 4.45 (dd, 2H, J=80Hz, 18Hz), 4.19-4.22 (m, 1H), 3.87 (s, 3H), 1.82-

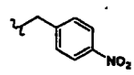
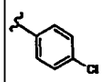
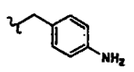
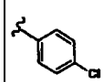
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									1.95 (m, 1H), 0.96-1.30 (m, 3H), 0.72-0.77 (m, 3H).
45				3	aceite claro	506.11	1.39 Método A	506.2	RMN ^{1}H ($CDCl_3$) δ 7.75 (d, 2H, J=8.0Hz), 7.50 (d, 2H, J=8.5Hz), 7.01-7.13 (m, 4H), 6.55 (s, amplio, 1H), 5.39 (s, amplio, 1H), 4.18 (t, 1H, J=6.0Hz), 3.32-3.60 (m, 1H), 3.16-19 (m, 1H), 2.91 (s, amplio, 2H), 2.76 (s, amplio, 2H), 2.52 (s, amplio, 2H), 1.27-1.86 (m, 8H), 0.97-1.00 (m, 1H), 0.73 (m, 6H).
46				1	sólido blanco	418.94	2.7 Método A	441 (M+Na$^+$)	RMN ^{1}H (d_6DMSO) δ 7.89 (d, 2H, J=8.2Hz), 7.65 (d, 2H, J=8.4Hz), 7.52 (s, amplio, 1H) 7.00 (s, amplio, 1H), 4.25 (dd, 2H, J=80Hz, 18Hz), 4.10-4.13 (m, 1H), 2.59-2.60 (m, 1H), 1.35 (s, 9H), 1.32-1.35 (m, 2H), 0.860 (d,

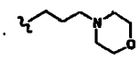
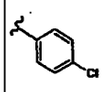
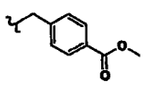
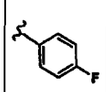
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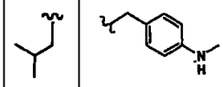
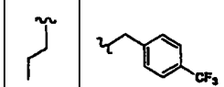
									3H, J=6.0Hz), 0.75 (d, 3H, J=6.0Hz).
47				1	sólido amarillo	439.92	1.69 Método A	440.2	RMN ^1H ($CDCl_3$) δ 8.17 (d, 2H, J=7.0Hz), 7.72 (d, 2H, J=7.0Hz), 7.54 (d, 1H, J=8.8Hz), 7.49 (d, 1H, J=8.8Hz), 6.14 (s, amplio, 1H), 5.18 (s, amplio, 1H), 4.60 (dd, 2H, J=70Hz, 18Hz), 4.29-4.34 (m, 1H), 1.74-1.83 (m, 1H), 1.00-1.34 (m, 2H), 0.78 (d, 3H, J=7.0Hz), 0.67 (d, 3H, J=7.0Hz).
48				4	sólido color canela	409.94	1.26 Método A	410.1	RMN ^1H ($CDCl_3$) δ 7.80 (d, 2H, J=8.5Hz), 7.63 (d, 2H, J=8.5Hz), 7.52 (s, amplio, 1H), 7.46 (d, 1H, J=8.0Hz), 7.26 (d, 1H, J=8.0Hz), 7.02 (s, amplio, 1H), 4.70 (dd, 2H, J=50Hz, 18Hz), 4.30-4.41 (m, 1H), 3.67 (s, amplio, 2H), 1.28-1.33 (m, 3H), 0.86 (d, 3H,

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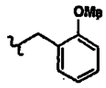
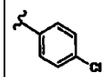
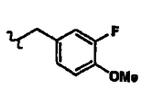
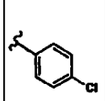
									J=7.0Hz), 0.57 (d, 3H, J=7.0Hz).
49				3	espuma color canela	431.99	1.19 Método A	432	RMN ^{1}H (d_6DMSO) δ 7.81 (d, 2H, J=8.0Hz), 7.66 (d, 2H, J=8.0Hz), 7.45 (s, amplio, 1H) 7.02 (s, 1H), 4.27 (m, 1H), 3.56 (s, amplio, 4H), 3.55-3.57 (m, 1H), 3.08-3.14 (m, 1H), 2.22-2.32 (m, 6H), 1.79-1.82 (m, 1H), 1.17-1.62 (m, 4H), 0. 86 (d, 6H, J=6.0Hz).
50				1	sólido blanco	436.51	1.58 Método A	437.1	RMN ^{1}H ($CDCl_3$) δ 7.95 (d, 2H, J=8.0Hz), 7.74-7.79 (m, 2H), 7.42 (d, 2H, J=8.0H), 7.14-7.19 (m, 2H), 6.24 (s, amplio, 1H), 5.20 (s, amplio, 1H), 4.50 (dd, 2H, J=50Hz, 17Hz), 4.12 (m, 1H), 3.91 (s, 3H), 1.75-1.82 (m, 1H), 1.25-1.31 (m, 1H), 1.05-1.12 (m, 1H), 0.75 (d, 3H, J=7.0Hz), 0.64 (d, 3H, J=7.0Hz).

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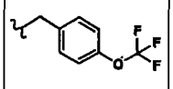
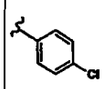
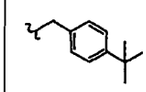
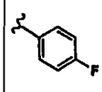
51				4	sólido color canela	423.97	1.21 Método A	424.1	RMN ^1H ($CDCl_3$) δ 7.65 (d, 2H, J=8.0Hz), 7.58 (d, 2H, J=8.2Hz), 7.47 (d, 2H, J=8.0Hz), 7.31 (d, 2H, J=8.5Hz), 6.24 (s, amplio, 1H), 5.16 (s, amplio, 1H), 4.50 (dd, 2H, J=50Hz, 17Hz), 4.27 (t, 1H, J=10Hz), 2.44 (s, 3H), 1.74-1.83 (m, 1H), 1.25-1.33 (m, 1H), 0.93-1.01 (m, 1H), 0.74 (d, 3H, J=7.0Hz), 0.63 (d, 3H, J=7.0Hz).
52				1	sólido blanco	448.90	1.79 Método A	449.0	RMN ^1H ($CDCl_3$) δ 7.66 (d, 2H, J=8.5Hz), 7.43 (d, 2H, J=8.5Hz), 7.12 (d, 1H, J=8.0Hz), 6.49 (d, 1H, J=8.0Hz), 6.24 (s, amplio, 1H), 5.22 (s, amplio, 1H), 4.35 (dd, 2H, J=50Hz, 15Hz), 4.22-4.27 (m, 1H), 2.04 (s, 3H), 1.27-1.89 (m, 3H), 0.74 (d, 3H,

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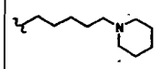
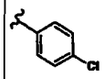
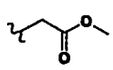
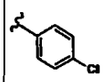
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									J=7.0Hz), 0.68 (d, 3H, J=7.0Hz).
53				1-Método A	sólido blanco	424.95	1.58 Método A	425.2	RMN ^{1}H (DMSO-d_6, 500MHz) δ 7.82 (d, 2H, J=8.2), 7.62 (d, 2H, J=8.3), 7.44 (d, 2H, J=7.1), 7.21 (t, 1H, J=6.7), 6.97 (s, 1H), 6.92 (d, 2H, J=6.9) 4 99 (d, 1H, J=17), 4.40 (d, 1H, J=17), 4.33 (s amplio, 1H), 3.76 (s, 3H), 1.20-1.40 (m, 3H), 0.79 (d, 3H, 5.2), 0.54 (d, 3H, J=5.2).
54				1-Método A	sólido blanco	400.86	1.81 min Método B	398.94 (M-H$^+$)	RMN ^{1}H ($CDCl_3$) δ 7.71 (d, 2H, J=6.8Hz), 7.48 (d, 2H, J=6.8Hz), 7.15 (d, 2H, J=10Hz), 7.02 (d, 2H, J=8.0Hz), 6.85 (t, 1H, J=7.5Hz), 6.19 (s, amplio, 1H), 5.13 (s, amplio, 1H), 4.31 (dd, 2H, J=50Hz, 15Hz), 4.43-4.45 (m, 1H), 3.87 (s, 3H), 1.17 (d, 3H, J=6.8Hz).

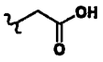
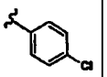
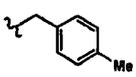
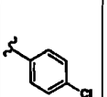
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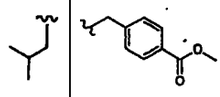
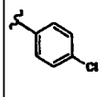
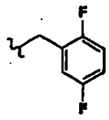
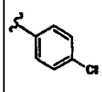
55				1-Método A	sólido blanco	478.92	1.76 Método A	479.1	RMN ^1H (DMSO-d_6, 500MHz) δ 7.81 (d, 2H, J=8.5), 7.60 (d, 2H, J=8.2), 7.54, (s, 1H), 7.51 (d, 2H, J=8.5), 7.30 (d, 2H, J=8.2), 7.04 (s, 1H), 4.83 (d, 1H, J=17), 4.71 (d, 1H, J=17), 1.20-1.35 (m, 3H), 0.80 (d, 3H, J=6.1), 0.47 (d, 3H, J=6.2).
56				1-Método A	sólido blanco	434.58	1.95 min Método A	435.24	RMN ^1H ($CDCl_3$, 300MHz) δ 7.67 (dd, 2H, J=5.0, 8.9), 7.20-7.30 (m, 4H), 7.09 (dd, 2H, J=8.6, 8.6), 6.28 (s amplio, 1H), 5.24 (s amplio, 1H), 4.44 (s, 2H), 4.34 (t, 1H, J=7.8), 1.75-1.90 (m, 1H), 1.22-1.38 (m, 2H), 1.30 (s, 9H), 0.77 (d, 3H, J=6.4), 0.67 (d, 3H, J=6.4).

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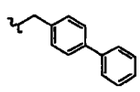
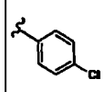
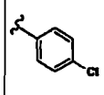
57				3	aceite café	458.07	2.16 Método C	458.2	RMN ^1H ($CDCl_3$, 500MHz) δ 7.77 (dd, 2H, J=1.6, 6.8), 7.53 (dd, 2H, J=2.0, 6.7), 6.55 (s, 1H), 5.64 (s, 1H), 4.15 (dd, 1H, J=5.6, 9.2), 3.57 (t, 2H, J=12), 3.35-3.45 (m, 1H), 3.10-3.17 (m, 1H), 2.87-3.00 (m, 2H), 2.57-2.70 (m, 2H), 2.27-2.40 (m, 2H), 1.80-2.00 (m, 6H), 1.63-1.73 (m, 2H), 1.20-1.50 (m, 4H), 0.85-0.90 (m, 1H), 0.73 (d, 3H, J=6.4), 0.70 (d, 3H, J=6.9).
58				5	aceite incoloro	390.89	1.51 Método A	391.2	RMN ^1H ($CDCl_3$, 500MHz) δ 7.91 (dd, 2H, J=2.0, 6.8), 7.51 (dd, 2H, J=2.2, 6.9), 7.06 (s, 1H), 5.33 (s, 1H), 4.13-4.25 (m, 2H), 4.03-4.15 (m, 3H), 1.77-1.85 (m, 1H), 1.35-1.45 (m, 1H), 1.30 (t, 3H, J=7.1),

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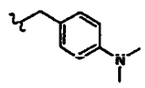
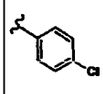
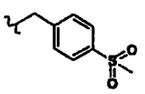
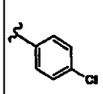
									1.15-1.22 (m, 1H), 0.74 (d, 3H, J=6.6), 0.71 (d, 3H, J=6.5).
59				5	sólido blanco	362.83	1.28 Método A	363.1	RMN ^{1}H (DMSO-d_6, 500MHz) δ 7.90 (dd, 2H, J=2.0, 6.8), 7.65 (dd, 2H, J=2.0, 6.8), 7.60 (s, 1H), 7.06 (s, 1H), 4.32 (d, 1H, J=18), 4.12 (t, 1H, J=8.0), 4.02 (d, 1H, J=18), 1.55-1.65 (m, 1H), 1.35-1.45 (m, 2H), 0.78 (d, 3H, J=6.1), 0.73 (d, 3H, J=6.1).
60				1-soporte sólido	sólido blanco	408.95	1.82 min Método B	409.1	RMN ^{1}H ($CDCl_3$) δ 7.64 (d, 2H, J=8.0Hz), 7.44 (d, 2H, J=8.0Hz), 7.22 (d, 2H, J=8.0Hz), 7.08 (d, 2H, J=8.0Hz), 6.29 (s, amplio, 1H), 5.34 (s, amplio, 1H), 4.53 (d, 1H, J=15.20Hz), 4.34, (d, 1H, J=15.20Hz), 4.27 (t, 1H, J=7.2Hz), 2.32 (s, 3H), 1.84 (m, 1H), 1.30 (m,

									1H), 1.21 (m, 1H), 0.75 (d, 3H, J=6.8Hz), 0.67 (d, 3H, J=6.8Hz).
61				1-Método A	sólido blanco	452.96	1.85 min Método A	453.08	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.97 (dd, 2H, J=1.7, 8.4), 7.68 (dd, 2H, J=2.0, 8.7), 7.41-7.48 (m, 4H), 6.23 (s amplio, 1H), 5.16 (s amplio, 1H), 4.64 (d, 1H, J=15.8), 4.47 (d, 1H, J=15.9), 4.31 (t, l H, J=7.8), 3.92 (s, 3H), 1:76-1.83 (m, 1H), 1.26-1.35 (m, 1H), 1.08-1.13 (m, 1H), 0.76 (d, 3H, J=6.0), 0.65 (d, 3H, J=6.7).
62				1-soporte sólido	sólido blanco	430.95	1.81 min Método B	431.06	RMN ^{1}H ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.49 (d, 2H, J=8.0Hz), 7.24 (m, 1H), 6.95 (m, 2H), 6.25 (s, amplio, 1H), 5.27 (s, amplio, 1H), 4.62 (d, 1H, J=16.0Hz), 4.45 (d, 1H, J=16.0Hz), 4.33 (t, 1H, J=6.8Hz), 1.84 (m, 1H),

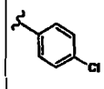
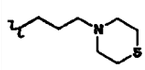
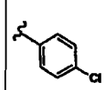
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									1.30 (m, 1H), 1.21 (m, 1H), 0.78 (d, 3H, J=6.8Hz), 0.70 (d, 3H, J=6.8Hz).
63				1-soporte sólido	sólido amarillo pálido	471.02	2.04 min Método B	471.09	RMN ^1H ($CDCl_3$) δ 7.65 (d, 2H, J=8.0Hz), 7.58 (d, 2H, J=8.0Hz), 7.47 (d, 2H, J=8.0Hz), 7.37-7.44 (m, 6H), 627 (s, amplio, 1H), 5.33 (s, amplio, 1H), 4.58 (d, 1H, J=15.2Hz), 4.45 (d, 1H, J=15.2Hz), 4.36 (t, 1H, J=7.2Hz), 1.84 (m, 1H), 1.30 (m, 1H), 1.21 (m, 1H), 0.78 (d, 3H, J=6.8Hz), 0.70 (d, 3H, J=6.8Hz).
64				1-soporte sólido	sólido rosa pálido	372.92	1.82 min Método B	395.11 M+Na	RMN ^1H ($CDCl_3$) δ 7.65 (d, 2H, J=8.0Hz), 7.50 (d, 2H, J=8.0Hz), 6.75 (s, amplio, 1H), 6.70 (s, amplio, 1H), 5.04 (m, 1H), 4.32 (t, 1H, J=7.2Hz), 3.91 (d amplio, 2H, J=7.0Hz), 1.81 (m, 1H), 1.66 (s

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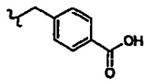
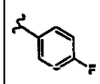
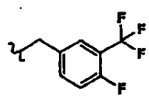
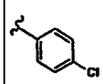
									amplio, 6H), 1.30 (m, 1H), 1.21 1.66 (s amplio, 6H), 1.30 (m, 1H), 1.21 (m, 1H), 0.77 (d, 3H, J=6.5Hz), 0.76 (d, 3H, J=6.5Hz).
65				4	sólido blanco	437.99	1.39 Método A	438.1	RMN ^{1}H (DMSO-d_6, 500MHz) δ 7.74 (dd, 2H, J=1.9, 6.7), 7.5 (dd, 2H, J=1.9, 6.8), 7.43 (s, 1H), 7.16 (d, 2H, J=8.6), 7.01 (s, 1H), 6.61 (d, 2H, J=8.8), 4.59 (q, 2H, J=16, 25), 4.34 (dd, 1H, J=5.0, 9.3), 2.85 (s, 6H), 1.27-1.47 (m, 3H), 0.80 (d, 3H, J=5.9), 0.52 (d, 3H, J=6.1).
66				1-Método A	sólido blanco	473.01	1.58 Método A	437.0	RMN ^{1}H (DMSO-d_6, 500MHz) δ 7.87 (d, 2H, J=8.2), 7.83 (d, 2H, J=8.3), 7.64 (d, 2H, J=8.5), 7.63 (d, 2H, J=8.5), 7.59 (s, 1H), 7.08 (s, 1H), 4.92 (d, 1H, J=17), 4.76 (d, 1H,

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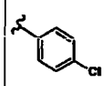
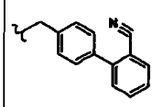
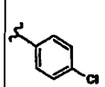
									J=17), 4.39 (t, 1H, J=6.9), 3.35 (s amplio, 1H), 1.20-1.40 (m, 3H), 0.81 (d, 3H, J=6.2), 0.54 (d, 3H, J=6.2).
67				1-Método A	aceite incoloro	346.88	1.79 Método A	374.1	RMN ^{1}H (DMSO-d_6, 500MHz) δ 7.83 (d, 2H, J=8.8), 7.63 (d, 2H, J=8.6), 7.41 (s, 1H), 7.0 (s, 1H), 4.25 (dd, 1H, J=4.8, 8.9), 3.38-3.47 (m, 1H), 3.0-3.13 (m, 1H), 1.55-1.70 (m, 1H), 1.40-1.55 (m, 1H), 1.30-1.40 (m, 1H), 0.87 (t, 3H, J=7.6), 0.73 (d, 3H, J=6.4), 0.72 (d, 3H, J=6.7).
68				3	aceite blanco	448.05	1.25 min Método C	448.19	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.76 (dd, 2H, J=2.0, 6.7), 7.50 (dd, 2H, J=2.0, 6.7), 6.51 (s, 1H), 5.45 (s, 1H), 4.20 (dd, 1H, J=6.4, 8.2), 3.35-3.45 (m, 1H), 3.20-3.30 (m, 1H), 2.68 (s amplio, 8H), 2.35 (s amplio,

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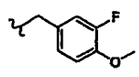
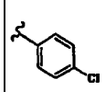
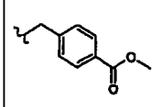
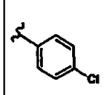
									2H), 1.70-1.90 (m, 3H), 1.20-1.40 (m, 1H), 0.95-1.05 (m, 1H), 0.75 (d, 3H, J=4.3), 0.73 (d, 3H, J=4.4).
69				6	sólido blanco	422.48	1.56 min Método A	423.14	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.89-7.93 (m, 4H), 7.84 (s amplio, 1H), 7.49 (d, 2H, J=8.2), 7.24-7.29 (m, 2H), 6.58 (s amplio, 1H), 5.12 (d, 1H, J=15.3), 4.23 (dd, 1H, J=4.6, 9.7), 4.05 (d, 1H, J=15.4), 2.04-2.14 (m, 1H), 1.23-1.32 (m, 1H), 0.79-0.88 (m, 1H), 0.72 (d, 3H, J=6.6), 0.67 (d, 3H, J=6.6).
70				1-Método A	sólido blanco	466.89	1.77 min Método B	467.03	RMN ^{1}H ($CDCl_3$) δ 7.65 (d, 2H, J=6.8Hz), 7.52-7.56 (m, 2H), 7.47 (d, 2H, J=6.8Hz), 7.11 (t, 1H, J=8.5Hz), 6.22 (s, amplio, 1H), 5.24 (s, amplio, 1H), 4.41 (dd, 2H,

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									J=50Hz, 15Hz), 4.28 (t, 1H, 7.5Hz), 1.80-1.92 (m, 1H), 1.21-1.30 (m, 1H), 0.95-1.19 (m, 2H), 0.76 (t, 3H, J=7.0Hz).
71				1-Método A	cera blanca	398.89	1.80 min Método B	388.0	RMN ^{1}H ($CDCl_3$) δ 7.67 (d, 2H, J=8.0Hz), 7.54 (d, 2H, J=8.0Hz), 7.42-7.49 (m, 4H), 6.20 (s, amplio, 1H), 5.21 (s, amplio, 1H), 4.54 (dd, 2H, J=50Hz, 15Hz), 4.25-4.29 (m, 1H), 1.82-1.95 (m, 1H), 1.26-1.33 (m, 1H), 0.98-1.12 (m, 2H), 0.75 (t, 3H, J=7.0Hz).
72				1-Método A	sólido blanco	482.01	1.79 min Método B	482.06	RMN ^{1}H ($CDCl_3$) δ 7.76 (d, 1H, J=7.5Hz), 7.63-7.67 (m, 4H), 7.43-7.50 (m, 8H), 6.24 (s, amplio, 1H), 5.28 (s, amplio, 1H), 4.53 (dd, 2H, J=50Hz, 15Hz), 4.27 (t, 1H, J=7.3Hz), 1.87-1.99

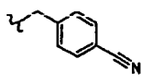
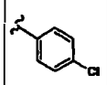
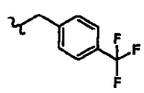
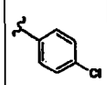
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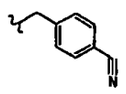
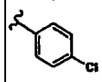
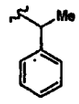
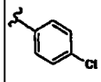
									(m, 1H), 1.30-1.39 (m, 1H), 1.03-1.11 (m, 2H), 0.76 (t, 3H, J=8.0Hz).
73				1-Método A	sólido amarillo pálido	426.90	1.86 min Método A	427.09	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.69 (ddd, 2H, J=2.0, 2.7, 8.7), 7.47 (dd, 2H, J=2.0, 8.7), 7.15 (dd, 1H, J=2.1, 12.0), 7.03 (d, 1H, J=8.4), 6.84 (t, 1H, J=8.5), 6.30 (s amplio, 1H), 5.25-5.30 (m, 2H), 4.96 (d, 1H, J=1.4), 4.87 (td, 1H, J=1.4, 9.9), 4.57 (d, 1H, J=15.4), 4.23-4.32 (m, 2H), 3.87 (s, 3H), 2.60-2.67 (m, 1H), 2.15-2.24 (m, 1H).
74				1-Método A	aceite incoloro	436.92	1.88 min Método A	437.09	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.97 (dd, 2H, J=1.7, 8.3), 7.71 (dd, 2H, J=2.0, 8.7), 7.43-7.50 (m, 4H), 6.26 (s amplio, 1H), 5.22-5.35 (m, 1H), 5.18 (s amplio, 1H), 4.84-4.96 (m,

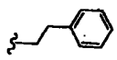
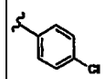
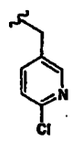
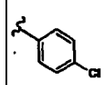
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									2H), 4.69 (d, 1H, J=5.8), 4.41 (d, 1H, J=15.8), 4.31 (t, 1H, J=7.5), 3.91 (s, 3H), 2.60-2.67 (m, 1H), 2.11-2.24 (m, 1H).
75				1-Método A	sólido blanco	403.89	1.63 min Método A	404.03	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.71 (ddd, 2H, J=2.0, 2.6, 8.7), 7.60 (dd, 2H, J=1.9, 8.3), 7.49-7.52 (m, 4H), 6.21 (s amplio, 1H), 5.22-5.33 (m, 1H), 5.17 (s amplio, 1H), 4.88-4.98 (m, 2H), 4.71 (d, 1H, J=16.2), 4.40 (d, 1H, J=16.1), 4.32 (t, 1H, J=7.6), 2.54-2.63 (m, 1H), 2.09-2.19 (m, 1H).
76				1-Método A	sólido blanco	446.88	2.04 min Método A	447.05	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.67 (d, 2H, J=8.6), 7.45-7.56 (m, 6H), 6.24 (s amplio, 1H), 5.25-5.39 (m, 1H), 5.19 (s amplio, 1H), 4.88-4.98 (m, 2H), 4.68 (d, 1H, J=15.8), 4.42 (d, 1H,

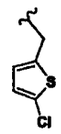
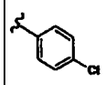
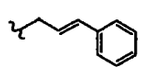
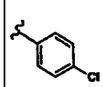
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									J=15.81), 4.34 (t, 1H, J=7.5), 2.58-2.68 (m, 1H), 2.13-2.23 (m, 1H).
77				1-Método A	sólido blanco	405.91	1.51 min Método B	406.2	RMN ^1H ($CDCl_3$) δ 7.70 (d, 2H, J=8.0Hz) 7.68 (d, 2H, J=8.0Hz), 7.47-7.51 (m, 4H), 6.15 (s, amplio, 1H), 5.16 (s, amplio, 1H), 4.53 (dd, 2H, J=50Hz, 15Hz), 4.21-4.26 (m, 1H), 1.82-1.87 (m, 1H), 1.20-1.25 (m, 1H), 0.97-1.09 (m, 2H), 0.74 (t, 3H, J=7.0Hz).
78				1-soporte sólido	espuma blanca	408.95	1.84 min Método B	431.04 M+Na	RMN ^1H ($CDCl_3$) δ 7.83 (d, 2H, J=8.0Hz), 7.52 (d, 2H, J=8.0Hz), 7.34-7.45 (m, 5H), 5.85 (s, amplio, 2H), 5.17 (q, 1H, 7.2Hz), 3.78 (dd 1H, J=8.4Hz, 4Hz), 2.36 (m, 1H), 1.62 (m, 1H), 1.50 (d, 3H, J=7.2Hz), 1.23 (m, 1H), 0.91 (d, 3H, J=6.6Hz),

									0.84 (d, 3H, J=6.6Hz).
79				1-soporte sólido	jarabe incoloro	408.95	1.89 Método B	431.04 M+Na	RMN ^1H ($CDCl_3$) δ 7.77 (d, 2H, J=8.0Hz), 7.50 (d, 2H, J=8.0Hz), 7.17-7.32 (m, 5H), 6.67 (s, amplio, 1H), 6.15 (s, amplio, 1H), 5.17 (q, 1H, 7.2Hz), 4.26 (dd 1H, J=6.6Hz), 3.48 (m, 1H), 3.37 (m, 1H), 2.97 (m, 1H), 2.90 (m, 1H), 1.92 (m, 1H), 1.33 (m, 1H), 1.10 (m, 1H), 0.76 (d, 3H, J=6.6Hz), 0.75 (d, 3H, J=6.6Hz).
80				1-soporte sólido	sólido amarillo	430.36	1.64 min Método B	430.02	RMN ^1H ($CDCl_3$) δ 8.34 (s, 1H), 7.67 (d, 1H, J=6.8Hz), 7.48 (d, 1H, 6.8Hz), 7.25 (d, 1H, J=6.8Hz), 6.1 (s ampio, 1H), 5.29 (s amplio, 1H), 4.59 (d, 1H, J=16Hz), 4.39 (d, 1H, J=16Hz), 1.8 (m, 1H), 1.32 (m, 1H), 1.06 (m, 1H), 0.78 (d, 3H, J=64.Hz),

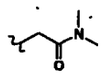
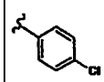
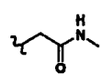
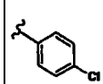
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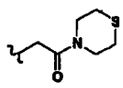
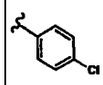
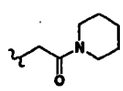
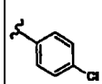
									0.68 (d, 3H, J=6.4Hz).
81				1-soporte sólido	sólido blanco	435.39	1.87 Método B	456.92 M+Na	RMN ^{1}H ($CDCl_3$) δ 7.64 (d, 2H, J=8.0Hz), 7.50 (d, 2H, J=8.0Hz), 6.79 (d, 1H, J=3.7Hz), 6.72 (d, 1H, J=3.7Hz), 4.60 (d, 1H, J=21.9), 4.56 (d, 1H, J=21.9Hz), 4.28 (t, 1H, J=7.4Hz), 1.86 (m, 1H), 1.33 (m, 1H), 1.25 (m, 1H), 0.76 (d, 3H, J=6.5Hz), 0.73 (d, 3H, J=6.5Hz).
82				1-Método A	sólido blanco	420.96	1.97 Método A	421.2	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.77 (d, 2H, J=8.6), 7.45 (d, 2H, J=9.10), 7.26-7.35 (m, 5H), 6.54 (d, 1H, J=16), 6.38 (s amplio, 1H), 6.00-6.07 (m, 1H), 5.34 (s amplio, 1H), 4.36 (t, 1H, J=7.2), 4.02-4.15 (m, 2H), 1.83-1.92 (m, 1H), 1.35-1.43 (m, 1H), 1.25-1.32 (m, 1H), 0.79 (d,

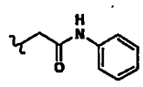
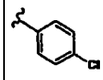
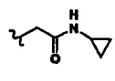
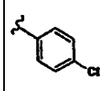
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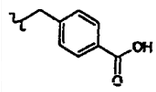
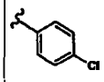
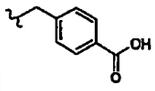
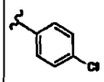
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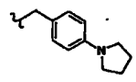
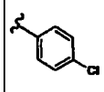
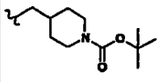
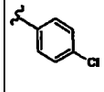
									3H, J=6.7), 0.77 (d, 3H, J=6.7).
83				5	sólido blanco	389.90	1.91 Método D	390.2	RMN ^{1}H (DMSO-d_6, 500MHz) δ 8.08 (s amplio, 1H), 7.97 (d, 2H, J=8.7), 7.65 (d, 2H, J=8.5), 7.01 (s amplio, 1H), 4.46 (d, 1H, J=18), 4.22 (d, 1H, J=18), 3.91 (t, 1H, J=6.3), 3.00 (s, 3H), 2.85 (s, 3H), 1.40-1.50 (m, 2H), 1.30-1.40 (m, 1H), 0.85 (d, 3H, J=6.1), 0.64 (d, 3H, J=6.0).
84				5	sólido blanco	375.88	1.38 Método A	376.0	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.85 (dd, 2H, J=1.8, 6.8), 7.50 (dd, 2H, J=2.0, 6.8), 7.40 (s amplio, 1H), 6.37 (s amplio, 1H), 5.25 (s amplio, 1H), 4.26 (dd, 1H, J=6.2, 8.6), 3.97 (d, 1H J=17), 3.85 (d, 1H, J=17), 2.85 (d, 3H, J=4.8), 1.75-1.85 (m, 1H), 1.40-1.48 (m, 1H), 0.88 (d, 3H,

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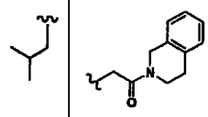
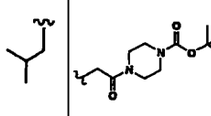
									J=6.4), 0.87 (d, 3H, J=6.6).
85				5	sólido blanco	448.01	2.18 Método C	448.1	RMN ^{1}H ($CDCl_3$, 500MHz) δ 8.10 (s amplio, 1H), 7.92 (d, 2H, J=8.5), 7.50 (d, 2H, J=8.5), 5.18 (s amplio, 1H), 4.35 (d, 1H, J=17), 4.15 (t, 1H, J=7.4), 3.97-4.05 (m, 1H), 3.95 (d, 1H, J=17), 3.70-3.89 (m, 3H), 2.55-2.85 (m, 4H), 1.85-1.91 (m, 1H), 1.55-1.85 (m, 1H), 1.30-1.40 (m, 1H), 0.85 (d, 3H, J=6.4), 0.83 (d, 3H, J=6.4).
86				5	sólido blanco	429.97	2.26 Método C	430.2	RMN ^{1}H ($CDCl_3$, 500MHz) δ 8.59 (s amplio, 1H), 7.92 (d, 2H, J=9.1), 7.47 (d, 2H, J=8.6), 5.16 (s amplio, 1H), 4.42 (d, 1H, J=17), 4.23 (dd, 1H, J=5.6, 8.6), 3.87 (d, 1H, J=17), 3. 55-3.65 (m, 1H), 3.40-3.52 (m, 3H) 1.80-2.00 (m, 1H), 1.45-1.80 (m,

									7H), 1.35-1.45 (m, 1H), 0.89 (d, 3H, J=6.7), 0.86 (d, 3H, J=6.5).
87				5	sólido blanco	437.95	2.37 Método C	438.2	RMN ^{1}H ($CDCl_3$, 500MHz) δ 8.95 (s amplio, 1H), 7.83 (d, 2H, J=8.6), 7.47 (d, 2H, J=8.1), 7.43 (d, 2H, J=8.6), 7.33 (t, 2H, J=8.1), 7.13 (t, 1H, J=7.6), 6.65 (s amplio, 1H), 5.45 (s amplio, 1H), 4.40 (dd, 1H, J=6.1, 8.6), 4.07 (d, 1H, J=17), 4.03 (d, 1H, J=17), 1.70-1.80 (m, 1H), 1.55-1.65 (m, 2H), 0.93 (d, 3H, J=7.0), 0.90 (d, 3H, 6.4).
88				5	sólido blanco	401.92	1.94 Método C	402.2	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.85 (dd, 2H, J=1.9, 8.9), 7.50 (dd, 2H, J=2.0, 8.7), 7.40 (s amplio, 1H), 6.55 (s amplio, 1H), 6.30 (s amplio, 1H), 4.23 (dd, 1H, J=2.9, 8.9), 3.92 (d, 1H, J=17), 3.83 (d, 1H, J=17), 2.68-2.73 (m, 1H), 1.75-1.83 (m, 1H), 1.50-1.57

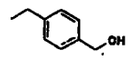
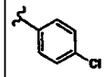
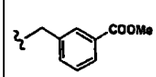
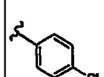
									(m, 1H), 1.40-1.49 (m, 1H), 0.88 (d, 3H, J=6.4), 0.87 (d, 3H, J=6.7), 0.80 (d, 2H, J=7.0), 0.51 (t, 2H, J=4.0).
89				6	sólido blanco	438.93	1.67 min Método A	439.17	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.91 (d, 2H, J=8.2), 7.81-7.84 (m, 3H), 7.56 (d, 2H, J=8.6), 7.49 (d, 2H, J=8.2), 6.55 (s amplio, 1H), 5.10 (d, 1H, J=15.4), 4.23 (dd, 1H, J=4.6, 9.7), 4.05 (d, 1H, J=15.4), 2.04-2.14 (m, 1H), 1.20-1.31 (m, 1H), 0.80-0.89 (m, 1H), 0.74 (d, 3H, J=6.6), 0.68 (d, 3H, J=6.6).
90				6	sólido blanco	422.89	1.41 min Método A	423.05	RMN ^{1}H (dmso-d_6, 300MHz) δ 7.86 (d, 2H, J=8.2), 7.85 (s amplio, 1H), 7.81 (d, 2H, J=8.6), 7.61 (d, 2H, J=8.6), 7.47 (d, 2H, J=8.0), 7.10 (s amplio, 1H), 5.45-5.55 (m, 1H), 4.83-4.95 (m, 3H), 4.71 (d, 1H, J=17.0), 4.47 (t, 1H, J=7.4), 2.29-

									2.37 (m, 1H), 2.13-2.22 (m, 1H).
91				2	sólido color canela	450.0	1.62 min Método B	450.2	RMN ^{1}H ($CDCl_3$) δ 7.67 (d, 2H, J=7.0Hz) 7.42 (d, 2H, J=7.0Hz), 7.17-7.26 (m, 2H), 6.49-6.58 (m, 2H), 6.18 (s, amplio, 1H), 5.11 (s, amplio, 1H), 4.33 (dd, 2H, J=50Hz, 15Hz), 4.12-4.20 (m, 1H), 3.21-3.30 (m, 4H), 1.91-2.04 (m, 5H), 1.32-1.38 (m, 1H), 0.94-1.09 (m, 2H), 0.75 (t, 3H, J=8.0Hz).
92				7	sólido blanco	502.08	1.72 Método B	502.1	RMN ^{1}H (DMSO-d_6, 500MHz) δ 7.86 (dd, 2H, J=2.0, 6.8), 7.65 (dd, 2H, J=2.0, 6.8) 7.37 (s amplio, 1H), 7.07 (s amplio, 1H), 4.19 (t, 1H, J=7.6), 3.92 (s amplio, 2H), 3.35 (dd, 1H, J=15, 6 8), 3.05 (dd, 1H, J=15, 8.1), 1.85 (s amplio, 1H), 1.50-1.70 (m, 4H), 1.38

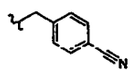
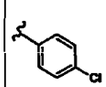
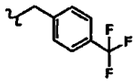
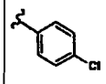
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									(s, 9H), 1.10-1.20 (m, 1H), 0.80-1.00 (m, 3H), 0.82 (d, 6H, J=7.6).
93				5	sólido blanco	478.01	1.60 Método A	478.1	RMN ^{1}H (DMSO-d_6, 500MHz) δ 8.05 (s, 1H), 7.98 (d, 2H, J=7.8), 7.65 (d, 2H, J=7.8), 7.05 (s, 1H), 4.73 (s, 1H), 4.55-4.65 (m, 2H), 4.37 (t, 1H, J=16), 3.95 (s amplio, 1H), 3.70 (s amplio, 2H), 2.90 (s amplio, 1H), 2.77 (s amplio, 1H), 1.00-1.55 (m, 4H), 0.70 (d, 6H, J=4.1).
94				5	sólido blanco	530.20	1.59 Método A	531.2	RMN ^{1}H (DMSO-d_6, 500MHz) δ 7.96 (d, 2H, J=8.7), 7.65 (d, 2H, 8.6), 7.02 (s, 1H), 4.5 (d, 1H, J=18), 4.27 (d, 2H, J=18), 3.95 (s amplio, 1H), 3.35-3.50 (m, 8H), 1.30-1.55 (m, 3H), 1.41 (s, 9H), 0.74 (d, 3H, J=6.5) 0.66 (d, 3H, J=6.0).

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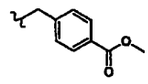
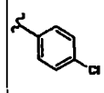
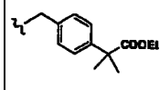
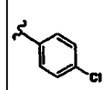
95				8	sólido blanco	424.95	1.49 min Método A	425.17	RMN ^{1}H, 500Hz, ($CDCl_3$) δ 7.68 (d, 2H, J=8.0Hz), 7.46 (d, 2H, J=8.0Hz), 7.33 (d, 2H, J=8.0Hz), 7.28 (d, 2H, J=8.0Hz), 6.26 (s, amplio, 1H), 5.35 (s, amplio, 1H), 4.67 (s, amplio, 2H), 4.56 (d, 1H, J_{ab}=16Hz), 4.36 (d, 1H, J_{ab}=16Hz), 4.26 (t, 1H, J=7.6Hz), 1.86-1.80 (m, 2H), 1.34-1.28 (m, 1H), 1:16-1.10 (m, 1H), 0.96 (d, 3H, J=7.0Hz), 0.93 (d, 3H, J=7.0Hz).
96				1-Método A	sólido blanco	452.96	1.75 min Método A	453.1	RMN ^{1}H ($CDCl_3$) δ 7.96-7.90 (m, 2H), 7.64 (A de ABq, 2H, J=8.8Hz), 7.56 (d, 1H, J=7.5Hz), 7.43 (B de ABq, 2H, J=8.8Hz), 7.37 (t, 1H, J=7.5Hz), 6.28 (amplio, 1H), 5.25 (amplio, 1H), 4.61 (A de ABq, 1H, J=15.7Hz,), 4.48 (B de ABq, 1H, J=15.7Hz), 4.36 (t, 1H,

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									J=7.3Hz), 3.91 (s, 3H), 1.86-1.76 (m, 1H), 1.39-1.30 (m, 1H), 1.23-1.13 (m, 1H), 0.78 (d, 3H, J=6.6Hz), 0.68 (d, 3H, J=6.6Hz).
97				1-Método A	sólido blanco	417.92	1.53 min Método A	418.11	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.71 (d, 2H, J=8.7), 7.60 (d, 2H, J=8.4), 7.47-7.51 (m, 4H), 6.28 (s amplio, 1H), 5.17 (s amplio, 1H), 4.73 (d, 1H, J=16.2), 4.41 (d, 1H, J=15.9), 4.32 (dd, 1H, J=1.5, 8.1), 1.65-1.82 (m, 1H), 1.14-1.30 (m, 1H), 0.27-0.40 (m, 2H), 0.12-0.22 (m, 1H), 0.18-0.05 (m, 2H).
98				1-Método A	sólido blanco	460.91	1.76 min Método A	461.05	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.67 (d, 2H, J=8.4), 7.44-7.56 (m, 6H), 6.32 (s amplio, 1H), 5.20 (s amplio, 1H), 4.70 (d, 1H, J=15.6), 4.43 (d, 1H, J=15.6), 4.35 (t, 1H, J=7.8), 1.70-

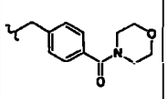
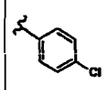
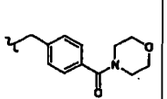
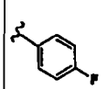
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									1.84 (m, 1H), 1.26-1.32 (m, 1H), 0.32-0.40 (m, 2H), 0.16-0.24 (m, 1H), 0:14-0.00 (m, 2H).
99				1-Método A	sólido blanco	450.94	1.63 min Método A	451.06	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.97 (d, 2H, J=8.3), 7.70 (d, 2H, J=8.7), 7.43-7.48 (m, 4H), 6.32 (s amplio, 1H), 5.15 (s amplio, 1 H), 4.70 (d, 1H, J=15.8), 4.43 (d, 1H, J=15.8), 4.35 (t, 1H, J=7.8), 3.91 (s, 3H), 1.70-1.82 (m, 1H), 1.23-1.35 (m, 1H), 0.32-0.40 (m, 2H), 0.10-0.21 (m, 1H),-0.25–0.05 (m, 2H).
100				1-Método A	sólido blanco	509.06	1.94 min Método A	509.2	RMN ^{1}H ($CDCl_3$) δ 7.58 (A de ABq, 2H, J=8.8Hz), 7.40 (B de ABq, 2H, J=8.8Hz), 7.24 (amplio, 4H), 6.20 (s amplio, 1H), 5.23 (s amplio, 1H), 4.45 (s, 2H), 4.36 (t, 1H, J=7.3Hz), 4.12 (q,

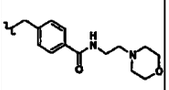
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									2H, J=7.2Hz), 1.83-1.74 (m, 1H), 1.55 (s, 3H), 1.55 (s, 3H), 1.39-1.20 (m, 2H), 1.19 (t, 3H, J=7.2Hz), 0.78 (d, 3H, J=6.6Hz), 0.66 (d, 3H, J=6.6Hz).
101				6	sólido blanco	508.04	1.48 min Método A	508.22	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.68 (d, 2H, J=8.6), 7.29-7.47 (m, 6H), 6.38 (s amplio, 1H), 5.75 (s amplio, 1H), 4.65 (d, 1H, J=16.0), 4.42 (d, 1H, J=16.0), 4.32 (t, 1H, J=7 5), 3.30-3.85 (m amplio, 8H), 1.69-1.78 (m, 1H), 1.28-1.37 (m, 1H), 1.08-1.14 (m, 1H), 0.76 (d, 3H, J=6.5), 0.63 (d, 3H, J=6.6).
102				6	sólido blanco	491.59	1.39 min Método A	492.23	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.75-7.80 (m, 2H), 7.42 (d, 2H, J=8.2), 7.33 (d, 2H, J=8.2), 7.14-7.20 (m, 2H), 6.37 (s amplio, 1H), 5.64 (s amplio, 1H), 4.64 (d, 1H, J=16.0),

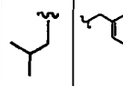
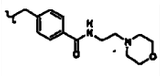
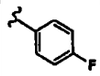
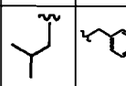
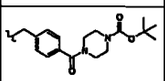
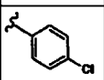
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									4.44 (d, 1H, J=16.0), 4.31 (t, 1H, J=7.1), 3.20-3.85 (m amplio, 8H), 1.70-1.78 (m, 1H), 1.28-1.35 (m, 1H), 1.05-1.14 (m, 1H), 0.76 (d, 3H, J=6.5), 0.63 (d, 3H, J=6.6).
103				6	aceite incoloro	551.11	1.32 min Método A	551.24	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.67-7.72 (m, 4H), 7.42-7.48 (m, 4H), 6.82 (s amplio, 1H), 6.25 (s amplio, 1H), 5.31 (s amplio, 1H), 4.65 (d, 1H, J=15.9), 4.43 (d, 1H, J=15.9), 4.30 (t, 1H, J =7.9), 3.70-3.79 (m, 4H), 3.53-3.59 (m, 2H), 2.53-2.65 (m, 6H), 1.79-1.86 (m, 1H), 1.29-1.38 (m, 1H), 1.08-1.14 (m, 1H), 0.76 (d, 3H, J=6.5), 0.65 (d, 3H, J=6.6).

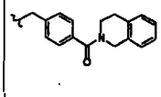
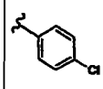
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104				6	sólido blanco	534.66	1.22 min Método A	535.28	RMN ^1H ($CDCl_3$, 300MHz) δ 7.75-7.80 (m, 2H), 7.71 (d, 2H, J=8.2), 7.43 (d, 2H, J=8.1), 7.14-7.20 (m, 2H), 6.81 (s amplio, 1H), 6.28 (s amplio, 1H), 5.31 (s amplio, 1H), 4.64 (d, 1H, J=15.9), 4.44 (d, 1H, J=15.9), 4.29 (t, 1H, J=7.6), 3.70-3.79 (m, 4H), 3.53-3.59 (m, 2H), 2.52-2.63 (m, 6H), 1.77-1.85 (m, 1H), 1.29-1.38 (m, 1H), 1.06-1.13 (m, 1H), 0.75 (d, 3H, J=6.5), 0.65 (d, 3H, J=6.6).
105				6	sólido blanco	607.17	1.70 min Método A	607.29	RMN ^1H ($CDCl_3$, 300MHz) δ 7.69 (d, 2H, J=8.6), 7.30-7.47 (m, 6H), 6.38 (s amplio, 1H), 5.75 (s amplio, 1H), 4.65 (d, 1H, J=16.0), 4.43 (d, 1H, J=16.0) 4.33 (t, 1H J=7.5) 3.30-3.85 (m amplio, 8H), 1.72-1.79 (m, 1H),

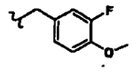
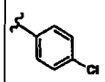
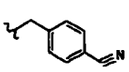
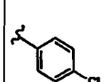
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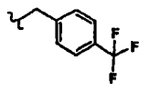
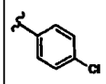
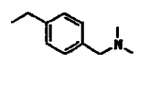
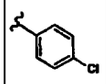
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									1.45 (s, 9H), 1.24-1.39 (m, 1H), 1.05-1.18 (m, 1H), 0.76 (d, 3H, J=6.5), 0.62 (d, 3H, J=6.6).
106				6	sólido blanco	554.11	1.75 min Método A	554.19	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.70 (ddd, 2H, J=1.9, 2.4, 8.6), 7.47 (ddd, 2H, J=2.0, 2.3, 8.7), 7.37-7.42 (m, 4H), 7.15-7.20 (m, 4H), 6.31 (s amplio, 1H), 5.60 (s amplio, 1H), 4.87 (s amplio, 1H), 4.65 (d, 1H, J=15.9), 4.52 (s amplio, 1H), 4.47 (d, 1 H, J=15.9), 4.33 (t, 1H, J=7.2), 4.05 (s amplio, 1H), 3.61 (s amplio, 1H), 2.85-3.01 (m amplio, 2H), 1.72-1.85 (m, 1H), 1.30-1.42 (m, 1H), 1.08-1.18 (m, 1H), 0.79 (d, 3H, J=6.5), 0.66 (d, 3H, J=6.6).

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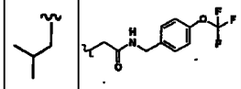
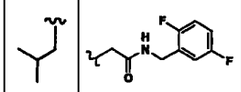
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107				1-Método A	cera clara	456.97	1.60 min Método B	455.1 (M-H⁻)	RMN ^{1}H ($CDCl_3$) δ 7.61 (d, 2H, J=8.0Hz) 7.43 (d, 2H, J=8.0Hz), 6.82-7.10 (m, 3H), 6.21 (s, amplio, 1H), 5.15 (s, amplio, 1H), 4.35 (dd, 2H, J=50Hz, 15Hz), 4.15-4.22 (m, 1H), 3.89 (s, amplio, 3H), 2.30-2.33 (m, 1H), 0.86-0.98 (m, 1H), 0.74 (s, 9H).
108				1-Método A	sólido blanco	433.96	1.58 min Método B	432.14 (M-H⁻)	RMN ^{1}H ($CDCl_3$) δ 7.67 (d, 2H, J=8.0Hz) 7.58 (d, 2H, J=8.0Hz), 7.45-7.49 (m, 4H), 6.19 (s, amplio, 1H), 5.15 (s, amplio, 1H), 4.55 (dd, 2H, J=50 Hz, 15Hz), 4.20-4.24 (m, 1H), 2.25-2.31 (m, 1H), 0.84-0.88 (m, 1H), 0.74 (s, 9H).

109				1-Método A	sólido blanco	476.95	1.62 min Método B	475.12 (M-H⁻)	RMN ^1H ($CDCl_3$) δ 7.61 (d, 2H, J=8.0Hz) 7.51 (d, 2H, J=8.0Hz), 7.40-7.44 (m, 4H), 6.20 (s, amplio, 1H), 5.21 (s, amplio, 1H), 4.51 (dd, 2H, J=50Hz, 15Hz), 4.24-4.28 (m, 1H), 2.28-2.32 (m, 1H), 0.91-0.96 (m, 1H), 0.76 (s, 9H).
110				8	sólido color canela	452.02	1.25 min Método A	452.23	RMN ^1H, 400 Hz, ($CDCl_3$) δ 7.94 (d, 2H, J=8.0Hz), 7.74 (d, 2H, J=8.0Hz), 7.63 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.27 (s, amplio, 1H), 5.40 (s, amplio, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.44 (d, 1H, J_{ab}=16Hz), 3.28-3.23 (m, 3H), 2.17 (s, amplio, 6H), 1.95 (m, 1H), 1.55 (m, 2H), 0.96 (d, 3H, J=7.0Hz), 0.93 (d, 3H, J=7.0Hz).

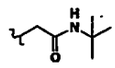
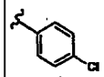
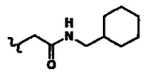
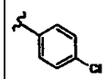
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111				5	sólido blanco	535.97	2.65 min Método C	536.04	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.80 (dd, 2H, J=2.0, 9.0), 7.45 (dd, 2H, J=2.0, 9.0), 7.32 (dd, 2H, J=1.8, 9.0), 7.24 (s amplio, 1H), 7.17 (d, 2H, J=1H 9.0), 5.50 (s amplio, 1H), 4.43 (qd, 2H, J=6.0, 15), 4.22 (t, 1H, J=7.0), 4.05 (d, 1H, J=17), 3.90 (d, 1H, J=17), 1.70-1.80 (m, 1H), 1.42-1.55 (m, 1H), 1.32-1.41 (m, 1H), 0.83 (d, 6H, J=7.9).
112				5	espuma blanca	487.93	1.52 min Método A	4.88.20	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.77 (d, 2H, J=8.3), 7.45 (d, 2H, J=9.0), 7.30 (s amplio, 1H), 7.05-7.10 (m, 1H), 6.90-7.05 (m, 2H), 5.53 (s amplio, 1H), 4.39-4.50 (m, 2H), 4.24 (t, 1H, J=7.1), 4.02 (d, 1H, J=17), 3.90 (d, 2H, J=17), 1.70-1.80 (m, 1H), 1.42-1.55 (m, 1 H), 1.35-1.42 (m, 1H),

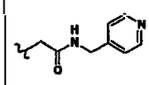
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									0.83 (d, 6H, J=7.7).
113				5	sólido oleoso, blanco	417.96	1.52 min Método A	418.23	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.92 (s amplio, 1H), 7.82 (d, 2H, J=8.2), 7.47 (d, 2H, J=8.2), 7.25 (s amplio, 1H), 6.23 (s amplio, 1H), 5.47 (s amplio, 1H), 4.25 (t, 1H, J=7.2), 3.91 (d, 1H, J=17), 3.75 (d, 1H, J=17), 1.75-1.82 (m, 1H), 1.50-1.62 (m, 1H), 1.38-1.50 (m, 1H), 1.35 (s, 9H), 0.89 (d, 3H, J=5.4), 0.87 (d, 3H, J=5.6).
114				5	sólido blanco	458.02	1.62 min Método A	458.26	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.84 (dd, 2H, J=2.0, 8.8), 7.68 (s amplio, 1H), 7.47 (dd, 2H, 2.0, 8.3), 6.62 (t amplio, 1H, J=5.3), 5.45 (s amplio, 1H), 4.25 (dd, 1H, J=2.3, 6.1), 3.98 (d, 1H, J=17),

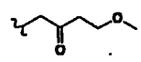
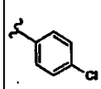
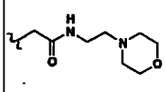
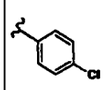
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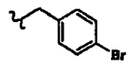
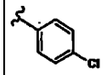
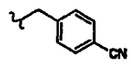
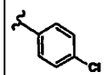
									3.85 (d, 1H, J=17), 303-3.15 (m, 2H), 1.86-1.92 (m, 1H), 1.40-1.85 (m, 7H), 1.05-1.35 (m, 4H), 0.90-0.99 (m, 2H), 0.88 (d, 3H, J=6.6), 0.87 (d, 3H, J=6.4).
115				5	sólido blanco	452.96	1.14 min Método A	453.22	RMN ^{1}H ($CDCl_3$, 400MHz) δ 8.53 (d, 2H, J=5.2), 8.04 (t, 1H, J=5.2), 7.80 (dd, 2H, J=1.8, 8.5), 7.46 (dd, 2H, J=1.8, 8.7), 7.33 (s amplio, 1H), 7.29 (d, 2H, J=5.4), 5.78 (s amplio, 1H), 4.47 (qd, 2H, J=6.0, 16), 4.21 (t, 1H, J=7.4), 4.07 (d, 1H, J=17), 3.92 (d, 1H, J=17), 1.67-1.77 (m, 1H), 1.30-1.47 (m, 2H), 0.81 (d, 3H, J=6.5), 0.77 (d, 3H, J=7.0).

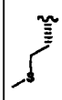
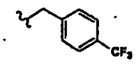
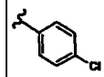
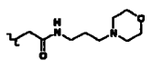
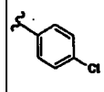
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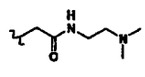
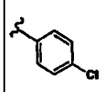
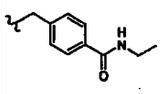
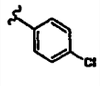
116				5	espuma blanca	419.93	1.29 min Método A	420.23	RMN ^1H ($CDCl_3$, 400MHz) δ 7.87 (dd, 2H, J=2.0, 8.5), 7.85 (s amplio, 1H), 7.49 (dd, 2H, J=2.1, 9.0), 6.73 (s amplio, 1H), 5.55 (s amplio, 1H), 4.22 (dd, 1H, J=6.1, 8.3), 4.02 (d, 1H, J=17), 3.87 (d, 1H, J=17), 3.40-3.50 (m, 4H), 3.36 (s, 3H), 1.77-1.86 (m, 1H), 1.46-1.57 (m, 1H), 1.30-1.41 (m, 1H), 0.84 (d, 3H, J=6.7), 0.83 (d, 3H, J=6.5).
117				5	espuma blanca	475.01	1.16 min Método A	475.26	RMN ^1H ($CDCl_3$, 400MHz) δ 7.85 (dd, 2H, J=2.0, 8.5), 7.64 (s amplio, 1H), 7.47 (dd, 2H, J=1.5, 7.1), 6.87 (s amplio, 1H), 5.55 (s amplio, 1H), 4.22 (dd, 1H, J=6.2, 7.9), 4.00 (d, 1H, J=17), 3.87 (d, 1H, J=17), 3.72 (t, 1H, J=4.2), 3.30-3.45 (m, 2H),

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									2.45-2.55 (m, 6H), 1.75-1.85 (m, 1H), 1.50-1.63 (m, 1H), 1.30-1.41 (m, 1H), 0.86 (d, 6H, J=9.0).
118				1-Método A	sólido blanco	459.79	1.62 min Método B	46.1	RMN ^{1}H ($CDCl_3$) δ 7.67 (d, 2H, J=7.0Hz) 7.48 (d, 2H, J=7.0Hz), 7.41 (d, 2H, J=6.5Hz), 7.21 (d, 2H, 6.5Hz), 6.21 (s, amplio, 1H), 5.20 (s, amplio, 1H), 4.43 (dd, 2H, J=50Hz, 15Hz), 4.12-4.24 (m, 1H), 1.88-1.90 (m, 1H), 1.24-1.29 (m, 1H), 0.98-1.08 (m, 2H), 0.74 (t, 3H, J=7.0Hz).
119				1-Método A	sólido amarillo	437.06	1.84 min Método F	(M+Na)$^+$ 459.9	RMN ^{1}H (400MHz, DMSO) δ 7.83 (d, 2H, J=8.8), 7.80 (d, 2H, J=8.3), 7.64 (d, 2H, J=8.5), 7.59 (d, 2H, J=8.6), 7.48 (s, 1H), 7.15 (s, 1H), 4.79 (ABq, 2H, Δv=22.2, J_{ab}=17.4), 4.44 (dd, 1H, J=8.0, 6.3), 2.21 (m, 2H), 1.84 (m,

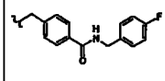
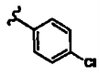
									1H), 1.81 (s, 3H), 1.53 (m, 1H).
120				1-Método A	sólido blanco	480.06	2.08 min Método F	$(M+Na)^+$ 503.0	RMN ^1H (400MHz, DMSO) δ 7.82 (d, 2H, J=8.8), 7.68 (d, 2H, J=8.6), 7.61 (m, 4H), 7.48 (s, 1H), 7.16 (s, 1H), 4.80 (ABq, 2H, $\Delta\nu$=16.7, J_{ab}=17.0), 4.45 (dd, 1H, J=8.2, 6.2), 2.22 (m, 2H), 1.82 (m, 1H), 1.78 (s, 3H), 1.61 (m, 1H).
121				5	sólido blanco	488.19	1.20 min Método A	489.26	RMN ^1H ($CDCl_3$, 400MHz) δ 7.95 (s amplio, 1H), 7.85 (dd, 2H, J=2.5, 9.2), 7.70 (s amplio, 1H), 7.47 (dd, 2H, 2.0, 8.8), 5.42 (s amplio, 1H), 4.23 (dd, 1H, J=6.3, 8.3), 3.94 (d, 1H, J=17) 3.83 (d, 1H, J=17), 3.73 (t, 4H, J=4.7), 3.39-3.48 (m, 1H), 3.22-3.33 (m, 1H), 2.42-2.55 (m, 4H), 1.79-1.88 (m, 2H), 1.63-1.75 (m, 2H), 1.49-1.61 (m, 1H), 1.31-

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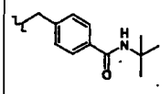
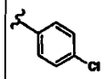
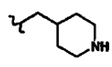
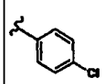
									1.45 (m, 1H), 1.05-1.11 (m, 1H), 0.88 (d, 6H, J=6.6).
122				5	sólido blanco	432.16	1.59 min Método C	433.12	RMN ^{1}H ($CDCl_3$, 400MHz) δ 8.04 (s amplio, 1H), 7.88 (dd, 2H, J=1.9, 6.9), 7.46 (dd, 2H, J=1.8, 6.8), 6.93 (s amplio, 1H), 5.55 (s amplio, 1H), 4.20 (dd, 1H, J=6.2, 8.3), 4.01 (d, 1H, J=17), 3.80 (d, 1H, J=17), 3.25-3.40 (m, 2H), 2.40 2.50 (m, 2H), 2.25 (s, 6H), 1.75-1.90 (m, 1 H), 1.45-1.60 (m, 1H), 1.30-1.45 (m, 1H), 0.84 (d, 3H, J=6.1), 0.82 (d, 3H, J=6.4).
123				6	sólido blanco	466.00	1.49 min Método A	466.17	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.68 (d, 4H, J=8.6), 7.47 (ddd, 2H, J=1.6, 2.4, 8.6), 7.41 (d, 2H, J=8.2), 6.25 (s amplio, 1H), 6.12 (s amplio, 1H), 5.30 (s amplio, 1H), 4.63 (d, 1H,

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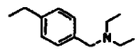
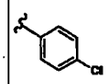
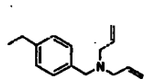
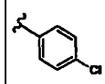
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									J=15.8), 4.44 (d, 1H, J=15.8), 4.30 (t, 1H, J=6.8), 3.47-3.52 (m, 2H), 1.78-1.84 (m, 1H), 1.30-1.34 (m, 1H), 1.25 (t, 3H), J=7.2), 1.08-1.13 (m, 1H), 0.76 (d, 3H, J=6.6), 0.65 (d, 3H, J=6.6).
124				6	aceite incoloro	546.05	1.65 min Método A	546.19	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.71 (d, 2H, J=8.2), 7.67 (d, 2H, J=8.6), 7.46 (d, 2H, J=8.6), 7.41 (d, 2H, J=8.0), 6.52 (s amplio, 1H), 6.24 (s amplio, 1H), 5.40 (s amplio, 1H), 4.63 (d, 1H, J=15.9), 4.59 (d, 2H, J=5.6), 4.42 (d, 1H, J=15.9), 4.29 (t, 1H, J=6.6), 1.78-1.84 (m, 1H), 1.29-1.34 (m, 1H), 1.25 (t, 3H), J=7.2), 1.06-1.11 (m, 1H), 0.76 (d, 3H, J=6.6), 0.66 (d, 3H, J=6.6).

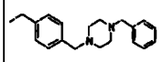
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125				6	aceite incoloro	494.06	1.67 min Método A	494.24	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.68 (dd, 2H, J=1.7, 8.6), 7.63 (d, 2H, J=8.2), 7.46 (d, 2H, J=8.6), 7.39 (d, 2H, J=8.2), 6.28 (s amplio, 1H), 5.94 (s amplio, 1H), 5.35 (s amplio, 1H), 4.63 (d, 1H, J=15.8), 4.41 (d, 1H, J=15.8), 4.29 (t, 1H, J=6.6), 1.78-1.84 (m, 1H), 1.46 (s, 9H), 1.29-1.34 (m, 1H), 1.25 (t, 3H), J=7.2), 1.06-1.11 (m, 1H), 0.76 (d, 3H, J=6.6), 0.66 (d, 3H, J=6.6).
126				7	sólido blanco	401.15	1.34 min Método A	402.15	RMN ^{1}H ($DMSO-d_6$, 500MHz) δ 7.87 (d, 2H, J=8.5), 7.66 (d, 2H, J=8.6), 7.41 (s, 1H), 7.04 (s, 1H), 4.17 (t, 1H, J=7.3), 3.40-3.50 (m, 1H), 3.20-3.25 (m, 1H), 3.03-3.10 (m, 1H), 2-65-2.80 (m, 2H), 1.85-2.00 (m, 1H), 1.20-1.85 (m, 2H), 1.45-1.60 (m,

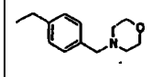
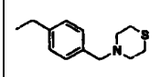
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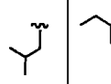
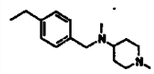
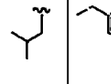
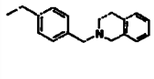
									1H), 1.30-1.40 (m, 1H), 1.10-1.30 (m, 4H), 0.75-0.90 (m, 1H), 0.82 (d, 3H, J=7.3), 0.80 (d, 3H, J=70).
127				8	sólido blanco	480.07	1.34 min Método A	480.25	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.60 (d, 2H, J=8.0Hz), 7.39-7.33 (m, 4H), 6.26 (s, amplio, 1H), 5.40 (s, amplio. 1H), 4.53 (d, 1H, J_{ab}=16Hz), 4.42 (d, 1H, J_{ab}=16Hz), 2.58 (q, 4H, J=8.0Hz), 1.94 (m, 1H), 1.59 (m, 2H), 1.06 (t, 6H, J=8.0Hz), 0.97 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
128				8	sólido blanco	504.1	1.32 min Método A	504.25	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.73 (d, 2H, J=8.0Hz), 7.48 (d, 2H, J=8.0Hz), 7.35 (d, 2H, J=8.0Hz), 6.25 (s, amplio, 1H), 5.35 (s, amplio, 1H),

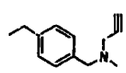
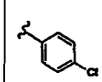
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									4.52 (d, 1H, J_{ab}=16Hz), 4.44 (d, 1H, J_{ab}=16Hz), 3.35 (s, 2H), 3.47-3.42 (m, 1H), 3.01 (s, amplio, 1H), 1.90 (m, 1H), 1.63 (m, 2H), 0.97 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
129				8	sólido blanco	583.2	1.26 min Método A	583.40	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.37 (m, 4H), 7.21 (m, 5H), 6.35 (s, amplio, 1H), 5.87 (s, amplio, 1H), 4.72 (d, 1H, J_{ab}=16Hz), 4.48 (d, 1H, J_{ab}=16Hz), 3.55 (s, 3H), 3.52 (s, 3H), 3.74-3.43 (m, 1H), 2.45 (m, 8H), 1.59 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz).

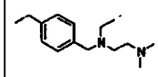
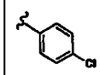
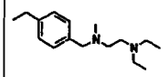
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130				8	vidrio color ámbar	496.06	1.32 min Método A	496.25	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.68 (d, 2H, J=8.0Hz), 7.72 (d, 2H, J=8.0Hz), 7.40-7.36 (m, 4H), 6.35 (s, amplio, 1H), 5.37 (s, amplio, 1H), 4.59 (d, 1H, J_{ab}=16Hz), 4.37 (d, 1H, J_{ab}=16Hz), 3.7-3.5 (m, 4H), 3.48 (s, 3H), 3.46 (m, 1H), 2.23-2.1 (m, 4H), 1.85 (m, 1H), 1.55 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz).
131				8	aceite color ámbar	510.12	1.33 min Método A	510.23	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.65 (s, amplio, 4H), 7.37 (d, 2H, J=8.0Hz), 6.25 (s, amplio, 1H), 5.36 (s, amplio, 1H), 4.60 (d, 1H, J_{ab}=16Hz), 4.38 (d, 1H, J_{ab}=16Hz), 3.47-3.43 (m, 3H), 2.61 (m, 4H), 2.30 (m, 4H), 1.90 (m, 1H), 1.59 (m, 2H), 0.96 (d, 3H, J=7.0Hz),

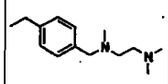
									0.94 (d, 3H, J=7.0Hz).
132				8	vidrio color ámbar	535.15	1.24 min Método A	535.32	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 8.02 (d, 2H, J=8.0Hz), 7.71 (d, 2H, J=8.0Hz), 7.40 (d, 2H, J=8.0Hz), 7.36 (d, 2H, J=8.0Hz), 6.27 (s, amplio, 1H), 5.40 (s, amplio, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.44 (d, 1H, J_{ab}=16Hz), 3.61 (s, 2H), 3.45 (m, 1H), 2.72-2.63 (m, 3H), 2.41 (s, 3H), 2.32 (s, 3H), 2.05 (t, 4H, J=12.0Hz), 1.90 (m, 3H), 1.74-1.55 (m, 3H), 0.96 (d, 3H, J=7.0Hz), 0.93 (d, 3H, J=7.0Hz).
133				8	vidrio color ámbar	540.13	1.28 min Método A	540.34	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.70 (d, 2H, J=8.0Hz), 7.52 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.24-7.14 (m, 3H), 6.88 (m, 1H), 6.25 (s, amplio, 1H), 5.39 (s,

									amplio, 1H), 4.62 (d, 1H, J_{ab}=16Hz), 4.40 (d, 1H, J_{ab}=16Hz), 3.45 (s, 2H), 3.46 (m, 1H), 3.35-3.19 (m, 2H), 3.93 (m, 1H), 2.71 (m, 1H), 2.61 (m, 1H), 2.49-2.43 (m, 2H), 1.89 (m, 1H), 1.67-1.54 (m, 2H), 0.97 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
134				8	sólido blanco	476.04	1.31 min Método A	476.17	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.79 (d, 2H, J=8.0Hz), 7.65 (d, 2H, J=8.0Hz), 7.47 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.35 (s, amplio, 1H), 5.85 (s, amplio,1H), 4.60 (s, 2H), 4.76 (d, 1H, J_{ab}=16Hz), 4.30 (d, 1H, J_{ab}=16Hz), 3.72 (s, amplio, 2H), 3.46 (m, 1H), 2.40 (s, amplio, 3H), 2.20 (s, 1H), 1.90 (m, 1H), 1.63 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d,

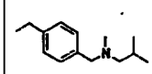
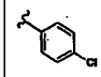
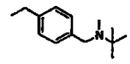
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									3H, J=7.0Hz).
135				8	sólido blanco	532.14	1.34 min Método A	532.32	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.62 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 7.33 (d, 2H, J=8.0Hz), 6.27 (s, amplio, 1H), 5.40 (s, amplio, 1H), 4.59 (d, 1H, J_{ab}=16Hz), 4.37 (d, 1H, J_{ab}=16Hz), 3.53 (s, 3H), 3.44 (m, 1H), 2.79 (t, 2H, J=8.0Hz), 2.62 (q, 2H, J=8.0Hz), 2.41 (t, 2H, J=8.0Hz), 2.25 (s, 6H), 1.95-1.85 (m, 1H), 1.67-1.54 (m, 2H), 1.07 (t, 3H, J=8.0Hz), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz).
136				8	sólido blanco	537.17	1.24 min Método A	537.34	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.41-7.36 (m, 4H), 6.57 (s, amplio, 1H), 5.40 (s, amplio, 1H), 4.59 (d,

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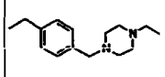
									1H, J_{ab}=16Hz), 4.37 (d, 1H, J_{ab}=16Hz), 3.51 (s, 2H) 3.45 (m, 1H), 2.69 (t, 2H, J=8.0Hz) 2.62 (t, 2H, J=8.0Hz) 2.55 (q, 4H, J=8.0Hz), 2.35 (s, 3H), 1.89 (m, 1H), 1.60 (m, 2H), 1.00 (t, 6H, J=8.0Hz), 0.96 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
137				8	sólido blanco	509.12	1.32 min Método A	509.33	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 8.01 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.40 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.27 (s, amplio, 1H), 5.39 (s, amplio, 1H), 4.58 (d, 1H, J_{ab}=16Hz), 436 (d, 1H, J_{ab}=16Hz), 3.51 (s, 2H), 3.45 (m, 1H), 2.66 (t, 2H, J=8.0Hz), 2.39 (t, 2H, J=8.0Hz), 2.35 (s, 3H), 2.25 (s, 6H), 1.90 (m, 1H), 1.59 (m, 2H), 0.97 (d,

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									3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
138				8	vidrio claro	494.1	1.37 min Método A	494.27	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.74 (d, 2H, J=8.0Hz), 7.52 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.26 (s, amplio, 1H), 5.39 (s, amplio, 1H), 4.55 (d, 1H, J_{ab}=16Hz), 4.42 (d, 1H, J_{ab}=16Hz), 3.70 (s, 3H), 3.46 (m, 1H), 2.38-235 (m, 5H), 1.91 (m, 2H), 1.60 (m, 2H), 0.96 (d, 3H, J=7.0Hz), 0.90 (d, 3H, J=7.0Hz).
139				8	sólido blanco	494.4	1.33 min Método A	494.26	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.63 (d, 2H, J=8.0Hz), 7.73 (d, 2H, J=8.0Hz), 7.48 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.35 (s, amplio, 1H), 5.38 (s, amplio, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.44 (d, 1H, J_{ab}=16Hz),

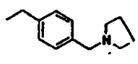
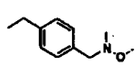
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									3.47-3.40 (m, 3H), 2.12 (s, 3H), 1.88 (m, 1H), 1.60 (m, 2H), 1.03 (s, 9H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz).
140				8	vidrio color ámbar	521.13	1.27 min Método A	521.31	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.65 (d, 2H, J=8.0Hz), 7.39-7.36 (m, 4H), 6.30 (s, amplio, 1H), 5.35 (s, amplio, 1H), 4.59 (d, 1H, J_{ab}=16Hz), 4.37 (d, 1H, J_{ab}=16Hz), 3.55 (s, 2H), 3.45 (m, 1H), 2.84 (m, 4H), 2.48 (q, 2H, J=7.0Hz), 2.28 (m, 4H), 1.88 (m, 1H), 1.60 (m, 2H), 1.20 (t, 3H, J=7.0Hz), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).

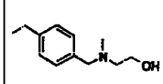
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141				8	sólido blanco	478.06	1.31 min Método A	478.22	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.71 (d, 2H, J=8.0Hz), 7.48 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.27 (s, amplio, 1H), 5.40 (s, amplio, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.43 (d, 1H, J_{ab}=16Hz), 3.58 (s, amplio, 2H), 3.45 (m, 1H), 2.66 (m, 4H), 1.86 (m, 5H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz).
142				8	espuma blanca	468.02	1.58 min Método A	468.25	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.76 (d, 2H, J=8.0Hz), 7.75 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.25 (s, amplio, 1H), 5.38 (s, amplio, 1H), 4.76 (d, 1H, J_{ab}=16Hz), 4.30 (d, 1H, J_{ab}=16Hz), 3.75 (s, 2H), 3.45

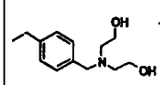
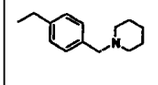
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									(m, 1H), 3.36 (s, 3H), 2.61 (s, 3H), 1.88 (m, 1H), 1.59 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz).
143				8	sólido blanco	482.05	1.28 min Método A	482.24	RMN ^{1}H, 400Hz, ($CDCl_3$) 7.69 (d, 2H, J=8.0Hz), 7.72 (d, 2H, J=8.0Hz), 7.42-7.36 (m, 4H), 6.35 (s, amplio, 1H), 5.83 (s, amplio, 1H), 4.58 (d, 1H, J=16Hz), 4.39 (d, 1H, J_{ab}=16Hz), 3.52 (s, 1H), 3.50 (s, 2H), 3.48 (s, 1H), 3.45 (m, 1H), 2.55 (t, 2H, J=8.0Hz), 2.20 (s, 3H), 1.90 (m, 1H), 1.59 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz).

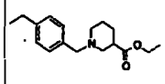
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144				8	vidrio claro	512.07	1.22 min Método A	512.25	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.71 (d, 2H, J=8.0Hz), 7.74 (d, 2H, J=8.0Hz), 7.39 (d, 2H, J=8.0Hz), 7.31 (d, 2H, J=8.0Hz), 6.27 (s, amplio, 1H), 5.40 (s, amplio, 1H), 4.72 (d, 1H, J_{ab}=16Hz), 4.39 (d, 1H, J_{ab}=16Hz), 3.76 (t, 4H, J=8.0Hz), 3.45 (m, 1H), 3.38 (s, amplio, 2H), 3.15 (s, amplio, 2H), 3.76 (t, 4H, J=8.0Hz), 1.89 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz).
145				8	sólido blanco	492.09	1.31 min Método A	492.21	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.63 (d, 2H, J=8.0Hz), 7.71 (d, 2H, J=8.0Hz), 7.47 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.26 (s, amplio, 1H), 5.39 (s, amplio, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.43 (d, 1H, J_{ab}=16Hz),

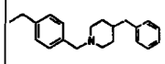
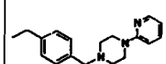
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									3.47-3.43 (m, 3H), 2.26 (m, 4H), 1.89 (m, 2H), 1.60 (m, 2H), 1.46-1.29 (m, 4H), 0.97 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
146				8	sólido blanco	564.15	1.33 min Método A	564.24	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.71 (d, 2H, J=8.0Hz), 7.48 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.35 (s, amplio, 1H), 5.40 (s, amplio, 1H), 4.72 (d, 1H, J_{ab}=16Hz), 4.48 (d, 1H, J_{ab}=16Hz), 4.03 (q, 2H, J=8.0Hz), 3.47-3.42 (m, 3H), 3.21 (m, 1H), 2.62 (m, 1H), 2.63-2.36 (m, 3H), 2.06-1.95 (m, 1H), 1.93-1.80 (m, 3H), 1.67-1.50 (m, 3H), 1.13 (t, 3H, J=8.0Hz), 0.98 (d, 3H, J=.07Hz), 0.95 (d, 3H, J=7.0Hz).

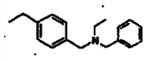
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147				8	sólido blanco	582.21	1.46 min Método A	582.41	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.71 (d, 2H, J=8.0Hz), 7.47 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.24 (t, 1H, J=8.0Hz), 7.03 (t, 2H, J=8.0Hz), 6.95 (d, 2H, J=8.0Hz), 6.27 (s, amplio, 1H), 5.40 (s, amplio, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.44 (d, 1H, J_{ab}=16Hz), 3.48-3.43 (m, 3H), 2.76 (m, 2H), 2.61 (m, 2H), 1.88 (m, 3H), 1.69-1.54 (m, 6H), 1.26 (m, 1H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz).
148				8	espuma blanca	570.16	1.41 min Método A	570.34	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 8.09 (d, 1H, J=4.0Hz), 8.02 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.41-7.36 (m, 5H), 6.72 (d, 1H, J=12.0Hz), 6.49 (t, 1H, J=8.0Hz), 6.35 (s, amplio, 1H),

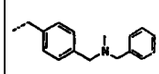
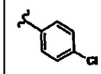
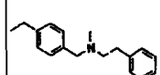
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									5.87 (s, amplio, 1H), 4.80 (d, 1H, J_{ab}=16Hz), 4.30 (d, 1H, J_{ab}=16Hz), 3.84 (m, 4H), 3.55 (s, 2H), 3.46 (m, 1H), 2.57 (m, 4H), 1.89 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 2H, J=7.0Hz).
149				8	sólido blanco	542.15	1.45 min Método A	542.24	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.70 (d, 2H, J=8.0Hz), 7.68 (d, 2H, J=8.0Hz), 7.47 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.29-7.16 (m, 5H), 6.28 (s, amplio, 1H), 5.38 (s, amplio, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.42 (d, 1H, J_{ab}=16Hz), 3.54 (s, 2H), 3.45 (m, 1H), 2.62 (q, 2H, J=7.0Hz), 1.89 (m, 1H), 1.60 (m, 2H), 1.08 (t, 3H, J=7.0Hz), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz).

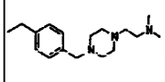
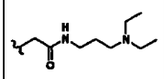
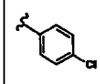
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150				8	película color ámbar	528.12	1.45 min Método A	528.33	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.68 (d, 2H, J=8.0Hz), 7.54 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 7.35-7.29 (m, 5H), 6.27 (s, amplio, 1H), 5.37 (s, amplio, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.43 (d, 1H, J_{ab}=16Hz), 3.55 (s, 2H), 3.45 (m, 1H), 2.17 (s, 3H), 1.89 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.95 (d, 3H, J=7.0Hz).
151				8	vidrio claro	542.15	1.46 min Método A	542.29	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.68 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.45 (d, 2H, J=8.0Hz), 7.39-7.26 (m, 4H), 6.97 (d, 1H, J=8.0Hz), 6.27 (s, amplio, 1H), 5.38 (s, amplio, 1H), 4.54 (d 1H, J_{ab}=16Hz), 4.44 (d, 1H, J_{ab}=16Hz), 3.43 (s, 2H), 3.25 (t, 1H, J=4.0Hz), 2.77-2.69

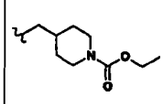
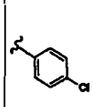
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									(m, 4H), 2.40 (s, 3H), 1.94 (m, 1H), 1.60 (m, 2H), 0.97 (d, 2H, J=7.0Hz), 0.94 (d, 2H, J=7.0Hz).
152				8	vidrio color ámbar	564.2	1.22 min Método A	564.32	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.59 (d, 2H, J=8.0Hz), 7.39-7.33 (m, 4H), 6.21 (s, amplio, 1H), 5.34 (s, amplio, 1H), 4.76 (d, 1H, J_{ab}=16Hz), 4.31 (d, 1H, J_{ab}=16Hz), 3.57 (s, 2H), 2.69-2.55 (m, 6H), 2.36-2.18 (m, 12H), 1.95 (m, 1H), 1.66-1.50 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
153				5	474.21	sólido blanco	1.78 min Método C	476.17	RMN ^{1}H ($CDCl_3$, 400 MHz) δ 8.41 (s amplio, 2H), 7.85 (dd, 2H, J=2.0, 6.8), 7.46 (dd, 2H, J=2.0, 6.8), 5.46 (s, 1H), 4.21 (dd, 1H, J=5.9, 8.8), 3.92 (d, 1H, J=17), 3.77 (d, 1H,

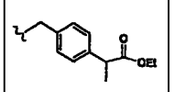
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									J=17), 3.27-3.41 (m, 2H), 2.48-2.62 (m, 6H), 1.80-1.90 (m, 1H), 1.50-1.72 (m, 3H), 1.35-1.49 (m, 1H), 1.05 (t, 6H, J=7.1), 0.87 (d, 3H, J=6.4), 0.85 (d, 3H, J=6.7).
154				5	sólido blanco	516.18	1.53 min Método A	517.30	RMN ^{1}H ($CDCl_3$, 500 MHz) δ 7.83 (dd, 2H, J=1.9, 6.8), 7.47 (dd, 2H, J=2.0, 6.8), 7.31 (s amplio, 1H), 7.11 (s amplio, 1H), 5.57 (s amplio, 1H), 4.23 (dd, 1H, J=6.8, 8.4), 4.00-4.15 (m, 2H), 3.95 (d, 1H, J=17), 3.83 (d, 1H, J=17), 2.93 (s amplio, 2H), 1.75-1.95 (m, 4H), 1.60-1.75 (1H, 1.25-1.55 (m, 1H), 1.25 (t, 5H, J=7.7), 0.85 (d, 3H, J=6.3), 0.83 (d, 3H, J=6.3).

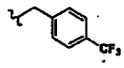
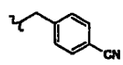
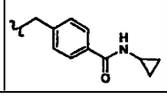
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155				1-Método A	sólido blanco	495.04	1.88 min Método A	495.1	RMN ^1H ($CDCl_3$) δ 7.62-7.59 (m, 2H), 7.43-7.39 (m, 2H), 7.28-7.25 (m, 2H), 7.22-7.19 (m, 2H), 6.22 (s amplio, 1H), 5.29 (s amplio, 1H), 4.53-4.43 (m, 2H), 4.42-4.37 (m, 1H), 4.16-4.07 (m, 2H), 1.82-1.73 (m, 1H), 1.48 (d, 3H, J=7.3Hz, isómero A), 1.47 (d, 3H, J=7.3Hz, isómero B), 1.36-1.22 (m, 2H), 1.21 (t, 3H, J=7.1Hz), 0.77 (d, 3H, J=6.4Hz, isómero A), 0.77 (d, 3H, J=6.4Hz, isómero B), 0.65 (d, 3H, J=6.7Hz, isómero A), 0.65 (d, 3H, J=6.7Hz, isómero B).

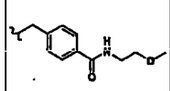
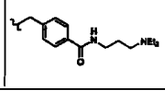
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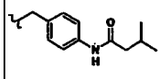
156				1-Método A	sólido blanco	434.07	1.57 min Método B	$(M+H)^+$ 435.1	RMN ^1H (400 MHz, DMSO) δ 7.80 (d, 2H, J=8.7), 7.66 (d, 2H, J=8.3), 7.60 (m, 4H), 7.53 (s, 1H), 7.10 (s, 1H), 4.80 (ABq, 2H, Δν=39.8, J_{ab}=17.2), 4.30 (t, 1H, J=7.5), 1.60 (m, 1H), 1.39 (m, 1H), 0.71 (t, 3H, J=7.3).
157				1-Método A	sólido blanco	391.08	1.32 min Método B	$(M+H)^+$ 392.1	RMN ^1H (400 MHz, DMSO) δ 7.81 (d, 2H, J=8.7), 7.78 (d, 2H, J=8.4), 7.62 (d, 2H, J=8.7), 7.57 (d, 2H, J=8.3), 7.52 (s, 1H), 7.09 (s, 1H), 4.80 (ABq, 2H, Δν=45.0, J_{ab}=17.6), 4.28 (t, 1H, J=7.5), 1.58 (m, 1H), 1.36 (m, 1H), 0.70 (t, 3H, J=7.3).
158				6	sólido blanco	478.01	1.53 min Método A	478.17	RMN ^1H (CD_3OD, 300MHz) δ 7.80 (ddd, 2H, J=1.9, 2.4, 8.7), 7.73 (d, 2H, J=8.3), 7.48-7.54 (m, 4H), 4.87 (m 1H), 4.79 (d, 1H, J=16.0), 4.49 (t,

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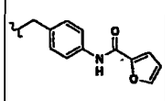
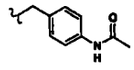
									1H, J=6.2), 2.81-2.87 (m, 1H), 1.25-1.43 (m, 3H), 0.83 (d, 3H, J=6.2), 0.77-0.83 (m, 2H), 0.63-0.66 (m, 2H), 0.57 (d, 3H, J=6.1).
159				6	sólido blanco	496.03	1.50 min Método A	496.21	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.70 (d, 2H, J=8.0), 7.68 (d, 2H, J=8.6), 7.46 (d, 2H, J=8.6), 7.41 (d, 2H, J=8.1), 4.64 (d, 1H, J=15.9), 4.43 (d, 1H, J=15.9), 4.30 (t, 1H, J=6.8), 3.63-3.66 (m, 2H), 3.55-3.58 (m, 2H), 3.39 (s, 3H), 1.76-1.84 (m, 1H), 1.28-1.34 (m, 1H), 1.05-1.11 (m, 1H), 0.75 (d, 3H, J=6.5), 0.66 (d, 3H, J=6.7)
160				6	sólido blanco	551.15	1.33 min Método A	551.28	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, J=8.2), 7.67 (dd, 2H, J=2.0, 8.7), 7.44 (dd, 2H, J=1.8, 8.6), 7.39 (d, 2H, J=8.2), 6.35 (s amplio, 1H),

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									5.46 (s amplio, 1H), 4.60 (d, 1H, J=15.9), 4.50 (d, 1H, J=15.9), 4.31 (t, 1H, J=7.3), 3.54-3.57 (m, 2H), 2.56-2.64 (m, 6H), 1.72-1.80 (m, 3H), 1.28-1.34 (m, 1H), 1.13-1.16 (m, 1H), 1.03 (t, 6H, J=7.2), 0.74 (d, 3H, J=6.6), 0.61 (d, 3H, J=6.6).
161				9	sólido blanco	494.06	1.51 min Método B	494.2	RMN ^{1}H ($CDCl_3$) δ 7.69 (d, 2H, J=7.0Hz), 7.45-7.47 (m, 4H), 7.30 (d, 2H, J=8.0Hz), 7.12 (s, amplio, 1H), 6.25 (s, amplio, 1H), 5.22 (s, amplio, 1H), 4.40 (dd, 2H, J=50Hz, 15Hz), 4.25 (t, 1H, J=7.4Hz), 2.48-2.51 (m, 1H), 1.54-1.86 (m, 1H), 1.17-1.34 (m, 10H), 0.75 (d, 3H, J=7.0Hz), 0.67 (d, 3H, J=7.0Hz).

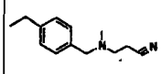
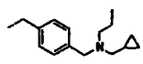
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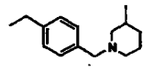
162				9	sólido color canela	504.01	1.52 min Método B	504.1	RMN ^1H ($CDCl_3$) δ 8.10 (s, amplio, 1H), 7.67 (d, 2H, J=7.0Hz), 7.58 (d, 2H, J=7.0Hz), 7.23-7.49 (m, 6H), 6.54-6.57 (m, 1H), 6.27 (s, amplio, 1H), 5.50 (s, amplio, 1H), 4.51 (dd, 2H, J=50Hz, 15Hz), 4.28 (t 1H, J=7.4Hz), 1.78 1.85 (m, 1H), 1.12-1.32 (m, 2H), 0.75 (d, 3H, J=7.0Hz), 0.67 (d, 3H, J=7.0Hz).
163				9	sólido blanco	451.98	1.50 min Método B	450.18 (M-H)	RMN ^1H ($CDCl_3$) δ 7.67 (d, 2H, J=8.0Hz), 7.28-7.46 (m, 6H), 7.12 (s, amplio, 1H), 6.24 (s, amplio, 1H), 5.19 (s, amplio, 1H), 4.48 (dd, 2H, J=50Hz, 15Hz), 4.27 (t, 1H, J=7.0Hz), 2.18 (s, 3H), 1.80-2.01 (m, 1H), 1.12-1.32 (m, 2H), 0.75 (d, 3H, J=7.0Hz), 0.67 (d, 3H, J=7.0Hz).

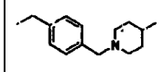
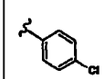
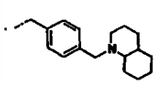
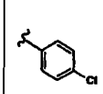
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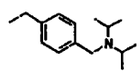
164				8	sólido blanco	491.06	1.31 min Método A	491.24	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.51 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.25 (s, amplio, 1H), 5.35 (s, amplio, 1H), 4.59 (d, 1H, J_{ab}=16Hz), 4.36 (d, 1H, J_{ab}=16Hz), 3.62 (s, 2H), 325 (t, 1H, J=6.0Hz), 2.55-2.48 (m, 7H), 1.94 (m, 1H), 1.60 (m, 2H), 0.97 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
165				8	sólido blanco	520.14	1.40 min Método A	520.32	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.66 (d, 2H, J=8.0Hz), 7.51 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.28 (s, amplio, 1H), 5.39 (s, amplio, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.43 (d, 1H, J_{ab}=16Hz), 3.57 (s, 2H), 3.25 (t, 1H, J=6.0Hz),

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									2.59 (t, 2H, J=8.0Hz), 2.30 (d, 2H, J=6.0Hz), 2.01-1.90 (m, 1H), 1.68-1.49 (m, 4H), 1.02 (m, 1H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz), 0.89 (t, 3H, J=8.0Hz), 0.44-0.31 (m, 4H).
166				8	vidrio claro	506.11	1.41 min Método A	506.31	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.73 (d, 2H, J=8.0Hz), 7.65 (d, 2H, J=8.0Hz), 7.44 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.27 (s, amplio, 1H), 5.39 (s, amplio, 1H), 4.56 (d, 1H, J_{ab}=16Hz), 4.42 (d, 1H, J_{ab}=16Hz), 3.45 (d, 1H, J_{ab}=12Hz), 3.28 (d, 1H J_{ab}=12Hz), 3.25 (t, 1H, J=6.0Hz), 2.75 (m, 4H), 2.0-1.53 (m, 7H), 1.35 (m, 1H), 1.17 (m, 1H), 0.97 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz),

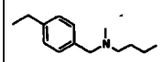
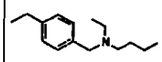
									0.87 (m, 3H).
167				8	vidrio claro	506.11	1.42 min Método A	506.30	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.71 (d, 2H, J=8.0Hz), 7.65 (d, 2H, J=8.0Hz), 7.43 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.26 (s, amplio, 1H), 5.40 (s, amplio, 1H), 4.56 (d, 1H, J_{ab}=16Hz), 4.42 (d, 1H, J_{ab}=16Hz), 3.48 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 2.56-2.42 (m, 4H), 1.93 (m, 1H), 1.89-1.48 (m, 6H), 1.34 (m, 1H), 0.98-0.93 (m, 9H).
168				8	vidrio claro	546.18	1.46 min Método A	546.35	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.65 (d, 2H, J=8.0Hz), 7.42 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.27 (s, amplio, 1H), 5.40 (s, amplio, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.43 (d, 1H, J_{ab}=16Hz),

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									3.45 (d, 1H, J_{ab}=12Hz), 3.28 (d, 1H, J_{ab}=12Hz), 3.25 (t, 1H, J=6.0Hz), 2.87 (m, 1H), 2.70-2.56 (m, 3H), 2.39 (m, 1H), 2.31-2.19 (m, 4H), 1.95 (m, 1H), 1.77 (m, 1H), 1.68-1.59 (m, 2H), 1.54-1.44 (m, 4H), 1.28 (m, 2H), 0.96 (d, 3H, J=7.0Hz), 0.94 (d, 2H, J=7.0Hz).
169				8	vidrio claro	508.13	1.39 min Método A	502.28	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.70 (d, 2H, J=8.0Hz), 7.68 (d, 2H, J=8.0Hz), 7.55 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.28 (s, amplio, 1H), 5.37 (s, amplio, 1H), 4.57 (d, 1H, J_{ab}=16Hz), 4.36 (d, 1H, J_{ab}=16Hz), 3.38 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 2.83 (m, 2H), 1.92 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz), 0.84

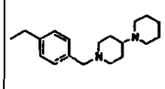
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									(s, 6H), 0.82 (s, 6H).
170				8	vidrio claro	494.1	1.34 min Método A	494.26	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.67 (d, 2H, J=8.0Hz), 7.44 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.27 (s, amplio, 1H), 5.39 (s, amplio, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.44 (d, 1H, J_{ab}=16Hz), 3.40 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 2.39 (s, 3H), 1.94 (m, 1H), 1.68-1.50 (m, 2H), 1.43 (m, 2H), 1.30 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz), 0.86 (t, 3H, J=7.0Hz).
171				8	vidrio claro	508.13	1.40 min Método A	508.27	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.4-7.33 (m, 4H), 6.25 (s, amplio, 1H), 5.35 (s, amplio, 1H), 4.52 (d, 1H, J_{ab}=16Hz), 4.43 (d, 1H,

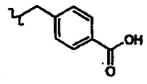
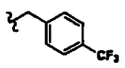
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									J_{ab}=16Hz), 3.46 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 2.62 (t, 2H, J=6.0Hz), 2.52 (q, 2H, J=7.0Hz), 1.94 (m, 1H), 1.68-1.45 (m, 4H), 1.29 (m, 2H), 1.02 (t, 3H, J=7.0Hz), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz), 0.88 (t, 3H, J=7.0Hz).
172				8	vidrio color ámbar	575.22	1.34 min Método A	575.32	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.59 (d, 2H, J=8.0Hz), 7.39-7.33 (m, 4H), 6.25 (s, amplio, 1H), 5.36 (s, amplio, 1H), 4.53 (d, 1H, J_{ab}=16Hz), 4.39 (d, 1H, J_{ab}=16Hz), 3.57 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 2.62-2.32 (m, 9H), 1.94 (m, 1 H), 1.68-1.50 (m, 2H), 1.48-1.20 (m, 12H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).

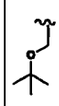
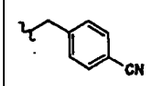
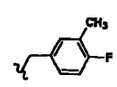
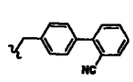
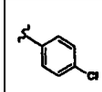
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173				6	sólido blanco	436.92	1.52 min Método A	437.16	RMN ^{1}H (dmso-d_6, 300MHz) δ 7.85 (d, 2H, J=8.4), 7.82 (dd, 2H, J=1.8, 8.7), 7.61 (dd, 2H, J=1.8, 8.7), 7.54 (s amplio, 1H), 7.47 (d, 2H, J=8.4), 7.09 (s amplio, 1H), 4.85 (d, 1H, J=17.4), 4.69 (d, 1H, J=17.1), 4.42 (t, 1H, J=7.2), 1.40-1.48 (m, 1H), 1.27-1.34 (m, 1H), 0.42-0.47 (m, 1H), 0.25-0.30 (m, 2H), -0.00-0.03 (m, 1H), 0.10-0.07 (m, 1H).
174				1-Método A	sólido blanque-cino	492.11	2.13 min Método D	M+Na 514.95	RMN ^{1}H (DMSO) δ 7.76 (d, 2H, J=6.8Hz), 7.61 (m, 6H), 7.44 (s, amplio, 1H), 7.13 (s, amplio, 1H), 4.78 (dd, 2H, J=52Hz, 16Hz), 4.58 (t, 1H, J=8.0Hz), 3.47 (d, 2H, J=6.0Hz), 0.88 (s, 9H).

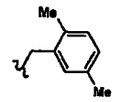
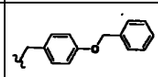
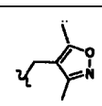
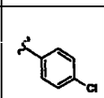
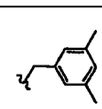
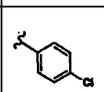
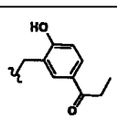
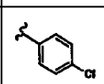
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175				1-Método A	sólido blanco	449.12	1.94 min Método D	M+Na 471.97	RMN ^{1}H (DMSO). δ.7.77 (m, 4H), 7.60 (m, 4H), 7.45 (s, amplio, 1H), 7.12 (s, amplio, 1H), 4.78 (dd, 2H, J=56Hz, 20Hz), 4.57 (t, 1H, J=8.0Hz) 3.47 (d, 2H, J=6.0Hz), 0.88 (s, 9H).
176				1-soporte sólido		478.90	1.86 Método B	479.02	
177				1-soporte sólido		426.90	1.82 Método B	449.02 M+Na	
178				1-soporte sólido		496.00	1.81 Método B	496.06	
179				1-soporte sólido		412.90	1.72 Método B	413.04	

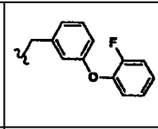
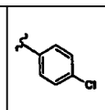
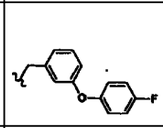
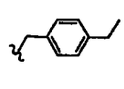
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180				1-soporte sólido		423.00	1.86 Método B	445.02 M+Na	
181				1-soporte sólido		501.10	1.94 Método B	523.04 M+Na	
182				1-soporte sólido		413.90	1.53 Método B	414.05	
183				1-soporte sólido		423.00	1.88 Método B	423.08	
184				1-soporte sólido		467.00	1.60 Método B	467.06	

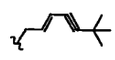
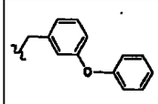
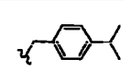
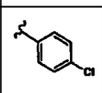
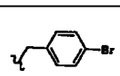
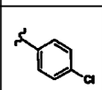
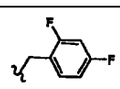
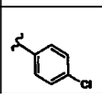
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185				1-soporte sólido		505.00	1.89 Método B	505.07	
186				1-soporte sólido		478.90	1.84 Método B	479.02	
187				1-soporte sólido		505.00	1.93 Método B	505.06	
188				1-soporte sólido		429.40	1.80 Método B	450.90 M+Na	
189				1-soporte sólido		423.00	1.89 Método B	423.09	

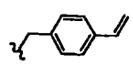
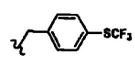
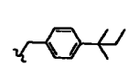
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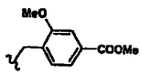
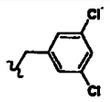
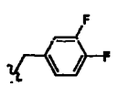
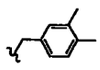
190				1-soporte sólido		425.00	1.92 Método B	425.11	
191				1-soporte sólido		487.00	1.91 Método B	487.04	
192				1-soporte sólido		437.00	1.95 Método B	459.05 M+Na	
193				1-soporte sólido		358.90	1.67 Método B	381.07 M+Na	
194				1-soporte sólido		473.80	1.86 Método B	472.9	
195				1-soporte sólido		430.9	1.75 Método B	431.04	

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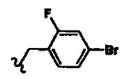
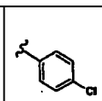
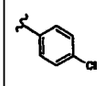
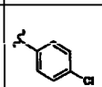
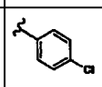
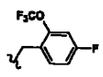
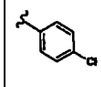
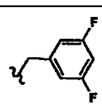
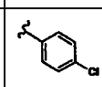
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196				1-soporte sólido		379.30	1.65 Método B	400.98	
197				1-soporte sólido		421.00	1.82 Método B	443.06 M+Na	
198				1-soporte sólido		379.30	1.64 Método B	400.99	
199				1-soporte sólido		495.00	1.95 Método B	494.98	
200				1-soporte sólido		465.10	2.05 Método B	487.10 M+Na	

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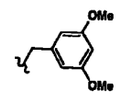
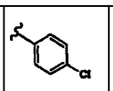
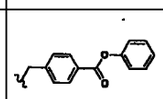
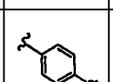
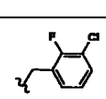
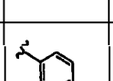
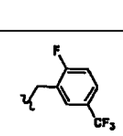
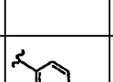
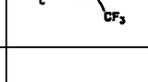
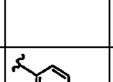
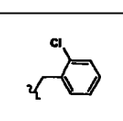
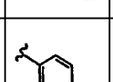
201				1-soporte sólido		483.00	1.72 Método B	483.04	
202				1-soporte sólido		463.80	1.91 Método B	486.96 M+Na	
203				1-soporte sólido		430.90	1.77 Método B	431.04	
204				1-soporte sólido		409.00	1.79 Método B	409.07	
205				1-soporte sólido		462.90	1.81 Método B	463.04	
206				1-soporte sólido		423.00	1.86 Método B	423.10	

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207				1-soporte sólido		491.80	1.88 Método B	492.91	
208				1-soporte sólido		409.00	1.78 Método B	431.04 M+Na	
209				1-soporte sólido		419.9	1.58 Método B	442.04 M+Na	
210				1-soporte sólido		344.90	1.56 Método B	367.05 M+Na	
211				1-soporte sólido		480.90	1.87 Método B	481.02	
212				1-soporte sólido		430.90	1.76 Método B	453.02	

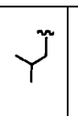
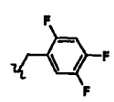
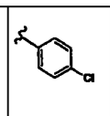
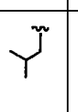
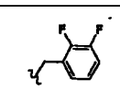
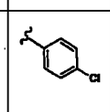
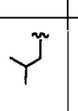
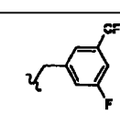
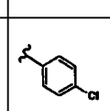
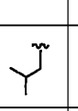
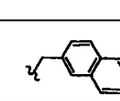
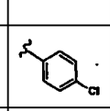
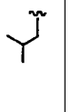
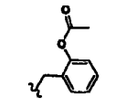
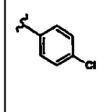
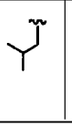
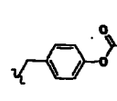
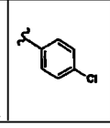
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213				1-soporte sólido		455.00	1.71 Método B	455.07	
214				1-soporte sólido		515.00	1.91 Método B	515.09	
215				1-soporte sólido		447.40	1.82 Método B	468.99 M+Na	
216				1-soporte sólido		480.90	1.80 Método B	481.00	
217				1-soporte sólido		402.90	1.600 Método B	403.12	
218				1-soporte sólido		429.40	1.78 Método B	429.04	

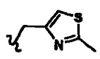
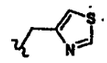
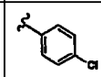
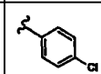
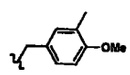
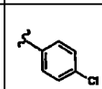
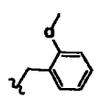
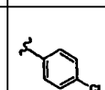
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219				1-soporte sólido		448.90	1.78 Método B	471.00	
220				1-soporte sólido		430.90	1.75 Método B	453.03	
221				1-soporte sólido		480.90	1.85 Método B	503.00 M+Na	
222				1-soporte sólido		445.00	1.87 Método B	467.06 M+Na	
223				1-soporte sólido		453.00	1.62 Método B	453.03	
224				1-soporte sólido		453.00	1.63 Método B	453.05	

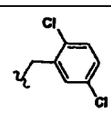
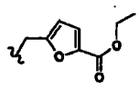
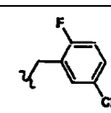
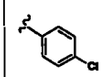
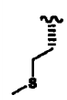
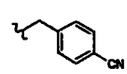
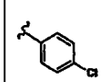
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225				1-soporte sólido		416.00	1.53 Método B	416.04	
226				1-soporte sólido		410.90	1.45 Método B	401.96	
227				1-soporte sólido		395.90	1.12 Método B	396.01	
228				1-soporte sólido		258.90	1.62 Método B	381.01 M+Na	
229				1-soporte sólido		439.00	1.80 Método B	460.97 M+Na	
230				1-soporte sólido		424.90	1.72 Método B	425.03	

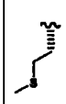
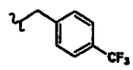
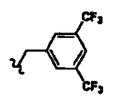
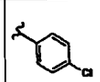
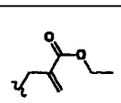
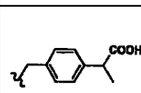
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231				1-soporte sólido		463.80	1.85 Método B	464.90	
232				1-soporte sólido		456.90	1.64 Método B	456.02	
233				1-soporte sólido		447.40	1.78 Método B	468.02 M+Na	
234				1-Método A	sólido blanco	419.11	1.91 min Método F	(M+Na)+ 442.0	RMN ^{1}H (400 MHz, DMSO) δ 7.82 (d, 2H, J=8.7), 7.80 (d, 2H, J=8.4), 7.62 (d, 2H, J=8.7), 7.59 (d, 2H, J=8.3,), 7.51 (s, 1H), 7.07 (s, 1H), 4.81 (ABq, 2H, Δν=38.0, J_{ab}=17.5), 4.31 (t, 1H, J=6.7), 1.54 (m, 1H), 1.29 (m, 1H), 1.03 (m, 3H), 0.85 (m, 1H), 0.66 (t, 3H, J=6.9).

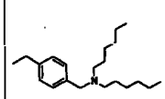
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235				1-Método A	sólido blanco	462.10	2.13 min Método F	$(M+Na)^+$ 442.0	RMN ^1H (400 MHz, DMSO) δ 7.81 (d, 2H, J=8.7), 7.69 (d, 2H, J=8.3), 7.61 (m, 4H), 7.51 (s, 1H), 7.07 (s, 1H), 4.82 (ABq, 2H, $\Delta\nu$=31.9, J_{ab}=17.1), 432 (t, 1H, J=8.3), 1.53 (m, 1H), 1.31 (m, 1H), 1.05 (m, 3H), 0.88 (m, 1H), 0.63 (t, 3H, J=6.8).
236				1-soporte sólido	sólido blanco	530.92	1.92 Método B	530.99	
237				1-soporte sólido	sólido blanco	416.93	1.61 Método B	417.07	
238				1-soporte sólido	sólido blanco	466.99	1.62 Método B	467.06	

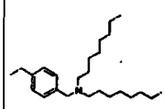
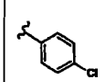
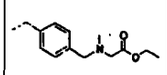
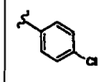
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239				1-soporte sólido	sólido blanco	379.13	1.62	400.98 M+Na	
240				1-soporte sólido	sólido blanco	395.91	1.13	396.01	
241				8	vidrio color ámbar	592.29	1.69 min Método A	592.39	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.65 (d, 2H, J=8.0Hz), 7.43 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.27 (s, amplio, 1H), 5.40 (s, amplio, 1H), 4.56 (d, 1H, J_{ab}=16Hz), 4.40 (d, 1H, J_{ab}=16Hz), 3.56 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 2.40 (t, 4H, J=6.0Hz), 1.95 (m, 1H), 1.68-1.52 (m, 2H), 1.42 (q, 4H, J=6.0Hz), 1.28-1.22 (m, 12H), 0.98 (d, 3H, J=7.0Hz), 0.88 (t, 6H, J=6.0Hz).

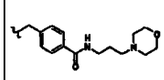
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242				8	vidrio color ámbar	648.4	1.88 min Método A	648.43	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.71 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.43 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.27 (s amplio, 1H), 5.40 (s, amplio, 1H), 4.56 (d, 1H, J_{ab}=16Hz), 4.40 (d, 1H, J_{ab}=16Hz), 3.56 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 2.47 (t, 4H, J=6.0Hz), 1.95 (m, 1H), 1.68-1.50 (m, 2H), 1.43-1.14 (m, 14H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz), 0.88 (t, 6H, J=6.0Hz).
243				9	vidrio claro	524.08	1.35 min Método A	542.25	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.50 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.25 (s, amplio, 1H), 5.34 (s, amplio, 1H), 4.70 (d, 1H, J_{ab}=16Hz), 4.48 (d, 1H, J_{ab}=16Hz),

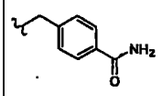
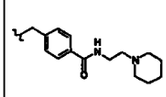
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									4.24-4.08 (m, 4H), 3.42 (s, 2H), 3.25 (t, 1H, J=6Hz), 2.51 (s, 3H), 1.94 (M, 1H), 1.68-1.54 (m, 2H), 1.22 (t, 3H, J=6.0Hz), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
244				6	sólido blanco	565.14	1.29 min Método B	564.99	RMN ^{1}H ($CDCl_3$, 300MHz) δ 8.12 (s amplio, 1H), 7.77 (d, 2H, J=8.8), 7.70 (d, 2H, J=8.6), 7.47 (d, 2H, J=8.4); 7.45 (d, 2H, J=8.0), 6.25 (s amplio, 1H), 5.31 (s amplio, 1H), 4.66 (d, 1H, J=15.7), 4.38 (d, 1H, J=15.8), 4.27 (t, 1H, J=7.1), 3.51-3.89 (m, 4H), 2.35-2.74 (m, 4H), 1.78-1.88 (m, 2H), 1.40-1.65 (m, 4H), 1.24-1.32 (m, 2H), 1.03-1.10 (m, 1H), 0.74 (d, 3H, J=6.5), 0.65 (d, 3H, J=6.6).

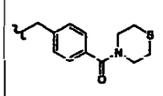
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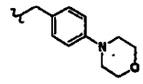
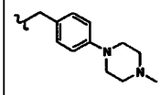
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245				6	sólido blanco	437.95	1.36 min Método B	438.20	RMN ^1H ($CDCl_3$, 300MHz) δ 7.72 (dd, 2H, J=8.3), 7.69 (dd, 2H, J=1.9, 8.7), 7.46 (dd, 2H, J=1.8, 8.7), 7.44 (d, 2H, J=8.6), 6.21 (s amplio, 1H), 5.98 (s amplio, 1H), 5.88 (s amplio, 1H), 5.39 (s amplio, 1H), 4.66 (d, 1H, J=15.7), 4.41 (d, 1H, J=15.9), 4.29 (t, 1H, J=6.5), 1.77-1.87 (m, 1H), 1.25-1.36 (m, 1H), 1.03-1.11 (m, 1H), 0.75 (d, 3H, J=6.6), 0.65 (d, 3H, J=6.6).
246				6	sólido blanco	549.14	1.34 min Método B	549.00	RMN ^1H ($CDCl_3$, 300MHz) δ 7.82 (d, 2H, J=7.8), 7.67 (dd, 2H, J=2.0, 8.7), 7.40-7.46 (m, 5H), 6.22 (s amplio, 1H), 5.23 (s amplio, 1H), 4.61 (d, 1H, J=15.9), 4.42 (d, 1H, J=15.7), 4.28 (t, 1H, J=7.2), 3.60-

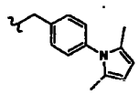
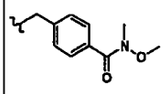
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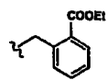
									3.69 (m, 2H), 2.45-2.83 (m, 6H), 1.40-1.85 (m, 7H), 1.24-1.35 (m, 1H), 1.05-1.14 (m, 1H), 0.75 (d, 3H, J=6.5), 0.66 (d, 3H, J=6.6).
247				6	sólido blanco	524.11	1.61 min Método B	523.94	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.68 (d, 2H, J=8.4), 7.46 (d, 2H, J=8.4), 7.39 (d, 2H, J=8.1), 7.29 (d, 2H, J=8.1), 6.20 (s amplio, 1H), 5.24 (s amplio, 1H), 4.60 (d, 1H, J=15.8), 4.44 (d, 1H, J=15.9), 4.30 (t, 1H, J=6.9), 3.70-4.05 (m amplio, 4H), 2.45-2.60 (m, 4H), 1.73-1.80 (m, 1H), 1.28-1.35 (m, 1H), 1.05-1.14 (m, 1H), 0.76 (d, 3H, J=6.5), 0.66 (d, 3H, J=6.6).

248				2	sólido rojo	466.00	1.48 min Método B	466.2	RMN ^1H ($CDCl_3$) δ 7.65 (d, 2H, J=7.0Hz), 7.41 (d, 2H, J=7.0Hz), 7.20 (d, 2H, J=8.8Hz), 6.79 (d, 2H, J=8.8Hz), 6.23 (s, amplio, 1H), 5.20 (s, amplio, 1H), 4.32 (dd, 2H, J=50Hz, 15Hz), 4.19-4.27 (m, 1H), 3.84-3.87 (m, 4H), 3.12-3.16 (m, 4H), 1.91-1.95 (m, 1H), 1.35-1.39 (m, 1H), 0.92-1.06 (m, 2H), 0.74 (t, 3H, J=8.0Hz).
249				2	sólido amarillo	479.05	1.18 min Método B	479.02	RMN ^1H ($CDCl_3$) δ 7.63 (d, 2H, J=8.0Hz), 7.40 (d, 2H, J=8.0Hz), 7.19 (d, 2H, J=8.8Hz), 6.78 (d, 2H, J=8.8Hz), 6.25 (s, amplio, 1H), 5.21 (s, amplio, 1H), 4.36 (dd, 2H, J=50Hz, 15Hz), 4.20-4.27 (m, 1H), 3.28-3.35 (m, 4H), 2.69-2.76 (m,

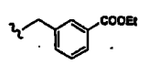
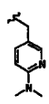
402

									4H), 2.48 (s, 3H), 1.93-1.97 (m, 1H), 1.35-1.39 (m, 1H), 0.90-1.07 (m, 2H), 0.72 (t, 3H, J=8.0Hz).
250				2	sólido color canela	474.03	1.92 min Método B	474.2	RMN ^1H ($CDCl_3$) δ 7.68 (d, 2H, J=8.8Hz), 7.43-7.45 (m, 4H), 7.12 (d, 2H, J=8.8Hz), 6.78 (d, 2H, J=8.8Hz), 6.19 (s, amplio, 1H), 5.18 (s, amplio, 1H), 4.56 (dd, 2H, J=50Hz, 15Hz), 4.21-4.30 (m, 1H), 2.01 (s, 6H), 1.93-1.97 (m, 1H), 1.35-1.39 (m, 1H), 0.90-1.07 (m, 2H), 0.72 (t, 3H, J=8.0Hz).
251				6	sólido blanco	482.00	2.01 min Método B	479.07	RMN ^1H ($CDCl_3$, 300MHz) δ 7.67 (ddd, 2H, J=1.9, 2.4, 8.7), 7.58 (d, 2H, J=8.1), 7.43 (ddd, 2H, J=1.5, 2.4, 8.7), 7.37 (d, 2H, J=8.2), 6.30 (s amplio, 1H), 5.70 (s amplio, 1H),

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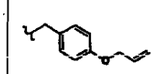
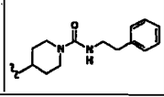
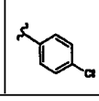
									4.62 (d, 1H, J=15.9), 4.46 (d, 1H, J=15.9), 4.32 (t, 1H, J=7.3), 3.51 (s, 3H), 3.32 (s, 3H), 1.73-1.80 (m, 1H), 1.28-1.35 (m, 1H), 1.05-1.14 (m, 1H), 0.74 (d, 3H, J=6.5), 0.61 (d, 3H, J=6.6).
252				1-Método A	sólido blanco	466.98	1.92 min Método A	467.2	RMN 1H ($CDCl_3$) δ 7.92 (d, 1H, J=8.0Hz), 7.79 (A de ABq, 2H, J=8.8Hz), 7.72 (d, 1H, J=7.7Hz), 7.50 (B de ABq, 2H, J=8.8Hz), 7.31 (t, 1H, J=7.7Hz), 6.29 (s amplio, 1H), 5.21 (s amplio, 1H), 5.02 (s, 2H), 4.35 (q, 2H, J=7.0Hz), 4.27 (dd, 1H, J=8.6, 5.5Hz), 1.88-1.78 (m, 1H), 1.39 (t, 3H, J=7.0Hz), 1.37-1.29 (m, 1H), 1.02-0.93 (m, 1H), 0.75 (d, 3H, J=6.6Hz), 0.66 (d, 3H, J=6.6Hz).

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253				1-Método A	sólido blanco	481.01	1.81 min Método A	481.2	RMN ^1H ($CDCl_3$) δ 7.67 (A de ABq, 2H, J=8.8Hz), 7.44 (B de ABq, 2H, J=8.8Hz), 7.27-7.15 (m, 3H), 6.24 (s amplio, 1H), 5.26 (s amplio, 1H), 4.55 (A de ABq, 1H, J=15.4Hz), 4.39 (B de ABq 1H, J=15.4Hz), 4.29 (t, 1H, J=7.0Hz), 4.15 (q, 2H, J=7.2Hz), 1.87-1.78 (m, 1H), 1.37-1.29 (m, 1H), 1.26 (t, 3H, =7.2Hz), 1.24-1.13 (m, 1H), 0.76 (d, 3H, J=6.2Hz), 0.67 (d, 3H, J=6.6Hz).
254				10	sólido blanco	438.98	1.20 Método B	439.05	RMN ^1H ($CDCl_3$) sal de TFA: δ 8.04 (s, 1H), 8.03 (d, 1H, J=9.80Hz), 7.76 (d, 2H, J=7.6 Hz), 7.54 (d, 2H, J=7.6Hz), 6.83 (d, 1H, J=9.8 Hz), 6.62 (s amplio,1H), 6.40 (s amplio, 1H), 4.64 (d, 1H, J=15.9 Hz), 4.29

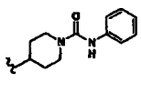
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									(m, 1H), 4.18 (d, 1H, J=15.9 Hz), 3.30 (s, 6H), 1.84 (m, 1H), 1.29 (m, 1H), 0.93 (m, 1H), 0.77 (d, 3H, J=6.5Hz), 0.72 (d, 3H, J=6.5Hz).
255				1-Método A	residuo anaranjado claro	450.14	2.02 min Método E	450.98	RMN ^{1}H (DMSO) δ 7.78 (d, 2H, J=8.4Hz), 7.58 (d, 2H, J=8.8Hz), 7.47 (s, amplio, 1H), 7.29 (d, 2H, J=8.8Hz), 7.00 (s amplio, 1H), 6.87 (d, 2H; J=8.8Hz), 6.03 (m, 1H), 5.32 (dd, 2H, J=12Hz, 56Hz), 4.63 (m, 4H), 5.32 (dd, 2H, J=12Hz, 56Hz), 4.35 (m, 1H), 1.33 (m, 3H), 0.80 (d, 3H, J=6.0Hz), 0.50 (d, 3H, J=6.0Hz).
256				7	sólido blanco	548.22	1.87 min Método A	549.00	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.71 (d, 2H, J=8.6), 7.71 (d, 2H, J=8.9), 7.15-7.35 (m, 5H), 6.64 (s, 1H), 5.86 (s, 1H), 4.15 (dd, 1H, J=5.2, 9.5),

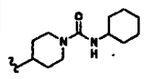
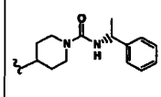
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									3.88 (d, 1H, J=13), 3.76 (d, 1H, J=13), 3.46 (t, 2H, J=6.7), 3.21-3.29 (m, 1H), 2.97 (dd, 1H, J=4.6, 14), 2.65-2.85 (m, 4H), 1.75-1.95 (m, 3H), 1.00-1.30 (m, 5H), 0.75-0.80 (m, 1H), 0.72 (d, 3H, J=6.7), 0.67 (d, 3H, J=6.7).
257				7	sólido blanco	520.19	1.74 min Método A	521.31	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, J=8.8), 7.51 (d, 2H, J=8.8), 7.33 (d, 2H, J=7.6), 7.28 (d, 2H, J=7.6), 7.03 (t, 1H, J=7.3), 6.67 (s, 1H), 5.42 (s, 1H), 3.97-4.22 (m, 3H), 3.27-3.35 (m, 1H), 2.78-3.02 (m, 3H), 1.83-1.99 (m, 3H), 1.09-1.42 (m, 4H), 0.75-0.82 (m, 1H), 0.74 (d, 3H J=6.4), 0.67 (d, 3H, J=6.7).

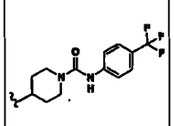
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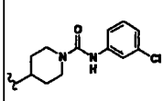
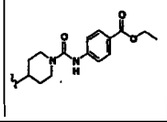
258				7	sólido blanco	526.24	1.81 min Método A	527.34	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.73 (d, 2H, J=8.9), 7.51 (d, 2H, 8.9), 6.65 (s, 1H), 5.37 (s, 1H), 4.15 (dd, 1H, J=5.1, 6.5), 3.92 (d, 1H, J=12), 3.82 (d, 1H, J=14), 3.57-3.67 (m, 1H), 3.26 (dd, 1H, J=10, 14), 2.98 (dd, 1H, J=4.5, 14), 2.74 (q, 2H, J=12, 24), 1.80-1.97 (m, 5H), 1.64-1.72 (m, 3H), 1.00-1.43 (m, 10H), 0.75-0.82 (m, 1H), 0.73 (d, 3H, J=6.4), 0.67 (d, 3H, 6.7).
259				7	sólido blanco	548.22	1.78 min Método A	549.32	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.71 (d, 2H, J=8.2), 7.50 (d, 2H, J=8.5), 7.30 (d, 4H, J=4.3), 7.20-7.25 (m, 1H), 6.65 (s, 1H), 5.74 (s, 1H), 4.99 (t, 1H, J=7.02), 4.70-4.77 (m, 1H), 4.10-4.25 (m, 1H), 4.00 (d, 1H,

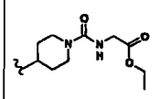
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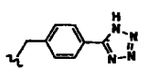
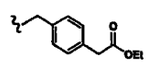
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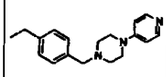
									J=13), 3.90 (d, 1H, J=13), 3.15-3.35 (m, 1H), 2.90-3.00 (m, 1H), 2.60-2.75 (m, 2H), 1.50-1.95 (m, 5H), 1.46 (d, 3H, J=6.7), 1.00-1.30 (m, 2H), 0.75-0.83 (m, 1H), 0.73 (d, 3H, J=6.4), 0.67 (d, 3H, J=6.4).
260				7	sólido blanco	588.18	1.90 min Método A	589.25	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.73 (d, 2H, J=8.9), 7.62 (d, 4H, J=8.6), 7.45 (d, 2H, J=8.5), 6.67 (s, 1H), 6.52 (s, 1H), 4.45 (s, 1H), 4.16 (dd, 1H, J=5.2, 9.8), 4.12 (d, 1H, J=12), 4.03 (d, 1H, J=14), 3.80 (dd, 1H, J=10, 14), 3.00 (dd, 1H, J=4.5, 14), 2.84-2.92 (m, 2H), 1.85-2.00 (m, 3H), 1.69 (d, 1H, J=12), 1.10-1.35 (m, 3H), 0.75-0.82 (m, 1H), 0.74 (d, 3H, J=6.7), 0.68 (d, 3H, J=6.7).

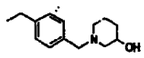
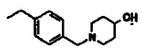
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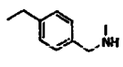
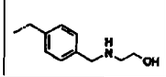
261				7	sólido blanco	554.14	1.86 min Método A	555.24	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.73 (d, 2H, J=8.6), 7.52 (d, 2H, J=8.9), 7.45 (s, 1H), 7.18 (d, 2H, J=6.7), 6.95-7.02 (m, 1H), 6.65 (s, 1H), 6.50 (s, 1H), 5.50 (s, 1H), 4.16 (dd, 1H, J=5.2, 9.5), 4.08 (d, 1H, J=15), 3.99 (d, 1H, J=14), 3.30 (dd, 1H, J=10, 15), 2.99 (dd, 1H, J=4.5, 15), 2.80-2.92 (m, 2H), 1.80-2.00 (m, 3H), 1.67 (d, 1H, J=13), 1.05-1.40 (m, 4H), 0.75-0.80 (m, 1H), 0.74 (d, 3H, J=6.7), 0.68 (d, 3H, J=6.7).
262				7	sólido blanco	592.21	1.86 min Método A	593.30	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.96 (d, 2H, J=8.9), 7.73 (d, 2H, J=8.9), 7.51 (d, J=8.6), 7.42 (d, 2H, J=8.6), 6.65 (s, 2H), 5.45 (s, 1H), 4.83 (q, 2H, J=7.0), 4.16 (dd, 1H, J=5.2, 9.8),

									4.11 (d, 1H, J=13), 4.03 (d, 1H, J=13), 3.30 (dd, 1H, J=10, 14), 3.00 (dd, 1H, J=4.2, 14), 2.81-2.95 (m, 2H), 1.84-2.01 (m, 3H), 1.68 (d, 1H, J=13), 1.37 (t, 3H, J=7.3), 1.08-1.34 (m, 4H), 0.76-0.82 (m, 1H), 0.74 (d, 3H, J=6.7), 0.68 (d, 3H, J=6.7).
263				7	sólido blanco	530.20	2.18 min Método C	531.11	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.73 (d, 2H, J=8.5), 7.51 (d, 2H, J=8.6), 6.67 (s, 1H), 5.41 (s, 1H), 4.97 (s, 1H), 4.20 (q, 2H, J=7.0), 4.15 (dd, 1H, J=5.1, 9.5), 3.90-4.04 (m, 4H), 3.26 (dd, 1H, J=10, 14), 2.99 (dd, H, J=4.5, 14), 2.70-2.82 (m, 2H), 1.80-1.95 (m, 3H), 1.28 (t, 3H, J=7.3), 1.05-1.25 (m, 3H), 0.75-0.80 (m, 1H), 0.72 (d, 3H, J=6.7), 0.67 (d, 3H, J=6.4).

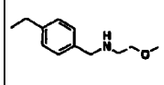
264				1-Método A	sólido blanco	462.96	1.47 Método B	462.98	RMN ^1H ($CDCl_3$) δ 7.81 (d, 2H, J=8.4Hz), 7.75 (d, 2H, J=8.0Hz), 7.55 (d, 2H, J=8.4Hz), 7.5 (d, 2H, J=8.0Hz), 6.86 (s, 1H), 6.44 (s, 1H), 4.96 (d, 1H, J=15.6Hz) 4.36 (dd, 1H, J=5.6Hz, 6.0Hz), 1.99 (m, 1H), 1.29 (m, 1H), 1.06 (m, 1H), 0.77 (d, 3H, J=6.8Hz), 0.74 (d, 3H, J=6.8Hz).
265				1-Método A	sólido blanco	481.01	1.81 min Método A	481.3	RMN ^1H ($CDCl_3$) δ 7.61 (A de ABq, 2H, J=8.8Hz), 7.42 (B de ABq, 2H, J=8.8Hz), 7.27 (A de ABq, 2H, J=8.4Hz), 7.19 (B de ABq, 2H, J=8.4Hz), 6.21 (s amplio, 1H), 5.19 (s amplio, 1H), 4.52 (A de ABq, 1H, J=15.5Hz, 1H), 4.39 (B de ABq, 1H, J=15.5Hz, 1H), 4.30 (t, 1H, J=7.3Hz), 4.14 (q, 2H, J=7.1Hz),

									3.58 (s, 2H), 1.86-1.76 (m, 1H), 1.36-1.27 (m, 1H), 1.14 (t, 3H, J=7.1Hz), 1.23-1.13 (m, 1H), 0.76 (d, 3H, J=6.2Hz), 0.66 (d, 3H, J=6.6Hz).
266				8	espuma blanca	570.16	1.17 min Método A	570.39	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 8.21 (d, 2H, J=4.0Hz), 8.02 (d, 2H. J=8.0Hz), 7.59 (d, 2H, J=8.0Hz), 7.39-7.33 (m, 4H), 6.83 (d, 2H, J=4.0Hz), 6.23 (s, amplio, 1H), 5.34 (s, amplio, 1H), 4.60 (d, 1H, J_{ab}=16Hz), 4.39 (d, 1H, J_{ab}=16Hz), 3.57 (s, 2H), 3.27-3.15 (m, 5H), 2.58-2.45 (m, 4H), 1.94 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).

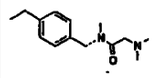
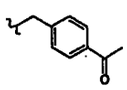
267				8	espuma blanca	508.08	1.28 min Método A	508.21	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.63 (d, 2H, J=8.0Hz), 7.43-7.36 (m, 4H), 6.27 (s, amplio, 1H), 5.39 (s, amplio, 1H), 4.59 (d, 1H, J_{ab}=16Hz), 4.36 (d, 1H, J_{ab}=16Hz), 2.83 (m, 1H), 2.41 (m, 2H), 2.18 (m, 1H), 1.95 (m, 1H), 1.85 (m 1H), 1.76-1.52 (m, 5H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
268				8	espuma blanca	508.08	1.26 min Método A	508.18	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.65 (d, 2H, J=8.0Hz), 7.45 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.27 (s, amplio, 1H), 5.39 (s, amplio, 1H), 4.59 (d, 1H, J_{ab}=16Hz), 4.36 (d, 1H, J_{ab}=16Hz), 3.77 (m, 1H), 3.47 (s, 2H), 3.25 (t,

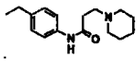
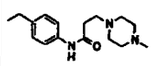
									1H, J=6.0Hz), 2.80 (m, 4H), 1.95 (m, 1H), 1.77-1.50 (m, 6H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
269				8	espuma blanca	437.99	1.28 min Método A	438.16	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.71 (d, 2H, J=8.0Hz), 7.66 (d, 2H, J=8.0Hz), 7.43 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 6.35 (s, amplio, 1H), 5.87 (s, amplio, 1H), 4.76 (d, 1H, J_{ab}=16Hz), 4.30 (d, 1H, J_{ab}=16Hz), 3.54 (s, 5H), 3.25 (t, 1H, J=6.0Hz), 1.94 (m, 1H), 1.60 (m, 2H), 1.18 (s, amplio, NH), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
270				8	sólido blanco	468.02	1.28 min Método A	468.16	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.72 (d, 2H, J=8.0Hz), 7.67 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.33 (d, 2H, J=8.0Hz), 6.35 (s, amplio,1H), 5.85

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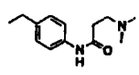
									(s, amplio,1H), 4.24-4.12 (m, 4H), 3.67 (s, 2H), 3.24 (t, 1H, J=6.0Hz), 3.06 (t, 2H, J=6.0Hz), 2.60 (s, amplio, NH), 1.95 (m, 1H), 1.68-1.52 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
271				8	vidrio claro	482.05	1.31 min Método A	482.18	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.79 (d, 2H, J=8.0Hz), 7.69 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.33 (d, 2H, J=8.0Hz), 6.35 (s, amplio, 1H), 5.85 (s, amplio, 1H), 4.60 (d, 1H, J_{ab}=16Hz), 4.43 (d, 1H, J_{ab}=16Hz), 3.67 (s, 2H), 3.61 (t, 2H, J=6.0Hz), 3.35 (s, 3H), 3.29-3.24 (m, 3H), 1.94 (m, 1H), 1.62 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).

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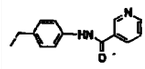
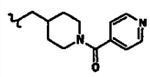
272				9	sólido blanco	523.1	1.30 min Método A	523.40	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 8.02 (d, 2H, J=8.0Hz), 7.71 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 7.28 (d, 2H, J=8.0Hz), 6.23 (s, amplio, 1H), 5.51 (s, amplio, 1H), 4.46 (s, 2H), 4.70 (d, 1H, J_{ab}=16Hz), 4.33 (d, 1H, J_{ab}=16Hz), 3.25 (t, 1H, J=6.0Hz), 2.69 (s, 3H), 2.63 (s, 2H), 2.20 (s, 6H), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
273				16	sólido blanco	436.96	1.43 min Método B	437.13	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.87 (d, 2H, J=8.4), 7.67 (dd, 2H, J=1.8, 8.7), 7.42-7.46 (m, 4H), 6.21 (s amplio, 1H), 5.28 (s amplio, 1H), 4.64 (d, 1H, J=15.9), 4.45 (d, 1H, J=15.9), 4.31 (t, 1H, J=6.6), 2.58 (s, 3H), 1.73-1.80 (m, 1H), 1.25-1.35

									(m, 1H), 1.05-1.14 (m, 1H), 0.74 (d, 3H, J=6.5), 0.65 (d, 3H, J=6.6).
274				17	espuma amarilla	549.14	1.38 min Método A	549.16	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.63 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.23 (d, 2H, J=8.0Hz), 6.25 (s, amplio, 1H), 5.35 (s, amplio, 1H), 4.75 (d, 1H, J_{ab}=16Hz), 4.38 (d, 1H, J_{ab}=16Hz), 3.25 (t, 1H, J=6.0Hz), 2.65 (t, 2H, J=6.0Hz), 2.56-2.44 (m, 6H), 1.95 (m, 1H), 1.68-1.45 (m, 8H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
275				17	vidrio claro	564.15	1.21 min Método A	564.32	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 9.30 (s, 1H, NH), 8.02 (d, 2H, J=8.0Hz), 7.61 (d, 2H, J=8.0Hz), 7.36 (d, 2H, J=8.0Hz), 7.23 (d, 2H, J=8.0Hz), 6.25 (s, amplio, 1H), 5.33 (s, amplio,

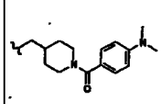
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									1H), 4.72 (d, 1H, J_{ab}=16Hz), 4.48 (d, 1H, J_{ab}=16Hz), 3.25 (t, 1H, J=6.0Hz), 2.65-2.38 (m, 12H), 2.28 (s, 2H), 1.95 (m, 1H), 1.59 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
276				17	espuma color canela	509.07	1.33 min Método A	509.17	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 9.31 (s, 1H, NH), 8.02 (d, 2H, J=8.0Hz), 7.63 (d, 2H, J=8.0Hz), 7.36 (d, 2H, J=8.0Hz), 7.23 (d, 2H, J=8.0Hz), 6.25 (s, amplio, 1H), 5.34 (s, amplio, 1H), 4.71 (d, 1H, J_{ab}=16Hz), 4.48 (d, 1H, J_{ab}=16Hz), 3.25 (t, 1H, J=6.0Hz), 2.66 (t, 2H, J=8.0Hz), 2.56 (t, 2H, J=8.0Hz), 2.38 (s, 6H), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).

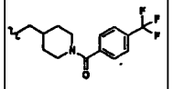
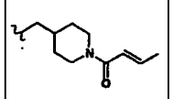
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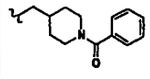
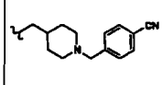
277				9	espuma color canela	515.04	1.47 min Método A	515.13	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 8.95 (s, amplio, NH), 8.67 (d, 1H, J=8.0Hz), 8.17 (d, 1H, J=8.0Hz), 8.02 (d, 2H, J=8.0Hz), 7.77 (d, 2H, J=8.0Hz), 7.57 (m, 4H), 7.38 (d, 2H, J=8.0Hz), 6.27 (s, amplio, 1H), 5.39 (s, amplio, 1H), 4.72 (d, 1H, J_{ab}=16Hz), 4.30 (d, 1H, J_{ab}=16Hz), 3.25 (t, 1H, J=6.0Hz), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
278				7	sólido blanco	507.06	2.44 min Método C	509.20	RMN ^{1}H ($CDCl_3$, 500MHz) δ 8.66 (s amplio, 2H), 7.80 (d, 1H, J=8.6), 7.73 (d, 2H, J=8.5), 7.51 (d, 2H, J=7.6), 7.41 (s amplio, 1H), 6.64 (s amplio, 1H), 5.35 (s amplio, 1H), 4.70 (s amplio, 1H), 4.10 (s amplio,

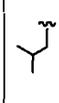
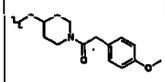
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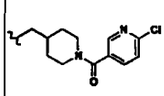
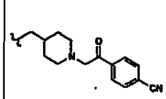
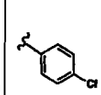
									1H), 3.71 (s amplio,1H), 3.33 (s amplio,1H), 3.02 (dd, 2H, J=4.8, 16), 2.70-2.85 (s amplio, 1H), 1.50-2.09 (m, 5H), 1.18-1.33 (m, 4H), 0.73 (d, 3H, J=6.7), 0.68 (d, 3H, J=6.5).
279				7	sólido blanco	549.14	2.76 min Método C	549.07	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.74 (dd, 2H, J=1.7, 6.7), 7.51 (dd, 2H, J=2.2, 6.9), 7.34 (d, 2H, J=8.0), 6.70 (s amplio, 1H), 6.60 (s amplio, 1H), 5.30 (s amplio, 1H), 4.13 (dd 1H, J=5.5, 10), 3.35 (dd, 1H, J=11, 14), 3.00 (s, 6H), 2.85 (s, 2H), 1.80-2.00 (m, 3H), 1.50-1.70 (m, 1H), 1.10-1.30 (m, 4H), 0.80-0.90 (m, 1H), 0.745 (d, 3H, J=6.7), 0.67 (d, 3H, J=6.5).

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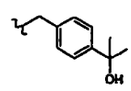
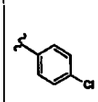
280				7	sólido blanco	574.07	3.03 Método C	574.03	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.73 (d, 2H, J=8.2), 7.65 (d, 2H, J=7.9), 7.51 (d, 2H, J=8.9), 7.48 (d, 2H, J=7.6), 6.65 (s amplio, 1H), 5.45 (s amplio, 1H), 4.71 (s amplio, 1H), 4.13 (s amplio, 1H), 3.65 (s amplio, 1H), 3.30 (s amplio, 1H), 2.97 (d, 2H J=12), 2.65-2.86 (m, 1H), 1.45-2.07 (m, 6H), 0.98-1.85 (m, 3H), 0.73 (amplio, s, 3H), 0.67 (amplio, s, 3H).
281				7	sólido blanco	470.04	2.78 min Método C	470.03	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, J=8.5), 7.50 (d, 2H, J=8.6), 6.78-6.90 (m, 1H), 6.55-6.65 (m, 1H), 6.23 (dd, 1H, J=1.5, 15), 5.33-5.60 (m, 1H), 4.50-4.75 (m, 1H), 4.09-4.20 (m, 1H), 3.90-4.05 (m, 1H), 2.80-3.25 (m, 3H), 2.40-2.75

									(m, 1H), 1.50-2.00 (m, 8H), 1.00-1.40 (m, 3H), 0.73 (amplio, s, 3H), 0.67 (amplio, s, 3H).
282				7	sólido blanco	506.07	2.86 min Método C	508.03	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.73 (d, 2H, J=8.5), 7.51 (d, 2H, J=8.5), 7.38 (s amplio, 4H), 6.65 (s amplio, 1H), 5.35 (s amplio, 1H), 4.71 (s amplio, 1H), 4.14 (s amplio, 1H), 3.76 (s amplio, 1H), 3.30 (s amplio, 1H), 2.60-3.05 (m, 3H), 0.99-2.05 (m, 10H), 0.73 (d, 3H, J=7.8), 0.67 (d, 3H, J=7.8).
283				7	sólido blanco	517.09	1.37 min Método A	517.19	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, J=8.5), 7.50-7.65 (m, 2H), 7.50 (d, 2H, J=7.0), 7.35-7.45 (m, 2H), 6.67 (s, 1H), 5.32 (s, 1H), 4.14 (dd, 1H, J=5.0, 9.0), 3.52 (s amplio, 1H), 3.28 (t, 1H, J=14)

									2.97 (dd, 1H J=3.5, 14), 2.82 (s amplio, 1H), 1.00-2.00 (m, 10H), 0.71 (d, 3H, J=6.5), 0.66 (d, 3H, J=6.5).
284				7	sólido blanco	550.12	2.87 min Método C	550.06	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, J=8.6), 7.50 (d, 2H, J=8.5), 7.13 (d, 2H, J=8.5), 6.85 (s amplio, 2H), 6.63 (d, 1H, J=33), 5.41 (s amplio, 1H), 4.62 (t, 1H, J=14), 4.10-4.17 (m, 1H), 3.75-3.90 (m, 4H), 3.65 (s, 3H), 3.14-3.30 (m, 1H), 2.80-2.95 (m, 2H), 2.43-2.60 (m, 1H), 1.45-2.00 (m, 4H), 1.15-1.30 (m, 2H), 0.71 (dd, 3H, J=7.6, 8.4), 0.65 (dd, 3H, J=6.0, 8.0).

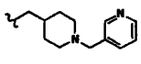
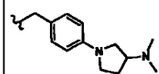
285				7	sólido blanco	541.50	2.76 min Método C	540.98	RMN ^{1}H ($CDCl_3$, 500MHz) δ 8.43 (s, 1H), 7.73 (d, 2H, J=8.5), 7.70 (d, 1H, J=2.4, 8.4), 7.51 (d, 2H, J=8.6), 7.87 (d, 1H, J=8.2), 6.63 (s amplio, 1H), 5.35 (s amplio, 1H), 4.68 (s amplio, 1H), 4.15 (dd, 1H, J=4.9, 9.8) 3.71 (s amplio, 1H), 3.31 (s amplio, 1H), 3.00 (dd, 2H, J=4.8, 14), 2.65-2.86 (m, 1H), 1.77-2.07 (m, 3H), 1.6-1.76 (m, 1H), 1.00-1.86 (m, 3H), 0.85-0.93 (m, 1H), 0.73 (d, 3H, J=6.7), 0.67 (d, 3H, J=6.7).
286				7	sólido blanco	545.11	1.36 min Método A	545.16	RMN ^{1}H ($CDCl_3$, 500MHz) δ 8.11 (d, 2H, J=8.6), 7.75 (d, 2H, J=8.6), 7.73 (d, 2H, J=8.9), 7.50 (d, 2H, J=8.9), 6.65 (s amplio, 1H), 5.38 (s amplio, 1H), 4.14 (dd, 1H, 7=5.5, 9.5), 3.80

475

									(s amplio, 1H), 3.27 (dd, 1H, J=10, 14), 2.97 (dd, 2H, J=4.6, 14), 1.17-2.00 (m, 11H), 0.75-0.81 (m, 1H), 0.73 (d, 3H, J=6.4), 0.67 (d, 3H, J=6.7).
287				12	sólido blanco	453.01	1.81 min Método A	453.16	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.61 (d, 2H, J=8.7), 7.40 (d, 2H, J=8.7), 7.37 (d, 2H, J=8.4), 7.26 (d, 2H, J=8.4), 6.28 (s amplio, 1H), 5.25 (s amplio, 1H), 4.49 (d, 1H, J=15.9), 4.41 (d, 1H, J=15.9), 4.33 (t, 1H, J=6.6), 1.73-1.80 (m, 1H), 1.55 (s, 6H), 1.28-1.35 (m, 1H), 1.20-1.25 (m, 1H), 0.77 (d, 3H, J=6.5), 0.66 (d, 3H, J=6.6).

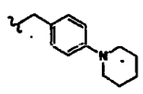
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288				7	sólido blanco	493.07	1.25 min Método A	493.23	RMN ^1H ($CDCl_3$, 500MHz) δ 8.51 (s, 2H), 7.73 (d, 2H, J=8.5), 7.50 (d, 2H, J=8.5), 6.67 (s, 1H), 5.83 (s, 1H), 4.15 (dd, 1H,.7=5.2, 8.9), 3.50 (s amplio, 2H), 3.25 (dd, 1H, J=8.5, 14), 2.75-3.05 (m, 3H), 1.60-2.10 (m, 6H), 1.10-1.40 (m, 4H), 0.75-0.85 (m, 1H), 0.72 (d, 3H, J=6.4), 0.67 (d, 3H, J=6.7).
289				2	sólido Amarillo	493.07	0.93 min Método B	493.2	RMN ^1H ($CDCl_3$) δ 7.67 (d, 2H, J=7.0Hz), 7.44 (d, 2H, J=7.0Hz), 7.19 (d, 2H, J=8.0Hz), 6.46 (d, 2H, J=8.0Hz), 6.21 (s, amplio, 1H), 5.17 (s, amplio, 1H), 4.31 (dd, 2H, J=50Hz, 15Hz), 4.15-4.22 (m, 1H), 3.84-3.87 (m, 4H), 3.91-3.99 (m, 1H), 3.51-3.54 (m, 3H), 3.22-3.26

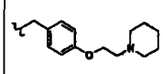
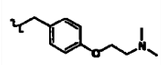
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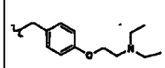
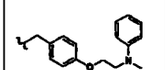
477

									(m, 1H), 2.75 (s, 3H), 2.72 (s, 3H), 2.23-2.36 (m, 2H), 1.91-1.98 (m, 1H), 1.32-1.40 (m, 1H), 0.81-1.04 (m, 2H), 0.73 (t, 3H, 7.2Hz).
290				2	sólido color canela	464.03	1.16 min Método B	464.2	RMN ^1H ($CDCl_3$) δ 7.62 (d, 2H, J=8.8Hz), 7.40 (d, 2H, J=8.0Hz), 7.11-7.20 (m, 2H), 6.79-6.86 (m, 2H), 6.20 (s, amplio, 1H), 5.13 (s, amplio, 1H), 4.30 (dd, 2H, J=50Hz, 15Hz), 4.13-4.21 (m, 1H) 3.10-3.19 (m, 4H), 1.92-1.95 (m, 1H), 1.39-1.90 (m, 8H), 1.22-1.26 (m, 1H), 0.97-1.05 (m, 2H), 0.73 (t, 3H, J=8.0Hz).

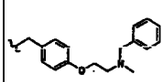
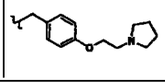
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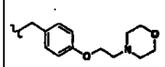
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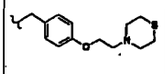
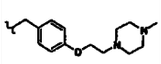
291				11	sólido anaran-jado	522.11	1.52 min Método E	522.1	RMN ^{1}H (DMSO) δ 7.78 (d, 2H, J=8.4Hz), 7.58 (d, 2H, J=8.8Hz), 7.47 (s, amplio, 1H), 7.27 (d, 2H, J=8.4Hz), 7.00 (s amplio, 1H), 6.85 (d, 2H, J=8.8Hz), 4.63 (dd, 2H, J=16Hz, 38Hz), 4.34 (m, 1H), 4.03 (s, 2H), 2.63 (m, 2H), 2.42 (m, 3H), 1.39 (m, 10H), 0.80 (d, 3H, J=6.0Hz), 0.50 (d, 3H, J=6.0Hz).
292				11	sólido blanco	481.18	1.46 min Método E	482.06	RMN ^{1}H (DMSO) δ 7.79 (d, 2H, J=8.8Hz), 7.60 (d, 2H, J=8.8Hz), 7.49 (s, amplio, 1H), 7.35 (d, 2H, J=8.4Hz), 7.01 (s amplio, 1H), 6.94 (d, 2H, J=8.8Hz), 4.68 (dd, 2H, J=16Hz, 53Hz), 435 (m, 1H), 4.28 (t, 2H, J=4.8Hz), 3.34 (m, 2H), 2.86 (s, 6H), 1.33 (m, 3H), 0.80 (d, 3H,

									J=6.0Hz), 0.50 (d, 3H, J=6.0Hz).
293				11	residuo blanco	509.21	1,52 min Método E	M+Na 532.03	RMN ^{1}H (DMSO) δ 7.79 (d, 2H, J=8.4Hz), 7.60 (d, 2H, J=8.4Hz), 7.48 (s, amplio, 1H), 7.35 (d, 2H, J=8.8Hz), 7.01 (s amplio, 1H), 6.94 (d, 2H, J=8.8Hz), 4.68 (dd, 2H, J=17Hz, 54Hz), 4.35 (m, 1H), 4.28 (t, 2H, J=4.8Hz), 3.51 (m, 3H), 3.21 (m, 3H), 1.29 (m, 9H), 0.80 (d, 3H, J=6.0Hz), 0.50 (d, 3H, J=6.0Hz).
294				11	sólido café claro	544.12	1.78 min Método E	544.13	RMN ^{1}H (DMSO) δ 7.78 (d, 2H, J=8.9Hz), 7.57 (d, 2H, J=8.0Hz), 7.45 (s, amplio, 1H), 7.27 (d, 2H, J=8.0Hz), 7.17 (t, 2H, J=8.9Hz) 7.00 (s amplio, 1H), 6.84 (d, 2H, J=8.0Hz), 6.75 (d, 2H, J=8.0Hz), 6.62 (t, 1H, J=8.0Hz), 4.65 (dd, 2H, J=17Hz, 41Hz), 4.34 (m,

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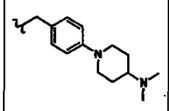
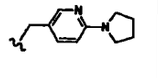
									1H), 4.10 (t, 2H, J=5.5Hz), 3.71 (t, 2H, J=7.9Hz), 2.96 (m, 3H), 1.32 (m, 3H), 0.79 (d, 3H, J=6.0Hz), 0.49 (d, 3H, J=6.0Hz).
295				11	polvo blanco	558.14	1.62 min Método B	558.10	RMN ^{1}H (DMSO) δ 7.80 (d, 2H, J=8.6Hz), 7.80 (d, 2H, J=8.6Hz), 7.54 (m, 2H), 7.49 (m, 4H), 7.34 (d, 2H, J=8.6Hz) 7.01 (s amplio,1H), 6.93 (d, 2H, J=8.6Hz), 4.68 (dd, 2H, J=17.0Hz, 54Hz), 4.47 (m, 1H), 4.36 (m, 4Hz), 3.50 (m, 2H), 2.80 (s, 3H), 1.34 (m, 3H), 0.80 (d, 3H, J=6.0Hz), 0.51 (d, 3H, J=6.0Hz).
296				11	polvo blanco	508.08	1.49 min Método E	508.07	RMN ^{1}H (DMSO) δ 7.79 (d, 2H, J=8.6Hz), 7.61 (d, 2H, J=8.6Hz), 7.49 (s, amplio, 1H), 7.35 (d, 2H, J=8.6Hz), 7.00 (s amplio, 1H), 6.94

									(d, 2H, J=8.6Hz), 4.68 (dd, 2H, J=17.0Hz, 53Hz), 4.35 (m, 1H), 4.27 (m, 2H), 3.59 (m, 4H), 3.13 (m, 2H), 2.03 (m, 2H), 1.89 (m, 2H), 1.34 (m, 3H), 0.80 (d, 3H, J=6.0Hz), 0.52 (d, 3H, J=6.0Hz).
297				11	sólido blanque-cino	5.24.07	1.46 min Método E	524.09	RMN ^{1}H (DMSO) δ 7.78 (d, 2H, J=8.9Hz), 7.57 (d, 2H, J=8.0Hz), 7.45 (s, amplio, 1H), 7.27 (d, 2H, J=8.0Hz), 7.17 (t, 2H, J=8.9Hz), 7.00 (s amplio, 1H), 6.84 (d, 2H, J=8.0Hz), 6.75 (d, 2H, J=8.0Hz), 6.62 (t, 1H, J=8.0Hz), 4.65 (dd, 2H, J=17Hz, 41Hz), 4.34 (m, 1H), 4.10 (t, 2H, J=5.5Hz), 3.71 (t, 2H, J=7.9Hz), 2.96 (m, 3H), 1.32 (m, 3H), 0.79 (d, 3H, J=6.0Hz), 0.49 (d, 3H, J=6.0Hz).

298				11	sólido blanco	540.15	1.52 min Método E	540.06	RMN ^{1}H (DMSO) δ 7.80 (d, 2H, J=8.8Hz), 7.60 (d, 2H, J=8.0Hz), 7.48 (s amplio, 1H), 7.35 (d, 2H, J=8.8Hz), 7.01 (s amplio, 1H) 6.95 (d, 2H, J=8.8Hz), 4.68 (dd, 2H, J=16.4Hz, 55Hz), 4.34 (m, 3H), 3.79 (m, 2H), 3.58 (m, 2H), 3.27 (m, 2H), 3.02 (m, 2H), 2.89 (m, 2H), 1.34 (m, 3H), 0.80 (d, 3H, J=6.0Hz), 0.52 (d, 3H, J=6.0Hz).
299				11	sólido anaran-jado claro	537.13	1.43 min Método E	537.13	RMN ^{1}H (DMSO) δ 7.79 (d, 2H, J=8.8Hz), 7.59 (d, 2H, J=8.0Hz), 7.48 (s amplio, 1H), 7.31 (d, 2H, J=8.8Hz), 7.00 (s amplio, 1H), 6.88 (d, 2H, J=8.8Hz), 4.66 (dd, 2H, J=16.4Hz, 49Hz), 4.35 (m, 1H), 4.11 (m, 2H), 3.18 (m, 9H), 2.78 (m, 3H),

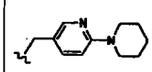
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									2.63 (m, 1H), 1.34 (m, 3H), 0.80 (d, 3H, J=6.0Hz), 0.51 (d, 3H, J=6.0Hz).
300				2	sólido color canela	507.10	1.19 min Método B	507.2	RMN ^{1}H ($CDCl_3$) δ 7.63 (d, 2H, J=8.0Hz), 7.41 (d, 2H, J=8.0Hz), 7.13-7.24 (m, 2H), 6.74-6.80 (m, 2H), 6.23 (s, amplio, 1H), 5.13 (s, amplio, 1H), 4.37 (dd, 2H, J=50Hz, 15Hz), 4.11-4.19 (m, 1H), 3.77-3.81 (m, 1H), 3.44 (s, 6H), 3.06-3.13 (m, 8H), 1.93-1.96 (m, 1H), 1.25-1.29 (m, 1H), 0.95-1.09 (m, 2H), 0.71 (t, 3H, J=8.0Hz).
301				10	espuma amarilla	465.02	1.22 Método B	465.25	RMN ^{1}H ($CDCl_3$) sal de TFA: δ 8.07 (s, 1H), 7.91 (d, 1H, J=9.6Hz), 7.74 (d, 2H, J=6.8Hz), 7.52 (d, 2H, J=6.8Hz), 6.64 (d, 1H, J=9.6Hz), 6.36 (s, 1H), 5.77 (s, 1H), 4.52 (d,

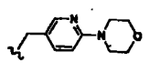
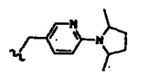
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									1H, J=16.0Hz); 4.28 (dd, 1H, J=5.6Hz, 6.0Hz), 4.21 (d, 1H, J=16.0Hz), 3.62 (m, 4H), 2.13 (m, 4H), 1.84 (m, 1H), 1.32 (m, 1H), 0.96 (m, 1H), 0.79 (d, 3H, J=6.8Hz), 0.72 (d, 3H, J=6.8Hz).
302				10	espuma amarilla	479.05	1.28 Método B	479.06	RMN ^{1}H ($CDCl_3$) sal de TFA: δ 8.01 (s, 1H), 7.95.(d, 1H, J=9.6Hz), 7.75 (d, 2H, J=8.0Hz), 7.50 (d, 2H, J=8.4Hz), 6.88 (d, 1H, J=9.6Hz), 6.43 (s, 1H), 6.04 (s, 1H), 4.53 (d, 1H, J=16.0Hz), 4.28 (dd, 1H, J=5.6Hz, 6.0Hz), 4.20 (d, 1H, J=16.0Hz), 3.65 (m, 4H), 1.82 (m, 1H), 1.74 (m, 6H), 1.31 (m, 1H), 0.95 (m, 1H), 0.78 (d, 3H, J=6.4Hz), 0.71 (d, 3H, J=6.4Hz).

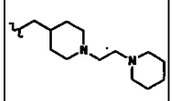
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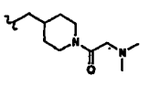
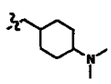
303				10	sólido blanco	481.02	1.16 Método B	481.05	RMN ^1H ($CDCl_3$) sal de TFA: δ 8.25 (s, 1H), 8.06 (d, 1H, J=9.6Hz), 7.74 (d, 2H, J=8.0Hz), 7.54 (d, 2H, J=8.0Hz), 6.91 (d, 1H, J=9.6Hz), 6.55 (s, 1H), 6.28 (s, 1H), 4.61 (d, 1H, J=16.0Hz), 4.28 (dd, 1H, J=5.2Hz, 6.2Hz), 4.21 (d, 1H, J=16.0Hz), 3.87 (m, 4H), 3.67 (m, 4H), 1.84 (m, 1H), 1.27 (m, 1H), 0.93 (m, 1H), 0.76 (d, 3H, J=6.4Hz), 0.72 (d, 3H, J=6.4Hz).
304				10	sólido café	493.07	1.357 Método B	493.04	RMN ^1H ($CDCl_3$) sal de TFA: δ 8.04 (s, 1H), 7.93 (d, 1H, J=9.2Hz), 7.73 (d, 2H, J=8.0Hz), 7.50 (d, 2H, J=8.0Hz), 6.69 (d, 1H, J=9.2Hz), 6.38 (s, 1H), 5.98 (s, 1H), 4.50 (d, 1H, J=16.0Hz), 4.30

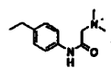
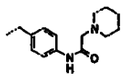
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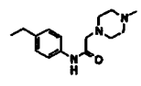
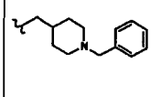
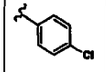
436

									(dd, 1H, J=5.6Hz, 6.0Hz), 4.22 (d, 1H, J=16.0Hz), 4.20 (m, 2H), 3.87 (m, 4H), 2.24 (m, 2H), 1.90 (m, 2H), 1.84 (m, 1H), 1.36 (d, 3H, J=2.0Hz), 1.34 (d, 3H, J=2.0Hz), 1.32 (m, 1H), 0.98 (m, 1H), 0.79 (d, 3H, J=6.4Hz), 0.72 (d, 3H, J=6.4Hz).
305				7	sólido blanco	513	1.03 min Método A	513.36	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, J=8.5), 7.50 (d, 2H, J=7.0), 6.65 (s, 1H), 6.35 (s, 1H), 4.14 (dd, 1H, J=5.5, 9.0), 3.25 (dd, 1H, J=10, 14), 1.35-2.95 (m, 24H), 1.15-1.30 (m, 3H), 0.72 (d, 3H, J=6.5), 0.67 (d, 3H, J=6.7).

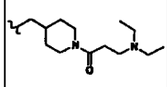
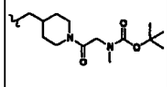
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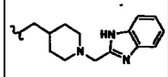
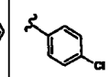
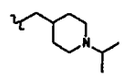
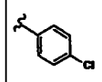
306				7	sólido blanco	487	1.43 min Método A	487.019	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.72 (d, 2H, J=8.4), 7.51 (d, 2H, J=8.7), 6.67 (d, 1H, J=24.3), 5.40 (d, 1H, J=12, 6), 4.54 (s amplio, 1H), 3.90-4.20 (m, 4H), 3.40-3.55 (m, 2H), 3.05-3.35 (m, 2H), 2.85-3.05 (m, 2H), 2.40-2.60 (m, 1H), 2.35 (d, 6H, J=8.1), 0.60-1.95 (m, 11H).
307				1-Método A	aceite claro	444.03	1.28 min Método B	444.04	RMN ^{1}H ($CDCl_3$) δ 7.72 (d, J=6.8Hz, 2H), 7.52 (d, J=6.8Hz, 2H), 6.75 (s, amplio, 1H), 5.79 (s, amplio, 1H), 4.14 (dd, J=9.6Hz, 4.8Hz, 1H), 3.23 (dd, J=14.4Hz, 10.0Hz, 1H), 3.12 (m, 1H), 2.92 (dd, J=14.4Hz, 4.8Hz, 1H), 2.77 (m, 6H), 2.09 (m, 2H), 1.83 (m, 1H), 1.71 (m, 1H), 0.75-1.52 (m, 8H), 0.73 (d, J=6.8Hz, 3H),

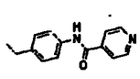
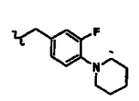
									0.67 (d, J=6.8Hz, 3H).
308				23	espuma color canela	495.04	1.13 min Método A	495.14	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 8.85 (s, 1H, NH), 8.02 (d, 2H, J=8.0Hz), 7.75 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.29 (d, 2H, J=8.0Hz), 6.23 (s, amplio, 1H), 5.39 (s, amplio, 1H), 4.62 (m, 4H), 3.25 (t, 1H, J=6.0Hz), 2.95 (s, 6H), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
309				23	espuma color canela	535.11	1.34 min Método A	535.29	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 8.85 (s, 1H, NH), 8.02 (d, 2H, J=8.0Hz), 7.78 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.30 (d, 2H, J=8.0Hz), 6.25 (s, amplio, 1H), 5.36 (s, amplio, 1H), 4.62 (m, 4H), 3.25 (t, 1H, J=6.0Hz), 2.42 (m, 4H), 1.95 (m,

									1H), 1.68-1.38 (m, 8H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
310				23	espuma color canela	550.12	1.24 min Método A	550.25	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 8.83 (s, 1H, NH), 8.02 (d, 2H, J=8.0Hz), 7.78 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.30 (d, 2H, J=8.0Hz), 6.20 (s, amplio, 1H), 5.39 (s, amplio, 1H), 4.71 (d, 1H, J_{ab}=16Hz), 4.48 (d, 1H, J_{ab}=16Hz), 4.26 (s, 2H), 3.25 (m, 1H), 2.67 (m, 8H), 2.40 (s, 3H), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
311				7	sólido blanco	492.09	2.30 min Método C	492.16	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.73 (d, 2H, J=8.4), 7.48 (d, 2H, J=8.4), 7.15-7.38 (m, 5H), 6.67 (s, 1H), 5.37 (s, 1H), 4.14 (dd, 1H, J=5.4, 9.0), 3.47 (s, 2H), 3.24 (dd, 1H, J=10,

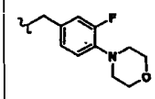
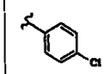
438

									14), 2.75-3.05 (m, 3H), 1.45-2.05 (m, 10H), 0.75-0.90 (m, 1H), 0.71 (d, 3H, J=6.6), 0.65 (d, 3H, J=6.6).
312				7	sólido blanco	529.15	2.27 min Método C	529.16	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.73 (d, 2H, J=8.7), 7.50 (d, 2H, J=8.7), 6.65 (d, 1H, J=5.1), 4.55 (s amplio, 1H), 4.05-430 (m, 1), 3.57-3.95 (m, 1H), 3.10-3.40 (m, 1H), 2.40-3.00 (m, 12H), 1.70-2.00 (m, 3H), 0.90-1.30 (m, 10H), 0.60-0.75 (m, 6H).
313				7	sólido blanco	573.16	1.78 min Método A	573.18	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.72 (d, 2H, J=7.8), 7.50 (d, 2H, J=8.7), 6.65 (d, 1H, J=14), 5.35 (s, 1H), 4.45-4.65 (m, 1H), 3.67-4.25 (m, 3H), 3.35-3.60 (m, 3H), 3.10-3.25 (m, 1H), 2.80-3.10 (m, 2H), 2.90 (s, 3H), 0.95-2.00 (m, 7H), 1.46 (s, 9H), 0.73

									(amplio, s, 3H), 0.67 (amplio, s, 3H).
314				7	sólido blanco	532.11	1.47 min Método A	532.19	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.74 (d, 2H, J=8.8), 7.50 (d, 3H, 8.8), 7.17-7.27 (m, 3H), 6.63 (s, 1H), 5.60 (s, 1H), 4.13 (dd, 1H, J=5.5, 9.2), 3.80 (s, 2H), 3.28 (dd, 1H, J=9.5, 15), 2.80-305 (m, 3H), 1.50-2.25 (m, 6H), 1.15-1.45 (m, 5H), 0.72 (d, 3H, J=6.6), 0.66 (d, 3H, J=6.6).
315				7	sólido blanco	444.04	2.11 min Método C	444.132	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.73 (d, 2H, J=8.7), 7.48 (d, 2H, J=8.4), 6.69 (s amplio, 1H), 5.45 (s amplio, 1H), 4.14 (dd, 1H, J=10, 15), 3.15-3.35 (m, 1H), 2.90-3.05 (m, 1H), 2.75-2.90 (m, 1H), 2.60-2.75 (m, 1H), 1.50-2.25 (m, 6H), 1.05-1.40 (m, 3H), 1.00 (d, 6H, J=11), 0.75-0.90 (m, 1H), 0.71 (d, 3H, J=10),

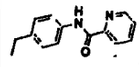
									0.66 (d, 3H, J=10).
316				9	espuma amarilla	515.04	1.50 min Método A	515.08	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 9.97 (s, 1H, NH), 8.82 (d, 2H, J=4.0Hz), 8.02 (d, 2H, J=8.0Hz), 7.76 (d, 2H, J=8.0Hz), 7.73 (d, 2H, J=4.0Hz), 7.46 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 6.27 (s, amplio, 1H), 5.39 (s, amplio, 1H), 4.72 (d, 1H J_{ab}=16Hz), 4.30 (d, 1H, J_{ab}=16Hz), 4.26 (s, 2H), 3.25 (t, 1H, J=6.0Hz), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
317				2	cera oscura	482.02	1.42 min Método B	482.01	RMN ^{1}H ($CDCl_3$) δ 7.63 (d, 2H, J=8.2Hz), 7.42 (d, 2H, J=8.2Hz), 6.71-7.08 (m, 3H), 6.20 (s, amplio, 1H), 5.15 (s, amplio, 1H), 4.27 (dd, 2H, J=50Hz, 15Hz), 4.23 (t, 1H,

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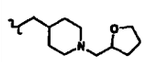
									J=7.0Hz), 2.99-3.10 (m, 4H), 1.92-1.95 (m, 1H), 1.53-1.59 (m, 2H), 1.41-1.90 (m, 4H), 1.21-1.24 (m, 1H), 0.98-1.08 (m, 2H), 0.74 (t, 3H, J=8.0Hz).
318				2	sólido oscuro	498.02	1.68 min Método B	498.2	RMN ^{1}H ($CDCl_3$) δ 7.66 (d, 2H, J=8.0Hz), 7.42 (d, 2H, J=8.0Hz), 6.84-7.02 (m, 3H), 6.20 (s, amplio, 1H), 5.22 (s, amplio, 1H), 4.34 (dd, 2H, J=50Hz, 15Hz), 4.19-4.25 (m, 1H), 3.84-3.86 (m, 4H), 3.15-3.17 (m, 1H), 3.03-3.06 (m, 4H), 1.31-1.77 (m, 2H), 0.95 (d, 3H, J=7.0Hz), 0.83 (d, 3H, J=7.0Hz).

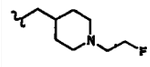
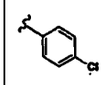
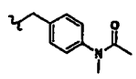
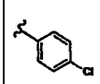
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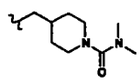
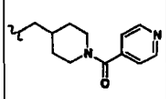
319				9	espuma color canela	515.04	1.77 min Método A	515.15	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 9.90 (s, 1H, NH), 8.51 (d, 1H, J=4.0Hz), 8.11 (d, 2H, J=8.0Hz), 8.01 (d, 2H, J=8.0Hz), 7.78 (m, 3H), 7.59 (d, 2H, J=8.0Hz), 7.38 (d, 2H, J=8.0Hz), 7.32 (t, 1H, J=4.0Hz), 6.27 (s, amplio, 1H), 5.38 (s, amplio, 1H), 4.71 (d, 1H, J_{ab}=16Hz), 4.31 (d, 1H, J_{ab}=16Hz), 3.25 (t, 1H, J=6.0Hz), 1.95 (m, 1H), 1.60 (m, 2H), 0.98 (d, 3H, J=7.0Hz), 0.94 (d, 3H, J=7.0Hz).
320				2	sólido color canela	511.06	1.12 min Método B	511.2	RMN ^{1}H (d_6DMSO) δ 7.78 (d, 2H, J=8.2Hz), 7.55 (d, 2H, J=8.2Hz), 7.02-7.14 (m, 3H), 6.80 (s, amplio, 1H), 4.82 (s, amplio, 1H), 3.58-4.63 (m, 2H), 4.32-4.38 (m, 1H), 3.42-3.56 (m, 4H), 3.16-3.21 (m,

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									1H), 2.84 (s, 3H), 2.49-2.51 (m, 4H), 1.85 (s, 3H), 1.76-1.82 (m, 1H), 1.21-1.33 (m, 2H), 0.82 (d, 3H, J=7.0Hz), 0.56 (d, 3H, J=7.0Hz).
321				7	sólido blanco	486.08	2.22 min Método C	486.12	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.73 (d, 2H, J=8.5), 7.49 (d, 2H, J=8.6), 6.67 (s, 1H), 5.35 (s, 1H), 4.15 (dd, 1H, J=5.8, 9.2), 4.05 (s amplio, 1H), 3.85 (dd, 1H, J=7.0, 15), 3.73 (dd, 1H, J=7.3, 15), 3.20-3.29 (m, 1H, 2.95-3.05 (m, 3H), 2.43-2.51 (s amplio, 2H), 1.20-2.10 (m, 14H), 0.80-0.90 (m, 1H), 0.72 (d, 3H, J=6.7), 0.67 (d, 3H, J=6.7).

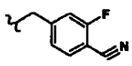
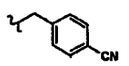
322				7	sólido blanco	448.00	1.34 min Método A	448.24	RMN ^1H ($CDCl_3$, 300MHz) δ 7.73 (d, 2H, J=8.7), 7.48 (d, 2H, J=8.7), 6.67 (s, 1H), 5.43 (s, 1H), 4.60 (d, 1H, J=5.1), 4.45 (d, 1H, J=4.8), 4.15 (dd, 1H, J=5.6, 9.0), 3.25 (dd, 1H, J=10, 15), 2.85-3.05 (m, 3H), 2.70 (t, 1H, J=5.0), 2.67 (t, 1H, J=4.7), 1.50-2.15 (m, 6H), 1.10-1.40 (3H), 0.75-0.90 (m, 1H), 0.71 (d, 3H, J=6.3), 0.66 (d, 3H, J=6.7).
323				9	sólido color canela	465.14	1.52 min Método B	466.1	RMN ^1H ($CDCl_3$) δ 7.68 (d, 2H, J=8.4Hz), 7.46 (d, 2H, J=8.4Hz), 7.43 (d, 2H, J=8.0Hz), 7.10 (d, 2H, J=8.0Hz), 6.19 (s, amplio, 1H), 5.16 (s, amplio, 1H), 4.44 (dd, 2H, J=50Hz, 15Hz), 4.31-4.35 (m 1H), 3.23 (s, 3H), 1.85 (s, 3H), 1.76-1.82

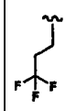
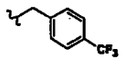
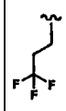
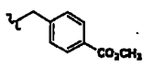
447

									(m, 1H) , 1.14-1.35 (m, 2H), 0.78 (d, 3H, J=7.0Hz), 0.65 (d, 3H, J=7.0Hz).
324				7	polvo blanco	473.04	1.54 mins Método A	473.17	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.73 (d, 2H, J=8.1), 7.50 (d, 2H, J=8.1), 6.67 (s, 1H), 5.85 (s, 1H), 4.15 (dd, 1H, J=5.1, 9.2), 3.65 (d, 2H, J=10), 3.26 (dd, 1H, J=9.9, 15), 2.97 (dd, 1H, J=4.4, 14), 2.60-2.85 (m, 3H), 2.80 (s, 6H); 1.75-1.95 (m, 3H), 1.05-1.30 (m, 3H), 0.72 (d, 3H, J=6.2), 0.65 (d, 3H, J=6.6).
325				7	sólido blanco	507.06	1.41 min Método A	507.20	RMN ^{1}H ($CDCl_3$, 300MHz) δ 8.64 (s, 2H), 7.72 (d, 3H, J=8.4), 7.50 (d, 2H, J=8.8), 7.35 (dd, 1H, J=4.8, 7.7), 6.63 (s, 1H), 5.39 (s amplio, 1H), 4.69 (s amplio, 1H), 4.05-4.20 (m, 1H), 3.72 (s amplio, 1H), 3.25 (m, 1H), 2.50-

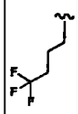
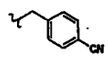
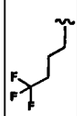
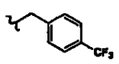
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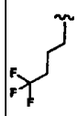
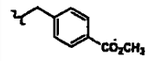
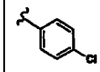
									3.200 (m, 3H), 1.50-2.10 (m, 5H), 1.00-1.40 (m, 3H), 0.72 (d, 3H, J=6.6), 0.66 (d, 3H, J=6.6).
326				1-Método A	sólido blanco	423.90	1.55 min Método B	424.11	RMN ^{1}H ($CDCl_3$) δ 7.69-7.71 (m, 3H), 7.48-7.56 (m, 4H), 6.11 (s, amplio, 1H), 5.22 (s, amplio, 1H), 4.57 (dd, 2H, J=50Hz, 15Hz), 4.22-4.26 (m, 1H), 1.80-1.83 (m, 1H), 0.99-1.23 (m, 3H), 0.74 (t, 3H, J=8.0Hz).
327				1-Método A	sólido blanco	459.06	1.57 min Método G	(M+Na)$^+$ 481.9	RMN ^{1}H (400 MHz, DMSO) δ 7.84 (d, 2H, J=8.8), 7.80 (d, 2H, J=8.6), 7.65 (d, 2H, J=8.7), 7.59 (d, 2H, J=8.3), 7.47 (s, 1H), 7.25 (s, 1H), 4.79 (ABq, 2H, Δν=5.1, J_{AB}=17.4), 4.43 (dd, 1H, J=8.5, 6.6), 2.05 (m, 2H), 1.82 (m, 1H), 1.49 (m, 1H).

328				1-Método A	sólido blanco	502.06	1.83 min Método G	$(M+H)^+$ 502.9	RMN ^1H (400 MHz, DMSO) δ 7.84 (d, 2H, J=8.8), 7.68 (d, 2H, J=8.0), 7.65-7.60 (m, 4H), 7.47 (s, 1H) ; 7.26 (s, 1H), 4.79 (s, 2H), 4.45 (dd, 1H, J=8.8, 6.1), 2.03 (m, 2H), 1.82 (m, 1H), 1.52 (m, 1H).
329				1-Método A	sólido blanco	492.07	2.39 min Método G	$(M+H)^+$ 492.9	RMN ^1H (400 MHz, DMSO) δ 7.91 (d, 2H, J=8.3), 7.85 (d, 2H, J=8.8), 7.64 (d, 2H, J=8.6), 7.54 (d, 2H, J=8.3), 7.43 (s, 1H), 7.23 (s, 1H), 4.79 (ABq, 2H, Δv=3.4, J_{ab}=17.2), 4.42 (dd, 1H, J=8.5, 6.1), 3.85 (s, 3H), 2.02 (m, 2H), 1.80 (m, 1H), 1.52 (m, 1H).

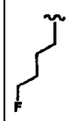
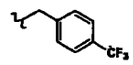
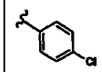
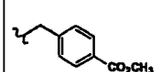
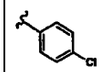
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330				1-Método A	sólido blanco	473.08	1.60 Método G	$(M+Na)^+$ 495.9	RMN ^1H (400 MHz, DMSO) δ 7.83 (d, 2H, J=8.8), 7.80 (d, 2H, J=8.3), 7.63 (d, 2H, J=8.6), 7.59 (d, 2H, J=8.3), 7.50 (s, 1H), 7.13 (s, 1H), 4.83 (ABq, 2H, Δν=36.2, J_{ab}=17.6), 4.37 (dd, 1H, J=8.5, 6.3), 2.09 (m, 1H), 1.88 (m, 1H), 1.64 (m, 1H), 1.45 (m, 1H), 1.27 (m, 2H).
331				1-Método A	sólido blanco	516.07	1.84 Método G	$(M+H)^+$ 516.9	RMN ^1H (400 MHz, DMSO) δ 7.82 (d, 2H, J=8.8), 7.69-7.60 (m, 6H), 7.49 (s, 1H), 7.13 (s, 1H).4.85 (ABq, 2H, Δν=27.9, J_{ab}=17.1), 4.38 (dd, 1H, J=9.0, 5.9), 2.05 (m, 1H), 1.75 (m, 1H), 1.65 (m, 1H), 1.46 (m, 1H), 1.27 (m, 2H).

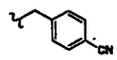
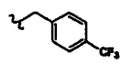
457

332				1-Método A	sólido blanco	506.09	1.67 Método G	$(M+H)^+$ 506.9	RMN ^1H (400 MHz, DMSO) δ 7.90 (d, 2H, J=8.6), 7.83 (d, 2H, J=8.8), 7.62 (d, 2H, J=8.8), 7.54 (d, 2H, J=8.3), 7.47 (s, 1H), 7.11 (s, 1H), 4.84 (ABq, 2H, Δν=36.3, J_{ab}=17.4), 4.36 (dd, 1H, J=8.6, 6.1), 3.85 (s, 3H), 2.04 (m, 1H), 1.82 (m, 1H), 1.62 (m, 1H), 1.45 (m, 1H), 1.26 (m, 2H).
333				19	sólido blanco	437.10	1.48 Método G	$(M+Na)^+$ 459.9	RMN ^1H (400 MHz, DMSO) δ 7.82 (d, 2H, J=8.8), 7.79 (d, 2H, J=8.5), 7.63 (d, 2H, J=8.8), 7.58 (d, 2H, J=83), 7.52 (s, 1H), 7.09 (s, 1H), 4.82 (ABq, 2H, Δν=37.2, J_{ab}=17.6), 4.34 (dd, 1H, J=8.0, 6.6), 4.25 (dt, 2H, J_d=47.2, J_t=5.7), 1.58 (m, 1H), 1.49-1.12 (m, 5H).

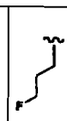
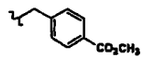
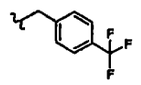
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334				19	sólido blanco	480.09	1.76 Método G	$(M+Na)^+$ 502.9	RMN ^1H (400 MHz, DMSO) δ 7.80 (d, 2H, J=8.6), 7.67 (d, 2H, J=8.6), 7.60 (m, 4H), 7.52 (s, 1H), 7.09 (s, 1H), 4.83 (ABq, 2H, Δν=30.1, J_{ab}=17.4), 4.36 (dd, 1H, J=8.6, 6.2), 4.22 (dt, 2H, J_d=47.5, J_t 6.4), 1.61 (m, 1H), 1.48-1.11 (m, 5H).
335				19	sólido blanco	470.11	1.58 Método G	$(M+H)^+$ 471.0	RMN ^1H (400 MHz, DMSO) δ 7.90 (d, 2H, J=8.3), 7.82 (d, 2H, J=8.8), 7.62 (d, 2H, J=8.8), 7.53 (d, 2H, J=8.4), 7.50 (s, 1H), 7.07 (s, 1H). 4.82 (ABq, 2H, Δν=39.4, J_{ab}=17.4), 4.34 (dd, 1H, J=8.3, 6.6), 4.22 (dt, 2H, J_d=41.6, J_t=6.1), 3.85 (s, 3H), 1.58 (m, 1H), 1.46-1.12 (m, 5H).

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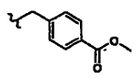
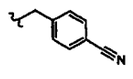
336				19	sólido blanco	423.08	1.43 Método G	$(M+H)^+$ 423.9	RMN ^1H (400 MHz, DMSO) δ 7.82 (d, 2H, J=8.8), 7.78 (d, 2H, J=8.3), 7.63 (d, 2H, J=6.8), 7.57 (d, 2H, J=8.6), 7.53 (s, 1H), 7.14 (s, 1H), 4.81 (ABq, 2H, Δν=36.2, J_{ab}=17.6), 4.38 (t, 1H, J=7.6), 4.27 (m, 1H), 4.15 (m, 1H), 1.64 (m, 1H), 1.54-1.36 (m, 3H).
337				19	sólido blanco	466.07	1.72 Método G	$(M+Na)^+$ 489.0	RMN ^1H (400 MHz, DMSO) δ 7.80 (d, 2H, J=8.8), 7.66 (d, 2H, J=8.1), 7.62-7.57 (m, 4H), 7.54 (s, 1H), 7.15 (s, 1H), 4.81 (ABq, 2H, Δν=29.1, J_{ab}=17.1), 4.40 (t, 1H, J=6.9), 4.25 (m, 1H), 4.13 (m, 1H), 1.67 (m, 1H), 1.55-1.39 (m, 3H).

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338				19	sólido amarillo	456.09	1.54 Método G	$(M+H)^+$ 457.0	RMN ^1H (400 MHz, DMSO) δ 7.90 (d, 2H, J=8.3), 7.83 (d, 2H, J=8.8), 7.62 (d, 2H, J=8.8), 7.52 (d, 2H, J=8.3), 7.50 (s, 1H), 7.11 (s, 1H), 4.82 (ABq, 2H, Δν=54.5, J_{ab}=17.3), 4.37 (t, 1H, J=8.0), 4.28-4.03 (m, 2H), 3.85 (s, 3H), 1.64 (m, 1H), 1.53-1.36 (m, 3H).
339				19	sólido blanco	452.86	1.85 min Método A	452.91	RMN ^1H ($CDCl_3$, 300MHz) δ 7.70 (d, 2H, J=8.7), 7.54 (d, 2H, J=8.4), 7.42-7.49 (m, 4H), 6.31 (s amplio, 1H), 5.23 (s amplio, 1H), 4.58-4.63 (m, 2H), 433-4.41 (m, 2H), 4.19 (t, 1H, J=4.5), 2.18-2.37 (m, 1H), 1.54-1.66 (m, 1H).

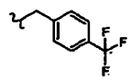
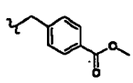
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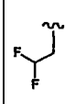
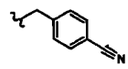
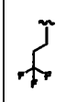
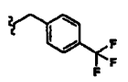
340				19	sólido blanco	442.89	1.68 min Método A	442.90	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.96 (d, 2H, J=8.4), 7.72 (d, 2H, J=8.7), 7.48 (d, 2H, J=8.7), 7.39 (d, 2H, J=8.4), 6.32 (s amplio, 1H), 5.18 (s amplio, 1H), 4.54-4.63 (m, 2H), 4.30-4.42 (m, 2H), 4.16 (t, 1H, J=4.5), 3.90 (s, 3H), 2.18-2.37 (m, 1H), 1.54-1.66 (m, 1H).
341				19	sólido blanco	409.87	1.57 min Método A	410.07	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.72 (dd, 2H, J=1.8, 8.7), 7.59 (d, 2H, J=8.1), 7.50 (dd, 2H, J=2.1, 8.7), 7.46 (d, 2H, J=8.1), 6.30 (s amplio, 1H), 5.21 (s amplio, 1H), 4.56-4.68 (m, 2H), 431-437 (m, 2H), 4.18 (t, 1H, J=4.8), 2.17-2.37 (m, 1H), 1.48-1.64 (m, 1H).

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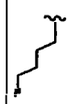
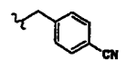
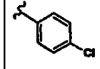
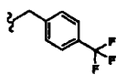
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342				19	sólido blanco	470.85	1.88 min Método A	470.89	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.70 (d, 2H, J=8.7), 7.56 (d, 2H, J=8.4), 7.51 (d, 2H, J=8.4), 7.43 (d, 2H, J=8.1), 6.32 (s amplio, 1H), 5.75 (tm, 1H, J_{H-F}=57), 5.34 (s amplio, 1H), 4.52-4.63 (m, 2H), 4.32 (d, 1H, J=15.6), 2.51-2.66 (m, 1H), 1.54-1.69 (m, 1H).
343				19	sólido blanco	460.88	1.74 min Método A	461.07	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.97 (dd, 2H, J=2.0, 8.4), 7.72 (d, 2H, J=8.7), 7.51 (d, 2H, J=8.7), 7.38 (d, 2H, J=8.4), 6.32 (s amplio, 1H), 5.75 (tm, 1H, J_{H-F}=57), 5.18 (s amplio, 1H), 4.60 (d, 1H, J=15.6), 4.50-4.55 (m, 1H), 4.32 (d, 1H, J=15.6), 3.91 (s, 3H), 2.51-2.66 (m, 1H), 1.54-1.69 (m, 1H).

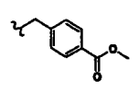
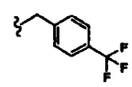
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344				19	sólido blanco	427.85	1.62 min Método A	428.06	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.70 (d, 2H, J=8.7), 7.61 (d, 2H, J=8.1), 7.53 (d, 2H, J=8.7), 7.45 (d, 2H, J=7.8), 6.32 (s amplio, 1H), 5.71 (tm, 1H, J_{H-F}=57), 5.21 (s amplio, 1H), 4.64 (d, 1H, J=15.6), 4.51-4.55 (m, 1H), 4.28 (d, 1H, J=15.6), 2.48-2.60 (m, 1H), 1.54-1.69 (m, 1H).
345				1-Método A, con. de sep. 1	sólido blanco	502.87	1.99 min Método E	503.02	RMN ^{1}H (DMSO) δ 7.83 (d, 2H, J=8.8Hz), 7.64 (m, 6H), 7.46 (s, amplio, 1H), 7.25 (s, amplio, 1H) 4.79 (s, 2H), 4.44 (m, 1H), 2.03 (m, 2H), 1.83 (m, 1H), 1.50 (m, 1H).
346				1-Método A, con. de sep. 2	sólido blanco	459.88	1.76 min Método E	460.13	RMN ^{1}H (DMSO) δ 7.84 (d, 2H, J=8.0Hz), 7.80 (d, 2H, J=7.7Hz), 7.65 (d, 2H, J=8.2Hz), 7.59 (d, 2H, J=7.7Hz), 7.47 (s, amplio, 1H), 7.25

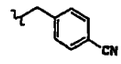
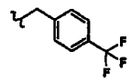
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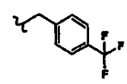
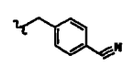
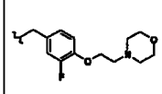
									(s, amplio, 1H), 4.78 (AB_2, 2H), $\Delta\nu$=5Hz, J_{ab}=17Hz), 4.43 (m, 1H), 2.05 (m, 2H), 1.83 (m, 1H), 1.48 (m, 1H).
347				1-Método A, con. de sep. 3	sólido ceroso, amarillo	437.92	1.67 min Método E	438.22	RMN ^{1}H (DMSO) δ 7.81 (m, 4H), 7.61 (m, 4H), 7.53 (s amplio, 1H), 7.09 (s amplio, 1H), 4.81 (AB_2, 2H, $\Delta\nu$=5Hz, J_{ab}=17Hz), 4.33 (m, 2H), 4.19 (t, 1H, J=6.0Hz), 1.44 (m, 6H).
348				1-Método A, con. de sep. 3	polvo blanco	480.91	1.94 min Método E	M+Na 503.14	RMN ^{1}H (DMSO) δ 7.99 (d, 2H, J=8.8Hz), 7.82 (m, 6H), 7.70 (s amplio, 1H), 7.27 (s amplio, 1H), 5.00 (m, 2H), 4.51 (m, 2H), 4.33 (m, 1H), 1.77 (m, 1H), 1.47 (m, 6H).

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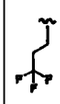
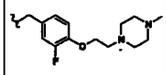
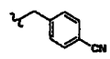
349				1-Método A	polvo blanco	470.94	1.59 min Método B	493.17 M+Na+	RMN ^1H ($CDCl_3$) δ 7.94 (d, J=8.0Hz, 2H), 7.72 (d, J=6.8Hz, 2H), 7.46 (d, J=6.8Hz, 2H), 7.38 (d, J=8.0Hz, 2H), 6.25 (s, amplio, 1H), 5.26 (s, amplio, 1H), 4.37-4.62 (m, 3H), 3.90 (s, 3H), 2.45 (m, 1H), 1.45 (m, 1H), 1.27 (d, J=21.2Hz, 3H), 1.17 (d, J=21.6Hz, 3H).
350				22	sólido blanco	484.88	1.93 min Método E	485.09	RMN ^1H (DMSO) δ 7.81 (d, 2H, J=8.8Hz), 7.63 (m, 6H), 7.51 (s, amplio, 1H), 7.21 (s, amplio, 1H), 5.85 (t, 1H, 56Hz), 4.81 (AB_2, 2H, Δν=5Hz, J_{ab}=15Hz), 4.42 (t, 1H, J=8.0Hz), 1.49 (m, 4H) .

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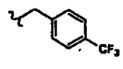
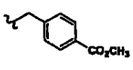
351				1-Método A	sólido blanco	437.92	1.49 min Método B	460.13 M+Na+	RMN ^{1}H ($CDCl_3$) δ 7.72 (d, J=6.8Hz, 2H), 7.58 (d, J=8.4Hz, 2H), 7.48 (d, J=8.4Hz, 2H), 7.45 (d, J=6.8Hz, 2H), 6.25 (s, amplio, 1H), 5.28 (s, amplio, 1H), 4.32-4.64 (m, 3H), 2.45 (m, 1H), 1.38 (m, 1H), 1.24 (d, J=21.2Hz, 3H), 1.21 (d, J=22Hz, 3H).
352				1-Método A	sólido blanco	480.91	1.76 min Método B	503.12 M+Na+	RMN ^{1}H ($CDCl_3$) δ 7.69 (d, J=8.4Hz, 2H), 7.52 (d, J=8.0Hz, 2H), 7.45 (d, J=8.4Hz, 2H), 7.43 (d, J=8.0Hz, J=8.0Hz, 2H), 6.30 (s, amplio, 1H), 5.44 (s, amplio, 1H), 4.34-4.66 (m, 3H), 2.49 (m, 1H), 1.46 (m, 1H), 1.26 (d, J=21.6Hz, 3H), 1.22 (d, J=21.6Hz, 3H).

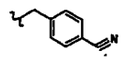
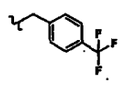
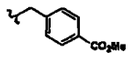
353				18	sólido blanco	466.89	1.41 min Método B	466.16	RMN ^1H ($CDCl_3$) δ 7.66 (d, 2H, J=8.4Hz) 7.45-7.55 (m, 6H), 6.17 (s, amplio, 1H), 5.19 (s, amplio, 1H), 4.53 (dd, 2H, J=50Hz, 15Hz), 4.34-4.37 (m, 2H), 4.22-4.25 (m, 1H), 2.00-2.05 (m, 1H), 1.43-1.49 (m, 3H).
354				18	sólido blanco	423.90	1.54 min Método B	424.1	RMN ^1H (d_6DMSO) δ 7.86 (d, 2H, J=8.0Hz) 7.48-7.75 (m, 6H), 6.56 (s, amplio, 1H), 5.69 (s, amplio, 1H), 4.72 (dd, 2H, J=42Hz, 16Hz), 4.51-4.55 (m, 3H), 1.43-2.07 (m, 4H).
355				11	sólido amarillo	582.02	1.47 min Método B	582.22	RMN ^1H (DMSO) δ 7.81 (d, 2H, J=8.8Hz), 7.63 (d, 2H, J=8.5Hz), 7.43 (s amplio, 1H), 7.24 (m, 4H), 4.64 (s, 2H), 4.42 (m, 3H), 3.99 (m, 2H), 3.62 (m, 6H), 3.23 (m, 2H), 1.85 (m, 4H).

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356				11	sólido blanco	595.06	1.42 min Método E	595.23	RMN ^{1}H (DMSO) δ 7.80 (d, 2H, J=8.8Hz), 7.63 (d, 2H, J=8.5Hz), 7.42 (s, amplio, 1H), 7.17 (m, 4H), 4.62 (s, 2H), 4.41 (m, 1H), 4.18 (m, 2H), 3.96 (s, 1H), 3.39 (m, 2H), 3.05 (m, 7H), 2.78 (s, 3H), 1.97 (m, 3H), 1.58 (m, 1H).
357				21	sólido blanco	437.10	1.50 Método G	(M+Na)$^+$ 460.2	RMN ^{1}H (400 MHz, DMSO) δ 7.83 (d, 2H, J=8.5), 7.75 (d, 2H, J=8.3), 7.68 (s, 1H), 7.64 (d, 2H, J=8.6), 7.49 (d, 2H, J=8.1), 7.20 (s, 1H), 4.67 (ABq, 2H, Δν=28.3, J_{ab}=17.3), 4.54 (dd, 1H, J=9.3, 3.2), 2.23 (m, 1H), 1.42 (m, 1H), 1.25 (d, 3H, J=21.6), 1.21 (d, 3H, J=21.7).

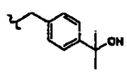
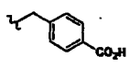
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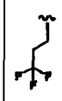
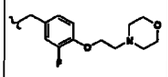
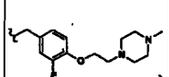
358				21	sólido blanco	480.09	1.76 Método G	$(M+Na)^+$ 503.2	RMN ^1H (400 MHz, DMSO) δ 7.80 (d, 2H, J=8.6), 7.69 (s, 1H), 7.61 (m, 4H), 7.50 (d, 2H, J=8.1), 7.22 (s, 1H), 4.68 (ABq, 2H, Δv=2.7, J_{ab}=17.1), 4.57 (dd, 1H, J=9.1, 3.0), 2.26 (m, 1H), 1.47 (m, 1H), 1.24 (d, 3H, J=21.5), 1.22 (d, 3H, J=21.5).
359				21	sólido blanco	470.11	1.62 Método G	$(M+Na)^+$ 493.2	RMN ^1H (400 MHz, DMSO) δ 7.86 (d, 2H, J=8.3), 7.83 (d, 2H, J=8.8), 7.63 (m, 3H), 7.44 (d, 2H, J=8.3), 7.18 (s, 1H), 4.67 (ABq, 2H, Δv=10.3, J_{ab}=17.1), 4.53 (dd, 1H, J=9.3, 2.9), 3.85 (s, 3H), 2.22 (m, 1H), 1.46 (m, 1H), 1.22 (d, 3H, J=21.5), 1.19 (d, 3H, J=21.6).

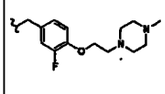
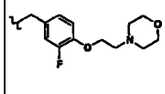
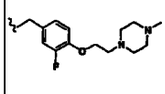
360				18	sólido blanco	409.87	1.53 min Método B	407.99 (M-H)	RMN ^{1}H ($CDCl_3$) δ 7.72 (d, 2H, J=8.4Hz) 7.58 (d, 2H, J=8.4Hz), 7.50 (d, 2H, J=8.4Hz), 7.45 (d, 2H, J=8.4Hz), 6.29 (s, amplio, 1H), 5.21 (s, amplio, 1H), 4.19-4.67 (m, 5H), 2.17-2.28 (m, 1H), 1.49-1.61 (m, 1H).
361				18	sólido blanco	452.86	1.56 min Método B	452.85	RMN ^{1}H ($CDCl_3$) δ 7.69 (d, 2H, J=8.4Hz) 7.56 (d, 2H, J=8.4Hz), 7.49 (d, 2H, J=8.4Hz) 7.43 (d, 2H, J=8.4Hz), 6.31 (s, amplio, 1H), 5.24 (s, amplio, 1H), 4.19-4.62 (m, 5H), 2.16-2.30 (m, 1H), 1.56-1.63 (m, 1H).
362				18	sólido blanco	456.93	1.86 min Método B	457.16	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.96 (d, 2H, J=8.4), 7.69 (dd, 2H, J=1.8, 8.4), 7.47 (ddd, 2H, J=1.5, 2.1, 8.7), 7.42 (d, 2H, J=8.4), 6.19 (s amplio, 1H), 5.18 (s amplio, 1H), 4.64 (d,

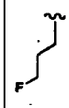
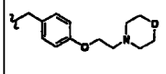
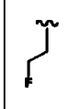
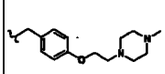
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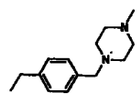
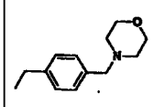
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									1H, J=15.6), 4.42 (d, 1H, J=15.9), 4.30-4.35 (m, 2H), 4.18 (t, 1H, J=3.6), 3.90 (s, 3H), 1.89-2.08 (m, 1H), 1.38-1.50 (m, 3H).
363				18	sólido blanco	456.97	1.80 min Método B	454.98 (ion neg)	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.64 (d, 2H, J=8.7), 7.42 (d, 2H, J=8.7), 7.38 (d, 2H, J=8.4), 7.26 (d, 2H, J=8.4), 6.19 (amplio, 1H), 5.28 (s amplio, 1H), 4.51 (d, 1H, J=15.6), 4.39 (d, 1H, J=15.3), 4.30-4.35 (m, 2H), 4.18 (t, 1H, J=3.6), 1.92-2.08 (m, 1H), 1.55 (s, 6H), 1.35-1.50 (m, 3H).
364				18	sólido blanco	442.90	1.73 min Método B	443.12	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.81 (d, 2H, J=8.4), 7.59 (dd, 2H, J=1.8, 8.4), 7.29-7.33 (m, 4H), 6.76 (amplio, 1H), 5.80 (s amplio, 1H), 4.62 (d, 1H, J=16.2), 4.44 (d, 1H,

									J=16.2), 4.31 (t, 1H, J=6.9), 3.85-4.10 (m, 2H), 1.70-1.85 (m, 1H), 1.30-1.48 (m, 3H).
365				11, con. de sep. 4	sólido blanque-cino	585.02	1.47 min Método E	582.18	RMN ^{1}H (DMSO) δ 7.80 (m, 2H), 7.62 (m, 2H), 7.42 (m, 1H), 7.18 (m, 4H), 4.62 (m, 3H), 4.42 (m, 1H), 4.14 (m, 1H). 4.00 (m, 3H), 3.58 (m, 4H), 2.93 (m, 1H), 2.70 (m, 2H), 2.01 (m, 2H), 1.85 (m, 1H), 1.59 (m, 1H).
366				11, cond de sep 4	sólido amarillo	595.06	1.43 min Método E	595.19	RMN ^{1}H ($CDCl_3$) δ 7.72 (d, 2H, J=8.7Hz), 7.52 (d, 2H, J=8.8Hz), 7.14 (m, 1H), 7.01 (m, 1H), 6.87 (m, 1H), 6.24 (s amplio, 1H), 5.36 (m, 1H), 4.51 (m, 1H), 4.28 (m, 4H), 3.23 (m, 9H), 2.77 (m, 3H), 1.94 (m, 3H), 1.40 (m, 1H).

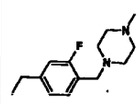
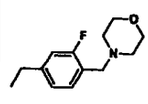
367				11, con. de sep. 4	sólido blanco	595.06	1.42 min Método E	595.20	RMN ^{1}H (DMSO) δ 7.80 (m, 2H), 7.62 (m, 2H), 7.42 (s amplio, 1H), 7.18 (m, 4H), 4.61 (m, 2H), 4.42 (m, 1H), 4.14 (m, 2H), 3.72 (m, 1H), 3.57 (m, 1H), 3.32 (s, 3H), 2.75 (m, 6H), 2.27 (m, 2H), 1.97 (m, 3H), 1.60 (m, 1H).
368				11, con. de sep. 4	sólido amarillo oscuro	546.04	1.55 min Método E	546.20	RMN ^{1}H ($CDCl_3$) δ 7.77 (d, 2H, J=8.5Hz), 7.61 (d, 2H, J=8.5Hz), 7.53 (m, 1H), 7.19 (m, 4H), 4.67 (ABq, 2H, Δv=35, J_{ab}=16Hz), 4.30 (m, 6H), 4.01 (m, 4H), 1.68 (m, 4H), 1.49 (m, 4H).
369				11, con. de sep. 4	sólido anaran-jado-amarillo	559.08	1.29 min Método E	559.22	RMN ^{1}H (DMSO) δ 7.77 (d, 2H, J=8.3Hz), 7.60 (d, 2H, J=8.3Hz), 7.50 (s, amplio, 1H), 7.16 (m, 4H), 4.65 (ABq, 2H, Δv□20, J_{ab}=16Hz) 4.33 (m, 2H), 4.18 (m, 4H), 3.17 (m,

									7H), 2.78 (s, 3H), 1.67 (m, 1H), 1.50 (m, 5H).
370				11, con. de sep. 4	sólido amarillo	528.05	1.32 min Método E	528.17	RMN ^{1}H (DMSO) δ 7.74 (d, 2H, J=8.3Hz), 7.60 (d, 2H, J=8.3Hz), 7.44 (s, amplio, 1H), 7.35 (d, 2H, J=8.5Hz), 7.08 (s, amplio, 1H), 6.95 (d, 2H, J=8.5Hz), 4.68 (ABq, 2H, Δν=24, J_{ab}=16Hz), 3.77 (m, 13H), 1.66 (m, 1H), 1.45 (m, 5H).
371				11, con. de sep. 4	sólido anaranjado claro	541.09	1.26 min Método E	541.24	RMN ^{1}H (DMSO) δ 7.77 (d, 2H, J=8.3Hz), 7.59 (d, 2H, J=8.3Hz), 7.43 (s amplio, 1H), 7.31 (d, 2H, J=8.3Hz), 7.08 (s, amplio, 1H), 6.87 (d, 2H, J=8.8Hz), 4.66 (ABq, 2H, Δν=16, J_{ab}=16Hz), 4.22 (m, 5H), 3.17 (m, 8H), 2.77 (m, 3H), 1.65 (m, 1H), 1.46 (m, 5H).

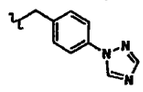
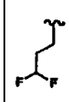
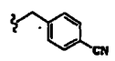
372				18, 8	vidrio color ámbar	511.05	1.09 min Método A	511.21	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.66 (d, 2H, J=8.0Hz), 7.43 (d, 2H, J=8.0Hz), 7.26 (d, 2H, J=8.0Hz), 7.21 (d, 2H, J=8.0Hz), 6.25 (s, amplio, 1H), 5.45 (s, amplio, 1H), 4.52 (d, 1H, J_{ab}=12.0Hz), 4.38 (d, 1H, J_{ab}=12.0Hz), 4.29 (m, 2H), 4.18 (t, 1H, J=6.0Hz), 3.72 (m, 1H), 3.47 (s, 2H), 2.29 (s, 3H), 2.0 (m, 2H), 1.83 (m, 2H) .
373				18, 8	vidrio color ámbar	498.01	1.40 min Método A	498.20	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.66 (d, 2H, J=8.0Hz), 7.44 (d, 2H, J=8.0Hz), 7.27 (d, 2H, J=8.0Hz), 7.22 (d, 2H, J=8.0Hz), 6.24 (s, amplio, 1H), 5.42 (s, amplio, 1H), 4.52 (d, 1H, J_{ab}=12.0Hz), 4.38 (d, 1H, J_{ab}=12.0Hz), 4.29 (m, 2H), 4.18 m

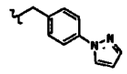
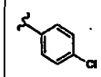
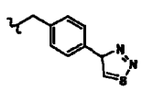
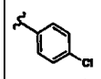
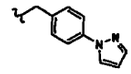
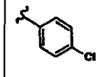
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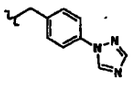
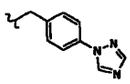
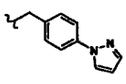
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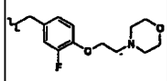
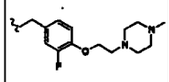
									1H), 3.68 (t, 4H, J=4.0Hz), 3.45 (s, 2H), 2.40 (s, amplio, 4H), 1.99 (m, 1H), 1.45 (m, 3H).
374				18, 8	vidrio color ámbar	529.08	1.17 min Método A	529.22	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.68 (d, 2H, J=8.0Hz), 7.46 (d, 2H, J=8.0Hz), 7.25 (t, 1H, J=6.0Hz), 7.05 (t, 1H, J=6.0Hz), 6.28 (s, amplio, 1H), 5.49 (s, amplio, 1H), 4.54 (d, 1H, J_{ab}=12.0Hz), 4.33 (m, 2H), 4.22 (m, 1H), 3.57 (s, 2H), 2.32 (s, 3H), 2.01 (m, 1H), 1.44 (m, 2H).
375				18, 8	vidrio colo ámbar	516.00	1.10 min Método A	516.17	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.68 (d, 2H, J=8.0Hz), 7.45 (d, 2H, J=8.0Hz), 7.28 (t, 1H, J=6.0Hz), 7.06 (t, 2H, J=6.0Hz), 6.24 (s, amplio, 1H), 5.40 (s, amplio, 1H), 4.53 (d, 1H, J_{ab}=12.0Hz), 4.36 (d, 1H, J_{ab}=12.0Hz),

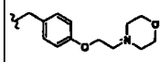
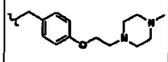
469

									4.34 (m, 2H), 4.21 (m, 1H), 3.69 (t, 4H, J=4.0Hz), 3.53 (s, 2H), 2.44 (s, amplio, 3H), 2.0 (m, 1H), 1.45 (m, 2H).
376				18	sólido blanco	451.91	1.39 min Método B	451.90	RMN ^{1}H ($CDCl_3$) δ 8.55 (s, 1H), 8.09 (s, 1H), 7.75 (d, 2H, J=8.0Hz), 7.62 (d, 2H, J=8.4Hz), 7.47-7.51 (m, 4H), 6.36 (s, amplio, 1H), 5.28 (s, amplio, 1H), 4.31-4.62 (m, 5H), 2.16-2.30 (m, 1H), 1.56-1.66 (m, 1H).
377				22	sólido blanco	441.89	1.65 min Método E	M+Na 464.01	RMN ^{1}H ($CDCl_3$) δ 7.69 (d, 2H, J=8.3Hz), 7.60 (d, 2H, J=8.3Hz), 7.49 (m, 4H), 6.18 (s amplio, 1H), 5.67 (tt, 1H, J=56Hz, 4.0Hz), 5.22 (s amplio, 1H), 4.52 (AB_2, 2H, Δν=1.6, J_{ab}=100Hz), 4.34 (m, 1H), 2.03 (m, 1H), 1.68 (m, 1H), 1.38 (m, 1H), 0.86 (m, 1H).

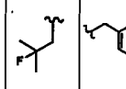
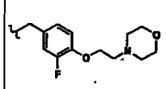
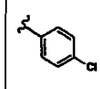
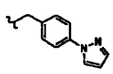
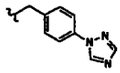
378				18	sólido blanco	450.92	1.52 min Método B	450.91	RMN ^{1}H ($CDCl_3$) δ 7.91 (s, 1H), 7.71 (m, 3H) 7.63 (d, 2H, J=8.4Hz), 7.50 (d, 2H, J=8.4Hz), 7.41 (d, 2H, J=8.4Hz), 6.47 (s, 1H), 6.34 (s, amplio, 1H), 5.18 (s, amplio, 1H), 4.30-4.60 (m, 5H), 2.14-2.29 (m, 1H), 1.56-1.66 (m, 1H).
379				18	sólido blanco	468.96	1.53 min Método B	469.04	RMN ^{1}H ($CDCl_3$) δ 8.64 (s, 1H), 7.98 (d, 2H, J=8.4Hz), 7.75 (d, 2H, J=8.4Hz), 7.45-7.50 (m, 4H), 6.35 (s, amplio, 1H), 5.20 (s, amplio, 1H), 4.22-4.64 (m, 5H), 2.20-2.35 (m, 1H), 1.54-1.62 (m, 1H).
380				18	sólido blanco	464.95	1.54 min Método B	464.99	RMN ^{1}H ($CDCl_3$) δ 8.54 (s, 1H), 8.10 (s, 1H), 7.73 (d, 2H, J=8.4Hz), 7.62 (d, 2H, J=8.4Hz), 7.48-7.52 (m, 5H), 6.22 (s, amplio, 1H), 5.18 (s, amplio,

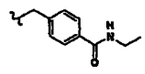
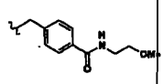
									1H), 4.32-4.69 (m, 5H), 2.09-2.19 (m, 1H), 1.44-1.61 (m, 3H).
381				18	sólido blanco	465.94	1.49 min Método B	465.96	RMN ^{1}H ($CDCl_3$) δ 8.55 (s, 1H), 8.09 (s, 1H), 7.73 (d, 2H, J=8.4Hz), 7.62 (d, 2H, J=8.4Hz), 7.47-7.51 (m, 4H), 6.36 (s, amplio, 1H), 5.28 (s, amplio, 1H), 4.31-4.66 (m, 5H), 2.10-2.39 (m, 1H), 1.56-1.66 (m, 3H).
382				1-Método A	sólido blanco	501.92	1.53 min Método B	502.1	RMN ^{1}H ($CDCl_3$) δ 8.56 (s, 1H), 8.10 (s, 1H), 7.72 (d, 2H, J=8.4Hz), 7.64 (d, 2H, J=8.4Hz), 7.49-7.52 (m, 4H), 6.23 (s, amplio, 1H), 5.22 (s, amplio, 1H), 4.32-4.64 (m, 3H), 1.44-2.20 (m, 4H).
383				1-Método A	sólido blanco	500.93	1.66 min Método B	501.13	RMN ^{1}H ($CDCl_3$) δ 7.91 (s, 1H), 7.41-7.78 (m, 9H), 6.47 (s, 1H), 6.23 (s, amplio, 1H), 5.27 (s, amplio, 1H), 4.30-4.59 (m, 3H), 1.47-2.21 (m, 4H).

384				18, 11	sólido color beige	532.01	1.36 min Método E	532.18	RMN ^{1}H (DMSO) δ 7.80 (d, 2H, J=8.3Hz), 7.61 (d, 2H, J=8.3Hz), 7.56 (s amplio, 1H), 7.23 (s, amplio, 1H), 7.19 (m, 3H), 4.64 (ABq, 2H, Δν=16, J_{ab}=16Hz), 4.51 (t, 1H, J=8.0Hz), 4.42 (m, 2H), 4.03 (m, 12H), 2.02 (m, 1H), 1.82 (m, 1H).
385				18, 11	sólido anaranja-do pálido	545.05	1.32 min Método E	545.25	RMN ^{1}H (DMSO) δ 7.79 (d, 2H, J=8.3Hz), 7.60 (d, 2H, J=8.3Hz), 7.54 (s amplio, 1H), 7.14 (m, 5H), 4.62 (ABq, 2H, Δν=8.0Hz, J_{ab}=16Hz), 4.51 (t, 1H, J=8.0Hz), 4.24 (m, 5H), 3.17 (m, 8H), 2.78 (m, 3H), 2.02 (m, 1H), 1.81 (m, 1H).

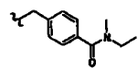
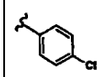
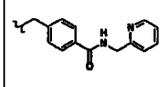
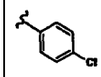
386				18, 11	residuo amarillo	514.02	1.33 min Método E	514.20	RMN ^{1}H (DMSO) δ 7.80 (d, 2H, J=8.3Hz), 7.61 (d, 2H, J=8.3Hz), 7.48 (s amplio, 1H), 7.33 (d, 2H, J=8.3Hz), 7.15 (s, amplio, 1H) 6.95 (d, 2H, J=8.3Hz), 4.65 (ABq, 2H, Δv=8.0Hz, J_{ab}=16Hz), 3.86 (m, 15H), 2.03 (m, 1H), 1.79 (m, 1H).
387				18, 11	sólido anaran-jado	527.06	1.28 min Método E	527.20	RMN ^{1}H (DMSO) δ 7.79 (d, 2H, J=8.3Hz), 7.60 (d, 2H, J=8.3Hz), 7.47 (s, amplio, 1H), 7.30 (d, 2H, J=8.3Hz), 7.15 (s, amplio, 1H), 6.89 (d, 2H, J=8.3Hz), 4.63 (ABq, 2H, Δv=8.0Hz, J_{ab}=16Hz), 4.48 (t, 1H, J=8.0Hz), 4.15 (m, 4H), 3.24 (m, 10H), 2.79 (m, 3H), 2.03 (m, 1H), 1.80 (m, 1H).

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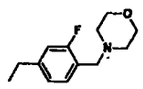
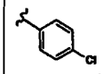
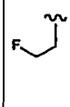
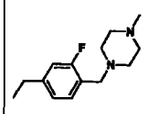
388				18, 11	sólido color canela	560.06	1.65 min Método E	559.14	RMN ^{1}H (DMSO) δ 7.76 (d, 2H, J=8.3Hz), 7.59 (m, 3H), 7.21 (s amplio, 1H), 7.08 (s, amplio, 1H), 7.04 (m, 2H), 4.53 (m, 5H), 3.92 (m, 4H), 3.45 (m, 6H), 2.25 (m, 1H), 1.54 (m, 1H), 1.25 (d, 3H, J=20Hz), 1.22 (d, 3H, J=20Hz).
389				18	sólido amarillo	478.91	1.55 min Método B	491.04 (M+Na)	RMN ^{1}H, ($CDCl_3$) δ 7.92 (s, 1H), 7.72-7.76 (m, 3H), 7.65 (d, 2H, J=8.4Hz) 7.52 (d, 2H, J=8.4Hz), 7.40 (d, 2H, J=8.4Hz) 6.47 (s, 1H), 6.30 (s, amplio, 1H), 5.21 (s, amplio, 1H), 4.27-4.57 (m, 3H), 2.51-2.60 (m, 1H), 1.53-1.65 (m, 2H).
390				18	sólido blanco	469.90	1.48 min Método B	470.1	RMN ^{1}H ($CDCl_3$) δ 7.90 (s, 1H), 7.40-7.76 (m, 9H), 6.50 (s, 1H), 6.27 (s, amplio, 1H), 5.52 (s, amplio, 1H),

									4.25-4.55 (m, 3H), 2.49-2.58 (m, 1H), 1.51-1.62 (m, 2H).
391				18, 6	sólido blanco	469.97	1.59 min Método A	470.09	RMN ^{1}H (MeOD, 400MHz) δ 7.77 (ddd, 2H, J=2.0, 2.4, 8.8), 7.71 (d, 2H, J=8.4), 7.51 (ddd, 2H, J=2.0, 2.4, 8.8), 7.48 (d, 2H, J=8.0), 4.80 (d, 1H, J=16.4), 4.72 (d, 1H, J=16.4), 4.47 (t, 1H, J=7.2), 4.05-4.28 (m, 2H), 3.38 (q, 2H, J=7.2), 1.70-1.85 (m, 1H), 1.30-1.48 (m, 3H), 1.20 (t, 3H, J=7.2).
392				18, 6	sólido blanco	500.00	1.57 min Método A	500.10	RMN ^{1}H (MeOD, 400MHz) δ 7.72-7.81 (m, 4H), 7.48-7.52 (m, 4H), 4.80 (d, 1H, J=16.4), 4.72 (d, 1H, J=16.4), 4.47 (t, 1H, J=7.2), 4.05-4.28 (m, 2H), 3.54 (s, 3H), 3.25-2.36 (m, 4H), 1.70-1.85 (m, 1H), 1.30-1.48 (m, 3H).

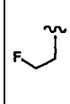
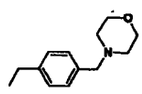
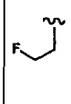
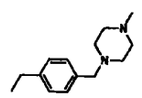
478

393				18, 6	sólido blanco	484.00	1.65 min Método A	484.12	RMN ^{1}H (MeOD, 400MHz) δ 7.79 (d, 2H, J=8.8), 7.50-7.54 (m, 4H), 7.29-7.33 (m, 2H), 4.79 (d, 1H, J=16.4), 4.72 (d, 1H, J=16.4), 4.47 (t, 1H, J=7.2), 4.05-4.28 (m, 2H), 3.52-356 (m, 2H), 3.03 y 2.94 (2 s, 3H), 1.70-1.85 (m, 1H), 1.30-1.48 (m, 3H), 1.15-1.25 (m, 3H).
394				18, 6	sólido blanco	533.03	1.36 min Método A	533.15	RMN ^{1}H (MeOD, 400MHz) δ 8.48 (d, 1H, J=4.8), 7.76-7.82 (m, 5H), 7.50-7.53 (m, 4H), 7.41 (d, 1H, J=8.0), 7.28-7.30 (m, 1H), 4.82 (d, 1H, J=16.0), 4.72 (d, 1H, J=16.4), 4.67 (s, 2H), 4.48 (t, 1H, J=7.2), 4.05-4.28 (m, 2H), 1.70-1.85 (m, 1H), 1.30-1.48 (m, 3H).

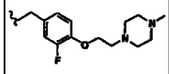
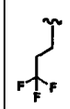
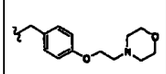
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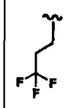
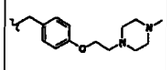
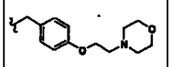
395				18, 8	vidrio color ámbar	501.98	1.17 min Método A	502.25	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.77 (d, 2H, J=8.0Hz), 7.51 (d, 2H, J=8.0Hz), 7.42 (t, 1H, J=6.0Hz), 7.26 (d, 1H, J=6.0Hz), 7.14 (d, 1H, J=6.0Hz), 6.35 (s, amplio, 1H), 6.07 (s, amplio, 1H), 4.82 (d, 1H, J_{ab}=12.0Hz), 4.35 (m, 1H), 4.19 (m, 5H), 3.59 (s, amplio, 4H), 3.48 (d, amplio, 1H), 2.90 (d, amplio, 1H), 2.20 (m, 1H), 1.50 (m, 1H) .
396				18, 8	vidrio color ámbar	515.02	1.21 min Método A	515.27	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.76 (d, 2H, J=8.0Hz), 7.50 (d, 2H, J=8.0Hz), 7.32 (m, 1H), 7.19 (d, 1H, J=8.0Hz), 7.07 (d, 1H, J=8.0Hz), 6.35 (s, amplio, 1H), 5.67 (s, amplio, 1H), 4.86 (d, 1H, J_{ab}=12.0Hz), 4.70 (s, 2H), 4.56 (m, 2H), 4.17 (m, 6H), 2.80 (s, 3H), 2.22

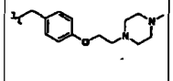
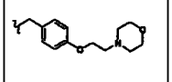
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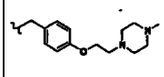
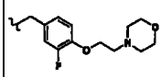
									(m, 1H), 1.54 (m, 1H).
397				18, 8	vidrio color ámbar	483.98	1.21 min Método A	483.98	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.77 (d, 2H, J=8.0Hz), 7.51 (d, 2H, J=8.0Hz), 7.41 (d, 2H, J=8.0Hz), 7.31 (d, 2H, J=8.0Hz), 6.34 (s, amplio, 1H), 6.05 (s, amplio, 1H), 4.83 (d, 1H, J_{ab}=12.0Hz), 4.51 (m, 1H), 4.20 (m, 4H), 3.94 (m, 5H), 3.51 (d, 1H, J=12.0Hz), 3.40 (d, 1H, J=12.0Hz), 2.89 (t, 1H, J=6.0Hz), 2.76 (t, 1H, J=6.0Hz), 2.20 (m, 1H), 1.51 (m, 1H).
398				18, 8	vidrio color ámbar	497.03	1.16 min Método A	498.74	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.76 (d, 2H, J=8.0Hz), 7.51 (d, 2H, J=8.0Hz), 7.37 (d, 2H, J=8.0Hz), 7.27 (d, 2H, J=8.0Hz), 6.31 (s, amplio, 1H), 5.80 (s, amplio, 1H), 4.82 (d, 1H, J_{ab}=12.0Hz), 4.55 (m, 2H), 4.16 (m,

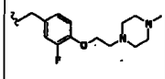
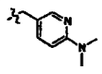
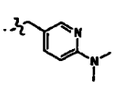
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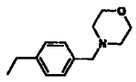
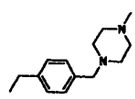
									5H), 3.82 (d, 1H), 2.78 (s, 3H), 2.21 (m, 1H), 1.52 (m, 1H).
399				20, 11	residuo incoloro	573.11	1.63 min Método E		RMN ^{1}H (DMSO) δ 7.76 (d, 2H, J=8.3Hz), 7.59 (m, 3H), 7.20 (s amplio, 1H), 7.08 (s, amplio, 1H), 7.03 (m, 2H), 4.53 (m, 11H), 3.92 (m, 4H), 3.45 (m, 3H), 2.24 (m, 1H), 1.54 (m, 1H), 1.25 (d, 3H, J=20Hz), 1.22 (d, 3H, J=20Hz).
400				11	sólido amarillo claro	564.03	1.51 min Método E	564.19	RMN ^{1}H (DMSO) δ 7.81 (d, 2H, J=8.3Hz), 7.63 (d, 2H, J=8.3Hz), 7.36 (m, 3H), 7.20 (s amplio, 1H), 6.96 (d, 2H, J=8.0Hz), 4.64 (s, 2H), 4.37 (m, 3H), 4.00 (m, 2H), 3.61 (m, 6H), 3.21 (m, 2H), 1.97 (m, 2H), 1.82 (m, 1H), 1.60 (m, 1H).

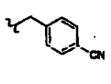
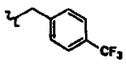
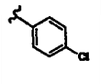
401				11	sólido anaranja-do pálido	577.07	1.47 min Método E	577.20	RMN ^{1}H (DMSO) δ 7.80 (d, 2H, J=8.0Hz), 7.62 (d, 2H, J=8.0Hz), 7.33 (m, 3H), 7.20 (s amplio, 1H), 6.89 (d, 2H, J=8.2Hz), 4.63 (s, 2H), 4.39 (m, 1H), 4.10 (m, 2H), 3.25 (m, 10H), 2.77 (s, 3H), 1.89 (m, 2H), 1.81 (m, 1H), 1.60 (m, 1H).
402				20, 11	residuo Amarillo pálido	542.07	1.51 min Método E	542.21	RMN ^{1}H (DMSO) δ 7.77 (d, 2H, J=8.0Hz), 7.59 (d, 2H, J=8.0Hz), 7.55 (s amplio, 1H), 7.26 (d, 2H, J=8.0Hz), 7.15 (s amplio, 1H), 6.90 (d, 2H, J=8.0Hz), 4.52 (m, 2H), 4.32 (m, 2H), 4.00 (m, 2H), 3.71 (m, 2H), 3.38 (m, 7H), 2.23 (m, 1H), 1.55 (m, 1H), 1.23 (d, 3H, J=20Hz), 1.21 (d, 3H, J=20Hz).

403				20, 11	sólido anaranja-do claro	555.12	1.45 min Método E	555.27	RMN ^{1}H (DMSO) δ 7.76 (d, 2H, J=8.0Hz), 7.58 (d, 2H, J=8.0Hz), 7.54 (s amplio, 1H), 7.22 (d, 2H, J=8.0Hz), 7.16 (s amplio, 1H), 6.84 (d, 2H, J=8.0Hz), 4.52 (m, 2H), 4.13 (m, 2H), 3.25 (m, 11H), 2.79 (m, 3H), 2.20 (m, 1H), 1.56 (m, 1H), 1.23 (d, 3H, J=20Hz), 1.20 (d, 3H, J=20Hz).
404				18, 11	residuo amarillo pálido	532.01	1.43 min Método E	532.18	RMN ^{1}H (DMSO) δ 7.81 (d, 2H, J=8.0Hz), 7.62 (d, 2H, J=8.0Hz), 7.48 (s amplio, 1H), 7.34 (d, 2H, J=8.0Hz), 7.25 (s amplio, 1H), 6.96 (d, 2H, J=8.0Hz), 5.72 (tt, 1H, J=8.0Hz, 56Hz), 4.61 (s, 2H), 4.52 (t, 1H, J=8.0), 4.33 (t, 2H, J=8.0Hz), 3.96 (m, 2H), 3.56 (m, 2H), 3.22 (m,

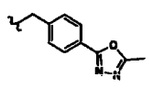
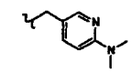
									2H), 2.24 (m, 1H), 1.95 (m, 1H).
405				18, 11	sólido amarillo pálido	545.05	1.37 min Método E	545.19	RMN ^{1}H (DMSO) δ 7.81 (d, 2H, J=8.0Hz), 7.61 (d, 2H, J=8.0Hz), 7.46 (s amplio, 1H), 7.30 (d, 2H, J=8.0Hz), 7.25 (s, amplio, 1H), 6.89 (d, 2H, J=8.0Hz), 5.64 (m, 1H), 4.60 (s, 2H), 4.52 (t, 1H, J=8.0Hz), 4.11 (m, 2H), 3.17 (m, 10H), 2.77 (m, 3H), 2.24 (m, 1H), 1.96 (m, 1H).
406				18, 11	residuo amarillo	550.00	1.43 min Método E	550.16	RMN ^{1}H (DMSO) δ 7.80 (d, 2H, J=8.0Hz), 7.62 (d, 2H, J=8.0Hz), 7.56 (s, amplio, 1H), 7.23 (m, 4H), 5.80 (tt, 1H, J=4.0Hz, 56Hz), 3.93 (m, 15H), 2.29 (m, 1H), 1.99 (m, 1H).

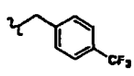
407				18, 11	sólido anaran-jado	563.04	1.37 min Método E.	563.21	RMN ^{1}H (DMSO) δ 7.80 (d, 2H, J=8.0Hz), 7.62 (d, 2H, J=8.0Hz), 7.55 (s, amplio, 1H), 7.29 (s, amplio, 1H), 7.15 (m, 3H), 5.78 (tt, 1H, J=4.0Hz, 56Hz), 4.56 (m, 3H), 4.21 (m, 2H), 3.22 (m, 10H), 2.79 (m, 3H), 2.30 (m, 1H), 1.97 (m, 1H).
408				18, 10, con. de sep. 5	aceite incoloro	442.94	0.993 min Método B	443.19	RMN ^{1}H ($CDCl_3$) δ 8.07 (s, 1H), 7.67 (d, J=6.8Hz, 2H), 7.55 (d, J=8.8Hz, 1H), 7.44 (d, J=6.8Hz, 2H), 6.47 (d, J=8.8Hz, 1H), 6.30 (s, amplio, 1H), 5.45 (s, amplio, 1H), 4.20-4.46 (m, 5H), 3.12 (s, 6H), 1.22-1.85 (m, 4H).
409				18, 10, con. de sep. 5	aceite claro	442.94	0.993 min Método B	443.19	RMN ^{1}H ($CDCl_3$) δ 8.07 (s, 1H), 7.67 (d, J=6.8Hz, 2H), 7.55 (d, J=8.8Hz, 1H), 7.44 (d, J=6.8Hz, 2H), 6.47 (d, J=8.8Hz, 1H), 6.30 (s, amplio, 1H),

									5.45 (s, amplio, 1H), 4.20-4.46 (m, 5H), 3.12 (s, 6H), 1.22-1.85 (m, 4H).
410				20, 8	vidrio color ámbar	512.04	1.44 min Método B	512.20	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.42 (d, 2H, J=8.0Hz), 7.22 (dd, 4H, J=8.0Hz), 6.27 (s, amplio, 1H), 5.26 (s, amplio, 1H), 4.58 (d, 1H), 4.43 (d, 1H, J_{ab}=16.0Hz), 4.36 (d, 1H, J_{ab}=16.0Hz), 3.68 (m, 6H), 3.46 (s, 2H), 2.45 (m, 6H), 1.53 (m, 1H), 1.26 (d, 3H, J=20.0Hz), 1.17 (d, 3H, J=20.0Hz).
411				20, 8	vidrio color ámbar	525.08	1.38 min Método B	525.24	RMN ^{1}H, 400Hz, ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.42 (d, 2H, J=8.0Hz), 7.22 (dd, 4H, J=8.0Hz), 6.26 (s, amplio, 1H), 5.24 (s, amplio, 1H), 4.57 (m, 1H), 4.43 (d, 1H,

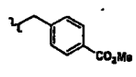
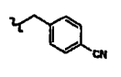
									J_{ab}=16.0Hz), 4.35 (d, 1H, J_{ab}=16.0Hz), 3.48 (s, 2H), 2.47 (m, 7H), 2.30 (s, 3H), 1.26 (d, 3H, J=22.0Hz), 1.18 (d, 3H, J=22.0Hz).
412				18	sólido blanco	427.87	1.39 min Método B	428.13	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.72 (dd, 2H, J=2.0, 8.8), 7.61 (d, 2H, J=8.4), 7.53 (dd, 2H, J=2.0, 8.4), 7.45 (d, 2H, J=8.0), 6.32 (s, amplio, 1H), 5.73 (tm, 1H, J_{H-F}=57), 5.22 (s amplio, 1H), 4.64 (d, 1H, J=16.4), 4.50-4.60 (m, 1H), 4.28 (d, 1H, J=16.4), 2.42-2.60 (m, 1H), 1.50-1.63 (m, 1H).
413				18	sólido blanco	470.86	1.69 min Método B	471.13	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.69 (dd, 2H, J=1.6, 8.8), 7.56 (d, 2H, J=8.4), 7.51 (ddd, 2H, J=2.0, 2.4, 8.4), 7.43 (d, 2H, J=8.4), 6.32 (s amplio, 1H), 5.75 (tm, 1H, J_{H-F}=57),

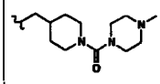
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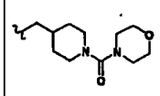
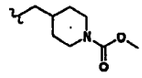
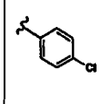
									5.25 (s amplio, 1H), 4.60 (d, 1H, J=15.6), 4.50-4.60 (m, 1H), 4.32 (d, 1H, J=15.6), 2.50-2.60 (m, 1H), 1.55-1.70 (m, 1H).
414				18, 13	sólido blanco	480.95	1.41 min Método B	481.22	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.96 (d, 2H, J=8.4), 7.70 (d, 2H, J=8.4), 7.47-7.50 (m, 4H), 6.22 (s amplio, 1H), 5.18 (s amplio, 1H), 4.66 (d, 1H, J=15.6), 4.43 (d, 1H, 7=15.6), 4.30-4.35 (m, 2H), 4.19-4.21 (m, 1H), 2.61 (s, 3H), 1.93-2.08 (m, 1H), 1.38-1.50 (m, 3H).
415				18, 10	espuma blanca	428.92	1.34 Método B	429.18	RMN ^{1}H ($CDCl_3$) sal de TFA δ 8.10 (s, 1H), 8.04 (d, 1H, J=9.2Hz), 7.76 (d, 2H, J=6.8Hz), 7.52 (d, 2H, J=6.8Hz), 6.80 (d, 2H, J=9.2Hz), 6.46 (s, 1H); 6.00 (s, 1H), 4.60 (d,

									1H, J=15.6Hz), 4.54 (dd, 1H, J=5.2Hz 6.2Hz), 4.30 (m, 1H), 4.18 (m, 1H), 4.07 (d, 1H, J=15.6Hz), 3.29 (s, 6H), 2.25 (m, 1H), 1.55 (m, 1H).
416				1-Método A	sólido blanque-cino	463.91	1.50 min Método B	464.11	RMN ^{1}H ($CDCl_3$, 300MHz) δ 8.72 (d, 1H, J=2.4), 7.82 (dd, 1H, J=2.7, 8.4), 7.55 (d, 2H, J=8.1), 7.47 (d, 2H, J=8.1), 7.37 (d, 1H, J=8.4), 5.97 (s amplio, 1H), 5.26 (s amplio, 1H), 4.62 (d, 1H, J=16.2), 4.54 (d, 1H, J=15.9), 4.44 (t, 1H, J=7.5), 1.70-1.77 (m, 1H), 1.35-1.43 (m, 1H), 1.21-1.31 (m, 1H), 0.85 (d, 3H, J=6.3), 0.67 (d, 3H, J=6.6).

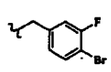
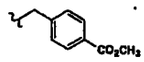
490

417				1-Método A	sólido blanco	453.95	1.37 min Método B	454.14	RMN ^{1}H ($CDCl_3$, 300MHz) δ 8.71 (d, 1H, J=3.0), 7.96 (d, 2H, J=8.1), 7.85 (dd, 1H, J=2.4, 8.4), 7.37-7.43 (m, 3H), 5.99 (s amplio, 1H), 5.24 (s amplio, 1H), 4.61 (d, 1H, J=15.9), 4.53 (d, 1H J=15.9), 4.41 (t, 1H J=7.2), 3.91 (s, 3H), 1.70-1.76 (m, 1H), 1.35-1.43 (m, 1H), 1.21-1.31 (m, 1H), 0.82 (d, 3H, J=6.6), 0.66 (d, 3H, J=6.6).
418				1-Método A	sólido blanco	420.92	1.64 min Método A	421.15	RMN ^{1}H ($CDCl_3$, 300MHz) δ 8.74 (d, 1H, J=2.4), 7.90 (dd, 1H, J=2.4, 8.4), 7.61 (d, 2H, J=8.4), 7.50 (d, 2H, J=8.4), 7.44 (d, 1H, J=8.4), 5.92 (s amplio, 1H), 5.22 (s amplio, 1H), 4.65 (d, 1H, J=16.5), 4.52 (d, 1H, J=16.5), 4.40 (t, 1H, J=7.5), 1.65-

									1.74 (m, 1H), 1.33-1.40 (m, 1H), 1.18-1.25 (m, 1H), 0.83 (d, 3H, J=6.6), 0.66 (d, 3H, J=6.6).
419				7	sólido blanco	528.12	1.35 min Método A	528.26	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, J=8.6), 7.51 (d, 2H, J=8.8), 6.65 (s, 1H), 5.35 (s, 1H), 4.14 (dd, 1H, J=5.1, 9.5), 3.63-3.75 (m, 2H), 3.35-3.55 (m, 3H), 3.25 (dd, 1H, J=9.8, 14), 2.98 (dd, 1H, J=4.5, 14), 2.35-2.87 (m, 8H), 1.77-1.92 (m, 3H), 1.59 (d, 2H, J=13), 1.05-1.30 (m, 3H), 0.75-0.80 (m, 1H), 0.72 (d, 3H, J=6.4), 0.67 (d, 3H, J=6.7).

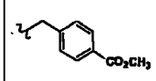
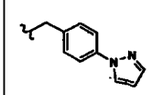
420				7	sólido blanco	515.08	1.56 min Método A	515.33	RMN ($CDCl_3$, 500MHz) δ 7.71 (d, 2H, J=8.5), 7.50 (d, 2H, J=8.5), 6.65 (s, 1H), 5.47 (s, 1H), 4.13 (dd, 1H, J=5.2, 9.2), 3.60-3.75 (m, 6H), 3.15-3.30 (m, 6H), 2.97 (dd, 1H, J=4.6, 14), 2.71 (dd, 2H, J=14, 25), 1.75-1.92 (m, 3H), 1.67 (d, 1H, J=12), 1.05-1.30 (m, 3H), 0.75-0.81 (m, 1H), 0.71 (d, 3H, J=6.7), 0.65 (d, 3H, J=6.7).
421				7	sólido blanco	460.00	1.68 min Método A	460.17	RMN ^1H ($CDCl_3$, 500MHz) δ 7.73 (d, 2H, J=8.5), 7.50 (d, 2H, J=8.6), 6.65 (s, 1H), 5.35 (s, 1H), 4.15 (dd, 3H, J=5.2, 9.5), 3.67 (s, 3H), 3.25 (t, 1H, J=10), 3.97 (dd, 1H, J=4.8, 14), 2.61-2.80 (m, 2H), 1.74-1.94 (m, 3H), 0.89-1.40 (m, 4H), 0.75-0.80

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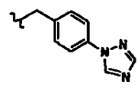
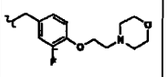
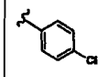
									(m, 1H), 0.72 (d, 3H, J=6.4), 0.67 (m, 3H, J=6.7).
422				1-Método A	sólido color canela	491.81	1.84 min Método B	491.04	RMN ^{1}H ($CDCl_3$) δ 7.71 (d, 2H, J=8.0Hz), 7.50-7.58 (m, 2H), 7.41 (d, 2H, J=8.0Hz), 7.17-7.22 (m, 1H), 6.23 (s, amplio, 1H), 5.25 (s, amplio, 1H), 4.41 (dd, 2H, J=50Hz, 15Hz), 4.31-4.35 (m, 1H), 1.80-1.86 (m, 1H), 1.41-1.44 (m, 1H), 1.11-1.15 (m, 1H), 0.81 (d, 3H, J=7.0Hz), 0.71 (d, 3H, J=7.0Hz).
423				1-Método A	sólido blanco	424.09	1.54 min Método F	$(M+H)^+$ 425.1	RMN ^{1}H (400 MHz, DMSO) δ 7.90 (d, 2H, J=8.1), 7.82 (d, 2H, J=8.5), 7.61 (d, 2H, J=8.5), 7.52 (d, 2H, J=8.1), 7.49 (s, 1H), 7.07 (s, 1H), 4.81 (ABq, 2H, Δν=45.3, J_{ab}=17.3), 4.27 (t, 1H, J=7.3), 3.85 (s, 3H),

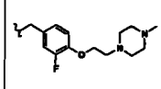
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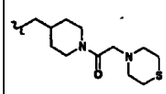
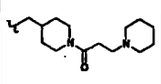
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									1.55 (m, 1H), 1.38 (m, 1H), 0.68 (t, 3H, J=7.3).
424				1-Método A	sólido blanco	452.12	1.69 min Método F	$(M+H)^+$ 453.1	RMN ^1H (400 MHz, DMSO) δ 7.90 (d, 2H, J=8.3), 7.83 (d, 2H, J=8.8), 7.62 (d, 2H, J=8.8), 7.54 (d, 2H, J=8.3), 7.48 (s, 1H), 7.04 (s, 1H), 4.82 (ABq, 2H, Δv=41.3, J_{AB}=17.3), 4.31 (t, 1H, J=8.1), 3.85 (s, 3H), 1.52 (m, 1H), 1.29 (m, 1H), 1.04 (m, 3H), 0.90 (m, 1H), 0.63 (t, 3H, J=7.3).
425				1-Método A	sólido amarillo pálido	460.99	1.48 min Método B	460.13	RMN. 1H ($CDCl_3$, 300MHz) δ 7.91 (d, 1H, J=1.5), 7.67-7.72 (m, 3H), 7.62 (d, 2H, J=8.7), 7.42-7.48 (m, 4H), 6.46 (t, 1H, J=2.1), 6.24 (s amplio, 1H), 5.21 (s amplio, 1H), 4.62 (d, 1H, J=15.3), 4.42 (d, 1H, J=15.6), 4.29 (t, 1H, J=6.9), 1.80-

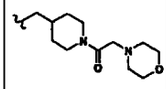
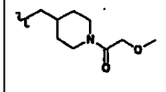
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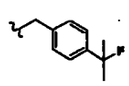
									1.88 (m, 1H), 1.28-1.40 (m, 1H), 1.12-1.21 (m, 1H), 0.75 (d, 3H, J=6.6), 0.66 (d, 3H, J=6.6).
426				1-Método A	sólido blanco	461.97	1.39 min Método B	462.18	RMN ^{1}H ($CDCl_3$, 300MHz) δ 8.54 (s, 1H), 8.10 (s, 1H), 7.71 (d, 2H, J=8.4), 7.61 (d, 2H, J=8.4), 7.46-7.52 (m, 4H), 6.23 (s amplio, 1H), 5.19 (s amplio, 1H), 4.66 (d, 1H, J=15.9), 4.42 (d, 1H J=15.9) 4.30 (t, 1H, J=6.9), 1.79-1.89 (m, 1H), 1.30-1.38 (m, 1H), 1.07-1.14 (m, 1H), 0.76 (d, 3H, J=6.6), 0.66 (d, 3H, J=6.6).
427				11	sólido amarillo pálido	542.07	1.48 min Método E	542.25	RMN ^{1}H ($CDCl_3$) δ 7.71 (d, 2H, J=8.00Hz), 7.49 (d, 2H, J=8.0Hz), 7.16 (d, 1H, J=12.0Hz), 7.05 (d, 1H, J=8.0Hz), 6.86 (t, 1H, J=8.0Hz), 6.40 (s, amplio, 1H), 5.87 (s amplio,

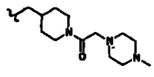
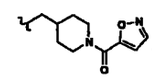
									1H), 4.42 (ABq, 2H, Δν=16, J_{ab}=164Hz), 4.49 (d, 2H, J=4.0Hz), 4.27 (t, 1H, J=8.0Hz), 4.04 (m, 4H), 3.69 (m, 2H), 3.51 (m, 2H), 3.10 (m, 2H), 1.83 (m, 1H), 1.29 (m, 1H), 1.07 (m, 1H), 0.75 (d, 3H, J=8.0Hz), 0.68 (d, 3H, J=8.0Hz).
428				11	sólido amarillo	555.12	1.41 min Método E	555.28	RMN ^{1}H ($CDCl_3$) δ 7.71 (d, 2H, J=8.00Hz), 7.50 (d, 2H, J=8.0Hz), 7.16 (d, 1H, J=12.0Hz), 7.05 (d, 1H, J=8.0Hz), 6.87 (t, 1H, J=8.0Hz), 6.38 (s, amplio, 1H), 5.91 (s amplio, 1H), 4.41 (AB_2, 2H, Δν=16, J_{ab}=176Hz), 4.45 (m, 2H), 4.27 (t, 1H, J=8.0Hz), 3.81 (m, 4H), 3.67 (m, 4H), 3.48 (m, 1H), 2.89 (s, 3H), 1.83 (m, 1H), 1.29 (m, 1H), 1.05 (m, 1H), 0.75 (d, 3H,

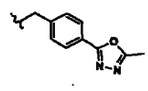
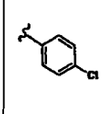
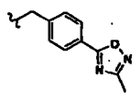
									J=8.0Hz), 0.68 (d, 3H, J=8.0Hz).
429				7	sólido blanco	545.17	1.84 min Método C	545.36	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.73 (d, 2H, J=9.0), 7.51 (d, 2H, J=8.0), 6.65 (2 s, 1H), 5.40 (s, 1H), 4.54 (t, 1H, J=13), 3.85-4.20 (m, 2H), 2.40-3.50 (m, 12H), 1.75-2.00 (m, 3H), 0.92-1.20 (m, 1H), 0.73 (d, 3H, J=5.8, 6.1), 0.67 (d, 3H, J=6.1, 6.4).
430				7	sólido blanco	541.16	1.43 min Método A	541.24	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.71 (d, 2H, J=6.4), 7.50 (d, 2H, J=8.2), 6.65 (d, 1H, J=41), 5.44 (s, 1H), 4.55 (t, 1H, J=13), 4.15 (s amplio, 1H), 3.95 (s amplio, 1H), 3.15-3.35 (m, 1H), 2.90-3.00 (m, 2H), 2.60-2.70 (m, 2H), 2.50-2.57 (m, 2H), 2.35.2.50 (m, 6H), 1.85-2.00 (m, 3H), 1.35-1.75 (m, 3H), 1.00-1.30 (m, 5H), 0.90-1.00 (m, 1H), 0.72

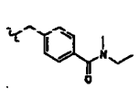
498

									(dd, 3H, J=7.0, 7.3), 0.66 (dd, 3H, J=6.1, 6.4).
431				7	sólido blanco	529.10	1.38 min Método A	529.27	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, 8.5), 7.51 (d, 2H, J=8.9), 6.65 (d, 1H, J=32), 5.43 (s, 1H), 4.55 (t, 1H, J=13) 4.14 (dd, 1H, J=4.8, 9.5), 3.88 (s amplio, 4H), 3.21-3.84 (m, 2H), 2.90-3.05 (m, 3H), 2.47-2.67 (m, 1H), 1.80-2.05 (m, 3H), 1.40-1.75 (m, 6H), 1.00-1.35 (m, 4H), 0.73 (dd, 3H, J=3.4, 6.4), 0.67 (dd, 3H, J=2.7, 6.7).
432				7	sólido blanco	474.02	1.55 min Método A	474.28	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, J=7.6), 7.50 (d, 2H, J=8.6), 6.65 (d, 1H, J=40), 5.46 (s, 1H), 4.56 (t, 1H, J=13), 4.00-4.20 (m, 2H), 3.80-3.90 (m, 1H), 3.40 (s,

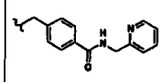
									3H), 3.20-3.35 (m, 1H), 2.85-3.05 (m, 2H), 2.40-2.65 (m, 1H), 1.50-2.00 (m, 5H), 1.00-1.45 (m, 2H), 0.83-0.90 (m, 1H), 0.72 (dd, 3H, J=6.7, 8.2), 0.67 (dd, 3H, J=5.8, 6.4).
433				1-Método A	sólido blanco	455.00	1.83 min Método B	454.15	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.61 (dd, 2H, J=1.8, 8.7), 7.40 (ddd, 2H, J=2.1, 2.4, 8.7), 7.26 (d, 4H, J=7.2), 6.25 (s amplio, 1H), 5.19 (s amplio, 1H), 4.51 (d, 1H, J=15.6), 4.43 (d, 1H, J=15.6), 4.34 (t, 1H, J=7.2), 1.75-1.85 (m, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 1.22-1.35 (m, 2H), 0.78 (d, 3H, J=6.3), 0.66 (d, 3H, J=6.3).

434				7	sólido blanco	542.15	1.73 min Método C	542.46	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.72 (d, 2H, J=8.5), 7.51 (d, 2H, J=8.5), 6.65 (d, 1H, J=39), 5.42 (s, 1H), 4.55 (t, 1H, J=14), 4.00-4.17 (m, 2H), 3.05-3.33 (m, 3H), 2.85-3.05 (m, 2H), 2.40-2.70 (m, 8H), 2.32 (s, 3H), 1.55-2.10 (m, 6H), 1.00-1.30 (m, 6H), 0.72 (t, 3H, J=6.7, 6.7), 0.67 (t, 3H, J=6.1, 6.4).
435				7	sólido blanco	497.02	1.70 min Método A	479.19	RMN ^{1}H ($CDCl_3$, 500MHz) δ 8.31 (s, 1H), 7.76 (d, 2H, J=8.9), 7.56 (d, 2H, J=8.5), 6.74 (s, 1H), 4.81 (t, 1H, J=7.6), 4.71 (s amplio, 1H), 4.20 (s amplio, 1H), 3.13 (t, 2H, J=8.6), 2.70-2.95 (m, 2H), 2.05-2.20 (m, 1H), 1.85-2.00 (m, 2H), 1.55-1.85 (m, 4H), 1.10-1.35 (m, 3H), 1.00 (d,

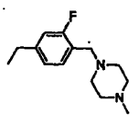
									3H, J=6.4), 0.97 (d, 3H, J=6.7), 0.87 (t, 1H, J=7.0).
436				13	sólido blanco	476.99	1.76 min Método B	477.22	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.94 (dd, 2H, J=1.8, 8.4), 7.69 (dd, 2H, J=1.8, 8.7), 7.45-7.50 (m, 4H), 6.23 (s amplio, 1H), 5.19 (s amplio, 1H), 4.65 (d. 1H, J=15.9), 4.46 (d, 1H, J=15.9), 4.31 (dd, 1H, J=6.6, 7.8), 2.61 (s, 3H), 1.75-1.85 (m, 1H), 1.28-1.35 (m, 1H), 1.08-1.15 (m, 1H), 0.76 (d, 3H, J=6.6), 0.64 (d, 3H, J=6.6).
437				14	sólido amarillo pálido	476.99	1.92 min Método B	477.18	RMN ^{1}H ($CDCl_3$, 300MHz) δ 8.04 (d,. 2H, J=8.4), 7.70 (dd, 2H, J=1.8, 8.4), 7.45-7.52 (m, 4H), 6.23 (s amplio, 1H), 5.19 (s amplio, 1H), 4.67 (d, 1H, J=16.2), 4.47 (d, J=15.9), 4.31 (t, 1H,

									J=7.2), 2.47 (s, 3H), 1.75-1.85 (m, 1H), 1.28-1.35 (m, 1H), 1.08-1.15 (m, 1H), 0.76 (d, 3H, J=6.6), 0.64 (d, 3H, J=6.6).
438				6	sólido blanco	480.03	1.81 min Método B	480.26	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.67 (d, 2H, J=8.7), 7.45 (d, 2H, J=8.7), 7.38 (d. 2H, J=8.1), 7.32 (d, 2H, J=7.5), 6.23 (s amplio, 1H), 5.19 (s amplio, 1H), 4.59 (d, 1H, J=16.2), 4.45 (d, 1H, J=15.9), 4.30 (t, 1H, J=6.9), 3.47-3.56 (m amplio, 1H), 3.15-3.35 (m amplio, 1H), 2.81-3.09 (m amplio, 3H), 1.75-1.85 (m, 1H), 1.05-1.40 (m, 5H), 0.76 (d, 3H, J=6.6), 0.65 (d, 3H, J=6.6).

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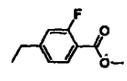
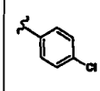
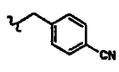
439				6	sólido blanco	529.06	1.60 min Método B	529.25	RMN ^{1}H ($CDCl_3$, 300MHz) δ 8.57 (d, 1H, J=4.8), 7.80 (d, 2H, J=8.4), 7.70-7.73 (m, 2H), 7.67 (d, 2H, J=8.4), 7.45 (d, 2H, J=8.4), 7.42 (d, 2H, J=7.8), 7.36 (d, 1H, J=7.8), 7.28 (s amplio, 1H), 6.23 (s amplio, 1H), 5.22 (s amplio, 1H), 4.77 (d, 2H, J=4.8), 4.63 (d, 1H, J=15.9), 4.44 (d, 1H, J=15.9), 4.29 (t, 1H, J=7.2), 1.73-1.85 (m, 1H), 1.25-1.38 (m, 1H), 1.06-1.14 (m, 1H), 0.75 (d, 3H, J=6.3), 0.65 (d, 3H, J=6.6).
440				8	vidrio color ámbar	512.04	1.36 min Método A	512.24	RMN ^{1}H 400Hz ($CDCl_3$) δ 7.70 (d, 2H, J=8.0Hz), 7.74 (d, 2H, J=8.0Hz), 7.31 (d, 2H, J=6Hz), 7.08 (d, 2H, J=8.0Hz), 6.25 (s, amplio, 1H), 5.41 (s, amplio, 1H), 4.56 (d, 1H,

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									J_{ab}=12H), 4.43 (d, 1H, J_{ab}=12Hz), 4.35 (t, 1H, J=6.0Hz), 3.72 (t, 4H, J=4.0Hz), 3.56 (s, 2H), 2.48 (t, 4H.J=41.0Hz), 1.79 (m, 1H), 1.36 (m, 1H), 1.18 (m, 1H), 0.79 (d, 3H, J=6.0Hz), 0.69 (d, 3H, J=6.0Hz).
441				8	vidrio color ámbar	525.08	1.35 min Método A	525.23	RMN ^{1}H 400Hz ($CDCl_3$) δ 7.69 (d, 2H, J=8.0Hz), 7.47 (d, 2H, J=8.0Hz), 7.28 (t, 1H, J=6.0Hz), 7.07 (dd, 2H, J=8.0Hz), 6.29 (s, amplio, 1H), 5.55 (s, amplio, 1H), 4.46 (d, 1H, J_{ab}=14.0Hz), 4.41 (d, 1H, J_{ab}=14.0Hz), 434 (t, 1H, J=6.0Hz), 3.58 (s, 2H), 2.33 (s, 3H), 1.78 (m, 1H), 1.18 (m, 1H), 0.79 (d, 3H, J=6.0Hz), 0.68 (d, 3H, J=6.0Hz).

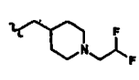
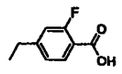
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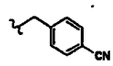
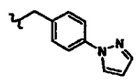
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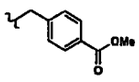
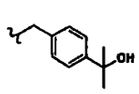
442				1-Método A	vidrio color ámbar	470.94	1.74 min Método A	471.12	RMN ^{1}H 400Hz (CDCl$_3$) δ 7.78 (t, 1H, J=6.0Hz), 7.72 (d, 2H, J=8.0Hz), 7.51 (d, 2H, J=8.0Hz), 7.19 (m, 2H), 6.21 (s, amplio, 1H), 5.37 (s, amplio, 1H), 4.64 (d, 1H, J_{ab}=14.0Hz), 4.47 (d, 1H, J_{ab}=14.0Hz), 4.34 (t, 1H, J=6.0Hz), 3.95 (s, 3H), 1.80 (m, 1H), 1.37 (m, 1H), 1.01 (m, 1H), 0.80 (d, 3H, J=6.0Hz), 0.69 (d, 3H, J=6.0Hz).
443				21	sólido blanco	435.10	1.40 min Método D	$(M+Na)^+$ 458.2	RMN ^{1}H (400 MHz, DMSO) δ 7.84 (d, 2H, J=8.6), 7.76 (d, 2H, J=8.3), 7.62 (d, 2H, J=8.8), 7.51 (d, 2H, J=8.3), 7.40 (s, 1H), 7.11 (s, 1H), 4.63 (ABq, 2H, Δv=5.9, J_{ab}=17.6), 4.56 (dd, 1H, J=8.3, 2.5), 4.54 (s, 1H), 1.95 (dd, 1H, J=13.7, 8.6), 1.26 (dd, 1H, J=13.6, 2.4), 1.04 (s, 3H), 0.99 (s, 3H).

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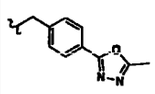
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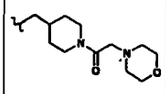
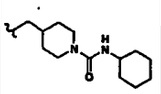
444				7	aceite claro	465.17	1.38 min Método A	466.20	RMN ^{1}H ($CDCl_3$, .500MHz) δ 7.73 (d, 2H, J=8.8), 7.50 (d, 2H, J=8.9), 6.67 (s, 1H), 5.37 (s, 1H), 4.14 (dd, 1H, J=5.5, 9.5), 3.25 (dd, 1H, J=10, 14), 2.97 (dd, 1H, J=4.5, 14), 2.87-2.95 (m, 2H), 2.65-2.75 (m, 2H), 2.07-2.23 (m, 2H), 1.83-1.90 (m, 1H), 1.50-1.82 (m, 4H), 1.15-1.40 (m, 3H), 0.77-0.85 (m, 1H), 0.72 (d, 3H, J=6.7), 0.66 (d, 3H, J=6.4).
445				6	vidrio color ámbar	456.92	1.62 min Método A	457.32	RMN ^{1}H 400Hz ($CDCl_3$) δ 7.77 (d, 2H, J=6.0Hz), 7.68 (t, 1H, J=6.0Hz), 7.64 (d, 2H, J=8.0Hz), 7.39 (m, 3H), 6.21 (s, amplio, 1H), 5.35 (s, amplio, 1H), 4.67 (d, 1H, J_{ab}=14.0Hz), 4.38 (d, 1H, J_{ab}=14.0Hz), 3.44 (m, 1H), 1.88 (m, 1H), 1.59 (m, 2H), 0.79 (d,

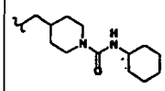
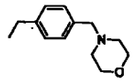
									3H, J=6.0Hz), 0.69 (d, 3H, J=6.0Hz).
446				18	sólido blanque-cino	417.09	1.53 min Método F	$(M+Na)^+$ 418.2	RMN ^1H (400 MHz, DMSO) δ 7.82 (d, 2H, J=8.8), 7.74 (d, 2H, J=8.5), 7.63 (d, 2H, J=8.8), 7.62 (s, 1H), 7.53 (d, 2H, J=8.5), 7.09 (s, 1H), 4.80 (ABq, 2H, Δν=17.9, J_{ab}=17.8), 4.70 (s, 1H), 4.62 (t, 1H, J=7.6), 4.60 (s, 1H), 234 (dd, 1H, J=14.4, 7.1), 2.02 (dd, 1H, J=14.6, 7.3), 1.57 (s, 3H).
447				18	sólido blanque-cino	458.12	1.59 min Método G	$(M+Na)^+$ 459.2	RMN ^1H (400 MHz, DMSO) δ 8.45 (d, 1H, J=2.2), .82 (d, 2H, J=8.6), 7.72 (m, 3H), 7.60 (d, 2H, J=8.8), 7.57 (s, 1H), 7.44 (d, 2H, J=8.5), 7.09 (s, 1H), 6.54 (t, 1H, J=2.0) 4.74 (ABq, 2H, Δν=25.5, J_{ab}=16.8), 4.71 (s, 1H), 4.61 (m, 2H), 2.37 (dd, 1H,

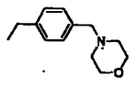
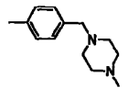
									J=14.2, 7.1), 2.08 (dd, 1H, J=14.7, 7.6), 1.57 (s, 3H).
448				18	sólido blanque-cino	442.90	1.74 min Método A	443.05	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.96 (d, 2H, J=8.2), 7.72 (d, 2H, J=8.0), 7.48 (d, 2H, J=8.0), 7.39 (d, 2H, J=8.0), 6.33 (s amplio, 1H), 5.20 (s amplio, 1H), 4.55-4.62 (m, 2H). 4.39 (d, 1H, J=15.4), 4.28-4.32 (m, 1H), 4.17-4.21 (m, 1H), 3.90 (s, 3H), 2.17-2.35 (m, 1H), 1.56-1.65 (m, 1H).
449				18, 12	espuma amarilla	442.94	1.65 min Método A	442.21	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.67 (ddd, 2H, J=2.0, 2.6, 8.8), 7.42 (ddd, 2H, J=2.0, 2.3, 8.8), 7.39 (d, 2H, J=8.2), 7.24 (d, 2H, J=8.2), 6.34 (s amplio, 1H), 5.35 (s amplio, 1H), 4.56 (dd, 1H, J=5.8, 8.5), 4.48 (d,

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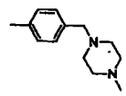
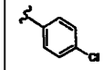
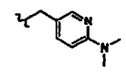
									1H, J=15.5), 4.35 (d, 1H, J=15.5), 4.30-4.33 (m, 1H), 4.18-4.22 (m, 1H), 2.23-2.39 (m, 1H), 1.56-1.670 (m, 2H), 1.57 (s, 6H).
450				18, 13	sólido blanco	466.92	1.61 min Método A	467.18	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.96 (ddd, 2H, J=1.7, 2.0, 8.4), 7.73 (ddd, 2H, J=1.9, 2.5, 8.7). 7.49 (ddd, 2H, J=2.0, 2.3, 8.7), 7.46 (d, 2H, J=8.6), 6.34 (s amplio, 1H), 5.21 (s amplio, 1H), 4.64 (d, 1H, J=15.4), 4.57-4.60 (m, 1H), 4.39 (d, 1H, J=16.1), 4.30-4.32 (m, 1H), 4.18-4.21 (m, 1H), 2.61 (s, 3H), 2.18-2.36 (m, 1H), 1.55-1.66 (m, 1H).

451				18,7	aceite claro	533.07	1.71 min Método A	533.22	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.73 (d, 2H, J=8.6), 7.51 (d, 2H, J=8.8), 6.67 (s, 1H), 5.51 (s, 1H), 4.14-4.52 (m, 4H), 3.76-3.95 (m, 2H), 3.50-3.72 (m, 1H), 3.19-327 (m, 1H), 2.86-3.07 (m, 1H), 2.56-2.80 (m, 2H), 1.70-1.99 (m, 7H), 1.36-1.63 (m, 10H).
452				18,7	aceite claro	517.07	2.53 min Método A	517.32	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.74 (d, 2H, J=8.6), 7.50 (d, 2H, J=8.5), 6.70 (s, 1H), 5.60 (s, 1H), 4.50 (dd, 1H, J=4.9, 9.8), 4.22-4.31 (m, 2H), 3.81-4.00 (m, 5H), 3.53-3.66 (m, 2H), 3.40-3.50 (m, 1H), 3.13-3.25 (m, 3H), 2.89 (dd, 1H, J=4.6, 14), 2.62-2.77 (m, 3H), 1.50-1.95 (m, 6H), 1.01-1.45 (m, 5H).

453				18, 7	aceite claro	531.09	2.27 min Método A	531.36	RMN ^1H ($CDCl_3$, 400MHz) δ 7.73 (d, 2H, J=8.6), 7.51 (d, 2H, J=8.6), 6.65 (d, 1H, J=28), 5.47 (s, 1H), 4.50-4.63 (m, 1H), 4.20-4.45 (m, 1H), 4.05-4.15 (m, 2H), 3.55-3.65 (m, 2H), 3.05-3.35 (m, 6H), 2.85-3.00 (m, 3H), 2.55-2.35 (m, 2H), 1.50-2.00 (m, 6H), 1.00-1.45 (m, 7H).
454				8	vidrio color ámbar	533.99	1.40 min Método A	534.27	RMN ^1H 400Hz ($CDCl_3$) δ 7.78 (d, 2H, J=8.0Hz), 7.39 (m, 6H), 6.34 (s, 1H), 5.80 (s, amplio, 1H), 4.72 (d, 1H, J_{ab}=14.0Hz), 4.16 (m, 1H), 4.34 (d, 1H, J_{ab}=14.0Hz), 3.60 (m, 4H), 3.84 (s, 2H), 2.62 (m, 2H), 2.25 (m, 4H) .

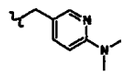
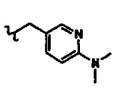
455				18, 8	vidrio color ámbar	501.98	1.27 min Método A	502.24	RMN ^{1}H 400Hz ($CDCl_3$) δ 7.79 (d, 2H, J=8.0Hz), 7.39 (m, 6H), 6.33 (s, amplio, 1H), 5.80 (s, amplio, 1H), 4.68 (d, 1H, J_{ab}=14.0Hz), 4.22 (d, 1H, J_{ab}=14.0Hz), 3.55 (s, 2H), 2.62 (m, 2H), 2.43 (m, 8H), 2.30 (s, 3H).
456				18, 8	vidrio color ámbar	515.02	1.22 min Método A	515.31	RMN ^{1}H 400Hz ($CDCl_3$) δ 7.79 (d, 2H, J=8.0Hz), 7.52 (d, 2H, J=8.0Hz), 7.39 (m, 4H), 6.34 (s, amplio, 1H), 5.78 (s, amplio, 1H), 5.72 (t, 1H, J=54.0Hz), 4.68 (d, 1H, J_{ab}=14.0Hz), 4.34 (d, 1H, J_{ab}=14.0Hz), 3.88 (m, 1H), 3.56 (m, 4H), 2.49 (m, 2H), 2.26 (m, 4H).

573

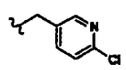
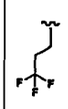
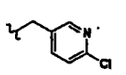
457				8	vidrio color ámbar	547.03	1.26 min Método A	547.20	RMN ^{1}H 400Hz ($CDCl_3$) δ 7.78 (d, 2H, J=8.0Hz), 7.50 (d, 2H, J=8.0Hz), 7.41 (m, 4H), 6.35 (s, amplio, 1H), 5.80 (s, amplio, 1H), 5.72 (t, 1H, J=54.0Hz), 4.68 (d, 1H, J_{ab}=14.0Hz), 4.35 (d, 1H, J_{ab}=14.0Hz), 3.87 (m, 1H), 3.55 (s, 2H), 2.44 (m, 10H), 2.30 (s, 3H).
458				18, 1-Método B	espuma blanca	446.91	1.01 Método B	447.13	RMN ^{1}H ($CDCl_3$) sal de TFA δ 8.14 (s, 1H), 7.98 (d, 1H, J=9.6Hz), 7.76 (d, 2H J=6.8Hz), 7.55 (d, 2H, J=6.8Hz), 6.81 (d, 2H, J=9.6Hz), 6.45 (s, 1H), 6.10 (s, 1H), 5.70 (t, 1H, J=110.0Hz), 4.60 (d, 1H, J=16.0Hz), 4.51 (m, 1H), 4.06 (d, 1H, J=16Hz), 3.30 (s, 6H), 2.55 (m, 1H), 1.60 (m, 1H).

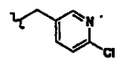
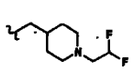
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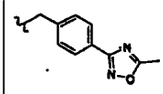
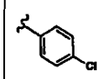
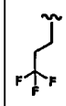
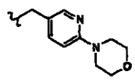
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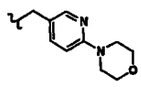
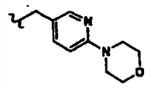
459				18, 1-Método B	espuma blanca	456.97	1.14 Método B	457.23	RMN ^1H ($CDCl_3$) sal de TFA δ 8.11 (s, 1H), 7.95 (d, 1H, J=9.6Hz), 7.77 (d, 2H, J=6.8Hz), 7.51 (d, 2H, J=6.8Hz), 6.76 (d, 2H, J=9.6Hz), 6.34 (s, 1H), 6.02 (s, 1H), 4.58 (d amplio, 1H, J=8.4Hz), 4.06 (d, 1H, J=16Hz), 4.06 (d, 1H, J=16Hz), 3.29 (s, 6H), 2.50 (m, 1H), 1.39 (m, 1H), 1.25 (d, 3H, J=22.0Hz), 1.17 (d, 3H, J=22.0Hz).
460				1-Método B	sólido gomoso, amarillo claro	478.92	1.89 min columna ODS-A C-18 3 X 50 mm 4mL/min, gradiente	479.21	RMN ^1H ($CDCl_3$) δ 8.09 (s, 1H), 8.01 (d, 1H, J=9.2Hz), 7.75 (d, 2H, J=8.4Hz), 7.53 (d, 2H, J=8.4Hz), 6.82 (d, 1H, J=9.2Hz), 6.62 (s, amplio, 1H), 6.12 (s, amplio, 1H), 4.18-4.58 (m, 3H), 3.30 (s, 6H), 2.15 (m, 1H), 2.05 (m, 1H), 1.85 (m, 1H),

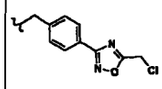
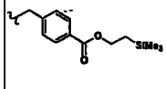
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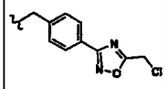
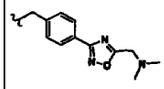
							de MeOH 0-100%/ H2O, TFA 0.1% 4 min		1.40 (m, 1H).
461				18	aceite claro	438.26	1.41 min Método B	438.01	RMN ^{1}H ($CDCl_3$) δ 8.33 (s, 1H), 7.73 (d, 1H, J=8.4Hz), 7.71 (d, 2H, J=8.8Hz), 7.51 (d, 2H, J=8.8Hz), 7.27 (d, 1H, J=8.4Hz), 6.56 (s, amplio, 1H), 6.11 (s, amplio, 1H), 5.69 (m,1H), 4.21-4.62 (m, 3H), 2.52 (m, 1H), 1.63 (m, 1H).
462				1	sólido blanco	470.30	1.53 min Método B	470.02	RMN ^{1}H ($CDCl_3$) δ 8.38 (s, 1H), 7.79 (d, 1H, J=8.0Hz), 7.68 (d, 2H, J=8.4Hz), 7.50 (d, 2H, J=8.4Hz), 7.31 (d, 1H, J=8.0Hz), 6.57 (s, amplio, 1H), 6.25 (s, amplio, 1H), 4.29-4.64 (m, 3H), 2.12 (m, 1H),

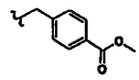
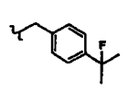
									1.98 (m, 1H), 1.81 (m, 1H), 1.43 (m, 1H).
463				18	aceite claro	434.32	1.43 min Método B	434.13	RMN ^1H ($CDCl_3$) δ 8.37 (s, 1H), 7.70 (d, 1H, J=8.8Hz), 7.68 (d, 1H, J=8.8Hz), 7.67 (d, 2H, J=6.8Hz), 7.48 (d, 2H, J=6.8Hz), 6.25 (s, amplio, 1H), 5.31 (s, amplio, 1H), 4.34-4.62 (m, 5H), 1.35-2.05 (m, 4H).
464				18, 7	aceite claro	469.14	1.14 min Método A	470.17	RMN ^1H ($CDCl_3$, 400MHz) δ 7.73 (d, 2H, J=8.8), 7.51 (d, 2H, J=8.8), 6.65 (s, 1H), 5.39 (s, 1H), 4.05-4.35 (m, 2H), 3.25 (dd, 1H, J=10, 14), 2.85-3.04 (m, 3H), 2.65-2.85 (m, 2H), 2.09-2.29 (m, 2H), 1.93-2.10 (m, 1H), 1.83-1.91 (m, 10H).

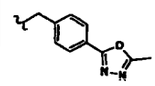
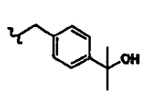
465				15	sólido blanco	476.99	1.91 min Método A	477.13	RMN ^{1}H ($CDCl_3$, 500MHz) δ 7.98 (d, 2H, J=8.2), 7.68 (d, 2H, J=8.9), 7.45 (d, 4H, J=8.5), 6.21 (s, 1H), 5.19 (s, 1H), 4.62 (d, 1H, J=15), 4.48 (d, l H, J=16), 4.31 (t, 1H, J 7.0), 2.65 (s, 3H), 1.75-1.85 (m, 1H), 1.20-1.35 (m, 4H), 1.10-1.17 (m, 1H), 0.85-0.90 (m, 1H), 0.75 (d, 3H, J=6.7), 0.64 (d, 3H, J=6.4).
466				1-Método B	sólido gomoso, claro	520.96	1.17 min Método B	521.19	RMN ^{1}H ($CDCl_3$) δ 8.16 (s, 1H), 8.06 (d, 1H, J=9.2Hz), 7.75 (d, 2H, J=8.4Hz), 7.50 (d, 2H, J=8.4Hz), 7.31 (d, 1H, J=9.2Hz), 6.67 (s, amplio, 1H), 6.20 (s, amplio, 1H), 4.19-4.60 (m, 3H), 3.87 (m, 4H), 3.69 (m, 4H), 2.14 (m, 1H), 1.98 (m, 1H), 1.83 (m, 1H), 1.38 (m, 1H).

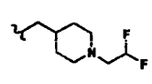
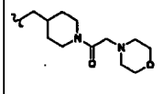
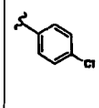
467				18, 1-Método B	sólido gomoso, claro	470.95	0.983 min Método B	471.19	RMN ^{1}H ($CDCl_3$) δ 8.15 (s, 1H), 8.10 (d, 1H, J=9.2Hz), 7.77 (d, 2H, J=8.4Hz), 7.53 (d, 2H, J=8.4Hz), 6.93 (d, 1H, J=9.2Hz), 6.65 (s, amplio, 1H), 6.22 (s, amplio, 1H), 4.09-4.67 (m, 5H), 3.87 (m, 4H), 3.68 (m, 4H), 2.25 (m, 1H), 1.63 (m, 1H).
468				1-Método B	sólido gomoso, claro	499.01	1.153 min Método B	499.23	RMN ^{1}H ($CDCl_3$) δ 8.12 (s, 1H), 8.07 (d, 1H, J=9.2Hz), 7.78 (d, 2H, J=8.4Hz), 7.52 (d, 2H, J=8.4Hz), 6.91 (d, 1H, J=9.2Hz), 6.63 (s, amplio, 1H), 6.19 (s, amplio, 1H), 4.07-4.62 (m, 3H), 3.86 (m, 4H), 3.68 (m, 4H), 2.46 (m, 1H), 1.31 (m, 1H), 1.25 (d, 3H, J=21.6), 1.17 (d, 3H, J=21.6).

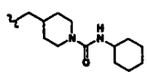
469				15	sólido blanco	511.43	1.90 min Método C	511.13	RMN ^{1}H ($CDCl_3$, 400MHz) δ 8.01 (d, 2H, J=8.3), 7.69 (d, 2H, J=8.8), 7.43-7.51 (m, 4H), 6.20 (s, 1H), 5.15 (s, 1H), 4.74 (s, 2H), 4.63 (d, 1H, J=15), 4.47 (d, 1 H, J=16), 4.31 (t, 1H, J=6.8), 1.74-1.87 (m, 1H), 1.04-1.88 (m, 4H), 0.82-0.94 (m, 1H), 0.76 (d, 3H, J=6.6), 0.65 (d, 3H, J=6.6).
470				1	sólido blanco	529.11	2.17 min Método D	529.11	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.95 (d, 2H, J=8.4), 7.71 (dd, 2H, J=1.6, 8.4), 7.48 (dd, 2H, J=2.4, 8.8), 7.38 (dd, 2H, J=2.4, 8.8), 6.31 (s amplio, 1H), 5.22 (s amplio, 1H), 4.60 (d, 1H, J=15.6), 4.55-4.58 (m, 1H), 4.38-4.42 (m, 3H), 4.29-4.32 (m, 1H), 4.17-4.21 (m, 1H), 2.18-2.32

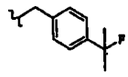
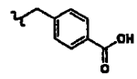
									(m, 2H), 1.12 (dd, 2H, J=6.8, 8.4), 0.08 (s, 9H).
471				15, 23	sólido blanco	510.14	1.86 min Método A	511.13	RMN ^{1}H ($CDCl_3$, 400MHz) δ 8.01 (d, 2H, J=8.4), 7.69 (d, 2H, J=8.8), 7.47 (d, 2H, J=8.0), 7.46 (d, 2H, J=8.8), 6.20 (s amplio, 1H), 5.20 (s amplio, 1H), 4.74 (s, 2H), 4.64 (d, 1H, J=15), 4.49 (d, 1H, J=15), 4.31 (t, 1H, J=7.0), 1.73-1.87 (m, 1H), 1.20-1.37 (m, 1H), 1.07-1.17 (m, 1H), 0.76 (d, 3H, J=6.6), 0.65 (d, 3H, 6.6).
472				15, 8	sólido blanco	519.17	1.42 min Método A	520.18	RMN ^{1}H ($CDCl_3$, 400MHz) δ 8.02 (d, 2H, J=7.6), 7.71 (d, 2H, J=8.4), 7.52 (d, 2H, J=8.0), 7.48 (d, 2H, J=8.4), 6.23 (s amplio, 1H), 5.17 (s amplio, 1H), 4.70 (d, 1H, J=16), 4.44 (d, 1H J=16), 4.31 (t, 1H, J=6.4), 3.70 (s,

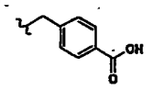
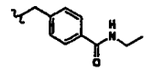
									2H), 3.02 (s, 6H), 1.75-1.90 (m, 1H), 1.00-1.40 (m, 2H), 0.76 (d, 3H, J=6.8), 0.66 (d, 3H, J=6.4).
473				1	espuma blanque-cina	460.89	2.11 min Método A	461.08	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.97 (d, 2H, J=8.4), 7.72 (d, 2H, J=8.4), 7.51 (dd, 2H, J=2.0, 8.4), 7.38 (d, 2H, J=8.0), 6.32 (s amplio, 1H), 5.71 (tm, 1H, J_{H-F}=55), 5.19 (s amplio, 1H), 4.60 (d, 1H, J=15.6), 4.49-4.53 (m, 1H), 4.33 (d, 1H, J=15.6), 3.91 (s, 3H), 2.42-2.68 (m, 1H), 1.54-1.65 (m, 1H).
474				1	espuma amarilla pálida	462.92	2.24 min Método A	485.07 (M+Na$^+$)	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.67 (d, 2H, J=8.4), 7.47 (d, 2H, J=8.8), 7.25-7.29 (m, 4H), 6.33 (s amplio,1H), 5.72 (tm, 1H, J_{H-F}=57), 5.23 (s amplio, 1H), 4.49-4.53 (m, 1H), 4.46 (d, 1H, J=15.6), 4.34 (d,

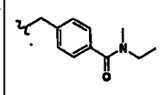
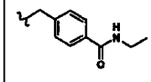
									1H, J=15.0), 2.52-2.60 (m, 1H), 1.55-1.65 (m, 1H), 1.68 (s, 3H), 1.63 (s, 3H).
475				1, 13	espuma blanca	484.91	1.67 min Método D	485.07	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.97 (d, 2H, J=8.0), 7.73 (dd, 2H, J=2.0, 8.8), 7.52 (dd, 2H, J=2.0, 8.8), 7.45 (d, 2H, J=8.4), 6.34 (s amplio, 1H), 5.73 (tm, 1H, J_{H-F}=57), 5.20 (s amplio, 1H), 4.63 (d, 1H, J=15.6), 4.52-4.55 (m, 1H), 4.32 (d, 1H, J=15.6), 2.61 (s, 3H), 2.55-2.60 (m, 1H), 1.61-1.65 (m, 1H).
476				1, 12	espuma blanca	460.93	1.72 min Método D	483.07 ($M+Na^+$)	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.68 (dd, 2H, J=2.0, 8.8), 7.48 (dd, 2H, J=8.4), 7.41 (d, 2H, J=8.4), 7.23 (d, 2H, J=8.8), 6.30 (s amplio, 1H), 5.73 (tm, 1H, J_{H-F}=57), 5.18 (s amplio,

									1H), 4.48-4.52 (m, 1H), 4.44 (d, 1H, J=15.2), 4.34 (d, 1H, J=15.2), 2.50-2.65 (m, 1H), 1.61-1.70 (m, 1H), 1.56 (s, 6H).
477				7	aceite claro	455.93	0.99 min Método A	456.20	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.72-7.86 (m, 2H), 7.45-7.52 (m, 2H), 6.70 (s amplio, 1H), 5.44 (s amplio, 1H), 4.46-4.57 (m, 2H), 4.00-4.37 (m, 2H), 3.24 (dd, 1H, J=4.4 9.8), 2.70-3.15 (m, 6H), 2.15-2.34 (m, 2H), 1.80-1.93 (m, 2H), 1.54-1.63 (m, 2H), 1.25-1.35 (m, 2H).
478				7	aceite claro	519.04	1.12 min Método A	519.23	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.71-7.84 (m, 2H), 7.39-7.55 (m, 2H), 6.70 (m amplio, 1H), 5.87 (m amplio, 1H), 4.88 (m, 1H), 4.50 (d, 1H, J=9.5), 4.21-4.31 (m, 2H), 4.11-4.20

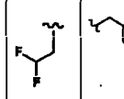
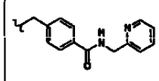
									(m, 2H), 3.80-3.87 (m, 2H), 3.69-3.77 (m, 2H), 3.31-3.50 (m, 2H), 3.00-3.21 (m, 2H), 2.80-3.95 (m, 2H), 2.10-2.50 (m, 4H), 1.85-1.95 (m, 2H), 1.73 (d, 2H, J=8.5), 1.40-1.50 (m, 2H).
479				7	aceite claro	535.06	1.72 min Método A	535.18	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.73 (d, 2H, J=8.6), 7.53 (d, 2H, J=8.6), 6.70 (s amplio, 1H), 5.70 (tm, 1H, J_{HF}=50), 5.55 (s amplio, 1H), 4.46 (dd, 1H, J=3.8, 10), 3.80-4.00 (m, 3H), 3.50-3.70 (m, 1H), 3.15-3.30 (m, 1H), 2.80-3.95 (m, 1H), 2.60-2.80 (m, 2H), 2.40-2.60 (m, 1H), 1.05-2.00 (m, 16H).

480				1	espuma blanque-cina	444.93	1.89 min Método D	467.09 (M+Na⁺)	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.66 (ddd, 2H, J=2.0, 2.4, 8.8), 7.44 (ddd, 2H, J=2.0, 2.4, 8.8), 7.25-7.31 (m, 4H), 6.30 (s amplio, 1H), 5.22 (s amplio, 1H), 4.56-4.60 (m, 1H), 4.47 (d, 1H, J=15.6), 4.39 (d, 1H, J=16.0), 4.32-4.36 (m, 1H), 4.20-4.24 (m, 1H), 2.23-2.39 (m, 1H), 1.70-1.85 (m, 1H), 1.65-1.68 (m, 3H), 1.53 (s, 3H).
481				6	sólido blanco	428.87	1.58 min Método D	429.04	RMN ^{1}H (CD_3OD, 400MHz) δ 7.92 (d, 2H, J=8.4), 7.79 (ddd, 2H, J=2.0, 2.4, 8.8), 7.52 (ddd, 2H, J=2.0, 2.8, 8.8), 7.47 (d, 2H, J=8.0), 4.80 (d, 1H, J=16), 4.66 (d, 1H, J=14.5), 4.64 (t, 1H, J=7.6), 4.10-4.33 (m, 2H), 2.05-2.12 (m, 1H), 1.72-1.80 (m, 1H).

482				6	sólido amarillo	446.86	1.39 min Método B	447.06	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.89 (d, 2H, J=8.0), 7.66 (dd, 2H, J=2.0, 8.0), 7.41 (dd, 2H, J=2.0, 8.4), 7.31 (d, 2H, J=8.0), 6.61 (s amplio, 1H), 5.90 (s amplio, 1H), 5.76 (tm, 1H, J_{H-F}=57), 4.56 (d, 1H, J=16.0), 4.49-4.52 (m, 1H), 4.36 (d, 1H, J=12.0), 2.50-2.65 (m, 1H), 1.61-1.70 (m, 1H).
483				6	sólido blanco	455.94	1.34 min Método B	488.11 ($M+Na^+$)	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.72 (d, 2H, J=8.0), 7.68 (d, 2H, J=8.0), 7.49 (ddd, 2H, J=2.0, 2.4, 8.4), 7.38 (d, 2H, J=8.0), 6.32 (s amplio, 1H), 0.06 (s amplio, 1H), 5.19 (s amplio, 1H), 4.59 (d, 1H, J=15.0), 4.56-4.60 (m, 1H), 4.37 (d, 1H, J=15.0), 4.29-4.32 (m, 1H), 4.16-4.19 (m, 1H), 3.45-3.49 (m, 2H), 2.15-2.30 (m, 1H),

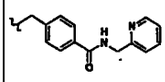
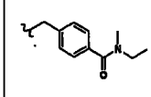
									1.50-1.65 (m, 1H), 1.25 (t, 3H, J=8.0).
484				6	sólido blanco	469.97	1.40 min Método B	470.15	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.72 (d, 2H, J=8.0), 7.48 (d, 2H, J=8.0), 7.30-7.36 (m, 4H), 6.30 (s amplio, 1H), 5.26 (s amplio, 1H), 4.54-4.58 (m, 2H), 4.38 (d, 1H, J=15.2), 4.29-4.32 (m, 1H), 4.18-4.22 (m, 1H), 3.55-3.59 (m, 1H), 3.22-3.27 (m, 1H), 2.90 y 3.05 (2 s, 3H), 2.20-2.33 (m, 1H), 1.50-1.65 (m, 1H), 1.08-1.30 (m, 3H).
485				6	sólido blanco	473.93	1.33 min Método B	474.11	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.72 (d, 2H, J=8.8), 7.70 (d, 2H, J=8.4), 7.51 (d, 2H, J=8.8), 7.38 (d, 2H, J=8.0), 6.31 (s amplio, 1H), 6.05 (s amplio, 1H), 5.72 (tm, 1H, J_{H-F}=57), 5.20 (s amplio, 1H), 4.59 (d, 1H, J=15.6),

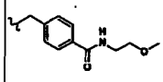
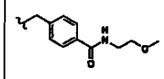
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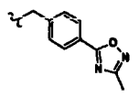
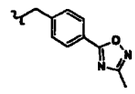
									4.49-4.52 (m, 1H), 4.31 (d, 1H, J=15.6), 3.46-3.53 (m, 2H), 2.45-2.65 (m, 1H), 1.57-1.65 (m, 1H), 1.25 (t, 3H, J=7.2).
486				6	sólido blanco	536.99	1.13 min Método B	537.17	RMN ^{1}H ($CDCl_3$, 400MHz) δ 8.57 (d, 1H, J=4.8), 7.83 (d, 2H, J=8.4), 7.71-7.78 (m, 3H), 7.71 (s amplio, 1H), 7.52 (dd, 2H, J=1.6, 8.8), 7.40 (d, 2H, J=8.0), 7.30-7.35 (m, 1H), 7.23-7.28 (m, 1H), 6.32 (s amplio, 1H), 5.72 (tm, 1H, J_{H-F}=57), 5.25 (s amplio, 1H), 4.75 (d, 2H, J=4.8), 4.59 (d, 1H, J=15.6), 4.49-4.53 (m, 1H), 4.33 (d, 1H, J=15.6), 2.48-2.65 (m, 1H), 1.58-1.65 (m, 1H).

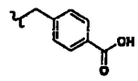
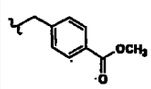
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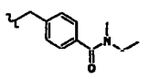
487				6	sólido blanco	519.00	1.10 min Método B	519.35	RMN ^{1}H ($CDCl_3$, 400MHz) δ 8.58 (d, 1H, J=4.4), 7.92 (d, 2H, J=8.4), 7.71-7.78 (m, 4H), 7.48 (dd, 2H, J=2.0, 8.8), 7.39-7.44 (m, 3H), 7.24-730 (m, 1H), 6.28 (s amplio, 1H), 5.20 (s amplio, 1H), 4.78 (d, 2H, J=4.8), 4.55-4.61 (m, 2H), 4.39 (d, 1H, J=15.6), 4.29-4.32 (m, 1H), 4.17-4.21 (m, 1H), 2.20-2.33 (m, 1H), 1.50-1.65 (m, 1H).
488				6	sólido blanco	487.96	1.63 min Método D	488.34	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.72 (dd, 2H, J=2.0, 8.8), 7.51 (dd, 2H, J=2.0, 8.4), 7.50 (s, 4H), 6.30 (s amplio, 1H), 5.72 (tm, 1H, J_{H-F}=57), 5.24 (s amplio, 1H), 4.55 (d, 1H, J=15.5), 4.49-4.52 (m, 1H), 4.33 (d, 1H, J=15.5), 3.57 (s amplio, 1H),

									3.23 (s amplio, 1H), 2.90 y 3.05 (2 s, 3H), 2.48-2.62 (m, 1H), 1.57-1.72 (m, 1H), 1.08-1.30 (m, 3H).
489				6	sólido blanque-cino	503.96	1.40 min Método A	504.41	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.72 (d, 4H, J=8.4), 7.52 (d, 2H, J=8.8), 7.38 (d, 2H, J=8.4), 6.49 (s amplio, 1H), 6.31 (s amplio, 1H), 5.72 (tm, 1H, J_{H-F}=57), 5.19 (s amplio, 1H), 4.59 (d, 1H, J=15.0), 4.48-4.52 (m, 1H), 4.31 (d, 1H, J=15.6), 3.62-3.68 (m, 2H), 3.53-3.59 (m, 2H), 3.39 (s, 3H), 2.48-2.62 (m, 1H), 1.57-1.72 (m, 1H).
490				6	sólido blanco	485.97	1.27 min Método B	486.14	RMN ^{1}H ($CDCl_3$, 300MHz) δ 7.69-7.74 (m, 4H), 7.51 (dd, 2H, J=1.8, 8.4), 7.38 (d, 2H, J=8.1), 6.48 (s amplio, 1H) 6.32 (s amplio 1H), 5.19 (s amplio 1H), 4.54-4.62 (m, 2H),

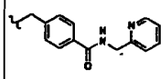
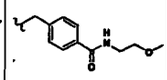
									4.30-4.41 (m, 2H), 4.13-4.19 (m, 1H), 3.61-3.67 (m, 2H), 3.53-3.59 (m, 2H), 3.39 (s, 3H), 2.48-2.62 (m, 1H), 1.57-1.72 (m, 1H).
491				14	sólido blanque-cino	484.91	1.54 min Método 1B	485.12	RMN ^{1}H ($CDCl_3$, 400MHz) δ 8.06 (d, 2H, J=8.4), 7.74 (d, 2H, J=8.8), 7.53 (d, 2H, J=8.8), 7.48 (d, 2H, J=8.4), 6.34 (s amplio, 1H), 5.72 (tm, 1H, J_{H-F}=57), 5.20 (s amplio, 1H), 4.65 (d, 1H, J=15.4), 4.51-4.56 (m, 1H), 4.33 (d, 1H, J=15.8), 2.48-2.65 (m, 1H), 2.47 (s, 3H), 1.57-1.65 (m, 1H).
492				14	sólido blanque-cino	466.92	1.65 min Método A	467.19	RMN ^{1}H ($CDCl_3$, 400MHz) δ 8.04 (d, 2H, J=8.0), 7.74 (dd, 2H, J=1.6, 8.4), 7.48-7.51 (m, 4H), 6.32 (s amplio, 1H), 5.17 (s amplio, 1H), 4.65 (d, 1H, J=16.0), 4.56-4.60 (1H,

									1H), 4.40 (d, 1H, J=16.0), 4.29-4.32 (m, 1H), 4.18-4.21 (m, 1H), 2.47 (s, 3H), 2.18-2.38 (m, 1H), 1.50-1.65 (m, 1H).
493				6	sólido blanco	478.88	1.59 min Método A	479.15	RMN ^{1}H (dmso-d_6, 400MHz) δ 7.88 (d, 2H, J=8.0); 7.85 (d, 2H, J=8.8), 7.63 (d, 2H, J=8.8), 7.51 (d, 2H, J=8.0), 7.42 (s amplio, 1H), 7.24 (s amplio, 1H), 4.77 (d, 2H, J=2.0), 4.40-4.44 (m, 1H), 1.97-2.05 (m, 2H), 1.75-1.84 (m, 1H), 1.42-1.50 (m, 1H).
494				1	sólido blanco	492.91	1.66 min Método A	493.11	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.97 (d, 2H, J=8.4), 7.69 (dd, 2H, J=1.6, 8.4), 7.50 (dd, 2H, J=2.0, 8.4), 7.40 (d, 2H, J=8.4), 6.22 (s amplio, 1H), 5.19 (s amplio, 1H), 4.58 (d, 1H, J=16.0), 4.43 (d, 1H,

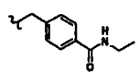
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									J=15.6), 4.31-4.35 (m, 1H), 3.91 (s, 3H), 2.08-2.20 (m, 1H), 1.88-2.03 (m, 1H), 1.69-1.82 (m, 1H), 1.38-1.47 (m, 1H).
495				6	sólido blanquecino	519.97	1.48 min Método B	520.21	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.70 (d, 2H, J=8.4), 7.50 (d, 2H, J=8.8), 7.37 (d, 2H, J=8.4), 7.33 (d, 2H, J=8.0), 6.20 (s amplio, 1H), 5.26 (s amplio, 1H), 4.45-4.52 (m, 2H), 4.33 (t, 1H, J=7.2), 3.61-3.70 (m, 1H), 3.22-3.27 (m, 1H), 2.90 y 3.06 (2 s, 3H), 2.05-2.18 (m, 1H), 1.90-2.03 (m, 1H), 1.69-1.82 (m, 1H), 1.38-1.47 (m, 1H), 1.11-1.28 (m, 3H).

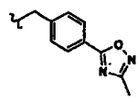
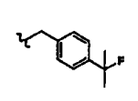
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496				6	sólido blanque-cino	569.01	1.21 min Método B	569.16	RMN ^{1}H ($CDCl_3$, 400MHz) δ 8.57 (d, 1H, J=4.8), 7.82 (d, 2H, J=8.4), 7.68-7.72 (m, 4H), 7.50 (d, 2H, J=8.8), 7.42 (d, 2H, J=8.4), 7.35 (d, 1H, J=8.0), 7.24 (s amplio, 1 H), 6.24 (s amplio, 1H), 5.26 (s amplio, 1H), 4.76 (d, 2H, J=4.8), 4.58 (d, 1H, J=15.6), 4.41 (d, 1H, J=15.6), 4.31-4.35 (m, 1H), 2.10-2.19 (m, 1H), 1.90-2.03 (m, 1H), 1.69-1.82 (m, 1H), 1.38-1.47 (m, 1H).
497				6	sólido blanco	535.97	1.53 min Método A	536.16	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.72 (d, 2H, J=8.0), 7.69 (d, 2H, J=8.4), 7.50 (d, 2H, J=8.4), 7.40 (d, 2H, J=8.4), 6.48 (s amplio, 1H), 6.22 (s amplio, 1H), 5.20 (s amplio, 1H), 4.57 (d, 1H, J=15.6), 4.41 (d, 1H, J=15.6),

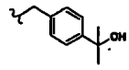
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									4.30-4.34 (m, 1H), 3.63-3.67 (m, 2H), 3.55-3.57 (m, 2H), 3.39 (s, 3H), 2.10-2.20 (m, 1H), 1.88-2.03 (m, 1H), 1.69-1.82 (m, 1H), 1.38-1.47 (m, 1H).
498				6	sólido blanco	505.95	1.55 min Método A	506.10	RMN ^{1}H ($CDCl_3$, 400MHz) δ 7.69 (dd, 2H, J=1.6, 8.4), 7.50 (d, 2H, J=8.4), 7.39 (d, 2H, J=8.0), 7.25-7.28 (m, 2H), 6.22 (s amplio, 1H), 6.03 (s amplio, 1H), 5.19 (s amplio, 1H), 4.57 (d, 1H, J=15.6), 4.41 (d, 1H, J=15.6), 4.30-4.33 (m, 1H), 3.48-3.53 (m, 2H), 2.10-2.20 (m, 1H), 1.88-2.03 (m, 1H), 1.69-1.82 (m, 1H), 1.38-1.47 (m, 1H), 1.25 (t, 3H, J=7.2).

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499				14	sólido color beige	516.93	1.65 min Método B	517.15	RMN (CDCl3, 400MHz) δ 8.06 (dd, 2H, J=1.6, 8.4), 7.71 (dd, 2H, J=2.0, 8.4), 7.49-7.52 (m, 4H), 6.22 (s amplio, 1H), 5.20 (s amplio, 1H), 4.63 (d, 1H, J=15.6), 4.44 (d, 1H, J=15.6), 4.33-4.37 (m, 1H), 2.47 (s, 3H), 2.10-2.20 (m, 1H), 1.91-2.03 (m, 1H), 1.73-1.86 (m, 1H), 1.40-1.51 (m, 1H).
500				1	espuma blanque-cina	494.94	1.74 min Método B	475.27 (M-HF+ H+)	RMN 1H (CDCl3, 50MHz) δ 7.65 (dd, 2H, J=2.0, 8.5), 7.46 (ddd, 2H, J=2.0, 2.5, 7.5), 7.25-7.31 (m, 4H), 6.18 (s amplio, 1H), 5.24 (s amplio, 1H), 4.47 (d, 1H, J=15.5), 4.41 (d, 1H, J=15.0), 4.35 (t, 1H, J=7.7), 2.08-2.20 (m, 1H), 1.88-2.03 (m, 1H), 1.69-1.82 (m, 1H), 1.68 (s, 3H), 1.63 (s, 3H), 1.38-1.47 (m, 1H).

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501				12	sólido blanque-cino	492.95	2.20 min Método A	475.96 (-H_2O) 492.01 (ion neg.)	RMN ^1H ($CDCl_3$, 400MHz) δ 7.65 (d, 2H, J=8.8), 7.46 (d, 2H, J=8.4), 7.40 (d, 2H, J=8.4), 7.25-7.27 (m, 2H), 6.19 (s amplio, 1H), 5.23 (s amplio, 1H), 4.46 (d, 1H, J=15.4), 4.41 (d, 1H, J=15.4), 4.34 (t, 1H, J=7.6), 2.08-2.20 (m, 1H), 1.88-2.03 (m, 1H), 1.69-1.82 (m, 1H), 1.56 (s, 3H), 1.54 (s, 3H), 1.38-1.47 (m, 1H).

Método A = columna ODS-A C-18 4.6 X 33 mm, 5 mL/minuto, 10:90:0.1 ($MeOH/H_2O$/TFA) a 90:10:0.1 ($MeOH/H_2O$/TFA), gradiente de 2 minutos

Método B = columna ODS-A C-18 3 X 50 mm, 5 mL/minuto, 10:90:0.1 ($MeOH/H_2O$/TFA) a 90:10:0.1 ($MeOH/H_2O$/TFA), gradiente de 2 minutos

Método C = columna ODS-A C-18 3 X 50 mm, 5 mL/minuto, 10:90:0.1 ($MeOH/H_2O$/TFA) a 90:10:0.1 ($MeOH/H_2O$/TFA), gradiente de 3 minutos

Método D = columna Phenomenex Luna C-18 S5 4.6 X 50 mm, 5 mL/minuto, 0-100% de $MeOH/H_2O$, 0.1% de TFA, gradiente de 2 minutos

Método E = columna Xterra C-18 S5 4.6 X 50 mm, 5 mL/minuto, 0-100% de $MeOH/H_2O$, 0.1% de TFA, gradiente de 2 minutos

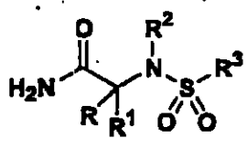
Método F = columna Phenomenex Luna C-18 S5 4.6 X 50 mm, 5 mL/minuto, 10:90:0.1 ($MeOH/H_2O$/TFA) a 90:10:0.1 ($MeOH/H_2O$/TFA), gradiente de 2 minutos

Método G = columna Xterra C-18 S7 3.0 X 50 mm, 5 mL/minuto, 10:90:0.1 ($MeOH/H_2O$/TFA) a 90:10:0.1 ($MeOH/H_2O$/TFA), gradiente de 2 minutos.

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REIVINDICACIONES

1. Un compuesto de la fórmula I; o un isómero óptico del mismo



I

caracterizado porque:

R^1 se selecciona del grupo que consiste de

(a) un grupo alquilo de 1 a 6 átomos de carbono o alquenilo de 2 a 6 átomos de carbono de cadena recta o ramificada sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de hidroxi, cicloalquilo de 3 a 7 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, alquiltio de 1 a 4 átomos de carbono y halógeno;

(b) cicloalquilo de 3 a 7 átomos de carbono sustituido opcionalmente por hidroxi o halógeno;

R es hidrógeno o R^1 y R tomados conjuntamente son alquileno de 2 a 5 átomos de carbono;

R^2 se selecciona del grupo que consiste de

(a) un grupo alquilo de 1 a 6 átomos de carbono o alquenilo de 3 a 6 átomos de carbono de cadena

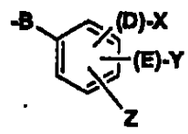
recta o ramificada sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, alcoxi de 1 a 4 átomos de carbono y NR^4R^5;

(b) cicloalquilmetilo de 3 a 7 átomos de carbono sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de amino, (alquil-C_1-C_4)NH-, di(alquil-C_1-C_4)N-, alquil-C_1-C_4-C(=O)NH- y alquil-C_1-C_4-OC(=O)NH-;

(c) un grupo alquil-C_1-C_6-C(=O)-A de cadena recta o ramificada;

(d) -B-naftilo;

(e)



D y E son cada uno, independientemente, un enlace directo, un grupo alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono o cicloalquilo de 3 a 7 átomos de carbono de cadena recta o ramificada;

Z se selecciona del grupo que consiste de hidrógeno, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, halógeno, ciano, hidroxi, $-OCHF_2$, $-OCF_3$, $-CF_3$ y $-CHF_2$;

X e Y se seleccionan cada uno, independientemente, del grupo que consiste de hidrógeno, hidroxi, halógeno, (halógeno)$_3$C-, (halógeno)$_2$CH-, alquil-C_1-C_4-S-, alquil-C_1-C_4-S(O)-, alquil-C_1-C_4-SO_2-, nitro, F_3S- y ciano; --OR^6;

$-NR^4R^5$;

$-NR^7C(=O)R^8$;

$-NR^7C(=O)OR^8$;

$-NHSO_2$-alquilo de 1 a 4 átomos de carbono;

$-N(SO_2$-alquil-C_1-$C_4)_2$;

-C(=O)W, en donde W se selecciona del grupo que consiste de hidroxi, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, fenoxi y $-NR^4R^5$;

-OC(=O)alquilo de 1 a 4 átomos de carbono;

-fenilo en el cual el grupo fenilo es sustituido opcionalmente por ciano, halógeno, alcoxi de 1 a 4 átomos de carbono, alquil-C_1-C_4-S-, $CH_3C(=O)$, alquil-C_1-C_4-S(O)- o alquil-C_1-C_4-SO_2; y

un grupo heterocíclico, en el cual el grupo heterocíclico se selecciona del grupo que consiste de furanilo, tiofuranilo, pirrolilo, imidazolilo, pirazolilo, triazolilo,

tetrazolilo, piridinilo, pirimidinilo, oxadiazolilo, oxazolilo, isoxazolilo, tiadiazolilo y tiazolilo, en donde el grupo heterocíclico es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de ciano, halógeno, alquilo de 1 a 4 átomos de carbono, (halógeno)alquilo de 1 a 4 átomos de carbono y CO_2-alquilo de 1 a 4 átomos de carbono;

(f) -B-(heterociclo), en el cual el heterociclo se selecciona del grupo que consiste de furanilo, tiofuranilo, pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, oxadiazolilo, oxazolilo, isoxazolilo, tiadiazolilo y tiazolilo, en donde el heterociclo es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de ciano, halógeno, alquilo de 1 a 4 átomos de carbono, CO_2-alquilo de 1 a 4 átomos de carbono, amino, (alquilo C_1-C_4)NH-, di(alquil-C_1-C_4)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo y 4-(alquil-C_1-C_6)-piperazin-1-ilo;

(g) -B-(piperidin-4-ilo), en el cual el grupo

piperidin-4-ilo es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de un grupo alquilo de 1 a 6 átomos de carbono de cadena recta o ramificada, $CH_2C(=O)$fenilo, fenilo y fenilmetilo en el cual el grupo alquilo de 1 a 6 átomos de carbono y el grupo fenilo son sustituidos opcionalmente por sustituyentes seleccionados del grupo que consiste de ciano, halógeno, bencimidazol-2-ilo, piridilo y tetrahidrofuran-2-ilo; y $-C(=O)W'$, en donde W' se selecciona del grupo que consiste de alcoxi de 1 a 4 átomos de carbono, R^9 y $-NR^4R^5$;

A es hidroxi, alcoxi de 1 a 4 átomos de carbono o NR^4R^5;

B es alquilo de 1 a 6 átomos de carbono o alquenilo de 3 a 6 átomos de carbono de cadena recta o ramificada;

R^3 es fenilo o piridilo sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, hidroxi, alcoxi de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono, $(halógeno)_3C-$, $(halógeno)_2CH-$ y $halógeno-CH_2-$;

R^4 y R^5 son cada uno, independientemente, hidrógeno, un grupo alquilo de 1 a 6 átomos de carbono, alquenilo

de 3 a 6 átomos de carbono, alquinilo de 3 a 6 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, cicloalquilmetilo de 3 a 7 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, fenilo, bencilo, piridilo, piperidin-4-ilo, indan-1-ilo, indan-2-ilo, tetrahidrofuran-3-ilo o pirrolidin-3-ilo de cadena recta o ramificada; en el cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de hidroxi, ciano, halógeno, $(halógeno)_3C-$, $(halógeno)_2CH-$, $halógeno-CH_2-$, hidroximetilo, benciloximetilo, fenilo, piridilo, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, $(halógeno)_3C-O-$, $(halógeno)_2CH-O-$, alquiltio de 1 a 4 átomos de carbono, amino, $(alquil\text{-}C_1\text{-}C_4)NH-$, $di\text{-}(alquil\text{-}C_1\text{-}C_4)N-$, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo, $4\text{-}(alquil\text{-}C_1\text{-}C_6)$piperazin-1-ilo, 4-fenilpiperazin-1-ilo, 4-bencilpiperazin-1-ilo, 4-piridilpiperazin-1-ilo, CO_2H, CO_2-alquilo de 1 a 4 átomos de carbono, $C(=O)NH$-alquilo de 1 a 4 átomos de carbono y $C(=O)N(alquil\text{-}C_1\text{-}C_4)_2$;

R^4 y R^5 tomados conjuntamente pueden ser morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, 1,2,3,4-tetrahidroisoquinolin-2-ilo, decahidroquinolin-1-

ilo, piperidin-1-ilo, piperazin-1-ilo, [1,4]-oxazepan-4-ilo, azetidin-1-ilo, 2,3-dihidro-1*H*-isoindol-2-ilo c 2,3-dihidro-1*H*-indol-1-ilo; en el cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de hidroxi, ciano, halógeno, (halógeno)$_3$C-, (halógeno)$_2$CH-, halógeno-CH$_2$-, fenilo, piridilo, bencilo, alquilo de 1 a 6 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, alquiltio de 1 a 4 átomos de carbono, amino, (alquil-C$_1$-C$_4$)NH-, di-(alquil-C$_1$-C$_4$)N-, CO_2H, CO_2-alquilo de 1 a 4 átomos de carbono, C(=O)NH-alquilo de 1 a 4 átomos de carbono y C(=O)N(alquil-C$_1$-C$_4$)$_2$;

R^6 es un grupo alquilo de 1 a 6 átomos de carbono, alquenilo de 3 a 6 átomos de carbono, bencilo o fenilo de cadena recta o ramificada, en el cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, amino, (alquil-C$_1$-C$_4$)NH-, di-(alquil-C$_1$-C$_4$)N-, (alquil-C$_1$-C$_4$)(fenil)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo y 4-(alquil-C$_1$-C$_6$)piperazin-1-ilo;

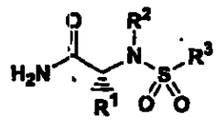
R^7 es hidrógeno, un grupo alquilo de 1 a 6 átomos de carbono de cadena recta o ramificada;

R^8 es un grupo alquilo de 1 a 6 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, fenilo, piridilo o furanilo de cadena recta o ramificada; en el cual cada uno es sustituido opciònalmente por sustituyentes seleccionados del grupo que consiste de halógeno, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, (alquil-C_1-C_4)NH-, di(alquil-C_1-C_4)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo y 4-(alquil-C_1-C_6)piperazin-1-ilo;

R^9 es un grupo alquilo de 1 a 6 átomos de carbono, alquenilo de 3 a 6 átomos de carbono, bencilo, fenilo, oxazolilo o piridilo de cadena recta o ramificada; en el cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, (halógeno)$_3$C-, (halógeno)$_2$CH-, halógeno-CH_2-, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, amino, (alquil-C_1-C_4)NH-, di(alquil-C_1-C_4)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo y 4-(alquil-C_1-C_6)piperazin-1-ilo;

o una sal farmacéuticamente aceptable, no tóxica del mismo.

2. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la fórmula



Ia

en donde:

R^1 se selecciona del grupo que consiste de

(a) un grupo alquilo de 1 a 6 átomos de carbono o alquenilo de 2 a 6 átomos de carbono de cadena recta o ramificada sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de hidroxi, cicloalquilo de 3 a 7 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, alquiltio de 1 a 4 átomos de carbono y halógeno;

(b) cicloalquilo de 3 a 7 átomos de carbono sustituido opcionalmente por hidroxi o halógeno;

R^2 se selecciona del grupo que consiste de

(a) un grupo alquilo de 1 a 6 átomos de carbono o alquenilo de 3 a 6 átomos de carbono de cadena recta o ramificada sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, alcoxi de 1 a 4 átomos

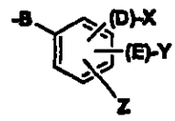
de carbono y NR^4R^5;

(b) cicloalquilmetilo de 3 a 7 átomos de carbono sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de amino, (alquil-C_1-C_4)NH-, di(alquil-C_1-C_4)N-, alquil-C_1-C_4-C(=O)NH- y alquil-C_1-C_4-OC(=O)NH-;

(c) un grupo alquil-C_1-C_6-C(=O)-A de cadena recta o ramificada;

(d) -B-naftilo;

(e)



D y E son cada uno, independientemente, un enlace directo, un grupo alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono o cicloalquilo de 3 a 7 átomos de carbono de cadena recta o ramificada;

Z se selecciona del grupo que consiste de hidrógeno, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, halógeno, ciano, hidroxi, $-OCHF_2$, $-OCF_3$, $-CF_3$ y $-CHF_2$;

X e Y se seleccionan cada uno, independientemente, del grupo que consiste de hidrógeno, hidroxi, halógeno, (halógeno)$_3$C-,

(halógeno)$_2$CH-, alquil-C_1-C_4-S-, alquil-C_1-C_4-S(O)-, alquil-C_1-C_4-SO_2-, nitro, F_3S- y ciano;

$-OR^6$;

$-NR^4R^5$;

$-NR^7C(=O)R^8$;

$-NR^7C(=O)OR^8$;

$-NHSO_2$-alquilo de 1 a 4 átomos de carbono;

$-N(SO_2$-alquil-C_1-$C_4)_2$;

-C(=O)W, en donde W se selecciona del grupo que consiste de hidroxi, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, fenoxi y $-NR^4R^5$;

-OC(=O)alquilo de 1 a 4 átomos de carbono;

-fenilo, en el cual el grupo fenilo es sustituido opcionalmente por ciano, halógeno, alcoxi de 1 a 4 átomos de carbono, alquil-C_1-C_4-S-, $CH_3C(=O)$, alquil-C_1-C_4-S(O)- o alquil-C_1-C_4-SO_2; y

un grupo heterocíclico, en el cual el grupo heterocíclico se selecciona del grupo que consiste de furanilo, tiofuranilo, pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, oxadiazolilo, oxazolilo, isoxazolilo, tiadiazolilo y tiazolilo, en donde el grupo

heterocíclico es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de ciano, halógeno, alquilo de 1 a 4 átomos de carbono, (halógeno)alquilo de 1 a 4 átomos de carbono y CO_2-alquilo de 1 a 4 átomos de carbono;

(f) -B-(heterociclo), en el cual el heterociclo se selecciona del grupo que consiste de furanilo, tiofuranilo, pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, oxadiazolilo, oxazolilo, isoxazolilo, tiadiazolilo y tiazolilo, en donde el heterociclo es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de ciano, halógeno, alquilo de 1 a 4 átomos de carbono, CO_2-alquilo de 1 a 4 átomos de carbono, amino, (alquil-C_1-C_4)NH-, di(alquil-C_1-C_4)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo y 4-(alquil-C_1-C_6)-piperazin-1-ilo;

(g) -B-(piperidin-4-ilo), en el cual el grupo piperidin-4-ilo es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de alquilo de 1 a 6 átomos de carbono

de cadena recta o ramificada, $CH_2C(=O)$fenilo, fenilo y fenilmetilo en el cual el grupo alquilo de 1 a 6 átomos de carbono y el grupo fenilo son sustituidos opcionalmente por sustituyentes seleccionados del grupo que consiste de ciano, halógeno, bencimidazol-2-ilo, piridilo y tetrahidrofuran-2-ilo; y $-C(=O)W'$, en donde W' se selecciona del grupo que consiste de alcoxi de 1 a 4 átomos de carbono, R^9 y $-NR^4R^5$;

A es hidroxi, alcoxi de 1 a 4 átomos de carbono o NR^4R^5;

B es un grupo alquilo de 1 a 6 átomos de carbono o alquenilo de 3 a 6 átomos de carbono de cadena recta o ramificada;

R^3 es fenilo o piridilo sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, hidroxi, alcoxi de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono, $(halógeno)_3C-$, $(halógeno)_2CH-$ y $halógeno-CH_2-$;

R^4 y R^5 son cada uno, independientemente, hidrógeno, un grupo alquilo de 1 a 6 átomos de carbono, alquenilo de 3 a 6 átomos de carbono, alquinilo de 3 a 6 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, cicloalquilmetilo de 3 a 7 átomos de

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carbono, alcoxi de 1 a 4 átomos de carbono, fenilo, bencilo, piridilo, piperidin-4-ilo, indan-1-ilo, indan-2-ilo, tetrahidrofuran-3-ilo o pirrolidin-3-ilo de cadena recta o ramificada; en el cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de hidroxi, ciano, halógeno, (halógeno)$_3$C-, (halógeno)$_2$CH-, halógeno-CH$_2$-, hidroximetilo, benciloximetilo, fenilo, piridilo, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, (halógeno)$_3$C-O-, (halógeno)$_2$CH-O-, alquiltio de 1 a 4 átomos de carbono, amino, (alquil-C$_1$-C$_4$)NH-, di(alquil-C$_1$-C$_4$)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo, 4-(alquil-C$_1$-C$_6$)piperazin-1-ilo, 4-fenilpiperazin-1-ilo, 4-bencilpiperazin-1-ilo, 4-piridilpiperazin-1-ilo, CO_2H, CO_2-alquilo de 1 a 4 átomos de carbono, C(=O)NH-alquilo de 1 a 4 átomos de carbono y C(=O)N(alquil-C$_1$-C$_4$)$_2$;

R^4 y R^5 tomados conjuntamente pueden ser morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, 1,2,3,4-tetrahidroisoquinolin-2-ilo, decahidroquinolin-1-ilo, piperidin-1-ilo, piperazin-1-ilo, [1,4]-oxazepan-4-ilo, azetidin-1-ilo, 2,3-dihidro-1*H*-isoindol-2-ilo o 2,3-dihidro-1*H*-indol-1-ilo; en el

cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de hidroxi, ciano, halógeno, (halógeno)$_3$C-, (halógeno)$_2$CH-, halógeno-CH$_2$-, fenilo, piridilo, bencilo, alquilo de 1 a 6 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, alquiltio de 1 a 4 átomos de carbono, amino, (alquil-C_1-C_4)NH-, di(alquil-C_1-C_4)N-, CO_2H, CO_2-alquilo de 1 a 4 átomos de carbono, C(=O)NH-alquilo de 1 a 4 átomos de carbono y C(=O)N(alquil-C_1-C_4)$_2$;

R^6 es un grupo alquilo de 1 a 6 átomos de carbono, alquenilo de 3 a 6 átomos de carbono, bencilo o fenilo de cadena recta o ramificada, en el cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, amino, (alquil-C_1-C_4)NH-, di(alquil-C_1-C_4)N-, (alquil-C_1-C_4)(fenil)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo y 4-(alquil-C_1-C_6)piperazin-1-ilo;

R^7 es hidrógeno, un grupo alquilo de 1 a 6 átomos de carbono de cadena recta o ramificada;

R^8 es un grupo alquilo de 1 a 6 átomos de carbono,

cicloalquilo de 3 a 7 átomos de carbono, fenilo, piridilo o furanilo de cadena recta o ramificada; en el cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, (alquil-C_1-C_4)NH-, di(alquil-C_1-C_4)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo y 4-(alquil-C_1-C_6)piperazin-1-ilo;

R^9 es un grupo alquilo de 1 a 6 átomos de carbono, alquenilo de 3 a 6 átomos de carbono, bencilo, fenilo, oxazolilo o piridilo de cadena recta o ramificada; en el cual cada uno es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, (halógeno)$_3$C-, (halógeno)$_2$CH-, halógeno-CH_2-, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, amino, (alquil-C_1-C_4)NH-, di(alquil-C_1-C_4)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo y 4-(alquil-C_1-C_6)piperazin-1-ilo;

o una sal farmacéuticamente aceptable, no tóxica del mismo.

3. El compuesto de conformidad con la reivindicación 2, caracterizado porque R^1 es un grupo alquilo

de 1 a 6 átomos de carbono o alquenilo de 2 a 6 átomos de carbono de cadena recta o ramificada sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de hidroxi, cicloalquilo de 3 a 7 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, alquiltio de 1 a 4 átomos de carbono y halógeno.

4. El compuesto de conformidad con la reivindicación 2, caracterizado porque R^1 es cicloalquilo de 3 a 7 átomos de carbono sustituido opcionalmente por hidroxi o halógeno.

5. El compuesto de conformidad con la reivindicación 3, caracterizado porque R^1 es un grupo alquilo de 1 a 6 átomos de carbono de cadena recta o ramificada sustituido opcionalmente por cicloalquilo de 3 a 7 átomos de carbono.

6. El compuesto de conformidad con la reivindicación 3, caracterizado porque R^1 es un grupo alquilo de 1 a 6 átomos de carbono de cadena recta o ramificada sustituido opcionalmente por halógeno.

7. El compuesto de conformidad con la reivindicación 2, caracterizado porque R^3 es fenilo sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, hidroxi, alcoxi de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono, $(halógeno)_3C-$, $(halógeno)_2CH-$ y $halógeno-CH_2-$.

8. El compuesto de conformidad con la reivindicación 2, caracterizado porque R^3 es piridilo sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, hidroxi, alcoxi de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono, $(halógeno)_3C-$, $(halógeno)_2CH-$ y $halógeno-CH_2-$.

9. El compuesto de conformidad con la reivindicación 7, caracterizado porque R^3 es fenilo sustituido opcionalmente por halógeno.

10. El compuesto de conformidad con la reivindicación 2, caracterizado porque R^2 es alquilo de 1 a 6 átomos de carbono o alquenilo de 3 a 6 átomos de carbono de cadena recta o ramificada sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de halógeno, alcoxi de 1 a 4 átomos de carbono y NR^4R^5.

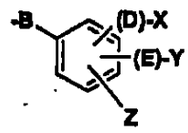
11. El compuesto de conformidad con la reivindicación 2, caracterizado porque R^2 es cicloalquilmetilo de 3 a 7 átomos de carbono sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de amino, $(alquil\text{-}C_1\text{-}C_4)NH-$, $di(alquil\text{-}C_1\text{-}C_4)N-$, $alquil\text{-}C_1\text{-}C_4\text{-}C(=O)NH-$ y $alquil\text{-}C_1\text{-}C_4\text{-}OC(=O)NH-$.

12. El compuesto de conformidad con la reivindicación 2, caracterizado porque R^2 es $alquil\text{-}C_1\text{-}C_6\text{-}C(=O)\text{-}A$ de cadena recta o ramificada.

13. El compuesto de conformidad con la

reivindicación 2, caracterizado porque R^2 es -B-naftilo.

14. El compuesto de conformidad con la reivindicación 2, caracterizado porque R^2 es



15. El compuesto de conformidad con la reivindicación 2, caracterizado porque R^2 es -B-(heterociclo), en el cual el heterociclo se selecciona del grupo que consiste de furanilo, tiofuranilo, pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, oxadiazolilo, oxazolilo, isoxazolilo, tiadiazolilo y tiazolilo, en donde el heterociclo es sustituido opcionalmente por sustituyentes seleccionados del grupo que consiste de ciano, halógeno, alquilo de 1 a 4 átomos de carbono, CO_2-alquilo de 1 a 4 átomos de carbono, amino, (alquilo C_1-C_4)NH-, di(alquil-C_1-C_4)N-, morfolin-4-ilo, tiomorfolin-4-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo y 4-(alquil-C_1-C_6)-piperazin-1-ilo;

16. El compuesto de conformidad con la reivindicación 2, caracterizado porque R^2 es -B-(piperidin-4-ilo), en el cual el grupo piperidin-4-ilo es sustituido opcionalmente por los sustituyentes seleccionados del grupo que consiste de alquilo de 1 a 6 átomos de carbono de cadena recta o ramificada, $CH_2C(=O)$fenilo, fenilo o fenilmetilo, en

el cual el grupo alquilo de 1 a 6 átomos de carbono y el grupo fenilo son sustituidos opcionalmente por sustituyentes seleccionados de un grupo que consiste de ciano, halógeno, bencimidazol-2-ilo, piridilo y tetrahidrofuran-2-ilo; y -C(=O)W' en donde W' se selecciona del grupo que consiste de alcoxi de 1 a 4 átomos de carbono, R^9 y $-NR^4R^5$.

17. El compuesto de conformidad con la reivindicación 14, caracterizado porque B es alquilo de 1 a 4 átomos de carbono de cadena recta.

18. El compuesto de conformidad con la reivindicación 17, caracterizado porque Z es hidrógeno.

19. El compuesto de conformidad con la reivindicación 17, caracterizado porque X es C(=O)W, E es un enlace directo e Y es hidrógeno.

20. El compuesto de conformidad con la reivindicación 17, caracterizado porque X es $-NR^4R^5$, E es un enlace directo e Y es hidrógeno.

21. El compuesto de conformidad con la reivindicación 17, caracterizado porque X es $-OR^6$, E es un enlace directo e Y es hidrógeno.

22. El compuesto de conformidad con la reivindicación 17, caracterizado porque X es $-NR^7C(=O)R^8$, E es un enlace directo e Y es hidrógeno.

23. Una composición farmacéutica para el tratamiento de trastornos sensibles a la inhibición de la

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producción del péptido β-amiloideo, caracterizada porque comprende una cantidad terapéuticamente efectiva de un compuesto de conformidad con la reivindicación 1 en asociación con un portador o diluyente farmacéuticamente aceptable.

24. Un método para el tratamiento de trastornos sensibles a la inhibición de la producción del péptido β-amiloideo en un mamífero en necesidad del mismo, caracterizado porque comprende administrar al mamífero una cantidad terapéuticamente efectiva de un compuesto de conformidad con la reivindicación 1.

25. Un método de conformidad con la reivindicación 24, caracterizado porque el trastorno es la enfermedad de Alzheimer y el síndrome de Down.

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RESUMEN DE LA INVENCIÓN

Se proporciona una serie de compuestos novedosos de α-(N-sulfonamido)acetamida de la fórmula (I), en donde R, R^1, R^2 y R^3 son como se definiera en la presente, los cuales son inhibidores de la producción del péptido β-amiloideo (β-AP) y son útiles en el tratamiento de la enfermedad Alzheimer y otras condiciones afectadas por la actividad anti-amiloidea.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
BMS PATENT LAW
SUZANNE BAJKO
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NEW JERSEY 08543-4000
AUG 27 2003

Docketed Item
Due Date
Attorney

PCT

NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing *(day/month/year)*	25 AUG 2003
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
CT-2703-NP	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US02/40605	20 Dec 2002	20 Dec 2001

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

25 June 2003 (25-06-03)

2. That date of receipt is:

[X] the actual date of receipt of the demand by this Authority (Rule 61.2(b)).

[ ] the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(a)).

[ ] the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

BMS PATENT
SEP 9 2003
WALLINGFORD, CT.

3. [ ] ATTENTION: That date of receipt is AFTER the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

[ ] *(If applicable)* This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/ Mail Stop PCT, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450	Authorized officer
Facsimile No. 703-305-3230	Telephone No. 703-308-6454

Form PCT/IPEA/402 (July 1998)

94.382

567

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
ALDO A. ALGIERI
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NJ 08543-4000

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing (*day/month/year*)	16 SEP 2003

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
[redacted]NP-PCT	

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US02/40605	20 December 2002 (20.12.2002)	20 December 2001 (20.12.2001)

Applicant

BRISTOL-MYERS SQUIBB COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

DEPT
SEP - 6 2003
RECEIVED

Name and mailing address of the IPEA/US	Authorized officer
Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	Felicia D. Roberts for Venkataraman Balasubramanian
Facsimile No. (703)305-3230	Telephone No. (703)308-1235

Form PCT/IPEA/416 (July 1992)

RETURNED
U.S. PATENT LAW

SEP 18 2003

Docketed Item _____
Due Date _____
Attorney _____

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CT-2703-NP-PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US02/40605	International filing date *(day/month/year)* 20 December 2002 (20.12.2002)	Priority date *(day/month/year)* 20 December 2001 (20.12.2001)

International Patent Classification (IPC) or national classification and IPC

IPC(7): C07C 237/04, 237/14; A61K 31/18; A61P 25/28 and US Cl.: 564/80, 84, 88; 544/ 106; 544/310; 546/184; 548/131,134; 514/618, 232.2, 315

Applicant

BRISTOL-MYERS SQUIBB COMPANY

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25 June 2003 (25.06.2003)	26 August 2003 (26.08.2003)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Venkataraman Balasubramanian Telephone No. (703)308-1235

Form PCT/IPEA/409 (cover sheet)(July 1998)

BMS PATENT LAW

SEP 18 2003

Docketed Item _____
Due Date _____
Attorney _____

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/40605

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-246 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 247-257, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/40605

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V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-25	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-25	YES
	Claims	NONE	NO
Industrial Applicability (IA)	Claims	1-25	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-25 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the N-sulfamido acetamide compounds.

Claims 1-25 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry as therapeutic agents for treating Alzheimer's disease and Down's syndrome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/40605

A. CLASSIFICATION OF SUBJECT MATTER:
IPC(7) : c07C 237/04, 237/14; A61K 31/18; A61P 25/28
US CL : 564/80, 84, 88; 544/ 106; 544/310; 546/184; 548/131,134; 514/618, 232.2, 315
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)
U.S. : 544/310

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE, EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98/03166 A1 (MONSANTO COMPANY) 29 January 1998 (29.01.1998), see entire document.	1-25

☐ 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 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
31 March 2003 (31.03.2003)	17 APR 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Venkataraman Balasubramanian Telephone No. (703)308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

566

REPORTE DE BÚSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US 02/40605

A. CLASIFICACION DEL TEMA

IPC(7) : C07C 237/04, 237/14; A61K 31/18; A61P 25/28

US CL : 564/80, 84, 88; 544/106; 544/310; 546/184; 548/131, 134; 514/618, 232.2 315

De acuerdo a la Clasificación de Patentes Internacional (IPC) o a tanto la clasificación nacional como la IPC.

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación):

U.S. : 544/310

Documentación buscada diferente a la documentación mínima, al grado que tales documentos están incluidos en los campos buscados:

Base de datos electrónica consultada durante la búsqueda internacional (nombre de la base de datos y, en donde sea práctico, términos de búsqueda utilizados):

CAS EN LÍNEA, EAST

C. DOCUMENTOS CONSIDERADOS QUE SON RELEVANTES

Categoría*	Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes	Pertinente para la reivindicación No.
A	WO 98/03166 A1 (MONSANTO COMPANY) 29 de Enero de 1998 (29.01.1998), véase el documento completo.	1-25

☐ Los documentos adicionales se listan en la continuación del cuadro C.

☐ Los miembros de la familia de patentes se listan en el anexo

*categorías especiales de los documentos citados:

"A" documento que define el estado general de la técnica, el cual no se considera que es de particular relevancia.

"E" primer documento publicado en o después de la fecha de presentación internacional.

"L" documento el cual puede arrojar dudas sobre la(s) reivindicación(es) de prioridad o el cual se cita para establecer la fecha de publicación de otra cita u otra razón especial (como se especifica)

"O" documento que se refiere a una descripción oral, uso, exhibición u otro medio

"P" documento publicado antes de la fecha de representación internacional pero después de la fecha de prioridad reivindicada.

"T" documento posterior publicado después de la fecha de presentación internacional o la fecha de prioridad y no en conflicto con la solicitud, pero citado para entender el principio o teoría fundamental de la invención.

"X" documento de relevancia particular; la invención reclamada no puede ser considerada nueva o no se puede considerar que involucra una paso inventivo cuando el documento se toma solo.

"Y" documento de particular relevancia; no se puede considerar que la invención reclamada involucra un paso inventivo cuando el documento es combinado con uno o más de tales documentos, tal combinación que es obvia para una persona experimentada en la técnica.

"&" documento miembro de la misma familia de patentes.

Fecha de la terminación actual de la búsqueda internacional	Fecha de envío del reporte de búsqueda internacional
31 de Marzo de 2003 (31.03.2003)	17 DE ABRIL DE 2003

Nombre y dirección de correo de la ISA/US	Funcionario autorizado
Comisionado de Patentes y Marcas Registradas Box PCT Washington, D.C. 20231	Venkataraman Balasubramanian
No. de Facsímil (703)305-3230	No. de Teléfono (703)308-1235

Forma PCT/ISA/210 (segunda hoja) (Julio de 1998)

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

RECEIVED
BMS PATENT LAW
APR 21 2003
Docketed Item
Due Date
Attorney

To:
SUZANNE BABAJKO
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NJ 08543-4000

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference CT-2703-NP	Date of Mailing (*day/month/year*) 17 APR 2003 FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. *PCT/US02/40605*	International filing date (*day/month/year*) 20 December 2002 (20.12.2002)
Applicant BRISTOL-MYERS SQUIBB COMPANY	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 *bis*.1 and 90 *bis*.3, respectively, before the completion of the technical preparations for international publication.

   Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Commissioner for Patents Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Felicia D. Roberts for Venkataraman Balasubramanian Telephone No. (703)308-1235

Form PCT/ISA/220 (April 2002) (*See notes on accompanying sheet*)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference CT-2703-NP	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US02/40605	International filing date (*day/month/year*) 20 December 2002 (20.12.2002)	(Earliest) Priority Date (*day/month/year*) 20 December 2001 (20.12.2001)
Applicant BRISTOL-MYERS SQUIBB COMPANY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the Report**
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
   ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☐ Certain claims were found unsearchable (See Box I).
3. ☐ Unity of invention is lacking (See Box II).
4. With regard to the title,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. ____
   ☐ as suggested by the applicant. ☒ None of the figures
   ☐ because the applicant failed to suggest a figure.
   ☐ because this figure better characterizes the invention.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/40605

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : c07C 237/04, 237/14; A61K 31/18; A61P 25/28
US CL : 564/80, 84, 88; 544/ 106; 544/310; 546/184; 548/131,134; 514/618, 232.2, 315

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)
U.S. : 544/310

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE, EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98/03166 A1 (MONSANTO COMPANY) 29 January 1998 (29.01.1998), see entire document.	1-25

☐ 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 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
31 March 2003 (31.03.2003)	17 APR 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Venkataraman Balasubramanian Telephone No. (703)308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

BABAJKO, Suzanne
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
United States of America

Date of mailing (day/month/year)
15 September 2003 (15.09.03)

Applicant's or agent's file reference	IMPORTANT INFORMATION
[redacted]	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US02/40605	20 December 2002 (20.12.02)	20 December 2001 (20.12.01)

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   EP :AT,BE,BG,CH,CY,CZ,DE,DK,EE,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,SI,SK,
   TR
   National :BG,CA,CN,DE,GB,IL,JP,KP,KR,MN,NO,PL,RO,RU,SK

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   AP :GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW
   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
   National :AE,AG,AL,AM,AT,AU,AZ,BA,BB,BR,BY,BZ,CH,CO,CR,CU,CZ,DK,DM,DZ,EC,
   EE,ES,FI,GD,GE,GH,GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,
   MG,MK,MW,MX,MZ,NZ,OM,PH,PT,SC,SD,SE,SG,SL,TJ,TM,TN,TR,TT,TZ,UA,UG,UZ,VC,
   VN,YU,ZA,ZM,ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

DEPUTY GENERAL COUNSEL
SEP - 7 2003
WALLINGFORD, CT.

BMS PATENT DEPT.
OCT 01 2003
Docketed Item
Due Date

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.87.20

Authorized officer:
Ana MILLIQUET-ROSLIK

Telephone No. (41-22) 338 9613

TRANSMITTAL LETTER TO THE UNITED STATES RECEIVING OFFICE

Date	25 June 2003
International Application No.	PCT/US02/40605
Attorney Docket No.	CT2703NP-PCT

I. Certification under 37 CFR 1.10 (if applicable)

EV 331197442 US	JUNE 25, 2003
Express Mail mailing number	Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Assistant Commissioner for Patents, Washington, D.C. 20231.

[signature]	Nancy S. Turover
Signature of person mailing correspondence	Typed or printed name of person mailing correspondence

II. ☐ **New International Application**

TITLE		Earliest priority date (Day/Month/Year)

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

A. ☐ The invention disclosed was not made in the United States.

B. ☐ There is no prior U.S. application relating to this invention.

C. ☐ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. *(NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority.)*

application no.		filed on	
application no.		filed on	

D. ☐ The present international application contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C. above. The additional subject matter is found on pages

and ☐ **DOES NOT ALTER** ☐ **MIGHT BE CONSIDERED TO ALTER** the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15

III. ☐ **A Response to an Invitation from the RO/US. The following document(s) is(are) enclosed:**

A. ☐ A Request for An Extension of Time to File a Response

B. ☐ A Power of Attorney (General or Regular)

C. ☐ Replacement pages:

pages		of the request (PCT/RO/101)	pages		of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

D. ☐ Submission of Priority Documents

Priority document		Priority document	

E. ☐ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. ☐ **A Request for Rectification under PCT 91** ☐ **A Petition** ☐ **A Sequence Listing Diskette**

V. ☑ **Other (please specify):**

DEMAND

The person signing this form is the:		
☐ Applicant	Aldo A. Algieri, Reg. No. 31,697	
☑ Attorney/Agent (Reg. No.)	Typed name of signer	
☐ Common Representative	[signature]	
	Signature	

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference: CT-2703NP-PCT
International application No.: PCT/US02/40605	International filing date *(day/month/year)*: 20 December 2002 (20-12-02)	(Earliest) Priority date *(day/month/year)*: 20 December 2001 (20-12-01)
Title of invention: Alpha-(N-Sulfonamido)Acetamide Derivatives as Beta-Amyloid Inhibitors		

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	Telephone No. / Facsimile No. / Teleprinter No. / Applicant's registration No. with the Office
Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America	Telephone No.: 609-252-4000 Facsimile No.: 609-252-4526 Teleprinter No.: Applicant's registration No. with the Office:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
United States of America	United States of America

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on a continuation sheet.

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Sheet No. 2

International application No.
PCT/US02/40605

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

ALGIERI, ALDO A.
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
United States of America

Telephone No.
203-677-6809

Facsimile No.
203-677-6900

Teleprinter No.

Agent's registration No. with the Office

[ ] Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

   [X] the international application as originally filed

   the description
   [ ] as originally filed
   [ ] as amended under Article 34

   the claims
   [ ] as originally filed
   [ ] as amended under Article 19 (together with any accompanying statement)
   [ ] as amended under Article 34

   the drawings
   [ ] as originally filed
   [ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

[X] which is the language in which the international application was filed.
[ ] which is the language of a translation furnished for the purposes of international search.
[ ] which is the language of publication of the international application.
[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

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Sheet No. 3

International application No.
PCT/US02/40605

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	: 0	sheets	☐	☐
2. amendments under Article 34	: 0	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	: 0	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	: 0	sheets	☐	☐
5. letter	: 0	sheets	☐	☐
6. other *(specify)*	: 0	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ *fee calculation sheet*
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listings in computer readable form
7. ☐ tables in computer readable form related to sequence listings
8. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Aldo A. Algieri, Agent Date: 25 June 2003

Aldo A. Algieri, Ph.D.

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US02/40605	For International Preliminary Examining Authority use only
Applicant's or agent's file reference CT-2703NP-PCT	Date stamp of the IPEA
Applicant BRISTOL-MYERS SQUIBB COMPANY	

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	$750.00	P	
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	172.00	H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	$922.00 TOTAL		

MODE OF PAYMENT

[X]	authorization to charge deposit account with the IPEA (see below)	[ ]	cash
[ ]	cheque	[ ]	revenue stamps
[ ]	postal money order	[ ]	coupons
[ ]	bank draft	[ ]	other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all IPEAs)

IPEA/ EP

[X] Authorization to charge the total fees indicated above.

[X] *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: 19.3880

Date: 25 June 2003

Name: Aldo A. Algieri

Signature: Aldo A. Algieri

PCT REQUEST

CT-2703-NP

Original (for SUBMISSION) - printed on 20.12.2002 10:09:33 AM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.10.2002)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	CT-2703-NP
I	Title of invention	ALPHA-(N-SULPHONAMIDO)ACETAMIDE DERIVATIVES AS BETA-AMYLOID INHIBITORS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States
II-4	Name	BRISTOL-MYERS SQUIBB COMPANY
II-5	Address:	P. O. Box 4000 Route 206 and Provinceline Road Princeton, NJ 08543-4000 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	609-252-4000
II-9	Facsimile No.	609-252-4526
III-1	Applicant and/or inventor	
III-1-1	This person is:	inventor only
III-1-4	Name (LAST, First)	PARKER, Michael F.
III-1-5	Address:	45 Brainard Hill Road Higganum, CT 06441 United States of America
III-2	Applicant and/or inventor	
III-2-1	This person is:	inventor only
III-2-4	Name (LAST, First)	MCELHONE, Katharine E.
III-2-5	Address:	25 Midway Drive Cromwell, CT 06416 United States of America

PCT REQUEST

CT-2703-NP

Original (for SUBMISSION) - printed on 20.12.2002 10:09:33 AM

III-3	Applicant and/or inventor	
III-3-1	This person is:	inventor only
III-3-4	Name (LAST, First)	MATE, Robert A.
III-3-5	Address:	380-91 Hitchcock Road Waterbury, CT 06705 United States of America
III-4	Applicant and/or inventor	
III-4-1	This person is:	inventor only
III-4-4	Name (LAST, First)	BRONSON, Joanne J.
III-4-5	Address:	230 Parmelee Hill Road Durham, CT 06422 United States of America
III-5	Applicant and/or inventor	
III-5-1	This person is:	inventor only
III-5-4	Name (LAST, First)	GAI, Yonghua
III-5-5	Address:	12 Linnea Lane Killingworth, CT 06419 United States of America
III-6	Applicant and/or inventor	
III-6-1	This person is:	inventor only
III-6-4	Name (LAST, First)	BERGSTROM, Carl P.
III-6-5	Address:	22 Paper Mill Drive Madison, CT 06443 United States of America
III-7	Applicant and/or inventor	
III-7-1	This person is:	inventor only
III-7-4	Name (LAST, First)	MARCIN, Lawrence R.
III-7-5	Address:	40 Ridgewood Drive Bethany, CT 06524 United States of America
III-8	Applicant and/or inventor	
III-8-1	This person is:	inventor only
III-8-4	Name (LAST, First)	MACOR, John E.
III-8-5	Address:	644 Moose Hill Road Guilford, CT 06437 United States of America

PCT REQUEST

CT-2703-NP

Original (for SUBMISSION) - printed on 20.12.2002 10:09:33 AM

IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	BABAJKO, Suzanne
IV-1-2	Address:	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
IV-1-3	Telephone No.	609-252-4000
IV-1-4	Facsimile No.	609-252-4526
IV-1-5	Agent's registration No.	32,980
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	BAXAM, Deanna(45,266); BELFIELD, Jing(45,914); BUCHHOLZ, Briana(39,123); D'AMICO, Stephen, C.(46,652); DAVIS, Stephen(26,693); DUNCAN, Laurelee(44,096); GIBBONS, Maureen(44,121); GOLIAN, Paul, D.(42,591); HERMENAU, Ronald(34,620); KILCOYNE, John(33,100); KLEIN, Christopher(34,363); LANGE, Keith(44,201); O'BRIEN, Maureen(42,043); PATEL, Rena(41,412); PEIST, Kenneth(45,006); PROVOOST, Jonathan(44,292); RODNEY, Burton(22,076); SHER, Audrey(39,024); WINSLOW, Anastasia(40,875); ALGIERI, Aldo(31,697); DUBOFF, Samuel(25,969); MAKUJINA, Shah(41,174); RYAN, Richard(30,491); VANATTEN, Mary, K.(39,408); VOLLES, Warren, K.(33,810)

V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	20 December 2001 (20.12.2001)
VI-1-2	Number	60/344,322
VI-1-3	Country	US

PCT REQUEST

CT-2703-NP

Original (for SUBMISSION) - printed on 20.12.2002 10:09:33 AM

VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1		
VII-1	International Searching Authority Chosen	United States Patent and Trademark Office (USPTO) (ISA/US)		
VIII	Declarations		Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-		
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-		
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-		
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-		
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-		
IX	Check list		number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6		-
IX-2	Description	246		-
IX-3	Claims	11		-
IX-4	Abstract	1		EZABST00.TXT
IX-5	Drawings	0		-
IX-7	TOTAL	264		
	Accompanying items		paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet		✓	-
IX-9	Original separate power of attorney		✓	-
IX-17	PCT-EASY diskette	-		Diskette
IX-18	Other (specified):	Certification		-
IX-19	Figure of the drawings which should accompany the abstract			
IX-20	Language of filing of the international application	English		
X-1	Signature of applicant, agent or common representative	Aldo A. Algieri		
X-1-1	Name (LAST, First)	ALGIERI, Aldo		

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	

10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/US
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

PETITORIO PCT

CT-2703-NP

Original (para presentación) - impreso el 20.12.2002 10:09:33 AM

0	Para uso únicamente de la Oficina Receptora	
0-1	Solicitud Internacional No.	
0-2	Fecha de Presentación Internacional	
0-3	Nombre de la Oficina Receptora y "Solicitud Internacional PCT"	
0-4	Forma – Solicitud PCT PCT/RO/101	
0-4-1	Utilización preparada	PCT-EASY Versión 2.92 (actualizado 01.10.2002)
0-5	Solicitud El signatario solicitó que la presente solicitud internacional se procese de acuerdo al Tratado de Cooperación en Patente	
0-6	Oficina Receptora (especificada por el solicitante)	Oficina Norteamericana de Patentes y Marcas Registradas (USPTO) (RO/US)
0-7	Referencia de archivo del agente o solicitante	CT-2703-NP
I	Título de la Invención	DERIVADOS DE α-(N-SULFONAMIDO) ACETAMIDA COMO INHIBIDORES DEL PÉPTIDO β-AMILOIDEO
II	Solicitante	
II-1	Esta persona es:	únicamente solicitante
II-2	Solicitante para	todos los Estados designados
II-4	Nombre	**BRISTOL-MYERS SQUIBB COMPANY**
II-5	Dirección:	Apartado de Correos 4000 Route 206 and Provinceline Road Princeton, NJ 08543-4000 Estados Unidos de América
II-6	Estado de nacionalidad	US
II-7	Estado de residencia	US
II-8	Número Teléfono	609-252-4000
II-9	Número Facsímil	609-252-4526
III-1	Solicitante y/o inventor	
III-1-1	Esta persona es:	únicamente inventor
III-1-4	Nombre (ULTIMO, Primero)	**PARKER, Michael F.**
III-1-5	Dirección:	45 Brainard Hill Road Higganum, CT 06441 Estados Unidos de América

III-2	Solicitante y/o Inventor	
III-2-1	Esta persona es:	únicamente inventor
III-2-4	Nombre (ULTIMO, Primero)	**MCELHONE, Katharine E.**
III-2-5	Dirección:	25 Midway Drive Cromwell, CT 06416 Estados Unidos de América
III-3	Solicitante y/o Inventor	
III-3-1	Esta persona es:	únicamente inventor
III-3-4	Nombre (ULTIMO, Primero)	**MATE, Robert A.**
III-3-5	Dirección:	380-91 Hitchcock Road Waterbury, CT 06705 Estados Unidos de América
III-4	Solicitante y/o Inventor	
III-4-1	Esta persona es:	únicamente inventor
III-4-4	Nombre (ULTIMO, Primero)	**BRONSON, Joanne J.**
III-4-5	Dirección:	230 Parmelee Hill Road Durham, CT 06422 Estados Unidos de América
III-5	Solicitante y/o Inventor	
III-5-1	Esta persona es:	únicamente inventor
III-5-4	Nombre (ULTIMO, Primero)	**GAI, Yonghua**
III-5-5	Dirección:	12 Linnea Lane Killingworth, CT 06419 Estados Unidos de América
III-6	Solicitante y/o Inventor	
III-6-1	Esta persona es:	únicamente inventor
III-6-4	Nombre (ULTIMO, Primero)	**BERGSTROM, Carl R.**
III-6-5	Dirección:	22 Paper Mill Drive Madison, CT 06443 Estados Unidos de América
III-7	Solicitante y/o Inventor	
III-7-1	Esta persona es:	únicamente inventor
III-7-4	Nombre (ULTIMO, Primero)	**MARCIN, Lawrence R.**
III-7-5	Dirección:	40 Ridgewood Drive Bethany, CT 06524 Estados Unidos de América

III-8	Solicitante y/o Inventor	
III-8-1	Esta persona es:	únicamente inventor
III-8-4	Nombre (ULTIMO, Primero)	**MACOR, John E.**
III-8-5	Dirección:	644 Moose Hill Road Guilford, CT 06437 Estados Unidos de América
IV-1	Agente o representante común; o dirección para correspondencia Por la presente la persona identificada en lo siguiente es / ha sido nombrada para actuar a nombre de el o los solicitantes ante las Autoridades Internacionales competentes como:	agente
IV-1-1	Nombre (ULTIMO, Primero)	**BABAJKO, Suzanne**
IV-1-2	Dirección:	Bristol-Myers Squibb Company Apartado de Correos 4000 Princeton, NJ 08543-4000 Estados Unidos de América
IV-1-3	Número Teléfono	609-252-4000
IV-1-4	Número Facsímil	609-252-4526
IV-1-5	Número de Registro del Agente	32,880
IV-2	Agente(s) adicional(es)	agente(s) adicional(es) con la misma dirección como el primer agente nombrado
IV-2-1	Nombre(s)	BAXAM, Deanna (45,266); BELFIELD, Jing (45,914); BUCHHOLZ, Briana (39,123); D'AMICO, Stephen, C. (46,652); DAVIS, Stephen (26,693); DUNCAN, Laurelee (44,096); GIBBONS, Maureen (44,121); GOLIAN, Paul, D. (42,591); HERMENAU, Ronald (34,620); KILCOYNE, John (33,100); KLEIN, Christopher (34,363); LANGE, Keith (44,201); O'BRIEN, Maureen (42,043); PATEL, Rena (41,412); PEIST, Kenneth (45,006); PROVOOST, Jonathan (44,292); RODNEY, Burton (22,076); SHER, Audrey (39,024); WINSLOW, Anastasia (40,875); ALGIERI, Aldo (31,697); DUBOFF, Samuel (25,969); MAKUJINA, Shah (41,174); RYAN, Richard (30,491); VANATTEN, Mary, K. (39,408); VOLLES, Warren, K. (33,810)
V	Estados Designados	

V-1	Patente Regional (otras clases de protección o tratamiento, si existen, son especificadas entre paréntesis después de la o las designaciones concernientes)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW y cualquier otro Estado que sea miembro del protocolo de Harare y miembro del PCT EA: AM AZ BY KG KZ MD RU TJ TM y cualquier otro Estado que sea miembro del acuerdo Euroasiático sobre patentes y miembro del PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR y cualquier otro Estado que sea miembro del acuerdo Europeo sobre patentes y miembro del PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG y cualquier otro Estado que sea miembro del acuerdo OAPI sobre patentes y miembro del PCT
V-2	Patente Nacional (otras clases de protección o tratamiento, si existen, son especificadas entre paréntesis después de la o las designaciones concernientes)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
V-5	Declaración de Designación Precautoria En adición a las designaciones hechas bajo los puntos V-1, V-2 y V-3, el solicitante también hace todas las designaciones bajo la Regla 4.9(b) que deban ser permitidas bajo el PCT excepto cualesquiera designaciones del o los Estados indicados bajo el punto V-6 siguiente. El solicitante declara que aquellas designaciones adicionales son objeto para confirmación y que cualquier designación que no es confirmada después del término de 15 meses de la fecha de prioridad para ser relacionada como retiro por el solicitante en el término de ese tiempo límite.	
V-6	Exclusión(es) de las designaciones precautorias	NINGUNA
VI-1	Reclamo de prioridad de la solicitud nacional anterior.	
VI-1-1	Fecha de presentación	20 de Diciembre de 2001 (20.12.2001)
VI-1-2	Número	60/344,322
VI-1-3	País	US

VI-2	Solicitud de documento de prioridad Se solicita a la oficina receptora que prepare y transmita a la Oficina Internacional una copia certificada de la(s) primera(s) solicitud(es) identificada(s) anteriormente como cuadro(s):	VI-1	
VII-1	Autoridad de Búsqueda Internacional Seleccionada	Oficina Norteamericana de Patentes y Marcas Registradas (USPTO) (ISA/US)	
VIII	Aclaraciones	Número de aclaraciones	
VIII-1	Acerca de la identidad del inventor	-	
VIII-2	Acerca de la autorización del solicitante de solicitar y obtener una patente en el momento de la solicitud internacional	-	
VIII-3	Acerca de la autorización del solicitante de reclamar la prioridad de una solicitud anterior, en el momento de la solicitud internacional	-	
VIII-4	Aclaración de los inventores (solo para los Estados Unidos de América)	-	
VIII-5	Aclaraciones con respecto a publicaciones no dañinas o a excepciones de daños a la novedad	-	
IX	Lista verificada	número de hojas	archivo(s) electrónicos anexos
IX-1	Solicitud (incluyendo hojas de aclaraciones)	6	-
IX-2	Descripción	246	-
IX-3	Reivindicaciones	11	-
IX-4	Resumen	1	EZABST00.TXT
IX-5	Dibujos	0	-
IX-7	TOTAL	264	
	Artículos anexos	Documento(s) anexos	Archivos(s) Electrónicos
IX-8	Costo de la hoja de cálculo	✓	-
IX-9	Copia del poder general del apoderado	✓	-
IX-17	Disco flexible PCT-EASY	-	Disco flexible
IX-18	Otro (especificar)	Certificación	-
IX-19	Figura de los dibujos que debe ser unida al resumen		
IX-20	Idioma de presentación de la solicitud Internacional	Inglés	
X-1	Firma del solicitante, agente o representante común	(firma)	
X-1-1	Nombre (ÚLTIMO, primero)	**ALGIERI, Aldo**	

PARA USO ÚNICAMENTE DE LA OFICINA RECEPTORA

10-1	Fecha de recepción actual de la Solicitud Internacional propuesta	
10-2	Dibujos:	
10-2-1	Recibido	
10-2-2	No recibido	
10-3	Fecha corregida de la recepción actual debido a os documentos o dibujos	

	recibidos posteriormente pero a tiempo que complementan la solicitud internacional propuesta	
10-4	Fecha de recepción a tiempo de las correcciones requeridas conforme al Artículo 11(2) del PCT	
10-5	Autoridad de Búsqueda Internacional	ISA/US
10-6	Transmisión de copia de búsqueda retardada hasta que la cuota de búsqueda sea pagada	
PARA USO ÚNICAMENTE DE LA OFICINA INTERNACIONAL		
11-1	Fecha de recepción de la copia de registro por la Oficina Internacional	

PCT (ANNEX - FEE CALCULATION SHEET)

CT-2703-NP

Original (for SUBMISSION) - printed on 20.12.2002 10:09:33 AM

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only				
0-1	International Application No.				
0-2	Date stamp of the receiving Office				

0-4	Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet				
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.10.2002)			
0-9	Applicant's or agent's file reference	CT-2703-NP			
2	Applicant	BRISTOL-MYERS SQUIBB COMPANY			
12	Calculation of prescribed fees		fee amount/multiplier	Total amounts (USD)	
12-1	Transmittal fee	T	⇨	240	
12-2-1	Search fee	S	⇨	700	
12-2-2	International search to be carried out by	US			
12-3	International fee				
	Basic fee				
	(first 30 sheets)	b1	407		
12-4	Remaining sheets	234			
12-5	Additional amount	(X)	9		
12-6	Total additional amount	b2	2,106		
12-7	b1 + b2 =	B	2,513		
12-8	Designation fees				
	Number of designations contained in international application	94			
12-9	Number of designation fees payable (maximum 5)	5			
12-10	Amount of designation fee	(X)	88		
12-11	Total designation fees	D	440		
12-12	PCT-EASY fee reduction	R	-125		
12-13	Total international fee (B+D-R)	I	⇨	2,828	
12-14	Fee for priority document				
	Number of priority documents requested	1			
12-15	Fee per document	(X)	15		
12-16	Total priority document fee	P	⇨	15	
12-17	TOTAL FEES PAYABLE (T+S+I+P)		⇨	3,783	
12-19	Mode of payment	authorization to charge deposit account			
12-20	Deposit account instructions				
	The receiving Office:	United States Patent and Trademark Office (USPTO) (RO/US)			
12-20-1	Authorization to charge the total fees indicated above.	✓ Ellen A. Marcus			

PCT (ANNEX - FEE CALCULATION SHEET) CT-2703-NP

Original (for SUBMISSION) - printed on 20.12.2002 10:09:33 AM

12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓ Aldo A. Algieri
12-20-3	Authorization to charge the fee for priority document.	✓ Aldo A. Algieri
12-21	Deposit account No.	19-3880
12-22	Date	20 December 2002 (20.12.2002)
12-23	Name and signature	ALGIERI, Aldo Aldo A. Algieri

VALIDATION LOG AND REMARKS

13-1-1	Applicant remarks	Abstract contains a chemical structure; location is indicated with brackets.

13-2-2	Validation messages States	Green? More designations could be made. The following States have not been designated: US. Please verify.
13-2-3	Validation messages Names	Green? Inventor 1.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
		Green? Inventor 2.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
		Green? Inventor 3.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
		Green? Inventor 4.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
		Green? Inventor 6.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.

PCT (ANNEX - FEE CALCULATION SHEET) CT-2703-NP

Original (for SUBMISSION) - printed on 20.12.2002 10:09:33 AM

		Green? Inventor 7.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
		Green? Inventor 8.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
13-2-9	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.
13-2-10	Validation messages Annotate	Green? All indications that can be made on the Request form are specifically provided for by the software. Please confirm validity of additional indication.

RECEIVED
BMS PATENT LAW
JUL 21 2003 PCT
Docketed Item
Due Date
Attorney

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

BABAJKO, Suzanne
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)* 03 July 2003 (03.07.03)	
Applicant's or agent's file reference CT-2703-NP	IMPORTANT NOTICE
International application No. PCT/US02/40605	International filing date *(day/month/year)* 20 December 2002 (20.12.02)
Priority date *(day/month/year)* 20 December 2001 (20.12.01)	
Applicant BRISTOL-MYERS SQUIBB COMPANY	

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

   CH, EP, KP, KR

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

   AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-*bis*)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 03 July 2003 (03.07.03) under No. 03/053912

4. **TIME LIMITS for filing a demand for international preliminary examination and for entry into the national phase**

   The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of **19 months** from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

   In practice, **time limits other than the 30-month time limit** will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For **regular updates on the applicable time limits** (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

   For **filing a demand for international preliminary examination**, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

   It is the applicant's **sole responsibility** to monitor all these time limits.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Judith Zahra
Facsimile No.(41-22) 740.14.35	Telephone No.(41-22) 338.91.11

Form PCT/IB/308 (April 2002)

590.592

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04057563 00000000 Folios: 589
Fecha (AMD): 2004-06-18 17:10:26
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente.	( )	(✓)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	(✓)
- Descripción de la invención.	( )	(✓)
- Dibujos de ser estos pertinentes.	( )	(✓)
- Comprobante de Pago de las tasas establecidas.		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de Identificación del solcitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable: Claudia M Nieva

Fecha:

593
594

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO

MANTENIMIENTO DE PROTOCOLOS

Número : 19358
Fecha : 07/05/1999
Conferido: BRISTOL-MYERS SQUIBB COMPANY

Pais : US ESTADOS UNIDOS DE AMERICA
Ciudad : 82 PRINCETON, NEW JERSEY
Represent: S Sustituir : S Desistir : S
No. Radicación : 99 28346 Clase: 0 Seev: 0 Seac: 0

scncia	Codigo	Ctr	Nombre
1	340	A	CASTRO DUQUE RAMIRO
2	3002		GOMEZ MEJIA HECTOR

594

~~592~~

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá D C

Doctor(a)
RAMIRO CASTRO DUQUE
Apoderado
BRISTOL – MYERS SQUIBB COMPANY

Oficio N° 07156

ASUNTO:

Radicación N°	04-57563
Solicitud internacional	PCT/US02/40605
Fecha inicio fase nacional	20/07/2004
Trámite	011
Evento	379
Actuación	416
Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 30 JUL. 2004

202044

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Conmutador: 3 820840 Fax: 3 505220
Sede CAN: Tr. 40A No. 38-50 3153265 al 69
Fax: 3 505220. Línea 9800-910 165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia