Industria y Comercio

SUPERINTENDENCIA

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DIVISIÓN DE NUEVAS CREACIONES

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SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: COMPUESTOS Y COMPOSICIONES COMO MODULADORES DEL RECEPTOR ACTIVO POR PROLIFERADOR DE PEROXISONA (PPAR)

SOLICITANTE: IRM LLC

DIRECCIÓN: Hurst Holme, 12 Trott Road, Hamilton, HM 11, Bermudas.

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APODERADO: CARLOS R. OLARTE

BOGOTÁ 20 de noviembre de 2006

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Eve: 3/N FASE NACIONAL
Act: 411 PRESENTACION Folios: 3/N

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(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[ ] Capítulo I. [X] Capítulo II.

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(3) **PCT (86)**

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(6) **Título (54)** **COMPUESTOS Y COMPOSICIONES COMO MODULADORES DEL RECEPTOR ACTIVADO POR PROLIFERADOR DE PEROXISOMA (PPAR)**

Clasificación Internacional (51) **C07D 277/24.**

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(10) **ANEX S**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso.
- [ ] 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 internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [x] Traducción del examen preliminar internacional 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 12 x 12.
- [ ] 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.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA: _____

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Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

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4

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(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: COMPOUNDS AND COMPOSITIONS AS PPAR MODULATORS

(57) Abstract: The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with the activity of the Peroxisome Proliferator-Activated Receptor (PPAR) families, particularly the activity of PPAR.

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COMPOUNDS AND COMPOSITIONS AS PPAR MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Patent Application Number 60/574,137, filed 24 May 2004, and U.S. Provisional Patent Application Number 60/648,985, filed 31 January 2005. The full disclosures of these applications are incorporated herein by reference in their entirety and for all purposes.

BACKGROUND OF THE INVENTION

Field of the Invention

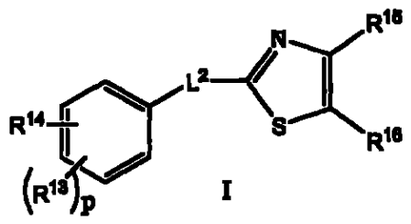
[0002] The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with the activity of the Peroxisome Proliferator-Activated Receptor (PPAR) families, particularly the activity of PPARδ.

Background

[0003] Peroxisome Proliferator Activated Receptors (PPARs) are members of the nuclear hormone receptor super family, which are ligand-activated transcription factors regulating gene expression. Certain PPARs are associated with a number of disease states including dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, atherogenesis, hypertriglyceridemia, heart failure, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, inflammation, arthritis, cancer, Alzheimer's disease, skin disorders, respiratory diseases, ophthalmic disorders, IBDs (irritable bowel disease), ulcerative colitis and Crohn's disease. Accordingly, molecules that modulate the activity of PPARs, particularly PPARδ, are useful as therapeutic agents in the treatment of such diseases.

SUMMARY OF THE INVENTION

[0004] In one aspect, the present invention provides compounds of Formula I:



I

in which

p is an integer selected from 0 to 3;

L^2 is selected from –XOX–, $–XS(O)_{0-2}X–$ and $–XS(O)_{0-2}XO–$; wherein X is independently selected from a bond and C_{1-4}alkylene; wherein any alkylene of L^2 can be optionally substituted by 1 to 3 radicals selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy;

R^{13} is selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{6-10}aryl, C_{5-10}heteraryl, C_{3-12}cycloalkyl and C_{3-8}heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^{13} is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy;

R^{14} is selected from $-XOXC(O)OR^{17}$ and $-XC(O)OR^{17}$; wherein X is a bond or C_{1-4}alkylene; and R^{17} is selected from hydrogen and C_{1-6}alkyl;

R^{15} and R^{16} are independently selected from $–R^{18}$ and $–YR^{18}$; wherein Y is a selected from C_{1-6}alkylene, C_{2-6}alkenylene, C_{2-6}alkynylene, $–C(O)NR^{17}–$ and –OX–; X is a bond or C_{1-4}alkylene; R^{17} is selected from hydrogen and C_{1-6}alkyl; and R^{18} is selected from C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{6-10}aryl and C_{5-13}heteroaryl; or R^{15} and R^{16} together with the atoms to which R^{15} and R^{16} are attached form fused bicyclic or tricyclic C_{5-14}heteroaryl;

[0005] wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^{18}, or the combination of R^{15} and R^{16}, is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxy-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl,

C_{6-10}aryl, C_{5-13}heteroaryl, $-XS(O)_{0-2}R^{17}$, $-XS(O)_{0-2}XR^{19}$, $-XNR^{17}R^{17}$, $-XNR^{17}S(O)_{0-2}R^{17}$, $-XNR^{17}C(O)R^{17}$, $-XC(O)NR^{17}R^{17}$, $-XNR^{17}C(O)R^{19}$, $-XC(O)NR^{17}R^{19}$, $-XC(O)R^{19}$, $-XNR^{17}XR^{19}$ and $-XOXR^{19}$; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituent is further optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxy-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy; wherein X is a bond or C_{1-4}alkylene; R^{17} is selected from hydrogen and C_{1-6}alkyl; and R^{19} is selected from C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{6-10}aryl and C_{5-10}heteroaryl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R^{19} is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds.

[0006] In a second aspect, the present invention provides a pharmaceutical composition that contains a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof; or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients.

[0007] In a third aspect, the present invention provides a method of treating a disease in an animal in which modulation of PPAR activity, particularly PPARδ, can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof, or a pharmaceutically acceptable salt thereof.

[0008] In a fourth aspect, the present invention provides the use of a compound of Formula I in the manufacture of a medicament for treating a disease in an animal in which PPAR activity, particularly PPARδ, activity contributes to the pathology and/or symptomology of the disease.

[0009] In a fifth aspect, the present invention provides a process for preparing compounds of Formula I and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0010] "Alkyl" as a group and as a structural element of other groups, for example halo-substituted-alkyl and alkoxy, can be either straight-chained or branched. C_{1-6}alkoxy includes, methoxy, ethoxy, and the like. Halo-substituted alkyl includes trifluoromethyl, pentafluoroethyl, and the like.

[0011] "Aryl" means a monocyclic or fused bicyclic aromatic ring assembly containing six to ten ring carbon atoms. For example, aryl can be phenyl or naphthyl, preferably phenyl. "Arylene" means a divalent radical derived from an aryl group. "Heteroaryl" is as defined for aryl where one or more of the ring members are a heteroatom. For example heteroaryl includes pyridyl, indolyl, indazolyl, quinoxalinyl, quinolinyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzo[1,3]dioxole, imidazolyl, benzo-imidazolyl, pyrimidinyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, thienyl, etc. "C_{6-10}arylC_{0-4}alkyl" means an aryl as described above connected via a alkylene grouping. For example, C_{6-10}arylC_{0-4}alkyl includes phenethyl, benzyl, etc.

[0012] "Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring atoms indicated. For example, C_{3-10}cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. "Heterocycloalkyl" means cycloalkyl, as defined in this application, provided that one or more of the ring carbons indicated, are replaced by a moiety selected from -O-, -N=, -NR-, -C(O) -, -S-, -S(O) - or -$S(O)_2$-, wherein R is hydrogen, C_{1-4}alkyl or a nitrogen protecting group. For example, C_{3-8}heterocycloalkyl as used in this application to describe compounds of the invention includes morpholino, pyrrolidinyl, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, etc.

[0013] "Halogen" (or halo) preferably represents chloro or fluoro, but can also be bromo or iodo.

[0014] "Treat", "treating" and "treatment" refer to a method of alleviating or abating a disease and/or its attendant symptoms.

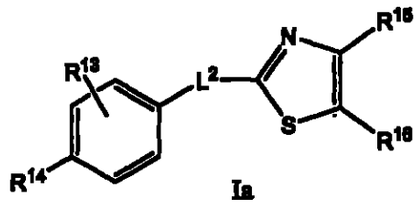
Description of the Preferred Embodiments

[0015] The present invention provides compounds, compositions and methods for the treatment of diseases in which modulation of PPARδ activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I.

[0016] In one embodiment, with reference to compounds of Formula I, p is an integer selected from 0 to 3; L^2 is selected from –XOX–, $-XS(O)_{0-2}X-$ and $-XS(O)_{0-2}XO-$; wherein X is independently selected from a bond and C_{1-4}alkylene; wherein any alkylene of L^2 can be optionally substituted by 1 to 3 radicals selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy; and R^{13} is C_{1-6}alkyl, C_{1-6}alkoxy and halo.

[0017] In a further embodiment, R^{14} is selected from $-XOXC(O)OR^{17}$ and $-XC(O)OR^{17}$; wherein X is a bond or C_{1-4}alkylene; and R^{17} is selected from hydrogen and C_{1-6}alkyl; R^{15} and R^{16} are independently selected from $-R^{18}$ and $-YR^{18}$; wherein Y is a selected from C_{1-6}alkylene, C_{2-6}alkenylene, $-C(O)NR^{17}-$ and –OX–; X is a bond or C_{1-4}alkylene; R^{17} is selected from hydrogen and C_{1-6}alkyl; and R^{18} is selected from C_{6-10}aryl, C_{3-12}cycloalkyl and C_{5-13}heteroaryl; or R^{15} and R^{16} together with the atoms to which R^{15} and R^{16} are attached form fused bicyclic or tricyclic C_{5-14}heteroaryl; wherein any aryl, heteroaryl and cycloalkyl of R^{18}, or the combination of R^{15} and R^{16}, is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxy-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{6-10}aryl optionally substituted with C_{1-6}alkoxy, C_{5-13}heteroaryl, $-XS(O)_{0-2}R^{17}$, $-XS(O)_{0-2}XR^{19}$, $-XNR^{17}R^{17}$, $-XNR^{17}S(O)_{0-2}R^{17}$, $-XNR^{17}C(O)R^{17}$, $-XC(O)NR^{17}R^{17}$, $-XNR^{17}C(O)R^{19}$, $-XC(O)NR^{17}R^{19}$, $-XC(O)R^{19}$, $-XNR^{17}XR^{19}$ and $-XOXR^{19}$; wherein X is a bond or C_{1-4}alkylene; R^{17} is selected from hydrogen and C_{1-6}alkyl; and R^{19} is selected from C_{6-10}aryl, C_{5-10}heteroaryl, C_{3-8}heterocycloalkyl and C_{3-12}cycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R^{19} is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy.

[0018] In a further embodiment, the invention provides a compound of Formula Ia:

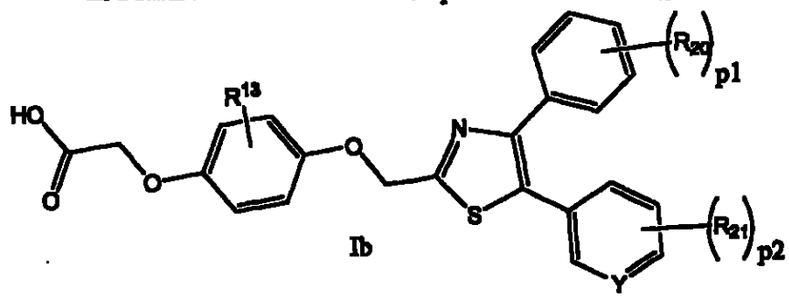


Ia

[0019] in which: L^2 is selected from $-S(O)_{0-2}(CH_2)_{1-4}O-$, $-O(CH_2)_{1-4}S(O)_{0-2}-$, $-CH_2S(O)_{0-2}-$, $-S(O)_{0-2}CH_2-$, $-S(O)_{0-2}-$, $-CH_2O-$ and $-OCH_2-$; R^{13} is selected from C_{1-6}alkyl, C_{1-6}alkoxy and halo; R^{14} is selected from $-OCH_2C(O)OH$ and $-CH_2C(O)OH$; R^{15} and R^{16} are independently selected from $-R^{18}$ and $-YR^{18}$; wherein Y is selected from C_{1-6}alkylene, C_{2-6}alkenylene, $-C(O)NH-$ and $-O(CH_2)_{1-3}-$; and R^{18} is selected from phenyl, biphenyl, cyclohexyl, naphthyl, benzo[1,3]dioxol-5-yl, benzo[b]furanyl, pyridinyl, pyrimidinyl, dibenzo-furan-2-yl, furanyl, benzo[b]thiophene, thiophenyl, phenoxathiin-4-yl, benzoxazolyl, 3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl, 2-oxo-2,3-dihydro-benzooxazol-6-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, benzoxazolyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl and quinolinyl; or R^{15} and R^{16} together with the atoms to which R^{15} and R^{16} are attached form 4,5-dihydro-naphtho[1,2-d]thiazol-2-yl, 4H-chromeno[4,3-d]thiazol-2-yl, 5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl, benzthiazolyl, benzoxazolyl and 1-oxa-3-aza-cyclopenta[a]naphthalen-2-yl;
wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^{15}, R^{16} or the combination of R^{15} and R^{16}, is optionally substituted with 1 to 3 radicals independently selected from halo, cyano, nitro, methyl, isopropyl, isopropyl-sulfanyl, isopropyloxy, hydroxy-methyl, methyl-sulfanyl, methoxy, ethoxy, pentafluoroethoxy, trifluoromethyl, trifluoromethoxy, trifluoromethyl-sulfonyl, morpholino, phenoxy, benzoxy, ethyl-sulfonyl, dimethylamino, methyl-sulfonyl-amino, ethyl-sulfonyl, propyl, vinyl, propyloxy, sec-butoxy, trifluoromethyl-sulfanyl, dimethyl-amino-carbonyl, diethyl-amino-carbonyl, methyl-carbonyl-amino, methyl-carbonyl, cyclopentyl-oxy, isopropyl-methylamino-carbonyl, cyclopropyl-amino-carbonyl, cyclohexyl, morpholino, piperidinyl, indolyl, pyrrolidinyl, pyrrolidinyl-carbonyl, 2,3-dihydro-benzofuran-5-yl piperidinyl-carbonyl, morpholino-

carbonyl, isopropyl-methyl-amino, isopropyl-methyl-amino-carbonyl, diethyl-amino, and phenyl optionally substituted with methoxy.

[0020] In a further embodiment are compounds of Formula Ib:



Ib

[0021] in which: p1 and p2 are independently selected from 0, 1 and 2; Y is selected from N and CH; R^{13} is selected from C_{1-6}alkyl, C_{1-6}alkoxy and halo; R^{20} is selected from trifluoromethyl and trifluoromethoxy; and R^{21} is selected from isopropyloxy and methoxy.

[0022] Preferred compounds of Formula I are detailed in the Examples, *infra*. More preferred compounds of the invention are selected from: {4-[4-(4-isopropoxy-phenyl)-5-(4-trifluoromethoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid; {4-[4-(4-isopropoxy-phenyl)-5-(4-trifluoromethyl-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid; and {4-[4-(6-methoxy-pyridin-3-yl)-5-(4-trifluoromethoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.

Pharmacology and Utility

[0023] Compounds of the invention modulate the activity of PPARs and, as such, are useful for treating diseases or disorders in which PPARs contributes to the pathology and/or symptomology of the disease. This invention further provides compounds of this invention for use in the preparation of medicaments for the treatment of diseases or disorders in which PPARs, particularly PPARδ, contributes to the pathology and/or symptomology of the disease.

[0024] Such compounds may therefore be employed for the treatment of prophylaxis, dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, atherogenesis, hypertriglyceridemia, heart failure, hyper cholesteremia, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, cachexia, HIV

wasting syndrome, inflammation, arthritis, cancer, Alzheimer's disease, anorexia, anorexia nervosa, bulimia, skin disorders, respiratory diseases, ophthalmic disorders, IBDs (irritable bowel disease), ulcerative colitis and Crohn's disease. Preferably for the treatment of prophylaxis, dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, atherogenesis, hypertriglyceridemia, cardiovascular diseases, hypertension, obesity, inflammation, cancer, skin disorders, IBDs (irritable bowel disease), ulcerative colitis and Crohn's disease.

[0025] Compounds of the invention can also be employed to treat long term critical illness, increase muscle mass and/or muscle strength, increase lean body mass, maintain muscle strength and function in the elderly, enhance muscle endurance and muscle function, and reverse or prevent frailty in the elderly.

[0026] Further, the compounds of the present invention may be employed in mammals as hypoglycemic agents for the treatment and prevention of conditions in which impaired glucose tolerance, hyperglycemia and insulin resistance are implicated, such as type-1 and type-2 diabetes, Impaired Glucose Metabolism (IGM), Impaired Glucose Tolerance (IGT), Impaired Fasting Glucose (IFG), and Syndrome X. Preferably type-1 and type-2 diabetes, Impaired Glucose Metabolism (IGM), Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG).

[0027] In accordance with the foregoing, the present invention further provides a method for preventing or treating any of the diseases or disorders described above in a subject in need of such treatment, which method comprises administering to said subject a therapeutically effective amount (*See, "Administration and Pharmaceutical Compositions", infra*) of a compound of the invention or a pharmaceutically acceptable salt thereof. For any of the above uses, the required dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired. The present invention also concerns: i) a compound of the invention or a pharmaceutically acceptable salt thereof for use as a medicament; and ii) the use of a compound of the invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for preventing or treating any of the diseases or disorders described above.

Administration and Pharmaceutical Compositions

[0028] In general, compounds of the invention will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5mg to about 100mg, conveniently administered, e.g. in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50mg active ingredient.

[0029] Compounds of the invention can be administered as pharmaceutical compositions by any conventional route, in particular enterally, e.g., orally, e.g., in the form of tablets or capsules, or parenterally, e.g., in the form of injectable solutions or suspensions, topically, e.g., in the form of lotions, gels, ointments or creams, or in a nasal or suppository form. Pharmaceutical compositions comprising a compound of the present invention in free form or in a pharmaceutically acceptable salt form in association with at least one pharmaceutically acceptable carrier or diluent can be manufactured in a conventional manner by mixing, granulating or coating methods. For example, oral compositions can be tablets or gelatin capsules comprising the active ingredient together with a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrollidone; if desired d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions can be aqueous isotonic solutions or suspensions, and suppositories can be prepared from fatty emulsions or suspensions. The compositions can be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they can also contain other therapeutically valuable substances. Suitable formulations for transdermal applications

include an effective amount of a compound of the present invention with a carrier. A carrier can include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. Matrix transdermal formulations can also be used. Suitable formulations for topical application, e.g., to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art. Such can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0030] This invention also concerns a pharmaceutical composition comprising a therapeutically effective amount of a compound as described herein in combination with one or more pharmaceutically acceptable carriers.

[0031] Compounds of the invention can be administered in therapeutically effective amounts in combination with one or more therapeutic agents (pharmaceutical combinations).

[0032] Thus, the present invention also relates to pharmaceutical combinations, such as a combined preparation or pharmaceutical composition (fixed combination), comprising: 1) a compound of the invention as defined above or a pharmaceutical acceptable salt thereof; and 2) at least one active ingredient selected from:

[0033] a) anti-diabetic agents such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; insulin sensitizer such as protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose co-transporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; DPPIV (dipeptidyl peptidase IV) inhibitors such as DPP728, LAF237 (vildagliptin - Example 1 of WO 00/34241), MK-0431, saxagliptin,

GSK23A ; an AGE breaker; a thiazolidone derivative (glitazone) such as pioglitazone, rosiglitazone, or *(R)*-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}-2,3-dihydro-1*H*-indole-2-carboxylic acid described in the patent application WO 03/043985, as compound 19 of Example 4, a non-glitazone type PPARγ agonist e.g. GI-262570;

[0034] b) hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; squalene synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin;

[0035] c) an anti-obesity agent or appetite regulating agent such as phentermine, leptin, bromocriptine, dexamphetamine, amphetamine, fenfluramine, dexfenfluramine, sibutramine, orlistat, dexfenfluramine, mazindol, phentermine, phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate, diethylpropion, benzphetamine, phenylpropanolamine or ecopipam, ephedrine, pseudoephedrine or cannabinoid receptor antagonists;

[0036] d) anti-hypertensive agents, e.g., loop diuretics such as ethacrynic acid, furosemide and torsemide; diuretics such as thiazide derivatives, chlorithiazide, hydrochlorothiazide, amiloride; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril and trandolapril; inhibitors of the Na-K-ATPase membrane pump such as digoxin; neutralendopeptidase (NEP) inhibitors e.g. thiorphan, terteo-thiorphan, SQ29072; ECE inhibitors e.g. SLV306; ACE/NEP inhibitors such as omapatrilat, sampatrilat and fasidotril; angiotensin II antagonists such as candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan, in particular valsartan; renin inhibitors such as aliskiren, terlakiren, ditekiren, RO 66-1132, RO-66-1168; β-adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol and timolol; inotropic agents such as digoxin, dobutamine and milrinone; calcium channel blockers such as amlodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists; and aldosterone synthase inhibitors;

[0037] e) a HDL increasing compound;

[0038] f) Cholesterol absorption modulator such as Zetia® and KT6-971;

[0039] g) Apo-A1 analogues and mimetics;

[0040] h) thrombin inhibitors such as Ximelagatran;

[0041] i) aldosterone inhibitors such as anastrazole, fadrazole, eplerenone;

[0042] j) Inhibitors of platelet aggregation such as aspirin, clopidogrel bisulfate;

[0043] k) estrogen, testosterone, a selective estrogen receptor modulator, a selective androgen receptor modulator;

[0044] l) a chemotherapeutic agent such as aromatase inhibitors e.g. femara, anti-estrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, alkylating agents, antineoplastic antimetabolites, platin compounds, compounds decreasing the protein kinase activity such as a PDGF receptor tyrosine kinase inhibitor preferably Imatinib ({ N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine }) described in the European patent application EP-A-0 564 409 as example 21 or 4-Methyl-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-benzamide described in the patent application WO 04/005281 as example 92; and

[0045] m) an agent interacting with a 5-HT_3 receptor and/or an agent interacting with 5-HT_4 receptor such as tegaserod described in the US patent No. 5510353 as example 13, tegaserod hydrogen maleate, cisapride, cilansetron;

[0046] or, in each case a pharmaceutically acceptable salt thereof; and optionally a pharmaceutically acceptable carrier.

[0047] Most preferred combination partners are tegaserod, imatinib, vildagliptin, metformin, a thiazolidone derivative (glitazone) such as pioglitazone, rosiglitazone, or *(R)*-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}-2,3-dihydro-1*H*-indole-2-carboxylic acid, a sulfonylurea receptor ligand, aliskiren, valsartan, orlistat or a statin such as pitavastatin, simvastatin, fluvastatin or pravastatin.

[0048] Preferably the pharmaceutical combinations contains a therapeutically effective amount of a compound of the invention as defined above, in a combination with a therapeutically effective amount of another therapeutic agent as described above, e.g., each at an effective therapeutic dose as reported in the art. Combination partners (1) and (2) can

be administered together, one after the other or separately in one combined unit dosage form or in two separate unit dosage forms. The unit dosage form may also be a fixed combination.

[0049] The structure of the active agents identified by generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or the Physician's Desk Reference or from databases, e.g. Patents International (e.g. IMS World Publications) or Current Drugs. The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active agents and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both in vitro and in vivo.

[0050] In another preferred aspect the invention concerns a pharmaceutical composition (fixed combination) comprising a therapeutically effective amount of a compound as described herein, in combination with a therapeutically effective amount of at least one active ingredient selected from the above described group a) to m), or, in each case a pharmaceutically acceptable salt thereof.

[0051] A pharmaceutical composition or combination as described herein for the manufacture of a medicament for the treatment of for the treatment of dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, hypertriglyceridemia, heart failure, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, inflammation, arthritis, cancer, Alzheimer's disease, skin disorders, respiratory diseases, ophthalmic disorders, inflammatory bowel diseases, IBDs (irritable bowel disease), ulcerative colitis, Crohn's disease, conditions in which impaired glucose tolerance, hyperglycemia and insulin resistance are implicated, such as type-1 and type-2 diabetes, Impaired Glucose Metabolism (IGM), Impaired Glucose Tolerance (IGT), Impaired Fasting Glucose (IFG), and Syndrome-X.

[0052] Such therapeutic agents include estrogen, testosterone, a selective estrogen receptor modulator, a selective androgen receptor modulator, insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide and Amaryl; insulinotropic sulfonylurea receptor ligands, such as meglitinides, e.g., nateglinide and repaglinide; insulin sensitizers, such as protein tyrosine phosphatase-1B (PTP-1B) inhibitors, GSK3 (glycogen synthase kinase-3) inhibitors or RXR ligands; biguanides, such as metformin; alpha-glucosidase inhibitors, such as acarbose; GLP-1 (glucagon like peptide-1),

GLP-1 analogs, such as Exendin-4, and GLP-1 mimetics; DPPIV (dipeptidyl peptidase IV) inhibitors, e.g. isoleucin-thiazolidide; DPP728 and LAF237, hypolipidemic agents, such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin, fluindostatin and rivastatin, squalene synthase inhibitors or FXR (liver X receptor) and LXR (farnesoid X receptor) ligands, cholestyramine, fibrates, nicotinic acid and aspirin. A compound of the present invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

[0053] The invention also provides for pharmaceutical combinations, e.g. a kit, comprising: a) a first agent which is a compound of the invention as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent. The kit can comprise instructions for its administration.

[0054] The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

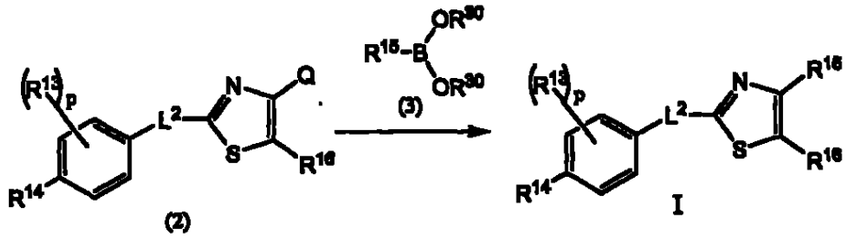
The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

Processes for Making Compounds of the Invention

[0055] The present invention also includes processes for the preparation of compounds of the invention. In the reactions described, it can be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups can be used in accordance with standard practice, for example, see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991.

[0056] Compounds of Formula I, in which R^{15} is cyclic (e.g. cycloalkyl, heterocycloalkyl, aryl and heteroaryl), can be prepared by proceeding as in reaction scheme Ia:

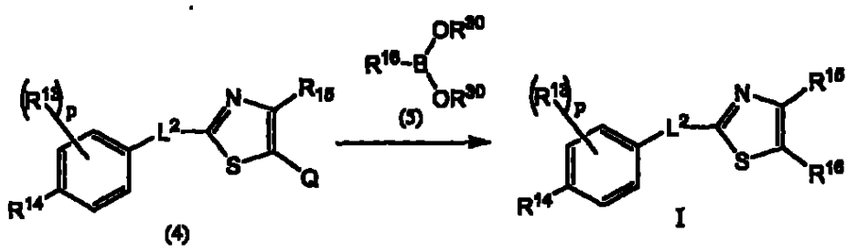
Reactions Scheme Ia



[0057] in which p, R^{13}, R^{14}, R^{16} and L^2 are as defined for Formula I in the Summary of the Invention. Q is a halogen, preferably Cl or Br; and R^{30} is independently selected from hydrogen, C_{1-6}alkyl or the R^{30} radicals can be cyclized. Compounds of Formula I are prepared by reacting a compound of formula 2 with a compound of formula 3 in the presence of a suitable catalyst (e.g., $Pd(Ph_3)_4$, or the like), a suitable base (e.g., Na_2CO_3, or the like) and a suitable solvent (e.g., water, ethanol, DME or the like). The reaction is carried out in the temperature range of about 120 to about 200°C (microwave) and takes up to about 20 minutes to complete.

[0058] Compounds of Formula I, in which R^{16} is cyclic (e.g. cycloalkyl, heterocycloalkyl, aryl and heteroaryl), can be prepared by proceeding as in reaction scheme Ib:

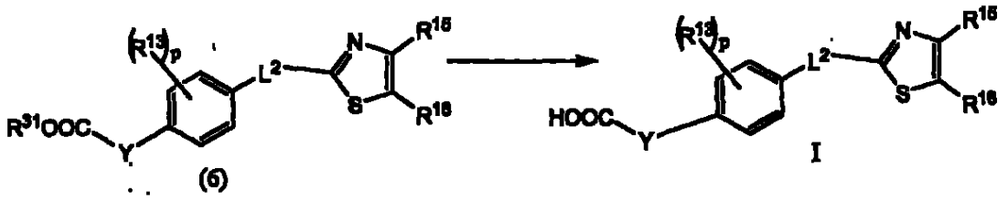
Reactions Scheme 1b



[0059] in which p, R^{13}, R^{14}, R^{16} and L^2 are as defined for Formula I in the Summary of the Invention. Q is a halogen, preferably Cl or Br; and R^{30} is independently selected from hydrogen, C_{1-6}alkyl or the R^{30} radicals can be cyclized. Compounds of Formula I are prepared by reacting a compound of formula 4 with a compound of formula 5 in the presence of a suitable catalyst (e.g., $Pd(Ph_3)_4$, or the like), a suitable base (e.g., Na_2CO_3, or the like) and a suitable solvent (e.g., water, ethanol, DME or the like). The reaction is carried out in the temperature range of about 120 to about 200°C (microwave) and takes up to about 20 minutes to complete.

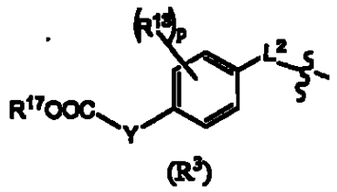
[0060] Compounds of Formula I, in which R^{14} is defined by –Y-$COOR^{31}$, can be prepared by proceeding as in reaction scheme 2:

Reactions Scheme 2



[0061] in which p, R^{13}, R^{15}, R^{16} and L^2 are as defined for Formula I in the Summary of the Invention; Y is –XOX– or –X– (wherein X is independently selected from a bond or C_{1-4}alkylene as defined in the Summary of the Invention) and R^{31} is an alkyl group, for example, methyl. Compounds of Formula I are prepared by reacting a compound of formula 4 in the presence of a suitable base (e.g., lithium hydroxide, or the like) and a suitable solvent (e.g., THF, water or the like). The reaction is carried out in the temperature range of about 0°C to about 50°C and takes up to about 30 hours to complete.

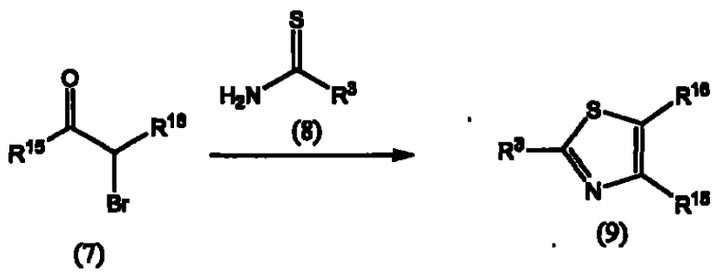
[0062] Compounds of Formula 9, in which R^3 is $-CH_3$, $-SH$, $-C(O)OC_2H_5$, $-CH_2OC(O)C(CH_3)_3$ or a group defined by:



(R^3)

[0063] wherein Y is –XOX– or –X–; and p, R^{13}, L^2, X and R^{17} are as defined in the Summary of the Invention), can be prepared by proceeding as in reaction scheme 3:

Reactions Scheme 3

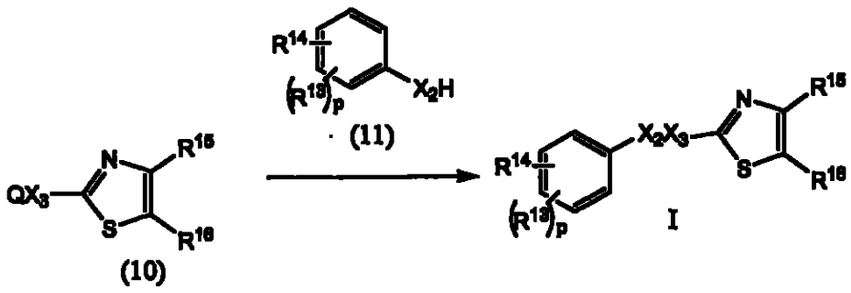


(7) (8) (9)

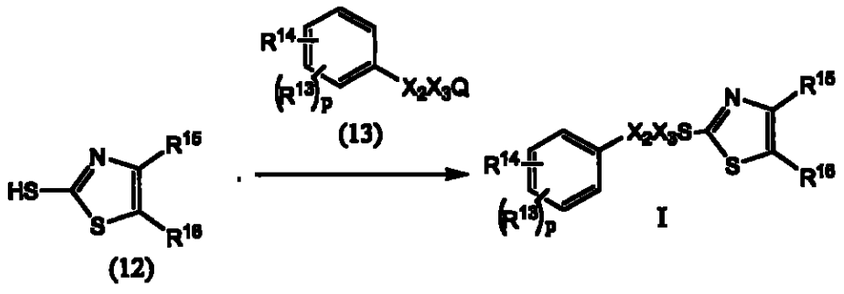
[0064] in which p, R^{13}, R^{17} and L^2 are as defined for Formula I in the Summary of the Invention; R^{15} and R^{16} independently are selected from hydrogen, alkyl or any cyclic radical (cycloalkyl, heterocycloalkyl, aryl and heteroaryl as defined in the Summary of the Invention). Compounds of Formula 9 are prepared by reacting a compound of formula 7 with a compound of formula 8 optionally in the presence of a solvent (e.g., ethanol, or the like). The reaction is carried out in the temperature range of about 10 to about 200°C and takes up to about 30 hours to complete.

[0065] Compounds of Formula I can be prepared by proceeding as in reaction scheme 4a and 4b:

Reactions Scheme 4a



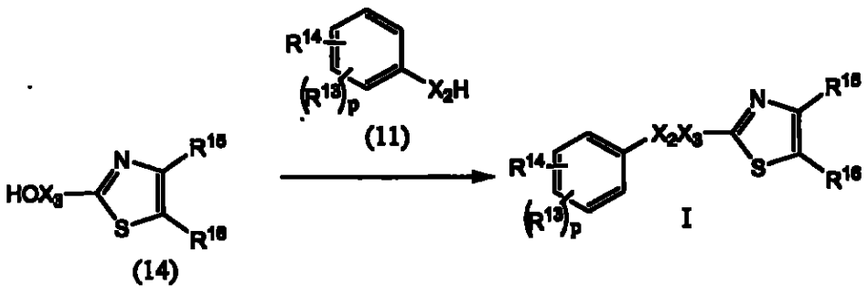
Reactions Scheme 4b



[0066] in which p, R^{13}, R^{14}, R^{15} and R^{16} are as defined for Formula I in the Summary of the Invention; X_2 is S or O; X_3 is a bond or C_{1-4}alkylene; and Q is a halo group, preferably Br or Cl. Compounds of Formula I are prepared by reacting a compound of formula 10 with a compound of formula 11 or a compound of formula 12 with a compound of formula 13 in the presence of a suitable solvent (e.g., cyanomethyl, ethanol or the like). The reaction is carried out in the temperature range of about 10 to about 80°C and takes up to about 24 hours to complete.

[0067] Compounds of Formula I can be prepared by proceeding as in reaction scheme 5:

Reactions Scheme 5



[0068] in which p, R^{13}, R^{14}, R^{15} and R^{16} are as defined for Formula I in the Summary of the Invention; X_2 is S or O; and X_3 is a bond or C_{1-4}alkylene. Compounds of Formula I are prepared by reacting a compound of formula 14 with a compound of formula 11 in the presence of a suitable solvent (e.g., DCM, THF or the like) and a suitable activating reagent (e.g., triphenylphosphine, diethylazodicarboxylate or the like). The reaction is carried out in the temperature range of about 0 to about 50°C and takes up to about 24 hours to complete.

[0069] Detailed reaction conditions are described in the examples, *infra*.

Additional Processes for Making Compounds of the Invention

[0070] A compound of the invention can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of the invention can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Alternatively, the salt forms of the compounds of the invention can be prepared using salts of the starting materials or intermediates.

[0071] The free acid or free base forms of the compounds of the invention can be prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound of the invention in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of the invention in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.).

[0072] Compounds of the invention in unoxidized form can be prepared from N-oxides of compounds of the invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (e.g. acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

[0073] Prodrug derivatives of the compounds of the invention can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of the invention with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

[0074] Protected derivatives of the compounds of the invention can be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

[0075] Compounds of the present invention can be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[0076] Compounds of the invention can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of the compounds of the invention, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then

recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981.

[0077] In summary, the compounds of Formula I can be made by a process, which involves:

[0078] (a) that of reaction scheme 1a, 1b, 2, 3, 4a, 4b or 5; and

[0079] (b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;

[0080] (c) optionally converting a salt form of a compound of the invention to a non-salt form;

[0081] (d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;

[0082] (e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;

[0083] (f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

[0084] (g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and

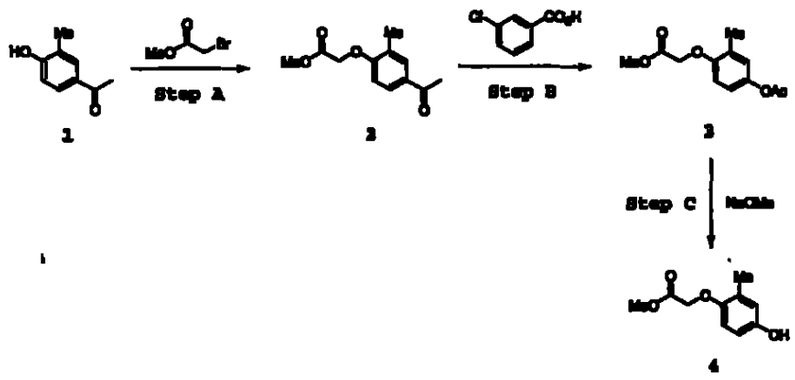
[0085] (h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

[0086] Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter.

[0087] One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used.

Examples

[0088] The present invention is further exemplified, but not limited, by the following intermediates and examples that illustrate the preparation of compounds of Formula I according to the invention.



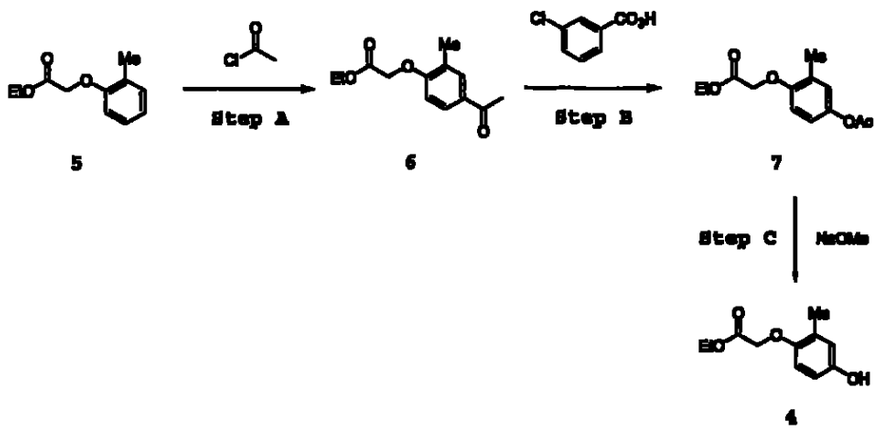
[0089] **Intermediate 4.** (4-Hydroxy-2-methyl-phenoxy)-acetic acid methyl ester.

[0090] **Step A:** 4'-Hydroxy-3'-methylacetophenone 1 (25 g, 166.4 mmol) and methyl-bromoacetate (25.5 g, 166.4 mmol) is dissolved in MeCN (600 mL). Cs_2CO_3 (117.8 g, 332.9 mmol) is added and the mixture is stirred overnight at room temperature. After insoluble salts are filtered and washed with MeCN, the solvent is removed and the remainder is taken up in EtOAc and washed subsequently with 1 M HCl (3x500 mL) and H_2O (2x500 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to afford 2 as a white solid.

[0091] **Step B:** (4-Acetyl-2-methyl-phenoxy)-acetic acid methyl ester 2 (33 g, 151.3 mmol), 77% mCPBA (54.9 g, 264.8 mmol) and p-TsOH (2.9 g, 15.1 mmol) in DCM (650 mL) are heated under reflux for 48 hours. The reaction mixture is then washed with 1 M KI (2x500 mL) and $NaHSO_3$ (2x500 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to afford 3 as a brown syrup.

[0092] **Step C:** A solution of (4-acetoxy-2-methyl-phenoxy)-acetic acid methyl ester 3 (25 g, 105.0 mmol) in dry MeOH (400 mL) is combined with a 0.5 M solution of NaOMe in MeOH (210 mL, 105.0 mmol) and stirred for 1 hour at room temperature. The solution is neutralized with 1 M HCl and washed with H_2O (2x500 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to afford 4 as a brown solid: ^{1}H-NMR (400MHz,

CD_3OD) δ = 6.65-6.51 (m, 3H), 4.60 (s, 2H), 3.75 (s, 3H), 2.19 (s, 3H). MS calculated for $C_{10}H_{13}O_4$ ($M+H^+$) 197.1, found 197.2.



5 6 7 4

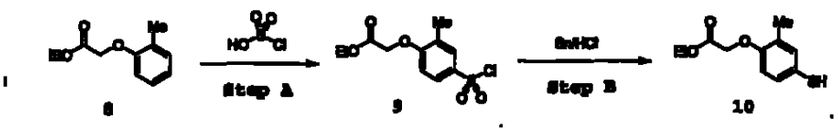
[0093] Intermediate 4 (alternative route). (4-Hydroxy-2-methyl-phenoxy)-acetic acid methyl ester.

[0094] Step A: (2-Methylphenoxy)acetic acid ethyl ester 5 (66.03 g, 340 mmol) is dissolved in dichloroethane (400 mL). Aluminum chloride (100.02 g, 750 mmol) is added and the light-brown mixture is stirred for 10 minutes at room temperature until homogenous. Acetyl chloride (35 mL, 493 mmol) is added dropwise using an addition funnel. The rate of addition is adjusted to maintain a relatively slow emission of hydrogen chloride gas. The resulting dark brown solution is allowed to cool to room temperature, then is poured over 300 g of crushed ice. The mixture is diluted with dichloromethane (300 mL) and is washed successively with water, saturated $NaHCO_3$ solution, water, saturated NH_4Cl solution, and brine. The organic layer is dried over Na_2SO_4, filtered and concentrated to afford 6 as a brown oil that solidified as a crystalline mass. ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.79 (d, J = 2.0 Hz, 1H), 7.77 (dd, J = 2.0, 8.4 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 4.71 (s, 2H), 4.26 (q, J = 7.2 Hz, 2H), 2.54 (s, 3H), 2.32 (s, 2H), 1.29 (t, J = 7.2 Hz, 3H).

[0095] Step B: (4-Acetyl-2-methyl-phenoxy)-acetic acid ethyl ester 6 (76.54 g, 324 mmol), 77% mCPBA (100.31 g, 407 mmol, 1.26 equiv.) and p-TsOH (13 g, 68 mmol, 21 mol%) in dichloroethane (450 mL) are heated to 50°C for 30 hours. The reaction mixture

is then washed with 1 M KI (2x500 mL) and $NaHSO_3$ (2x500 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to afford 7 as a brown syrup.

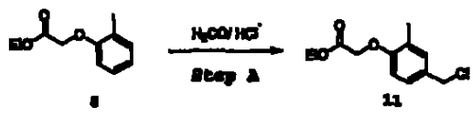
[0096] Step C: A solution of (4-Acetoxy-2-methyl-phenoxy)-acetic acid ethyl ester 7 (from step B above) in dry MeOH (400 mL) is combined with a 0.5 M solution of NaOMe in MeOH (650 mL, 325 mmol) and stirred for 2 h at room temperature. The solution is neutralized with 1 M HCl and washed with H_2O (2x500 mL). The organic layer is dried (Na_2SO_4), filtered and concentrated to afford 4 (21.7 g, 111 mmol, 34%, two steps) as a light-brown solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 6.58 (d, J = 2.8 Hz, 1H), 6.54 (d, J = 8.4 Hz), 6.50 (dd, J = 2.8, 8.4 Hz, 1H), 4.7 (br. s, 1H), 4.54 (s, 2H), 3.73 (s, 3H), 2.17 (s, 3H). MS calculated for $C_{10}H_{13}O_4$ ($M+H^+$) 197.1, found 197.4.



[0097] Intermediate 10. (4-Mercapto-2-methyl-phenoxy)-acetic acid ethyl ester.

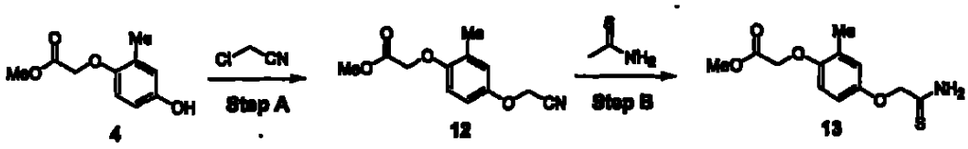
[0098] Step A: A 500 mL three-necked round bottom flasked is charged with chlorosulfonic acid (25 mL, 373.9 mmol), flushed with nitrogen and cooled to 0 °C. Under nitrogen and vigorous stirring, ethyl (2-methylphenoxy) acetate 8 (40 g, 206.2 mmol) is added dropwise. The mixture is stirred for 90 minutes at 0°C, then poured on ice-water (200 mL). After the mixture is stirred for an additional 45 min at room temperature, the white precipitate is filtered, washed with ice-water and dried in vacuo to afford 9 as a white solid.

[0099] Step B: (4-Chlorosulfonyl-2-methyl-phenoxy)-acetic acid ethyl ester 9 (25 g, 85.4 mmol) and tin (50.8 g, 427 mmol) are suspended in EtOH and cooled to 0°C. After a solution of 4 N HCl in dioxane (107 mL, 427 mmol) is added dropwise, the resulting mixture is heated to reflux for 3 hours. Then the mixture is concentrated in vacuo, the remainder taken up in chloroform and filtered. The filtrate is concentrated in vacuo to a yellow oil, which is purified by chromatography (silica, Hex/EtOAc gradient) to afford 10 as a colorless oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.14 (m, 1H), 7.07-7.10 (m, 1H), 6.59 (m, 1H), 4.60 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.33 (s, 1H), 2.24 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). MS calculated for $C_{11}H_{14}O_3S$ ($M+H^+$) 227.1, found 227.4.



[00100] Intermediate 11. (4-Chloromethyl-2-methyl-phenoxy)-acetic acid ethyl ester.

[00101] Step A: To a solution of ethyl (2-methylphenoxy) acetate 8 (20.0 g, 103 mmol) in petroleum ether (50 mL, b.p. 40-55 °C), HCl (120 mL, 12M) and formaldehyde (8.4 mL, 37 %) are added, then the mixture is stirred for 25 h at room temperature. The mixture is diluted with EtOAc and the organic layer is washed with water three times, dried ($MgSO_4$), filtered and concentrated to afford crude product, which is purified by flash chromatography with 20% EtOAc/hexane to give (4-chloromethyl-2-methyl-phenoxy)-acetic acid ethyl ester 11 as a liquid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.19 (d, J= 2.0 Hz, 1H), 7.14 (dd, J= 2.0 Hz, J= 8.0 Hz, 1H), 6.55 (d, J= 8.0 Hz, 1H), 4.64 (s, 2H), 4.53 (s, 2H), 4.26 (q, J= 7.2 Hz, 2H), 2.29 (s, 3H), 1.30 (t, J= 7.2 Hz, 3H). MS calculated for $C_{12}H_{15}ClO_3$ ($M\text{-}Cl^+$) 207.2, found 207.10.

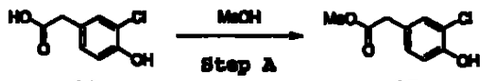


[00102] Intermediate 13. (2-Methyl-4-thiocarbamoylmethoxy-phenoxy)-acetic acid methyl ester.

[00103] Step A: (4-Hydroxy-2-methyl-phenoxy)-acetic acid methyl ester 4 (1.64 g, 8.3 mmol) and chloroacetonitrile (0.553 mL, 8.7 mmol) are dissolved in acetonitrile (30 mL). Cs_2CO_3 (5.4 g, 16.7 mmol) is added and the mixture is stirred for 2 h at room temperature. Insoluble salts are filtered and washed with EtOAc, the solvent is removed to give an oil which crystallized under vacuum to give 12 (1.84 g, 7.83 mmol, 94%) as a pale yellow solid. ^{1}H-NMR (400MHz, $CDCl_3$) δ = 6.76 (s, 1H), 6.67 (s, 1H), 6.60 (d, J = 8.5 Hz, 1H), 4.62.(s, 2H), 4.54 (s, 2H), 3.73 (s, 3H), 2.21 (s, 3H). MS calculated for $C_{12}H_{14}NO_4$ ($M+H^+$) 236.1, found 236.3.

[00104] Step B: (4-Cyanomethoxy-2-methyl-phenoxy)-acetic acid methyl ester 12 (1.75 g, 7.45 mmol) and thioacetamide (1.12 g, 14.9 mmol) are dissolved in DMF (120 mL).

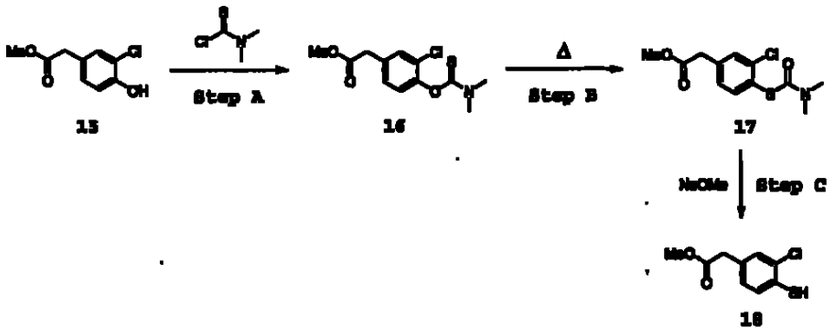
HCl (4.0 N in 1,4-dioxane, 20 mL) is added and the mixture is stirred at 100°C overnight. The mixture is diluted with saturated $NaHCO_3$, extracted with EtOAc and washed subsequently with H_2O (4x100 mL) and brine (100 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated. The residue is triturated with DCM (5 mL) and hexanes (5 mL) and collected by filtration to afford 13 as a beige solid: ^{1}H-NMR (400MHz, DMSO-d6) δ = 6.84 (d, J = 2.9 Hz, 1H), 6.78 (d, J = 8.9 Hz, 1H), 6.71 (dd, J = 3.0, 8.9 Hz, 1H), 4.75 (s, 2H), 4.67 (s, 2H), 4.04 (s, 1H), 3.69 (s, 3H), 2.18 (s, 3H). MS calculated for $C_{12}H_{16}NO_4S$ ($M+H^+$) 270.1, found 270.3.



14 15

[00105] Intermediate 15. (3-Chloro-4-hydroxy-phenyl)-acetic acid methyl ester.

[00106] Step A: 3-Chloro-4-hydroxy-phenyl)-acetic acid 14 (20 g, 107 mmol) is dissolved in MeOH (250 mL) containing catalytic amounts of conc. H_2SO_4 (2.5 mL). The solution is heated to reflux overnight. The solvent is evaporated, the remainder is dissolved in DCM and washed with H_2O (3x200 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to afford 15 as a light yellow solid: ^{1}H-NMR (400MHz, CD_3OD) δ = 7.21 (d, J = 2.1 Hz, 1H), 7.01 (dd, J = 2.1 Hz, J = 8.3, 1H), 6.84 (d, J = 8.3 Hz, 1H), 3.67 (s, 3H), 3.54 (s, 2H). MS calculated for $C_9H_{10}ClO_3$ ($M+H^+$) 201.0, found 201.2.



15 16 17 18

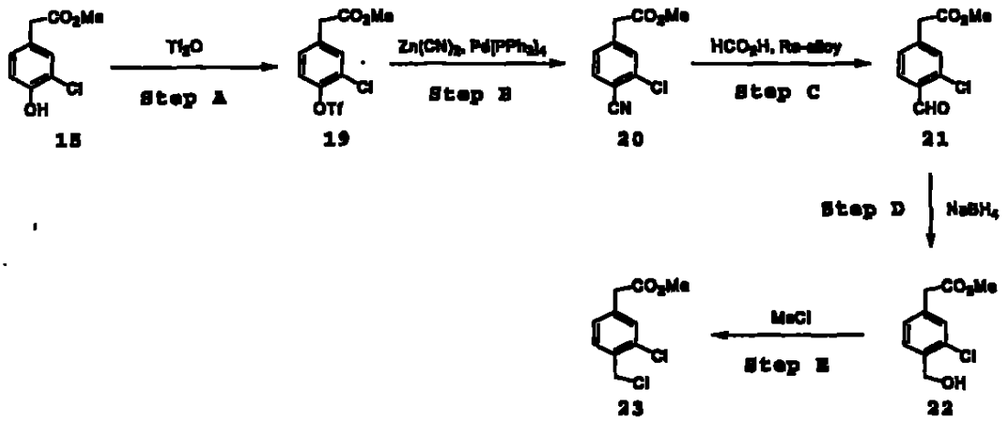
[00107] Intermediate 18. (3-Chloro-4-mercapto-phenyl)-acetic acid methyl ester.

[00108] Step A: 3-(Chloro-4-hydroxy-phenyl)-acetic acid methyl ester 15 (4.1 g, 21.4 mmol), dimethyl thiocarbamoylchloride (3.2 g, 25.6 mmol), Et_3N (5.9 mL, 42.8 mmol)

and DMAP (261 mg, 2.14 mmol) are dissolved in dry dioxane (30 mL) and heated to reflux for 16 h under nitrogen. The reaction mixture is cooled to room temperature, diluted with EtOAc and washed with H_2O (3x50 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to afford 16 as a colorless oil.

[00109] Step B: (3-Chloro-4-dimethylthiocarbamoyloxy-phenyl)-acetic acid methyl ester 16 (5.2 g, 18.1 mmol) is transferred to a 250 mL three-necked round bottom flask equipped with a thermometer. Tetradecane (45 mL) is added and the mixture is heated to reflux (250°C) overnight. After cooling to room temperature the solvent is decanted, the remaining oil is washed several times with hexanes and purified by chromatography (silica, Hex/EtOAc gradient) to afford 17 as a brown oil.

[00110] Step C: (3-Chloro-4-dimethylcarbamoylsulfanyl-phenyl)-acetic acid methyl ester 17 (3.1 g, 10.8 mmol) is dissolved in 0.5 M NaOMe in MeOH. The mixture is heated to reflux for 4 h, then acidified with 1 M HCl. The organic solvent is evaporated, the remainder is extracted into EtOAc (50 mL) and washed with H_2O (2x50 mL). The organic layer is dried ($MgSO_4$), filtered, concentrated and purified (silica, hexanes/EtOAc gradient) to afford 18 as a pale yellow oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.30-7.26 (m, 2H), 7.06-7.03 (m, 1H) 3.87 (s, 1H), 3.69 (s, 3H), 3.55 (s, 2H). MS calculated for $C_9H_{10}ClO_2S$ ($M+H^+$) 217.0, found 217.3.



[00111] Intermediate 23. (3-Chloro-4-chloromethyl-phenyl)-acetic acid methyl ester.

[00112] Step A: To a solution of (3-Chloro-4-hydroxy-phenyl)-acetic acid methyl ester 15 (15.9 g, 79.25 mmol) in CH_2Cl_2 (160 mL), triethylamine (11.04 mL, 79.25 mmol) and trifilic anhydride (13.33 mL, 79.25 mmol) are added at 0°C and stirred for 1 hour. The reaction mixture is then diluted with EtOAc (300mL) and washed with $NaHCO_3$, brine and water. The organic layer is dried ($MgSO_4$), filtered and concentrated to afford (3-chloro-4-trifluoromethanesulfonyloxy-phenyl)-acetic acid methyl ester 19 as an oil. MS calculated for $C_{10}H_9ClF_3O_5S$ ($M+H^+$) 333, found 333.95.

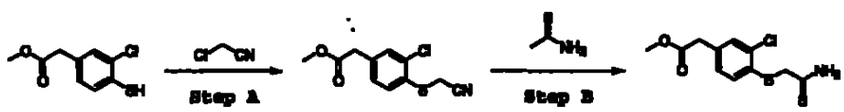
[00113] Step B: To a solution of (3-chloro-4-trifluoromethanesulfonyloxy-phenyl)-acetic acid methyl ester 19 (24.5 g, 73.64 mmol) in dry DMF (45 mL) is added zinc cyanide (8.91 g, 75.9 mmol) and tetrakis(triphenylphosphine) palladium (8.50 g, 7.36 mmol). The mixture is stirred for 34 h at 80°C and then cooled to room temperature, diluted with EtOAc (150 mL) and poured into a saturated $NaHCO_3$ solution (150 mL). A white precipitate is removed by vacuum filtration. The filtrate is washed with H_2O, dried ($MgSO_4$), filtered and concentrated to afford crude product, which is purified by silic gel chromatography with 20% EtOAc/hexane to give (3-chloro-4-cyano-phenyl) acetic acid methyl ester 20 (11.6 g, 75.13 mmol) as a wax-like solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.63 (d, J= 8.0 Hz, 1H), 7.47 (d, J= 1.2 Hz, 1H), 7.30 (dd, J= 1.2 Hz, J= 8.0 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 2H). MS calculated for $C_{10}H_9O_2ClN$ ($M+H^+$) 210.0, found 210.0.

[00114] Step C: A solution of (3-chloro-4-cyano-phenyl) acetic acid methyl ester 20 (7.4 g, 35.3 mmol) in formic acid (100 mL, 88%) is combined with Raney-alloy (9.0 g) and heated to reflux (110°C) overnight. Then the mixture is cooled to room temperature. The alloy is filtered off by Celite pad, washed with EtOAc and the filtrate is concentrated in vacuo. The remainder is diluted with EtOAc (250 mL) and washed with H_2O (2x) and $NaHCO_3$ (2x). The organic layer is dried ($MgSO_4$), filtered and concentrated to afford crude product, which is purified by silic gel chromatography with EtOAc/hexane to give (3-Chloro-4-formyl-phenyl)-acetic acid methyl ester 21 as a wax-like solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 10.31 (s, 1H), 7.84 (d, J= 8.0 Hz, 1H), 7.58 (s, 1H), 7.45 (d, J= 8.0 Hz, 1H), 3.86 (s, 2H), 3.64 (s, 3H).

[00115] Step D: A solution of (3-chloro-4-formyl-phenyl)-acetic acid methyl ester 21 (0.6 g, 2.82 mmol) in MeOH (4.0 mL) is added dropwise to a solution of $NaBH_4$ in water (4.0 mL) and stirred for 10 minutes at 20-22°C. Then HCl (1N, 15 mL) is added and the

mixture is stirred for 5 minutes. The solution is diluted with EtOAc (80 mL) and the organic layer is dried ($MgSO_4$), filtered and concentrated to afford crude product, which is purified by silic gel chromatography with 50% EtOAc/hexane to give (3-chloro-4-hydroxymethyl-phenyl)-acetic acid methyl ester 22 as a wax-like solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.44 (d, J= 8.0 Hz, 1H), 7.30 (d, J= 1.2 Hz, 1H), 7.20 (dd, J= 1.2 Hz, J= 8.0 Hz, 1H), 4.76 (s, 2H), 3.70 (s, 3H), 3.61 (s, 2H).

[00116] Step B: To a solution of (3-chloro-4-hydroxymethyl-phenyl)-acetic acid methyl ester 22 (0.5 g, 2.33 mmol) in dry DMF (5 mL) is added lithium chloride (108.6 mg, 2.56 mmol) and s-collidine (310.2 mg, 2.56 mmol). The mixture is cooled to 0 °C and $MeSO_2Cl$ (2.56 mmol) is added slowly. The mixture is stirred for two hours at 0 °C, then poured on ice-water and extracted with EtOAc. The organic layer is washed with water, dried ($MgSO_4$), filtered and concentrated to afford (3-chloro-4-chloromethyl-phenyl)-acetic acid methyl ester 23: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.42 (m, 1H), 7.34 (m, 1H), 7.19 (m, 1H), 4.68 (s, 2H), 3.71 (s, 3H), 3.61 (s, 2H). MS calculated for $C_{10}H_{11}Cl_2O_2$ $(M+1)^+$ 233.0, found 233.00.



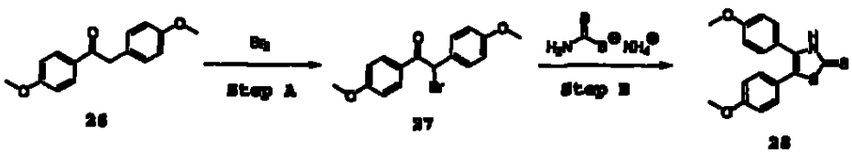
18 24 25

[00117] Intermediate 25. (3-Chloro-4-thiocarbamoyl-methylsulfanyl-phenyl)-acetic acid methyl ester.

[00118] Step A: (3-Chloro-4-mercapto-phenyl)-acetic acid methyl ester 18 (1.04 g, 4.8 mmol) is dissolved in dry acetonitrile. Cesium carbonate (3.16 g, 9.7 mmol, 2 equiv.) is added, followed by chloroacetonitrile (0.45 mL, 7.13 mmol, 1.5 equiv.). The mixture is stirred under nitrogen for 18 hours. The resulting red suspension is filtered, the solids are washed with more acetonitrile, and the resulting clear red solution is concentrated to yield 24 as an orange oil (1.26 g, quantitative). ^{1}H-NMR (400MHz, DMSO-d_6) δ = 7.50 (d, J = 8.0 Hz, 1H), 7.49 (s, 1H), 7.35 (dd, J = 1.6, 8.0 Hz, 1H), 4.35 (s, 2H), 3.75 (s, 2H), 3.63 (s, 3H). MS calculated for $C_{11}H_{11}ClNO_2S$ $(M+H^+)$ 256.0, found 256.3.

[00119] Step B: (3-Chloro-4-cyanomethylsulfanyl-phenyl)-acetic acid methyl ester 24 (1.12 g, 4.38 mmol), thioacetamide (1.52 g, 20.2 mmol, 4.6 equiv.), and a hydrogen

chloride solution in dioxane (4.0 M, 5 mL, 20 mmol, 4.6 equiv.) are dissolved in 2 mL dimethylacetamide and 3 mL dioxane. The mixture is heated to 95°C for 48 hours. The reaction mixture is then cooled to room temperature, diluted with ethyl acetate and washed with water, saturated $NaHCO_3$, saturated NH_4Cl, and brine. The organic layer is dried (Na_2SO_4), filtered and concentrated to afford a red oil. Silica gel chromatography (20% to 60% ethyl acetate in hexanes) yielded (3-chloro-4-thiocarbamoylmethylsulfanyl-phenyl)-acetic acid methyl ester 25 as a brown syrup. ^{1}H-NMR (400MHz, DMSO-d_6) δ = 9.80 (s, 1H), 9.39 (s, 1H) 7.32 (d, J = 1.6 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.20 (dd, J = 1.6, 8.4 Hz, 1H), 4.10 (s, 2H), 3.67 (s, 3H), 3.59 (s, 3H). MS calculated for $C_{11}H_{13}ClNO_2S_2$ ($M+H^+$) 290.0, found 290.2.

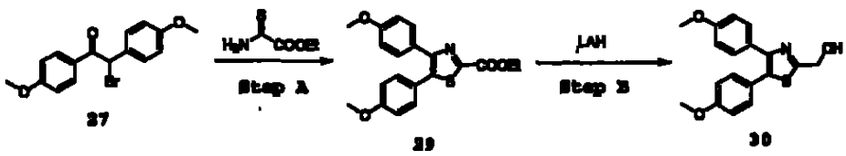


26 27 28

[00120] Intermediate 28. 4,5-Bis-(4-methoxy-phenyl)-3H-thiazole-2-thione.

[00121] Step A: To a solution of desoxyanisoin 26 (10 g, 39.0 mmol) in anhydrous $CHCl_3$ (200 mL) is added bromine (2.4 mL, 46.8 mmol) dropwise. After the addition is complete (indicated by a colour change to red), the solvent is evaporated, the remainder is triturated with ether and the precipitated product is filtered to give 27 as a white solid: ^{1}H-NMR (400MHz, CD_3OD) δ = 7.98 (d, J = 9.0 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.72 (s, 1H), 3.83 (s, 3H), 3.75 (s, 3H). MS calculated for $C_{16}H_{15}O_3$ ($M-Br^+$) 255.1, found 255.4.

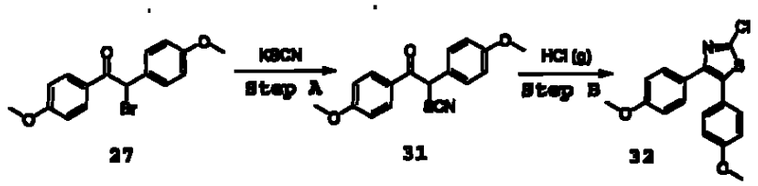
[00122] Step B: 2-Bromo-1,2-bis-(4-methoxy-phenyl)-ethanone 27 (3.0 g, 8.9 mmol) and ammonium dithiocarbamate (1.5 g, 13.4 mmol) are dissolved in EtOH (50 mL) and heated to 60°C for 3 hours. The solvent is then partially removed, the precipitate filtered and recrystallized from EtOH to yield 28 as a white solid: ^{1}H-NMR (400MHz, CD_3OD) δ = 7.26 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 3.77 (s, 3H). MS calculated for $C_{17}H_{16}NO_2S_2$ ($M+H^+$) 330.1, found 330.2.



[00123] Intermediate 30. [4,5-Bis-(4-methoxy-phenyl)-thiazol-2-yl]-methanol.

[00124] Step A: A solution of 2-bromo-1,2-bis-(4-methoxy-phenyl)-ethanone 27 (3.0 g, 9.0 mmol) and ethyl thiooxamate (1.2 g, 9.0 mmol) in anhydrous EtOH (20 mL) is heated to reflux for 12 hours. The solvent is removed in vacuo and the remainder is purified by chromatography (silica, DCM/MeOH gradient) to afford 29 as a colorless semi-solid: ^{1}H-NMR (400MHz, CD_3OD) δ = 7.39 (d, J = 8.9 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.45 (q, J = 7.1, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H). MS calculated for $C_{20}H_{20}NO_4S$ ($M+H^+$) 370.1, found 370.4.

[00125] Step B: 4,5-Bis-(4-methoxy-phenyl)-thiazole-2-carboxylic acid ethyl ester 29 (1.0 g, 2.7 mmol) is dissolved in dry THF (20 mL) and cooled to 0°C. A solution of 1 M lithium aluminium hydride in THF (4 mL, 4.1 mmol) is added dropwise via cannula and the mixture is stirred at 0°C for 1 hour. Sodium sulfate decahydrate (1.3 g, 4.1 mmol) is added slowly and the mixture is stirred an additional 1 h at room temperature. The suspension is then filtered over celite, dried ($MgSO_4$) and concentrated. The concentrate is purified by chromatography (silica, DCM/MeOH gradient) to yield 30 as a yellow oil: ^{1}H-NMR (400MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 3.96 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H). MS calculated for $C_{18}H_{18}NO_3S$ ($M+H^+$) 328.1, found 328.4.

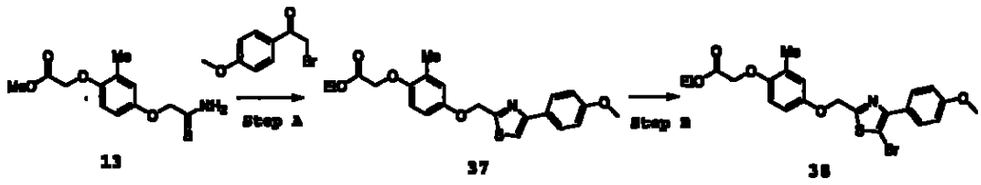


[00126] Intermediate 32: 2-Chloro-4,5-bis-(4-methoxy-phenyl)-thiazole.

[00127] Step A: 2-Bromo-1,2-bis-(4-methoxy-phenyl)-ethanone 27 (500 mg, 1.49 mmol) and potassium rhodanide (145 mg, 1.49 mmol) are heated to reflux in acetone (20 mL) for 8 hours. The mixture is cooled, diluted with water (50 mL), extracted with EtOAc

(3 x 50 mL) and washed with brine (30 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to give crude 1,2-Bis-(4-methoxy-phenyl)-2-thiocyanato-ethanone 31, which is used without further purification in Step B.

[00128] Step B: The crude 1,2-bis-(4-methoxy-phenyl)-2-thiocyanato-ethanone 31 (440 mg, 1.40 mmol) is dissolved in EtOAc (100 mL), then HCl gas is bubbled through the solution for two hours. The mixture is neutralized with aqueous NaOH to pH 6, then extracted with EtOAc (3 x 50 mL) and washed sequentially with water (30 mL) and brine (30 mL). The organic layer is dried ($MgSO_4$), filtered, concentrated and purified on silica (EtOAc/Hexane gradient) to afford the title compound 32 as a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.42 (d, J = 9.0 Hz, 2H), 7.25 (d, J = 9.3 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 9.3 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 3H). MS calculated for $C_{17}H_{15}ClNO_2S$ ($M+H^+$) 332.0, found 332.3.



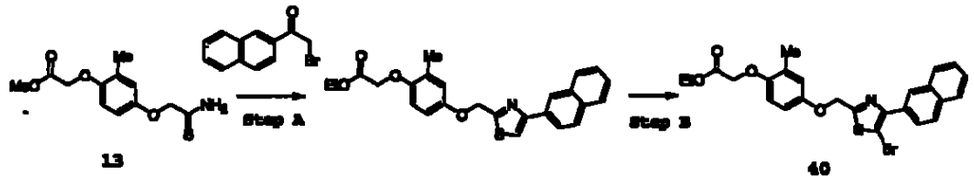
13 37 38

[00129] Intermediate 38: {4-[5-Bromo-4-(4-methoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid ethyl ester.

[00130] Step A: Intermediate 13 (200 mg, 0.743 mmol), and 2-bromo-4'-methoxyacetophenone (186 mg, 0.817 mmol) are heated at reflux in EtOH (4 mL) for 2 hours. The mixture is cooled, filtered, and washed with methanol to provide {4-[4-(4-methoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid ethyl ester 37 as a white solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, J = 6.8 Hz, 1H), 7.75 (d, J = 6.8 Hz, 1H), 7.32 (s, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 3.0 Hz, 1H), 6.73 (dd, J = 3.0, 8.9 Hz, 1H), 6.65 (d, J = 8.8 Hz, 1H), 5.29 (s, 2H), 4.51 (s, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 2.22 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H). MS calculated for $C_{22}H_{24}NO_5S$ ($M+H^+$) 414.1, found 414.4.

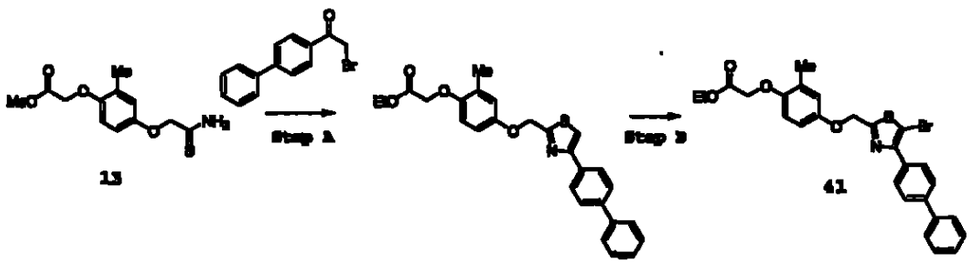
[00131] Step B: Intermediate 37 (184.6 mg, 0.45 mmol) is dissolved in dichloromethane (2 mL), then bromine (39 µL, 0.76 mmol) in acetic acid (100 µL) is added and the mixture is stirred at room temperature for 1 hour. The mixture is diluted with

saturated $NaHCO_3$, extracted with dichloromethane and washed with brine (10 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to give intermediate 38 as a white glassy substance: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.80 (d, J = 6.8 Hz, 1H), 7.79 (d, J = 6.8 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 3.0 Hz, 1H), 6.67 (dd, J = 3.0, 8.9 Hz, 1H), 6.59 (d, J = 8.8 Hz, 1H), 5.20 (s, 2H), 4.51 (s, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 2.22 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H). MS calculated for $C_{22}H_{23}BrNO_5S$ ($M+H^+$) 492.0, found 492.2.



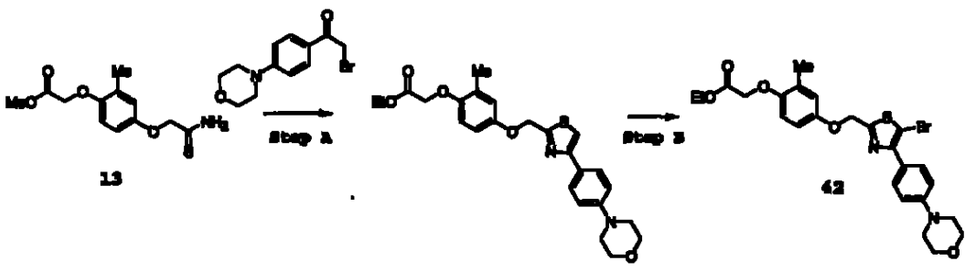
[00132] Intermediate 40: [4-(5-Bromo-4-naphthalen-2-yl-thiazol-2-ylmethoxy)-2-methyl-phenoxy]-acetic acid ethyl ester.

[00133] Following the procedure of Intermediate 38, except substituting 2-Bromo-1-naphthalen-2-yl-ethanone for 2-bromo-4'-methoxyacetophenone in Step A, the title compound is purified on reverse phase HPLC (H_2O/MeCN gradient) to afford a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.42 (s, 1H), 8.03 (dd, J = 1.6, 8.4 Hz, 1H), 7.92 (d, J = 8.8 Hz, 2H), 7.88 (m, 1H), 7.52 (m, 2H), 6.89 (d, J = 3.2 Hz, 1H), 6.77 (dd, J = 3.2, 8.8 Hz, 1H), 6.68 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H) 4.60 (s, 2H), 4.26 (q, J = 7.2 Hz, 2H) 2.30 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H). MS calculated for $C_{25}H_{23}BrNO_4S$ ($M+H^+$) 512.1, found 511.5.



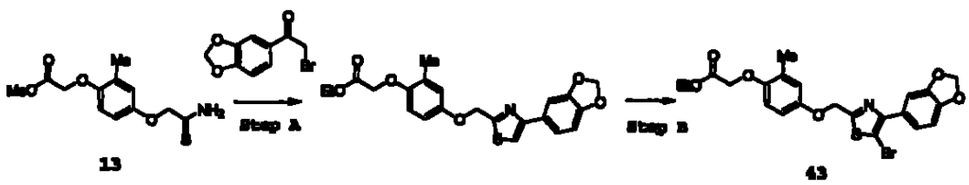
[00134] Intermediate 41: [4-(4-Biphenyl-4-yl-5-bromo-thiazol-2-ylmethoxy)-2-methyl-phenoxy]-acetic acid ethyl ester.

[00135] Following the procedure of Intermediate 38, except substituting 1-biphenyl-4-yl-2-bromo-ethanone for 2-bromo-4'-methoxyacetophenone in Step A, the title compound is purified on reverse phase HPLC (H_2O/MeCN gradient) to afford a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.99 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 7.6 Hz, 2H), 7.43 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.72 (dd, J = 2.8, 8.8 Hz, 1H), 6.64 (d, J = 8.8 Hz, 1H), 5.26 (s, 2H) 4.56 (s, 2H), 4.22 (q, J = 7.2 Hz, 2H), 2.27 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H). MS calculated for $C_{27}H_{25}BrNO_4S$ ($M+H^+$) 538.1, found 538.0.



[00136] Intermediate 42: {4-[5-Bromo-4-(4-morpholin-4-yl-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid ethyl ester.

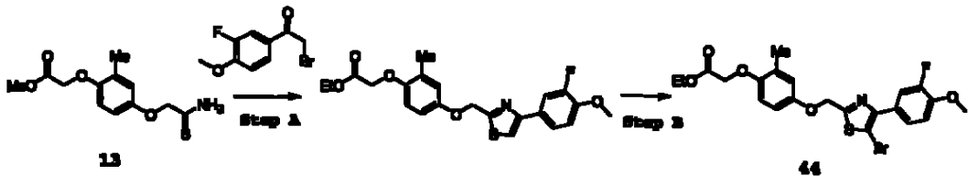
[00137] Following the procedure of Intermediate 38, except substituting 2-Bromo-1-(4-morpholin-4-yl-phenyl)-ethanone for 2-bromo-4'-methoxyacetophenone in Step A, the title compound is prepared as a yellow solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.99 (d, J = 9.2 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.74 (dd, J = 2.8, 8.8 Hz, 1H), 6.66 (d, J = 8.8 Hz, 1H), 5.27 (s, 2H) 4.59 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 4.04 (m, 4H), 3.45 (m, 4H), 2.29 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H). MS calculated for $C_{25}H_{28}BrN_2O_5S$ ($M+H^+$) 547.1, found 547.3.



[00138] Intermediate 43: [4-(4-Benzo[1,3]dioxol-5-yl-5-bromo-thiazol-2-ylmethoxy)-2-methyl-phenoxy]-acetic acid ethyl ester.

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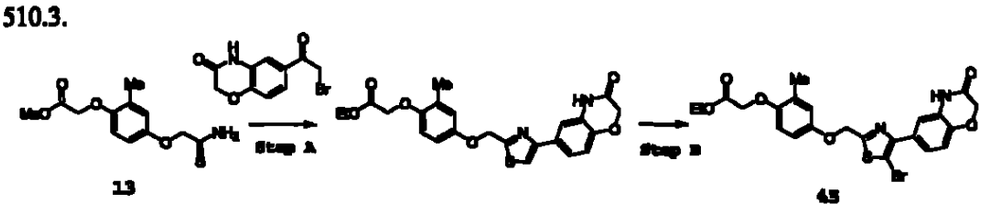
[00139] Following the procedure of Intermediate 38, except substituting 1-Benzo[1,3]dioxol-5-yl-2-bromo-ethanone for 2-bromo-4'-methoxyacetophenone in Step A, the title compound is prepared as a yellow solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.43 (dd, J = 1.6, 8.0 Hz, 1H), 7.41 (d, J = 1.6 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 2.8 Hz, 1H), 6.74 (dd, J = 2.8, 8.8 Hz, 1H), 6.66 (d, J = 8.8 Hz, 1H), 6.02 (s, 2H), 5.27 (s, 2H) 4.59 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 2.27 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H). MS calculated for $C_{22}H_{21}BrNO_6S$ ($M+H^+$) 506.0, found 506.2.



13 44

[00140] Intermediate 44: {4-[5-Bromo-4-(3-fluoro-4-methoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid ethyl ester.

[00141] Following the procedure of Intermediate 38, except substituting 2-bromo-1-(3-fluoro-4-methoxy-phenyl)-ethanone for 2-bromo-4'-methoxyacetophenone in Step A, the title compound is prepared as a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.70 (m, 2H), 7.07 (t, J = 8.4 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 6.71 (dd, J = 2.4, 8.8 Hz, 1H), 6.64 (d, J = 8.8 Hz, 1H), 5.24 (s, 2H), 4.56 (s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 3.92 (s, 3H), 2.26 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H). MS calculated for $C_{22}H_{22}BrFNO_5S$ ($M+H^+$) 510.0, found 510.3.

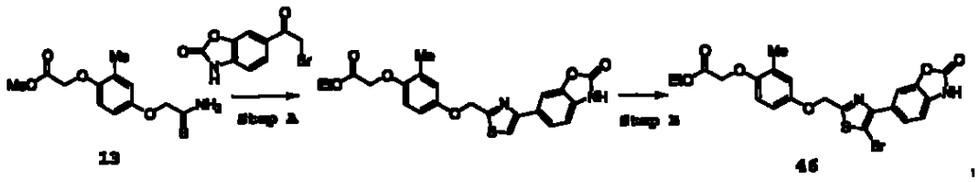


13 45

[00142] Intermediate 45; {4-[5-Bromo-4-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid ethyl ester.

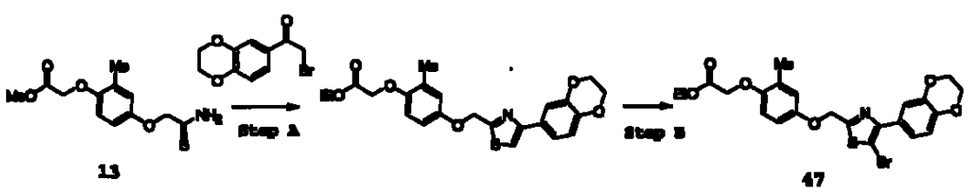
[00143] Following the procedure of Intermediate 38, except substituting 6-(2-bromo-acetyl)-4H-benzo[1,4]oxazin-3-one for 2-bromo-4'-methoxyacetophenone in Step A, the title compound is prepared as a yellow solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.76 (s, 1H), 7.65 (dd, J = 2.0, 8.4 Hz, 1H), 7.39 (d, J = 2.0 Hz 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.89 (d,

J = 2.8 Hz, 1H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1E), 5.31 (s, 2H), 4.71 (s, 2H), 4.64 (s, 2H), 4.31 (q, J = 7.2 Hz, 2H), 2.33 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H). MS calculated for $C_{23}H_{22}BrN_2O_6S$ ($M+H^+$) 533.0, found 533.0.



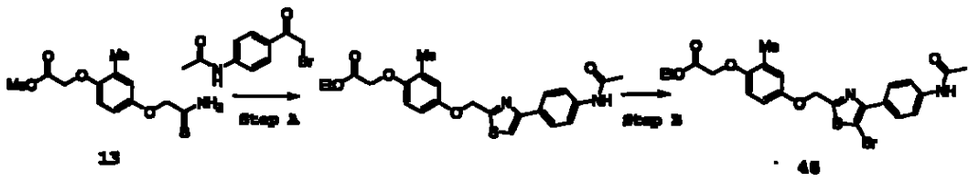
[00144] Intermediate 46: {4-[5-Bromo-4-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid ethyl ester.

[00145] Following the procedure of Intermediate 38, except substituting 6-(2-bromo-acetyl)-3H-benzooxazol-2-one for 2-bromo-4'-methoxyacetophenone in Step A, the title compound is prepared as a yellow solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.07 (s, 1H), 7.82 (s, 1H), 7.78 (dd, J = 1.6, 8.4 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 6.74 (dd, J = 2.8, 8.8 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 5.28 (s, 2H), 4.60 (s, 2H), 4.26 (q, J = 7.2 Hz, 2H), 2.29 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H). MS calculated for $C_{22}H_{20}BrN_2O_6S$ ($M+H^+$) 519.0, found 519.0.



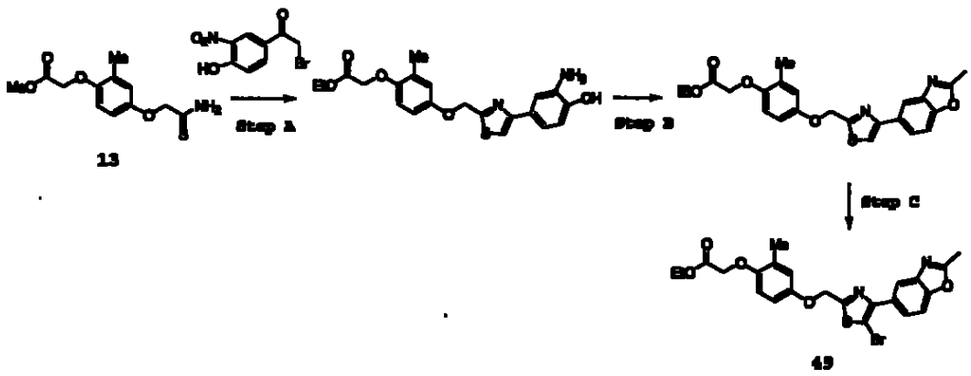
[00146] Intermediate 47: {4-[5-Bromo-4-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid ethyl ester.

[00147] Following the procedure of Intermediate 38, except substituting 2-bromo-1-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-ethanone for 2-bromo-4'-methoxyacetophenone in Step A, the title compound is used without purification in the next step. MS calculated for $C_{23}H_{23}BrNO_6S$ ($M+H^+$) 520.0, found 520.0.



[00148] Intermediate 48: {4-[4-(4-Acetylamino-phenyl)-5-bromo-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid ethyl ester.

[00149] Following the procedure of Intermediate 38, except substituting N-[4-(2-Bromo-acetyl)-phenyl]-acetamide for 2-bromo-4'-methoxyacetophenone in Step A, the title compound is prepared as a yellow solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.91 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 2.8 Hz, 1H), 6.74 (dd, J = 2.8, 8.8 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.59 (s, 2H), 4.26 (q, J = 7.2 Hz, 2H), 2.29 (s, 3H), 2.21 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H). MS calculated for $C_{23}H_{24}BrN_2O_5S$ ($M+H^+$) 519.0, found 519.1.



[00150] Intermediate 49: {4-[5-Bromo-4-(2-methyl-benzooxazol-5-yl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid ethyl ester.

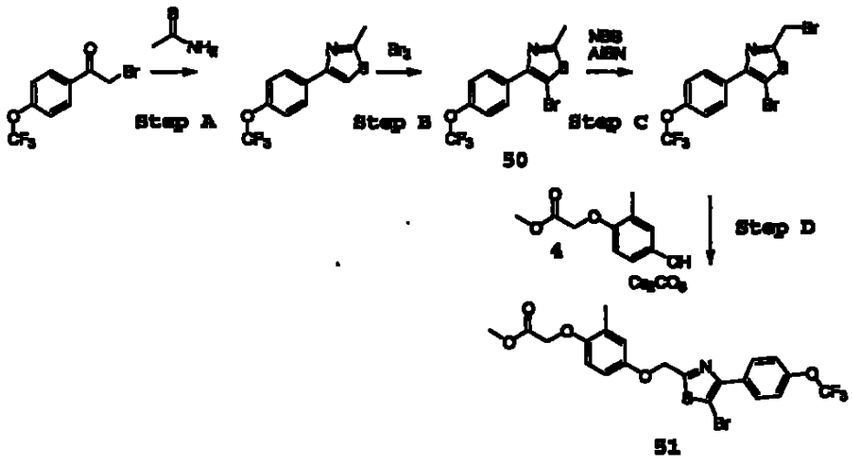
[00151] Step A: Intermediate 13 (2.1 g, 7.79 mmol), and 2-Bromo-1-(4-hydroxy-3-nitro-phenyl)-ethanone (2.0 g, 7.79 mmol) are heated to reflux in EtOH (40 mL) for 4 hours. Tin (II) chloride (4.4 g, 23 mmol) is added and the mixture is heated to reflux for an additional 2 hours. Then the mixture is extracted with ethyl acetate, washed with saturated sodium bicarbonate solution, and filtered through celite. The organic layer is dried ($MgSO_4$), filtered, concentrated and purified on reverse phase HPLC (H_2O/MeCN gradient)

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to afford {4-[4-(3-Amino-4-hydroxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid ethyl ester: MS calculated for $C_{21}H_{23}N_2O_5S$ ($M+H^+$) 415.1, found 415.4.

[00152] Step B: {4-[4-(3-Amino-4-hydroxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid ethyl ester (245 mg, 0.59 mmol) is dissolved in toluene (20 mL). Acetic anhydride (59 μL, 0.62 mmol) is added and the mixture is heated to reflux for 2 hours. Then *p*-toluene sulfonic acid (169 mg, 0.88 mmol) is added and the mixture is heated to reflux for another 2 h using a Dean-Stark trap to remove water. The mixture is diluted with saturated $NaHCO_3$, extracted with EtOAc and washed with brine (10 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to yield {2-methyl-4-[4-(2-methyl-benzooxazol-5-yl)-thiazol-2-ylmethoxy]-phenoxy}-acetic acid ethyl ester as a pale yellow solid, which is used without further purification in Step C.

[00153] Step C: Crude {2-Methyl-4-[4-(2-methyl-benzooxazol-5-yl)-thiazol-2-ylmethoxy]-phenoxy}-acetic acid ethyl ester (208 mg, 0.47 mmol) is dissolved in dichloromethane (10 mL) and pyridine (2 drops), then bromine (27 μL, 0.52 mmol) is added and the mixture is stirred at room temperature for 1 hour. The mixture is diluted with saturated $NaHCO_3$, extracted into dichloromethane and washed with brine (10 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to give Intermediate 49 as a white powder: MS calculated for $C_{23}H_{22}BrN_2O_5S$ ($M+H^+$) 517.0, found 517.0.



[00154] Intermediate 50: {4-[5-Bromo-4-(4-trifluoromethoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester.

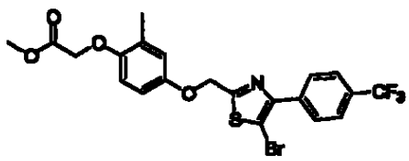
[00155] Step A: 2-Bromo-1-(4-trifluoromethoxy-phenyl)-ethanone (500 mg, 1.76 mmol) and thioacetamide (146 mg, 1.94 mmol) is dissolved in ethanol and heated to reflux for 2 hours. The solvent is removed in vacuo to afford crude 2-methyl-4-(4-trifluoromethoxy-phenyl)-thiazole, which is used without further purification in Step B.

[00156] Step B: 2-Methyl-4-(4-trifluoromethoxy-phenyl)-thiazole (1.76 mmol) is dissolved in dichloromethane (5 mL) containing acetic acid (1 mL). Bromine (0.20 mL, 3.9 mmol) is added and the mixture is heated at 40°C for 2 hours. The mixture is diluted with saturated $NaHCO_3$, extracted into dichloromethane and washed with brine (10 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to give 5-bromo-2-methyl-4-(4-trifluoromethoxy-phenyl)-thiazole 50 as a yellow oil. ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.95 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H), 2.71 (s, 3H). MS calculated for $C_{11}H_8BrF_3NOS$ ($M+H^+$) 337.9, found 337.9.

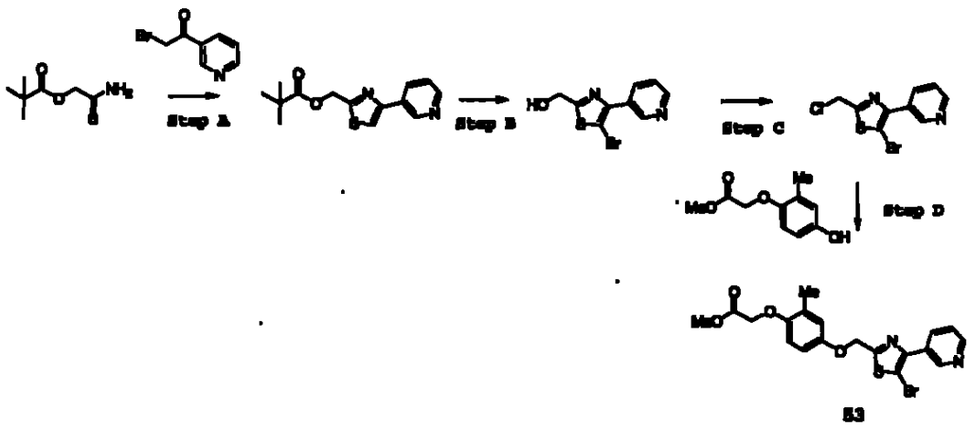
[00157] Step C: 5-Bromo-2-methyl-4-(4-trifluoromethoxy-phenyl)-thiazole 50 (548 mg, 1.62 mmol) and N-bromosuccinimide (317 mg, 1.78 mmol) are dissolved in carbon tetrachloride (40 mL) and heated to 50°C. Azo-bis-isobutyronitrile (20 mg) is predissolved in carbon tetrachloride (10 mL) and added dropwise to the mixture, then the mixture is heated at 50°C for 96 hours. The mixture is diluted with saturated $NaHCO_3$, extracted into dichloromethane and washed with brine (10 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to give crude 5-Bromo-2-bromomethyl-4-(4-trifluoromethoxy-phenyl)-thiazole which is used without further purification in Step D.

[00158] Step D: 5-Bromo-2-bromomethyl-4-(4-trifluoromethoxy-phenyl)-thiazole (1.62 mmol), Intermediate 4 (222 mg, 1.13 mmol), and cesium carbonate (736 mg, 2.26 mmol) are slurried in acetonitrile at room temperature for 1 hour. The mixture is filtered, the solvent evaporated, and the remainder purified by flash chromatography using a mixture of hexane and ethyl acetate (5:1) to afford 51 as a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.97 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 2.8 Hz, 1H), 6.74 (dd, J = 2.8, 8.8 Hz, 1H), 6.66 (d, J = 8.8 Hz, 1H), 5.27 (s, 2H), 4.61 (s, 2H), 3.80 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{21}H_{18}BrF_3NO_5S$ ($M+H^+$) 532.0, found 532.0.

[00159] Intermediate 52: {4-[5-Bromo-4-(4-trifluoromethyl-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester.



[00160] Following the procedure of Intermediate 51, except substituting 2-bromo-1-(4-trifluoromethylphenyl)-ethanone for 2-bromo-1-(4-trifluoromethoxy-phenyl)-ethanone in Step A, the title compound is prepared as a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.08 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 2.8 Hz, 1H), 6.75 (dd, J = 2.8, 8.8 Hz, 1H), 6.66 (d, J = 8.8 Hz, 1H), 5.28 (s, 2H), 4.61 (s, 2H), 3.80 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{21}H_{18}BrF_3NO_4S$ ($M+H^+$) 516.0, found 516.3.



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[00161] Intermediate 53: [4-(5-Bromo-4-pyridin-3-yl-thiazol-2-ylmethoxy)-2-methyl-phenoxy]-acetic acid methyl ester.

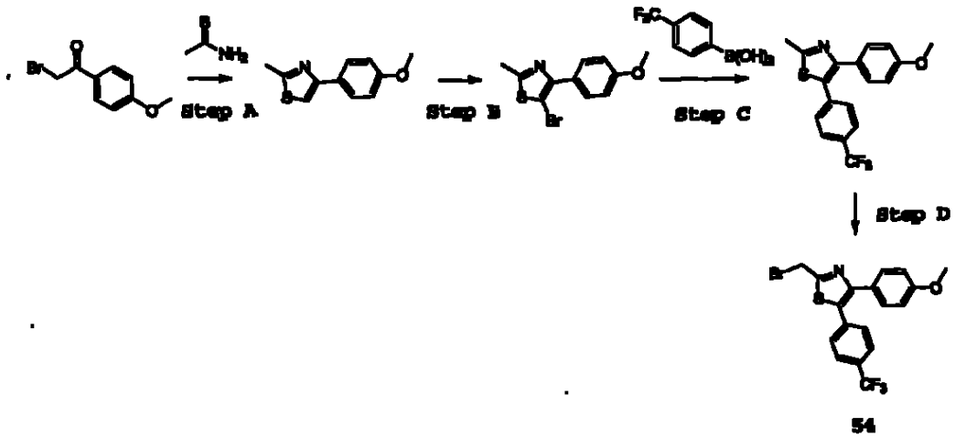
[00162] Step A: 2-Bromo-1-pyridin-3-yl-ethanone (200 mg, 0.71 mmol) and 2-amino-2-thioxoethyl pivalate (131 mg, 0.75 mmol) are dissolved in ethanol and heated to reflux for 1 hour. The mixture is diluted with saturated $NaHCO_3$, extracted into dichloromethane and washed with brine (10 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to give 2,2-dimethyl-propionic acid 4-pyridin-3-yl-thiazol-2-ylmethyl ester, which is used without further purification in Step B.

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[00163] Step B: Crude 2,2-Dimethyl-propionic acid 4-pyridin-3-yl-thiazol-2-ylmethyl ester (0.71 mmol) is dissolved in dichloromethane (10 mL) containing pyridine (2 drops), then bromine (47 μL, 0.93 mmol) is added and the mixture is stirred for 16 h at room temperature. The mixture is diluted with saturated $NaHCO_3$, extracted into dichloromethane and washed with brine (10 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated. The residue is immediately dissolved in tetrahydofuran (5 mL), then lithium hydroxide (1.0 N, 2 mL) is added and the mixture is stirred for 1 hour. The mixture is diluted with saturated $NaHCO_3$, extracted into ethyl acetate (2x) and washed with brine (10 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to give (5-Bromo-4-pyridin-3-yl-thiazol-2-yl)-methanol, which is used without further purification in Step C.

[00164] Step C: Crude (5-bromo-4-pyridin-3-yl-thiazol-2-yl)-methanol (0.71 mmol) is dissolved in dry tetrahydrofuran, then thionyl chloride (0.30 mL, 4.1 mmol) is added and the mixture is stirred for 1 hour. The mixture is diluted with saturated $NaHCO_3$, extracted into dichloromethane and washed with brine (10 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to give 3-(5-Bromo-2-chloromethyl-thiazol-4-yl)-pyridine, which is used without further purification in Step D.

[00165] Step D: Crude 3-(5-bromo-2-chloromethyl-thiazol-4-yl)-pyridine (0.71 mmol), Intermediate 4 (139 mg, 0.71 mmol) and cesium carbonate (464 mg, 1.42 mmol) are suspended in dry acetonitrile and stirred for 2 hours. Then the mixture is filtered, the solvent evaporated, and the remainder purified on reverse phase HPLC (H_2O/MeCN gradient) to afford Intermediate 53 as the major component of a mixture of compounds (by ^1H nmr). This mixture is used directly in the next step without further purification.



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[00166] Intermediate 54: 2-Bromomethyl-4-(4-methoxy-phenyl)-5-(4-trifluoromethyl-phenyl)-thiazole.

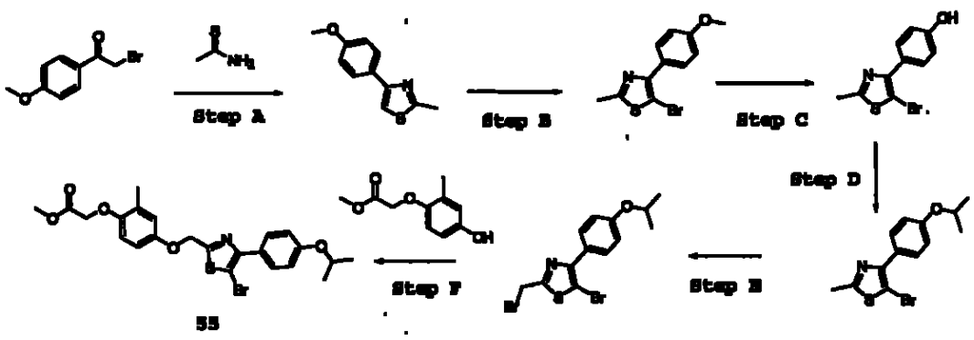
[00167] Step A: 2-Bromo-1-(4-methoxy-phenyl)-ethanone (25.0 g, 109 mmol) and thioacetamide (9.0 g, 120 mmol) are dissolved in ethanol (60 mL) and heated to reflux for 2 hours. The solvent is removed in vacuo to afford crude 4-(4-Methoxy-phenyl)-2-methyl-thiazole, which is used without further purification in Step B.

[00168] Step B: 4-(4-Methoxy-phenyl)-2-methyl-thiazole (109 mmol) is dissolved in dichloromethane (300 mL). Bromine (6.20 mL, 120 mmol) is added and the mixture is heated at 40°C for 3 hours. The mixture is diluted with saturated $NaHCO_3$, extracted into dichloromethane and washed with brine (50 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to give 5-bromo-4-(4-methoxy-phenyl)-2-methyl-thiazole. MS calculated for $C_{11}H_{11}BrNOS$ ($M+H^+$) 284.0, found 284.1.

[00169] Step C: 5-Bromo-4-(4-methoxy-phenyl)-2-methyl-thiazole (4 g, 14.1 mmol), 4-trifluoromethylphenylboronic acid (3.2 g, 16.9 mmol) and sodium carbonate (4.5 g, 42.3 mmol) are dissolved in H_2O (12.6 mL), ethanol (9.3 mL) and 1,2-dimethoxyethane (37.8 mL) and the mixture is degassed by bubbling Argon through the solution for 10 minutes. $Pd(PPh_3)_4$ (490 mg, 0.42 mmol) is added and the mixture is heated at 170°C by microwave in a sealed tube for 10 minutes. The mixture is diluted with water (50 mL), extracted into EtOAc (200 mL) and washed with brine (50 mL). The organic layer is dried ($MgSO_4$), filtered, concentrated and purified on a column of silica gel using a mixture of hexane and ethyl acetate to afford 4-(4-Methoxy-phenyl)-2-methyl-5-(4-trifluoromethyl-

phenyl)-thiazole: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.54 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 2.77 (s, 3H). MS calculated for $C_{18}H_{15}F_3NOS$ ($M+H^+$) 350.1, found 350.0.

[00170] Step D: 4-(4-Methoxy-phenyl)-2-methyl-5-(4-trifluoromethyl-phenyl)-thiazole (3.66 g, 10.5 mmol) and N-bromosuccinimide (2.05 g, 11.5 mmol), are dissolved in carbon tetrachloride (60 mL) and heated to 50°C. Azo-bis-isobutyronitrile (172 mg) is predissolved in carbon tetrachloride (10 mL) and added dropwise to the mixture, then the mixture is heated at 60°C for 16 hours. The mixture is diluted with saturated $NaHCO_3$, extracted into dichloromethane and washed with brine (50 mL). The organic layer is dried ($MgSO_4$), filtered, concentrated and purified by flash chromatography using a mixture of hexane and ethyl acetate to afford Intermediate 54. MS calculated for $C_{18}H_{14}BrF_3NOS$ ($M+H^+$) 428.0, found 428.0.



[00171] Intermediate 55: {4-[5-Bromo-4-(4-isopropoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester.

[00172] Step A: Thioacetamide (9.0 g, 120 mmol) and 2-bromo-1-(4-methoxy-phenyl)-ethanone (25 g, 109 mmol) are dissolved in ethanol (60 mL) and heated to reflux for 2 hours. The ethanol is removed under vacuum and the crude 4-(4-methoxy-phenyl)-2-methyl-thiazole is used in Step B without further purification.

[00173] Step B: 4-(4-Methoxy-phenyl)-2-methyl-thiazole (109 mmol) is dissolved in dichloromethane (300 mL). Bromine (6.2 ml, 120 mmol) is added and the mixture is heated to reflux for 3 hours. The mixture is quenched with saturated $NaHCO_3$(aq), extracted into dichloromethane, washed with saturated $NaHCO_3$(aq), dried over magnesium sulfate, filtered and evaporated to give 5-bromo-4-(4-methoxy-phenyl)-2-methyl-thiazole as a pale

beige powder: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.85 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 2.69 (s, 3H). MS calculated for $C_{11}H_{11}BrNOS$ ($M+H^+$) 284.0, found 284.1.

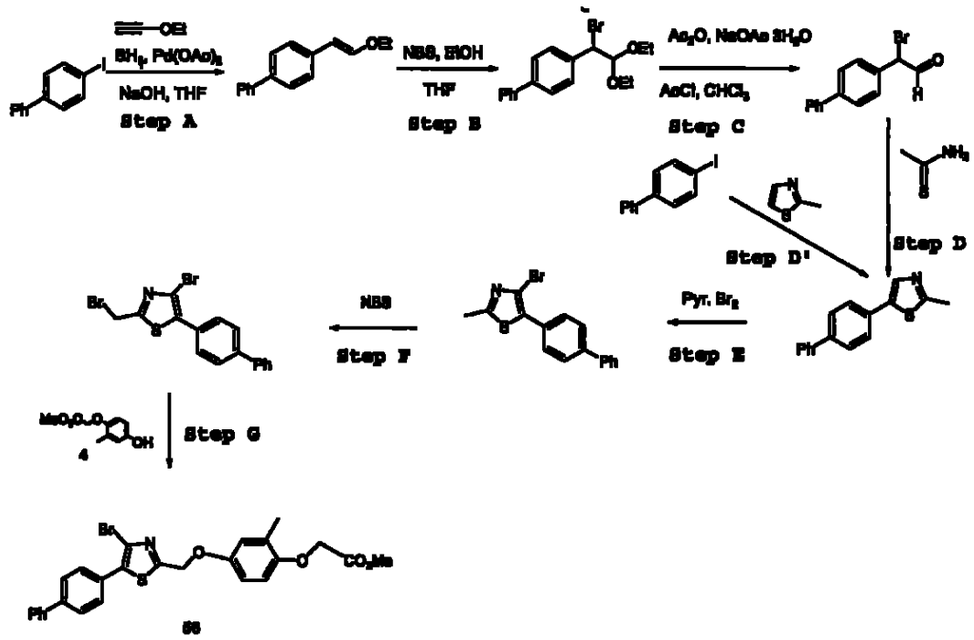
[00174] Step C: 5-Bromo-4-(4-methoxy-phenyl)-2-methyl-thiazole (15.0 g, 52.8 mmol) is dissolved in dichloromethane (200 mL). Boron tribromide (15 mL, 158.3 mmol) is added and the mixture is stirred at room temperature for 1 hour. The mixture is quenched with saturated $NaHCO_3$(aq), extracted into dichloromethane, washed with saturated $NaHCO_3$(aq), dried over magnesium sulfate, filtered and evaporated to yield crude 4-(5-Bromo-2-methyl-thiazol-4-yl)-phenol (15.4 g), which is used without purification in Step D: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.79 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 3.16 (s, 1H), 2.70 (s, 3H). MS calculated for $C_{10}H_9BrNOS$ ($M+H^+$) 270.0, found 270.2.

[00175] Step D: 4-(5-Bromo-2-methyl-thiazol-4-yl)-phenol (38.3 mmol) is dissolved in acetone (100 mL). K_2CO_3 (10.6 g, 76.6 mmol) is added, followed by 2-iodopropane (7.7 mL, 76.6 mmol) and the resulting mixture is heated to reflux for 18 hours. The solvent is evaporated *in vacuo* and the residue is purified by flash chromatography using a mixture of hexane and ethyl acetate to afford 5-bromo-4-(4-isopropoxy-phenyl)-2-methyl-thiazole. MS calculated for $C_{13}H_{15}BrNOS$ ($M+H^+$) 312.0, found 312.0.

[00176] Step E: 5-Bromo-4-(4-isopropoxy-phenyl)-2-methyl-thiazole (3.4 g, 10.89 mmol) is dissolved in carbon tetrachloride (100 mL). N-bromosuccinimide (2.52 g, 14.16 mmol) is added and the mixture is heated to 50°C, then AIBN (179 mg, 1.09 mmol) is added. The mixture is heated to 70°C for 5 hours. Additional bromine (0.5 g) and AIBN (60 mg) is added and stirring is continued at 70°C for another 12 hours. The mixture is then cooled, quenched with water, extracted into dichloromethane, dried over $MgSO_4$, filtered and evaporated to give crude 5-bromo-2-bromomethyl-4-(4-isopropoxy-phenyl)-thiazole, which is used directly in Step F.

[00177] Step F: 5-Bromo-2-bromomethyl-4-(4-isopropoxy-phenyl)-thiazole (10.89 mmol) and Intermediate 4 (2.13g, 10.89 mmol) are dissolved in acetonitrile (100 mL). Cesium carbonate (7.1 g, 21.78 mmol) is added and the mixture is stirred at room temperature for 2 hours. The mixture is filtered, evaporated, and purified by flash chromatography using a mixture of hexane and ethyl acetate to afford Intermediate 55: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.92 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.93 (d, J =

2.8 Hz, 1H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H), 4.67 (s, 2H), 3.86 (s, 3H), 2.36 (s, 3H), 2.12 (s, 1H, 1.44 (s, 6H). MS calculated for $C_{23}H_{25}BrNO_5S$ ($M+H^+$) 506.1, found 506.1.



[00178] Intermediate 56: [4-(5-biphenyl-4-yl-4-bromo-thiazol-2-ylmethoxy)-2-methyl-phenoxy]-acetic acid methyl ester.

[00179] Step A: To a solution of ethyl ethynyl ether (6.0 g, 85.6 mmol) in THF (100mL) at 0°C is added borane-tetrahydrofuran complex (1.0 mol in THF, 28.53 mL, 28.53 mmol). The mixture is warmed to room temperature and stirred for 2 hours. The resulting solution is added to a mixture of 4-iodobiphenyl (20.0 g, 71.33 mmol), triphenylphosphine (598 mg, 2.28 mmol), palladium(II) acetate (128 mg, 0.571 mmol) and sodium hydroxide (8.5 g, 214.0 mmol) in THF (200 mL). The mixture is heated to reflux for 15 h, then cooled, diluted with EtOAc (1000 mL), washed with saturated Na_2CO_3, brine and water. The organic layer is dried ($MgSO_4$), filtered and concentrated to give crude product, which is purified by silica gel chromatography (ether/hexane, gradient) to give 4-(2-ethoxy-vinyl)-biphenyl as a white solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.52-7.19 (m, 9H), 6.97

(d, J=12.8 Hz, 1H), 5.81 (d, J=12.8 Hz, 1H), 3.87 (m, 2H), 1.29 (t, 3H). MS calculated for $C_{16}H_{17}O$ ($M+H^+$) 225.1, found 225.1.

[00180] Step B: 4-(2-Ethoxy-vinyl)-biphenyl (7.60 g, 33.88 mmol) is dissolved in a mixture of EtOH/THF (120/30 mL), then NBS (6.03 g, 33.88 mmol) is added. The mixture is stirred at room temperature for 2 h, then concentrated and purified by silica gel chromatography (EtOAc/hexane, gradient) to give 4-(1-bromo-2,2-diethoxy-ethyl)-biphenyl as a white solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.33-7.63 (m, 9H), 4.98 (d, J=6.4 Hz, 1H), 4.88 (d, J=6.4 Hz, 1H), 3.81 (m, 1H), 3.64 (m, 2H), 3.45 9(m, 1H), 1.29 (t, J=7.2 Hz, 3H), 1.07 (t, J=7.2 Hz, 3H). MS calculated for $C_{18}H_{21}BrO_2$ (M^+) 349.3, found 270.1 $(M-Br)^+$.

[00181] Step C: 4-(1-Bromo-2,2-diethoxy-ethyl)-biphenyl (750 mg, 2.15 mmol) is dissolved in chloroform (3 mL), then Ac_2O (220 mg, 2.15 mmol), $NaOAc{\cdot}3H_2O$ (175.4 mg, 1.29 mmol) and AcCl (118 mg, 1.51 mmol) are added successively and the mixture is stirred at 55°C for 5 hours. The mixture is diluted with CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ and brine. The organic layer is dried ($MgSO_4$), filtered and concentrated to give crude biphenyl-4-yl-bromo-acetaldehyde 50 as a thick oil, which is used in the next step without further purification. MS calculated for $C_{14}H_{11}BrO$ (M^+) 275.2, found 195.1 $(M-Br)^+$.

[00182] Step D: The aldehyde 50 (0.57 g, 2.07 mmol) is dissolved in EtOH (8 mL), then thioacetamide (156 mg, 2.07 mmol) is added and the mixture is stirred at 90°C for 15 hours. The solution is diluted with EtOAc (50 mL) and washed with saturated $NaHCO_3$ (30 mL) and brine (10 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to give crude product, which is purified by silic gel chromatography with EtOAc/hexane (gradient) to give 5-biphenyl-4-yl-2-methyl-thiazole as a white solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.78 (s, 1H), 7.51-7.56 (m, 5H), 4.28-7.41 (m, 4H), 2.69 (s, 3H). MS calculated for $C_{16}H_{14}NS$ ($M+H^+$) 252.1, found 252.0.

[00183] Step D': An alternative one step coupling reaction to prepare 5-biphenyl-4-yl-2-methyl-thiazole.

[00184] 4-Iodobiphenyl (40.0 g, 171.6 mmol) is dissolved in DMF (800 mL), then 2-methylthiazole (8.50 g, 85.5 mmol), triphenylphosphine (3.6 g, 13.73 mmol), cesium carbonate (55.9 g, 171.6 mmol), palladium(II) acetate (3.01 g, 13.7 mmol) are added and the mixture is stirred at 140°C for 24 hours. The reaction mixture is subsequently filtered through Celite 545 and washed with sat. K_2CO_3 and EtOAc. The filtrate is diluted with

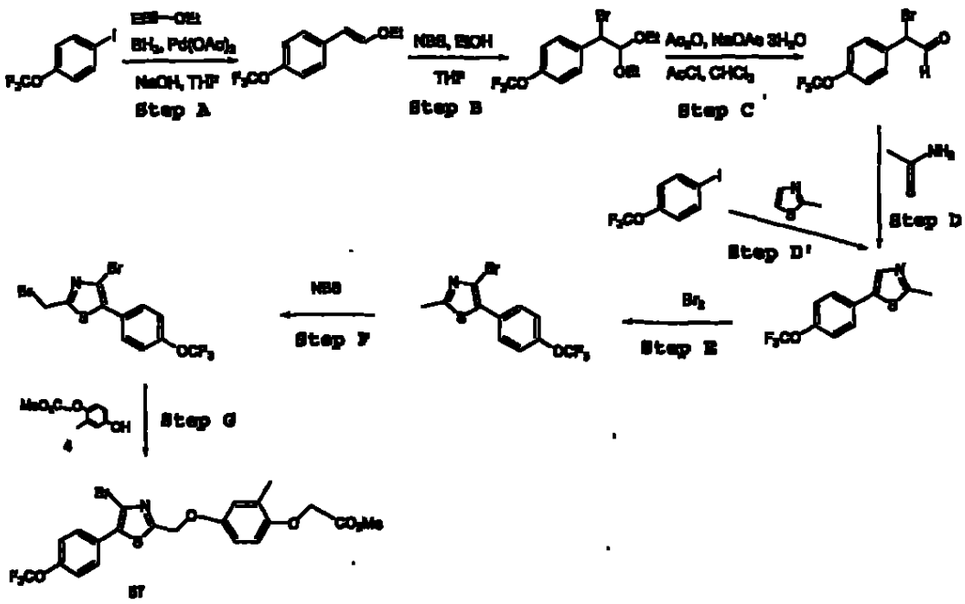
EtOAc and washed with saturated $NaHCO_3$, brine and water. The organic layer is dried ($MgSO_4$), filtered and concentrated to give crude product, which is purified by silic gel chromatography (ether/hexane, gradient) to give 5-biphenyl-4-yl-2-methyl-thiazole.

[00185] Step E: 5-Biphenyl-4-yl-2-methyl-thiazole (1.0 g, 3.98 mmol) is dissolved in chloroform (100 mL), then bromine (245 μL, 4.77 mmol) is added and the mixture is stirred at room temperature for 15 hours. Pyridine (354.1 μL, 4.38 mmol) is added and the solution is stirred for 4 h at room temperature. The solution is diluted with CH_2Cl_2 (100 mL) and washed with saturated $NaHCO_3$ (50 mL) and brine (30 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to give crude product, which is purified by silic gel chromatography with ether/hexane (gradient) to give 5-biphenyl-4-yl-4-bromo-2-methyl-thiazole as a white solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ =7.55-7.64 (m, 5H), 4.29-7.42 (m, 4H), 2.68 (s, 3H). MS calculated for $C_{16}H_{13}BrNS$ ($M+H^+$) 330.0, found 330.0.

[00186] Step F: N-Bromosuccinimide (504 mg, 2.83 mmol) is added to a solution of 5-biphenyl-4-yl-4-bromo-2-methyl-thiazole (850 mg, 2.57 mmol) in carbon tetrachloride (50 mL). The above solution is stirred at 75°C for 18 hours. The solution is diluted with CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ (50 mL) and brine (30 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to give crude product, which is purified by silic gel chromatography with hexane/ether (gradient) to give 5-biphenyl-4-yl-4-bromo-2-bromomethyl-thiazole as a white solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ =7.55-7.66 (m, 5H), 4.30-7.45 (m, 4H), 4.65 (s, 2H). MS calculated for $C_{16}H_{12}Br_2NS$ ($M+H^+$) 410.1, found 410.9.

[00187] Step G: Intermediate 4 (169 mg, 0.86 mmol) and Cs_2CO_3 (308 mg, 0.94 mmol) are added to a solution of 5-biphenyl-4-yl-4-bromo-2-bromomethyl-thiazole (336 mg, 0.82 mmol) in MeCN (30 mL). The mixture is stirred for 3 h at room temperature. After the mixture is filtered, the organic solution is concentrated and purified by silic gel chromatography with hexane/ether (gradient) to give [4-(5-biphenyl-4-yl-4-bromo-thiazol-2-ylmethoxy)-2-methyl-phenoxy]-acetic acid methyl ester (56) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.60-7.72 (m, 5H), 7.35-7.47 (m, 4H), 6.85 (d, J=2.8 Hz, 1H), 6.74(dd, J=2.8 Hz, J=8.8 Hz, 1H), 6.65 (d, J=8.8 Hz, 1H), 5.28 (s, 2H), 4.60 (s, 2H), 3.78 (s, 3H), 2.27 (s, 3H). MS calculated for $C_{26}H_{23}BrNO_4S$ ($M+H^+$) 525.0, found 525.0.

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[00188] Intermediate 57: {4-[4-bromo-5-(4-trifluoromethoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester.

[00189] Step A: Following the procedure of intermediate 56, except substituting 1-iodo-4-trifluoromethoxy-benzene for 4-iodobiphenyl in step A, 1-(2-ethoxy-vinyl)-4-trifluoromethoxy-benzene is prepared as a white solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.38 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 12.8 Hz, 1H), 5.98 (d, J = 13.2 Hz, 1H), 4.08 (q, J = 7.0 Hz, 2H), 1.50 (t, J = 7.0 Hz, 3H). MS calculated for $C_{11}H_{12}F_3O_2$ ($M+H^+$) 233.1, found 233.1.

[00190] Step B: Following the procedure of intermediate 56, except substituting 1-(2-ethoxy-vinyl)-4-trifluoromethoxy-benzene for 4-(2-ethoxy-vinyl)-biphenyl in step B, 1-(1-bromo-2,2-diethoxy-ethyl)-4-trifluoromethoxy-benzene is prepared as a white solid : ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.52 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 4.95 (d, J = 6.4 Hz, 1H), 4.83 (d, J = 6.0 Hz, 1H), 3.84-3.77 (m, 1H), 3.71-3.61 (m, 2H), 3.50-3.43 (m, 1H), 1.29 (t, J = 7.0 Hz, 3H), 1.09 (t, J = 7.0 Hz, 3H). MS calculated for $C_{13}H_{16}BrF_3O_3$ (M^+) 356.0, found 277.0 $(M-Br)^+$.

[00191] Step C: Following the procedure of intermediate 56, except substituting 1-(1-bromo-2,2-diethoxy-ethyl)-4-trifluoromethoxy-benzene for 4-(1-bromo-2,2-diethoxy-ethyl)-biphenyl in step C, bromo-(4-trifluoromethoxy-phenyl)-acetaldehyde is prepared as a

white solid without purification. MS calculated for $C_9H_6BrF_3O_2$ (M^+) 283.1, found 203.1 $(M-Br)^+$.

[00192] Step D: Following the procedure of intermediate 56, except substituting bromo-(4-trifluoromethoxy-phenyl)-acetaldehyde for biphenyl-4-yl-bromo-acetaldehyde in step D, 2-methyl-5-(4-trifluoromethoxy-phenyl)-thiazole is prepared as a white solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.71 (s, 1H), 7.46 (m, 2H), 7.18 (m, 2H), 2.68 (s, 3H). MS calculated for $C_{11}H_9F_3NOS$ ($M+H^+$) 260.0, found 260.0.

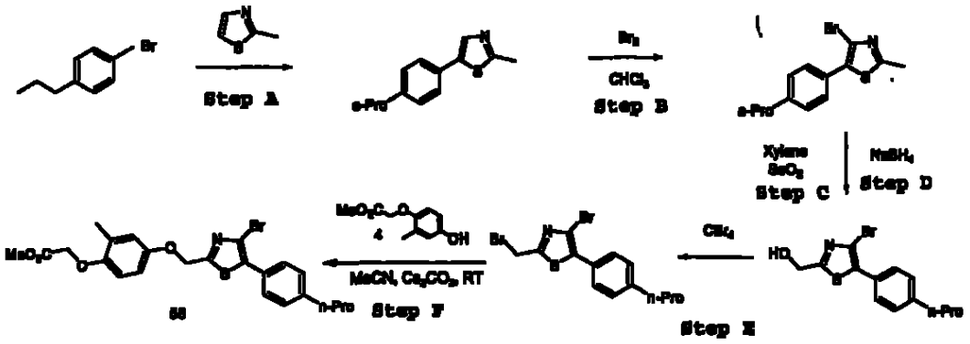
[00193] Step D': An alternative one step coupling reaction to prepare 2-methyl-5-(4-trifluoromethoxy-phenyl)-thiazole.

[00194] Following the procedure of intermediate 56, except substituting 1-iodo-4-trifluoromethoxy-benzene for 4-iodobiphenyl in step D'. 2-methyl-5-(4-trifluoromethoxy-phenyl)-thiazole is obtained.

[00195] Step E: Following the procedure of intermediate 56, except substituting D-methyl-5-(4-trifluoromethoxy-phenyl)-thiazole for 5-biphenyl-4-yl-2-methyl-thiazole and without adding pyridine in step E, 4-bromo-2-methyl-5-(4-trifluoromethoxy-phenyl)-thiazole is prepared as a colorless oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.56 (m, 2H), 7.21 (m, 2H), 2.67 (s, 3H). MS calculated for $C_{11}H_8BrF_3NOS$ ($M+H^+$) 337.9, found 337.9.

[00196] Step F: Following the procedure of intermediate 56, except substituting 4-bromo-2-methyl-5-(4-trifluoromethoxy-phenyl)-thiazole for 5-biphenyl-4-yl-4-bromo-2-methyl-thiazole in step F, 4-bromo-2-bromomethyl-5-(4-trifluoromethoxy-phenyl)-thiazole is prepared as a yellow oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ =7.59 (m, 2H), 7.23 (m, 2H), 4.63 (s, 2H). MS calculated for $C_{11}H_7Br_2F_3NOS$ $(M+2H)^+$ 416.9, found 416.8.

[00197] Step G: Following the procedure of intermediate 56, except substituting 4-bromo-2-bromomethyl-5-(4-trifluoromethoxy-phenyl)-thiazole for 5-bromo-2-bromomethyl-4-(4-methoxy-phenyl)-oxazole in step G, {4-[4-bromo-5-(4-trifluoromethoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester (57) is prepared as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.66 (m, 2H), 7.28 (m, 2H), 6.85 (d, J=2.8 Hz, 1H), 6.74(dd, J=3.2 Hz, J=8.8 Hz, 1H), 6.67 (d, J=8.8 Hz, 1H), 5.28 (s, 2H), 4.61 (s, 2H), 3.80 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{21}H_{18}BrF_3NO_5S$ ($M+H^+$) 532.0, found 532.0.



[00198] Intermediate 58: {4-[4-bromo-5-(4-propyl-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester.

[00199] Step A: 1-Bromo-4-propyl-benzene (50.0 g, 251.1 mmol) is dissolved in DMF (800 mL), then 2-methylthiazole (12.45 g, 125.6 mmol), triphenylphosphine (3.2 g, 12.56 mmol), cesium carbonate (81.2 g, 251.14 mmol), palladium(II) acetate (4.5 g, 20.09) are added and the mixture is stirred at 140°C for 24 hours. The reaction mixture is filtered through Celite 545, washed with sat. K_2CO_3 and EtOAc. The solution is diluted with EtOAc and washed with saturated $NaHCO_3$, brine and water. The organic layer is dried ($MgSO_4$), filtered and concentrated to give crude product, which is purified by silic gel chromatography with ether/hexane (gradient) to give 2-methyl-5-(4-propyl-phenyl)-thiazole as an oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ =7.83 (s, 1H), 7.49 (d, J=8.4 Hz, 2H), 7.26 (d, J=8.4 Hz, 2H), 2.80 (s, 3H), 2.66 (t, J=7.6 Hz, 2H), 1.71 (m, 2H), 1.02 (t, J= 7.2 Hz, 3H). MS calculated for $C_{13}H_{16}NS$ ($M+H^+$) 218.1, found 218.1.

[00200] Step B: 2-Methyl-5-(4-propyl-phenyl)-thiazole (2.0 g, 9.20 mmol) is dissolved in chloroform (25 mL), then bromine (0.52 mL, 10.12 mmol) is added and the mixture is stirred at room temperature for 2 hours. The solution is diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine (100 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to give crude product, which is purified by silic gel chromatography with ether/hexane (gradient) to give 4-bromo-2-methyl-5-(4-propyl-phenyl)-thiazole as an oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.52 (d, J=8.0 Hz, 2H), 7.23 (d, J=8.0 Hz, 2H), 2.71 (s, 3H), 2.62 (t, J= 7.4 Hz, 2H), 1.67 (m, 2H), 0.99 (t, J= 7.4 Hz, 3H). MS calculated for $C_{13}H_{14}BrNS$ ($M+H^+$) 296.0, found 296.0.

[00201] Step C and D: Selenium dioxide (4.5 g, 40.51 mmol) is added to a solution of 4-bromo-2-methyl-5-(4-propyl-phenyl)-thiazole (6.0 g, 20.25 mmol) in xylene (150 mL). The mixture is stirred at 150°C for 30 hours. After 15 h an additional 1.2 g of SeO_2 is added to the reaction mixture. Then the solution is diluted with EtOAc and washed with saturated Na_2CO_3 and brine. The organic layer is dried ($MgSO_4$), filtered and concentrated to give 4-bromo-5-(4-propyl-phenyl)-thiazole-2-carbaldehyde as a crude product, which is used for next reaction.

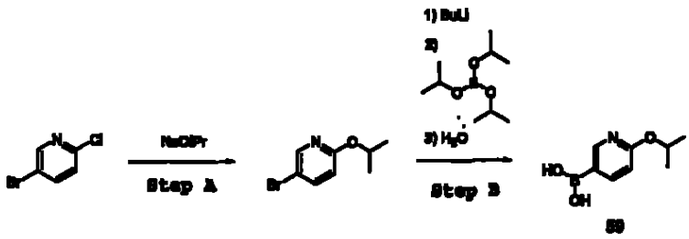
[00202] $NaBH_4$ (604 mg, 16.0 mmol) is added to a solution of crude 4-bromo-5-(4-propyl-phenyl)-thiazole-2-carbaldehyde in MeOH (100 mL) and the mixture is stirred for 10 min. The solution is concentrated, diluted with EtOAc, washed with saturated Na_2CO_3 and brine. The organic layer is dried ($MgSO_4$), filtered and concentrated to give a crude mixture, which is purified by silic gel chromatography with hexane/EtOAc (gradient) to give [4-bromo-5-(4-propyl-phenyl)-thiazol-2-yl]-methanol as a white solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.37 (d, J=8.0 Hz, 2H), 7.09 (d, J=8.0 Hz, 2H), 4.79 (s, 2H), 2.47 (t, J= 8.0 Hz, 2H), 2.17 (s, bro. 1H), 1.51 (m, 2H), 0.81 (t, J= 7.4 Hz, 3H). MS calculated for $C_{13}H_{15}BrNOS$ ($M+H^+$) 312.0, found 312.0.

Step E: $P(Ph)_3$ (2.22 g, 8.46 mmol) is added to the solution of [4-bromo-5-(4-propyl-phenyl)-thiazol-2-yl]-methanol in CH_2Cl_2 (40 mL) and stirred for 10 min at 0°C. Then CBr_4 (2.81 g, 8.46 mmol) dissolved in CH_2Cl_2 (20 mL) is added to the reaction mixture. The mixture is warmed to room temperature and stirred overnight. The solution is concentrated to give a crude mixture, which is purified by silic gel chromatography with hexane/ether (gradient) to give 4-bromo-2-bromomethyl-5-(4-propyl-phenyl)-thiazole as a colorless oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.37 (d, J=8.0 Hz, 2H), 7.08 (d, J=8.0 Hz, 2H), 4.52 (s, 2H), 2.46 (t, J= 8.0 Hz, 2H), 1.49 (m, 2H), 0.80 (t, J= 8.0 Hz, 3H). MS calculated for $C_{13}H_{14}Br_2NO$ ($M+H^+$) 373.9, found 373.9.

[00203] Step F: A mixture of 4-bromo-2-bromomethyl-5-(4-propyl-phenyl)-thiazole (910 mg, 2.43 mmol), (4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester (4) (524 mg, 2.67 mmol) and Cs_2CO_3 (911 mg, 2.79 mmol) in MeCN (15 mL) is stirred at room temperature for 4 hours. The mixture is filtered, then concentrated to give crude product, which is purified by silic gel chromatography with EtOAc/hexane (gradient) to give {4-[4-bromo-5-(4-propyl-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl

ester (58) as a white solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.54 (d, J=8.4 Hz, 2H), 7.24 (d, J=8.4 Hz, 2H), 6.85 (d, J=2.8 Hz, 1H), 6.74 (m, 1H), 6.65 (m, 1H), 5.27 (s, 2H), 4.61 (s, 2H), 3.80 (s, 3H), 2.65 (t, J=8.0 Hz, 3H), 2.29 (s, 3H), 1.67 (m, 2H), 0.97 (t, J= 8.0 Hz, 3H). MS calculated for $C_{23}H_{25}BrNO_4S$ ($M+H^+$) 490.1, found 490.1.

[00204] Intermediate 59: 2-Isopropoxy-5-pyridineboronic acid.



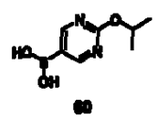
[00205] Step A: NaH (5.2 g, 130 mmol) is suspended in isopropanol (50 mL). The mixture is stirred for 30 min at 60°C. After the gas evolution ceased, 2-chloro-5-bromopyridine (10.0 g, 52 mmol) dissolved in isopropanol (100 mL) is added and the mixture is heated to reflux for 24 hours. The solvent is removed in vacuo, and the remainder is taken up in H_2O and extracted with EtOAc. The organic layer is separated and dried over $MgSO_4$, filtered and concentrated to afford 2-isopropoxy-5-bromo-pyridine as a light brown oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.10 (d, J = 2.5 Hz, 1H), 7.54 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.52 (d, J = 8.8 Hz, 1H), 5.17 (m, 1H), 1.26 (d, J = 6.2 Hz, 6H). MS calculated for $C_8H_{11}BrNO$ ($M+H^+$) 216.0, found 215.9.

[00206] Step B: 2-Isopropoxy-5-bromo-pyridine (0.65 g, 3 mmol) is dissolved in dry ether (10 mL) and cooled to -78°C under argon. Butyl lithium (1.6 M in hexane, 2.81 mL, 4.5 mmol) is added dropwise and the mixture is stirred at -78°C for 2 hours. Then triisopropyl borate (1.72 mL, 7.5 mmol) is added quickly and the mixture is stirred for another 2 h at -78°C. The mixture is allowed to warm to room temperature, quenched with H_2O (20 mL) and stirred overnight at room temperature. The ether is removed in vacuo, the aqueous layer is adjusted to pH 10 (with 2 M NaOH) and washed with ether. Then the aqueous layer is adjusted to pH 3 (with 48% aq. HBr) and extracted with EtOAc three times. The organic layer is separated and dried over $MgSO_4$, filtered and concentrated to afford 2-

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isopropoxy-5-pyridineboronic acid 59 as a colorless glass: MS calculated for $C_8H_{13}BNO_3$ ($M+H^+$) 182.1, found 182.1.

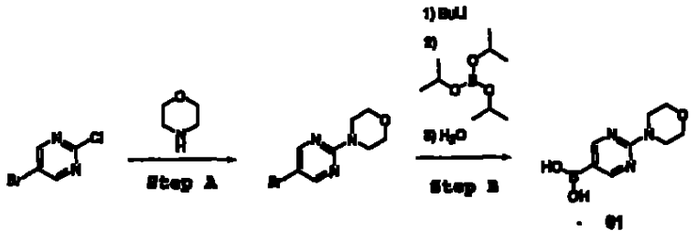
[00207] Intermediate 60. 2-Isopropoxy-5-pyrimidineboronic acid.



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[00208] Following the procedure of Intermediate 59, except substituting 2-chloro-5-bromopyrimidine for 2-chloro-5-bromopyridine in Step A, the title compound is prepared as a white solid: MS calculated for $C_7H_{12}BN_2O_3$ ($M+H^+$) 183.1, found 183.1.

[00209] Intermediate 61: 2-Morpholino-5-pyrimidineboronic acid.



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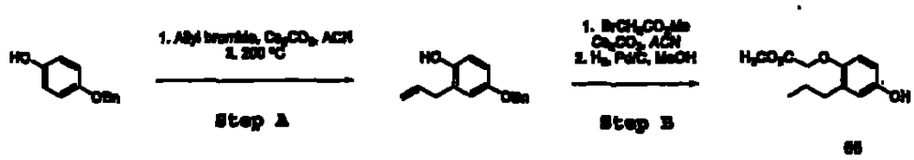
[00210] Step A: Morpholine (5.4 mL, 62.4 mmol) is dissolved in MeCN (250 mL). K_2CO_3 (8.6 g, 62.4 mmol) is added and the mixture is stirred at room temperature for 1 hour. Then 2-chloro-5-bromo-pyrimidine (10.0 g, 52 mmol) is added and the mixture is heated to reflux for 5 hours. The solvent is partially removed in vacuo and the remainder is taken up in H_2O and extracted with EtOAc. The organic layer is separated and dried over $MgSO_4$, filtered and concentrated to afford 2-isopropoxy-5-bromo-pyrimidine as a light brown oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.24 (s, 2H), 3.69 (m, 8H). MS calculated for $C_8H_{11}BrN_3O$ ($M+H^+$) 244.0, found 243.9.

[00211] Step B: Following the procedure of Intermediate 59 Step B, except substituting 2-isopropoxy-5-bromo-pyrimidine for 2-isopropoxy-5-bromo-pyridine, the title

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compound is prepared as a white solid: MS calculated for $C_9H_{13}BN_3O_3$ ($M+H^+$) 210.1, found 210.1.

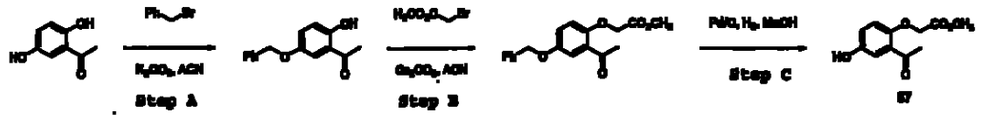
[00212] Intermediate 66: (4-Hydroxy-2-propyl-phenoxy)-acetic acid methyl ester.



[00213] Step A: 4-Benzyloxy-phenol (5.0 g, 25 mmol) is dissolved in acetonitrile (70 mL). Powdered cesium carbonate (10.50 g, 32.2 mmol) is added with stirring, followed by allyl bromide (2.25 mL, 26.6 mmol). The mixture is vigorously stirred overnight. Filtration through a plug of Celite 545, washing the solids with more acetonitrile, drying the solution over Na_2SO_4 and concentration yielded the allyl ether as a white solid. The ether (1.83g, 7.62 mmol) is heated under nitrogen in a sealed vial to 200°C. After about 4.5 h, the mixture is cooled to yield a light-brown oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.42 (m, 2H), 7.38 (m, 2H), 7.32 (m, 1H), 6.78 (s, 1H), 6.75 (s, 2H), 6.00 (dddd, 1H), 5.18 (m, 1H), 5.14 (m, 1H), 5.00 (s, 1H), 4.62 (br. s, 1H), 3.38 (d, J = 6.0 Hz, 2H).

[00214] Step B: 2-Allyl-4-benzyloxy-phenol (0.30 g, 1.25 mmol) is dissolved in dry acetonitrile (3 mL). Powdered cesium carbonate (0.68 g, 2.1 mmol) is added with vigorous stirring, followed by methyl bromoacetate (0.15 mL, 1.6 mmol). The suspension is stirred at room temperature overnight. Dilution with 1 N aqueous HCl, extraction with ethyl acetate, drying over $MgSO_4$ and concentration yields an oil. A portion of this product (0.075 g, 0.24 mmol) is dissolved in methanol (5 mL) and ethyl acetate (30 mL). Palladium black on carbon (5%, 10 mg, 2 mol%) is added. The mixture is degassed and stirred vigorously under 1 atm of hydrogen overnight. Filtration and concentration yields the phenol 66: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.66 (d, J = 2.8 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 6.57 (dd, J = 2.8, 8.4 Hz, 1H), 4.58 (s, 2H), 4.48 (s, 1H), 3.79 (s, 3H), 2.60 (t, J = 7.6 Hz, 2H), 1.61 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H). MS calculated for $C_{12}H_{17}O_4$ ($M+H^+$) 225.1, found 225.1.

[00215] Intermediate 67: (2-Acetyl-4-hydroxy-phenoxy)-acetic acid methyl ester.

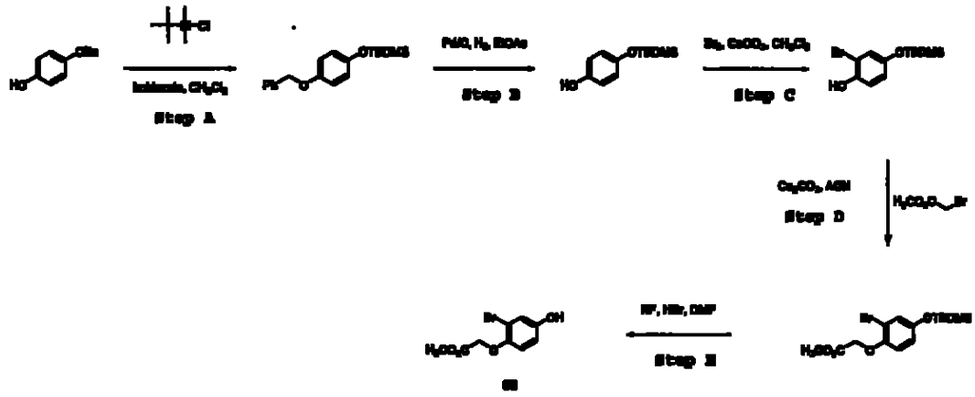


[00216] Step A: 1-(2,5-Dihydroxy-phenyl)-ethanone (5.0 g, 33 mmol) is dissolved in 30 mL acetonitrile. Powdered potassium carbonate (7.10 g, 51.4 mmol) is added with stirring, followed by dropwise addition of benzyl bromide (4.0 mL, 33.4 mmol). The resulting suspension is stirred at room temperature under nitrogen overnight, then filtered through a plug of Celite 545 and concentrated to yield a light-brown oil. Slicagel chromatography (hexane to 30% ethyl acetate in hexane) yielded the pure benzyl ether as a near-colorless oil: ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 11.50 (s, 1H), 7.35 (m, 6H), 7.25 (dd, J = 3.1, 9.0 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 5.10 (s, 2H), 2.63 (s, 3H); MS calculated for $C_{15}H_{15}O_3$ ($M+H^+$) 243.2, found 243.1.

[00217] Step B: 1-(5-Benzyloxy-2-hydroxy-phenyl)-ethanone (7.27 g, 29.4 mmol) is dissolved in acetonitrile (100 mL). Powdered cesium carbonate (14.36 g, 44.1 mmol) is added with stirring, followed by methyl bromoacetate (3.5 mL, 38 mmol). The resulting suspension is stirred at 80°C under nitrogen for 3h. It is filtered through a plug of Celite 545 and concentrated to yield (2-acetyl-4-benzyloxy-phenoxy)-acetic acid methyl ester as a near-colorless oil that slowly solidifies: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.36 (m, 6H), 7.25 (dd, J = 3.2, 9.0 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 5.04 (s, 2H), 4.69 (s, 2H), 3.80 (s, 3H), 2.71 (s, 3H); MS calculated for $C_{18}H_{19}O_5$ ($M+H^+$) 315.2, found 315.1.

[00218] Step C: (2-acetyl-4-benzyloxy-phenoxy)-acetic acid methyl ester (9.17 g, 29.2 mmol) is dissolved in methanol (50 mL) and ethyl acetate (50 mL). Palladium black on carbon (5%, 1.53 g, 2.4 mol%) is added. The mixture is degassed and stirred vigorously under 1 atm of hydrogen overnight. Filtration and concentration yields the phenol 67: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.32 (d, J = 3.2 Hz, 1H), 6.97 (dd, J = 3.2, 8.9 Hz, 1H), 6.74 (d, J = 8.9 Hz, 1H), 4.68 (s, 2H), 3.81 (s, 3H), 2.71 (s, 3H). MS calculated for $C_{11}H_{13}O_5$ ($M+H^+$) 225.1, found 225.1.

[00219] Intermediate 68: (2-Bromo-4-hydroxy-phenoxy)-acetic acid methyl ester.



[00220] Step A: 4-Benzyloxy-phenol (5.01 g, 25.0 mmol) is suspended in 65 mL dichloromethane. Solid imidazole (4.05 g, 26.9 mmol) is added and the stirring is continued until the mixture turned homogenous. *tert*-Butyl-chloro-dimethyl-silane (2.49 g, 36.6 mmol) is added in portions, and a white precipitate started to form. The suspension is stirred at room temperature overnight. It is then filtered and concentrated to yield (4-Benzyloxy-phenoxy)-*tert*-butyl-dimethyl-silane as a white powder: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.43 (m, 2H), 7.38 (m, 2H), 7.32 (m, 1H), 6.85 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 9.0 Hz, 2H), 5.00 (s, 2H), 0.98 (s, 9H), 0.17 (s, 6H); MS calculated for $C_{19}H_{27}O_2Si$ ($M+H^+$) 315.2, found 315.1.

[00221] Step B: (4-Benzyloxy-phenoxy)-*tert*-butyl-dimethyl-silane (7.73 g, 24.6 mmol) is dissolved in methanol (10 mL) and ethyl acetate (80 mL). Palladium black on charcoal (5%, 0.6 g, 1 mol%) is added and the mixture is vigorously stirred under hydrogen at room temperature for 48 hours. Filtration and concentration yielded the 4-(tert-butyl-dimethyl-silanyloxy)-phenol: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.70 (s, 4H), 3.90 (br. s, 1H), 0.97 (s, 9H), 0.16 (s, 6H). MS calculated for $C_{12}H_{21}O_2Si$ ($M+H^+$) 225.1, found 225.0.

[00222] Step C: 4-(tert-Butyl-dimethyl-silanyloxy)-phenol (4.66 g, 20.8 mmol) is dissolved in dichloromethane (100 mL). Powdered calcium carbonate (4.61 g, 46.7 mmol) is suspended into the solution and the mixture is stirred vigorously at 0°C. Bromine (1.10 mL, 21.4 mmol) is added dropwise with vigorous stirring. After 1.5 h at 0°C, the mixture is warmed up to room temperature, treated with anhydrous $MgSO_4$, filtered and concentrated to yield 2-bromo-4-(tert-butyl-dimethyl-silanyloxy)-phenol as an oil that slowly solidified: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.96 (d, J= 2.8 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.71 (dd, J =

2.8, 8.8 Hz, 1H), 5.14 (br. s, 1H), 0.97 (s, 9H), 0.17 (s, 6H). MS calculated for $C_{12}H_{20}BrO_2Si$ ($M+H^+$) 303.1, found 303.0.

[00223] Step D: 2-Bromo-4-(tert-butyl-dimethyl-silanyloxy)-phenol (5.19 g, 17 mmol) is dissolved in acetonitrile (100 mL). Cesium carbonate (14.10 g, 43 mmol) is added, followed by methyl bromoacetate (1.60 mL, 17.4 mmol); the mixture is stirred overnight at room temperature. Filtration and concentration yields [2-bromo-4-(tert-butyl-dimethyl-silanyloxy)-phenoxy]-acetic acid methyl ester as an oil: MS calculated for $C_{15}H_{24}BrO_4Si$ ($M+H^+$) 375.2, found 375.1.

[00224] Step E: [2-bromo-4-(tert-butyl-dimethyl-silanyloxy)-phenoxy]-acetic acid methyl ester (6.19 g, 16.5 mmol) is dissolved in dimethylformamide (80 mL). Powdered potassium fluoride (2.10 g, 36 mmol) is added, followed by aqueous concentrated hydrogen bromide solution (48%, 1.0 mL, 5.9 mmol). The mixture is stirred overnight at room temperature. Dilution with water, extraction with dichloromethane (4 x 100 mL), followed by drying over Na_2SO_4; filtration and concentration yields an oil; drying overnight at low pressure yields (2-Bromo-4-hydroxy-phenoxy)-acetic acid methyl ester 68 as a solid: MS calculated for $C_9H_{10}BrO_4$ ($M+H^+$) 261.0, found 260.9.

[00225] Intermediate 69: (4-Hydroxy-3-methyl-phenoxy)-acetic acid methyl ester.



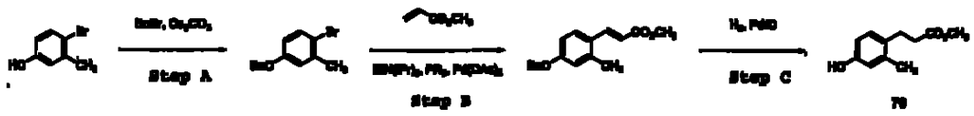
[00226] Step A: (4-Hydroxy-phenoxy)-acetic acid (14.96 g, 89 mmol) is suspended in methanol (35 mL). Concentrated sulfuric acid (0.25 mL, cat.) is added and the mixture is refluxed overnight. Cooling to room temperature and concentrating to dryness yields (4-hydroxy-phenoxy)-acetic acid methyl ester as a solid (16 g, quantitative). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.78 (m, 4H), 4.81 (s, 1H), 4.58 (s, 2H), 3.80 (s, 3H).

[00227] Step B: (4-Hydroxy-phenoxy)-acetic acid methyl ester (4.25 g, 23.3 mmol) is dissolved in trifluoroacetic acid (25 mL). Hexamethylene-tetramine (5.11 g, 36.5 mmol) is added. The resulting homogenous mixture is stirred at 70°C for 3 hours. Cooling

to room temperature and concentrating to dryness yields a paste. Silicagel chromatography (10% to 60% ethyl acetate in hexanes) yields (3-formyl-4-hydroxy-phenoxy)-acetic acid methyl ester: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 10.70 (s, 1H), 9.84 (s, 1H), 7.20 (dd, J = 3.2, 9.2 Hz, 1H), 7.03 (d, J = 3.2 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 4.64 (s, 2H), 3.82 (s, 3H); MS calculated for $C_9H_{10}BrO_4$ ($M+H^+$) 261.0, found 260.9.

[00228] Step C: (3-Formyl-4-hydroxy-phenoxy)-acetic acid methyl ester (0.26 g, 1.24 mmol) is dissolved in methanol (15 mL). Palladium black on charcoal (10 mg, 0.4 mol%) is added and the mixture is stirred overnight under hydrogen (1 atm). Reversed-phase HPLC purification yields (4-hydroxy-3-methyl-phenoxy)-acetic acid methyl ester 69 as an oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.8 (m, 3H), 4.93 (s, 1H), 4.69 (s, 2H), 3.93 (s, 3H), 2.35 (s, 3H).

[00229] Intermediate 70: 3-(4-Hydroxy-2-methyl-phenyl)-propionic acid methyl ester



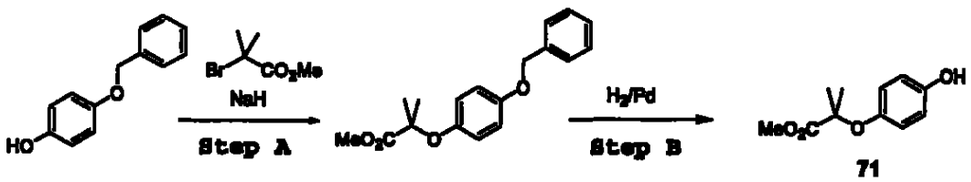
[00230] Step A: 4-Bromo-3-methyl-phenol (13.71 g, 73.3 mmol) is dissolved in acetonitrile (100 mL). Cesium carbonate (30.46 g, 93.5 mmol) and benzyl bromide (10 mL, 84.2 mmol) are added and the mixture is stirred overnight at room temperature. Filtration and concentration to dryness yields 4-benzyloxy-1-bromo-2-methyl-benzene as a solid (23.5 g, quantitative). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.4 (m, 6H), 6.87 (d, J = 3.2 Hz, 1H), 6.68 (dd, J = 3.2, 8.8 Hz, 1H), 5.03 (s, 2H), 2.36 (s, 3H); no mass spectrum could be obtained.

[00231] Step B: 4-Benzyloxy-1-bromo-2-methyl-benzene (9.29 g, 33.5 mmol) is dissolved in propionitrile (80 mL). Ethyldiisopropylamine (12 mL, 72.6 mmol) and methyl acrylate (12 mL, 133 mmol) are added. The mixture is degassed with argon, and tri-ortho-tolylphosphine (4.11 g, 20.1 mmol) and palladium acetate (1.53 g, 6.8 mmol) is added. The mixture is heated to 100°C overnight. Cooling to room temperature and concentrating to dryness yields a paste. The residue is taken up in ethyl acetate and washed with water and brine, dried over $MgSO_4$ and concentrated. Silicagel chromatography (0% to 60% ethyl

acetate in hexanes) yields 3-(4-benzyloxy-2-methyl-phenyl)-acrylic acid methyl ester: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, J = 15.6 Hz, 1H), 7.52 (d, J = 9.6 Hz, 1H), 7.4 (m, 5H), 7.68 (m, 2H), 6.26 (d, J = 15.6 Hz, 1H), 5.08 (s, 2H), 3.80 (s, 3H), 2.42 (s, 3H); MS calculated for $C_{18}H_{19}O_3$ ($M+H^+$) 283.1, found 283.1.

[00232] Step C: 3-(4-Benzyloxy-2-methyl-phenyl)-acrylic acid methyl ester (4.83 g, 17 mmol) is dissolved in methanol (85 mL) and ethyl acetate (25 mL). Palladium black on charcoal (5%, 0.51 g, 1.4 mol%) is added and the mixture is stirred under hydrogen for 36 hours. Concentration yields 3-(4-Hydroxy-2-methyl-phenyl)-propionic acid methyl ester 70 as an oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.98 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 2.8 Hz, 1H), 6.60 (dd, J = 2.8, 8.4 Hz, 1H), 3.68 (s, 3H), 2.87 (t, J = 7.6 Hz, 2H), 2.55 (t, J = 7.6 Hz, 2H), 2.26 (s, 3H).

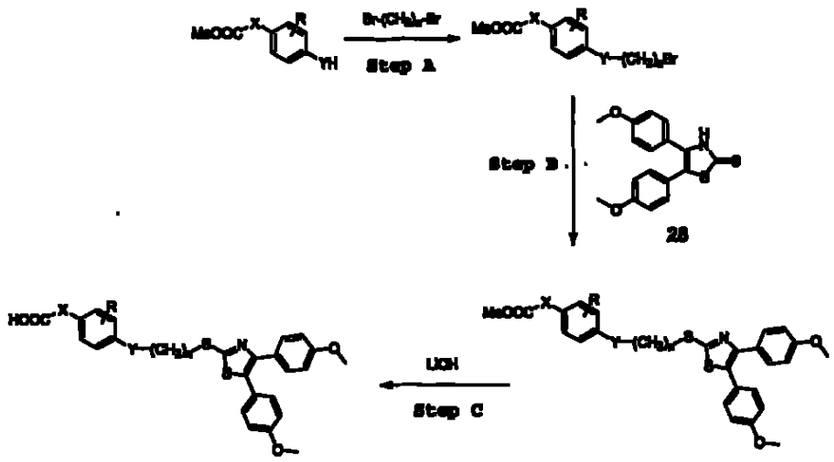
[00233] Intermediate 71: 2-(4-Hydroxy-phenoxy)-2-methyl-propionic acid methyl ester.



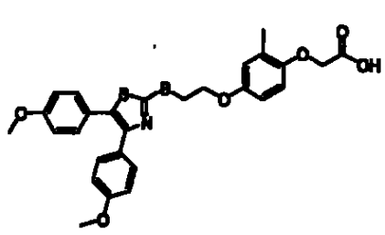
71

[00234] Step A: 4-(Benzyloxy)phenol (5.0 g, 25 mmol) is dissolved in DMF (40 mL). To the solution is added NaH (60% dispersion, 1.1 g, 27.5 mmol) in portions while the temperature is kept at room temperature. After stirring the suspension for 30 min at room temperature methyl-□-bromoisobutyrate (9.05 g, 50 mmol) is added dropwise. The mixture is stirred at 50°C for 3 h, then concentrated. The remainder is diluted with water (200 mL) and extracted with EtOAc (3x150 mL). The organic layer is separated and dried over $MgSO_4$, filtered and concentrated. The crude product is purified by flash chromatography (silica, Hex/EtOAc gradient) to afford 2-(4-benzyloxy-phenoxy)-2-methyl-propionic acid methyl ester as a clear oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.44-7.33 (m, 5H), 6.85 (m, 4H), 5.01 (s, 2H), 3.78 (s, 3H), 1.55 (s, 6H). MS calculated for $C_{18}H_{21}O_4$ ($M+H^+$) 301.1, found 301.4.

[00235] Step B: 2-(4-benzyloxy-phenoxy)-2-methyl-propionic acid methyl ester (0.5 g, 1.7 mmol) is dissolved in EtOH (15 mL). After addition of a catalytic amount of Palladium(0) on charcoal the mixture is subjected to 1 atm hydrogen and stirred for 5 h at room temperature. Then the mixture is filtered through celite, the solvent is removed and the remainder dried on high vacuum to yield 2-(4-hydroxy-phenoxy)-2-methyl-propionic acid methyl ester 71 as a brownish oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 6.76 (d, J = 9.0 Hz, 2H), 6.69 (d, J = 9.0 Hz, 2H), 3.78 (s, 3H), 1.53 (s, 6H). MS calculated for $C_{11}H_{15}O_4$ ($M+H^+$) 211.1, found 211.3.



[00236] Example A1. (4-{2-[4,5-Bis-(4-methoxy-phenyl)-thiazol-2-ylsulfanyl]-ethoxy}-2-methyl-phenoxy)-acetic acid.

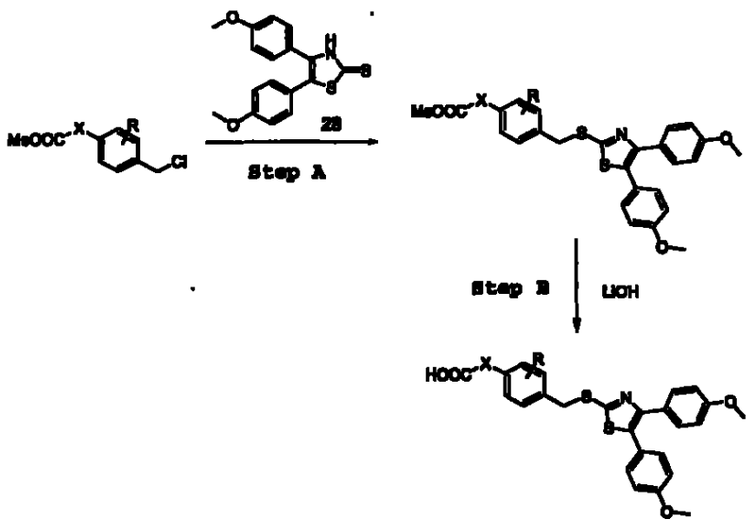


[00237] Step A: Intermediate 4 (0.5 g, 2.8 mmol), 1,2-dibromoethane (2.4 mL, 27.7 mmol) and Cs_2CO_3 (4.5 g, 13.9 mmol) are suspended in dry acetone. The mixture is heated to reflux overnight. The reaction mixture is cooled to room temperature, filtered and the

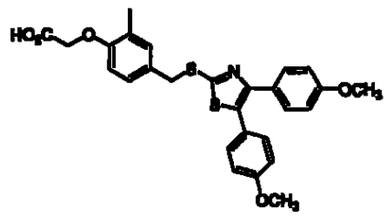
solvent is removed in vacuo. The remainder is purified by chromatography (silica, DCM/MeOH gradient) to afford [4-(2-Bromo-ethoxy)-2-methyl-phenoxy]-acetic acid methyl ester as a white solid: MS calculated for $C_{11}H_{14}BrO_4$ ($M+H^+$) 303.0, found 303.2.

[00238] Step B: [4-(2-Bromo-ethoxy)-2-methyl-phenoxy]-acetic acid methyl ester (91 mg, 0.30 mmol) is added dropwise to a solution of NaOMe (23 mg, 0.33 mmol) and intermediate 28 in EtOH (5 mL). After stirring at room temperature for 24h the solvent is removed to afford crude (4-{2-[4,5-Bis-(4-methoxy-phenyl)-thiazol-2-ylsulfanyl]-ethoxy}-2-methyl-phenoxy)-acetic acid methyl ester.

[00239] Step C: The crude (4-{2-[4,5-Bis-(4-methoxy-phenyl)-thiazol-2-ylsulfanyl]-ethoxy}-2-methyl-phenoxy)-acetic acid methyl ester is dissolved in THF (3 mL), a solution of 1 M LiOH in H_2O (0.6 mL) is added and the mixture is stirred overnight at room temperature. The mixture is acidified with 1 M HCl, EtOAc (10 mL) is added and the organic layer washed with H_2O (3x5 mL). The organic layer is dried ($MgSO_4$), filtered, concentrated and purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound A1 as a white solid: ^{1}H-NMR (400MHz, CD_3OD) δ = 7.34 (d, J = 8.9 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.73-6.64 (m, 3H), 4.56 (s, 2H), 4.29 (t, J = 6.4 Hz), 3.79 (s, 3H), 3.78 (s, 3H), 3.57 (t, J = 6.4 Hz, 2H), 2.18 (s, 3H). MS calculated for $C_{28}H_{28}NO_6S_2$ ($M+H^+$) 538.1, found 538.4.

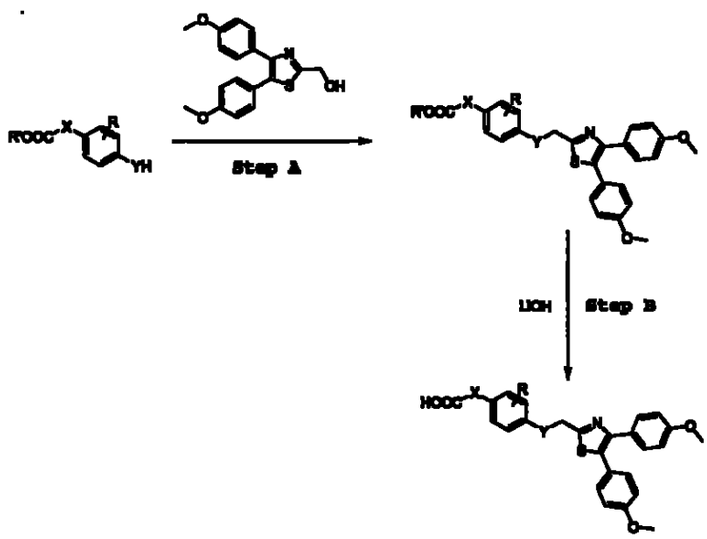


[00240] Example B1. {4-[4,5-Bis-(4-methoxy-phenyl)-thiazol-2-ylsulfanylmethyl]-2-methyl-phenoxy}-acetic acid.

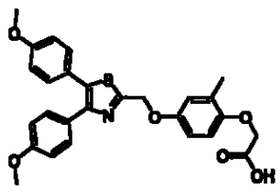


[00241] Step A: NaOEt (23 mg, 0.33 mmol) is dissolved in absolute EtOH (5 mL). 4,5-Bis-(4-methoxy-phenyl)-3H-thiazole-2-thione 28 (73 mg, 0.30 mmol) and (4-chloromethyl-2-methyl-phenoxy)-acetic acid ethyl ester (intermediate 11) (100 mg, 0.30 mmol) is added successively. The reaction is stirred for 12 h at room temperature to afford the crude product.

[00242] Step B: 2 N LiOH (3.0 mL) is added into the reaction mixture from step A and it is stirred for 3 h at 60°C. The reaction is cooled to room temperature and acidified to PH 2-3 by 2 N HCl. Then it is extracted with CH_2Cl_2. The organic layer is separated, dried ($MgSO_4$) and concentrated. The product is recrystallized in ethyl acetate and hexane to afford the title compound B1 as a slightly yellow solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.44 (d, J = 8.8 Hz, 2H), 7.24-7.18 (m, 4H), 6.86-6.80 (m, 4H), 6.66 (d, J = 8.4 Hz, 1H), 5.30 (s, 2H), 4.67 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 2,27 (s, 3H). MS calculated for $C_{27}H_{26}NO_5S_2$ ($M+H^+$) 508.12, found 508.10.



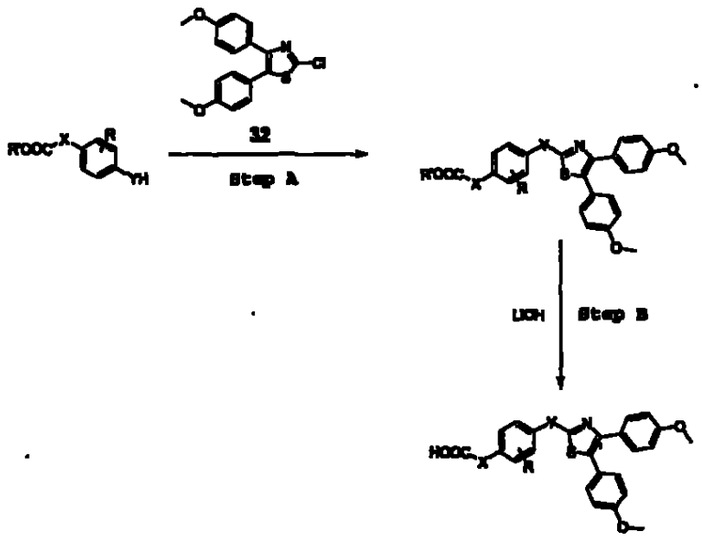
[00243] Example C1. {4-[4,5-Bis-(4-methoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.



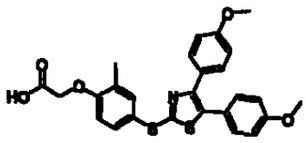
[00244] Step A: Intermediate 30 (25 mg, 0.08 mmol), intermediate 4 (18 mg, 0.09 mmol) and triphenylphosphine (30 mg, 0.11 mmol) are dissolved in dry DCM (1 mL) and cooled to 0°C. After the slow addition of diethyl azodicarboxylate (24 □L, 0.15 mmol) the solution is stirred at room temperature overnight. The solvent is removed to afford crude {4-[4,5-Bis-(4-methoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester which is used without further purification in step B.

[00245] Step B: The crude {4-[4,5-Bis-(4-methoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester is dissolved in THF (1 mL), a solution of 1 M LiOH in H_2O (0.2 mL) is added and the mixture is stirred overnight at room temperature. The mixture is acidified with 1 M HCl (0.25 mL), EtOAc (10 mL) is added and the organic layer washed with H_2O (3x5 mL). The organic layer is dried ($MgSO_4$), filtered, concentrated

and purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound C1 as a colorless glass: ^{1}H-NMR (400MHz, CD_3OD) δ = 7.36 (d, J = 8.9 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 6.91-6.75 (m, 7H), 5.30 (s, 2H), 4.62 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 2.25 (s, 3H). MS calculated for $C_{27}H_{25}NO_6S$ ($M+H^+$) 492.1, found 492.4.

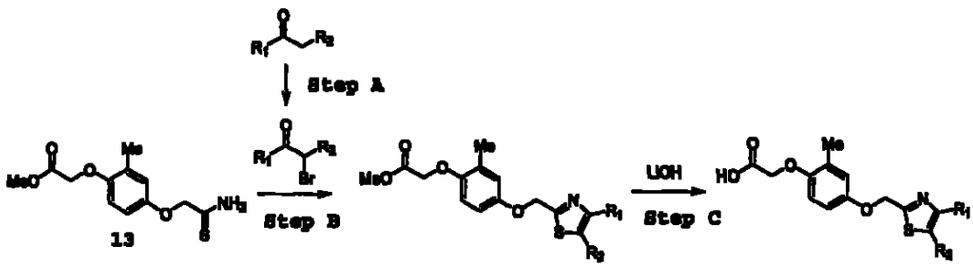


[00246] Example D1: {4-[4,5-Bis-(4-methoxy-phenyl)-thiazol-2-ylsulfanyl]-2-methyl-phenoxy}-acetic acid.

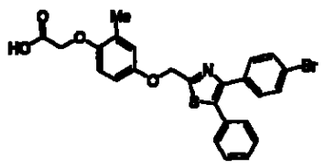


[00247] Step A: Intermediate 10 (28 mg, 0.131 mmol), intermediate 32 (40 mg, 0.131 mmol), and NaOEt (18 mg, 0.262 mmol) are dissolved in EtOH (1 mL) and heated to reflux for 6 hours. The mixture is acidified with aqueous 1 N HCl (1 mL) and extracted with EtOAc (2 x 4 mL). The organic layer is dried ($MgSO_4$), filtered, and concentrated to provide crude {4-[4,5-Bis-(4-methoxy-phenyl)-thiazol-2-ylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester.

[00248] Step B: {4-[4,5-Bis-(4-methoxy-phenyl)-thiazol-2-ylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester is then dissolved in THF (1 mL) and treated with 1 N LiOH (200 μL) and stirred at room temperature for 2 hours. The mixture is acidified with aqueous HCl (1 N, 300 μL), extracted with EtOAc (2 x 4 mL), dried ($MgSO_4$), filtered, concentrated, and purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound D1 as a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.45 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.33 (d, 8.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 6.70 (m, 5H), 4.65 (s, 2H), 3.71 (s, 3H), 3.69 (s, 3H), 2.22 (s, 3H). MS calculated for $C_{26}H_{24}NO_5S_2$ ($M+H^+$) 494.1, found 494.4.



[00249] Example E1. {4-[4-(4-Bromo-phenyl)-5-phenyl-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.

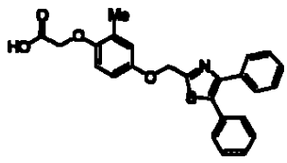


[00250] Step A: 1-(4-Bromo-phenyl)-2-phenyl-ethanone (0.24 g, 0.87 mmol) is dissolved in glacial acetic acid (3 mL). Bromine (50 □L, 0.97 mmol) is added and the mixture is stirred for 30 minutes at room temperature. Dilution with water (40 mL) yields a white solid. Filtration, washing with water, and drying yields 2-bromo-1-(4-bromo-phenyl)-2-phenyl-ethanone as a white powder: 0.30 g. ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.85 (d, J = 6.8 Hz, 2H), 7.59 (d, J= 6.8 Hz, 2H) 7.50 (dd, J = 2.0, 8.4 Hz, 2H), 7.36 (m, 3H), 6.30 (s, 1H). MS calculated for $C_{11}H_{11}Br_2O$ ($M+H^+$) 354.9, found 355.1.

[00251] Step B: (2-Methyl-4-thiocarbamoylmethoxy-phenoxy)-acetic acid methyl ester (Intermediate 13) (46 mg, 0.17 mmol) and 2-bromo-1-(4-bromo-phenyl)-2-phenyl-ethanone are suspended in ethanol and heated to 75°C for 18 hours. Cooling to room temperature, concentration, and purification by chromatography (silica, 10% to 40% ethyl acetate in hexane gradient) affords {4-[4-(4-bromo-phenyl)-5-phenyl-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid ethyl ester as a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.28 (m, 4H), 7.21 (m, 5H), 6.77 (d, J = 2.8 Hz, 1H), 6.66 (dd, J = 2,8, 8.8 Hz, 1H), 6.55 (d, J = 8.8 Hz, 1H), 5.23 (s, 2H), 4.47 (s, 2H), 4.13 (q, J = 7.2 Hz, 2H), 2.17 (s, 3H), 1.17 (q, J = 7.2 Hz, 3H).

[00252] Step C: {4-[4-(4-Bromo-phenyl)-5-phenyl-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid ethyl ester (55.2 mg, 0.11 mmol) is dissolved in dioxane. Lithium hydroxide monohydrate (13.0 mg, 0.31 mmol) dissolved in water (0.5 mL) is added. After 40 minutes the mixture became homogenous. Concentration to a syrup, dilution with ethyl acetate, washing with 10% citric acid solution, water, saturated aqueous ammonium chloride, and brine, drying over Na_2SO_4 and concentration yields the title compound {4-[4-(4-bromo-phenyl)-5-phenyl-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid E1 as a white solid: Reversed phase HPLC purification yields the pure acid: ^{1}H-NMR (400MHz, DMSO-d_6) δ = 12.87 (s, 1H), 7.53 (m, 2H), 7.41 – 7.34 (m, 7H), 6.95 (d, J = 2.9 Hz, 1H), 6.85 (dd, J = 2,9, 8.9 Hz, 1H), 6.77 (d, J = 8.9 Hz, 1H), 5.39 (s, 2H), 4.61 (s, 2H), 2.18 (s, 3H). MS calculated for $C_{25}H_{21}BrNO_4S$ ($M+H^+$) 512.0, found 512.3.

[00253] Example E2: [4-(4,5-Diphenyl-thiazol-2-ylmethoxy)-2-methyl-phenoxy]-acetic acid.

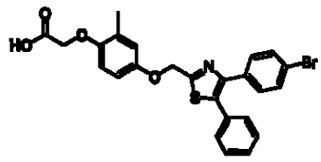


[00254] Step A: For the title compound, the intermediate bromide is purchased and used directly in Step B.

[00255] Step B: Intermediate 13 (20 mg, 0.076 mmol), and desyl bromide (23 mg, 0.084 mmol) are dissolved in EtOH (2 mL) and heated to reflux for 2 hours. The solvent is removed by evaporation to afford crude [4-(4,5-diphenyl-thiazol-2-ylmethoxy)-2-methyl-phenoxy]-acetic acid methyl ester which is used without further purification in Step C.

[00256] Step C: The crude [4-(4,5-diphenyl-thiazol-2-ylmethoxy)-2-methyl-phenoxy]-acetic acid methyl ester is dissolved in THF (1 mL), a solution of 1 M LiOH in H_2O (0.2 mL) is added and the mixture is stirred for 1 h at room temperature. The mixture is acidified with 1 M HCl (0.25 mL), EtOAc (10 mL) is added and the organic layer washed with brine (5 mL). The organic layer is dried ($MgSO_4$), filtered, concentrated and purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound E2 as a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.40 (m, 2H), 7.23 (m, 8H), 6.82 (d, J = 2.9 Hz, 1H), 6.69 (dd, J = 3.0, 8.9 Hz, 1H), 6.61 (d, J = 8.9 Hz, 1H), 5.26 (s, 2H), 4.53 (s, 2H), 2.20 (s, 3H). MS calculated for $C_{25}H_{22}NO_4S$ ($M+H^+$) 432.1, found 432.4.

[00257] Example E3: {4-[4-(4-Bromo-phenyl)-5-phenyl-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.

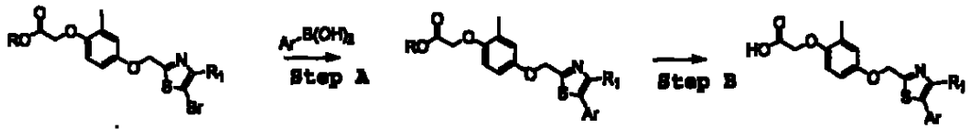


[00258] Step A: 1-(4-Bromo-phenyl)-2-phenyl-ethanone (275 mg, 1.00 mmol) is dissolved in DCM (2 mL). Pyridinium tribromide (352 mg, 1.1 mmol) is added and the mixture is stirred at room temperature for 2 hours. Then the mixture is diluted with DCM (1 mL) and washed with H_2O (2 mL). The organic layer is concentrated in vacuo to afford crude 1-(4-bromo-phenyl)-2-bromo-2-phenyl-ethanone as a yellow solid, and is used in Step B without further purification.

[00259] Step B: A mixture of 1-(4-bromo-phenyl)-2-bromo-2-phenyl-ethanone (43 mg, 0.12 mmol) and (2-Methyl-4-thiocarbamoylmethoxy-phenoxy)-acetic acid methyl ester

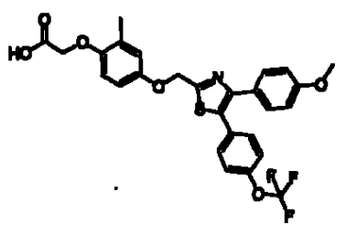
(Intermediate 13, 32 mg, 0.12 mmol) in EtOH (1 mL) is heated at 180°C for 5 min in a microwave apperatus. The resulting solution is used directly in the next step.

[00260] Step C: THF (2 mL) and 1 N LiOH (0.5 mL) are added to the solution derived from step B. The mixture is stirred overnight at room temperature, then acidified with 1 N HCl (1 mL). The reaction mixture is extracted with EtOAc (3 mL), the organic layer is separated and concentrated in vacuo. The remainder is taken up in DMSO (1 mL) and purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound E59 as a white solid: ^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.54-7.31 (m, 9H), 6.96 (d, J = 3.0 Hz, 1H), 6.87 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.40 (s, 2H), 4.63 (s, 2H), 2.19 (s, 3H). MS calculated for $C_{25}H_{21}BrNO_4S$ ($M+H^+$) 510.0, found 510.3.



38 R1 = 4-methoxyphenyl
40 R1 = 2-naphthyl
41 R1 = 4-biphenyl
42 R1 = 4-morpholinophenyl
43 R1 = benzo[3,4]-dioxol
44 R1 = 3-fluoro,4-methoxyphenyl
45 R1 = benzo[3,4]-oxazin-3-one
46 R1 = benzo[3,4]-oxazol-2-one
47 R1 = benzo[3,4]-dioxine
48 R1 = 4-acetylamino-phenyl
49 R1 = 2'-methylbenzo[3,4]-oxazole
51 R1 = 4-(trifluoromethoxy)phenyl
52 R1 = 4-trifluoromethylphenyl
53 R1 = 3-pyridyl

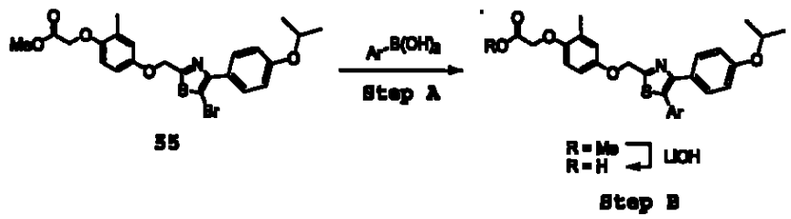
[00261] Example F1: *{4-[4-(4-Methoxy-phenyl)-5-(4-trifluoromethoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.*



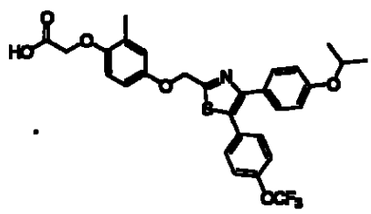
[00262] Step A: Intermediate 38 (21 mg, 0.042 mmol), 4-trifluoromethoxyphenyl-boronic acid (10.3 mg, 0.050 mmol) and sodium carbonate (13 mg, 0.126 mmol) are dissolved in water (120 µL), ethanol (90 µL) and 1,2-dimethoxyethane (360 µL) and the

mixture is degassed with bubbling Argon for 2 minutes. $Pd(PPh_3)_4$ (10 mol%) is added and the mixture is subjected to microwave (180°C) for 5 min in a sealed tube. The mixture is diluted with saturated water (5 mL), extracted into EtOAc (10 mL) and washed with brine (5 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to give crude {4-[4-(4-Methoxy-phenyl)-5-(4-trifluoromethoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester, which is used without further purification in Step B.

[00263] Step B: The {4-[4-(4-Methoxy-phenyl)-5-(4-trifluoromethoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester is dissolved in THF (1 mL), a solution of 1 M LiOH in H_2O (0.2 mL) is added and the mixture is stirred for 1 h at room temperature. The mixture is acidified with 1 M HCl (0.25 mL), EtOAc (10 mL) is added and the organic layer washed with brine (5 mL). The organic layer is dried ($MgSO_4$), filtered, concentrated and purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound F1 as a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.32 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.1 Hz, 2H), 6.82 (d, J = 2.9 Hz, 1H), 6.76 (d, J = 8.8 Hz, 2H), 6.71 (dd, J = 2.8, 8.8 Hz, 1H), 6.63 (d, J = 8.9 Hz, 1H), 5.25 (s, 2H), 4.56 (s, 2H), 3.75 (s, 3H), 2.21 (s, 3H). MS calculated for $C_{27}H_{23}F_3NO_6S$ ($M+H^+$) 546.1, found 546.3.



[00264] Example G1: {4-[4-(4-Isopropoxy-phenyl)-5-(4-trifluoromethoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.

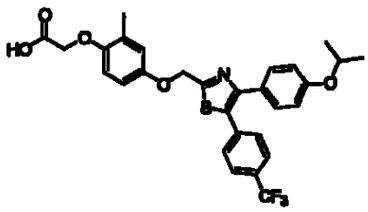


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[00265] Step A: Intermediate 55 (21 mg, 0.041 mmol), 4-trifluoromethoxyphenyl-boronic acid (10.3 mg, 0.050 mmol) and sodium carbonate (13 mg, 0.126 mmol) are dissolved in water (120 μL), ethanol (90 μL) and 1,2-dimethoxyethane (360 μL). The mixture is degassed with argon for 2 min. $Pd(PPh_3)_4$ (10 mol%) is added and the mixture is subjected to microwave (170°C) for 5 min. The mixture is diluted with water (5 mL), extracted into EtOAc (10 mL) and washed with brine (5 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to give crude {4-[4-(4-Isopropoxy-phenyl)-5-(4-trifluoromethoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester, which is used without further purification in Step B.

[00266] Step B: The crude {4-[4-(4-Isopropoxy-phenyl)-5-(4-trifluoromethoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester is dissolved in THF (1 mL), a solution of 1 M LiOH in H_2O (0.2 mL) is added and the mixture is stirred for 1 h at room temperature. The mixture is acidified with 1 M HCl (0.25 mL), EtOAc (10 mL) is added and the organic layer washed with brine (5 mL). The organic layer is dried ($MgSO_4$), filtered, concentrated and purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound G1 as a white solid: ^{1}H-NMR (400MHz, MeOD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.77 (d, J = 8.4 Hz, 2H), 6.75 (dd, J = 2.8, 8.8 Hz, 1H), 6.68 (d, J = 8.8 Hz, 1H), 5.25 (s, 2H), 4.53 (m, 3H), 2.17 (s, 3H), 1.23 (s, 3H), 1.21 (s, 3H). MS calculated for $C_{29}H_{27}F_3NO_6S$ ($M+H^+$) 574.1, found 574.1.

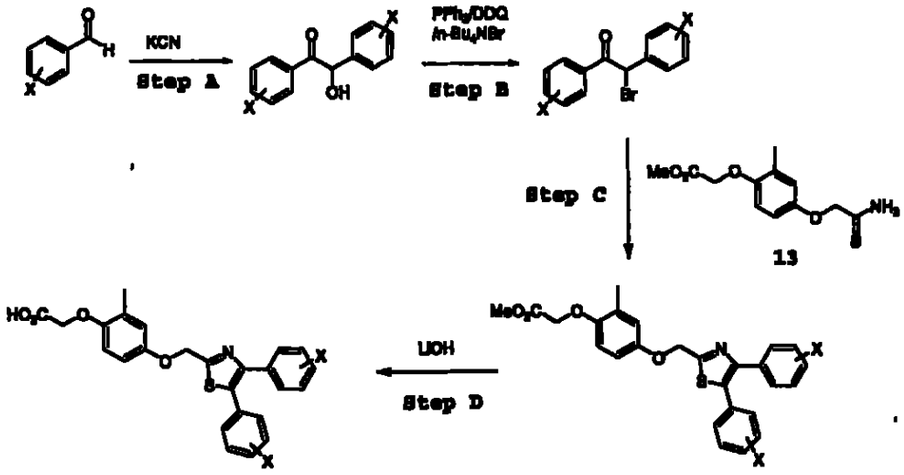
[00267] Example G2: {4-[4-(4-Isopropoxy-phenyl)-5-(4-trifluoromethyl-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.



[00268] Step A: Intermediate 55 (21 mg, 0.04 mmol), 4-trifluoromethylphenyl-boronic acid (9.5 mg, 0.05 mmol) and sodium carbonate (13 mg, 0.13 mmol) are dissolved

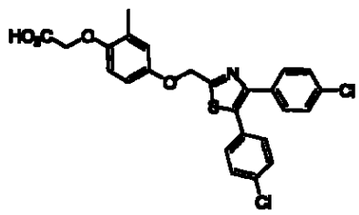
in water (120 μL), ethanol (90 μL) and 1,2-dimethoxyethane (360 μL). The mixture is degassed with Argon for 2 minutes. $Pd(PPh_3)_4$ (10 mol%) is added and the mixture is subjected to microwave (170°C) for 5 min. The mixture is diluted with water (5 mL), extracted into EtOAc (10 mL) and washed with brine (5 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated to give crude {4-[4-(4-Isopropoxy-phenyl)-5-(4-trifluoromethyl-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester, which is used without further purification in Step B.

[00269] Step B: The crude {4-[4-(4-Isopropoxy-phenyl)-5-(4-trifluoromethyl-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester is dissolved in THF (1 mL), a solution of 1 M LiOH in H_2O (0.2 mL) is added and the mixture is stirred for 1 h at room temperature. The mixture is acidified with 1 M HCl (0.25 mL), EtOAc (10 mL) is added and the organic layer washed with brine (5 mL). The organic layer is dried ($MgSO_4$), filtered, concentrated and purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound G2 is prepared as a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.70 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 2.8 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.90 (dd, J = 2.8, 8.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 5.41 (s, 2H), 4.67 (m, 3H), 2.32 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H). MS calculated for $C_{29}H_{27}F_3NO_5S$ ($M+H^+$) 558.1, found 558.2.



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[00270] Example H1. {4-[4,5-Bis-(4-chloro-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.



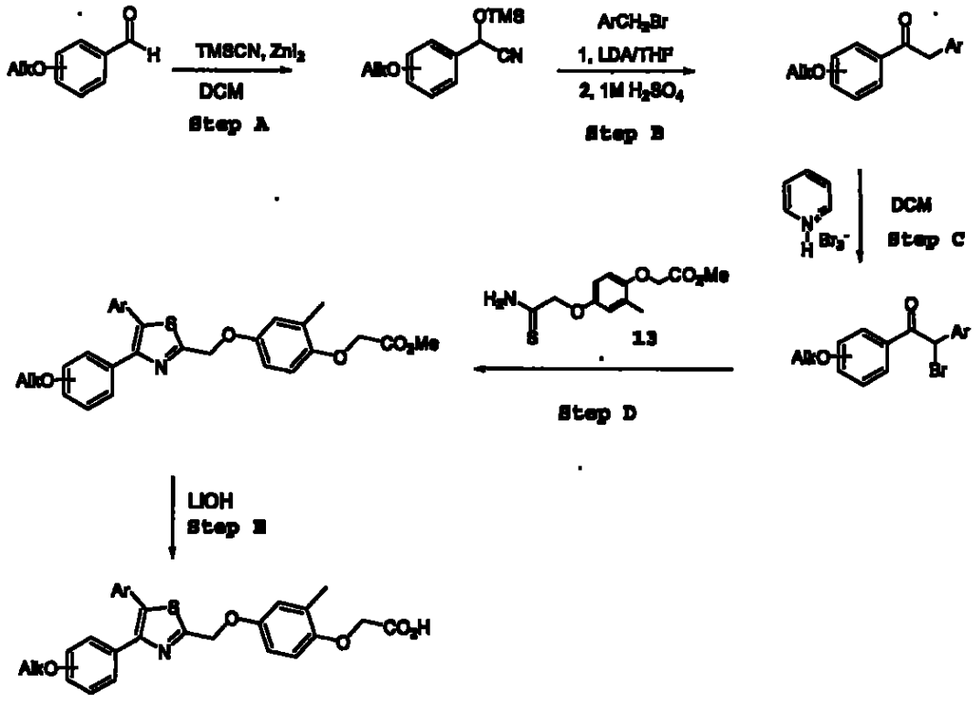
[00271] Step A: To a solution of 4-chloro-benzaldehyde (0.57 g, 2.04 mmol) in EtOH (8 mL) is added KCN (18.0 mg, 0.27 mmol) dissolved in water (4 mL). The mixture is heated to reflux for 7 hours, then cooled to room temperature and extracted with ethyl acetate (100 mL). The organic layer is dried ($MgSO_4$), filtered, and concentrated. The residue is purified by flash chromatography with 40%ether/hexane to give a solid: NMR (400MHz, $CDCl_3$) δ = 7.83 (m, 2H), 7.39 (m, 2H), 7.31 (m, 2H), 7.25 (m, 2H), 5.88 (s, 1H), 4.50 (bro. 1H). MS calculated for $C_{14}H_9OCl_2$ ($M\text{-}OH^+$) 263.0, found 262.9.

[00272] Step B: To a solution of 2,3-dichloro-5,6-dicyanobenzoquinone (242 mg, 1.07 mmol) and triphenylphosphine (280 mg, 1.07 mmol) in dry CH_2Cl_2 (5 mL) is subsequently added tetrabutylammonium bromide (344 mg (1.07 mmol) and 1,2-Bis-(4-chloro-phenyl)-2-hydroxy-ethanone (200 mg, 0.71 mmol). The suspension is kept stirring for 1.5 h at room temperature. The resulting brown solution is concentrated in vacuo and purified by flash chromatography (hexane/ethyl acetate 5:1) to afford 2-bromo-1,2-bis-(4-chloro-phenyl)-ethanone as a colorless oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.86 (d, J = 8.8 Hz, 2H), 7.40-7.35 (m, 4H), 7.29 (d, J = 8.4 Hz, 2H), 6.17 (s, 1H). MS calculated for $C_{14}H_9OCl_2$ ($M\text{-}Br^+$) 263.0, found 262.9.

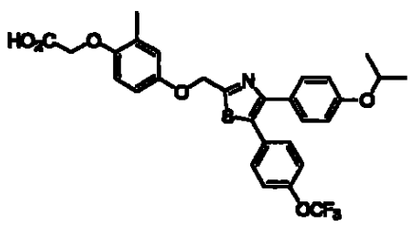
[00273] Step C: A mixture of 2-bromo-1,2-bis-(4-chloro-phenyl)-ethanone (44.0 mg, 0.13 mmol), (2-methyl-4-thiocarbamoylmethoxy-phenoxy)-acetic acid methyl ester 13 (34.0 mg, 0.13 mmol) and EtOH (1 mL) is subjected to microwave (180°C) for 5 min. The resulting solution is used directly in the next step.

[00274] Step D: The crude {4-[4,5-bis-(4-chloro-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester from step C is dissolved in THF (1 mL) and H_2O

(0.5 mL). $LiOH \cdot H_2O$ (53.7 mg, 0.64 mmol) is added. The mixture is stirred for 2 h at room temperature, then acidified with 1 N HCl. EtOAc (20 mL) is added and the product is extracted. The organic layer is dried ($MgSO_4$), filtered, concentrated and purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound H1 as a white solid: ^{1}H-NMR (400MHz, CD_3OD) δ = 7.45 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.34-7.30 (m, 4H), 6.91 (d, J = 2.8 Hz, 1H), 6.85-6.76 (m, 2H), 5.34 (s, 2H), 4.62 (s, 2H), 2.26 (s, 3H). MS calculated for $C_{25}H_{20}Cl_2NO_4S$ ($M+H^+$) 500.04, found 501.00.



[00275] Example J1: {4-[4-(4-Isopropoxy-phenyl)-5-(4-trifluoromethoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.



[00276] Step A: 4-Isopropoxy-benzaldehyde (5.0 g, 30.45 mmol) and trimethylsilyl cyanide (3.02 g, 30.45 mmol) are dissolved in dry DCM (50 mL). The solution is cooled to 0°C, then zinc iodide (42.76 mg, 1.13 mmol) is added. The reaction mixture is then warmed to room temperature and kept stirring over night. The mixture is concentrated, redissolved in ether and filtered through activated charcoal. The filtrate is dried ($MgSO_4$) and concentrated to give (4-isopropoxy-phenyl)-trimethylsilanyloxy-acetonitrile as a colorless oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.16 (d, J = 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.22 (s, 1H), 4.38-4.32 (m, 1H), 1.13 (d, J = 4.0 Hz, 6H), 0.00 (s, 9H). MS calculated for $C_{14}H_{21}NO_2Si$, (M^+) 263.1, found 237.1 (M-CN).

[00277] Step B: (4-Isopropoxy-phenyl)-trimethylsilanyloxy-acetonitrile (1.0 g, 3.78 mmol) is dissolved in dry THF (8 mL). The solution is added dropwise into a solution of LDA (2 M in THF, 1.89 mL) in THF (4 mL) at -78°C. The reaction mixture is stirred for 0.5 h followed by addition a solution of 4-(trifluoromethoxy)benzyl bromide (0.97 g, 3.78 mmol) in THF (2 mL). The reaction mixture is allowed to warm to room temperature and kept stirring for 18 hours. The reaction mixture is poured into H_2O (10 mL) and extracted with EtOAc three times. The organic layers are combined and washed by brine, dried ($MgSO_4$) and concentrated. The residue is redissolved in MeOH (10 mL), then H_2SO_4 (1 M, 4 mL) is added. After stirring at room temperature over night, the reaction mixture is adjusted to pH 10 by adding 1 N NaOH, then extracted with EtOAc three times. The organic layers are combined and washed with H_2O and brine, dried and concentrated to give crude 1-(4-isopropoxy-phenyl)-2-(4-trifluoromethoxy-phenyl)-ethanone, which is used directly in the next step without purification. MS calculated for $C_{18}H_{18}F_3O_3$, ($M+H^+$) 339.1, found 339.4.

[00278] Step C: The crude 1-(4-isopropoxy-phenyl)-2-(4-trifluoromethoxy-phenyl)-ethanone (100 mg) is dissolved in DCM (2 mL). Pyridinium tribromide (94.5 mg, 0.30 mmol) is added. The reaction mixture is stirred for 2 h at room temperature. The solvent is removed to give crude 2-bromo-1-(4-isopropoxy-phenyl)-2-(4-trifluoromethoxy-phenyl)-ethanone, which is used directly in the next step without purification. MS calculated for $C_{18}H_{17}BrF_3O_3$, ($M+H^+$) 417.0, found 417.3.

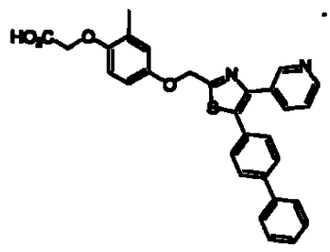
[00279] Step D: Crude 2-bromo-1-(4-isopropoxy-phenyl)-2-(4-trifluoromethoxy-phenyl)-ethanone is dissolved in EtOH (1.0 mL) in a 5 mL microwave reaction vial. (2-

methyl-4-thiocarbamoylmethoxy-phenoxy)-acetic acid methyl ester (13) (79.6 mg, 0.30 mmol) is added and the vial is sealed. Crude {4-[4-(4-isopropoxy-phenyl)-5-(4-trifluoromethoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester is obtained after subjection to microwave (5 min at 180°C) and is used directly in the next step without purification. MS calculated for $C_{30}H_{29}F_3NO_6S$ ($M+H^+$) 588.2, found 588.1.

[00280] Step E: THF (0.8 mL), H_2O (0.5 mL) and $LiOH·H_2O$ (62 mg, 1.48 mmol) are added to the reaction mixture of step D. The reaction mixture is stirred for 1 h at room temperature, then it is purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound J1 as a white solid: ^{1}H-NMR (400MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 2.8 Hz, 1H), 6.78-6.67 (m, 4H), 5.24 (s, 2H), 4.53 (s, 2H), 4.51 (m, 1H), 2.16 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H). MS calculated for $C_{29}H_{27}F_3NO_6S$ ($M+H^+$) 574.1, found 574.2.



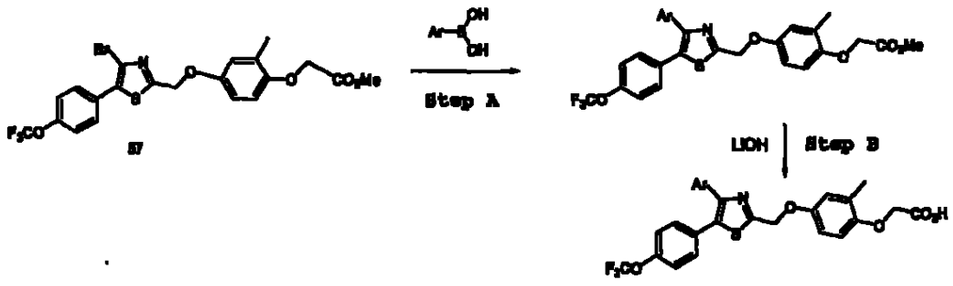
[00281] Example K1: [4-(5-Biphenyl-4-yl-4-pyridin-3-yl-thiazol-2-ylmethoxy)-2-methyl-phenoxy]-acetic acid.



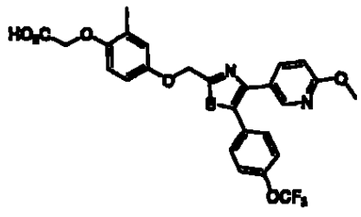
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[00282] Step A: A mixture of [4-(5-biphenyl-4-yl-4-bromo-thiazol-2-ylmethoxy)-2-methyl-phenoxy]-acetic acid methyl ester (56) (10.0 mg, 0.019 mmol), 3-pyridineboronic acid (3.7 mg, 0.023 mmol), tetrakis (triphenylphosphine) palladium (2.2 mg, 0.0019 mmol), potassium carbonate (10.5 mg, 76.0 mmol), 1,4-dioxane (1 mL), EtOH (0.3 mL) and H_2O (0.2 mL) in a sealed vial is heated to 120°C and stirred at this temperature overnight. The reaction mixture is cooled to room temperature and used in the next step without further purification. MS calculated for $C_{30}H_{25}N_2O_4S$ ($M+H^+$) 523.2, found 523.2.

[00283] Step B: $LiOH·H_2O$ (4.0 mg, 0.095 mmol) is added to the reaction mixture from step hours. The mixture is stirred at room temperature for 2 h, then filtered. The filtrate is purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound K1 as a white solid: ^{1}H-NMR (400MHz, CD_3OD) δ = 8.77 (bs, 1H), 8.55 (bs, 1H), 8.33 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 6.4 Hz, 1H), 7.64-7.42 (m, 4H), 7.41-7.35 (m, 4H), 7.30-7.26 (m, 1H), 6.84 (d, J = 2.8 Hz, 1H), 6.78-6.68 (m, 2H), 5.31 (s, 2H), 4.54 (s, 2H), 2.17 (s, 3H). MS calculated for $C_{30}H_{25}N_2O_4S$ ($M+H^+$) 509.2, found 509.1.

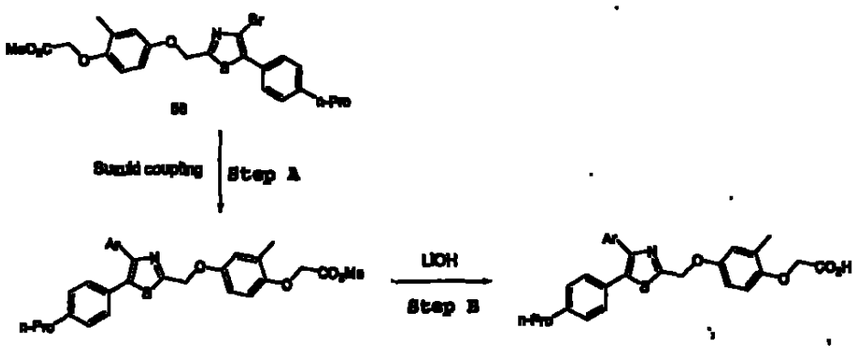


[00284] Example L1: {4-[4-(6-Methoxy-pyridin-3-yl)-5-(4-trifluoromethoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.

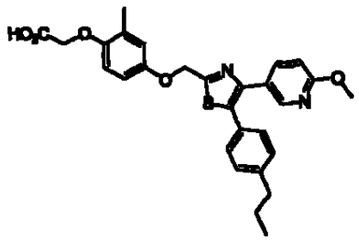


[00285] Step A: A mixture of {4-[4-bromo-5-(4-trifluoromethoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester (400 mg, 0.75 mmol), 2-methoxy-5-pyridineboronic acid (229.7 mg, 1.50 mmol), tetrakis triphenylphosphine) palladium (86.9 mg, 0.075 mmol), potassium carbonate (1.0 N, 3.0 mL, 3.0 mmol), 1,4-dioxane (10.0 mL) and EtOH (6.0 mL) in a sealed vial is heated to 120°C overnight. The reaction mixture is cooled to room temperature and used in the next step without further purification.

[00286] Step B: $LiOH{\cdot}H_2O$ (158 mg, 3.75 mmol) is added to the reaction mixture from step hours. The mixture is stirred at room temperature for 2 h, then filtered. The filtrate is purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound L1 as a white solid: ^{1}H-NMR (400MHz, CD_3OD) δ = 8.13 (d, J = 2.0 Hz, 1H), 7.72 (dd, J = 2.4 Hz, J = 8.4 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 3H), 5.27 (s, 2H), 4.54 (s, 2H), 3.83 (s, 3H), 2.17 (s, 3H). MS calculated for $C_{26}H_{22}F_3N_2O_6S$ ($M+H^+$) 547.1, found 547.1.



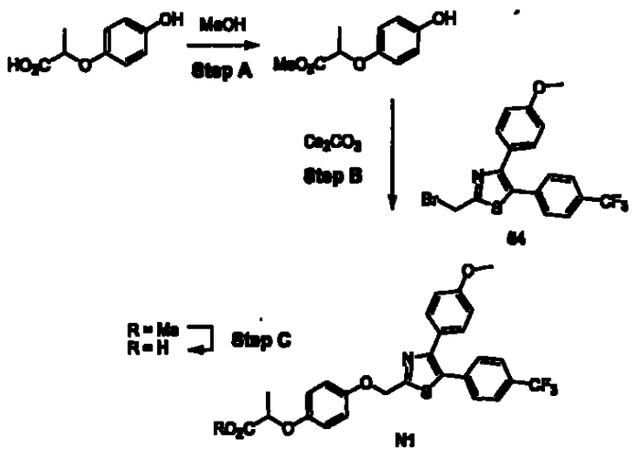
[00287] Example M1: {4-[4-(6-Methoxy-pyridin-3-yl)-5-(4-propyl-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.



[00288] Step A: A mixture of {4-[4-Bromo-5-(4-propyl-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester 58 (20 mg, 0.041 mmol), 2-methoxy-5-pyridineboronic acid (12.5 mg, 0.082 mmol), tetrakis triphenylphosphine) palladium (4.7 mg, 0.0041 mmol), potassium carbonate (1.0 N, 0.16 mL, 0.16 mmol), 1,4-dioxane (0.6 mL) and EtOH (0.3 mL) in a sealed vial is subjected to microwave (5 min at 170°C). Crude {4-[4-(6-Methoxy-pyridin-3-yl)-5-(4-trifluoromethoxy-phenyl)-thiazole-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester is obtained and is used directly in the next step without purification. MS calculated for $C_{27}H_{24}F_3N_2O_7$ ($M+H^+$) 519.2, found 519.2.

[00289] Step B: $LiOH.H_2O$ (17.0 mg, 0.41 mmol), MeOH (0.4 mL), THF (0.3 mL) and H_2O (0.2 mL) are added to the reaction mixture from step G. The mixture is stirred at room temperature for 2 h, then filtered. The filtrate is purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound M1 as a white solid: ^{1}H-NMR (400MHz, CD_3OD) δ = 8.12 (s, 1H), 7.71 (dd, J = 2.4 Hz, J = 8.8 Hz, 1H), 7.17-7.11 (m, 4H), 6.82 (d, J = 2.8 Hz, 1H), 6.73-6.66 (m, 3H), 5.24 (s, 2H), 4.53 (s, 2H), 3.82 (s, 3H), 2.51 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.61-1.51 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H). MS calculated for $C_{28}H_{29}N_2O_5S$ ($M+H^+$) 505.2, found 505.2.

[00290] Example N1: 2-{4-[4-(4-Methoxy-phenyl)-5-(4-trifluoromethyl-phenyl)-thiazol-2-ylmethoxy]-phenoxy}-propionic acid.



[00291] Step A: 2-(4-Hydroxy-phenoxy)-propionic acid (25 mg, 0.14 mmol) is dissolved in MeOH (20 mL). Thienyl chloride (5 □L, 0.06 mmol) is added and the solution is stirred at 60°C for 2 hours. The solvent is removed in vacuo to afford crude 2-(4-hydroxy-phenoxy)-propionic acid methyl ester as a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 6.77 (d, J = 9.2 Hz, 2H), 6.72 (d, J = 9.2 Hz, 1H), 4.66 (q, J = 6.8 Hz, 1H), 3.75 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H). MS calculated for $C_{10}H_{13}O_4$ ($M+H^+$) 197.1, found 197.4.

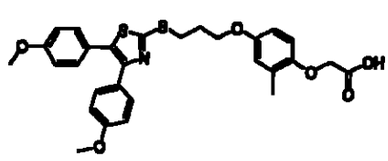
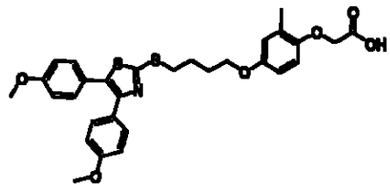
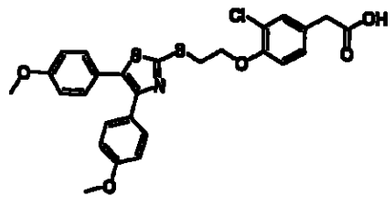
[00292] Step B: 2-(4-hydroxy-phenoxy)-propionic acid methyl ester (27 mg, 0.14 mmol) and Cs_2CO_3 (137 mg, 0.42 mmol) are added to a solution of intermediate 54 (60 mg, 0.14 mmol) in MeCN (5 mL). The mixture is stirred for 3 h at room temperature. After the mixture is filtered, the organic solution is concentrated to afford crude 2-{4-[4-(4-Methoxy-phenyl)-5-(4-trifluoromethyl-phenyl)-thiazol-2-ylmethoxy]-phenoxy}-propionic acid methyl ester, which is used in the next step without further purification.

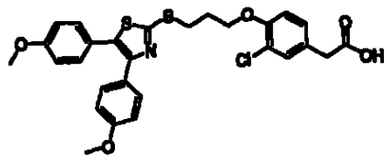
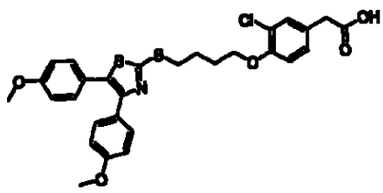
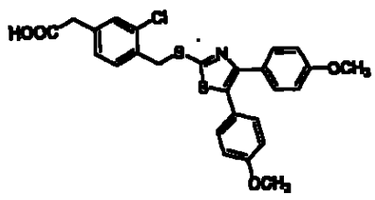
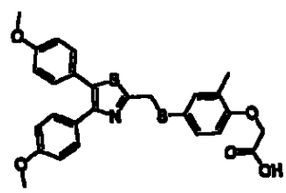
[00293] Step C: THF (2 mL) and 1 N LiOH (0.5 mL) are added to the crude product from step B. The mixture is stirred overnight at room temperature, then acidified with 1 N HCl (1 mL). The reaction mixture is extracted with EtOAc (3 mL), the organic layer is separated and concentrated in vacuo. The remainder is taken up in DMSO (1 mL) and purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound N1 as a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.55 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 6.95-6.83 (m, 6H), 5.31 (s, 2H), 4.69 (q, J = 6.8 Hz, 1H), 3.81 (s, 3H), 1.60 (d, J = 6.8 Hz, 3H). MS calculated for $C_{27}H_{23}F_3NO_5S$ ($M+H^+$) 530.1, found 530.4.

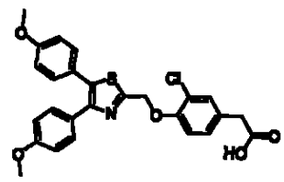
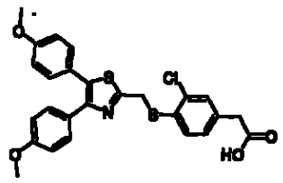
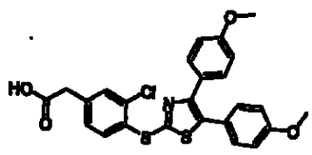
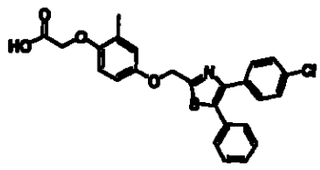
[00294] By repeating the procedures described in the above examples, using appropriate starting materials, the following compounds of Formula I, as identified in Table 1, are obtained.

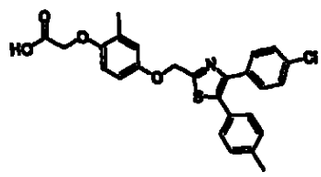
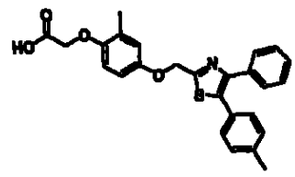
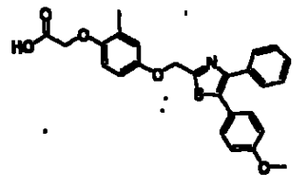
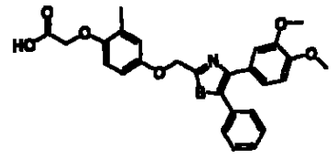
Table 1

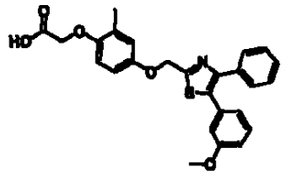
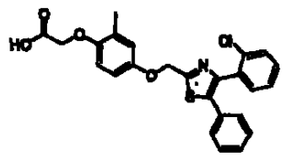
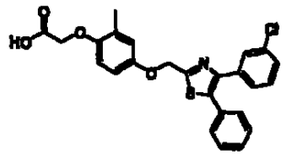
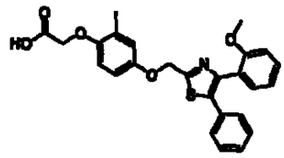
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)

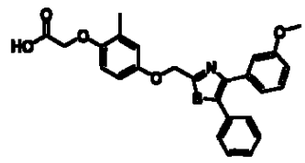
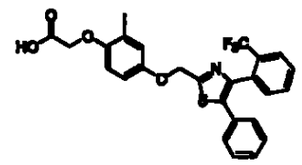
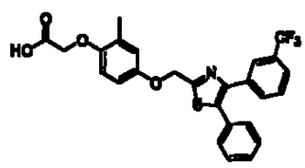
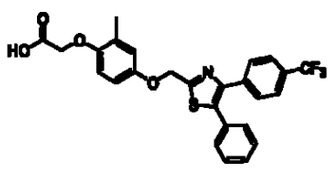
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
A2		^{1}H-NMR (400MHz, CD_3OD) δ = 7.34 (d, J = 8.9 Hz, 2H), 7.14 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.9 Hz, 2H), 6.73-6.63 (m, 3H), 4.55 (s, 2H), 4.06 (t, J = 5.9 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.42 (t, J = 7.0 Hz, 2H), 2.23 (m, 2H), 2.18 (s, 3H). MS calculated for $C_{29}H_{30}NO_6S_2$ ($M+H^+$) 552.1, found 552.4.
A3		^{1}H-NMR (400MHz, CD_3OD) δ = 7.34 (d, J = 8.9 Hz, 2H), 7.16 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.9 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 6.72-6.61 (m, 3H), 4.56 (s, 2H), 3.95 (t, J = 6.0 Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.31 (t, J = 7.2 Hz, 2H), 2.19 (s, 3H), 2.01-1.89 (m, 4H). MS calculated for $C_{30}H_{32}NO_6S_2$ ($M+H^+$) 566.2, found 566.4.
A4		^{1}H-NMR (400MHz, CD_3OD) δ = 7.37-6.82 (m, 11H), 4.42 (t, J = 6.4 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.66 (t, J = 6.4 Hz, 2H), 3.50 (s, 2H). MS calculated for $C_{29}H_{29}ClNO_6S_2$ ($M+H^+$) 542.1, found 542.3.

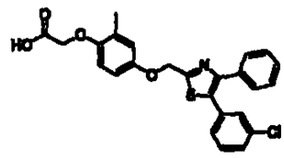
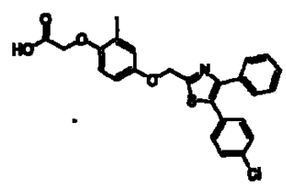
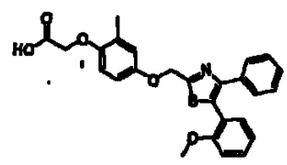
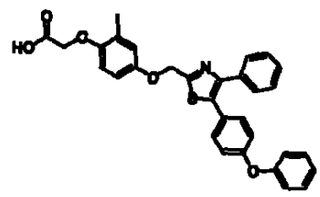
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
A5		^{1}H-NMR (400MHz, CD_3OD) δ = 7.35-6.80 (m, 11H), 4.19 (t, J = 5.8 Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.55 (s, 2H), 3.47 (t, J = 7.0 Hz, 2H), 2.30 (m, 2H). MS calculated for $C_{28}H_{27}ClNO_5S_2$ ($M+H^+$) 556.1, found 556.4.
A6		^{1}H-NMR (400MHz, CD_3OD) δ = 7.36-6.80 (m, 11H), 4.10 (t, J = 5.7 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.51 (s, 2H), 3.36 (t, J = 7.1 Hz, 2H), 2.08-1.98 (m, 4H). MS calculated for $C_{29}H_{29}ClNO_5S_2$ ($M+H^+$) 570.1, found 570.4.
B2		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.51-7.45 (m, 3H), 7.35 (d, J= 1.2 Hz, 1H), 7.22 (s, 1H), 7.20 (s, 1H), 7.13 (dd, J= 1.2 Hz, J= 8.0 Hz, 1H), 4.57 (s, 2H), 3.802 (s, 3H), 3.809 (s, 3H), 3.62 (s, 2H). MS calculated for $C_{26}H_{23}ClNO_4S_2$ ($M+H^+$) 512.0, found 512.00.
C2		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.74-6.63 (m, 11H), 4.62 (s, 2H), 4.35 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.23 (s, 3H). MS calculated for $C_{27}H_{29}NO_5S_2$ ($M+H^+$) 508.1, found 508.4.

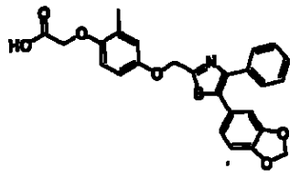
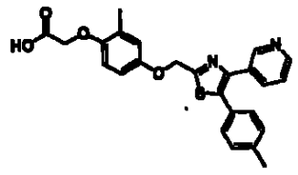
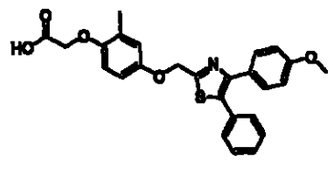
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
C3		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.74-6.80 (m, 11H), 5.43 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.57 (s, 2H). MS calculated for $C_{25}H_{23}ClNO_3S$ ($M+H^+$) 496.1, found 496.3.
C4		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.74-6.78 (m, 11H), 4.51 (s, 2H), 3.79 (s, 3H), 3.79 (s, 3H), 3.58 (s, 2H). MS calculated for $C_{25}H_{23}ClNO_4S_2$ ($M+H^+$) 512.1, found 512.3.
D2		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.59 (d, J = 8.0 Hz, 1H), 7.44 (s, 1H), 7.37 (d, 8.8 Hz, 2H), 7.21 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.4 Hz, 4H), 3.77 (s, 6H), 3.64 (s, 2H). MS calculated for $C_{28}H_{24}NO_5S_2$ ($M+H^+$) 498.0, found 498.3.
E48		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.46-7.31 (m, 9H), 6.96 (d, J = 3.0 Hz, 1H), 6.87 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.40 (s, 2H), 4.63 (s, 2H), 2.19 (s, 3H). MS calculated for $C_{25}H_{21}ClNO_4S$ ($M+H^+$) 466.1, found 466.3.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
E49		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.46-7.08 (m, 8H), 6.96 (d, J = 3.0 Hz, 1H), 6.86 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.78 (d, J = 8.9 Hz, 1H), 5.39 (s, 2H), 4.63 (s, 2H), 2.69 (m, 3H), 2.19 (s, 3H). MS calculated for $C_{28}H_{25}ClNO_4S$ ($M+H^+$) 480.1, found 480.3.
E60		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.46-7.19 (m, 9H), 6.96 (d, J = 2.9 Hz, 1H), 6.87 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.39 (s, 2H), 4.63 (s, 2H), 2.32 (s, 3H), 2.19 (s, 3H). MS calculated for $C_{28}H_{26}NO_4S$ ($M+H^+$) 446.1, found 446.4.
E61		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.47-7.26 (m, 7H), 6.95 (m, 3H), 6.87 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.38 (s, 2H), 4.63 (s, 2H), 3.77 (s, 3H), 2.19 (s, 3H). MS calculated for $C_{28}H_{26}NO_5S$ ($M+H^+$) 462.1, found 462.4.
E62		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.50-7.44 (m, 5H), 7.09-6.85 (m, 6H), 5.46 (s, 2H), 4.70 (s, 2H), 3.81 (s, 3H), 3.59 (s, 3H), 2.26 (s, 3H). MS calculated for $C_{27}H_{26}NO_6S$ ($M+H^+$) 492.1, found 492.4.

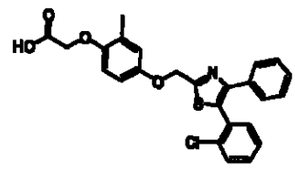
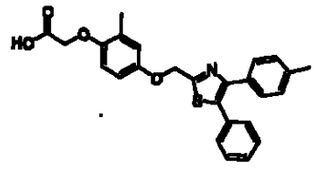
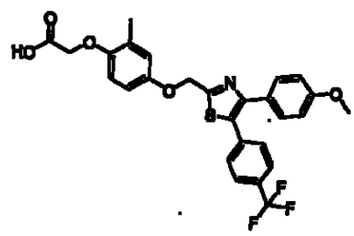
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
B63		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.45-7.26 (m, 6H), 6.94-6.76 (m, 6H), 5.37 (s, 2H), 4.61 (s, 2H), 3.64 (s, 3H), 2.17 (s, 3H). MS calculated for $C_{26}H_{24}NO_3S$ ($M+H^+$) 462.1, found 462.4.
B64		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.54-7.19 (m, 9H), 6.96 (d, J = 3.0 Hz, 1H), 6.88 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.39 (s, 2H), 4.64 (s, 2H), 2.19 (s, 3H). MS calculated for $C_{25}H_{21}ClNO_4S$ ($M+H^+$) 466.1, found 466.3.
B65		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.46-7.27 (m, 9H), 6.94 (d, J = 3.0 Hz, 1H), 6.84 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.76 (d, J = 8.9 Hz, 1H), 5.38 (s, 2H), 4.61 (s, 2H), 2.17 (s, 3H). MS calculated for $C_{25}H_{21}ClNO_4S$ ($M+H^+$) 466.1, found 466.3.
B66		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.39-7.19 (m, 7H), 7.01-6.96 (m, 3H), 6.87 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.36 (s, 2H), 4.63 (s, 2H), 3.39 (s, 3H), 2.20 (s, 3H). MS calculated for $C_{26}H_{24}NO_3S$ ($M+H^+$) 462.1, found 462.4.

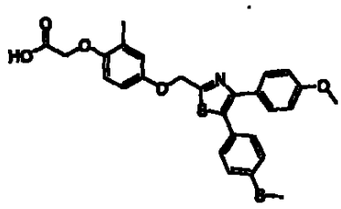
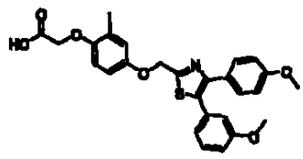
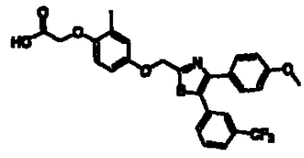
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
E67		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.41-7.22 (m, 7H), 7.03-6.97 (m, 3H), 6.88 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.40 (s, 2H), 4.63 (s, 2H), 3.62 (s, 3H), 2.19 (s, 3H). MS calculated for $C_{26}H_{24}NO_5S$ ($M+H^+$) 462.1, found 462.4.
E68		MS calculated for $C_{26}H_{21}F_3NO_4S$ ($M+H^+$) 500.1, found 500.4.
E69		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.75-7.34 (m, 9H), 6.98 (d, J = 3 Hz, 1H), 6.88 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.43 (s, 2H), 4.64 (s, 2H), 2.20 (s, 3H). MS calculated for $C_{26}H_{21}F_3NO_4S$ ($M+H^+$) 500.1, found 500.3.
E70		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.71-7.63 (m, 4H), 7.44-7.33 (m, 5H), 6.97 (d, J = 3 Hz, 1H), 6.88 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.42 (s, 2H), 4.64 (s, 2H), 2.19 (s, 3H). MS calculated for $C_{26}H_{21}F_3NO_4S$ ($M+H^+$) 500.1, found 500.4.

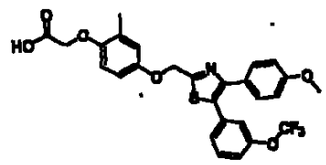
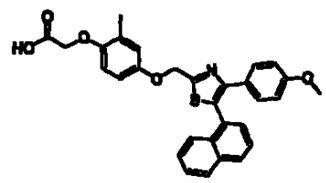
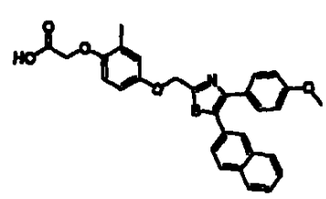
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
E71		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.46-7.26 (m, 9H), 6.97 (d, J = 3.0 Hz, 1H), 6.88 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.41 (s, 2H), 4.64 (s, 2H), 2.19 (s, 3H). MS calculated for $C_{25}H_{21}ClNO_4S$ ($M+H^+$) 466.1, found 466.3.
E72		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.47-7.30 (m, 9H), 6.96 (d, J = 3.0 Hz, 1H), 6.87 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.40 (s, 2H), 4.64 (s, 2H), 2.19 (s, 3H). MS calculated for $C_{25}H_{21}ClNO_4S$ ($M+H^+$) 466.1, found 466.3.
E73		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.43-7.12 (m, 8H), 6.97-6.79 (m, 4H), 5.39 (s, 2H), 4.64 (s, 2H), 3.64 (s, 3H), 2.19 (s, 3H). MS calculated for $C_{26}H_{24}NO_5S$ ($M+H^+$) 462.1, found 462.4.
E74		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.45-7.31 (m, 8H), 7.17-6.78 (m, 9H), 5.38 (s, 2H), 4.63 (s, 2H), 2.19 (s, 3H). MS calculated for $C_{31}H_{26}NO_5S$ ($M+H^+$) 524.2, found 524.4.

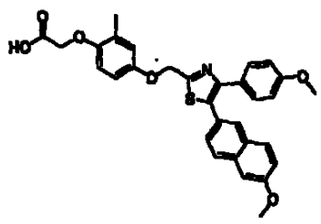
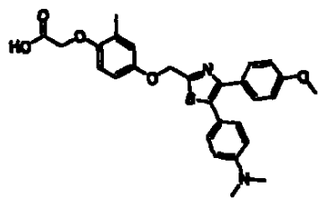
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
E75		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.48-7.30 (m, 5H), 6.96-6.78 (m, 6H), 6.06 (s, 2H), 5.37 (s, 2H), 4.63 (s, 2H), 2.19 (s, 3H). MS calculated for $C_{28}H_{22}NO_6S$ ($M+H^+$) 476.1, found 476.4.
E76		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 8.64 (d, J = 1.7 Hz, 1H), 8.54 (dd, J = 1.4 Hz, J = 4.8 Hz, 1H), 7.91 (d, J = 8.0 Hz), 7.47 (dd, J = 5.0 Hz, J = 7.9 Hz, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 3.0 Hz, 1H), 6.87 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.41 (s, 2H), 4.64 (s, 2H), 2.34 (s, 3H), 2.19 (s, 3H). MS calculated for $C_{27}H_{25}N_2O_4S$ ($M+H^+$) 447.1, found 447.4.
E87		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.40-7.34 (m, 7H), 6.96 (d, J = 3.0 Hz, 1H), 6.87 (m, 3H), 6.78 (d, J = 8.9 Hz, 1H), 5.38 (s, 2H), 4.63 (s, 2H), 3.74 (s, 3H), 2.19 (s, 3H). MS calculated for $C_{28}H_{24}NO_5S$ ($M+H^+$) 462.1, found 462.4.

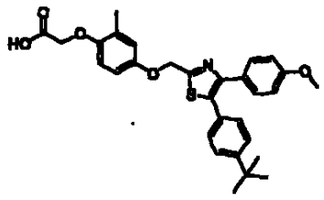
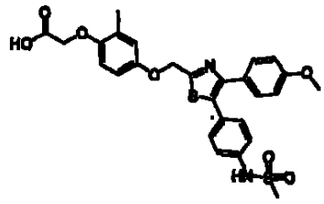
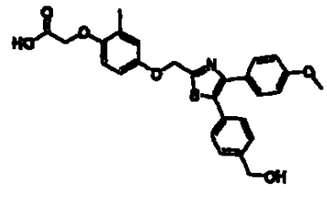
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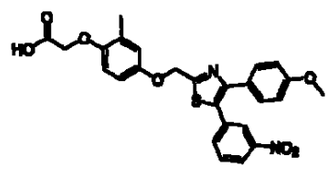
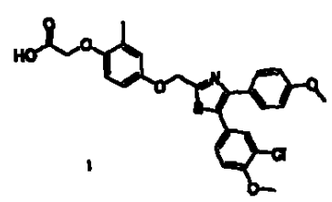
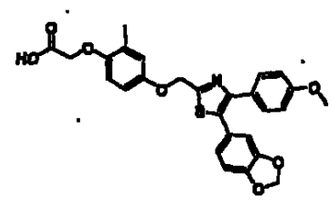
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
E90		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.62-7.25 (m, 9H), 6.98 (d, J = 3.0 Hz, 1H), 6.89 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.80 (d, J = 8.9 Hz, 1H), 5.44 (s, 2H), 4.64 (s, 2H), 2.20 (s, 3H). MS calculated for $C_{25}H_{21}ClNO_4S$ ($M+H^+$) 466.1, found 466.3.
E91		^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ = 7.40-7.33 (m, 7H), 7.13 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 3.0 Hz, 1H), 6.87 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.39 (s, 2H), 4.63 (s, 2H), 2.29 (s, 3H), 2.19 (s, 3H). MS calculated for $C_{26}H_{24}NO_4S$ ($M+H^+$) 446.1, found 446.4.
F2		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.48 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 3.0 Hz, 1H), 6.77 (d, J = 8.8 Hz, 2H), 6.71 (dd, J = 3.0, 8.9 Hz, 1H), 6.64 (d, J = 8.8 Hz, 1H), 5.26 (s, 2H), 4.56 (s, 2H), 3.74 (s, 3H), 2.21 (s, 3H). MS calculated for $C_{27}H_{22}F_3NO_5S$ ($M+H^+$) 530.1, found 530.3.

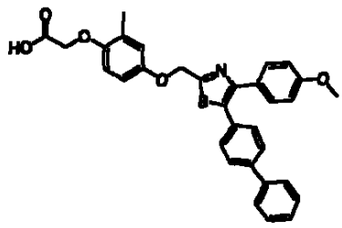
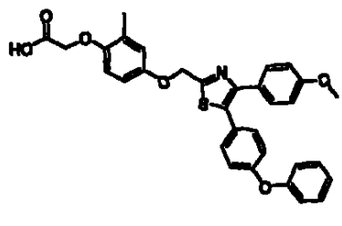
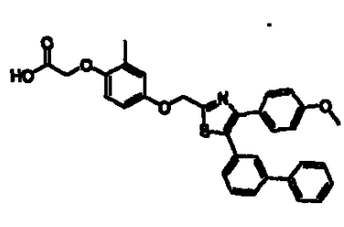
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F3		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.35 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 2.8 Hz, 1H), 6.76 (d, J = 8.8 Hz, 2H), 6.71 (dd, J = 3.1, 8.9 Hz, 1H), 6.63 (d, J = 8.8 Hz, 1H), 5.26 (s, 2H), 4.55 (s, 2H), 3.74 (s, 3H), 2.41 (s, 3H), 2.21 (s, 3H). MS calculated for $C_{27}H_{26}NO_5S_2$ (M+H$^+$) 508.1, found 508.3.
F4		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.42 (d, J = 8.8 Hz, 2H), 7.22 (t, J = 7.5 Hz, 1H), 6.90 (m, 2H), 6.86 (m, 4H), 6.77 (dd, J = 3.1, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.63 (s, 2H), 3.81 (s, 3H), 3.70 (s, 3H), 2.28 (s, 3H). MS calculated for $C_{27}H_{26}NO_6S$ (M+H$^+$) 492.1, found 492.4.
F5		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.61 (s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 3.2, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.64 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{27}H_{23}F_3NO_5S$ (M+H$^+$) 530.1, found 530.4.

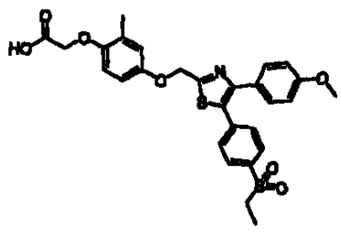
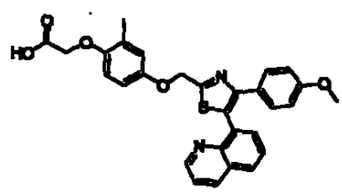
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F6		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.39 (d, J = 8.8 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 7.27 (d, J = 7.2 Hz, 1H), 7.15 (m, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.64 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{27}H_{23}F_3NO_5S$ ($M+H^+$) 546.1, found 546.0.
F7		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.91 (m, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.48 (m, 3H), 7.40 (m, 1H), 7.33 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 2.8 Hz, 1H), 6.82 (dd, J = 2.8, 8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 6.64 (d, J = 8.9 Hz, 2H), 5.42 (s, 2H), 4.65 (s, 2H), 3.69 (s, 3H), 2.30 (s, 3H). MS calculated for $C_{30}H_{26}NO_5S$ ($M+H^+$) 512.2, found 512.1.
F8		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.88 (s, 1H), 7.76 (m, 3H), 7.49 (m, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.34 (dd, J = 1.6, 8.4 Hz, 1H), 6.92 (d, J = 2.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.39 (s, 2H), 4.64 (s, 2H), 3.80 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{30}H_{26}NO_5S$ ($M+H^+$) 512.2, found 512.1.

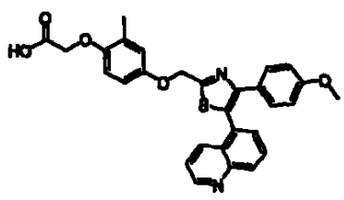
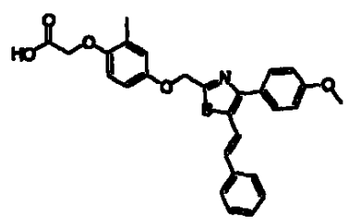
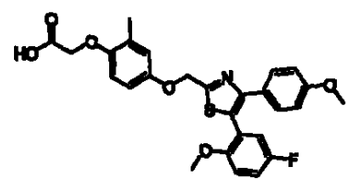
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F9		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.78 (s, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.43 (d, J = 8.8 Hz, 2H), 7.29 (dd, J = 2.0, 8.4 Hz, 1H), 7.16 (dd, J = 2.4, 8.8 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 6.91 (d, J = 2.8 Hz, 1H), 6.81 (d, J = 9.2 Hz, 2H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.39 (s, 2H), 4.64 (s, 2H), 3.95 (s, 3H), 3.80 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{31}H_{28}NO_5S$ ($M+H^+$) 542.2, found 542.4.
F10		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.50 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 2.8 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 6.88 (dd, J = 2.8, 8.8 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 5.46 (s, 2H), 4.73 (s, 2H), 3.93 (s, 3H), 3.22 (s, 6H), 2.39 (s, 3H). MS calculated for $C_{29}H_{29}NO_5S$ ($M+H^+$) 505.2, found 505.4.

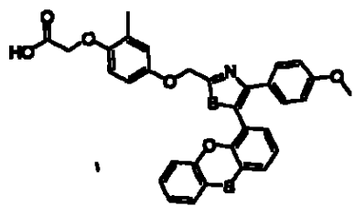
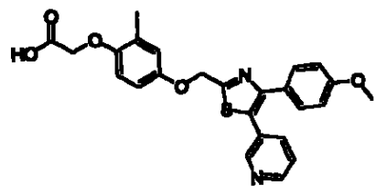
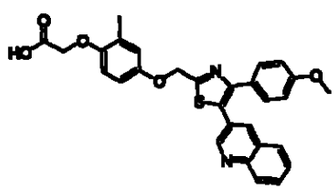
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F11		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.40 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 2.4 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.44 (s, 2H), 4.63 (s, 2H), 3.83 (s, 3H), 2.28 (s, 3H), 1.31 (s, 9H). MS calculated for $C_{30}H_{32}NO_5S$ ($M+H^+$) 518.2, found 518.4.
F12		^{1}H-NMR (400MHz, DMSO-d6) δ = 9.98 (s, 1H), 7.40 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 2.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 6.86 (dd, J = 2.8, 8.8 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.63 (s, 2H), 3.76 (s, 3H), 2.51 (s, 3H), 2.20 (s, 3H). MS calculated for $C_{27}H_{27}N_2O_7S_2$ ($M+H^+$) 555.1, found 555.3.
F13		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.39 (d, J = 8.8 Hz, 2H), 7.30 (s, 4H), 6.88 (d, J = 2.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.76 (dd, J = 2.8, 9.2 Hz, 1H), 6.68 (d, J = 9.2 Hz, 1H), 5.33 (s, 2H), 4.69 (s, 2H), 4.61 (s, 2H), 3.79 (s, 3H), 2.26 (s, 3H). MS calculated for $C_{27}H_{29}NO_6S$ ($M+H^+$) 492.1, found 492.4.

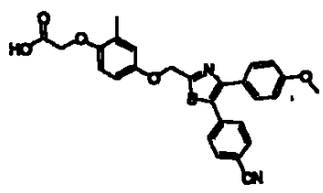
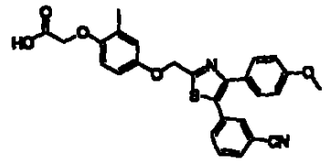
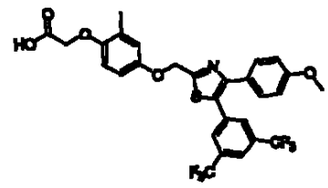
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F14		^{1}H-NMR (400MHz, DMSO-d6) δ = 8.21 (d, J = 7.2 Hz, 1H), 8.14 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 8.0 Hz, 1H), 7.39 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 2.8 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 6.85 (dd, J = 2.8, 8.8 Hz, 1H), 6.79 (d, J = 9.2 Hz, 1H), 5.42 (s, 2H), 4.63 (s, 2H), 3.76 (s, 3H), 2.20 (s, 3H). MS calculated for $C_{28}H_{23}N_2O_7S$ ($M+H^+$) 507.1, found 507.4.
F15		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.41 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 2.4 Hz, 1H), 7.15 (dd, J = 2.0, 8.4 Hz, 1H), 6.89 (d, J = 2.8 Hz, 1H), 6.84 (m, 3H), 6.76 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.32 (s, 2H), 4.63 (s, 2H), 3.94 (s, 3H), 3.82 (s, 3H), 2.28 (s, 3H). MS calculated for $C_{27}H_{23}ClNO_6S$ ($M+H^+$) 526.1, found 526.3.
F16		^{1}H-NMR (400MHz, DMSO-d6) δ = 7.40 (d, J = 8.8 Hz, 2H), 6.96 (s, 1H), 6.94 (s, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.86 (m, 3H), 6.78 (d, J = 9.2 Hz, 1H), 6.10 (s, 2H), 5.37 (s, 2H), 4.63 (s, 2H), 3.76 (s, 3H), 2.19 (s, 3H). MS calculated for $C_{27}H_{24}NO_7S$ ($M+H^+$) 506.1, found 506.4.

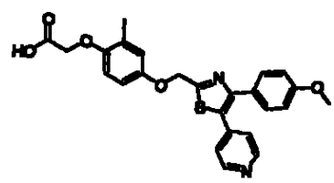
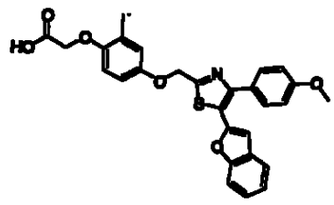
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F17		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.60 (d, J = 7.6 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.41 (m, 7H), 6.91 (d, J = 2.8 Hz, 1H), 6.85 (d, J = 8.4 Hz, 2H), 6.79 (dd, J = 2.4, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.64 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{32}H_{29}NO_3S$ ($M+H^+$) 538.2, found 538.4.
F18		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.43 (d, J = 8.4 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.14 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 7.6 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 2.4, 8.4 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.63 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{32}H_{29}NO_4S$ ($M+H^+$) 554.2, found 554.4.
F19		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.56 (t, J = 1.6 Hz, 1H), 7.53 (dt, J = 1.6, 8.0 Hz, 1H), 7.47 (d, J = 8.8 Hz, 4H), 7.40 (m, 3H), 7.32 (m, 2H), 6.91 (d, J = 3.2 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.63 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{32}H_{29}NO_3S$ ($M+H^+$) 538.2, found 538.1.

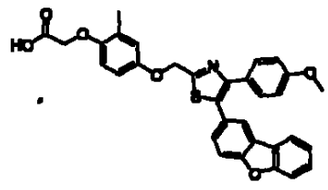
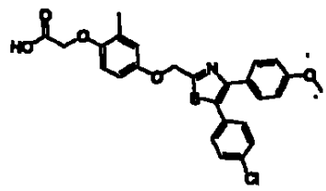
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F20		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.83 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.8 Hz, 1H), 7.37 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 6.79 (dd, J = 2.4, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.64 (s, 2H), 3.85 (s, 3H), 3.13 (q, J = 7.2 Hz, 2H), 2.29 (s, 3H), 1.30 (t, J = 7.6 Hz, 3H). MS calculated for $C_{29}H_{32}NO_7S_2$ ($M+H^+$) 554.1, found 554.0.
F21		^{1}H-NMR (400MHz, $CDCl_3$) δ = 9.10 (dd, J = 1.6, 4.8 Hz, 1H), 8.55 (dd, J = 1.6, 8.4 Hz, 1H), 8.03 (dd, J = 1.2, 8.4 Hz, 1H), 7.94 (dd, J = 1.6, 7.2 Hz, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.70 (dd, J = 4.8, 8.0 Hz, 1H), 7.25 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 2.4 Hz, 1H), 6.79 (dd, J = 2.4, 8.8 Hz, 1H), 6.67 (m, 3H), 5.44 (s, 2H), 4.61 (s, 2H), 3.73 (s, 3H), 2.26 (s, 3H). MS calculated for $C_{28}H_{25}N_2O_5S$ ($M+H^+$) 513.1, found 513.0.

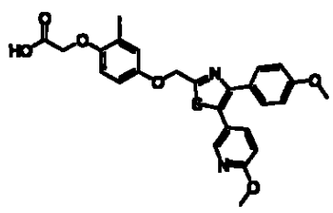
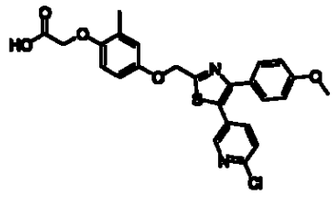
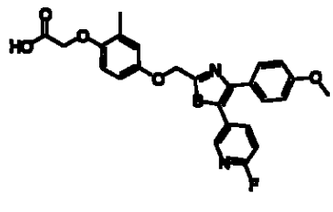
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F22		^{1}H-NMR (400MHz, $CDCl_3$) δ = 9.19 (d, J = 4.8 Hz, 1H), 8.57 (d, J = 8.4 Hz, 1H), 8.51 (d, J = 8.8 Hz, 1H), 8.03 (t, J = 7.6 Hz, 1H), 7.91 (d, J = 7.2 Hz, 1H), 7.63 (m, 2H), 7.50 (m, 1H), 7.22 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 2.8 Hz, 1H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 6.66 (d, J = 8.8 Hz, 2H), 5.42 (s, 2H), 4.65 (s, 2H), 3.70 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{29}H_{25}N_2O_5S$ ($M+H^+$) 513.1, found 513.4.
F23		^{1}H-NMR (400MHz, DMSO-d6) δ = 7.54 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 7.6 Hz, 2H), 7.24 (m, 2H), 7.20 (m, 2H), 7.02 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 16.0 Hz, 1H), 6.88 (d, J = 2.8 Hz, 1H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.31 (s, 2H), 4.56 (s, 2H), 3.76 (s, 3H), 2.12 (s, 3H). MS calculated for $C_{28}H_{26}NO_5S$ ($M+H^+$) 488.1, found 488.4.
F24		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.84 (d, J = 8.8 Hz, 0.7H), 7.38 (d, J = 8.8 Hz, 1.3H), 6.70-7.02 (m, 8H), 5.36 (s, 1.3H), 5.27 (s, 0.7H), 4.63 (s, 2H), 3.86 (s, 1.1H), 3.80 (s, 1.9H), 3.66 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{29}H_{25}FNO_6S$ ($M+H^+$) 510.1, found 510.0.

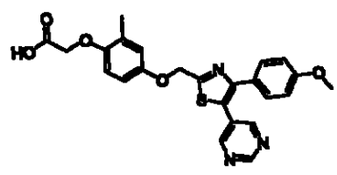
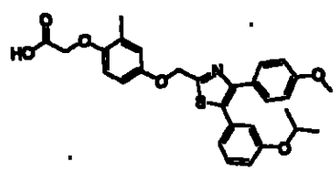
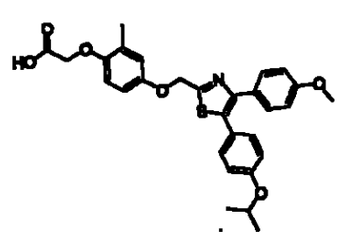
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F25		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.43 (d, J = 8.8 Hz, 2H), 7.12 (dd, J = 1.6, 7.6 Hz, 1H), 7.09 (dd, J = 2.0, 9.2 Hz, 1H), 7.00 (m, 5H), 6.80 (m, 3H), 6.72 (d, J = 8.8 Hz, 1H), 6.63 (dd, J = 2.0, 7.6 Hz, 1H), 5.47 (s, 2H), 4.65 (s, 2H), 3.76 (s, 3H), 2.30 (s, 3H). MS calculated for $C_{32}H_{28}NO_6S_2$ ($M+H^+$) 584.1, found 584.0.
F26		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.74 (d, J = 2.0 Hz, 1H), 8.66 (dd, J = 1.6, 5.2 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.54 (m, 1H), 7.36 (d, J = 8.8 Hz, 2H), 6.88 (m, 3H), 6.77 (dd, J = 2.8, 8.4 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.38 (s, 2H), 4.67 (s, 2H), 3.83 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{25}H_{23}N_2O_5S$ ($M+H^+$) 463.1, found 463.0.
F27		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.86 (d, J = 2.0 Hz, 1H), 8.24 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.77 (m, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.63 (s, 2H), 3.77 (s, 3H), 2.27 (s, 3H). MS calculated for $C_{29}H_{25}N_2O_5S$ ($M+H^+$) 513.1, found 513.0.

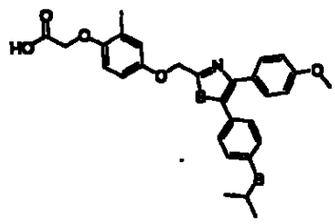
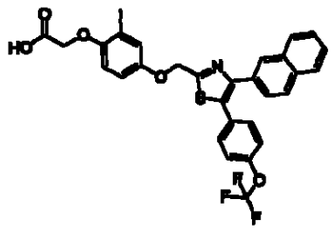
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/e)
F28		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.59 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 3.2, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 3.83 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{27}H_{23}N_2O_3S$ ($M+H^+$) 487.1, found 487.3.
F29		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.55 (d, J = 1.2 Hz, 1H), 7.51 (dd, J = 1.2, 7.6 Hz, 1H), 7.48 (dd, J = 1.2, 8.0 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.78 (d, J = 8.8 Hz, 2H), 6.71 (dd, J = 2.4, 8.8 Hz, 1H), 6.63 (d, J = 8.8 Hz, 1H), 5.28 (s, 2H), 4.57 (s, 2H), 3.75 (s, 3H), 2.22 (s, 3H). MS calculated for $C_{27}H_{23}N_2O_3S$ ($M+H^+$) 487.1, found 487.4.
F30		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.78 (s, 1H), 7.76 (s, 2H), 7.37 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{28}H_{22}F_6NO_3S$ ($M+H^+$) 598.1, found 598.3.

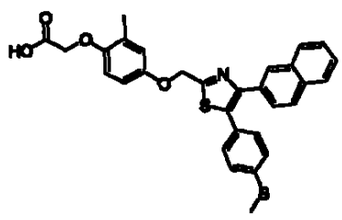
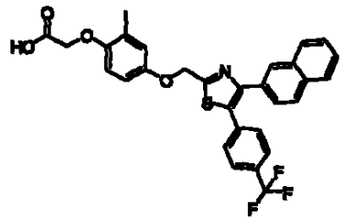
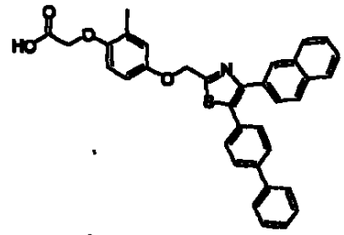
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F31		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.60 (d, J = 5.6 Hz, 2H), 7.62 (d, J = 5.6 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.71 (dd, J = 2.8, 8.8 Hz, 1H), 6.65 (d, J = 8.8 Hz, 1H), 5.30 (s, 2H), 4.59 (s, 2H), 3.80 (s, 3H), 2.23 (s, 3H). MS calculated for $C_{25}H_{23}N_2O_3S$ ($M+H^+$) 463.1, found 463.1.
F32		^{1}H-NMR (400MHz, DMSO-d6) δ = 7.48 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 7.6 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 3.2 Hz, 1H), 6.73 (dd, J = 3.2, 8.8 Hz, 1H), 6.72 (s, 1H), 6.64 (d, J = 8.8 Hz, 1H), 5.28 (s, 2H), 4.48 (s, 2H), 3.71 (s, 3H), 2.10 (s,3H). MS calculated for $C_{28}H_{24}NO_5S$ ($M+H^+$) 502.1, found 502.3.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F33		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.85 (d, J = 8.0 Hz, 1H), 7.82 (dd, J = 1.2, 7.6 Hz, 1H), 7.34 (m, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.24 (m, 2H), 7.17 (d, J = 7.6 Hz, 1H), 6.83 (d, J = 2.8 Hz, 1H), 6.72 (dd, J = 2.8, 8.8 Hz, 1H), 6.64 (d, J = 8.8 Hz, 2H), 6.62 (d, J = 8.8 Hz, 1H), 5.32 (s, 2H), 4.53 (s, 2H), 3.65 (s, 3H), 2.19 (s, 3H). MS calculated for $C_{32}H_{30}NO_5S$ ($M+H^+$) 552.1, found 552.4.
F34		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.40 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 3.2, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H), 4.63 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{29}H_{27}ClNO_5S$ ($M+H^+$) 496.1, found 496.3.

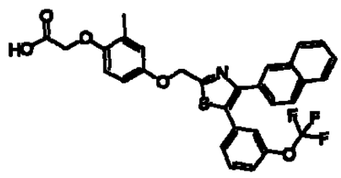
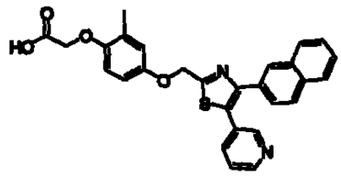
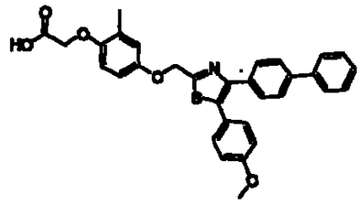
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F35		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.18 (d, J = 2.0 Hz, 1H), 7.47 (dd, J = 2.0, 8.8 Hz, 1H), 7.40 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.76 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 5.33 (s, 2H), 4.63 (s, 2H), 3.95 (s, 3H), 3.81 (s, 3H), 2.28 (s, 3H). MS calculated for $C_{25}H_{25}N_2O_5S$ ($M+H^+$) 493.1, found 493.1.
F36		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.40 (d, J = 2.4 Hz, 1H), 7.57 (dd, J = 2.4, 8.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 2.8 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{25}H_{22}ClN_2O_5S$ ($M+H^+$) 497.1, found 497.0.
F37		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.22 (d, J = 2.0 Hz, 1H), 7.69 (dt, J = 2.4, 8.4 Hz, 1H), 7.37 (d, J = 8.8 Hz, 2H), 6.88 (m, 2H), 6.85 (d, J = 8.8 Hz, 2H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.64 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{25}H_{22}FN_2O_5S$ ($M+H^+$) 481.1, found 481.0.

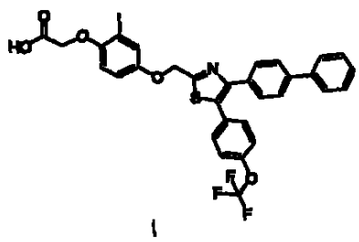
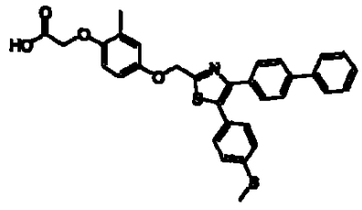
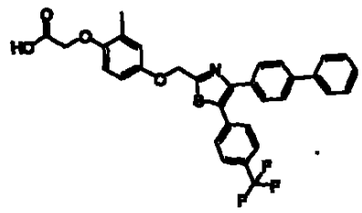
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F38		^{1}H-NMR (400MHz, $CDCl_3$) δ = 9.14 (s, 1H), 8.71 (s, 2H), 7.37 (d, J = 8.8 Hz, 2H), 6.87 (m, 3H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.64 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{24}H_{22}N_3O_3S$ ($M+H^+$) 464.1, found 464.1.
F39		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.42 (d, J = 8.8 Hz, 2H), 7.20 (t, J = 8.0 Hz, 1H), 6.85 (m, 6H), 6.76 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 9.2 Hz, 1H), 5.35 (s, 2H), 4.63 (s, 2H), 4.39 (m, 1H), 3.80 (s, 3H), 2.28 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H). MS calculated for $C_{29}H_{30}NO_6S$ ($M+H^+$) 520.2, found 520.1.
F40		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.41 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.83 (d, J = 9.2 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.76 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 9.2 Hz, 1H), 5.35 (s, 2H), 4.62 (s, 2H), 4.55 (m, 1H), 3.81 (s, 3H), 2.28 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H). MS calculated for $C_{29}H_{30}NO_6S$ ($M+H^+$) 520.2, found 520.1.

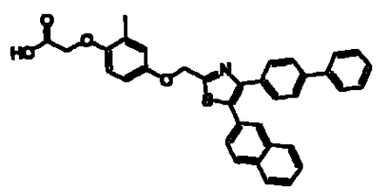
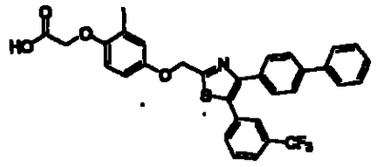
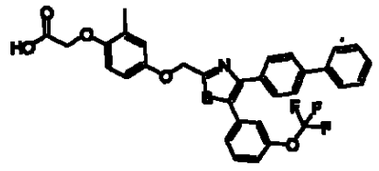
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F41		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.40 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.63 (s, 2H), 3.81 (s, 3H), 3.42 (m, 1H), 2.28 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H). MS calculated for $C_{29}H_{30}NO_5S_2$ ($M+H^+$) 536.2, found 536.1.
F42		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.05 (s, 1H), 7.81 (dd, J = 2.4, 6.8 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.48 (m, 3H), 7.37 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 2.8 Hz, 1H), 6.81 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.38 (s, 2H), 4.64 (s, 2H), 2.29 (s, 3H). MS calculated for $C_{30}H_{23}F_3NO_5S$ ($M+H^+$) 566.2, found 566.1.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F43		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.09 (s, 1H), 7.80 (m, 2H), 7.74 (d, J = 8.4 Hz, 1H), 7.51 (dd, J = 1.6, 8.4 Hz, 1H), 7.47 (m, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 2.8 Hz, 1H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.38 (s, 2H), 4.64 (s, 2H), 2.47 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{30}H_{29}NO_4S_2$ ($M+H^+$) 528.1, found 528.1.
F44		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.05 (s, 1H), 7.82 (dd, J = 2.0, 7.2 Hz, 1H) 7.77(d, J = 8.4 Hz, 2), 7.55 (d, J = 8.4 Hz, 2H), 7.48 (m, 5H), 6.92 (d, J = 2.8 Hz, 1H), 6.82 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.41 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{30}H_{26}F_3NO_4S$ ($M+H^+$) 550.1, found 550.1.
F45		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.14 (s, 1H), 7.80 (m, 2H), 7.76 (d, J = 8.8 Hz, 1H) 7.56 (m, 5H), 7.46 (m, 6H), 7.37 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 2.8 Hz, 1H), 6.83 (dd, J = 3.2, 8.8 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 5.41 (s, 2H), 4.65 (s, 2H), 2.31 (s, 3H). MS calculated for $C_{35}H_{29}NO_4S$ ($M+H^+$) 558.2, found 558.1.

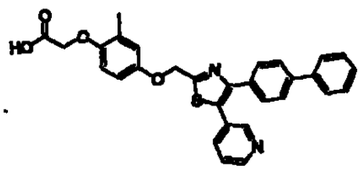
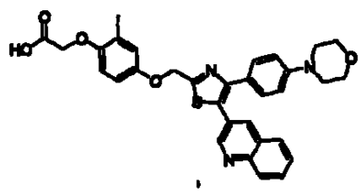
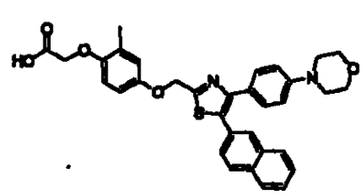
110

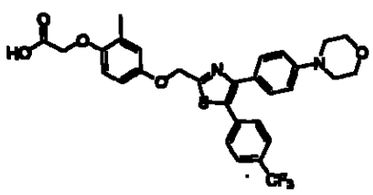
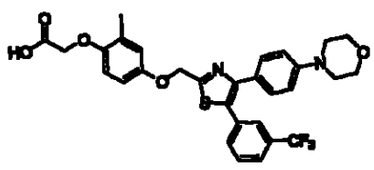
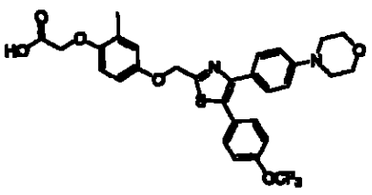
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F46		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.07 (s, 1H), 7.81 (dd, J = 2.0, 8.8 Hz, 1H), 7.75 (m, 2H), 7.47 (m, 3H), 7.31 (m, 2H), 7.23 (s, 1H), 7.17 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 2.8 Hz, 1H), 6.81 (dd, J = 2.8, 8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 5.39 (s, 2H), 4.64 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{30}H_{23}F_3NO_3S$ ($M+H^+$) 566.1, found 566.1.
F47		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.88 (d, J = 1.6 Hz, 1H), 8.72 (d, J = 5.6 Hz, 1H), 8.01 (m, 2H), 7.84 (t, J = 8.0 Hz, 2H), 7.78 (d, J = 7.2 Hz, 1H), 7.54 (m, 3H), 7.43 (dd, J = 1.6, 8.4 Hz, 1H), 6.92 (d, J = 2.8 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 5.44 (s, 2H), 4.69 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{28}H_{23}N_2O_3S$ ($M+H^+$) 483.1, found 483.1.
F48		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.54 (m, 5H), 7.40 (t, J = 7.2 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 2.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 6.75 (dd, J = 2.8, 8.8 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 5.31 (s, 2H), 4.60 (s, 2H), 3.79 (s, 3H), 2.26 (s, 3H). MS calculated for $C_{32}H_{30}NO_3S$ ($M+H^+$) 538.2, found 538.4.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F49		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.61 (d, J = 7.2 Hz, 2H), 7.56 (s, 4H), 7.44 (t, J = 7.2 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 2.8 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.64 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{32}H_{25}F_3NO_5S$ ($M+H^+$) 592.1, found 592.4.
F50		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.54 (m, 6H), 7.41 (t, J = 7.2 Hz, 2H), 7.32 (t, J = 7.2 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H), 4.61 (s, 2H), 2.47 (s, 3H), 2.27 (s, 3H). MS calculated for $C_{32}H_{28}NO_4S_2$ ($M+H^+$) 554.1, found 554.3.
F51		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.58 (m, 8H), 7.49 (d, J = 8.4 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.35 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 2.8 Hz, 1H), 6.81 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{32}H_{25}F_3NO_4S$ ($M+H^+$) 576.1, found 576.4.

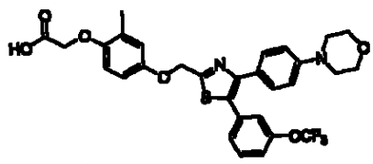
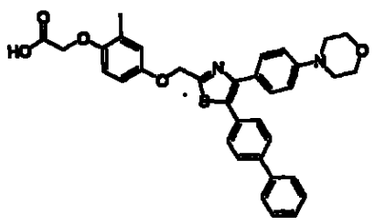
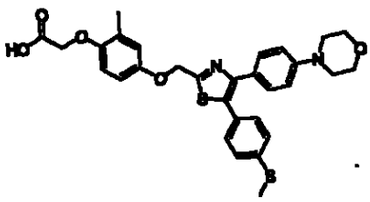
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F52		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.92 (s, 1H), 7.81 (m, 3H), 7.58 (m, 4H), 7.51 (m, 4H), 7.41 (m, 3H), 7.33 (t, J = 7.2 Hz, 1H), 6.94 (d, J = 2.8 Hz, 1H), 6.82 (dd, J = 2.8, 8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 5.40 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{35}H_{29}NO_4S$ (M+H$^+$) 558.2, found 558.4.
F53		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.66 (s, 1H), 7.58 (m, 3H), 7.54 (m, 5H), 7.44 (t, J = 7.2 Hz, 3H), 7.35 (t, J = 7.2 Hz, 1H), 6.92 (d, J = 3.2 Hz, 1H), 6.81 (dd, J = 3.2, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.38 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{36}H_{28}F_3NO_4S$ (M+H$^+$) 576.1, found 576.3.
F54		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.60 (d, J = 7.2 Hz, 2H), 7.56 (s, 4H), 7.44 (t, J = 7.2 Hz, 2H), 7.35 (m, 3H), 7.23 (s, 1H), 7.18 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 2.8 Hz, 1H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{36}H_{28}F_3NO_5S$ (M+H$^+$) 592.1, found 592.4.

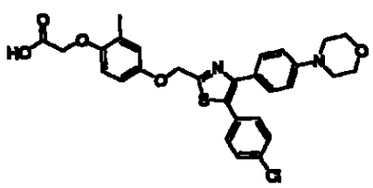
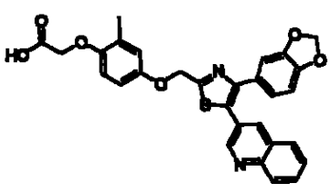
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Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F55		^{1}H-NMR (400MHz, DMSO-d6) δ = 8.59 (m, 2H), 7.85 (dt, J = 2.0, 8.0 Hz, 1H), 7.69 (m, 4H), 7.53 (d, J = 8.4 Hz, 2H), 7.47 (t, J = 7.2 Hz, 2H), 7.37 (t, J = 7.6 Hz, 1H), 6.98 (d, J = 2.8 Hz, 1H), 6.89 (dd, J = 2.8, 8.8 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 5.45 (s, 2H), 4.65 (s, 2H), 2.20 (s, 3H). MS calculated for $C_{30}H_{25}N_2O_4S$ ($M+H^+$) 509.2, found 509.4.
F56		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.97 (d, J = 1.6 Hz, 1H), 8.47 (d, J = 1.6 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 7.90 (m, 2H), 7.74 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 8.8 Hz, 2H), 6.89 (m, 3H), 6.75 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.63 (s, 2H), 3.87 (m, 4H), 3.21 (m, 4H), 2.27 (s, 3H). MS calculated for $C_{32}H_{30}N_3O_4S$ ($M+H^+$) 568.2, found 568.2.
F57		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.88 (s, 1H), 7.81 (m, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.52 (m, 5H), 7.32 (dd, J = 1.2, 8.4 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.75 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.38 (s, 2H), 4.64 (s, 2H), 3.99 (m, 4H), 3.37 (m, 4H), 2.28 (s, 3H). MS calculated for $C_{32}H_{31}N_3O_4S$ ($M+H^+$) 567.2, found 567.2.

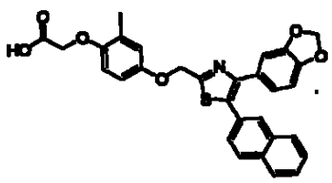
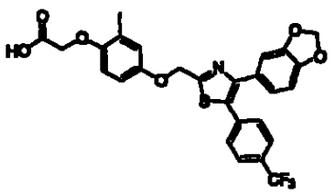
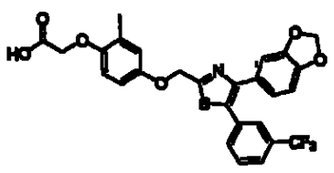
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F58		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.57 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.63 (s, 2H), 3.92 (m, 4H), 3.27 (m, 4H), 2.28 (s, 3H). MS calculated for $C_{30}H_{28}F_3N_2O_5S$ ($M+H^+$) 585.2, found 585.2.
F59		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.60 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.43 (m, 3H), 7.03 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.63 (s, 2H), 3.94 (m, 4H), 3.29 (m, 4H), 2.28 (s, 3H). MS calculated for $C_{30}H_{28}F_3N_2O_5S$ ($M+H^+$) 585.2, found 585.1.
F60		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.42 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H), 4.63 (s, 2H), 3.93 (m, 4H), 3.27 (m, 4H), 2.28 (s, 3H). MS calculated for $C_{30}H_{28}F_3N_2O_5S$ ($M+H^+$) 601.2, found 601.2.

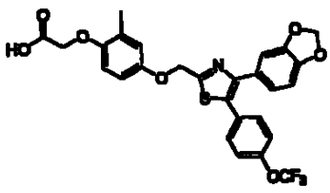
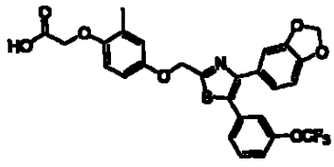
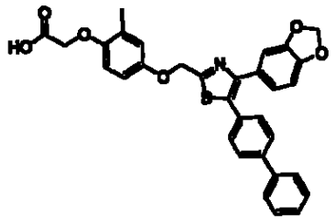
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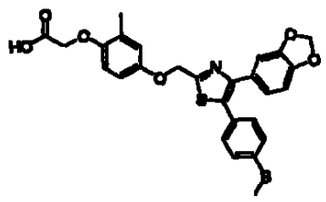
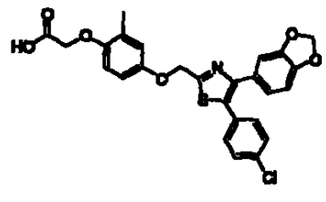
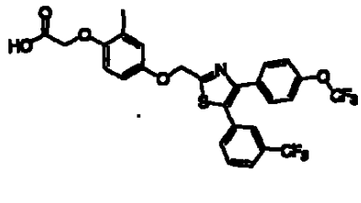
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F61		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.45 (d, J = 8.8 Hz, 2H), 7.36 (t, J = 8.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.63 (s, 2H), 3.96 (m, 4H), 3.30 (m, 4H), 2.28 (s, 3H). MS calculated for $C_{30}H_{28}F_3N_2O_6S$ ($M+H^+$) 601.2, found 601.2.
F62		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.52 (d, J = 8.4 Hz, 2H), 7.47 (t, J = 8.4 Hz, 4H), 7.37 (t, J = 7.6 Hz, 2H), 7.30 (m, 3H), 7.04 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 2.8 Hz, 1H), 6.70 (dd, J = 2.8, 8.8 Hz, 1H), 6.61 (d, J = 8.8 Hz, 1H), 5.27 (s, 2H), 4.55 (s, 2H), 3.90 (m, 4H), 3.26 (m, 4H), 2.20 (s, 3H). MS calculated for $C_{35}H_{33}N_2O_5S$ ($M+H^+$) 593.2, found 593.2.
F63		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.54 (d, J = 8.8 Hz, 2H), 7.21 (m, 6H), 6.88 (d, J = 2.8 Hz, 1H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H), 4.63 (s, 2H), 4.03 (m, 4H), 3.40 (m, 4H), 2.49 (s, 3H), 2.28 (s, 3H). MS calculated for $C_{30}H_{31}N_2O_5S_2$ ($M+H^+$) 563.2, found 563.2.

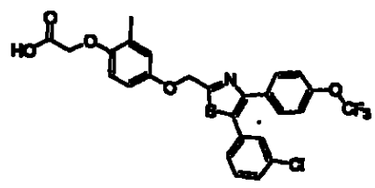
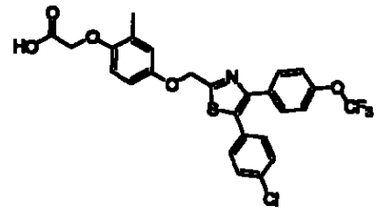
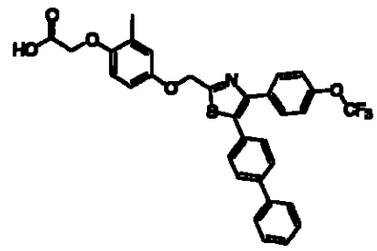
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F64		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.48 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 2.8 Hz, 1H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H), 4.63 (s, 2H), 4.00 (m, 4H), 3.36 (m, 4H), 2.28 (s, 3H), 2.28 (s, 3H). MS calculated for $C_{29}H_{29}ClN_2O_5S$ ($M+H^+$) 551.1, found 551.2.
F65		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.92 (d, J = 1.6 Hz, 1H), 8.36 (s, 1H), 8.29 (d, J = 8.8 Hz, 1H), 7.84 (m, 2H), 7.68 (t, J = 8.0 Hz, 1H), 6.97 (d; J = 1.2 Hz, 1H), 6.91 (m, 2H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.97 (s, 2H), 5.37 (s, 2H), 4.65 (s, 2H), 2.28 (s, 3H). MS calculated for $C_{29}H_{23}N_2O_6S$ ($M+H^+$) 527.1, found 527.3.

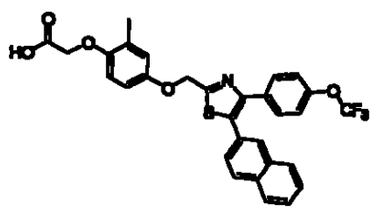
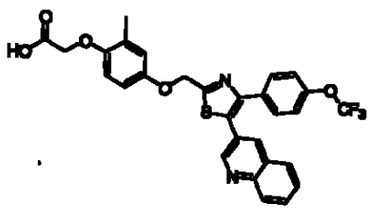
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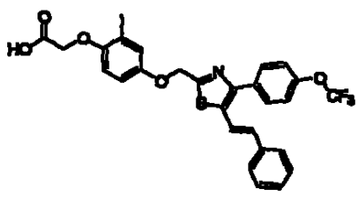
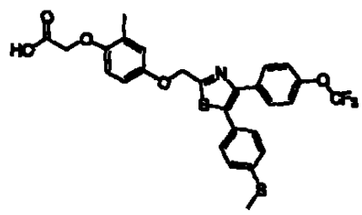
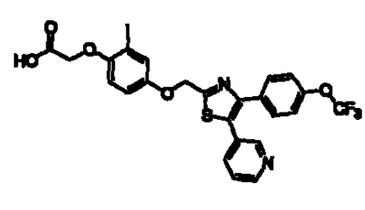
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F66		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.87 (s, 1H), 7.81 (m, 2H), 7.76 (d, J = 8.8 Hz, 1H), 7.51 (m, 2H), 7.33 (dd, J = 2.0, 8.8 Hz, 1H), 6.99 (m, 2H), 6.92 (d, J = 2.8 Hz, 1H), 6.81 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.0 Hz, 2H), 5.95 (s, 2H), 5.40 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{29}H_{24}NO_6S$ ($M+H^+$) 526.1, found 526.3.
F67		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.57 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 6.94 (m, 2H), 6.90 (d, J = 3.2 Hz, 1H), 6.77 (m, 2H), 6.70 (d, J = 8.8 Hz, 1H), 5.98 (s, 2H), 5.33 (s, 2H), 4.64 (s, 2H), 2.29 (s, 3H). MS calculated for $C_{27}H_{21}F_3NO_6S$ ($M+H^+$) 544.1, found 544.3.
F68		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.60 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 6.93 (m, 2H), 6.90 (d, J = 3.2 Hz, 1H), 6.78 (dd, J = 3.2, 8.8 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.97 (s, 2H), 5.35 (s, 2H), 4.65 (s, 2H), 2.29 (s, 3H). MS calculated for $C_{27}H_{21}F_3NO_6S$ ($M+H^+$) 544.1, found 544.3.

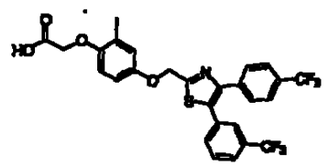
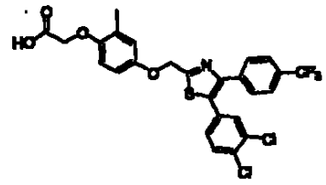
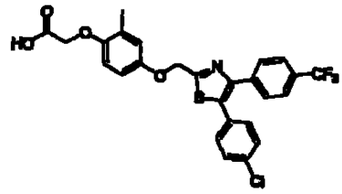
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F69		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.35 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.94 (m, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.77 (m, 2H), 6.70 (d, J = 8.8 Hz, 1H), 5.97 (s, 2H), 5.33 (s, 2H), 4.64 (s, 2H), 2.29 (s, 3H). MS calculated for $C_{27}H_{21}F_3NO_7S$ ($M+H^+$) 560.1, found 560.3.
F70		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.36 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.16 (m, 2H), 6.95 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 1.2 Hz, 1H), 6.90 (d, J = 2.0 Hz, 1H), 6.77 (m, 2H), 6.70 (d, J = 8.8 Hz, 1H), 5.97 (s, 2H), 5.33 (s, 2H), 4.64 (s, 2H), 2.29 (s, 3H). MS calculated for $C_{27}H_{21}F_3NO_7S$ ($M+H^+$) 560.1, found 560.3.
F71		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.58 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.37 (m, 3H), 7.02 (dd, J = 1.6, 8.0 Hz, 1H), 6.98 (d, J = 1.6 Hz, 1H), 6.90 (d, J = 2.4 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.96 (s, 2H), 5.36 (s, 2H), 4.63 (s, 2H), 2.28 (s, 3H). MS calculated for $C_{26}H_{22}NO_6S$ ($M+H^+$) 552.1, found 552.4.

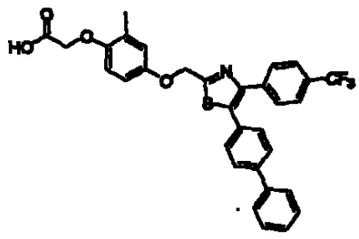
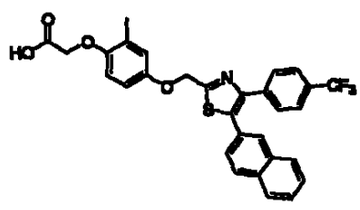
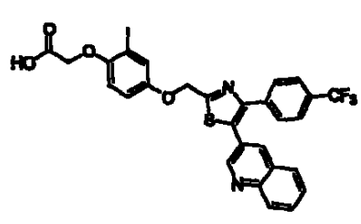
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F72		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.25 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.69 (dd, J = 1.6, 8.0 Hz, 1H), 6.97 (d, J = 1.6 Hz, 1H), 6.90 (d, J = 3.2 Hz, 1H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.96 (s, 2H), 5.33 (s, 2H), 4.63 (s, 2H), 2.49 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{27}H_{24}NO_6S_2$ ($M+H^+$) 522.1, found 522.3.
F73		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.30 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 6.95 (dd, J = 1.6, 8.0 Hz, 1H), 6.93 (d, J = 1.6 Hz, 1H), 6.89 (d, J = 2.8 Hz, 1H), 6.76 (m, 2H), 6.70 (d, J = 8.8 Hz, 1H), 5.97 (s, 2H), 5.33 (s, 2H), 4.64 (s, 2H), 2.29 (s, 3H). MS calculated for $C_{26}H_{21}ClNO_6S$ ($M+H^+$) 510.1, found 510.2.
F74		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.59 (d, J = 8.8 Hz, 2H), 7.48 (m, 4H), 7.16 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 2.8 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.65 (s, 2H), 2.29 (s, 3H). MS calculated for $C_{27}H_{20}F_6NO_5S$ ($M+H^+$) 584.1, found 584.3.

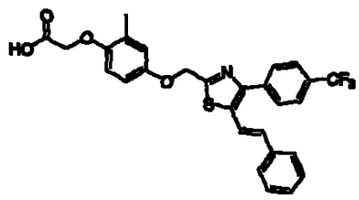
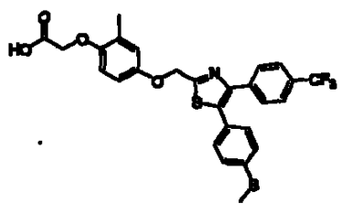
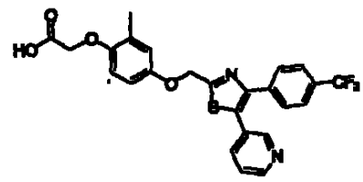
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F75		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.52 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.26 (t, J = 8.0 Hz, 1H), 7.17 (t, J = 8.4 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.65 (s, 2H), 2.29 (s, 3H). MS calculated for $C_{26}H_{20}ClF_3NO_3S$ ($M+H^+$) 550.1, found 550.3.
F76		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.49 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 2.8 Hz, 1H), 6.76 (dd, J = 2.8, 8.8 Hz, 1H), 6.68 (d, J = 8.8 Hz, 1H), 5.30 (s, 2H), 4.62 (s, 2H), 2.26 (s, 3H). MS calculated for $C_{26}H_{20}ClF_3NO_3S$ ($M+H^+$) 550.1, found 550.3.
F77		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.57 (m, 6H), 7.43 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 7.6 Hz, 3H), 7.13 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.75 (dd, J = 2.8, 8.8 Hz, 1H), 6.68 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H), 4.62 (s, 2H), 2.27 (s, 3H). MS calculated for $C_{32}H_{25}F_3NO_3S$ ($M+H^+$) 592.1, found 592.4.

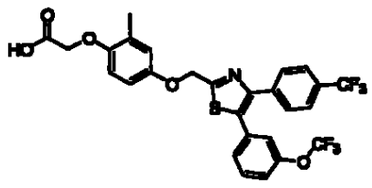
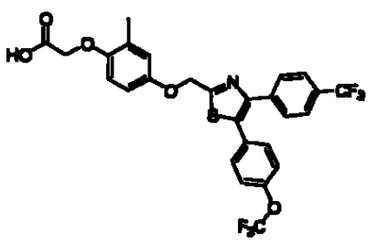
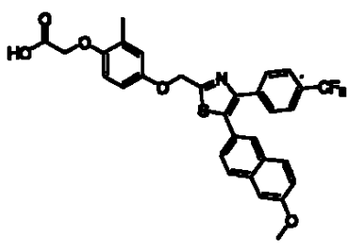
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F78		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.87 (s, 1H), 7.83 (m, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.51 (t, J = 8.0 Hz, 2H), 7.34 (dd, J = 1.6, 8.4 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 2.8 Hz, 1H), 6.81 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{29}H_{23}F_3NO_3S$ ($M+H^+$) 566.1, found 566.3.
F79		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.90 (d, J = 2.0 Hz, 1H), 8.23 (m, 2H), 7.80 (m, 2H), 7.65 (t, J = 7.2 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 3.2 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 5.39 (s, 2H), 4.66 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{28}H_{22}F_3N_2O_3S$ ($M+H^+$) 567.1, found 567.3.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F80		^{1}H-NMR (400MHz, DMSO-d6) δ = 8.10 (s, 1H), 7.66 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 7.2 Hz, 2H), 7.32 (d, J = 7.2 Hz, 2H), 7.17 (m, 4H), 6.92 (d, J = 16.4 Hz, 1H), 6.78 (d, J = 2.8 Hz, 1H), 6.69 (dd, J = 2.8, 8.8 Hz, 1H), 6.62 (d, J = 8.8 Hz, 1H), 5.22 (s, 2H), 4.46 (s, 2H), 2.07 (s, 3H). MS calculated for $C_{28}H_{22}F_3NO_3S$ ($M+H^+$) 542.1, found 542.3.
F81		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.54 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.64 (s, 2H), 2.50 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{29}H_{25}F_3NO_3S_2$ ($M+H^+$) 562.1, found 562.3.
F82		^{1}H-NMR (400MHz, DMSO-d6) δ = 8.58 (dd, J = 1.6, 8.8 Hz, 1H), 8.54 (d, J = 2.0 Hz, 1H), 8.24 (s, 1H), 7.80 (dt, J = 2.0, 8.0 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.44 (dd, J = 5.2, 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 2.8 Hz, 1H), 6.85 (dd, J = 3.2, 8.8 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 5.40 (s, 2H), 4.60 (s, 2H), 2.20 (s, 3H). MS calculated for $C_{27}H_{22}F_3N_2O_3S$ ($M+H^+$) 517.1, found 517.3.

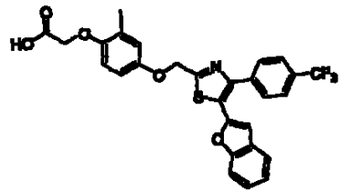
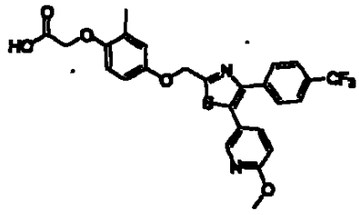
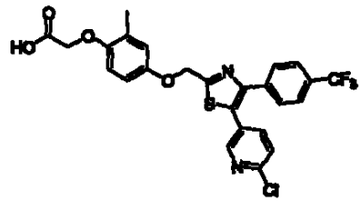
Compound Number	Compound Structure	Physical Data ^1H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F83		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.61 (d, J = 2.8 Hz, 2H), 7.57 (m, 4H), 7.47 (s, 1H), 7.46 (d, J = 3.2 Hz, 1H), 6.91 (d, J = 2.8 Hz, 1H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{27}H_{20}F_6NO_4S$ ($M+H^+$) 568.1, found 567.9.
F84		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.56 (m, 4H), 7.42 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.07 (dd, J = 2.0, 8.4 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 6.75 (dd, J = 2.8, 8.8 Hz, 1H), 6.68 (d, J = 8.8 Hz, 1H), 5.30 (s, 2H), 4.61 (s, 2H), 2.26 (s, 3H). MS calculated for $C_{26}H_{19}Cl_2F_3NO_4S$ ($M+H^+$) 568.0, found 567.9.
F85		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.61 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 3.2 Hz, 1H), 6.79 (dd, J = 3.2, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{26}H_{20}ClF_3NO_4S$ ($M+H^+$) 534.1, found 534.0.

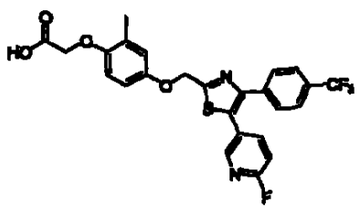
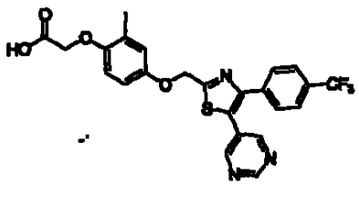
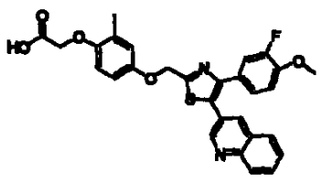
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F86		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.67 (d, J = 8.4 Hz, 2H), 7.58 (m, 6H), 7.45 (t, J = 7.2 Hz, 2H), 7.39 (m, 3H), 6.92 (d, J = 2.8 Hz, 1H), 6.81 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{32}H_{25}F_3NO_4S$ ($M+H^+$) 576.1, found 576.0.
F87		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.88 (s, 1H), 7.85 (m, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 7.52 (m, 4H), 7.32 (dd, J = 1.2, 8.4 Hz, 1H), 6.93 (d, J = 2.8 Hz, 1H), 6.82 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.38 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{30}H_{23}F_3NO_4S$ ($M+H^+$) 550.1, found 550.0.
F88		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.89 (d, J = 2.0 Hz, 1H), 8.25 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.82 (m, 2H), 7.66 (d, J = 7.2 Hz, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 2.8 Hz, 1H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 5.40 (s, 2H), 4.66 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{29}H_{22}F_3N_2O_4S$ ($M+H^+$) 551.1, found 551.0.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F89		^{1}H-NMR (400MHz, DMSO-d6) δ = 8.30 (t, J = 2.0 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.37 (m, 3H), 7.30 (d, J = 7.2 Hz, 1H), 7.13 (d, J = 15.6 Hz, 1H), 6.95 (d, J = 2.8 Hz, 1H), 6.86 (dd, J = 2.8, 8.8 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 5.40 (s, 2H), 4.62 (s, 2H), 2.20 (s, 3H). MS calculated for $C_{28}H_{23}F_3NO_4S$ ($M+H^+$) 526.1, found 526.0.
F90		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.63 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.21 (m, 4H), 6.90 (d, J = 2.8 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.64 (s, 2H), 2.50 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{27}H_{23}F_3NO_4S_2$ ($M+H^+$) 546.1, found 546.0.
F91		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.36 (d, J = 2.4 Hz, 1H), 8.31 (dd, J = 1.2, 8.8 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.26 (s, 4H), 7.08 (dd, J = 4.8, 8.0 Hz, 1H), 6.57 (d, J = 2.8 Hz, 1H), 6.58 (dd, J = 2.8, 8.8 Hz, 1H), 6.40 (d, J = 8.8 Hz, 1H), 5.05 (s, 2H), 4.33 (s, 2H), 1.97 (s, 3H). MS calculated for $C_{25}H_{19}F_3N_2O_4S$ ($M+H^+$) 501.1, found 501.0.

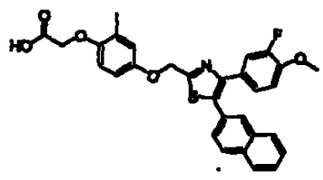
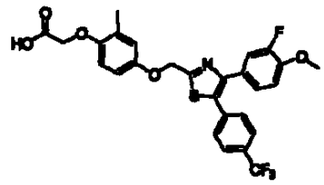
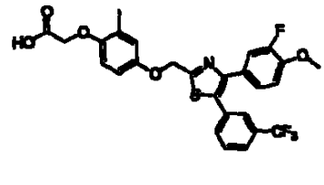
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F92		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.60 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.40 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.15 (s, 1H), 6.91 (d, J = 3.2 Hz, 1H), 6.79 (dd, J = 3.2, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{27}H_{20}F_6NO_3S$ ($M+H^+$) 584.1, found 584.0.
F93		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.60 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 3.2 Hz, 1H), 6.79 (dd, J = 3.2, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{27}H_{20}F_6NO_3S$ ($M+H^+$) 584.1, found 584.0.
F94		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.79 (s, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 3H), 7.51 (d, J = 8.0 Hz, 2H), 7.29 (dd, J = 1.6, 8.4 Hz, 1H), 7.18 (dd, J = 2.4, 8.8 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 3.2 Hz, 1H), 6.82 (dd, J = 3.2, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.65 (s, 2H), 3.94 (s, 3H), 2.30 (s, 3H). MS calculated for $C_{31}H_{25}F_3NO_3S$ ($M+H^+$) 580.1, found 580.0.

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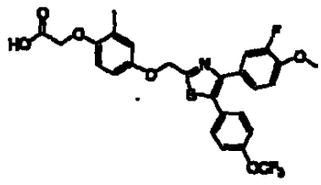
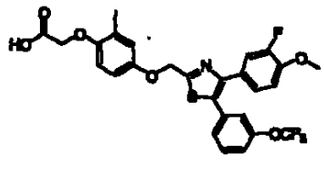
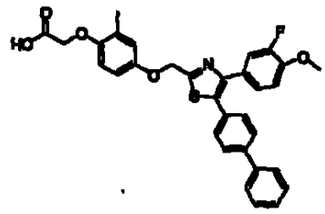
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F95		^{1}H-NMR (400MHz, DMSO-d6) δ = 8.33 (s, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 6.8 Hz, 1H), 7.29 (t, J = 7.2 Hz, 1H), 7.06 (s, 1H), 7.01 (d, J = 3.2 Hz, 1H), 6.91 (dd, J = 3.2, 8.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 5.49 (s, 2H), 4.66 (s, 2H), 2.23 (s, 3H). MS calculated for $C_{28}H_{21}F_3NO_3S$ ($M+H^+$) 540.1, found 540.0.
F96		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.17 (d, J = 2.0 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.47 (dd, J = 2.8, 8.4 Hz, 1H), 6.91 (d, J = 2.8 Hz, 1H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.73 (t, J = 8.8 Hz, 2H), 5.34 (s, 2H), 4.65 (s, 2H), 3.96 (s, 3H), 2.30 (s, 3H). MS calculated for $C_{28}H_{21}F_3N_2O_3S$ ($M+H^+$) 531.1, found 531.0.
F97		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.35 (d, J = 2.4 Hz, 1H), 7.56 (m, 4H), 7.53 (dd, J = 2.4, 8.4 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 2.8 Hz, 1H), 6.76 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.32 (s, 2H), 4.62 (s, 2H), 2.26 (s, 3H). MS calculated for $C_{27}H_{19}ClF_3N_2O_3S$ ($M+H^+$) 535.1, found 535.0.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F98		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.23 (d, J = 2.4 Hz, 1H), 7.70 (dt, J = 2.8, 8.4 Hz, 1H), 7.58 (m, 4H), 7.53 (dd, J = 2.4, 8.4 Hz, 1H), 6.95 (dd, J = 2.0, 8.4 Hz, 1H), 6.90 (d, J = 2.8 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 2.29 (s, 3H). MS calculated for $C_{29}H_{19}F_4N_2O_4S$ ($M+H^+$) 519.1, found 519.0.
F99		^{1}H-NMR (400MHz, DMSO-d6) δ = 9.21 (s, 1H), 8.82 (s, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 2.8 Hz, 1H), 6.88 (dd, J = 2.8, 8.8 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 5.47 (s, 2H), 4.63 (s, 2H), 2.20 (s, 3H). MS calculated for $C_{24}H_{19}F_3N_3O_4S$ ($M+H^+$) 502.1, found 502.0.
F100		^{1}H-NMR (400MHz, $CDCl_3$) δ = 9.06 (d, J = 1.6 Hz, 1H), 8.56 (s, 1H), 8.46 (d, J = 8.8 Hz, 1H), 7.80 (t, J = 7.2 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.28 (m, 1H), 7.12 (d, J = 8.4 Hz, 1H), 6.89 (m, 2H), 6.76 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.39 (s, 2H), 4.66 (s, 2H), 3.89 (s, 3H), 2.28 (s, 3H). MS calculated for $C_{29}H_{24}FN_2O_5S$ ($M+H^+$) 531.1, found 531.3.

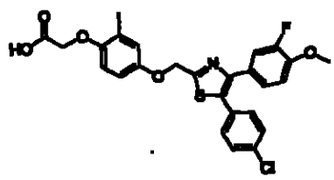
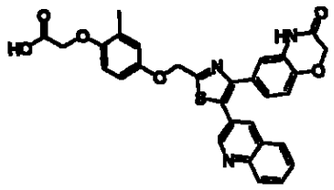
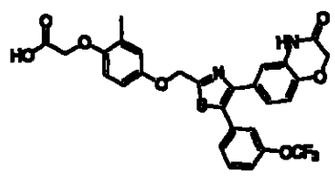
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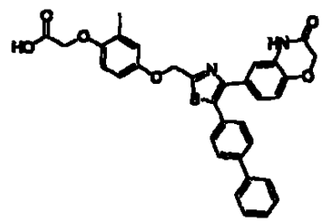
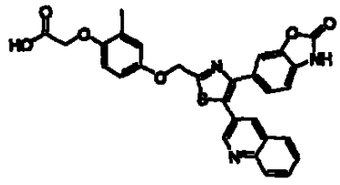
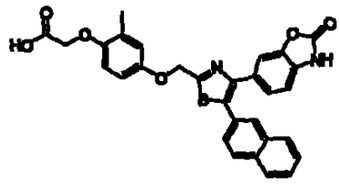
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F101		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.88 (s, 1H), 7.80 (m, 3 H), 7.51 (m, 2H), 7.34 (dd, J = 2.0, 8.8 Hz, 1H), 7.30 (dd, J = 2.0, 12.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 2.8 Hz, 1H), 6.84 (t, J = 8.4 Hz, 1H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.65 (s, 2H), 3.87 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{30}H_{25}FNO_3S$ ($M+H^+$) 530.1, found 530.3.
F102		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.59 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.24 (dd, J = 1.6, 12 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 6.89 (m, 2H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 3.90 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{27}H_{22}F_4NO_3S$ ($M+H^+$) 548.1, found 548.4.
F103		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.59 (m, 2H), 7.47 (m, 2H), 7.22 (dd, J = 2.0, 12.4 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 7.90 (d, J = 2.8 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 3.90 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{27}H_{22}F_4NO_3S$ ($M+H^+$) 548.1, found 548.4.

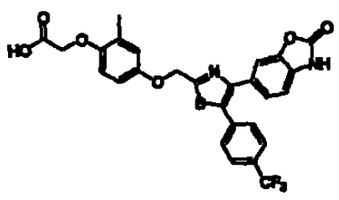
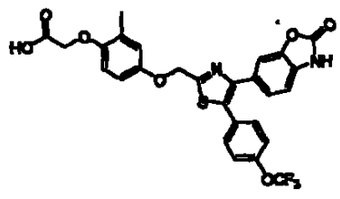
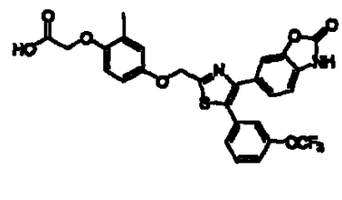
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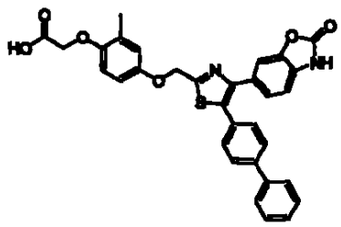
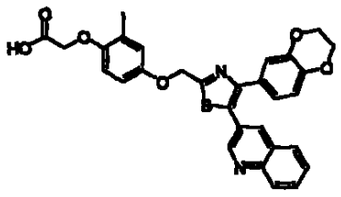
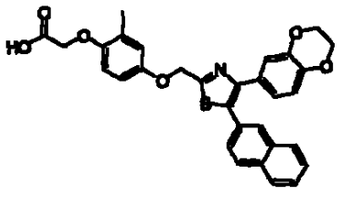
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F104		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.35 (d, J = 8.4 Hz, 2H), 7.21 (m, 3H), 6.89 (m, 2H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.65 (s, 2H), 3.90 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{27}H_{22}F_4NO_4S$ ($M+H^+$) 564.1, found 564.3.
F105		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.53 (t, J = 7.6 Hz, 1H), 7.41 (m, 2H), 7.35 (m, 3H), 7.04 (m, 2H), 6.93 (dd, J = 2.8, 8.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 5.49 (s, 2H), 4.80 (s, 2H), 4.05 (s, 3H), 2.44 (s, 3H). MS calculated for $C_{27}H_{22}F_4NO_4S$ ($M+H^+$) 564.1, found 564.3.
F106		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.40 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.25 (m, 2H), 7.18 (m, 3H), 7.10 (dd, J = 1.2, 12.4 Hz, 1H), 7.06 (m, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 6.59 (dd, J = 2.8, 8.8 Hz, 1H), 6.50 (d, J = 8.8 Hz, 1H), 5.14 (s, 2H), 4.44 (s, 2H), 3.69 (s, 3H), 2.09 (s, 3H). MS calculated for $C_{32}H_{27}FNO_3S$ ($M+H^+$) 556.2, found 556.2.

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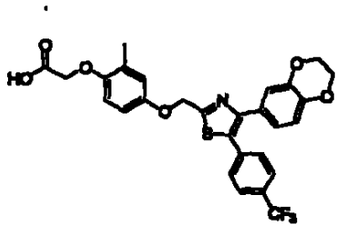
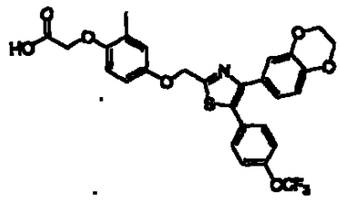
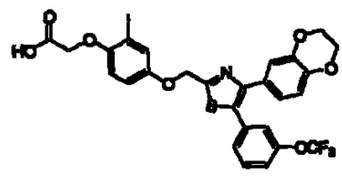
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F107		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.26 (d, J = 8.8 Hz, 2H), 7.20 (m, 3H), 7.11 (d, J = 8.4 Hz, 1H), 6.83 (m, 2H), 6.72 (dd, J = 2.8, 8.8 Hz, 1H), 6.65 (d, J = 8.8 Hz, 1H), 5.28 (s, 2H), 4.58 (s, 2H), 3.83 (s, 3H), 2.29 (s, 3H). MS calculated for $C_{29}H_{27}ClFNO_5S$ ($M+H^+$) 514.1, found 514.2.
F108		^{1}H-NMR (400MHz, DMSO-d6) δ = 10.61 (s, 1H), 8.60 (d, J = 2.0 Hz, 1H), 8.41 (s, 1H), 7.91 (d, J = 8.8 Hz, 2H), 7.70 (t, J = 7.6 Hz, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.04 (d, J = 1.6 Hz, 1H), 6.83 (m, 2H), 6.76 (m, 2H), 6.68 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H), 4.52 (s, 2H), 4.48 (s, 2H), 2.09 (s, 3H). MS calculated for $C_{30}H_{24}N_2O_6S$ ($M+H^+$) 554.1, found 554.1.
F109		^{1}H-NMR (400MHz, DMSO-d6) δ = 10.66 (s, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.17 (s, 1H), 7.05 (d, J = 2.4 Hz, 1H), 6.85 (d, J = 2.8 Hz, 1H), 6.77 (m, 3H), 6.68 (d, J = 8.8 Hz, 1H), 5.29 (s, 2H), 4.53 (s, 2H), 4.48 (s, 2H), 2.11 (s, 3H). MS calculated for $C_{30}H_{24}F_3N_2O_6S$ ($M+H^+$) 587.1, found 587.1.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F110		^{1}H-NMR (400MHz, DMSO-d6) δ = 10.73 (s, 1H), 7.66 (d, J = 8.0 Hz, 4H), 7.44 (m, 4H), 7.35 (t, J = 7.6 Hz, 1H), 7.21 (d, J = 1.6 Hz, 1H), 6.93 (m, 2H), 6.75 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.59 (s, 2H), 4.55 (s, 2H), 2.21 (s, 3H). MS calculated for $C_{30}H_{27}N_3O_5S$ ($M+H^+$) 579.2, found 579.1.
F111		^{1}H-NMR (400MHz, DMSO-d6) δ = 11.60 (s, 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.44 (s, 1H), 7.96 (d, J = 7.2 Hz, 1H), 7.81 (t, J = 7.2 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 2.8 Hz, 1H), 6.86 (dd, J = 2.8, 8.4 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 5.42 (s, 2H), 4.59 (s, 2H), 2.27 (s, 3H). MS calculated for $C_{29}H_{23}N_3O_5S$ ($M+H^+$) 540.1, found 540.1.
F112		^{1}H-NMR (400MHz, DMSO-d6) δ = 11.55 (s, 1H), 7.93 (s, 1H), 7.84 (m, 3H), 7.50 (m, 2H), 7.32 (dd, J = 2.0, 8.8 Hz, 1H), 7.29 (s, 1H), 7.22 (d, J = 9.6 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.56 (s, 2H), 2.21 (s, 3H). MS calculated for $C_{30}H_{23}N_2O_5S$ ($M+H^+$) 539.1, found 539.1.

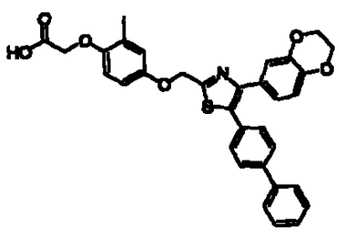
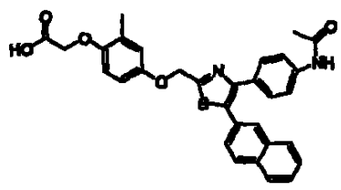
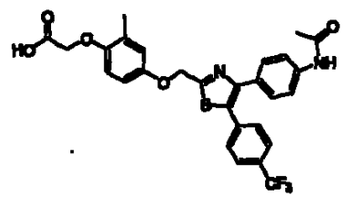
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F113		^{1}H-NMR (400MHz, DMSO-d6) δ = 11.62 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 7.6 Hz, 2H), 7.31 (s, 1H), 7.20 (d, J = 7.6 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.92 (s, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 5.38 (s, 2H), 4.59 (s, 2H), 2.25 (s, 3H). MS calculated for $C_{27}H_{20}F_3N_2O_5S$ ($M+H^+$) 557.1, found 557.3.
F114		^{1}H-NMR (400MHz, DMSO-d6) δ = 11.64 (s, 1H), 8.13 (m, 2H), 7.49 (m, 2H), 7.33 (br s, 3H), 7.26 (d, J = 8.4 Hz, 1H), 7.03 (dd, J = 4.0, 8.0 Hz, 1H), 6.95 (s, 1H), 6.88 (m, 1H), 6.79 (dd, J = 3.2, 8.8 Hz, 1H), 5.41 (s, 2H), 4.63 (s, 2H), 2.30 (s, 3H). MS calculated for $C_{27}H_{20}F_3N_2O_5S$ ($M+H^+$) 573.1, found 573.2.
F115		^{1}H-NMR (400MHz, DMSO-d6) δ = 11.35 (s, 1H), 7.88 (m, 2H), 7.24 (t, J = 8.0 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 7.03 (d, J = 9.6 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.72 (d, J = 8.0 Hz, 1H), 6.65 (s, 1H), 6.58 (dd, J = 2.4, 8.8 Hz, 1H), 6.49 (d, J = 8.8 Hz, 1H), 5.10 (s, 2H), 4.32 (s, 2H), 1.97 (s, 3H). MS calculated for $C_{27}H_{20}F_3N_2O_5S$ ($M+H^+$) 573.1, found 573.2.

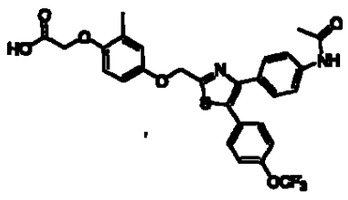
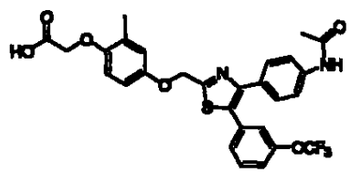
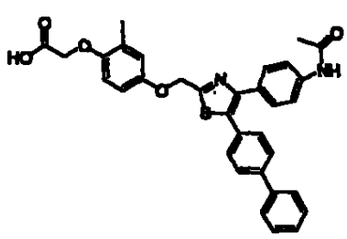
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F116		^{1}H-NMR (400MHz, DMSO-d6) δ = 11.68 (s, 1H), 8.23 (m, 2H), 7.67 (d, J = 8.0 Hz, 4H), 7.44 (m, 4H), 7.37 (d, J = 6.8 Hz, 1H), 7.33 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.93 (s, 1H), 6.85 (dd, J = 2.4, 8.8 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.60 (s, 2H), 2.21 (s, 3H). MS calculated for $C_{32}H_{33}N_2O_6S$ ($M+H^+$) 565.1, found 565.1.
F117		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.87 (s, 1H), 8.27 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.79 (m, 2H), 7.63 (t, J = 7.6 Hz, 1H), 7.05 (s, 1H), 6.89 (s, 2H), 6.78 (m, 2H), 6.71 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.64 (s, 2H), 4.23 (m, 4H), 2.28 (s, 3H). MS calculated for $C_{30}H_{29}N_2O_6S$ ($M+H^+$) 541.1, found 541.1.
F118		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.88 (s, 1H), 7.80 (m, 2H), 7.75 (d, J = 8.8 Hz, 1H), 7.49 (m, 2H), 7.36 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 1.2 Hz, 1H), 6.94 (m, 2H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.73 (t, J = 8.8 Hz, 2H), 5.37 (s, 2H), 4.64 (s, 2H), 4.23 (m, 4H), 2.01 (s, 3H). MS calculated for $C_{31}H_{29}NO_6S$ ($M+H^+$) 540.1, found 540.2.

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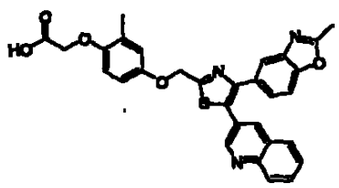
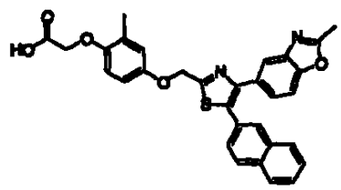
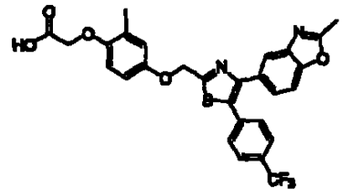
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F119		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.56 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 2.0 Hz, 1H), 6.89 (m, 2H), 6.77 (m, 2H), 6.70 (d, J = 8.8 Hz, 1H), 5.32 (s, 2H), 4.63 (s, 2H), 4.26 (m, 4H), 2.28 (s, 3H). MS calculated for $C_{28}H_{23}F_3NO_6S$ ($M+H^+$) 558.1, found 558.1.
F120		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.37 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 2.0 Hz, 1H), 6.90 (m, 2H), 6.77 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 8.8 Hz, 1H), 5.31 (s, 2H), 4.63 (s, 2H), 4.26 (m, 4H), 2.28 (s, 3H). MS calculated for $C_{28}H_{23}F_3NO_7S$ ($M+H^+$) 574.1, found 574.1.
F121		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.35 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 2.0 Hz, 1H), 6.92 (dd, J = 2.0, 8.4 Hz, 1H), 6.89 (d, J = 2.8 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.32 (s, 2H), 4.63 (s, 2H), 4.25 (m, 4H), 2.28 (s, 3H). MS calculated for $C_{28}H_{23}F_3NO_7S$ ($M+H^+$) 574.1, found 574.1.

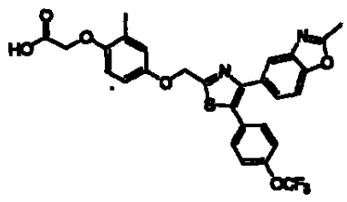
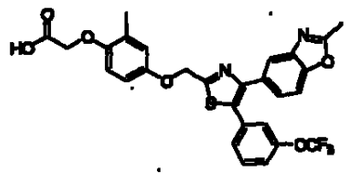
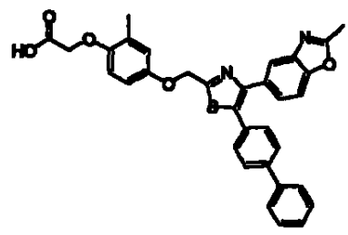
136 135

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F122		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.60 (d, J = 7.2 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.42 (m, 5H), 7.08 (d, J = 2.4 Hz, 1H), 6.97 (dd, J = 2.0, 8.4 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.64 (s, 2H), 4.25 (m, 4H), 2.29 (s, 3H). MS calculated for $C_{33}H_{29}NO_6S$ ($M+H^+$) 566.2, found 566.2.
F123		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.05 (s, 1H), 8.00 (m, 1H), 7.94 (m, 2H), 7.66 (m, 4H), 7.59 (m, 2H), 7.50 (d, J = 9.2 Hz, 1H), 7.10 (s, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 5.56 (s, 2H), 4.82 (s, 2H), 2.48 (s, 3H), 2.37 (s, 3H). MS calculated for $C_{31}H_{28}N_2O_5S$ ($M+H^+$) 539.2, found 539.2.
F124		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.43 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.31 (m, 3H), 7.13 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 2.4 Hz, 1H), 6.76 (dd, J = 2.4, 8.8 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.61 (s, 2H), 2.25 (s, 3H), 2.19 (s, 3H). MS calculated for $C_{32}H_{26}F_3N_2O_5S$ ($M+H^+$) 557.1, found 557.1.

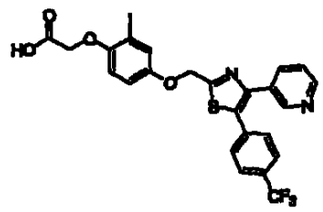
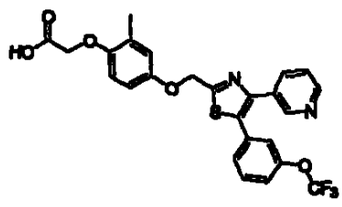
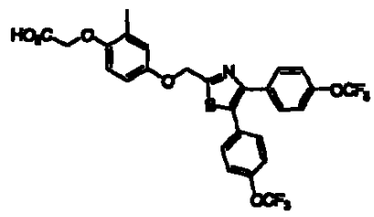
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F125		MS calculated for $C_{28}H_{24}F_3N_2O_6S$ ($M+H^+$) 573.1, found 573.1.
F126		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.45 (m, 4H), 7.35 (t, J = 8.8 Hz, 1H), 7.22 (s, 1H), 7.18 (m, 2H), 6.90 (d, J = 3.2 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.64 (s, 2H), 2.29 (s, 3H), 2.19 (s, 3H). MS calculated for $C_{28}H_{24}F_3N_2O_6S$ ($M+H^+$) 573.1, found 573.1.
F127		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.62 (d, J = 7.6 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.50 (m, 6H), 7.40 (m, 3H) 7.34 (s, 1H), 6.94 (d, J = 2.8 Hz, 1H), 6.83 (dd, J = 2.8, 8.8 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 5.40 (s, 2H), 4.67 (s, 2H), 2.32 (s, 3H), 2.23 (s, 3H). MS calculated for $C_{28}H_{28}N_2O_5S$ ($M+H^+$) 565.2, found 565.1.

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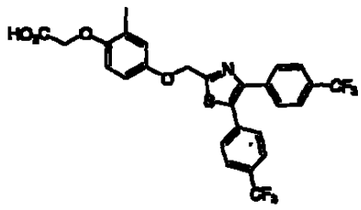
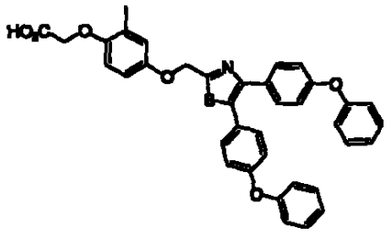
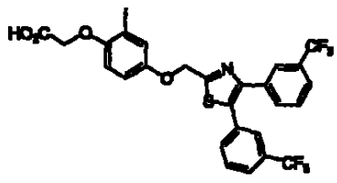
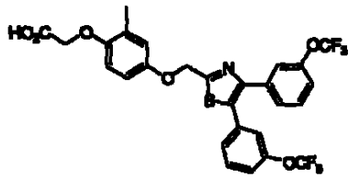
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F128		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.76 (s, 1H), 8.19 (s, 1H), 8.13 (m, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.70 (s, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.35 (s, 2H), 6.91 (s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 5.40 (s, 2H), 4.69 (s, 2H), 2.64 (s, 3H), 2.31 (s, 3H). MS calculated for $C_{28}H_{24}N_2O_5S$ ($M+H^+$) 538.1, found 538.0.
F129		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.86 (s, 1H), 7.79 (m, 2H), 7.73 (m, 2H), 7.48 (m, 2H), 7.39 (dd, J = 1.6, 8.4 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.30 (dd, J = 1.6, 6.8 Hz, 1H), 6.92 (d, J = 2.8 Hz, 1H), 6.85 (dd, J = 2.8, 8.8 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 5.39 (s, 2H), 4.67 (s, 2H), 2.65 (s, 3H), 2.30 (s, 3H). MS calculated for $C_{31}H_{25}N_2O_5S$ ($M+H^+$) 537.1, found 537.0.
F130		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.79 (s, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.47 (m, 4H), 6.90 (d, J = 2.4 Hz, 1H), 6.90 (dd, J = 2.8, 8.8 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 5.44 (s, 2H), 4.74 (s, 2H), 2.75 (s, 3H), 2.37 (s, 3H). MS calculated for $C_{29}H_{23}F_3N_2O_5S$ ($M+H^+$) 555.1, found 555.0.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F131		MS calculated for $C_{28}H_{23}F_3N_2O_5S$ ($M+H^+$) 571.1, found 571.0.
F132		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.71 (s, 1H), 7.36 (m, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.25 (m, 1H), 7.15 (m, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.82 (dd, J = 2.8, 8.8 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 5.35 (s, 2H), 4.67 (s, 2H), 2.66 (s, 3H), 2.30 (s, 3H). MS calculated for $C_{28}H_{23}F_3N_2O_5S$ ($M+H^+$) 571.1, found 571.0.
F133		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.75 (d, J = 1.2 Hz, 1H), 7.58 (d, J = 7.2 Hz, 2H), 7.45 (m, 6H), 6.90 (m, 4H), 6.85 (dd, J = 2.8, 8.8 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.67 (s, 2H), 2.65 (s, 3H), 2.30 (s, 3H). MS calculated for $C_{27}H_{27}N_2O_5S$ ($M+H^+$) 563.2, found 563.0.

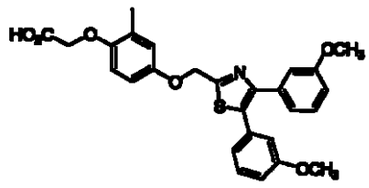
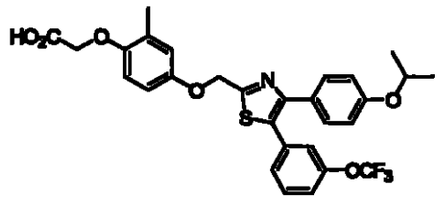
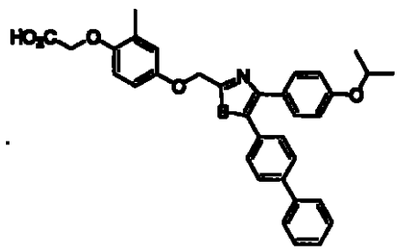
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Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
F134		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.86 (s, 1H), 8.77 (d, J = 4.4 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.55 (m, 1H), 7.47 (d, J = 8.0 Hz, 2H), 6.89 (dd, J = 2.4, 8.8 Hz, 1H), 6.80 (d, J = 2.4 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.72 (s, 2H), 2.25 (s, 3H). MS calculated for $C_{25}H_{20}F_3N_2O_4S$ ($M+H^+$) 501.1, found 501.1.
F135		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.83 (s, 1H), 8.59 (d, J = 4.4 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.34 (m, 2H), 7.23 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.12 (s, 1H), 6.83 (d, J = 2.8 Hz, 1H), 6.75 (dd, J = 2.8, 8.8 Hz, 1H), 6.68 (d, J = 8.8 Hz, 1H), 5.30 (s, 2H), 4.61 (s, 2H), 2.25 (s, 3H). MS calculated for $C_{25}H_{20}F_3N_2O_5S$. ($M+H^+$) 517.1, found 517.1.
H2		^{1}H-NMR (400MHz, CD_3OD) δ = 7.57 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 2.8 Hz, 1H), 6.85-6.76 (m, 2H), 5.35 (s, 2H), 4.62 (s, 2H), 2.26 (s, 3H). MS calculated for $C_{27}H_{20}F_6NO_5S$ ($M+H^+$) 600.08, found 600.00.

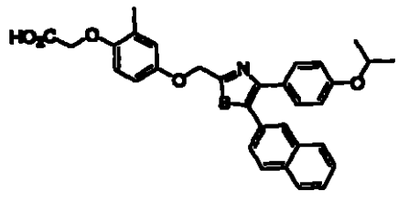
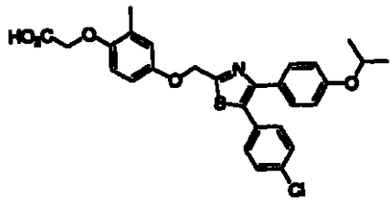
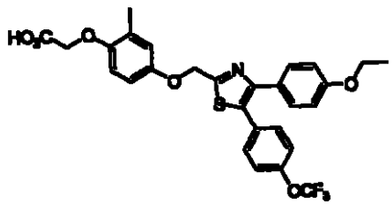
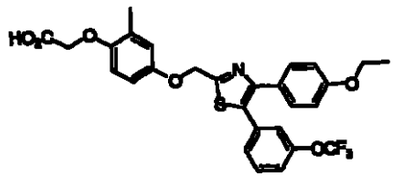
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Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
H3		^{1}H-NMR (400MHz, CD_3OD) δ = 7.71 (d, J = 8.4 Hz, 2H), 7.65 (s, 4H), 7.56 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 2.8 Hz, 1H), 6.87-6.77 (m, 2H), 5.39 (s, 2H), 4.63 (s, 2H), 2.27 (s, 3H). MS calculated for $C_{27}H_{20}F_6NO_4S$ ($M+H^+$) 568.09, found 568.00.
H4		^{1}H-NMR (400MHz, CD_3OD) δ = 7.46 (d, J = 6.8 Hz, 2H), 7.40-7.34 (m, 4H), 7.33 (d, J = 8.8 Hz, 2H), 7.17-7.12 (m, 2H), 7.04-7.00 (m, 4H), 6.96-6.91 (m, 5H), 6.85-6.76 (m, 2H), 5.33 (s, 2H), 4.62 (s, 2H), 2.26 (s, 3H). MS calculated for $C_{37}H_{30}NO_5S$ ($M+H^+$) 616.17, found 616.00.
H5		^{1}H-NMR (400MHz, CD_3OD) δ = 7.73-7.69 (m, 3H), 7.64-7.58 (m, 4H), 7.54-7.50 (m, 1H), 6.94 (d, J = 2.8 Hz, 1H), 6.87-6.77 (m, 2H), 5.39 (s, 2H), 4.62 (s, 2H), 2.26 (s, 3H). MS calculated for $C_{27}H_{20}F_6NO_4S$ ($M+H^+$) 568.09, found 568.00.
H6		^{1}H-NMR (400MHz, CD_3OD) δ = 7.53-7.37 (m, 4H), 7.32-7.30 (m, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.19 (s, 1H), 6.93 (d, J = 2.8 Hz, 1H), 6.86-6.77 (m, 2H), 5.38 (s, 2H), 4.63 (s, 2H), 2.26 (s, 3H). MS calculated for $C_{27}H_{20}F_6NO_6S$ ($M+H^+$) 600.08, found 600.00.

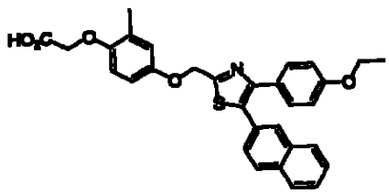
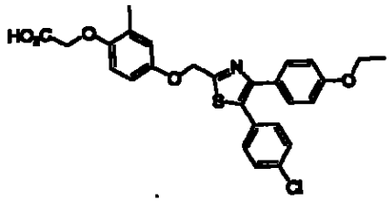
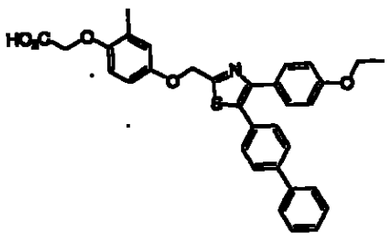
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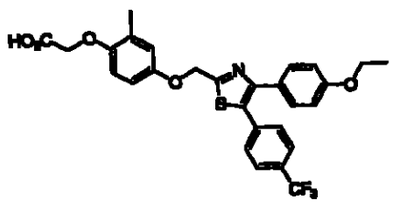
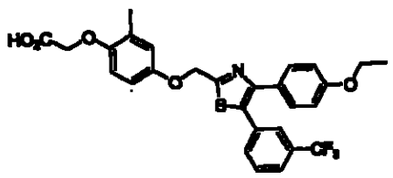
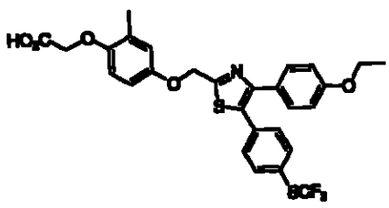
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
H7		^{1}H-NMR (400MHz, CD_3OD) δ = 7.25 (t, J = 8.0 Hz, 2H), 7.18 (t, J = 8.0 Hz, 2H), 6.97-6.79 (m, 8H), 6.73-6.71 (m, 1H), 5.33 (s, 2H), 4.57 (s, 2H), 3.62 (s, 3H), 3.58 (s, 3H), 2.12 (s, 3H). MS calculated for $C_{27}H_{25}NO_6S$ (M+H+) 492.14, found 492.00.
J2		^{1}H-NMR (400MHz, CD_3OD) δ = 7.47 (t, J = 8.0 Hz, 1H), 7.39-7.34 (m, 3H), 7.26-7.24 (m, 1H), 7.17(s, 1H), 6.94 (d, J = 3.2 Hz, 1H), 6.89-6.78 (m, 4H), 5.35 (s, 2H), 4.64 (s, 2H), 4.62 (m, 1H), 2.27 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H). MS calculated for $C_{29}H_{27}F_3NO_6S$ ($M+H^+$) 574.1, found 574.2.
J3		^{1}H-NMR (400MHz, CD_3OD) δ = 7.61-7.57 (m, 4H), 7.40-7.35 (m, 6H), 7.29 (t, J = 6.8 Hz, 1H), 6.88 (d, J = 2.8 Hz, 1H), 6.80-6.71 (m, 4H), 5.28 (s, 2H), 4.56 (s, 2H), 4.53 (m, 1H), 2.17 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H). MS calculated for $C_{29}H_{27}F_3NO_6S$ ($M+H^+$) 566.2, found 566.2.

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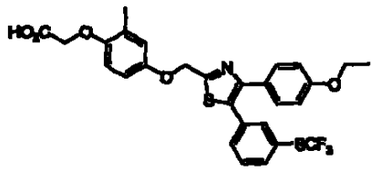
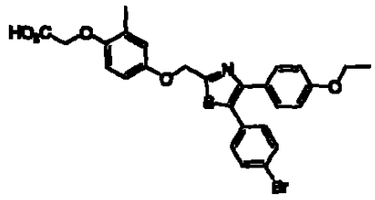
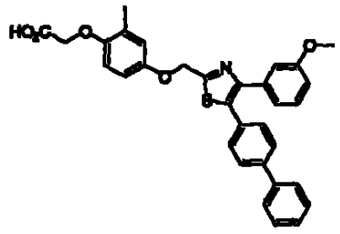
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
J4		^{1}H-NMR (400MHz, CD_3OD) δ = 7.79-7.68 (m, 4H), 7.42-7.37 (m, 2H), 7.30-7.23 (m, 3H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 4H), 5.26 (s, 2H), 4.53 (s, 2H), 4.48 (m, 1H), 2.17 (s, 3H), 1.20 (s, 3H), 1.18 (s, 3H). MS calculated for $C_{29}H_{27}F_3NO_5S$ ($M+H^+$) 540.2, found 540.2.
J5		^{1}H-NMR (400MHz, CD_3OD) δ = 7.29-7.22 (m, 6H), 6.83 (d, J = 2.4 Hz, 1H), 6.77-6.68 (m, 4H), 5.25 (s, 2H), 4.54 (s, 2H), 4.51 (m, 1H), 2.16 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H). MS calculated for $C_{28}H_{27}ClNO_5S$ ($M+H^+$) 524.1, found 524.1.
J6		^{1}H-NMR (400MHz, CD_3OD) δ = 7.36-7.16 (m, 6H), 6.85 (d, J = 2.8 Hz, 1H), 6.79-6.68 (m, 4H), 5.26 (s, 2H), 4.54 (s, 2H), 3.97-3.91 (m, 2H), 2.16 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H). MS calculated for $C_{29}H_{27}F_3NO_6S$ ($M+H^+$) 560.1, found 560.2.
J7		^{1}H-NMR (400MHz, CD_3OD) δ = 7.36-7.00 (m, 6H), 6.80 (d, J = 2.8 Hz, 1H), 6.76-6.64 (m, 4H), 5.22 (s, 2H), 4.49 (s, 2H), 3.95-3.89 (m, 2H), 2.14 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H). MS calculated for $C_{29}H_{27}F_3NO_6S$ ($M+H^+$) 560.1, found 560.2.

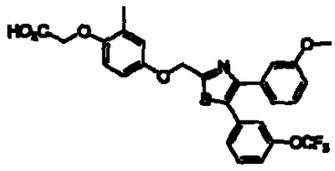
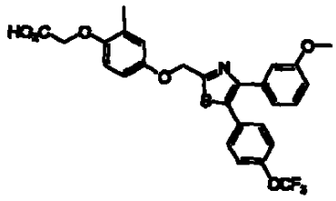
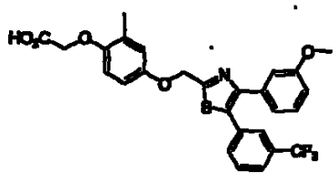
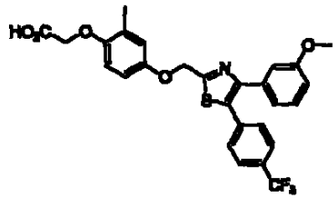
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Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
J8		^{1}H-NMR (400MHz, CD_3OD) δ = 7.80 (s, 1H), 7.77-7.69 (m, 3H), 7.43-7.40 (m, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.26 (dd, J = 1.8 Hz, J = 8.4 Hz, 1H), 6.85 (d, J = 2.8 Hz, 1H), 6.78-6.68 (m, 4H), 5.27 (s, 2H), 4.53 (s, 2H), 3.95-3.89 (m, 2H), 2.18 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H). MS calculated for $C_{31}H_{29}NO_5S$ ($M+H^+$) 526.2, found 526.2.
J9		^{1}H-NMR (400MHz, CD_3OD) δ = 7.27-7.19 (m, 6H), 6.82 (d, J = 2.8 Hz, 1H), 6.78-6.67 (m, 4H), 5.23 (s, 2H), 4.53 (s, 2H), 3.96-3.91 (m, 2H), 2.16 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H). MS calculated for $C_{27}H_{25}ClNO_5S$ ($M+H^+$) 510.1, found 510.1.
J10		^{1}H-NMR (400MHz, CD_3OD) δ = 7.54-7.49 (m, 4H), 7.34-7.23 (m, 7H), 6.82 (d, J = 2.8 Hz, 1H), 6.76-6.65 (m, 4H), 5.22 (s, 2H), 4.50 (s, 2H), 3.92-3.87 (m, 2H), 2.12 (s, 3H), 1.23 (t, J = 7.0 Hz, 3H). MS calculated for $C_{33}H_{30}NO_5S$ ($M+H^+$) 552.2, found 552.2.

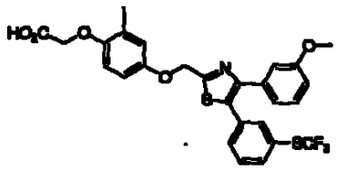
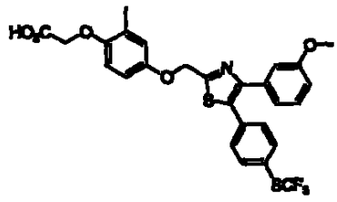
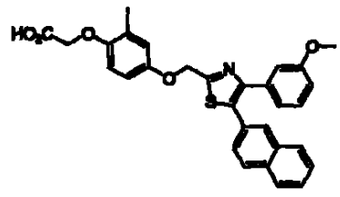
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
J11		^{1}H-NMR (400MHz, CD_3OD) δ = 7.55 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.80-6.67 (m, 4H), 5.25 (s, 2H), 4.53 (s, 2H), 3.96-3.91 (m, 2H), 2.16 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H). MS calculated for $C_{28}H_{25}F_3NO_5S$ ($M+H^+$) 544.1, found 544.1.
J12		^{1}H-NMR (400MHz, CD_3OD) δ = 7.54-7.42 (m, 4H), 7.25 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.79-6.67 (m, 4H), 5.25 (s, 2H), 4.53 (s, 2H), 3.96-3.91 (m, 2H), 2.16 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H). MS calculated for $C_{28}H_{25}F_3NO_5S$ ($M+H^+$) 544.1, found 544.1.
J13		^{1}H-NMR (400MHz, CD_3OD) δ = 7.60 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.80-6.69 (m, 4H), 5.27 (s, 2H), 4.54 (s, 2H), 3.98-3.93 (m, 2H), 2.17 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H). MS calculated for $C_{28}H_{25}F_3NO_5S_2$ ($M+H^+$) 576.1, found 576.1.

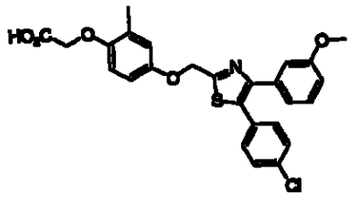
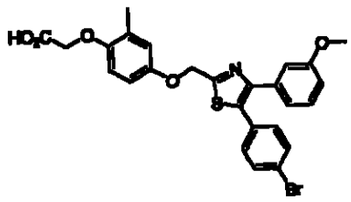
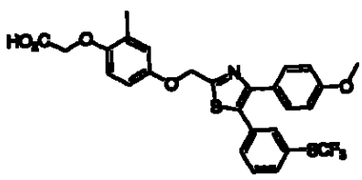
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Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
J14		^{1}H-NMR (400MHz, CD_3OD) δ = 7.58-7.45 (m, 4H), 7.27 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.81-6.68 (m, 4H), 5.25 (s, 2H), 4.53 (s, 2H), 3.96-3.91 (m, 2H), 2.16 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H). MS calculated for $C_{28}H_{25}F_3NO_5S_2$ ($M+H^+$) 576.1, found 576.1.
J15		^{1}H-NMR (400MHz, CD_3OD) δ = 7.45 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.80-6.69 (m, 4H), 5.26 (s, 2H), 4.54 (s, 2H), 3.97-3.92 (m, 2H), 2.16 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H). MS calculated for $C_{27}H_{25}BrNO_5S$ ($M+H^+$) 554.1, found 554.1.
J16		^{1}H-NMR (400MHz, CD_3OD) δ = 7.56-7.51 (m, 5H), 7.37-7.26 (m, 6H), 7.14 (t, J = 7.6 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.81-6.68 (m, 3H), 5.27 (s, 2H), 4.54 (s, 2H), 3.59 (s, 3H), 2.18 (s, 3H). MS calculated for $C_{33}H_{33}NO_5S$ ($M+H^+$) 538.2, found 538.2.

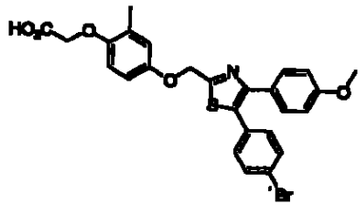
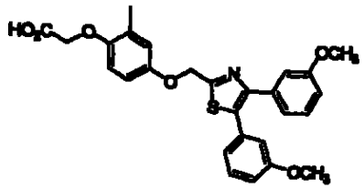
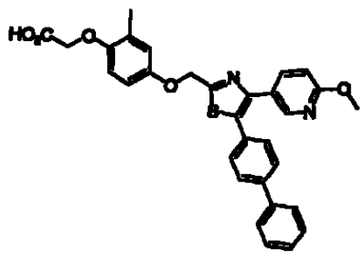
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
J17		^{1}H-NMR (400MHz, CD_3OD) δ = 7.38 (t, J = 8.0 Hz, 1H), 7.29-7.27 (m, 1H), 7.18-7.12 (m, 2H), 7.07 (s, 1H), 7.92-6.79 (m, 4H), 6.74-6.67 (m, 2H), 5.26 (s, 2H), 4.53 (s, 2H), 3.59 (s, 3H), 2.17 (s, 3H). MS calculated for $C_{27}H_{23}F_3NO_5S$ ($M+H^+$) 546.1, found 546.1.
J18		^{1}H-NMR (400MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.18-7.11 (m, 3H), 6.93-6.88 (m, 2H), 6.82 (d, J = 2.8 Hz, 1H), 6.80-6.66 (m, 3H), 5.25 (s, 2H), 4.52 (s, 2H), 3.57 (s, 3H), 2.16 (s, 3H). MS calculated for $C_{27}H_{23}F_3NO_5S$ ($M+H^+$) 546.1, found 546.1.
J19		^{1}H-NMR (400MHz, CD_3OD) δ = 7.55 (t, J = 8.0 Hz, 2H), 7.44-7.38 (m, 2H), 7.16-7.11 (m, 1H), 6.91-6.67 (m, 6H), 5.27 (s, 2H), 4.53 (s, 2H), 3.59 (s, 3H), 2.16 (s, 3H). MS calculated for $C_{27}H_{23}F_3NO_5S$ ($M+H^+$) 530.1, found 530.1.
J20		^{1}H-NMR (400MHz, CD_3OD) δ = 7.56-7.45 (m, 4H), 7.12 (t, J = 8.4 Hz, 1H), 6.89-6.66 (m, 6H), 5.26 (s, 2H), 4.52 (s, 2H), 3.57 (s, 3H), 2.15 (s, 3H). MS calculated for $C_{27}H_{23}F_3NO_5S$ ($M+H^+$) 530.1, found 530.1.

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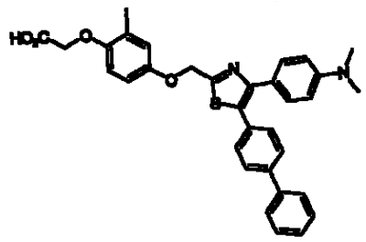
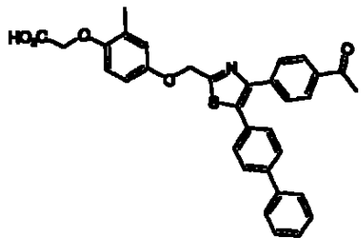
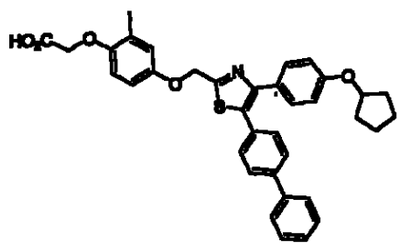
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
J21		^{1}H-NMR (400MHz, CD_3OD) δ = 7.59 (t, J = 8.0 Hz, 1H), 7.51 (s, 1H), 7.48-7.41 (m, 2H), 7.13 (t, J = 8.0 Hz, 1H), 6.91-6.87 (m, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.81-6.67 (m, 3H), 5.27 (s, 2H), 4.52 (s, 2H), 3.58 (s, 3H), 2.17 (s, 3H). MS calculated for $C_{27}H_{23}F_3NO_5S_2$ ($M+H^+$) 562.1, found 562.0.
J22		^{1}H-NMR (400MHz, CD_3OD) δ = 7.59 (t, J = 8.0 Hz, 2H), 7.38 (t, J = 8.4 Hz, 2H), 7.14 (t, J = 8.0 Hz, 1H), 6.95-6.87 (m, 2H), 6.83 (d, J = 3.2 Hz, 1H), 6.81-6.67 (m, 3H), 5.27 (s, 2H), 4.53 (s, 2H), 3.56 (s, 3H), 2.17 (s, 3H). MS calculated for $C_{27}H_{23}F_3NO_5S_2$ ($M+H^+$) 562.1, found 562.0.
J23		^{1}H-NMR (400MHz, CD_3OD) δ = 7.80 (s, 1H), 7.77-7.68 (m, 4H), 7.42-7.38 (m, 2H), 7.26 (dd, J = 1.6 Hz, J = 8.4 Hz, 1H), 7.08 (t, J = 8.0 Hz, 1H), 6.95-6.93 (m, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.78-6.68 (m, 2H), 5.27 (s, 2H), 4.53 (s, 2H), 3.50 (s, 3H), 2.17 (s, 3H). MS calculated for $C_{30}H_{25}NO_5S$ ($M+H^+$) 512.1, found 512.1.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
J24		^{1}H-NMR (400MHz, CD_3OD) δ = 7.33-7.25 (m, 4H), 7.15 (t, J = 8.0 Hz, 1H), 6.94-6.92 (m, 2H), 6.86 (d, J = 2.8 Hz, 1H), 6.82-6.69 (m, 3H), 5.28 (s, 2H), 4.55 (s, 2H), 3.61 (s, 3H), 2.17 (s, 3H). MS calculated for $C_{26}H_{23}ClNO_5S$ ($M+H^+$) 496.1, found 496.0.
J25		^{1}H-NMR (400MHz, CD_3OD) δ = 7.48 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.16 (t, J = 8.2 Hz, 1H), 6.94-6.92 (m, 2H), 6.87 (d, J = 3.2 Hz, 1H), 6.83-6.70 (m, 3H), 5.29 (s, 2H), 4.55 (s, 2H), 3.62 (s, 3H), 2.17 (s, 3H). MS calculated for $C_{26}H_{23}BrNO_5S$ ($M+H^+$) 540.0, found 540.1.
J26		^{1}H-NMR (400MHz, CD_3OD) δ = 7.57 (d, J = 8.0 Hz, 1H), 7.50 (s, 1H), 7.47-7.37 (m, 2H), 7.27 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.79 (d, J = 8.8 Hz, 2H), 6.76-6.67 (m, 2H), 5.25 (s, 2H), 4.53 (s, 2H), 3.70 (s, 3H), 2.17 (s, 3H). MS calculated for $C_{27}H_{23}F_3NO_5S_2$ ($M+H^+$) 562.1, found 562.0.

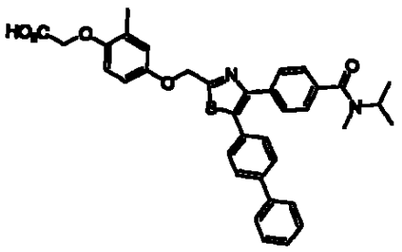
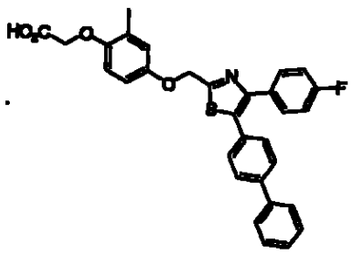
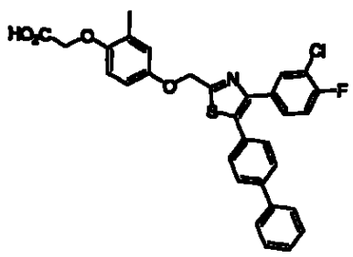
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Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
J27		^{1}H-NMR (400MHz, CD_3OD) δ = 7.48 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.21.(d, J = 8.4 Hz, 2H), 6.87 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.80-6.70 (m, 2H), 5.28 (s, 2H), 4.56 (s, 2H), 3.71 (s, 3H), 2.16 (s, 3H). MS calculated for $C_{28}H_{28}BrNO_5S$ ($M+H^+$) 540.0, found 540.0.
J21		^{1}H-NMR (400MHz, CD_3OD) δ = 7.25 (t, J = 8.0 Hz, 2H), 7.18 (t, J = 8.0 Hz, 2H), 6.97-6.79 (m, 8H), 6.73-6.71 (m, 1H), 5.33 (s, 2H), 4.57 (s, 2H), 3.62 (s, 3H), 3.58 (s, 3H), 2.12 (s, 3H). MS calculated for $C_{27}H_{26}NO_6S$ (M+H+) 492.14, found 492.00.
K2		^{1}H-NMR (400MHz, CD_3OD) δ = 8.16 (d, J = 2.0 Hz, 1H), 7.75 (dd, J = 2.4 Hz, J = 8.8 Hz, 1H), 7.57-7.54 (m, 4H), 7.37-7.30 (m, 4H), 7.28-7.24 (m, 1H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 3H), 5.27 (s, 2H), 4.53 (s, 2H), 3.81 (s, 3H), 2.17 (s, 3H). MS calculated for $C_{31}H_{27}N_2O_5S$ ($M+H^+$) 539.2, found 539.1.

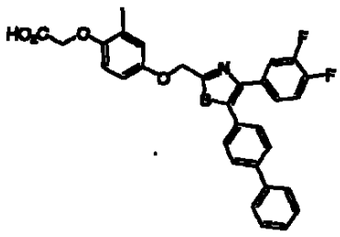
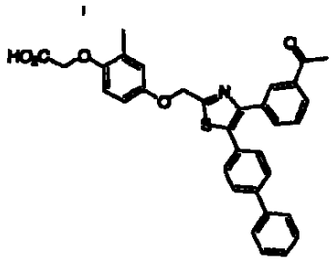
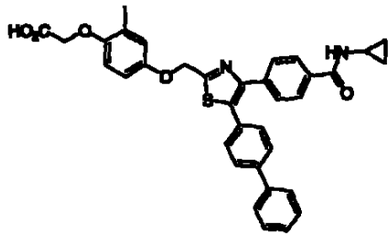
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Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
K3		^{1}H-NMR (400MHz, CD_3OD) δ = 7.58-7.55 (m, 4H), 7.41-7.34 (m, 4H), 7.29-7.26 (m, 1H), 6.91 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 2.8 Hz, 1H), 6.79-6.69 (m, 2H), 5.27 (s, 2H), 4.55 (s, 2H), 2.96 (s, 6H), 2.17 (s, 3H). MS calculated for $C_{33}H_{31}N_2O_4S$ (M+H$^+$) 551.2, found 551.2.
K4		^{1}H-NMR (400MHz, CD_3OD) δ = 7.88 (d, J = 8.4 Hz, 4H), 7.58-7.55 (m, 6H), 7.37-7.32 (m, 4H), 7.28-7.25 (m, 1H), 6.85 (d, J = 2.8 Hz, 1H), 6.78-6.68 (m, 2H), 5.29 (s, 2H), 4.53 (s, 2H), 2.50 (s, 3H), 2.18 (s, 3H). MS calculated for $C_{33}H_{28}NO_5S$ (M+H$^+$) 550.2, found 550.2.
K5		^{1}H-NMR (400MHz, CD_3OD) δ = 7.59-7.55 (m, 4H), 7.37-7.33 (m, 6H), 7.29-7.26 (m, 1H), 6.86 (d, J = 2.8 Hz, 1H), 6.78-6.68 (m, 2H), 5.27 (s, 2H), 4.55 (s, 2H), 4.72 9m, 1H), 2.50 (s, 3H), 2.18 (s, 3H), 1.90-1.52 (m, 8H). MS calculated for $C_{36}H_{34}NO_5S$ (M+H$^+$) 592.2, found 592.2.

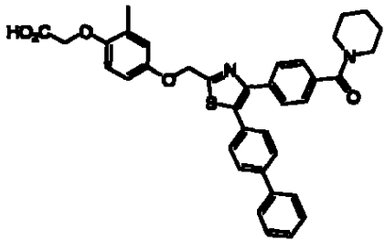
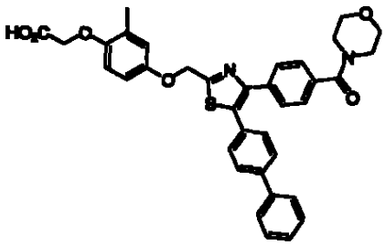
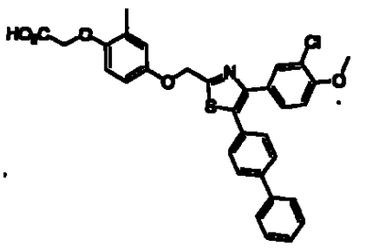
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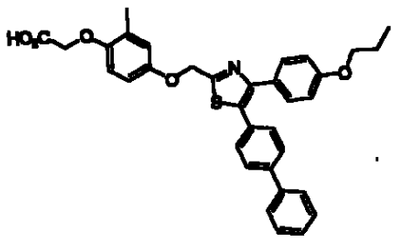
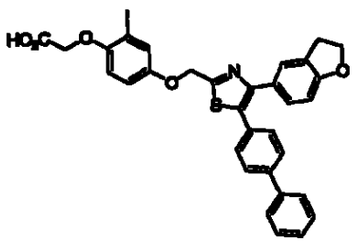
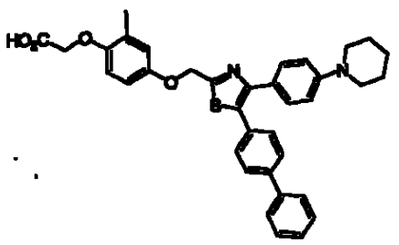
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
K6		^{1}H-NMR (400MHz, CD_3OD) δ = 7.54-7.51 (m, 6H), 7.36-7.31 (m, 4H), 7.28-7.24 (m, 3H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 2H), 5.27 (s, 2H), 4.53 (s, 2H), 3.92-3.86 (m, 1H), 2.83-2.74(m, 3H), 2.17 (s, 3H), 1.14-1.07 (m, 6H). MS calculated for $C_{36}H_{38}N_2O_5S$ ($M+H^+$) 607.2, found 607.3.
K7		^{1}H-NMR (400MHz, CD_3OD) δ = 7.59-7.56 (m, 5H), 7.38-7.25 (m, 7H), 7.10 (t, J = 8.8 Hz, 1H), 6.85 (d, J = 2.8 Hz, 1H), 6.78-6.69 (m, 2H), 5.27 (s, 2H), 4.54 (s, 2H), 2.18 (s, 3H). MS calculated for $C_{31}H_{28}FNO_4S$ ($M+H^+$) 526.1, found 526.1.
K8		^{1}H-NMR (400MHz, CD_3OD) δ = 7.62 (d, J = 8.4 Hz, 4H), 7.49-7.30 (m, 7H), 7.07-7.02 (m, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.82-6.71 (m, 2H), 5.30 (s, 2H), 4.56 (s, 2H), 2.17 (s, 3H). MS calculated for $C_{31}H_{27}ClFNO_4S$ ($M+H^+$) 560.1, found 560.1.

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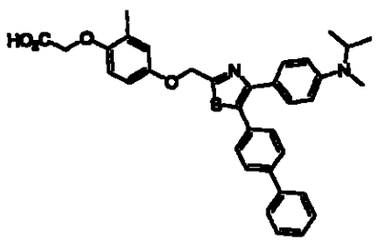
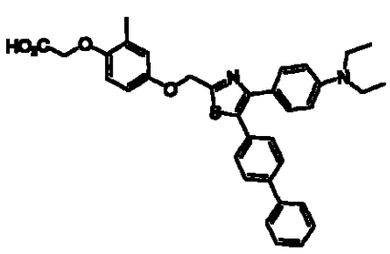
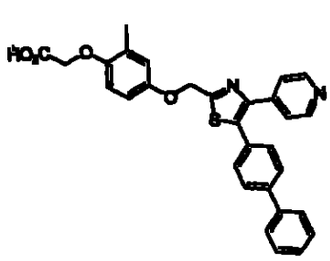
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
K9		^{1}H-NMR (400MHz, CD_3OD) δ = 7.63-7.60 (m, 4H), 7.41-7.15 (m, 8H), 6.87 (d, J = 2.8 Hz, 1H), 6.80-6.70 (m, 2H), 5.30 (s, 2H), 4.54 (s, 2H), 2.17 (s, 3H). MS calculated for $C_{31}H_{24}F_2NO_4S$ ($M+H^+$) 544.1, found 544.1.
K10		^{1}H-NMR (400MHz, CD_3OD) δ = 8.06 (s, 1H), 7.85 (d, J = 7.6 hz, 1H), 7.69 (d, J = 7.6 hz, 1H), 7.58-7.54 (m, 4H), 7.40-7.25 (m, 6H), 6.86 (d, J = 2.4 Hz, 1H), 6.79-6.69 (m, 2H), 5.30 (s, 2H), 4.54 (s, 2H), 2.37 (s, 3H), 2.18 (s, 3H). MS calculated for $C_{33}H_{29}NO_5S$ ($M+H^+$) 550.2, found 550.2.
K11		^{1}H-NMR (400MHz, CD_3OD) δ = 7.67 (d, J = 8.4 Hz, 2H), 7.54-7.48 (m, 5H), 7.36-7.24 (m, 6H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 2H), 5.26 (s, 2H), 4.53 (s, 2H), 2.80-2.72 (m, 1H), 2.17 (s, 3H), 0.70-0.53 (m, 4H). MS calculated for $C_{35}H_{31}N_3O_5S$ ($M+H^+$) 591.2, found 591.2.

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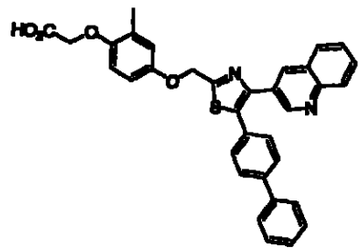
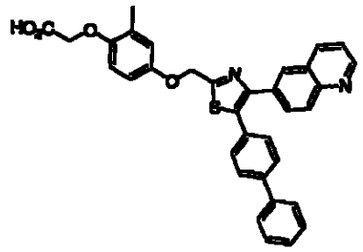
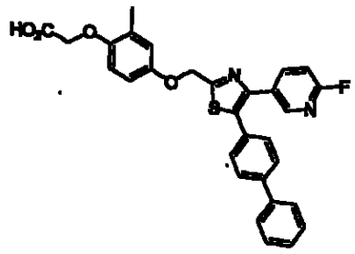
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
K12		^{1}H-NMR (400MHz, CD_3OD) δ = 7.55-7.51 (m, 7H), 7.37-7.26 (m, 6H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 2H), 5.28 (s, 2H), 4.54 (s, 2H), 3.64-3.23 (m, 4H), 2.18 (s, 3H), 1.72-1.40 (m, 6H). MS calculated for $C_{37}H_{35}N_2O_3S$ ($M+H^+$) 619.2, found 619.2.
K13		^{1}H-NMR (400MHz, CD_3OD) δ = 7.59-7.53 (m, 6H), 7.39-7.26 (m, 7H), 6.87 (d, J = 2.4 Hz, 1H), 6.80-6.69 (m, 2H), 5.29 (s, 2H), 4.55 (s, 2H), 3.70-3.25 (m, 8H), 2.17 (s, 3H). MS calculated for $C_{36}H_{33}N_2O_4S$ ($M+H^+$) 621.2, found 621.2.
K14		^{1}H-NMR (400MHz, CD_3OD) δ = 7.56 (d, J = 8.0 Hz, 4H), 7.48 (d, J = 1.6 Hz, 1H), 7.37-7.25 (m, 6H), 6.93 (d, J = 8.4 Hz, 4H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 2H), 5.26 (s, 2H), 4.54 (s, 2H), 3.79 (s, 3H), 2.18 (s, 3H). MS calculated for $C_{32}H_{27}ClNO_3S$ ($M+H^+$) 572.1, found 572.1.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
K15		^{1}H-NMR (400MHz, CD_3OD) δ = 7.65-7.57 (m, 4H), 7.40-7.29 (m, 7H), 6.87 (d, J = 2.4 Hz, 1H), 6.82-6.70 (m, 4H), 5.28 (s, 2H), 4.54 (s, 2H), 3.85 (t, J = 6.6 Hz, 2H), 2.17 (s, 3H), 1.71-1.66 (m, 2H), 0.94 (t, J = 7.0 Hz, 3H). MS calculated for $C_{34}H_{33}NO_5S$ ($M+H^+$) 566.2, found 566.1.
K16		^{1}H-NMR (400MHz, CD_3OD) δ = 7,58-7.54 (m, 4H), 7.39-7.26 (m, 6H), 7.15 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 6.79-6.60 (m, 3H), 5.27 (s, 2H), 4.55 (s, 2H), 4.47 (t, J = 8.8 Hz, 2H), 3.10 (t, J = 8.4 Hz, 2H), 2.17 (s, 3H). MS calculated for $C_{33}H_{29}NO_5S$ ($M+H^+$) 550.2, found 550.1.
K17		^{1}H-NMR (400MHz, CD_3OD) δ = 7.58-7.54 (m, 6H), 7.38-7.25 (m, 7H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 2H), 5.27 (s, 2H), 4.54 (s, 2H), 3.43 (t, J = 5.4 Hz, 4H), 2.17 (s, 3H), 1.88-1.83 (m, 4H), 1.68-1.64 (m, 2H). MS calculated for $C_{36}H_{35}N_2O_4S$ ($M+H^+$) 591.2, found 591.2.

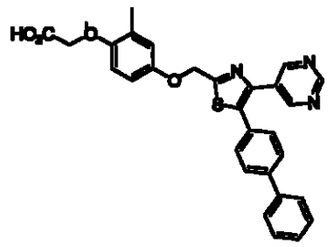
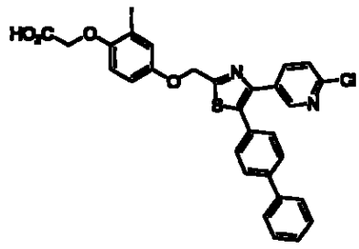
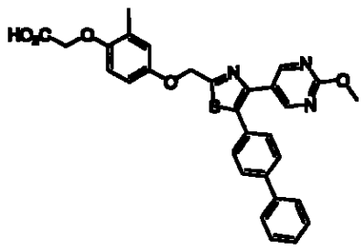
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Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
K18		MS calculated for $C_{35}H_{35}N_2O_4S$ ($M+H^+$) 579.2, found 579.2.
K19		MS calculated for $C_{35}H_{35}N_2O_4S$ ($M+H^+$) 579.2, found 579.2.
K20		^{1}H-NMR (400MHz, CD_3OD) δ = 8.62 (d, J = 6.8 Hz, 1H), 8.07 (d, J = 6.4 Hz, 1H), 7.70-7.28 (m, 11H), 6.85 (d, J = 2.8 Hz, 1H), 6.78-6.68 (m, 2H), 5.33 (s, 2H), 4.54 (s, 2H), 2.17 (s, 3H). MS calculated for $C_{30}H_{25}N_2O_4S$ ($M+H^+$) 509.2, found 509.1.

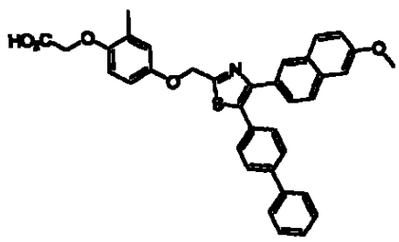
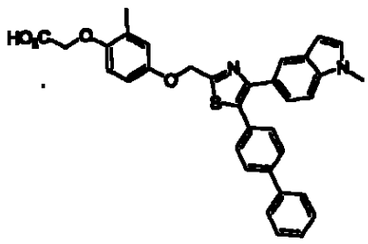
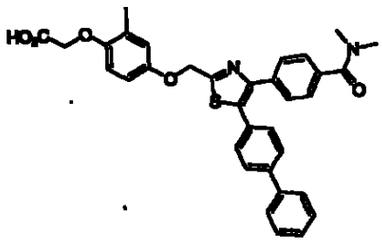
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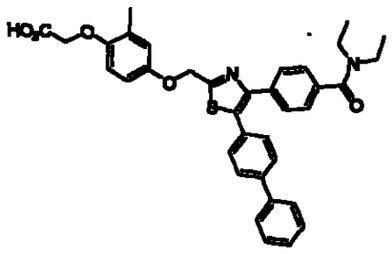
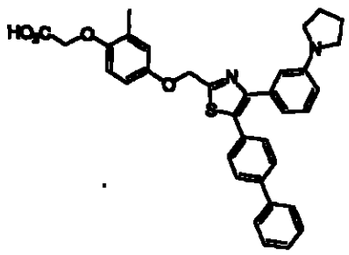
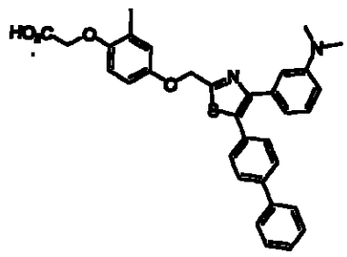
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
K21		^{1}H-NMR (400MHz, CD_3OD) δ = 9.08 (s, 1H), 8.80 (s, 1H), 8.16-8.08 (m, 2H), 7.96 (t, J = 7.6 Hz, 1H), 7.83-7.77 (m, 4H), 7.69-7.46 (m, 4H), 7.08 (d, J = 2.4 Hz, 1H), 7.02-6.89 (m, 2H), 5.55 (s, 2H), 4.74 (s, 2H), 2.34 (s, 3H). MS calculated for $C_{34}H_{27}N_2O_4S$ ($M+H^+$) 559.2, found 559.2.
K22		^{1}H-NMR (400MHz, CD_3OD) δ = 9.00 (d, J = 4.0 Hz, 1H), 8.82-8.79 (m, 1H), 8.36 (s, 1H), 8.09-8.00 (m, 2H), 7.85-7.81 (m, 1H), 7.58-7.25 (m, 9H), 6.86 (d, J = 3.2 Hz, 1H), 6.79-6.69 (m, 2H), 5.32 (s, 2H), 4.54 (s, 2H), 2.18 (s, 3H). MS calculated for $C_{34}H_{27}N_2O_4S$ ($M+H^+$) 559.2, found 559.1.
K23		^{1}H-NMR (400MHz, CD_3OD) δ = 8.26 (s, 1H), 8.05-8.00 (m, 1H), 7.64-7.28 (m, 9H), 7.03 (dd, J = 2.4 Hz, J = 8.8 Hz, 1H), 6.88 (d, J = 2.8 Hz, 1H), 6.81-6.70 (m, 2H), 5.32 (s, 2H), 4.54 (s, 2H), 2.17 (s, 3H). MS calculated for $C_{30}H_{24}FN_2O_4S$ ($M+H^+$) 527.1, found 527.1.

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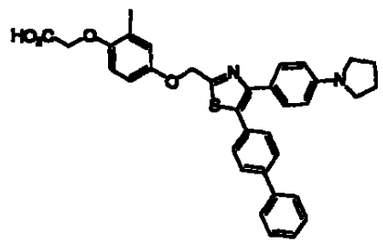
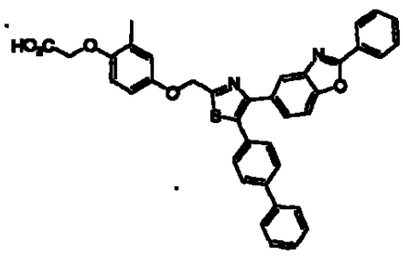
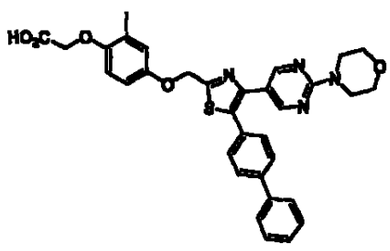
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
K24		^{1}H-NMR (400MHz, CD_3OD) δ = 9.01 (s, 1H), 8.81 (s, 2H), 7.68-7.61 (m, 4H), 7.44-7.30 (m, 5H), 6.89 (d, J = 2.4 Hz, 1H), 6.82-6.71 (m, 2H), 5.35 (s, 2H), 4.55 (s, 2H), 2.17 (s, 3H). MS calculated for $C_{29}H_{24}N_3O_4S$ ($M+H^+$) 510.1, found 510.1.
K25		^{1}H-NMR (400MHz, CD_3OD) δ = 8.40 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 2.6 Hz, J = 8.2 Hz, 1H), 7.61-7.55 (m, 4H), 7.37-7.25 (m, 6H), 6.83 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 2H), 5.29 (s, 2H), 4.48 (s, 2H), 2.17 (s, 3H). MS calculated for $C_{29}H_{24}ClN_2O_4S$ ($M+H^+$) 543.1, found 543.1.
K26		^{1}H-NMR (400MHz, CD_3OD) δ = 8.40 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 2.6 Hz, J = 8.2 Hz, 1H), 7.61-7.55 (m, 4H), 7.37-7.25 (m, 6H), 6.83 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 2H), 5.29 (s, 2H), 4.48 (s, 2H), 2.17 (s, 3H).MS calculated for $C_{30}H_{26}N_3O_5S$ ($M+H^+$) 540.2, found 540.1.

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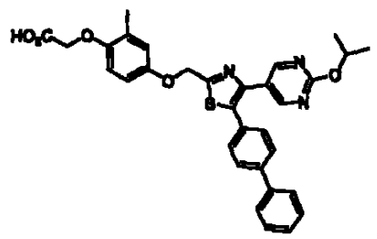
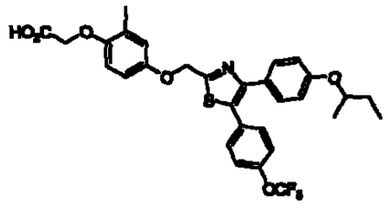
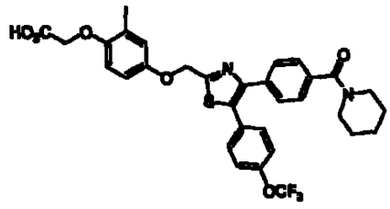
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
K27		^{1}H-NMR (400MHz, CD_3OD) δ = 7.88 (s, 1H), 7.63-7.50 (m, 6H), 7.42-7.24 (m, 6H), 7.13 (d, J = 2.8 Hz, 1H), 7.03 (dd, J = 2.6 Hz, J = 9.0 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 6.77-6.69 (m, 2H), 5.29 (s, 2H), 4.54 (s, 2H), 3.81 (s, 3H), 2.18 (s, 3H). MS calculated for $C_{36}H_{30}NO_5S$ ($M+H^+$) 588.2, found 588.2.
K28		^{1}H-NMR (400MHz, CD_3OD) δ = 7.67 (s, 1H), 7.58-7.53 (m, 4H), 7.39-7.21 (m, 7H), 7.15 (s, 1H), 6.89 (d, J = 2.4 Hz, 1H), 6.82-6.71 (m, 2H), 5.30 (s, 2H), 4.56 (s, 2H), 3.72 (s, 3H), 2.18 (s, 3H). MS calculated for $C_{34}H_{29}N_2O_4S$ ($M+H^+$) 561.2, found 561.2.
K29		^{1}H-NMR (400MHz, CD_3OD) δ = 7.54-7.51 (m, 6H), 7.36-7.23 (m, 7H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 2H), 5.27 (s, 2H), 4.53 (s, 2H), 3.00 (s, 3H), 2.92 (s, 3H), 2.17 (s, 3H). MS calculated for $C_{34}H_{31}N_2O_5S$ ($M+H^+$) 579.2, found 579.2.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
K30		^{1}H-NMR (400MHz, CD_3OD) δ = 7.54-7.51 (m, 6H), 7.36-7.24 (m, 7H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 2H), 5.27 (s, 2H), 4.53 (s, 2H), 3.47-3.36 (m, 4H), 2.17 (s, 3H), 1.10-0.99 (m, 6H). MS calculated for $C_{34}H_{31}N_2O_5S$ ($M+H^+$) 607.2, found 607.2.
K31		^{1}H-NMR (400MHz, CD_3OD) δ = 7.56 (d, J = 8.0 Hz, 4H), 7.38-7.25 (m, 5H), 7.12 (t, J = 8.0 Hz, 1H), 6.87-6.61 (m, 6H), 5.27 (s, 2H), 4.54 (s, 2H), 3.14-3.11 (m, 4H), 2.17 (s, 3H), 1.89-1.86 (m, 4H). MS calculated for $C_{33}H_{33}N_2O_4S$ ($M+H^+$) 577.2, found 577.2.
K32		^{1}H-NMR (400MHz, CD_3OD) δ = 7.58-7.53 (m, 4H), 7.37-7.17 (m, 9H), 6.84 (d, J = 2.8 Hz, 1H), 6.78-6.68 (m, 2H), 5.28 (s, 2H), 4.54 (s, 2H), 2.99 (s, 6H), 2.17 (s, 3H). MS calculated for $C_{33}H_{31}N_2O_4S$ ($M+H^+$) 551.2, found 551.2.

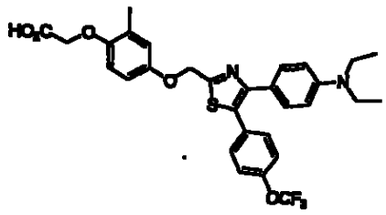
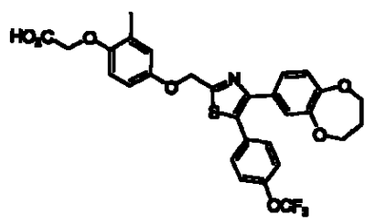
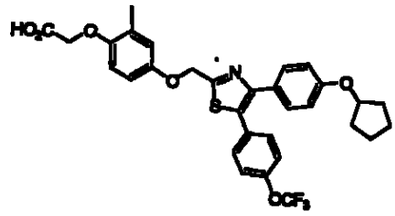
161
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Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
K33		^{1}H-NMR (400MHz, CD_3OD) δ = 7.54-7.49 (m, 4H), 7.36-7.23 (m, 7H), 6.83 (d, J = 3.2 Hz, 1H), 6.77-6.68 (m, 2H), 6.50 (d, J = 8.4 Hz, 2H), 5.24 (s, 2H), 4.53 (s, 2H), 3.21-3.18 (m, 4H), 2.17 (s, 3H), 1.98-1.92 (m, 4H). MS calculated for $C_{33}H_{33}N_2O_4S$ ($M+H^+$) 577.2, found 577.2.
K34		^{1}H-NMR (400MHz, CD_3OD) δ = 8.15 (d, J = 7.2 Hz, 4H), 7.78-7.27 (m, 13H), 6.90-6.72 (m, 3H), 5.34 (s, 2H), 4.57 (s, 2H), 2.18 (s, 3H). MS calculated for $C_{38}H_{29}N_2O_5S$ ($M+H^+$) 625.2, found 625.2.
K35		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.51 (s, 2H), 7.61-7.37 (m, 9H), 6.92-6.71 (m, 3H), 5.33 (s, 2H), 4.64 (s, 2H), 3.82 (m, 4H), 3.77 (m, 4H), 2.29 (s, 3H). MS calculated for $C_{36}H_{31}N_4O_5S$ ($M+H^+$) 595.2, found 595.2.

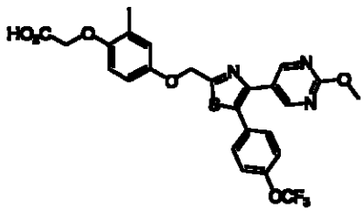
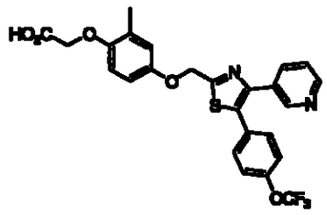
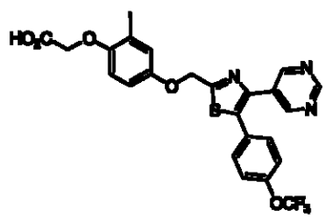
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Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
K36		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.69 (s, 2H), 7.71-7.38 (m, 9H), 6.91-6.71 (m, 3H), 5.34 (s, 2H), 5.27 (m, 1H), 4.64 (s, 2H), 2.29 (s, 3H), 1.39 (d, J = 6.2 Hz, 6H). MS calculated for $C_{32}H_{30}N_3O_5S$ ($M+H^+$) 568.2, found 568.2.
L2		^{1}H-NMR (400MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 4H), 5.24 (s, 2H), 4.52 (s, 2H), 4.30-4.25 (m, 1H), 2.16 (s, 3H), 1.62-1.52 (m, 2H), 1.18 (d, J = 6.0 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H). MS calculated for $C_{30}H_{29}F_3NO_6S$ ($M+H^+$) 588.2, found 588.1.
L3		^{1}H-NMR (400MHz, CD_3OD) δ = 7.57 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 2.8 Hz, 1H), 6.86-6.77 (m, 2H), 5.37 (s, 2H), 4.63 (s, 2H), 3.70(bs, 2H), 3.39(bs, 2H), 2.26 (s, 3H), 1.72-1.54 (m, 6H). MS calculated for $C_{32}H_{30}F_3N_2O_6S$ ($M+H^+$) 627.2, found 627.1.

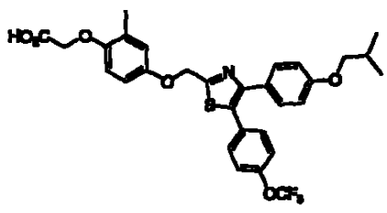
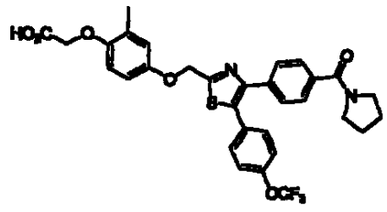
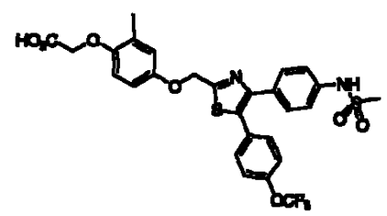
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Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
L4		^{1}H-NMR (400MHz, CD_3OD) δ = 7.50 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.14 (bs, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.76-6.67 (m, 2H), 5.26 (s, 2H), 4.53 (s, 2H), 3.51 (q, J = 7.2 Hz, 4H), 2.16 (s, 3H), 1.05 (t, J = 7.0 Hz, 6H). MS calculated for $C_{30}H_{30}F_3N_2O_3S$ ($M+H^+$) 587.2, found 587.2.
L5		^{1}H-NMR (400MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 8.97 (d, J = 2.0 Hz, 2H), 6.90-6.77 (m, 3H), 6.75-6.67 (m, 2H), 5.24 (s, 2H), 4.53 (s, 2H), 4.09-4.02 (q, 4H), 2.16 (s, 3H), 2.08-2.03 (m, 2H). MS calculated for $C_{29}H_{25}F_3NO_7S$ ($M+H^+$) 588.1, found 588.1.
L6		^{1}H-NMR (400MHz, CD_3OD) δ = 7.38 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 2.8 Hz, 1H), 6.79-6.69 (m, 4H), 5.27 (s, 2H), 4.73 (m, 1H), 4.54 (s, 2H), 2.16 (s, 3H), 1.86-1.54 (m, 8H). MS calculated for $C_{31}H_{29}F_3NO_5S$ ($M+H^+$) 600.2, found 600.1.

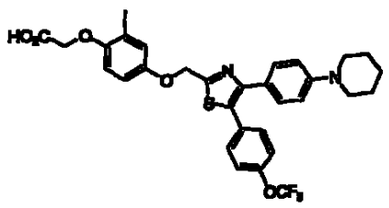
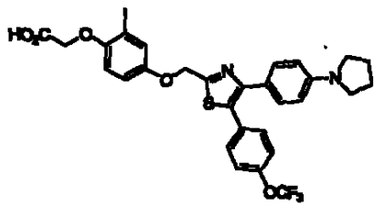
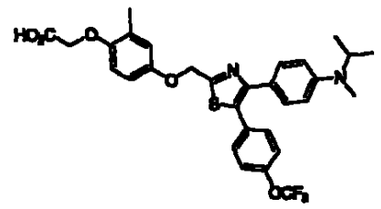
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Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
L7		^{1}H-NMR (400MHz, CD_3OD) δ = 8.53 (s, 2H), 7.44 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 2H), 5.29 (s, 2H), 4.54 (s, 2H), 3.93 (s, 3H), 2.17 (s, 3H). MS calculated for $C_{25}H_{21}F_3N_3O_5S$ ($M+H^+$) 548.1, found 548.1.
L8		^{1}H-NMR (400MHz, CD_3OD) δ = 8.68 (s, 1H), 8.55 (d, J = 5.2 Hz, 1H), 8.11 (dd, J = 1.8 Hz, J = 8.2 Hz, 1H), 7.60-7.56 (m, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 2.8 Hz, 1H), 6.81-6.70 (m, 2H), 5.34 (s, 2H), 4.56 (s, 2H), 2.16 (s, 3H). MS calculated for $C_{25}H_{20}F_3N_2O_5S$ ($M+H^+$) 517.1, found 516.9.
L9		^{1}H-NMR (400MHz, CD_3OD) δ = 9.24 (s, 1H), 8.98 (s, 2H), 7.71 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 2.8 Hz, 1H), 7.02-6.90 (m, 2H), 5.56 (s, 2H), 4.67 (s, 2H), 2.39 (s, 3H). MS calculated for $C_{24}H_{19}F_3N_3O_5S$ ($M+H^+$) 518.1, found 518.1.

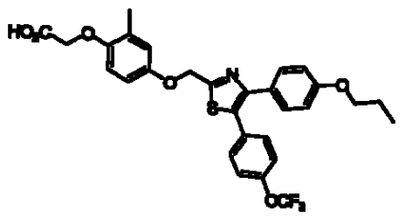
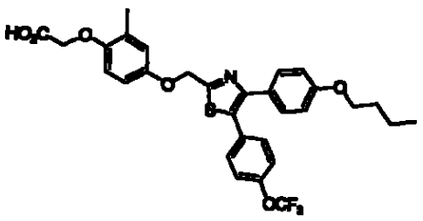
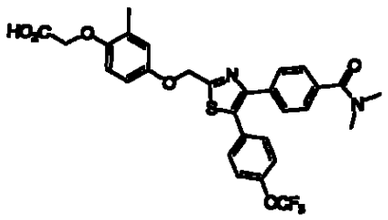
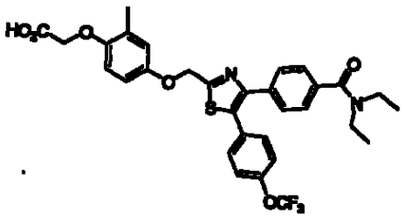
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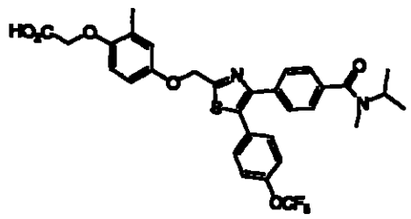
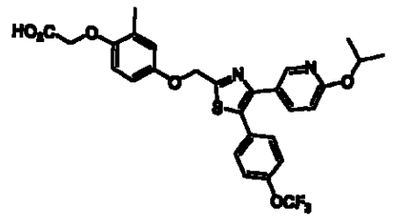
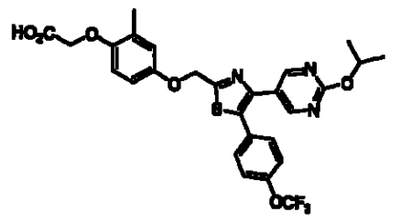
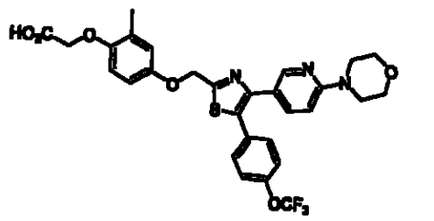
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
L10		^{1}H-NMR (400MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 2.8 Hz, 1H), 6.80-6.66 (m, 4H), 5.24 (s, 2H), 4.49 (s, 2H), 3.66 (d, J = 6.4 Hz, 2H), 2.19 (s, 3H), 2.01-1.91 (m, 1H), 0.94 (s, 3H), 0.93 (s, 3H). MS calculated for $C_{30}H_{29}F_3NO_5S$ ($M+H^+$) 588.2, found 588.1.
L11		^{1}H-NMR (400MHz, CD_3OD) δ = 7.47-7.40 (m, 4H), 7.37 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 2H), 5.28 (s, 2H), 4.54 (s, 2H), 3.49 (t, J = 7.0 Hz, 2H), 3.38 (t, J = 6.4 Hz, 2H), 2.17 (s, 3H), 1.93-1.78 (m, 4H). MS calculated for $C_{31}H_{28}F_3N_2O_5S$ ($M+H^+$) 613.2, found 613.1.
L12		^{1}H-NMR (400MHz, CD_3OD) δ = 7.36-7.32 (m, 4H), 7.20 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.76-6.67 (m, 2H), 5.25 (s, 2H), 4.52 (s, 2H), 2.89 (s, 3H), 2.16 (s, 3H). MS calculated for $C_{27}H_{24}F_3N_2O_7S_2$ ($M+H^+$) 609.1, found 609.1.

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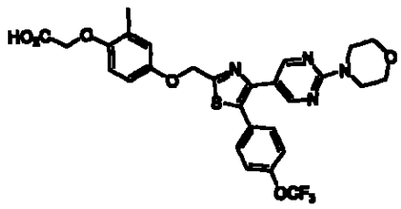
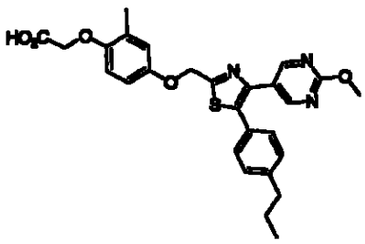
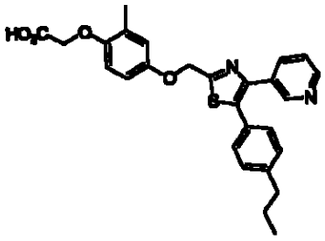
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
L13		^{1}H-NMR (400MHz, CD_3OD) δ = 7.51 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.76-6.67 (m, 2H), 5.27 (s, 2H), 4.54 (s, 2H), 3.42 (t, J = 5.4 Hz, 4H), 2.17 (s, 3H), 1.87-1.82 (m, 4H), 1.68-1.64 (m, 2H). MS calculated for $C_{31}H_{30}F_3N_2O_3S$ ($M+H^+$) 599.2, found 599.2.
L14		^{1}H-NMR (400MHz, CD_3OD) δ = 7.33 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.81 (d, J = 2.8 Hz, 1H), 6.74-6.65 (m, 2H), 6.50 (d, J = 8.8 Hz, 2H), 5.21 (s, 2H), 4.52 (s, 2H), 3.21 (t, J = 5.4 Hz, 4H), 2.15 (s, 3H), 1.95-1.90 (m, 4H). MS calculated for $C_{30}H_{28}F_3N_2O_3S$ ($M+H^+$) 585.2, found 585.2.
L15		^{1}H-NMR (400MHz, CD_3OD) δ = 7.39-7.36 (m, 4H), 6.86-6.82 (m, 5H), 6.77-6.67 (m, 2H), 5.04 (s, 2H), 4.50 (s, 2H), 4.00-3.94 (m, 1H), 3.01 (s, 3H), 2.16 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H). MS calculated for $C_{30}H_{30}F_3N_2O_3S$ ($M+H^+$) 587.2, found 587.2.

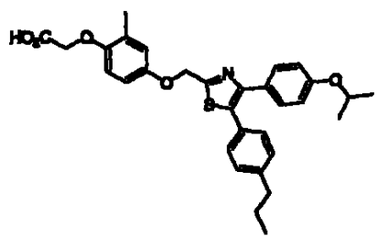
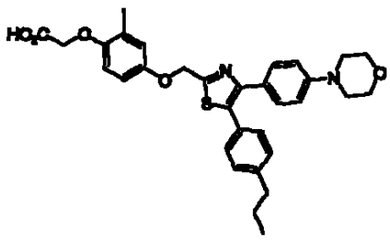
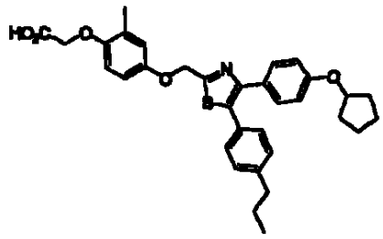
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Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
L16		MS calculated for $C_{29}H_{27}F_3NO_6S$ ($M+H^+$) 573.1, found 573.1.
L17		MS calculated for $C_{30}H_{29}F_3NO_6S$ ($M+H^+$) 588.2, found 588.1.
L18		^{1}H-NMR (400MHz, CD_3OD) δ = 7.48 (d, J = 8.4 Hz, 2H), 7.37-7.30 (m, 4H), 7.20 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 2H), 5.28 (s, 2H), 4.53 (s, 2H), 3.01 (s, 3H), 2.92 (s, 3H), 2.17 (s, 3H). MS calculated for $C_{29}H_{28}F_3N_2O_6S$ ($M+H^+$) 587.1, found 587.1.
L19		^{1}H-NMR (400MHz, CD_3OD) δ = 7.56 (d, J = 8.0 Hz, 2H), 7.45-7.34 (m, 4H), 7.28 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 2.8 Hz, 1H), 6.86-6.77 (m, 2H), 5.37 (s, 2H), 4.62 (s, 2H), 3.59-3.25 (m, 4H), 2.26 (s, 3H), 1.39-1.10 (m, 6H). MS calculated for $C_{31}H_{32}F_3N_2O_6S$ ($M+H^+$) 615.2, found 615.2.

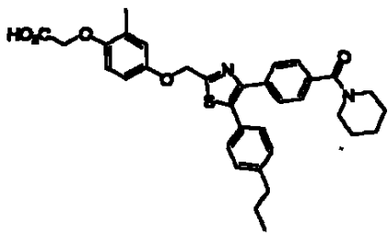
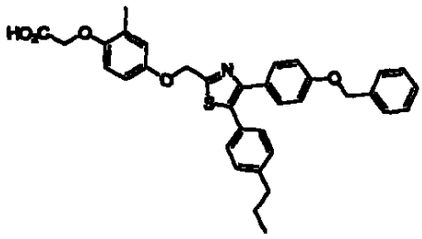
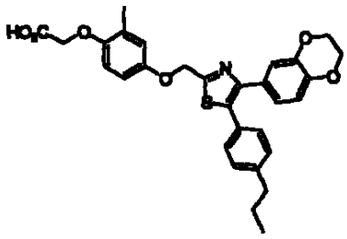
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
L20		^{1}H-NMR (400MHz, CD_3OD) δ = 7.52 (d, J = 8.0 Hz, 2H), 7.41-7.28 (m, 4H), 7.24 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 3.2 Hz, 1H), 6.82-6.73 (m, 2H), 5.32 (s, 2H), 4.58 (s, 2H), 3.95-3.86 (m, 1H), 2.89-2.88 (m, 3H), 2.22 (s, 3H), 1.25-1.12 (m, 6H). MS calculated for $C_{31}H_{30}F_3N_2O_6S$ ($M+H^+$) 615.2, found 615.2.
L21		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.48 (m, 1H), 7.77 (m, 1H), 7.32-7.16 (m, 5H), 6.80-6.64 (m, 3H), 5.31 (m, 2H), 5.25 (s, 2H), 4.58 (s, 2H), 3.77 (m, 4H), 2.21 (s, 3H), 1.38 (d, J = 6.1 Hz, 6H). MS calculated for $C_{28}H_{28}F_3N_2O_6S$ ($M+H^+$) 575.1, found 575.1.
L22		MS calculated for $C_{27}H_{25}F_3N_3O_6S$ ($M+H^+$) 576.1, found 576.1.
L23		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.39 (d, J = 2.1 Hz, 1H), 7.83 (m, 1H), 7.51-7.35 (m, 4H), 6.99-6.82 (m, 4H), 5.41 (s, 2H), 4.77 (s, 2H), 3.98 (m, 4H), 3.79 (m, 4H), 2.40 (s, 3H). MS calculated for $C_{29}H_{28}F_3N_3O_6S$ ($M+H^+$) 602.2, found 602.2.

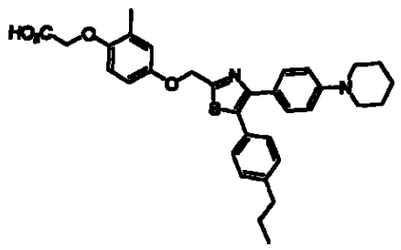
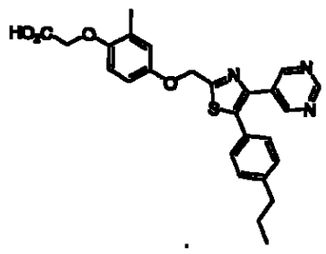
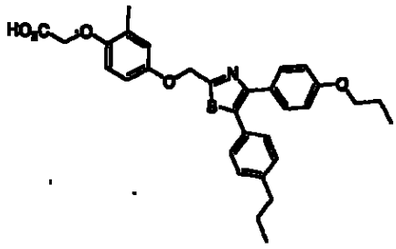
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Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
L24		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.48 (s, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.89 (s, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.71 (d, J = 7.3 Hz, 1H), 5.32 (s, 2H), 4.64 (s, 2H), 3.82 (m, 4H), 3.78 (m, 4H), 2.29 (s, 3H). MS calculated for $C_{28}H_{26}F_3N_4O_4S$ ($M+H^+$) 603.1, found 603.3.
M2		^{1}H-NMR (400MHz, CD_3OD) δ = 8.52 (s, 2H), 7.23-7.16 (m, 4H), 6.84 (d, J = 2.8 Hz, 1H), 6.78-6.68 (m, 2H), 5.27 (s, 2H), 4.54 (s, 2H), 3.90 (s, 3H), 2.52 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.60-1.54 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H). MS calculated for $C_{27}H_{29}N_3O_3S$ ($M+H^+$) 506.2, found 506.2.
M3		^{1}H-NMR (400MHz, CD_3OD) δ = 8.69 (bs, 1H), 8.51 (bs, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.62 (bs, 1H), 7.23-7.16 (m, 4H), 6.83 (d, J = 2.8 Hz, 1H), 6.76-6.67 (m, 2H), 5.28 (s, 2H), 4.53 (s, 2H), 2.54 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.62-1.52 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H). MS calculated for $C_{27}H_{27}N_2O_4S$ ($M+H^+$) 475.2, found 475.2.

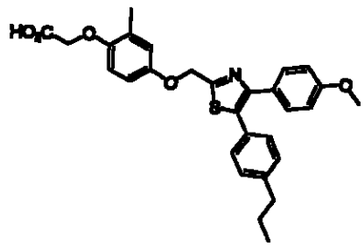
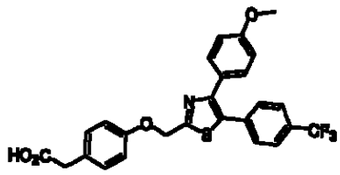
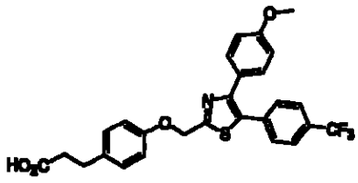
Compound Number	Compound Structure	Physical Data ^1H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
M4		^{1}H-NMR (400MHz, CD_3OD) δ = 7.26 (d, J = 8.8 Hz, 2H), 7.13-7.04 (m, 4H), 6.81 (d, J = 2.8 Hz, 1H), 6.74-6.66 (m, 2H), 5.21 (s, 2H), 4.52 (s, 2H), 4.51-4.46 (m, 1H), 2.49 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.57-1.51 (m, 2H), 1.21 (d, J = 6.0 Hz, 6H), 0.85 (t, J = 7.4 Hz, 3H). MS calculated for $C_{31}H_{34}NO_5S$ ($M+H^+$) 532.2, found 532.2.
M5		^{1}H-NMR (400MHz, CD_3OD) δ = 7.32 (d, J = 8.8 Hz, 2H), 7.13-7.05 (m, 4H), 6.91 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 2.8 Hz, 1H), 6.74-6.66 (m, 2H), 5.21 (s, 2H), 4.52 (s, 2H), 3.75 (t, J = 4.6 Hz, 4H), 3.14 (bs, 4H), 2.49 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.57-1.50 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H). MS calculated for $C_{33}H_{35}N_2O_5S$ ($M+H^+$) 559.2, found 559.2.
M6		^{1}H-NMR (400MHz, CD_3OD) δ = 7.27 (d, J = 8.4 Hz, 2H), 7.15-7.06 (m, 4H), 6.83 (d, J = 2.4 Hz, 1H), 6.76-6.67 (m, 4H), 5.23 (s, 2H), 4.73-4.69 (m, 1H), 4.53 (s, 2H), 2.50 (t, J = 7.6 Hz, 2H), 2.17 (s, 3H), 1.88-1.51 (m, 10H), 0.86 (t, J = 7.4 Hz, 3H). MS calculated for $C_{32}H_{36}NO_5S$ ($M+H^+$) 558.2, found 558.2.

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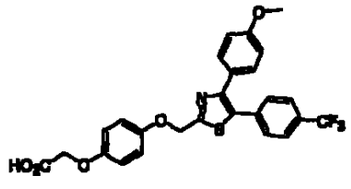
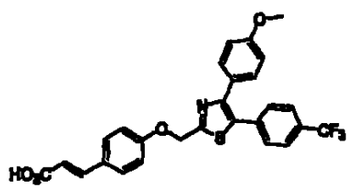
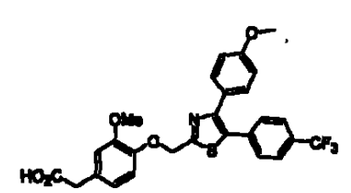
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
M7		^{1}H-NMR (400MHz, CD_3OD) δ = 7.48 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.16-7.08 (m, 4H), 6.83 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 2H), 5.25 (s, 2H), 4.53 (s, 2H), 3.61 (bs, 2H), 3.30 (bs, 2H), 2.51 (t, J = 7.6 Hz, 2H), 2.17 (s, 3H), 1.63-1.43 (m, 8H), 0.86 (t, J = 7.4 Hz, 3H). MS calculated for $C_{34}H_{37}N_2O_5S$ ($M+H^+$) 585.2, found 585.2.
M8		^{1}H-NMR (400MHz, CD_3OD) δ = 7.34-7.20 (m, 7H), 7.13-7.04 (m, 4H), 6.85-6.81 (m, 3H), 6.75-6.66 (m, 2H), 5.21 (s, 2H), 4.97(s, 2H), 4.52 (s, 2H), 2.49 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.57-1.52 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H). MS calculated for $C_{35}H_{34}NO_5S$ ($M+H^+$) 580.2, found 580.2.
M9		^{1}H-NMR (400MHz, CD_3OD) δ = 7.14-7.06 (m, 4H), 6.84-6.62 (m, 6H), 5.21 (s, 2H), 4.51 (s, 2H), 4.14-4.11 (m, 4H), 2.51 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.58-1.53 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H). MS calculated for $C_{30}H_{30}NO_6S$ ($M+H^+$) 532.1, found 532.1.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
M10		^{1}H-NMR (400MHz, CD_3OD) δ = 7.50 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.16-7.09 (m, 4H), 6.83 (d, J = 2.4 Hz, 1H), 6.77-6.67 (m, 2H), 5.25 (s, 2H), 4.53 (s, 2H), 3.41-3.38 (m, 4H), 2.52 (t, J = 7.6 Hz, 2H), 2.17 (s, 3H), 1.84-1.52 (m, 10H), 0.86 (t, J = 7.2 Hz, 3H). MS calculated for $C_{33}H_{37}N_2O_4S$ ($M+H^+$) 557.2, found 557.2.
M11		^{1}H-NMR (400MHz, CD_3OD) δ = 8.94 (s, 1H), 8.75 (s, 2H), 7.23-7.17 (m, 4H), 6.83 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 2H), 5.28 (s, 2H), 4.53 (s, 2H), 2.53 (t, J = 7.6 Hz, 2H), 2.17 (s, 3H), 1.63-1.55 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H). MS calculated for $C_{26}H_{29}N_3O_4S$ ($M+H^+$) 476.1, found 476.1.
M12		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.52-6.62 (m, 11H), 5.85 (s, 2H), 4.62 (s, 2H), 3.91 (t, J = 6.5 Hz, 2H), 2.58 (m, 2H), 2.27 (s, 3H), 1.78 (m, 2H), 1.63 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H). MS calculated for $C_{31}H_{34}NO_5S$ ($M+H^+$) 532.2, found 532.2.

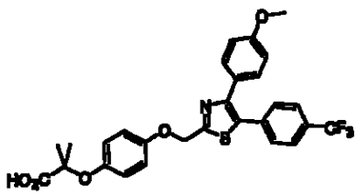
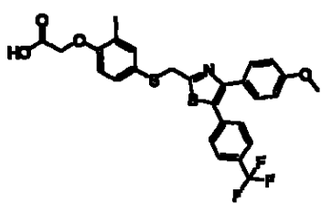
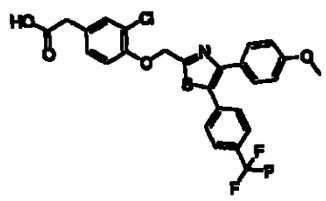
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Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
M13		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.28-7.05 (m, 6H), 6.82 (d, J = 2.8 Hz, 1H), 6.77-6.66 (m, 4H). 5.22 (s, 2H), 4.52 (s, 2H), 3.69 (s, 3H), 2.49 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.58-1.52 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H). MS calculated for $C_{28}H_{30}NO_3S$ ($M+H^+$) 504.2, found 504.2.
N2		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.56 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 10.0 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 5.40 (s, 2H), 3.82 (s, 3H), 3.62 (s, 2H). MS calculated for $C_{28}H_{31}F_3NO_4S$ ($M+H^+$) 500.1, found 500.3.
N3		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.57 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H), 6.97 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.44 (s, 2H), 3.83 (s, 3H), 2.93 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H). MS calculated for $C_{27}H_{28}F_3NO_4S$ ($M+H^+$) 514.1, found 514.3.

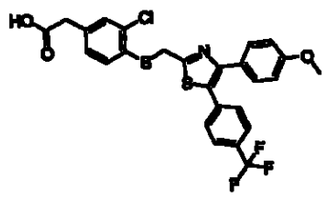
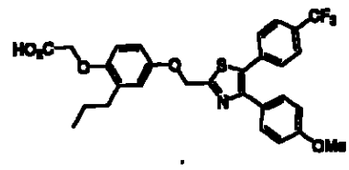
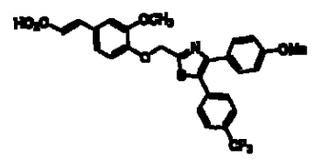
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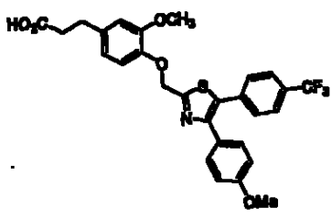
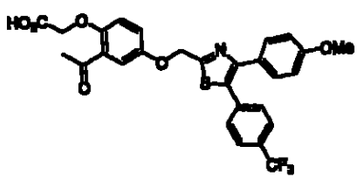
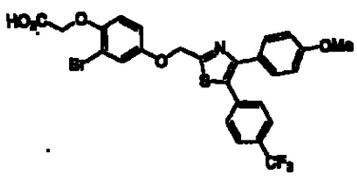
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
N4		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.56 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 9.1 Hz, 2H), 6.89 (d, J = 9.1 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.35 (s, 2H), 4.62 (s, 2H), 3.83 (s, 3H). MS calculated for $C_{26}H_{21}F_3NO_5S$ ($M+H^+$) 515.1, found 515.3.
N5		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.74 (d, J = 15.9 Hz, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 7.47-7.40 (m, 4H), 7.07 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.35 (d, J = 15.9 Hz, 1H), 5.45 (s, 2H), 3.83 (s, 3H). MS calculated for $C_{27}H_{21}F_3NO_4S$ ($M+H^+$) 512.1, found 512.3.
N6		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.56 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 7.00 (d, J = 8.1 Hz, 1H), 6.87-6.81 (m, 4H), 5.46 (s, 2H), 3.91 (s, 3H), 3.83 (s, 3H), 3.62 (s, 2H). MS calculated for $C_{27}H_{23}F_3NO_5S$ ($M+H^+$) 530.1, found 530.3.

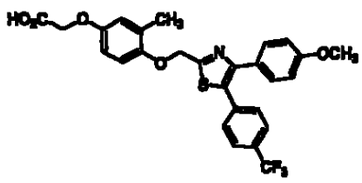
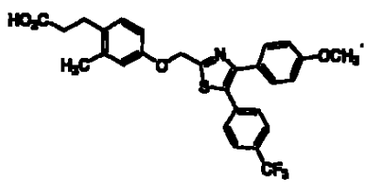
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Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
N7		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.55 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 6.92 (s, 4H), 6.84 (d, J = 8.8 Hz, 2H), 5.34 (s, 2H), 3.81 (s, 3H), 1.52 (s, 6H). MS calculated for $C_{28}H_{25}F_3NO_5S$ ($M+H^+$) 544.1, found 544.4.
N13		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.30 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.05 (m, 4H), 6.58 (d, J = 8.8 Hz, 2H), 6.41 (d, J = 8.4 Hz, 1H), 4.41 (s, 2H), 4.16 (s, 2H), 3.56 (s, 3H), 2.01 (s, 3H). MS calculated for $C_{27}H_{22}F_3NO_4S_2$ ($M+H^+$) 546.1, found 546.3.
N14		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 2.0 Hz, 1H), 7.16 (dd, J = 2.0, 8.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 5.46 (s, 2H), 3.82 (s, 3H), 3.59 (s, 2H). MS calculated for $C_{26}H_{20}ClF_3NO_4S$ ($M+H^+$) 534.1, found 534.3.

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Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
N15		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.46 (d, J = 8.0 Hz, 2H), 7.29 (m, 6H), 7.06 (dd, J = 1.6, 8.0 Hz, 1H), 6.76 (d, J = 8.8 Hz, 2H), 4.44 (s, 2H), 3.73 (s, 3H), 3.52 (s, 2H). MS calculated for $C_{29}H_{20}ClF_3NO_3S_2$ ($M+H^+$) 550.0, found 550.3.
N20		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.56 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 3.0 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 6.79 (dd, J = 3.0, 9.0 Hz, 1H), 6.71 (d, J = 9.0 Hz, 1H) 5.37 (s, 2H), 4.63 (s, 2H), 3.82 (s, 3H), 2.63 (t, J = 7.6 Hz, 2H), 1.63 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); ^{19}F-NMR (376.5MHz, $CDCl_3$) δ = -62.7. MS calculated for $C_{29}H_{27}F_3NO_3S$ ($M+H^+$) 558.2, found 558.2.
N21		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.70 (d, J = 15.6 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.10 (m, 3H), 6.85 (d, J = 8.8 Hz, 2H), 6.32 (d, J = 16.0 Hz, 1H), 5.50 (s, 2H), 3.95 (s, 3H), 3.82 (s, 3H); ^{19}F-NMR (376.5MHz, $CDCl_3$) δ = -62.7. MS calculated for $C_{28}H_{23}F_3NO_3S$ ($M+H^+$) 542.1, found 542.1.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
N22		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.42 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 8.8 Hz, 2H), 6.67 (d, J = 2.0 Hz, 1H), 6.62 (dd, J = 2.0, 8.0 Hz, 1H), 5.31 (s, 2H), 3.78 (s, 3H), 3.69 (s, 3H), 2.79 (t, J = 7.8 Hz, 2H), 2.54 (t, J = 7.8 Hz, 2H); ^{19}F-NMR (376.5MHz, $CDCl_3$) δ = -62.65. MS calculated for $C_{28}H_{25}F_3NO_5S$ (M+H$^+$) 544.1, found 544.1.
N23		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.55 (d, J = 8.4 Hz, 2H), 7.2 (m, 5H), 7.20 (m, 1H), 6.90 (m, 3H), 5.50 (s, 2H), 4.72 (s, 2H), 3.80 (s, 3H), 2.65 (s, 3H); ^{19}F-NMR (376.5MHz, $CDCl_3$) δ = -62.8. MS calculated for $C_{28}H_{25}F_3NO_6S$ (M+H$^+$) 558.1, found 558.0.
N24		^{19}F-NMR (376.5MHz, $CDCl_3$) δ = -62.7. MS calculated for $C_{28}H_{24}BrF_3NO_5S$ (M+H$^+$) 594.1, found 594.0.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
N25		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.57 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.84 (m, 2H), 6.71 (dd, J = 3.2, 8.8 Hz, 1H), 5.36 (s, 2H), 4.63 (s, 2H), 3.82 (s, 3H), 2.31 (s, 3H); ^{19}F-NMR (376.5MHz, $CDCl_3$) δ = -62.7. MS calculated for $C_{27}H_{23}F_3NO_5S$ (M+H$^+$) 530.1, found 530.1.
N26		^{1}H-NMR (400MHz, CD_3CN) δ = 7.64 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 2.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 6.83 (dd, J = 2.8, 8.4 Hz, 1H), 5.36 (s, 2H), 3.78 (s, 3H), 2.83 (t, J = 7.2 Hz, 2H), 2.52 (t, J = 7.2 Hz, 2H), 2.29 (s, 3H); ^{19}F-NMR (376.5MHz, $CDCl_3$) δ = -63.16. MS calculated for $C_{28}H_{25}F_3NO_4S$ (M+H$^+$) 528.1, found 528.2.

[00295] By repeating the procedures described in the above examples, using appropriate starting materials, the following compounds of Formula I, as identified in Table 1, are obtained.

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Transcriptional Assay

[00296] Transfection assays are used to assess the ability of compounds of the invention to modulate the transcriptional activity of the PPARs. Briefly, expression vectors for chimeric proteins containing the DNA binding domain of yeast GAL4 fused to the ligand-binding domain (LBD) of either PPARδ, PPARα or PPARγ are introduced via transient transfection into mammalian cells, together with a reporter plasmid where the luciferase gene is under the control of a GAL4 binding site. Upon exposure to a PPAR modulator, PPAR transcriptional activity varies, and this can be monitored by changes in luciferase levels. If transfected cells are exposed to a PPAR agonist, PPAR-dependent transcriptional activity increases and luciferase levels rise.

[00297] 293T human embryonic kidney cells ($8x10^6$) are seeded in a $175cm^2$ flask a day prior to the start of the experiment in 10% FBS, 1% Penicillin/Streptomycin/Fungizone, DMEM Media. The cells are harvested by washing with PBS (30ml) and then dissociating using trypsin (0.05%; 3ml). The trypsin is inactivated by the addition of assay media (DMEM, CA-dextran fetal bovine serum (5%). The cells are spun down and resuspended to 170,000cells/ml. A Transfection mixture of GAL4-PPAR LBD expression plasmid (1μg), UAS-luciferase reporter plasmid (1μg), Fugene (3:1 ratio; 6μL) and serum-free media (200μL) was prepared and incubated for 15-40 minutes at room temperature. Transfection mixtures are added to the cells to give 0.16M cells/mL, and cells (50μl/well) are then plated into 384 white, solid-bottom, TC-treated plates. The cells are further incubated at 37°C, 5.0% CO_2 for 5-7 hours. A 12-point series of dilutions (3 fold serial dilutions) are prepared for each test compound in DMSO with a starting compound concentration of 10μM. Test compound (500nl) is added to each well of cells in the assay plate and the cells are incubated at 37°C, 5.0% CO_2 for 18-24 hours. The cell lysis/luciferase assay buffer, Bright-Glo™ (25%; 25μl; Promega), is added to each well. After a further incubation for 5 minutes at room temperature, the luciferase activity is measured.

[00298] Raw luminescence values are normalized by dividing them by the value of the DMSO control present on each plate. Normalized data is analyzed and dose-response curves are fitted using Prizm graph fitting program. EC50 is defined as the concentration at

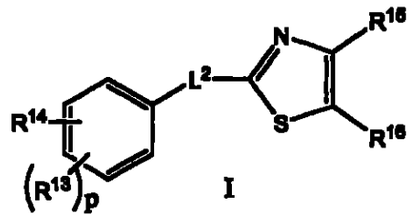
which the compound elicits a response that is half way between the maximum and minimum values. Relative efficacy (or percent efficacy) is calculated by comparison of the response elicited by the compound with the maximum value obtained for a reference PPAR modulator.

[00299] Compounds of Formula I, in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, for example, as indicated by the *in vitro* tests described in this application. Compounds of the invention preferably have an EC50 for PPARδ of less than 1μM, more preferably less than 500nm, more preferably less than 100nM. Compounds of the invention are at least 100-fold selectsve for PPARδ over PPARγ.

[00300] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

WE CLAIM:

1. A compound of Formula I:



I

in which

p is an integer selected from 0 to 3;

L^2 is selected from –XOX–, $–XS(O)_{0-2}X–$ and $–XS(O)_{0-2}XO–$; wherein X is independently selected from a bond and C_{1-4}alkylene; wherein any alkylene of L^2 can be optionally substituted by 1 to 3 radicals selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy;

R^{13} is selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{6-10}aryl, C_{5-10}heteraryl, C_{3-12}cycloalkyl and C_{3-8}heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^{13} is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy;

R^{14} is selected from $-XOXC(O)OR^{17}$ and $-XC(O)OR^{17}$; wherein X is a bond or C_{1-4}alkylene; and R^{17} is selected from hydrogen and C_{1-6}alkyl;

R^{15} and R^{16} are independently selected from $–R^{18}$ and $–YR^{18}$; wherein Y is selected from C_{1-6}alkylene, C_{2-6}alkenylene, C_{2-6}alkynylene, $–C(O)NR^{17}–$ and –OX–; X is a bond or C_{1-4}alkylene; R^{17} is selected from hydrogen and C_{1-6}alkyl; and R^{18} is selected from C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{6-10}aryl and C_{5-13}heteroaryl; or R^{15} and R^{16} together with the atoms to which R^{15} and R^{16} are attached form fused bicyclic or tricyclic C_{5-14}heteroaryl;

wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^{18}, or the combination of R^{15} and R^{16}, is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxy-C_{1-6}alkyl,

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halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{6-10}aryl, C_{5-13}heteroaryl, $-XS(O)_{0-2}R^{17}$, $-XS(O)_{0-2}XR^{19}$, $-XNR^{17}R^{17}$, $-XNR^{17}S(O)_{0-2}R^{17}$, $-XNR^{17}C(O)R^{17}$, $-XC(O)NR^{17}R^{17}$, $-XNR^{17}C(O)R^{19}$, $-XC(O)NR^{17}R^{19}$, $-XC(O)R^{19}$, $-XNR^{17}XR^{19}$ and $-XOXR^{19}$; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituent is further optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxy-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy; wherein X is a bond or C_{1-4}alkylene; R^{17} is selected from hydrogen and C_{1-6}alkyl; and R^{19} is selected from C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{6-10}aryl and C_{5-10}heteroaryl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R^{19} is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy; and the pharmaceutically acceptable salts, hydrates, solvates, isomers and prodrugs thereof.

2. The compound of claim 1 in which:

p is an integer selected from 0 to 3;

L^2 is selected from $-XOX-$, $-XS(O)_{0-2}X-$ and $-XS(O)_{0-2}XO-$; wherein X is independently selected from a bond and C_{1-4}alkylene; wherein any alkylene of L^2 can be optionally substituted by 1 to 3 radicals selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy;

R^{13} is C_{1-6}alkyl, C_{1-6}alkoxy and halogen; and

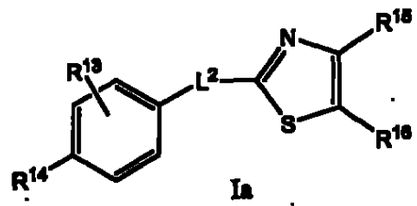
R^{14} is selected from $-XOXC(O)OR^{17}$ and $-XC(O)OR^{17}$; wherein X is a bond or C_{1-4}alkylene; and R^{17} is selected from hydrogen and C_{1-6}alkyl;

R^{15} and R^{16} are independently selected from $-R^{18}$ and $-YR^{18}$; wherein Y is selected from C_{1-6}alkylene, C_{2-6}alkenylene, $-C(O)NR^{17}-$ and $-OX-$; X is a bond or C_{1-4}alkylene; R^{17} is selected from hydrogen and C_{1-6}alkyl; and R^{18} is selected from C_{6-10}aryl, C_{3-12}cycloalkyl and C_{5-13}heteroaryl; or R^{15} and R^{16} together with the atoms to which R^{15} and R^{16} are attached form fused bicyclic or tricyclic C_{5-14}heteroaryl;

wherein any aryl, heteroaryl and cycloalkyl of R^{18}, or the combination of R^{15} and R^{16}, is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxy-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, halo-

substituted-C_{1-6}alkoxy, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{6-10}aryl optionally substituted with C_{1-6}alkoxy, C_{5-13}heteroaryl, $-XS(O)_{0-2}R^{17}$, $-XS(O)_{0-2}XR^{19}$, $-XNR^{17}R^{17}$, $-XNR^{17}S(O)_{0-2}R^{17}$, $-XNR^{17}C(O)R^{17}$, $-XC(O)NR^{17}R^{17}$, $-XNR^{17}C(O)R^{19}$, $-XC(O)NR^{17}R^{19}$, $-XC(O)R^{19}$, $-XNR^{17}XR^{19}$ and $-XOXR^{19}$; wherein X is a bond or C_{1-4}alkylene; R^{17} is selected from hydrogen and C_{1-6}alkyl; and R^{19} is selected from C_{6-10}aryl, C_{5-10}heteroaryl, C_{3-8}heterocycloalkyl and C_{3-12}cycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R^{19} is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy.

3. The compound of claim 1 of Formula Ia:



Ia

L^2 is selected from $-S(O)_{0-2}(CH_2)_{1-4}O-$, $-O(CH_2)_{1-4}S(O)_{0-2}-$, $-CH_2S(O)_{0-2}-$, $-S(O)_{0-2}CH_2-$, $-S(O)_{0-2}-$, $-CH_2O-$ and $-OCH_2-$;

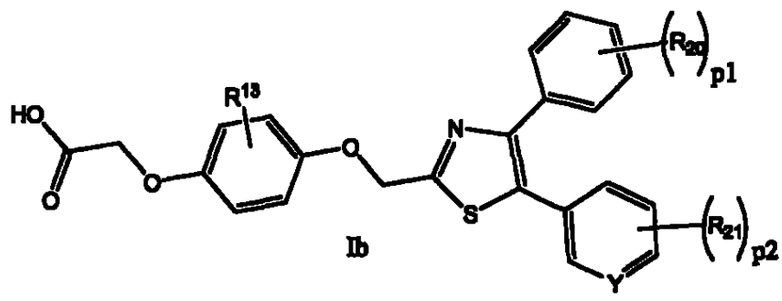
R^{13} is selected from C_{1-6}alkyl, C_{1-6}alkoxy and halo;

R^{14} is selected from $-OCH_2C(O)OH$ and $-CH_2C(O)OH$;

R^{15} and R^{16} are independently selected from $-R^{18}$ and $-YR^{18}$; wherein Y is selected from C_{1-6}alkylene, C_{2-6}alkenylene, $-C(O)NH-$ and $-O(CH_2)_{1-3}-$; and R^{18} is selected from phenyl, biphenyl, cyclohexyl, naphthyl, benzo[1,3]dioxol-5-yl, benzo[b]furanyl, pyridinyl, pyrimidinyl, dibenzo-furan-2-yl, furanyl, benzo[b]thiophene, thiophenyl, phenoxathiin-4-yl, benzoxazolyl, 3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl, 2-oxo-2,3-dihydro-benzooxazol-6-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, benzoxazolyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl and quinolinyl; or R^{15} and R^{16} together with the atoms to which R^{15} and R^{16} are attached form 4,5-dihydro-naphtho[1,2-d]thiazol-2-yl, 4H-chromeno[4,3-d]thiazol-2-yl, 5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl, benzthiazolyl, benzoxazolyl and 1-oxa-3-aza-cyclopenta[a]naphthalen-2-yl;

wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^{15}, R^{16} or the combination of R^{15} and R^{16}, is optionally substituted with 1 to 3 radicals independently selected from halo, cyano, nitro, methyl, isopropyl, isopropyl-sulfinyl, isopropyloxy, hydroxy-methyl, methyl-sulfanyl, methoxy, ethoxy, pentafluoroethoxy, trifluoromethyl, trifluoromethoxy, trifluoromethyl-sulfinyl, morpholino, phenoxy, benzoxy, ethyl-sulfonyl, dimethylamino, methyl-sulfonyl-amino, ethyl-sulfonyl, propyl, vinyl, propyloxy, *sec*-butoxy, trifluoromethyl-sulfanyl, dimethyl-amino-carbonyl, diethyl-amino-carbonyl, methyl-carbonyl-amino, methyl-carbonyl, cyclopentyl-oxy, isopropyl-methylamino-carbonyl, cyclopropyl-amino-carbonyl, cyclohexyl, morpholino, piperidinyl, indolyl, pyrrolidinyl, pyrrolidinyl-carbonyl, 2,3-dihydro-benzofuran-5-yl piperidinyl-carbonyl, morpholino-carbonyl, isopropyl-methyl-amino, isopropyl-methyl-amino-carbonyl, diethyl-amino, and phenyl optionally substituted with methoxy.

4. The compound of claim 3 of Formula Ib:



Ib

in which:

p1 and p2 are independently selected from 0, 1 and 2;

Y is selected from N and CH;

R^{13} is selected from C_{1-6}alkyl, C_{1-6}alkoxy and halo;

R^{20} is selected from trifluoromethyl and trifluoromethoxy; and

R^{21} is selected from isopropyloxy and methoxy.

5. The compound of claim 4 selected from {4-[4-(4-isopropoxy-phenyl)-5-(4-trifluoromethoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid; {4-[4-(4-isopropoxy-phenyl)-5-(4-trifluoromethyl-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-

acetic acid; and {4-[4-(6-methoxy-pyridin-3-yl)-5-(4-trifluoromethoxy-phenyl)-thiazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.

6. A method for treating a disease or disorder in an animal in which modulation of PPARδ activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease, which method comprises administering to the animal a therapeutically effective amount of a compound of Claim 1.

7. The method of claim 6 in which the disease or disorder is selected from the treatment of prophylaxis, dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, atherogenesis, hypertriglyceridemia, heart failure, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, cachexia, inflammation, arthritis, cancer, anorexia, anorexia nervosa, bulimia, Alzheimer's disease, skin disorders, respiratory diseases, ophthalmic disorders, irritable bowel diseases, ulcerative colitis, Crohn's disease, type-1 diabetes, type-2 diabetes and Syndrome X.

8. The method of claim 6 in which the disease or disorder is selected from HIV wasting syndrome, long term critical illness, decreased muscle mass and/or muscle strength, decreased lean body mass, maintenance of muscle strength and function in the elderly, diminished muscle endurance and muscle function, and frailty in the elderly.

9. The use of a compound according to any of claims 1 to 5 in the manufacture of a medicament for treating a disease in an animal in which PPARδ activity contributes to the pathology and/or symptomology of the disease.

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any of claim 1 to 5 in combination with one or more pharmaceutically acceptable excipients.

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11. A pharmaceutical combination, especially a pharmaceutical composition, comprising: 1) a compound of any of claims 1 to 5 or a pharmaceutical acceptable salt thereof; and 2) at least one active ingredient selected from:

a) anti-diabetic agents such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; insulin sensitizer such as protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose co-transporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; dipeptidyl peptidase IV inhibitors such as DPP728, vildagliptin, MK-0431, saxagliptin, GSK23A ; an AGE breaker; a thiazolidone derivative (glitazone) such as pioglitazone, rosiglitazone, or *(R)*-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}-2,3-dihydro-1*H*-indole-2-carboxylic acid, a non-glitazone type PPARγ agonist e.g. GI-262570;

b) hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; squalene synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin;

c) an anti-obesity agent or appetite regulating agent such as phentermine, leptin, bromocriptine, dexamphetamine, amphetamine, fenfluramine, dexfenfluramine, sibutramine, orlistat, dexfenfluramine, mazindol, phentermine, phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate, diethylpropion, benzphetamine, phenylpropanolamine or ecopipam, ephedrine, pseudoephedrine or cannabinoid receptor antagonists;

d) anti-hypertensive agents, e.g., loop diuretics such as ethacrynic acid, furosemide and torsemide; diuretics such as thiazide derivatives, chlorithiazide, hydrochlorothiazide, amiloride; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril and trandolapril;

inhibitors of the Na-K-ATPase membrane pump such as digoxin; neutralendopeptidase (NEP) inhibitors e.g. thiorphan, terteo-thiorphan, SQ29072; ECE inhibitors e.g. SLV306; ACE/NEP inhibitors such as omapatrilat, sampatrilat and fasidotril; angiotensin II antagonists such as candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan, in particular valsartan; renin inhibitors such as aliskiren, terlakiren, ditekiren, RO 66-1132, RO-66-1168; β-adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol and timolol; inotropic agents such as digoxin, dobutamine and milrinone; calcium channel blockers such as amlodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists; and aldosterone synthase inhibitors;

e) a HDL increasing compound;

f) a cholesterol absorption modulator such as Zetia® and KT6-971;

g) Apo-A1 analogues and mimetics;

h) thrombin inhibitors such as Ximelagatran;

i) aldosterone inhibitors such as anastrazole, fadrazole, eplerenone;

j) Inhibitors of platelet aggregation such as aspirin, clopidogrel bisulfate;

k) estrogen, testosterone, a selective estrogen receptor modulator, a selective androgen receptor modulator;

l) a chemotherapeutic agent such as aromatase inhibitors e.g. femara, anti-estrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, alkylating agents, antineoplastic antimetabolites, platin compounds, compounds decreasing the protein kinase activity such as a PDGF receptor tyrosine kinase inhibitor preferably Imatinib or 4-Methyl-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-benzamide; and

m) an agent interacting with a 5-HT_3 receptor and/or an agent interacting with 5-HT_4 receptor such as tegaserod, tegaserod hydrogen maleate, cisapride, cilansetron;

or, in each case a pharmaceutically acceptable salt thereof; and optionally a pharmaceutically acceptable carrier.

12. A pharmaceutical composition according to claim 10 or a combination according to claim 11, for the treatment or prevention of dyslipidemia, hyperlipidemia,

hypercholesteremia, atherosclerosis, hypertriglyceridemia, heart failure, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, inflammation, arthritis, cancer, Alzheimer's disease, skin disorders, respiratory diseases, ophthalmic disorders, inflammatory bowel diseases, IBDs (irritable bowel disease), ulcerative colitis, Crohn's disease, conditions in which impaired glucose tolerance, hyperglycemia and insulin resistance are implicated, such as type-1 and type-2 diabetes, Impaired Glucose Metabolism (IGM), Impaired Glucose Tolerance (IGT), Impaired Fasting Glucose (IFG), and Syndrome-X.

13. A compound according to any of claims 1 to 5, or a pharmaceutical composition according to claim 10 or a combination according to claim 11, for use as a medicament.

14. Use of a compound according to any of claims 1 to 5, or a pharmaceutical composition according to claim 10 or a combination according to claim 11, for the manufacture of a medicament for the treatment or prevention of dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, hypertriglyceridemia, heart failure, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, inflammation, arthritis, cancer, Alzheimer's disease, skin disorders, respiratory diseases, ophthalmic disorders, inflammatory bowel diseases, IBDs (irritable bowel disease), ulcerative colitis, Crohn's disease, conditions in which impaired glucose tolerance, hyperglycemia and insulin resistance are implicated, such as type-1 and type-2 diabetes, Impaired Glucose Metabolism (IGM), Impaired Glucose Tolerance (IGT), Impaired Fasting Glucose (IFG), and Syndrome-X.

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Para códigos de dos letras y otras abreviaciones, consultar "Notas Guía sobre Códigos y Abreviaciones" que aparecen al principio de cada emisión regular de la Gaceta del PCT.

(54) Título: COMPUESTOS Y COMPOSICIONES COMO MODULADORES DEL RECEPTOR ACTIVADO POR PROLIFERADOR DE PEROXISOMA (PPAR)

(54) Resumen: La invención proporciona compuestos, composiciones farmacéuticas que comprenden estos compuestos, y métodos para utilizar tales compuestos con el fin de tratar o prevenir enfermedades o trastornos asociados con la actividad de las familias del Receptor Activado por Proliferador de Peroxisoma (PPAR), en particular la actividad de PPAR.

COMPUESTOS Y COMPOSICIONES COMO MODULADORES DEL RECEPTOR ACTIVADO POR PROLIFERADOR DE PEROXISOMA (PPAR)

Referencia Cruzada a Solicitudes Relacionadas

Esta solicitud reivindica el beneficio de la Solicitud de Patente Provisional de los Estados Unidos de Norteamérica Número 60/574,137, presentada el 14 de mayo de 2004, y de la Solicitud de Patente Provisional de los Estados Unidos de Norteamérica Número 60/648,985, presentada el 31 de enero de 2005. Las descripciones completas de estas solicitudes se incorporan a la presente como referencia en su totalidad y para todos los propósitos.

Campo de la Invención

La invención proporciona compuestos, composiciones farmacéuticas que comprenden estos compuestos, y métodos para utilizar estos compuestos con el fin de tratar o prevenir enfermedades o trastornos asociados con la actividad de las familias del Receptor Activado por Proliferador de Peroxisoma (PPAR), en particular la actividad de PPARδ.

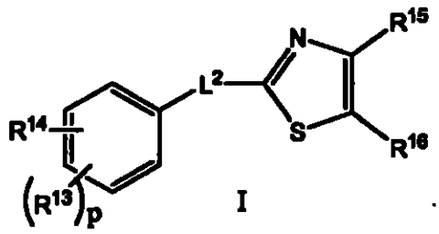
Antecedentes de la Invención

Los Receptores Activados por Proliferador de Peroxisoma (PPARs) son miembros de la súper-familia de receptores de hormonas nucleares, que son factores de transcripción activados por ligando que regulan la expresión genética. Ciertos PPARs están asociados con un número de estados de enfermedad, incluyendo dislipidemia, hiperlipidemia, hipercolesteremia, ateroesclerosis, aterogénesis, hipertrigliceridemia, insuficiencia cardiaca, infarto de miocardio, enfermedades vasculares,

enfermedades cardiovasculares, hipertensión, obesidad, inflamación, artritis, cáncer, enfermedad de Alzheimer, trastornos de la piel, enfermedades respiratorias, trastornos oftálmicos, IBDs (enfermedad de intestino irritable), colitis ulcerativa, y enfermedad de Crohn. De conformidad con lo anterior, las moléculas que modulan la actividad de los PPARs, en particular PPARδ, son útiles como agentes terapéuticos en el tratamiento de tales enfermedades.

Breve Descripción de la Invención

En un aspecto, la presente invención proporciona compuestos de la Fórmula I:



I

en donde:

p es un entero seleccionado de 0 a 3;

L^2 se selecciona a partir de -XOX-, $-XS(O)_{0-2}X-$ y $-XS(O)_{0-2}XO-$; en donde X se selecciona independientemente a partir de un enlace y alquileno de 1 a 4 átomos de carbono; en donde cualquier alquileno de L^2 pude estar opcionalmente sustituido por 1 a 3 radicales seleccionados a partir de halógeno, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, y alcoxi de 1 a 6 átomos de carbono sustituido por halógeno;

R^{13} se selecciona a partir de halógeno, alquilo de 1 a 6 átomos de

carbono, alcoxi de 1 a 6 átomos de carbono, hidroxi-alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxi de 1 a 6 átomos de carbono sustituido por halógeno, arilo de 6 a 10 átomos de carbono, heteroarilo de 5 a 10 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, y heterocicloalquilo de 3 a 8 átomos de carbono; en donde cualquier arilo, heteroarilo, cicloalquilo, y heterocicloalquilo de R^{13} está opcionalmente sustituido con 1 a 3 radicales independientemente seleccionados a partir de halógeno, nitro, ciano, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, hidroxi-alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, y alcoxi de 1 a 6 átomos de carbono sustituido por halógeno;

R^{14} se selecciona a partir de -XOXC(O)OR^{17} y -XC(O)OR^{17}; en donde X es un enlace o alquileno de 1 a 4 átomos de carbono; y R^{17} se selecciona a partir de hidrógeno y alquilo de 1 a 6 átomos de carbono;

R^{15} y R^{16} se seleccionan independientemente a partir de -R^{18} y -YR^{18}; en donde Y se selecciona a partir de alquileno de 1 a 6 átomos de carbono, alquenileno de 2 a 6 átomos de carbono, alquinileno de 2 a 6 átomos de carbono, -C(O)NR^{17}- y -OX-; X es un enlace o alquileno de 1 a 4 átomos de carbono; R^{17} se selecciona a partir de hidrógeno y alquilo de 1 a 6 átomos de carbono; y R^{18} se selecciona a partir de cicloalquilo de 3 a 12 átomos de carbono, hetero-ciclo-alquilo de 3 a 8 átomos de carbono, arilo de 6 a 10 átomos de carbono, y hetero-arilo de 5 a 13 átomos de carbono; o R^{15} y R^{16}, junto con los átomos con los que están unidos R^{15} y R^{16}, forman un heteroarilo de 5 a 14 átomos de carbono bicíclico o

triciclico fusionado;

en donde cualquier arilo, hetero-arilo, cicloalquilo, y hetero-cicloalquilo de R^{15}, o la combinación de R^{15} y R^{16}, está opcionalmente sustituido con 1 a 3 radicales independientemente seleccionados a partir de halógeno, nitro, ciano, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, tioalquilo de 1 a 6 átomos de carbono, hidroxi-alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxi de 1 a 6 átomos de carbono sustituido por halógeno, ciclo-alquilo de 3 a 12 átomos de carbono, hetero-ciclo-alquilo de 3 a 8 átomos de carbono, arilo de 6 a 10 átomos de carbono, hetero-arilo de 5 a 13 átomos de carbono, $-XS(O)_{0-2}R^{17}$, $-XS(O)_{0-2}XR^{18}$, $XNR^{17}R^{17}$, $-XNR^{17}S(O)_{0-2}R^{17}$, $-XNR^{17}C(O)R^{17}$, $XC(O)NR^{17}R^{17}$, $-XNR^{17}C(O)R^{18}$, $-XC(O)NR^{17}R^{18}$, $-XC(O)R^{18}$, $-XNR^{17}XR^{19}$, y $XOXR^{19}$; en donde cualquier sustituyente de arilo, heteroarilo, cicloalquilo, o heterocicloalquilo está además sustituido opcionalmente con 1 a 3 radicales independientemente a partir de halógeno, nitro, ciano, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, tioalquilo de 1 a 6 átomos de carbono, hidroxi-alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, y alcoxi de 1 a 6 átomos de carbono, sustituido por halógeno; en donde X es un enlace o alquileno de 1 a 4 átomos de carbono, R^{17} se selecciona a partir de hidrógeno y alquilo de 1 a 4 átomos de carbono, y R^{19} se selecciona a partir de cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 8 átomos de carbono, arilo de 6 a 10 átomos de carbono, y heteroarilo de 5 a 10 átomos de carbono; en donde cualquier arilo, heteroarilo, cicloalquilo, o heterocicloalquilo de

R^{19} está opcionalmente sustituido con 1 a 3 radicales independientemente seleccionados a partir de halógeno, nitro, ciano, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, y alcoxi de 1 a 6 átomos de carbono sustituido por halógeno; y los derivados de N-óxido, derivados de profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos; y las sales farmacéuticamente aceptables y solvatos (por ejemplo, hidratos) de estos compuestos.

En un segundo aspecto, la presente invención proporciona una composición farmacéutica que contiene un compuesto de la Fórmula I, o un derivado de N-óxido, isómeros individuales o mezclas de isómeros del mismo; o una sal farmacéuticamente aceptable del mismo, mezclados con uno o más excipientes adecuados.

En un tercer aspecto, la presente invención proporciona un método para el tratamiento de una enfermedad en un animal en donde la modulación de PPAR, en particular PPARδ pueda prevenir, inhibir, o reducir la patología y/o sintomatología de la enfermedad, cuyo método comprende administrar al animal una cantidad terapéuticamente efectiva de un compuesto de la Fórmula I, o un derivado de N-óxido, isómeros individuales y mezclas de isómeros del mismo, o una sal farmacéuticamente aceptable del mismo.

En un cuarto aspecto, la presente invención proporciona el uso de un compuesto de la Fórmula I en la fabricación de un medicamento para el tratamiento de una enfermedad en un animal en donde la actividad de PPAR, en particular la actividad de PPARδ, contribuya a la patología y/o

sintomatología de la enfermedad.

En un quinto aspecto, la presente invención proporciona un proceso para preparar compuestos de la Fórmula I, y los derivados de N-óxido, derivados de profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos, y las sales farmacéuticamente aceptables de los mismos.

Descripción Detallada de la Invención

Definiciones

"Alquilo", como un grupo y como un elemento estructural de otros grupos, por ejemplo alquilo sustituido por halógeno y alcoxi, puede ser de cadena recta o ramificada. Alcoxi de 1 a 6 átomos de carbono incluye metoxi, etoxilo, y similares. Alquilo sustituido por halógeno incluye trifluoro-metilo, pentafluoro-etilo, y similares.

"Arilo" significa un ensamble de anillo aromático monocíclico o biciclico fusionado que contiene de 6 a 10 átomos de carbono del anillo. Por ejemplo, arilo puede ser fenilo o naftilo, de preferencia fenilo. "Arileno" significa un radical divalente derivado a partir de un grupo arilo. "Heteroarilo" es como se define para arilo, en donde uno o más de los miembros del anillo son un heteroátomo. Por ejemplo, heteroarilo incluye piridilo, indolilo, indazolilo, quinoxalinilo, quinolinilo, benzofuranilo, benzopiranilo, benzotiopiranilo, benzo-[1,3]-dioxol, imidazolilo, benzo-imidazolilo, pirimidinilo, furanilo, oxazolilo, isoxazolilo, triazolilo, tetrazolilo, pirazolilo, tienilo, etcétera. "Arilo de 6 a 10 átomos de carbono-alquilo de 0 a 4 átomos de carbono" significa un arilo como se describe anteriormente, conectado mediante una agrupación de alquileno. Por

ejemplo, arilo de 6 a 10 átomos de carbono-alquilo de 0 a 4 átomos de carbono incluye fenetilo, bencilo, etcétera.

"Cicloalquilo" significa un ensamble de anillo monocíclico, bicíclico fusionado, o policíclico puenteado, saturado o parcialmente insaturado, que contiene el número de átomos del anillo indicado. Por ejemplo, cicloalquilo de 3 a 10 átomos de carbono incluye ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, etcétera. "Heterocicloalquilo" significa cicloalquilo, como se define en esta solicitud, en el entendido de que uno o más de los átomos de carbono del anillo indicados, están reemplazados por una fracción seleccionada a partir de -O-, -N=, -NR-, -C(O)-, -S-, -S(O)-, ó $-S(O)_2-$, en donde R es hidrógeno, alquilo de 1 a 4 átomos de carbono, o un grupo protector de nitrógeno. Por ejemplo, heterocicloalquilo de 3 a 8 átomos de carbono, como se utiliza en esta solicitud para describir los compuestos de la invención, incluye morfolino, pirrolidinilo, piperazinilo, piperidinilo, piperidinilona, 1,4-dioxa-8-aza-espiro-[4,5]-dec-8-ilo, etcétera.

"Halógeno" (o halo) de preferencia representa cloro o flúor, pero también puede ser bromo o yodo.

"Tratar", "tratando", y "tratamiento", se refieren a un método para aliviar o abatir una enfermedad y/o sus síntomas aunados.

Descripción de las Modalidades Preferidas

La presente invención proporciona compuestos, composiciones, y métodos para el tratamiento de enfermedades en donde la modulación de la actividad de PPARδ pueda prevenir, inhibir, o reducir la patología y/o sintomatología de las enfermedades, cuyo método comprende administrar

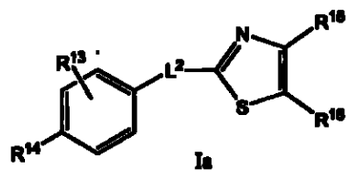
al animal una cantidad terapéuticamente efectiva de un compuesto de la Fórmula I.

En una modalidad, con referencia a los compuestos de la Fórmula I, p es un entero seleccionado de 0 a 3; L^2 se selecciona de -XOX-, $-XS(O)_{0-2}X-$, y $-XS(O)_{0-2}XO-$; en donde X se selecciona independientemente a partir de un enlace y alquileno de 1 a 4 átomos de carbono; en donde cualquier alquileno de L^2 puede estar opcionalmente sustituido por 1 a 3 radicales seleccionados a partir de halógeno, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, y alcoxi de 1 a 6 átomos de carbono sustituido por halógeno; y R^{13} es alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, y halógeno.

En una modalidad adicional, R^{14} se selecciona a partir de $-XOXC(O)OR^{17}$ y $-XC(O)OR^{17}$; en donde X es un enlace o alquileno de 1 a 4 átomos de carbono; y R^{17} se selecciona a partir de hidrógeno y alquilo de 1 a 6 átomos de carbono; R^{15} y R^{16} se seleccionan independientemente a partir de $-R^{18}$ e $-YR^{18}$; en donde Y se selecciona a partir de alquileno de 1 a 6 átomos de carbono, alquenileno de 2 a 6 átomos de carbono, $-C(O)NR^{17}-$, y -OX-; X es un enlace o alquileno de 1 a 4 átomos de carbono; R^{17} se selecciona a partir de hidrógeno y alquilo de 1 a 6 átomos de carbono; y R^{18} se selecciona a partir de arilo de 6 a 10 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, y heteroarilo de 5 a 13 átomos de carbono; o R^{15} y R^{16}, junto con los átomos con los que están unidos R^{15} y R^{16}, forman un heteroarilo de 5 a 14 átomos de carbono bicíclico o tricíclico fusionado; en donde cualquier arilo, heteroarilo, y

cicloalquilo de R^{15}, o la combinación de R^{15} y R^{16}, está opcionalmente sustituido con 1 a 3 radicales independientemente seleccionados a partir de halógeno, nitro, ciano, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, tioalquilo de 1 a 6 átomos de carbono, hidroxi-alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxi de 1 a 6 átomos de carbono sustituido por halógeno, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 8 átomos de carbono, arilo de 6 a 10 átomos de carbono opcionalmente sustituido con alcoxi de 1 a 6 átomos de carbono, heteroarilo de 5 a 13 átomos de carbono, $-XS(O)_{0-2}R^{17}$, $-XS(O)_{0-2}XR^{18}$, $-XNR^{17}R^{17}$, $-XNR^{17}S(O)_{0-2}R^{17}$, $-XNR^{17}C(O)R^{17}$, $-XC(O)NR^{17}R^{17}$, $-XNR^{17}C(O)R^{18}$, $-XC(O)NR^{17}R^{19}$, $-XC(O)R^{19}$, $-XNR^{17}XR^{19}$, y $-XOXR^{19}$; en donde X es un enlace o alquileno de 1 a 4 átomos de carbono; R^{17} se selecciona a partir de hidrógeno y alquilo de 1 a 6 átomos de carbono; y R^{18} se selecciona a partir de arilo de 6 a 10 átomos de carbono, heteroarilo de 5 a 10 átomos de carbono, heterocicloalquilo de 3 a 8 átomos de carbono, y cicloalquilo de 3 a 12 átomos de carbono, en donde cualquier arilo, heteroarilo, cicloalquilo, o heterocicloalquilo de R^{18} está opcionalmente sustituido con 1 a 3 radicales independientemente seleccionados a partir de halógeno, nitro, ciano, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, y alcoxi de 1 a 6 átomos de carbono sustituido por halógeno.

En una modalidad adicional, la invención proporciona un compuesto de la Fórmula Ia:



Ia

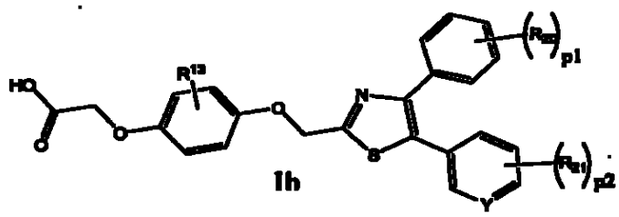
en donde:

L^2 se selecciona a partir de $-S(O)_{0-2}(CH_2)_{1-4}O-$, $-O(CH_2)_{1-4}S(O)_{0-2}-$, $-CH_2S(O)_{0-2}-$, $-S(O)_{0-2}CH_2-$, $-S(O)_{0-2}-$, $-CH_2O-$, y $-OCH_2-$; R^{13} se selecciona a partir de alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, y halógeno; R^{14} se selecciona a partir de $-OCH_2C(O)OH$, y $-CH_2C(O)OH$; R^{15} y R^{16} se seleccionan independientemente a partir de $-R^{18}$ e $-YR^{18}$; en donde Y se selecciona a partir de alquileno de 1 a 6 átomos de carbono, alquenileno de 2 a 6 átomos de carbono, -C(O)NH-, y $-O(CH_2)_{1-3}-$; y R^{18} se selecciona a partir de fenilo, bifenilo, ciclohexilo, naftilo, benzo[1,3]dioxol-5-ilo, benzo[b]furanilo, piridinilo, pirimidinilo, dibenzofuran-2-ilo, furanilo, benzo[b]tiofeno, tiofenilo, fenoxantiin-4-ilo, benzoxazolilo, 3-oxo-3,4-dihidro-2H-benzo[1,4]oxazin-6-ilo, 2-oxo-2,3-dihidro-benzo-oxazol-6-ilo, 2,3-dihidro-benzo[1,4]dioxin-6-ilo, benzoxazolilo, 3,4-dihidro-2H-benzo[b][1,4]dioxepin-7-ilo, y quinolinilo; o R^{15} y R^{16} junto con los átomos con los que están unidos R^{15} y R^{16}, forman 4,5-dihidro-nafto[1,2-d]tiazol-2-ilo, 4H-cromeno[4,3-d]tiazol-2-ilo, 5,6-dihidro-4H-3-tia-1-aza-benzo[e]-azulen-2-ilo, benzotiazolilo, benzoxazolilo, y 1-oxa-3-aza-ciclopenta-[a]naftalen-2-ilo;

en donde cualquier arilo, heteroarilo, cicloalquilo y heterocicloalquilo de R^{15} y R^{16} la combinación de R^{15} y R^{16}, está opcionalmente sustituido con 1 a 3 radicales independientemente seleccionados a partir de halógeno, ciano, nitro, metilo, isopropilo, isopropil-sulfanilo, isopropiloxi,

hidroxi-metilo, metil-sulfanilo, metoxi, etoxilo, pentafluoro-etoxilo, trifluoro-metilo, trifluoro-metoxi, trifluoro-metil-sulfonilo, morfolino, fenoxilo, benzoxilo, etil-sulfonilo, dimetil-amino, metil-sulfonil-amino, etil-sulfonilo, propilo, vinilo, propiloxi, butoxilo secundario, trifluoro-metil-sulfanilo, dimetil-amino-carbonilo, dietil-amino-carbonilo, metil-carbonil-amino, metil-carbonilo, ciclopentil-oxilo, isopropil-metil-amino-carbonilo, ciclopropil-amino-carbonilo, ciclohexilo, morfolino, piperidinilo, indolilo, pirrolidinilo, pirrolidinil-carbonilo, 2,3-dihidro-benzofuran-5-ilo, piperidinil-carbonilo, morfolino-carbonilo, isopropil-metil-amino, isopropil-metil-amino-carbonilo, dietil-amino, y fenilo opcionalmente sustituido con metoxi.

En una modalidad adicional, están los compuestos de la Fórmula Ib:



Ih

en donde: p1 y p2 se seleccionan independientemente de 0, 1, y 2; Y se selecciona a partir de N y CH; R^{13} se selecciona a partir de alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, y halógeno; R^{20} se selecciona a partir de trifluorometilo y trifluorometoxi; y R^{21} se selecciona a partir de isopropiloxi y metoxi.

Los compuestos preferidos de la Fórmula I se detallan en los Ejemplos más adelante. Los compuestos más preferidos de la invención se seleccionan a partir de: ácido {4-[4-(4-isopropoxi-fenil)-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético; ácido {4-[4-(4-isopropoxi-fenil)-5-(4-trifluoro-metil-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-

acético; y ácido {4-[4-(6-metoxi-piridin-3-il)-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.

Farmacología y Utilidad

Los compuestos de la invención modulan la actividad de los PPARs, y como tales, son útiles para el tratamiento de enfermedades o trastornos en donde los PPARs contribuyan a la patología y/o sintomatología de la enfermedad. Esta invención proporciona además compuestos de esta invención para utilizarse en la preparación de medicamentos para el tratamiento de enfermedades o trastornos en donde los PPARs, en particular PPARδ, contribuyan a la patología y/o sintomatología de la enfermedad.

Por consiguiente, estos compuestos se pueden emplear para el tratamiento o profilaxis de dislipidemia, hiperlipidemia, hipercolesteremia, ateroesclerosis, aterogénesis, hipertrigliceridemia, insuficiencia cardíaca, hipercolesteremia, infarto de miocardio, enfermedades vasculares, enfermedades cardiovasculares, hipertensión, obesidad, caquexia, síndrome de desecho por VIH, inflamación, artritis, cáncer, enfermedad de Alzheimer, anorexia, anorexia nerviosa, bulimia, trastornos de la piel, enfermedades respiratorias, trastornos oftálmicos, IBDs (enfermedad de intestino irritable), colitis ulcerativa, y enfermedad de Crohn. De preferencia para el tratamiento o profilaxis de dislipidemia, hiperlipidemia, hipercolesteremia, ateroesclerosis, aterogénesis, hipertrigliceridemia, enfermedades cardiovasculares, hipertensión, obesidad, inflamación, cáncer, trastornos de la piel, IBDs (enfermedad de intestino irritable), colitis ulcerativa, y enfermedad de Crohn.

Los compuestos de la invención también se pueden emplear para tratar enfermedades críticas de largo plazo, para aumentar la masa muscular y/o la fuerza muscular, para aumentar la masa corporal magra, para mantener la fuerza y la función muscular en los ancianos, para mejorar la duración del músculo y la función muscular, y para revertir o prevenir la fragilidad en los ancianos.

Además, los compuestos de la presente invención se pueden emplear en mamíferos como agentes hipoglicémicos para el tratamiento y la prevención de condiciones en donde estén implicadas una intolerancia a la glucosa, hiperglicemia, y resistencia a la insulina, tales como diabetes tipo 1 y tipo 2, Metabolismo Deteriorado de Glucosa (IGM), Intolerancia a la Glucosa (IGT), Glucosa Deteriorada en Ayunas (IFG), y Síndrome X. De preferencia, diabetes tipo 1 y tipo 2, Metabolismo Deteriorado de Glucosa (IGM); Intolerancia a la Glucosa (IGT), y Glucosa Deteriorada en Ayunas (IFG).

De conformidad con lo anterior, la presente invención proporciona además un método para prevenir o tratar cualquiera de las enfermedades o trastornos descritos anteriormente, en un sujeto que necesite dicho tratamiento, cuyo método comprende administrar a este sujeto una cantidad terapéuticamente efectiva (*Ver, "Administración y Composiciones Farmacéuticas", más adelante*) de un compuesto de la invención o una sal farmacéuticamente aceptable del mismo. Para cualquiera de los usos anteriores, la dosificación requerida variará dependiendo del modo de administración, de la condición particular que se vaya a tratar, y del efecto deseado. La presente invención también se refiere a:

i) un compuesto de la invención o una sal farmacéuticamente aceptable del mismo, para utilizarse como un medicamento,

ii) el uso de un compuesto de la invención o una sal farmacéuticamente aceptable del mismo, para la fabricación de un medicamento para prevenir o tratar cualquiera de las enfermedades o trastornos descritos anteriormente.

Administración y Composiciones Farmacéuticas

En general, los compuestos de la invención se administrarán en cantidades terapéuticamente efectivas mediante cualquiera de los modos usuales y aceptables conocidos en la técnica, ya sea solos o en combinación con uno o más agentes terapéuticos. Una cantidad terapéuticamente efectiva puede variar ampliamente, dependiendo de la severidad de la enfermedad, la edad, y la salud relativa del sujeto, la potencia del compuesto utilizado, y otros factores. En general, se indica que se obtienen resultados satisfactorios sistémicamente en dosificaciones diarias de aproximadamente 0.03 a 2.5 miligramos/kilogramo por peso corporal. Una dosificación diaria indicada en el mamífero superior, por ejemplo en los seres humanos, está en el intervalo de aproximadamente 0.5 miligramos a aproximadamente 100 miligramos, convenientemente administrados, por ejemplo, en dosis divididas hasta cuatro veces al día, o en una forma retardada. Las formas de dosificación unitaria adecuadas para administración oral comprenden de aproximadamente 1 a 50 miligramos de ingrediente activo.

Los compuestos de la invención se pueden administrar como composiciones farmacéuticas por cualquier vía convencional, en particular

enteralmente, por ejemplo oralmente, por ejemplo en la forma de tabletas o cápsulas, o parenteralmente, por ejemplo en la forma de soluciones o suspensiones inyectables, tópicamente, por ejemplo en la forma de lociones, geles, ungüentos, o cremas, o en una forma nasal o de supositorio. Las composiciones farmacéuticas que comprenden un compuesto de la presente invención en forma libre o en una forma de sal farmacéuticamente aceptable en asociación con cuando menos un vehículo o diluyente farmacéuticamente aceptable, se pueden fabricar de una manera convencional mediante métodos de mezcla, granulación, o recubrimiento. Por ejemplo, las composiciones orales pueden ser tabletas o cápsulas de gelatina que comprendan al ingrediente activo junto con a) diluyentes, por ejemplo lactosa, dextrosa, sacarosa, manitol, sorbitol, celulosa, y/o glicina; b) lubricantes, por ejemplo sílice, talco, ácido esteárico, su sal de magnesio o calcio, y/o polietilenglicol; para tabletas también c) aglutinantes, por ejemplo silicato de magnesio y aluminio, pasta de almidón, gelatina, tragacanto, metil-celulosa, carboxi-metil-celulosa de sodio, y/o polivinil-pirrolidona; si se desea d) desintegrantes, por ejemplo almidones, ágar, ácido algínico o su sal sódica, o mezclas efervescentes; y/o) absorbentes, colorantes, saborizantes, y edulcorantes. Las composiciones inyectables pueden ser soluciones o suspensiones isotónicas acuosas, y los supositorios se pueden preparar a partir de emulsiones o suspensiones grasas. Las composiciones se pueden esterilizar y/o pueden contener adyuvantes, tales como agentes conservadores, estabilizantes, humectantes, o emulsionantes, promotores de solución, sales para regular la presión osmótica, y/o reguladores del

pH. En adición, también pueden contener otras sustancias terapéuticamente valiosas. Las formulaciones adecuadas para aplicaciones transdérmicas incluyen una cantidad efectiva de un compuesto de la presente invención con un vehículo. Un vehículo puede incluir solventes farmacológicamente aceptables absorbibles para asistir en el paso a través de la piel del huésped. Por ejemplo, los dispositivos transdérmicos están en la forma de un parche que comprende un miembro de respaldo, un depósito que contiene al compuesto opcionalmente con vehículos, opcionalmente una barrera de control de liberación para suministrar el compuesto a la piel del huésped a una velocidad controlada y previamente determinada durante un periodo de tiempo prolongado, y elementos para asegurar el dispositivo a la piel. También se pueden utilizar formulaciones transdérmicas de matriz. Las formulaciones adecuadas para aplicación tópica, por ejemplo a la piel y a los ojos, de preferencia son soluciones acuosas, ungüentos, cremas, o geles, bien conocidos en la técnica. Éstos pueden contener solubilizantes, estabilizantes, agentes mejoradores de tonicidad, reguladores del pH, y conservadores.

Esta invención también se refiere a una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto como se describe en la presente, en combinación con uno o más vehículos farmacéuticamente aceptables.

Los compuestos de la invención se pueden administrar en cantidades terapéuticamente efectivas en combinación con uno o más agentes terapéuticos (combinaciones farmacéuticas).

Por consiguiente, la presente invención también se refiere a una

combinación farmacéutica, tal como una preparación combinada o una composición farmacéutica (combinación fija), que comprende:

1) un compuesto de la invención como se define anteriormente, o una sal farmacéuticamente aceptable del mismo, y

2) cuando menos un ingrediente activo seleccionado a partir del grupo que consiste en:

a) agentes antidiabéticos tales como insulina, derivados de insulina y miméticos; secretagogos de insulina tales como las sulfonil-ureas, por ejemplo Glipizida, gliburida, y Amarilo; ligandos de receptores de sulfonilurea insulinotrópica tales como meglitinidas, por ejemplo nateglinida y repaglinida; sensibilizantes a insulina, tales como inhibidores de fosfatasa de proteína tirosina-1B (PTP-1B), tales como PTP-112; inhibidores de GSK3 (quinasa de sintasa de glicógeno-3), tales como SB-517955, SB-4195052, SB-216763, NN-57-05441, y NN-57-05445; ligandos RXR, tales como GW-0791 y AGN-194204; inhibidores del co-transportador de glucosa dependiente de sodio, tales como T-1095; inhibidores de fosforilasa de glicógeno A, tales como BAY R3401; biguanidas, tales como metformina; inhibidores de alfa-glucosidasa, tales como acarbosa; GLP-1 (péptido tipo glucagon-1), análogos de GLP-1 tales como Exendin-4 y miméticos de GLP-1; inhibidores de DPPIV (dipeptidil-peptidasa IV) tales como DPPT728, LAF237 (vildagliptina - Ejemplo 1 de la Publicación Internacional Número WO 00/34241), MK-0431, saxagliptina, GSK23A; un rompedor de AGE; un derivado de tiazolidona (glitazona) tal como pioglitazona, rosiglitazona, o ácido (R)-1-{4-[5-metil-2-(4-trifluoro-metil-fenil)-oxazol-4-ilmetoxi]-bencen-sulfonil}-2,3-dihidro-1H-indol-2-carboxílico

descrito en la Solicitud de Patente Número WO 03/043985, como el compuesto 19 del Ejemplo 4, un agonista de PPARδ que no es tipo glitazona, por ejemplo GI-262570;

b) agentes hipolipidémicos, tales como inhibidores de reductasa de 3-hidroxi-3-metil-glutaril-coenzima A (HMG-CoA), por ejemplo lovastatina, pitavastatina, simvastatina, pravastatina, cerivastatina, mevastatina, velostatina, fluvastatina, dalvastatina, atorvastatina, rosuvastatina, y rivastatina; inhibidores de sintasa de escualeno; ligandos FXR (receptor farnesoide X) y LXR (receptor de hígado X); colestiramina; fibratos; ácido nicotínico y aspirina;

c) un agente contra la obesidad o un agente regulador del apetito, tal como fentermina, leptina, bromocriptina, dexanfetamina, anfetamina, fenfluramina, dexfenfluramina, sibutramina, orlistato, dexfenfluramina, mazindol, fentermina, fendimetrazina, dietilpropión, fluoxetina, bupropión, topiramato, dietilpropión, benzofetamina, fenilpropanolamina, o ecopipam, efedrina, pseudo-efedrina, o antagonistas del receptor canabinoide;

d) agentes anti-hipertensivos, por ejemplo diuréticos de ciclo tales como ácido etacrínico, furosemida, y torsemida diuréticos tales como derivados de tiazida, clortiazida, hidroclorotiazida, amilorida; inhibidores de la enzima convertidora de angiotensina (ACE), tales como benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, y trandolapril; inhibidores de la bomba de membrana de Na-K-ATPasa, tales como digoxina; inhibidores de neutralendopeptidasa (NEP), por ejemplo tiorfán, terteo-tiorfán, SQ29072; inhibidores de ECE, por

ejemplo SV306; inhibidores de ACE/EP, tales como omapatrilato, sampatrilato, y fasidotril; antagonistas de angiotensina II, tales como candesartan, eprosartan, irbesartan, losartan, telmisartan, y valsartan, en particular valsartan; inhibidores de renina, tales como aliskireno, terlaquireno, ditequireno, ditequireno, RO 66-1132, RO-66-1168; bloqueadores del receptor β-adrenérgico, tales como acebutolol, atenolol, betaxolol, bisoprolol, metaprolol, nadolol, propranolol, sotalol, y timolol; agentes inotrópicos tales como digoxina, dobutamina, y milrinona; bloqueadores del canal de calcio, tales como amlodipina, bepridil, diltiazem, felodipina, nicardipina, nimodipina, nifedipida, nisoldipina, y verapamil; antagonistas del receptor de aldosterona; e inhibidores de sintasa de aldosterona;

e) un compuesto incrementador de lipoproteínas de alta densidad (HDL),

f) modulador de absorción de colesterol, tal como Zetia® y KT6-971,

g) análogos y miméticos de Apo-A1,

h) inhibidores de trombina, tales como Ximelagatran,

i) inhibidores de aldosterona, tales como anastrazol, fadrazol, eplerenona,

j) inhibidores de la acumulación de plaquetas, tales como aspirina, bisulfato de clopidogrel,

k) estrógeno, testosterona, un modulador del receptor de estrógeno selectivo, un modulador de receptor de andrógeno selectivo;

l) un agente quimioterapéutico, tal como los inhibidores de

aromatasa, por ejemplo femara, anti-estrógenos, inhibidores de topoisomerasa I, inhibidores de topoisomerasa II, agentes activos en microtúbulos, agentes alquilantes, antimetabolitos antineoplásticos, compuestos de platina, compuestos que reducen la actividad de la quinasa de proteína tales como el inhibidor de quinasa de tirosina receptora de PDGF, de preferencia imatinib ({N-{5-[4-(4-metil-piperazino-metil)-benzoil-amido]-2-metilfenil}-4-(3-piridil)-2-pirimidin-amina}), descrita en la Solicitud de Patente Europea Número EP-A-0,564,409 como el Ejemplo 21, ó 4-metil-N-[3-(4-metil-imidazol-1-il)-5-trifluoro-metil-fenil]-3-(4-piridin-3-il-pirimidin-2-ilamino)-benzamida, descrita en la Solicitud de Patente Número WO 04/005281 como el Ejemplo 92; y

m) un agente que interactúe con un receptor 5-HT_3 y/o un agente que interactúe con un receptor 5-HT_4, tal como tegaserod, descrito en la Patente de los Estados Unidos de Norteamérica Número 5510353 como el Ejemplo 13, maleato ácido de tegaserod, cisaprida, cilansetron;

o en cada caso una sal farmacéuticamente aceptable de los mismos;

y opcionalmente un vehículo farmacéuticamente aceptable.

Los componentes de combinación más preferidos son tegaserod, imatinib, vildagliptina, metformina, un derivado de tiazolidona (glitazona), tal como pioglitazona, rosiglitazona, o ácido (R)-1-{4-[5-metil-2-(4-trifluorometil-fenil)-oxazol-4-ilmetoxi]-oxazol-4-ilmetoxi]-bencen-sulfonil}-2,3-dihidro-1H-indol-2-carboxílico, un ligando de receptor de sulfonil-urea, alisquireno, valsartan, orlistato, o una estatina, tal como pitavastina, simvastatina, fluvastatina, o pravastatina.

De preferencia, la combinación farmacéutica contiene una cantidad

terapéuticamente efectiva de un compuesto de la invención como se define anteriormente, en una combinación con una cantidad terapéuticamente efectiva de otro agente terapéutico como se describe anteriormente, por ejemplo cada uno en una dosis terapéutica efectiva, como se reporta en la técnica. Los componentes de combinación (1) y (2) se pueden administrar juntos, uno después del otro, o por separado en una forma de dosificación unitaria combinada o en dos formas de dosificación unitaria separadas. La forma de dosificación unitaria también puede ser una combinación fija.

La estructura de los agentes activos identificados por nombres genéricos o comerciales se puede tomar de la edición actual del compendio estándar "The Merck Index", o de la Physician's Desk Reference, o de las bases de datos, por ejemplo Patents International (por ejemplo, IMS World Publications), o Current Drugs. El contenido correspondiente de los mismos se incorpora a la presente como referencia. Cualquier persona experta en la materia está absolutamente capacitada para identificar los agentes activos, y, basándose en estas referencias, de la misma manera está capacitada para fabricar y probar las indicaciones y propiedades farmacéuticas en modelos de prueba convencionales, tanto *in vitro* como *in vivo*.

En otro aspecto preferido, la invención se refiere a una composición farmacéutica (combinación fija) que comprende una cantidad terapéuticamente efectiva de un compuesto como se describe en la presente, en combinación con una cantidad terapéuticamente efectiva de cuando menos un ingrediente activo seleccionado a partir del grupo anteriormente descrito, consistente en a) a m), o en cada caso, una sal

farmacéuticamente aceptable de los mismos;

La invención también se refiere a composiciones farmacéuticas o a combinaciones farmacéuticas como se describen en lo anterior, para la fabricación de un medicamento para el tratamiento de dislipidemia, hiperlipidemia, hipercolesteremia, ateroesclerosis, hipertrigliceridemia, insuficiencia cardíaca, infarto de miocardio, enfermedades vasculares, enfermedades cardiovasculares, hipertensión, obesidad, inflamación, artritis, cáncer, enfermedad de Alzheimer, trastornos de la piel, enfermedades respiratorias, trastornos oftálmicos, enfermedades inflamatorias de intestino, IBDs (enfermedad de intestino irritable), colitis ulcerativa, enfermedad de Crohn, condiciones en las que estén implicadas la intolerancia a la glucosa, hiperglicemia, y resistencia a la insulina, tales como diabetes tipo 1 y tipo 2, Metabolismo Deteriorado de Glucosa (IGM), Intolerancia a la Glucosa (IGT), Glucosa Deteriorada en Ayunas (IFG), y Síndrome X.

Tales agentes terapéuticos incluyen estrógeno, testosterona, un modulador del receptor de estrógeno selectivo, un modulador de receptor de andrógeno selectivo; insulina, derivados de insulina y miméticos; secretagogos de insulina tales como las sulfonil-ureas, por ejemplo Glipizida, y Amarilo; ligandos de receptores de sulfonilurea insulinotrópica tales como meglitinidas, por ejemplo nateglinida y repaglinida; sensibilizantes a insulina, tales como inhibidores de fosfatasa de proteína tirosina-1B (PTP-1B), inhibidores de GSK3 (quinasa de sintasa de glicógeno-3), o ligandos RXR, biguanidas, tales como metformina; inhibidores de alfa-glucosidasa, tales como acarbosa; GLP-1 (péptido tipo

glucagon-1), análogos de GLP-1 tales como Exendin-4 y miméticos de GLP-1; inhibidores de DPPIV (dipeptidil-peptidasa IV) tales como isoleucina-tiazolidina; DPPT728, LAF237, agentes hipolipidémicos, tales como inhibidores de reductasa de 3-hidroxi-3-metil-glutaril-coenzima A (HMG-CoA), por ejemplo lovastatina, pitavastatina, simvastatina, pravastatina, cerivastatina, mevastatina, velostatina, fluvastatina, dalvastatina, atorvastatina, rosuvastatina, y rivastatina; inhibidores de sintasa de escualeno; ligandos FXR (receptor de hígado X) y LXR(receptor farnesoide X); colestiramina; fibratos; ácido nicotínico y aspirina. Un compuesto de la presente invención puede administrarse simultáneamente, antes o después del otro ingrediente activo, por separado por la misma o diferente ruta de administración o junto en la misma formulación farmacéutica.

La invención también proporciona combinaciones farmacéuticas, por ejemplo un kit, que comprenda: a) un primer agente que sea un compuesto de la invención como se da a conocer en la presente, el forma libre o en forma de sal farmacéuticamente aceptable, y b) cuando menos un co-agente. El kit puede comprender instrucciones para su administración.

Los términos "co-administración" o "administración combinada" o similares, como se utilizan en la presente, abarcan la administración de los agentes terapéuticos seleccionados a un solo paciente, y pretenden incluir regímenes de tratamiento en donde los agentes no necesariamente sean administrados por la misma vía de administración o al mismo tiempo.

El término "combinación farmacéutica", como se utiliza en la presente, significa un producto que resulta de la mezcla o combinación de

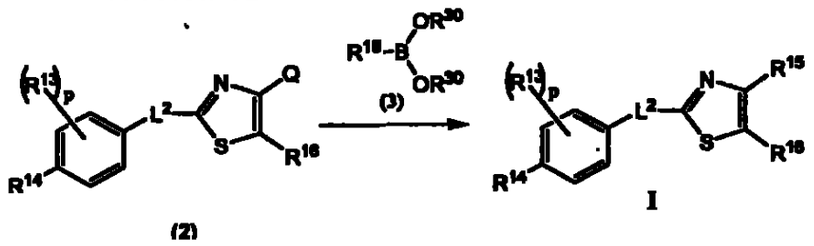
más de un ingrediente activo, e incluye tanto las combinaciones fijas como no fijas de los ingredientes activos. El término "combinación fija" significa que los ingredientes activos, por ejemplo un compuesto de la Fórmula I y un co-agente, se administran ambos a un paciente de una manera simultánea en la forma de una sola entidad o dosificación. El término "combinación no fija" significa que los ingredientes activos, por ejemplo un compuesto de la Fórmula I y un co-agente, se administra ambos a un paciente como entidades separadas, ya sea de una manera simultánea, concurrente, o en secuencia, sin límites de tiempo específicos, en donde esta administración proporciona niveles terapéuticamente efectivos de los dos compuestos en el cuerpo del paciente. Esto último también se aplica a la terapia de cóctel, por ejemplo la administración de tres o más ingredientes activos.

Proceso para Hacer los Compuestos de la Invención

La presente invención también incluye procesos para la preparación de los compuestos de la invención. En las reacciones descritas, puede ser necesario proteger los grupos funcionales reactivos, por ejemplo los grupos hidroxilo, amino, imino, tio, o carboxilo, en donde se deseen éstos en el producto final, para evitar su participación indeseada en las reacciones. Se pueden utilizar grupos protectores convencionales de acuerdo con la práctica convencional, por ejemplo, ver T.W. Green y P.G.M. Wuts en "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991.

Los compuestos de la Fórmula I, en donde R^{15} es cíclico (por ejemplo, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo), se pueden preparar procediendo como en el esquema de reacción 1a:

Esquema de Reacción 1a

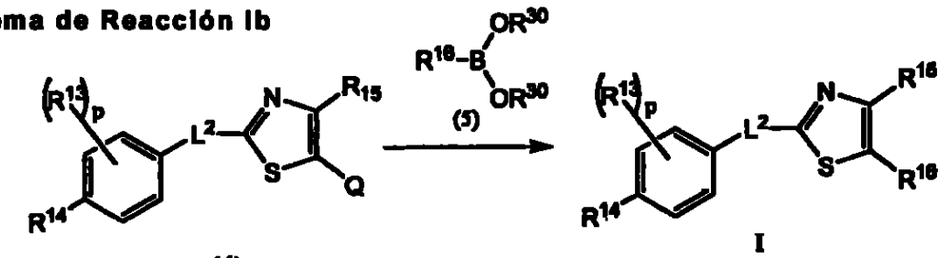


(2) I

en donde p, R^{13}, R^{14}, R^{16}, y L^2 son como se definen para la Fórmula I en el Compendio de la Invención. Q es un halógeno, de preferencia Cl ó Br; y R^{30} se selecciona independientemente a partir de hidrógeno, alquilo de 1 a 6 átomos de carbono, o los radicales R^{30} se pueden ciclar. Los compuestos de la Fórmula I se preparan mediante la reacción de un compuesto de la Fórmula 2 con un compuesto de la Fórmula 3 en la presencia de un catalizador adecuado (por ejemplo, $Pd(Ph_3)_4$, o similar), una base adecuada (por ejemplo, Na_2CO_3,, o similar), y un solvente adecuado (por ejemplo, agua, etanol, DME, o similares). La reacción se lleva a cabo en el intervalo de temperatura de aproximadamente 120°C a aproximadamente 200°C (microondas), y se lleva aproximadamente 20 minutos para terminarse.

Los compuestos de la Fórmula I, en donde R^{16} es cíclico (por ejemplo, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo), se pueden preparar procediendo como en el esquema de reacción 1b:

Esquema de Reacción Ib

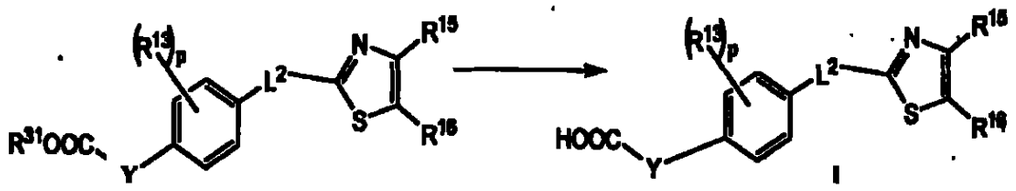


(4) I

en donde p, R^{13}, R^{14}, R^{15}, y L^2 son como se definen para la Fórmula I en el Compendio de la Invención. Q es un halógeno, de preferencia Cl ó Br; y R^{30} se selecciona independientemente a partir de hidrógeno, alquilo de 1 a 6 átomos de carbono, o los radicales R^{30} se pueden ciclar. Los compuestos de la Fórmula I se preparan mediante la reacción de un compuesto de la Fórmula 4 con un compuesto de la Fórmula 5 en la presencia de un catalizador adecuado (por ejemplo, $Pd(Ph_3)_4$, o similar), una base adecuada (por ejemplo, Na_2CO_3,, o similar), y un solvente adecuado (por ejemplo, agua, etanol, DME, o similares). La reacción se lleva a cabo en el intervalo de temperatura de aproximadamente 120°C a aproximadamente 200°C (microondas), y se lleva aproximadamente 20 minutos para terminarse.

Los compuestos de la Fórmula I, en donde R^{14} es definido por -Y-$COOR^{31}$, se pueden preparar procediendo como en el esquema de reacción 2:

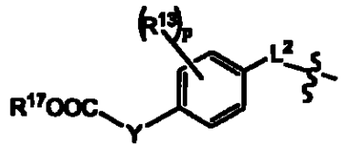
Esquema de Reacción 2



en donde p, R^{13}, R^{15}, R^{16}, y L^2 son como se definen para la Fórmula I en el Compendio de la Invención; Y es -XOX- ó -X- (en donde X se selecciona independientemente a partir de un enlace o alquileno de 1 a 4 átomos de carbono como se define en el Compendio de la Invención), y R^{31} es un grupo alquilo, por ejemplo metilo. Los compuestos de la Fórmula I se preparan mediante la reacción de un compuesto de la Fórmula 4 en la

presencia de una base adecuada (por ejemplo, hidróxido de litio o similar), y un solvente adecuado (por ejemplo, tetrahidrofurano, agua, o similares). La reacción se lleva a cabo en el intervalo de temperatura de aproximadamente 0°C a aproximadamente 50°C, y se lleva aproximadamente 30 horas para terminarse.

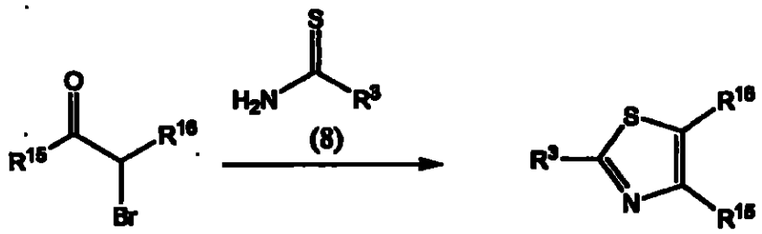
Los compuestos de la Fórmula 9, en donde R^3 es $-CH_3$, -SH, $-C(O)OC_2H_5$, $-CH_2OC(O)C(CH_3)_3$ o un grupo definido por:



(R^3)

(en donde Y es -XOX- ó -X-; y p, R^{13}, L^2, X, y R^{17} son como se definen en el Compendio de la Invención), se pueden preparar procediendo como en el Esquema de Reacción 3:

Esquema de Reacción 3



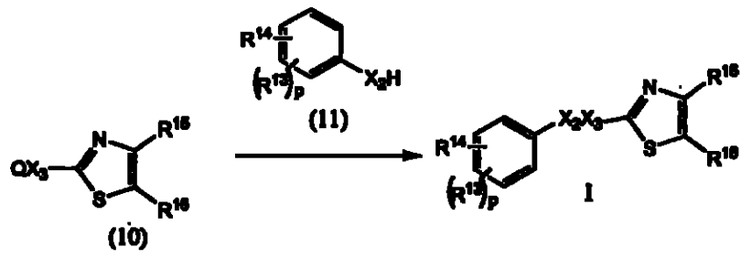
(7) (9)

en donde p, R^{13}, R^{17}, y L^2 son como se definen para la Fórmula I en el Compendio de la Invención; R^{15} y R^{16} se seleccionan independientemente a partir de hidrógeno, alquilo, o cualquier radical cíclico (cicloalquilo, heterocicloalquilo, arilo y heteroarilo como se definen en el Compendio de la Invención). Los compuestos de la Fórmula 9 se

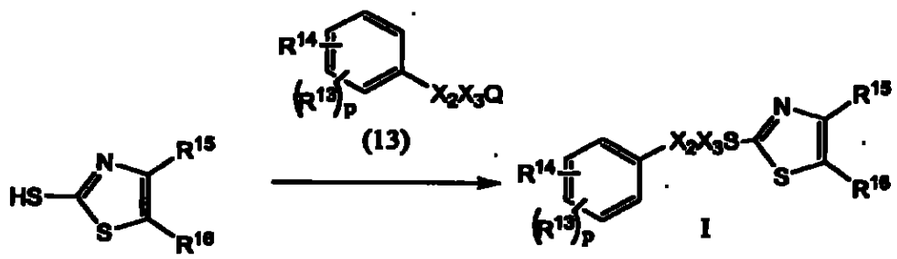
preparan mediante la reacción de un compuesto de la Fórmula 7 con un compuesto de la Fórmula 8, opcionalmente en la presencia de un solvente (por ejemplo, etanol, o similar). La reacción se lleva a cabo en el intervalo de temperatura de aproximadamente 10°C a aproximadamente 200°C, y se lleva aproximadamente 30 horas para terminarse.

Los compuestos de la Fórmula I se pueden preparar procediendo como en los esquemas de reacción 4a y 4b:

Esquema de Reacción 4a



Esquema de Reacción 4b

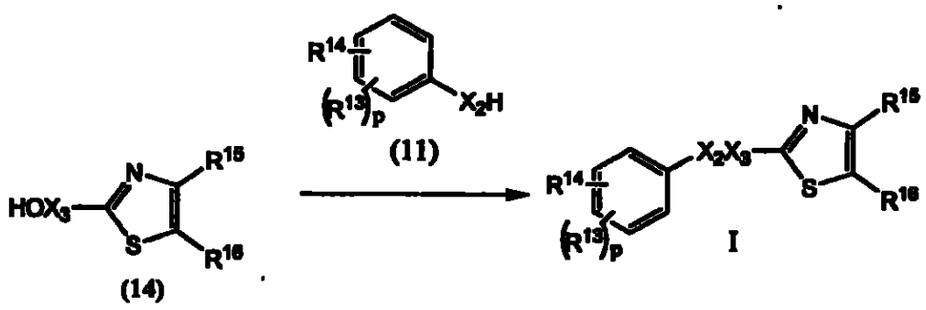


en donde p, R^{13}, R^{14}, R^{15}, y R^{16} son como se definen para la Fórmula I en el Compendio de la Invención; X_2 es S u O; X_3 es un enlace o alquileno de 1 a 4 átomos de carbono; y Q es un grupo halógeno, de preferencia Br ó Cl. Los compuestos de la Fórmula I se preparan mediante la reacción de un compuesto de la Fórmula 10 con un compuesto de la

Fórmula 11 ó un compuesto de la Fórmula 12 con un compuesto de la Fórmula 13 en la presencia de un solvente adecuado (por ejemplo cianometilo, etanol, o similar). La reacción se lleva a cabo en el intervalo de temperatura de aproximadamente 10°C a aproximadamente 80°C, y se lleva hasta aproximadamente 24 horas para terminarse.

Los compuestos de la Fórmula I se pueden preparar procediendo como en el esquema de reacción 5:

Esquema de Reacción 5



en donde p, R^{13}, R^{14}, R^{15}, y R^{16} son como se definen para la Fórmula I en el Compendio de la Invención; X_2 es S u O; y X_3 es un enlace o alquileno de 1 a 4 átomos de carbono. Los compuestos de la Fórmula I se preparan mediante la reacción de un compuesto de la Fórmula 14 con un compuesto de la Fórmula 11 en la presencia de un solvente adecuado (por ejemplo, DCM, tetrahidrofurano, o similares) y un reactivo activador adecuado (por ejemplo, trifenil-fosfina, azo-dicarboxilato de dietilo, o similares). La reacción se lleva a cabo en el intervalo de temperatura de aproximadamente 0°C a aproximadamente 50°C, y se lleva hasta aproximadamente 24 horas para terminarse.

Las condiciones de reacción detalladas se describen en los

ejemplos, más adelante.

Procesos Adicionales para Hacer los Compuestos de la Invención

Un compuesto de la invención se puede preparar como una sal de adición de ácido farmacéuticamente aceptable, mediante la reacción de la forma de base libre del compuesto con un ácido inorgánico u orgánico farmacéuticamente aceptable. De una manera alternativa, una sal de adición de base farmacéuticamente aceptable de un compuesto de la invención, se puede preparar mediante la reacción de la forma de ácido libre del compuesto con una base inorgánica u orgánica farmacéuticamente aceptable. De una manera alternativa, las formas de sal de los compuestos de la invención se pueden preparar utilizando las sales de los materiales de partida o de los intermediarios.

Las formas de ácido libre o de base libre de los compuestos de la invención se pueden preparar a partir de la sal de adición de base o de la sal de adición de ácido correspondiente, respectivamente. Por ejemplo, un compuesto de la invención en una forma de sal de adición de ácido, se puede convertir a la base libre correspondiente mediante su tratamiento con una base adecuada (por ejemplo, una solución de hidróxido de amonio, hidróxido de sodio, y similares). Un compuesto de la invención en una forma de sal de adición de base se puede convertir al ácido libre correspondiente mediante su tratamiento con un ácido adecuado (por ejemplo, ácido clorhídrico, etcétera).

Los compuestos de la invención, en una forma no oxidada, se pueden preparar a partir de N-óxidos de los compuestos de la invención, mediante su tratamiento con un agente reductor (por ejemplo, azufre,

dióxido de azufre, trifenil-fosfina, borohidruro de litio, borohidruro de sodio, tricloruro de fósforo, tribromuro, o similares) en un solvente orgánico inerte adecuado (por ejemplo, acetonitrilo, etanol, dioxano acuoso, o similares) de 0°C a 80°C.

Los derivados de profármaco de los compuestos de la invención se pueden preparar mediante métodos conocidos por los expertos ordinarios en la técnica (por ejemplo, para mayores detalles, ver Saulnier y colaboradores, (1994), Bioorganic and Medicinal Chemistry Letters, Volumen 4, página 1985). Por ejemplo, los profármacos apropiados se pueden preparar mediante la reacción de un compuesto no derivado de la invención con un agente carbamilante adecuado (por ejemplo, 1,1-aciloxialquilcarbanoclorhidato, carbonato de para-nitrofenilo, o similares).

Los derivados protegidos de los compuestos de la invención se pueden hacer por medios conocidos por los expertos ordinarios en la materia. Una descripción detallada de las técnicas aplicables a la creación de grupos protectores y su remoción, se puede encontrar en T.W. Greene, "Protecting Groups in Organic Chemistry", 3ª Edición, John Wiley and Sons, Inc., 1999.

Los compuestos de la presente invención se pueden preparar convenientemente, o se pueden formar, durante el proceso de la invención, como solvatos (por ejemplo, hidratos). Los hidratos de los compuestos de la presente invención se pueden preparar de una manera conveniente mediante recristalización a partir de una mezcla de solventes acuosa/orgánica, utilizando solventes orgánicos tales como dioxina, tetrahidrofurano, o metanol.

Los compuestos de la invención se pueden preparar como sus estereoisómeros individuales, mediante la reacción de una mezcla racémica del compuesto con un agente de resolución ópticamente activo, para formar un par de compuestos diaestereoisoméricos, la separación de los diaestereómeros, y la recuperación de los enantiómeros ópticamente puros. Aunque la resolución de los enantiómeros se puede llevar a cabo utilizando derivados diaestereoméricos covalentes de los compuestos de la invención, se prefieren los complejos disociables (por ejemplo, las sales diaestereoméricas cristalinas). Los diaestereómeros tienen propiedades físicas distintas (por ejemplo, puntos de fusión, puntos de ebullición, solubilidades, reactividad, etcétera), y se pueden separar fácilmente aprovechando estas diferencias. Los diaestereómeros se pueden separar mediante cromatografía, o de preferencia mediante técnicas de separación/resolución, basándose en las diferencias en su solubilidad. Entonces se recupera el enantiómero ópticamente puro, junto con el agente de resolución, por cualquier medio práctico que no dé como resultado la racemización. Una descripción más detallada de las técnicas aplicables a la resolución de los estereoisómeros de los compuestos a partir de su mezcla racémica se puede encontrar en Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley and Sons, Inc., 1981.

En resumen, los compuestos de la Fórmula I se pueden hacer mediante un proceso que involucra:

(a) aquél del esquema de reacción 1, 1b, 2, 3, 4a, 4b, ó 5; y

(b) opcionalmente convertir un compuesto de la invención en una

sal farmacéuticamente aceptable;

(c) opcionalmente convertir una forma de sal de un compuesto de la invención a una forma que no sea de sal;

(d) opcionalmente convertir una forma no oxidada de un compuesto de la invención en un N-óxido farmacéuticamente aceptable;

(e) opcionalmente convertir una forma de N-óxido de un compuesto de la invención a su forma no oxidada;

(f) opcionalmente resolver un isómero individual de un compuesto de la invención a partir de una mezcla de isómeros;

(g) opcionalmente convertir un compuesto no derivado de la invención en un derivado de profármaco farmacéuticamente aceptable; y

(h) opcionalmente convertir un derivado de profármaco de un compuesto de la invención hasta su forma no derivada.

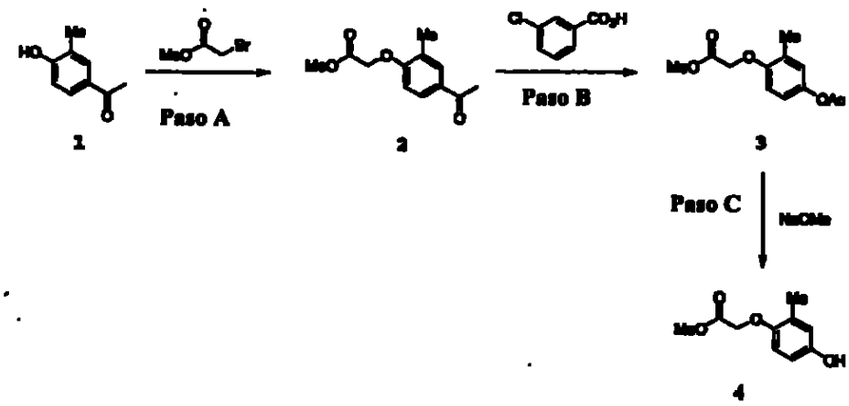
Hasta no se describa particularmente la producción de los materiales de partida, los compuestos son conocidos o se pueden preparar de una manera análoga a los métodos conocidos en la técnica, o como se da a conocer en los Ejemplos posteriormente en la presente.

Un experto en la técnica apreciará que las transformaciones anteriores solamente son representativas de los métodos para la preparación de los compuestos de la presente invención, y que de manera similar se pueden emplear otros métodos bien conocidos.

Ejemplos

La presente invención se ejemplifica adicionalmente, pero no se limita, mediante los siguientes intermediarios y ejemplos que ilustran la preparación de los compuestos de la Fórmula I de acuerdo con la

Invención.



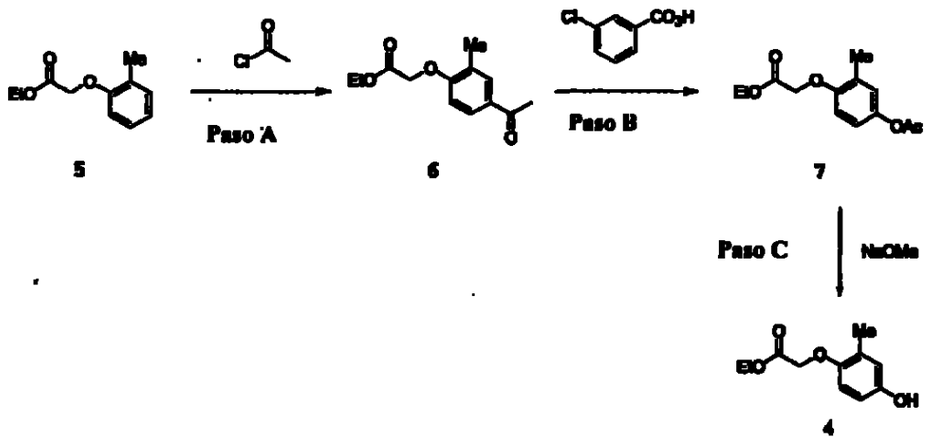
Intermediario 4. Metil-éster del ácido (4-hidroxi-2-metil-fenoxi)-acético.

Paso A: La 4'-hidroxi-3'-metil-acetofenona 1 (25 gramos, 166.4 milimoles) y bromoacetato de metilo (25.5 gramos, 166.4 milimoles) se disuelven en MeCN (600 mililitros). Se agrega Cs_2CO_3 (117.8 gramos, 332.9 milimoles), y la mezcla se agita durante la noche a temperatura ambiente. Después las sales insolubles se filtran y se lavan con MeCN, el solvente se remueve, y el resto se recupera en EtOAc, y se lava subsecuentemente con HCl 1M (500 mililitros, 3 veces) y H_2O (550 mililitros, 2 veces). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra para proporcionar el 2 como un sólido blanco.

Paso B: El metil-éster del ácido (4-acetil-2-metil-fenoxi)-acético 2 (33 gramos, 151.3 milimoles), mCPBA al 77 por ciento (54.9 gramos, 264.8 milimoles), y TsOH (2.9 gramos, 15.1 milimoles) en DCM (650 mililitros), se calientan bajo reflujo durante 48 horas. Luego la mezcla de reacción se lava con KI 1M (500 mililitros, 2 veces) y $NaHSO_3$ (500 mililitros, 2 veces). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra para

proporcionar el 3 como un jarabe castaño.

Paso C: Una solución del metil-éster del ácido (4-acetoxi2-metil-fenoxi)-acético 3 (25 gramos, 105.0 milimoles) en MeOH seco (400 mililitros) se combina con una solución 0.5M de NaOM en MeOH (210 mililitros, 105.0 milimoles), y se agita durante 1 hora a temperatura ambiente. La solución se neutraliza con HCl 1M, y se lava con H_2O (500 mililitros, 2 veces). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para proporcionar el 4 como un sólido castaño: ^1H RMN (400 MHz, CD_3OD) δ = 6.65-6.51 (m, 3H), 4.60 (s, 2H), 3.75 (s, 3H), 2.19 (s, 3H). MS calculada para $C_{10}H_{13}O_4$ ($M+H^+$) 197.1, encontrada 197.2.



Intermediario 4 (ruta alternativa). Metil-éster del ácido (4-hidroxi-2-metil-fenoxi)-acético.

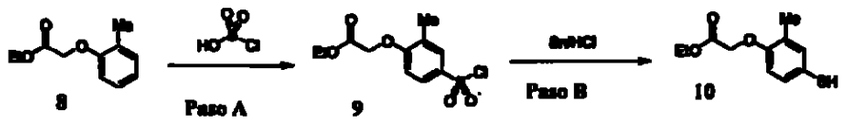
Paso A: El etil-éster del ácido (2-metil-fenoxi)acético 5 (66.03 gramos, 340 milimoles) se disuelve en dicloroetano (400 mililitros). Se agrega cloruro de aluminio (100.02 gramos, 750 milimoles), y la mezcla castaña clara se agita durante 10 minutos a temperatura ambiente hasta

quedar homogénea. Se agrega por goteo cloruro de acetilo (35 mililitros, 493 milimoles) utilizando un embudo de adición. La velocidad de adición se ajusta para mantener una emisión relativamente lenta de gas de cloruro de hidrógeno. La solución castaña oscura resultante se deja enfriar a temperatura ambiente, luego se vierte sobre 300 gramos de hielo triturado. La mezcla se diluye con diclorometano (300 mililitros), y se lava sucesivamente con agua, una solución saturada de $NaHCO_3$, agua, solución saturada de NH_4Cl, y salmuera. La capa orgánica se seca sobre Na_2SO_4, se filtra, y se concentra, para proporcionar el 6 como un aceite castaño que se solidifica como una masa cristalina. ^1H RMN (400 MHz, $CDCl_3$) δ = 7.79 (d, J = 2.0 Hz, 1H), 7.77 (dd, J = 2.0, 8.4 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 4.71 (s, 2H), 4.26 (q, J = 7.2 Hz, 2H), 2.54 (s, 3H), 2.32 (s, 2H), 1.29 (t, = 7.2 Hz, 3H).

Paso B: El etil-éster del ácido (4-acetil-2-metil-fenoxi)-acético 6 (76.54 gramos, 324 milimoles), mCPBA al 77 por ciento (100.31 gramos, 407 milimoles, 1.26 equivalentes), y p-TsOH (13 gramos, 68 milimoles, 21 por ciento molar) en dicloroetano (450 mililitros), se calientan a 50°C durante 30 horas. Luego la mezcla de reacción se lava con KI 1M (500 mililitros, 2 veces) y $NaHO_3$ (500 mililitros, 2 veces). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra para proporcionar el 7 como un jarabe castaño.

Paso C: Una solución del etil-éster del ácido (4-acetoxi-2-metil-fenoxi)-acético 7 (de paso B anterior) en MeOH seco (400 mililitros) se combina con una solución 0.5M de NaOMe en MeOH (650 mililitros, 325 milimoles), y se agita durante 2 horas a temperatura ambiente. La solución

se neutraliza con HCl 1M, y se lava con H_2O (500 mililitros, 2 veces). La capa orgánica se seca (Na_2SO_4), se filtra, y se concentra, para proporcionar el 4 (21.7 gramos, 111 milimoles, 34 por ciento, dos pasos) como un sólido castaño claro: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 6.58 (d, J = 2.8 Hz, 1H), 6.54 (d, J = 8.4 Hz), 6.50 (dd, J = 2.8, 8.4 Hz, 1H), 4.7 (br. s, 1H), 4.54 (s, 2H), 3.73 (s, 3H), 2.17 (s, 3H). MS calculada para $C_{10}H_{13}O_4$ ($M+H^+$) 197.1, encontrada 197.4.

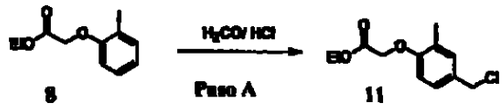


Intermediario 10. Etil-éster del ácido (4-mercapto-2-metil-fenoxi)-acético.

Paso A: Un matraz de fondo redondo de tres cuellos, de 500 mililitros, se carga con ácido clorosulfónico (25 mililitros, 373.9 milimoles), se inunda con nitrógeno, y se enfría a 0°C. Bajo nitrógeno y con agitación vigorosa, se agrega por goteo (2-metil-fenoxi)-acetato de etilo 8 (40 gramos, 206.2 milimoles). La mezcla se agita durante 90 minutos a 0°C, luego se vierte sobre hielo-agua (200 mililitros). Después, la mezcla se agita durante 45 minutos adicionales a temperatura ambiente, el precipitado blanco se filtra, se lava con agua helada, y se seca al vacío para proporcionar el 9 como un sólido blanco.

Paso B: El etil-éster del ácido (4-cloro-sulfonil-2-metil-fenoxi)-acético 9 (25 gramos, 85.4 milimoles) y estaño (50.8 ramos, 427 milimoles) se suspenden en EtOH, y se enfrían a 0°C. Después se agrega por goteo una solución de HCl 4N en dioxano (107 mililitros, 427 milimoles), y la

mezcla resultante se calienta a reflujo durante 3 horas. Luego la mezcla se concentra al vacío, el resto se recupera en cloroformo, y se filtra. El filtrado se concentra al vacío para obtener un aceite amarillo, el cual se purifica mediante cromatografía (sílice, gradiente de Hex/EtOAc) para proporcionar el 10 como un aceite incoloro: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.14 (m, 1H), 7.07-7.10 (m, 1H), 6.59 (m,1H), 4.60 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.33 (s, 1H), 2.24 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). MS calculada para $C_{11}H_{14}O_3S$ ($M+H^+$) 227.1, encontrada 227.4.

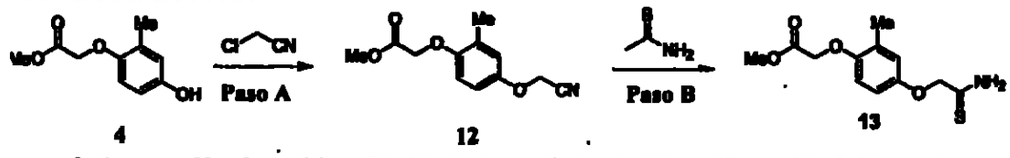


8 11

Intermediario 11. Etil-éster del ácido (4-cloro-metil-2-metil-fenoxi)-acético.

Paso A: A una solución del (2-metil-fenoxi)-acetato de etilo 8 (20.0 gramos, 103 milimoles), en éter de petróleo (50 mililitros, punto de ebullición de 40°C a 55°C), se le agregan HCl (120 mililitros, 12M) y formaldehído (8.4 mililitros, 37 por ciento), y luego la mezcla se agita durante 25 horas a temperatura ambiente. La mezcla se diluye con EtOAc, y la capa orgánica se lava con agua tres veces, se seca ($MgSO_4$), se filtra, y se concentra, para proporcionar el producto crudo, el cual se purifica mediante cromatografía por evaporación con EtOAc al 20 por ciento/hexano, para dar el etil-éster del ácido (4-cloro-metil-2-metil-fenoxi)-acético 11 como un líquido: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.19 (d, J = 2.0 Hz, 1H), 7.14 (dd, J = 2.0 Hz, J = 8.0 Hz, 1H), 6.55 (d, J = 8.0 Hz, 1H), 4.64 (s, 2H), 4.53 (s, 2H), 4.26 (q, J = 7.2 Hz, 2H), 2.29 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H). MS calculada para $C_{12}H_{15}ClO_3$ ($M-Cl^+$) 207.2,

encontrada 207.10.



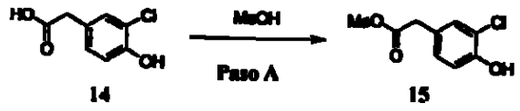
4 12 13

Intermediario 13. Metil-éster del ácido (2-metil-4-tiocarbamoil-metoxi-fenoxi)-acético.

Paso A: El metil-éster del ácido (4-hidroxi-2-metil-fenoxi)-acético 4 (1.64 gramos, 8.3 milimoles) y cloroacetonitrilo (0.553 mililitros, 8.7 milimoles) se disuelven en acetonitrilo (30 mililitros). Se agrega Cs_2CO_3 (5.4 gramos, 16.7 milimoles), y la mezcla se agita durante 2 horas a temperatura ambiente. Las sales insolubles se filtran y se lavan con EtOAc, el solvente se remueve para dar un aceite, el cual se cristaliza al vacío para dar el 12 (1.84 gramos, 7.83 milimoles, 94 por ciento) como un sólido amarillo pálido. ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 6.76 (s, 1H), 6.67 (s, 1H), 6.60 (d, J = 8.5 Hz, 1H), 4.62 (s, 2H), 4.54 (s, 2H), 3.73 (s, 3H), 2.21 (s, 3H). MS calculada para $C_{12}H_{14}NO_4$ ($M+H^+$) 236.1, encontrada 236.3.

Paso B: El metil-éster del ácido (4-ciano-metoxi-2-metil-fenoxi)-acético 12 (1.75 gramos, 7.45 milimoles) y tioacetamida (1.12 gramos, 14.9 milimoles) se disuelven en dimetilformamida (120 mililitros). Se agrega HCl (4.0 N en 1,4-dioxano, 20 mililitros), y la mezcla se agita a 100°C durante la noche. La mezcla se diluye con $NaHCO_3$ saturado, se extrae con EtOAc, y se lava subsecuentemente con H_2O (100 mililitros, 4 veces) y salmuera (100 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra. El residuo se tritura con DCM (5 mililitros) y hexanos (5 mililitros), y se recolecta mediante filtración, para proporcionar el 13 como un sólido beige: ^{1}H-RMN (400 MHz, DMSO-d_6) δ = 6.84 (d, J = 2.9 Hz, 1H),

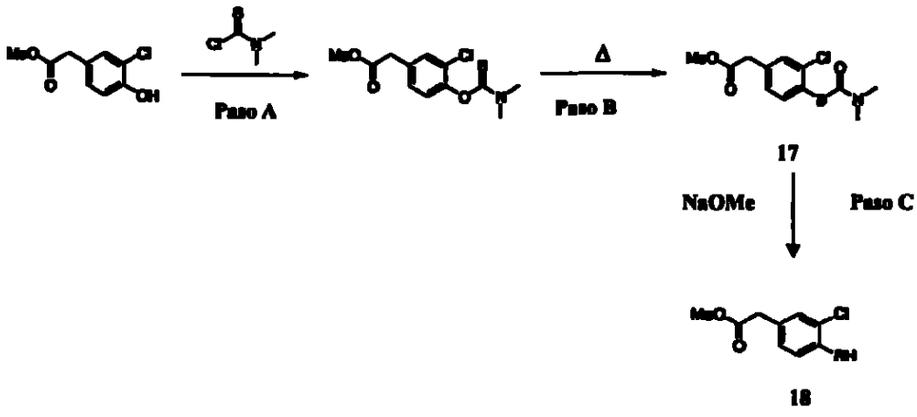
6.78 (d, J = 8.9 Hz, 1H), 6.71 (dd, J = 3.0, 8.9 Hz, 1H), 4.75 (s, 2H), 4.67 (s, 2H), 4.04 (s, 1H), 3.69 (s, 3H), 2.18 (s, 3H). MS calculada para $C_{12}H_{16}NO_4S$ ($M+H^+$) 270.1, encontrada 270.3.



14 15

Intermediario 15. Metil-éster del ácido (3-cloro-4-hidroxi-fenil)-acético.

Paso A: El ácido (3-cloro-4-hidroxi-fenil)-acético 14 (20 gramos, 107 milimoles) se disuelve en MeOH (250 mililitros) conteniendo cantidades catalíticas de H_2SO_4 concentrado (2.5 mililitros). La solución se calienta a reflujo durante la noche. El solvente se evapora, el resto se disuelve en DCM, y se lava con H_2O (200 mililitros, 3 veces). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para proporcionar el 15 como un sólido amarillo claro: ^1H RMN (400 MHz, CD_3OD) δ = 7.21 (d, J = 2.1 Hz, 1H), 7.01 (dd, J = 2.1 Hz, J = 8.3, 1H), 6.84 (d, = 8.3 Hz, 1H), 3.67 (s, 3H), 3.54 (s, 2H). MS calculada para $C_9H_{10}ClO_3$ ($M+H^+$) 201.0, encontrada 201.2.



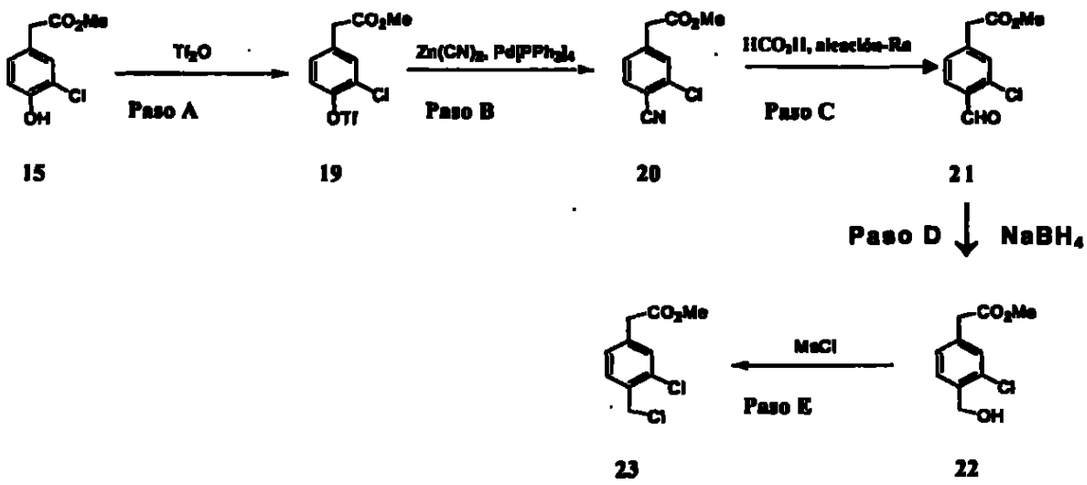
Intermediario 18. Metil-éster del ácido (3-cloro-4-mercapto-fenil)-acético.

Paso A: El metil-éster del ácido (3-cloro-4-hidroxi-fenil)-acético 15 (4.1 gramos, 21.4 milimoles), tiocarbamoil-cloruro de dimetilo (3.2 gramos, 25.6 milimoles), Et_3N (5.9 mililitros, 42.8 milimoles), y DAMP (261 miligramos, 2.14 milimoles), se disuelven en dioxano seco (30 mililitros), y se calientan a reflujo durante 16 horas bajo nitrógeno. La mezcla de reacción se enfría a temperatura ambiente, se diluye con EtOAc, y se lava con H_2O (50 mililitros, 3 veces). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para proporcionar el 16 como un aceite incoloro.

Paso B: El metil-éster del ácido (3-cloro-4-dimetiltio-carbamoil-oxi-fenil)-acético 16 (5.2 gramos, 18.1 milimoles) se transfiere a un matraz de fondo redondo de tres cuellos, de 250 mililitros, equipado con un termómetro. Se agrega tetradecano (45 mililitros), y la mezcla se calienta a reflujo (250°C) durante la noche. Después de enfriar a temperatura ambiente, el solvente se decanta, el aceite restante se lava varias veces con hexanos, y se purifica mediante cromatografía (sílice, gradiente de Hex/EtOAc), para proporcionar el 17 como un aceite castaño.

Paso C: El metil-éster del ácido (3-cloro-4-dimetil-carbamoil-sulfanil-fenil)-acético 17 (3.1 gramos, 10.8 milimoles) se disuelve en NaOMe 0.5 M en MeOH. La mezcla se calienta a reflujo durante 4 horas, luego se acidifica con HCl 1M. El solvente orgánico se evapora, el resto se extrae en EtOAc (50 mililitros), y se lava con H_2O (50 mililitros, 2 veces). La capa orgánica se seca ($MgSO_4$), se filtra, se concentra, y se purifica (sílice, gradiente de hexanos/EtOAc), para proporcionar el 18 como un

aceite amarillo pálido: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.30-7.26 (m, 2H), 7.06-7.03 (m, 1H), 3.87 (s, 1H), 3.69 (s, 3H), 3.55 (s, 2H). MS calculada para $C_9H_{10}ClO_2S$ ($M+H^+$) 217.0, encontrada 217.3.



Intermediario 23. Metil-éster del ácido (3-cloro-4-cloro-metil-fenil)-acético.

Paso A: A una solución del metil-éster del ácido (3-cloro-4-hidroxi-fenil)-acético 15 (15.9 gramos, 79.25 milimoles) en CH_2Cl_2 (160 mililitros), se le agregan trietil-amina (11.04 mililitros, 79.25 milimoles) y anhídrido trifílico (13.33 mililitros, 79.25 milimoles), a 0°C, y se agitan durante 1 hora. Luego la mezcla de reacción se diluye con EtOAc (300 mililitros), y se lava con $NaHCO_3$, salmuera, y agua. La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para proporcionar el metil-éster del ácido (3-cloro-4-trifluoro-metan-sulfoniloxi-fenil)-acético 19 como un aceite. MS calculada para $C_{10}H_8ClF_3O_5S$ ($M+H^+$) 333, encontrada 333.95.

Paso B: A una solución de metil-éster del ácido (3-cloro-4-trifluoro-metan-sulfoniloxi-fenil)-acético 19 (24.5 gramos, 73.64 milimoles) en

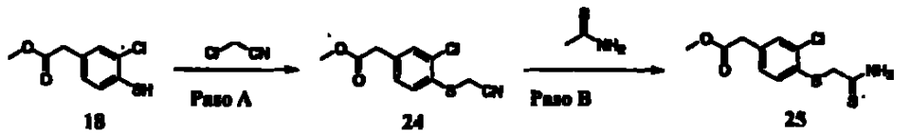
dimetilformamida seca (45 mililitros), se le agregan cianuro de zinc (8.91 gramos, 75.9 milimoles), y tetraquis-trifenil-fosfina)-paladio (8.50 gramos, 7.36 milimoles). La mezcla se agita durante 34 horas a 80°C, y luego se enfría a temperatura ambiente, se diluye con EtOAc (150 mililitros), y se vierte en una solución saturada de $NaHCO_3$ (150 mililitros). Se remueve un precipitado blanco mediante filtración al vacío. El filtrado se lava con H_2O, se seca ($MgSO_4$), se filtra, y se concentra para proporcionar el producto crudo, el cual se purifica mediante cromatografía en gel de sílice con EtOAc al 20 por ciento/hexano, para dar el metil-éster del ácido (3-cloro-4-ciano-fenil)-acético 20 (11.6 gramos, 75.13 milimoles) como un sólido tipo cera: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.63 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 1.2 Hz, 1H), 7.30 (dd, J = 1.2 Hz, J = 8.0 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 2H). MS calculada para $C_{10}H_8O_2ClN$ ($M+H^+$) 210.0, encontrada 210.0.

Paso C: Una solución del metil-éster del ácido (3-cloro-4-ciano-fenil)-acético 20 (7.4 gramos, 35.3 milimoles) en ácido fórmico (100 mililitros, 88 por ciento), se combina con una aleación de Raney (9.0 gramos), y se calienta a reflujo (110°C) durante la noche. Entonces la mezcla se enfría a temperatura ambiente. La aleación se filtra mediante un cojín de Celite, se lava con EtOAc, y el filtrado se concentra al vacío. El resto se diluye con EtOAc (250 mililitros), y se lava con H_2O (dos veces) y $NaHCO_3$ (dos veces). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra para proporcionar el producto crudo, el cual se purifica mediante cromatografía en gel de sílice con EtOAc/hexano, para dar el metiléster del ácido (3-cloro-4-formil-fenil)-acético 21 como un sólido tipo cera: ^{1}H-RMN

(400 MHz, $CDCl_3$) δ = 10.31 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.58 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 3.86 (s, 2H), 3.64 (s, 3H).

Paso D: Una solución del metil-éster del ácido (3-cloro-4-formil-fenil)-acético 21 (0.6 gramos, 2.82 milimoles) en MeOH (4.0 mililitros), se agrega por goteo a una solución de $NaBH_4$ en agua (4.0 mililitros), y se agita durante 10 minutos de 20°C a 22°C. Entonces se agrega HCl (1N, 15 mililitros), y la mezcla se agita durante 5 minutos. La solución se diluye con EtOAc (80 mililitros), y la capa orgánica se seca ($MgSO_4$), se filtra, y se concentra para proporcionar el producto crudo, el cual se purifica mediante cromatografía en gel de sílice con EtOAc al 50 por ciento/hexano, para dar el metil-éster del ácido (3-cloro-4-hidroximetil-fenil)-acético 22 como un sólido tipo cera: ^1H RMN (400 MHz, $CDCl_3$) δ = 7.44 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 1.2 Hz, 1H), 7.20 (dd, J = 1.2 Hz, J = 8.0 Hz, 1H), 4.76 (s, 2H), 3.70 (s, 3H), 3.61 (s, 2H).

Paso E: A una solución del metil-éster del ácido (3-cloro-4-hidroximetil-fenil)-acético 22 (0.5 gramos, 2.33 milimoles) en dimetilformamida seca (5 mililitros), se le agrega cloruro de litio (108.6 miligramos, 2.56 milimoles) y s-colidina (310.2 miligramos, 2.56 milimoles). La mezcla se enfría a 0°C, y se agrega lentamente $MeSO_2Cl$ (2.56 milimoles). La mezcla se agita durante 2 horas a 0°C, luego se vierte sobre agua helada, y se extrae con EtOAc. La capa orgánica se lava con agua, se seca ($MgSO_4$), se filtra, y se concentra, para proporcionar el metil-éster del ácido (3-cloro-4-clorometil-fenil)-acético 23: ^1H-RMN (400 MHz, $CDCl_3$) δ = 7.42 (m, 1H), 7.34 (m, 1H), 7.19 (m, 1H), 4.68 (s, 2H), 3.71 (s, 3H), 3.61 (s, 2H). MS calculada para $C_{10}H_{11}Cl_2O_2$ $(M+1)^+$ 233.0, encontrada 233.00.



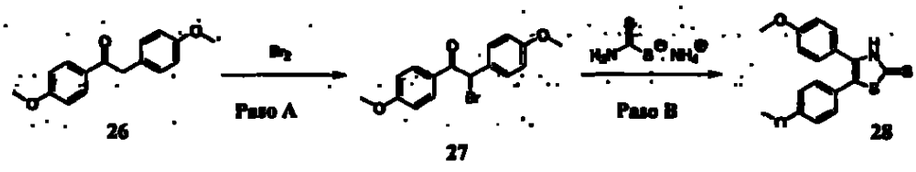
18 24 25

Intermediario 25. Metil-éster del ácido (3-cloro-4-tiocarbamoil-metilsulfanil-fenil)-acético.

Paso A: El metil-éster del ácido (3-cloro-4-mercapto-fenil)-acético 18 (1.04 gramos, 4.8 milimoles) se disuelve en acetonitrilo seco. Se agrega carbonato de cesio (3.16 gramos, 9.7 milimoles, 2 equivalentes), seguido por cloroacetonitrilo (0.45 mililitros, 7.13 milimoles, 1.5 equivalentes). La mezcla se agita bajo nitrógeno durante 18 horas. La suspensión roja resultante se filtra, los sólidos se lavan con más acetonitrilo, y la solución roja transparente resultante se concentra para dar el 24 como un aceite naranja (1.26 gramos, cuantitativo). ^{1}H-RMN (400 MHz, DMSO-d_6) δ = 7.50 (d, J = 8.0 Hz, 1H), 7.49 (s, 1H), 7.35 (dd, J = 1.6, 8.0 Hz, 1H), 4.35 (s, 2H), 3.75 (s, 2H), 3.63 (s, 3H). MS calculada para $C_{11}H_{11}ClNO_2S$ ($M+H^+$) 256.0, encontrada 256.3.

Paso B: El metil-éster del ácido (3-cloro-4-cianometilsulfanil-fenil)-acético 24 (1.12 gramos, 4.38 milimoles), tioacetamida (1.52 gramos, 20.2 milimoles, 4.6 equivalentes), y una solución de cloruro de hidrógeno en dioxano (4.0 M, 5 mililitros, 20 milimoles, 4.6 equivalentes), se disuelven en 2 mililitros de dimetil-acetamida y 3 mililitros de dioxano. La mezcla se calienta a 95°C durante 48 horas. La mezcla de reacción se enfría entonces a temperatura ambiente, se diluye con acetato de etilo, y se lava con agua, $NaHCO_3$ saturado, NH_4Cl saturado, y salmuera. La capa orgánica se seca (Na_2SO_4), se filtra, y se concentra para proporcionar un

aceite rojo. La cromatografía en gel de sílice (del 20 por ciento al 60 por ciento de acetato de etilo en hexanos) produjo el metil-éster del ácido (3-cloro-4-tiocarbamoil-metil-sulfanil-fenil)-acético 25 como un jarabe castaño. ^{1}H-RMN (400 MHz, DMSO-d_6) δ = 9.80 (s, 1H), 9.39 (s, 1H), 7.32 (d, J = 1.6 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.20 (dd, J = 1.6, 8.4 Hz, 1H), 4.10 (s, 2H), 3.67 (s, 3H), 3.59 (s, 3H). MS calculada para $C_{11}H_{13}ClNO_2S_2$ ($M+H^+$) 290.0, encontrada 290.2.

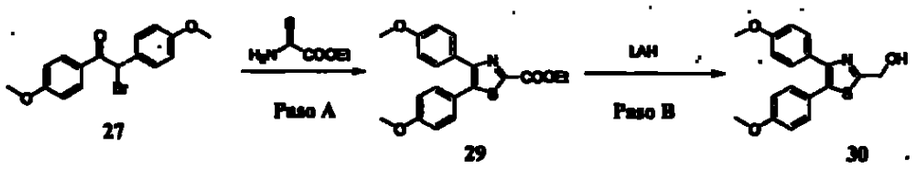


Intermediario 28. 4,5-bis-(4-metoxi-fenil)-3H-tiazol-2-tiona.

Paso A: A una solución de la desoxianisoina 26 (10 gramos, 39.0 milimoles) en $CHCl_3$ anhidro (200 mililitros), se le agrega por goteo bromo (2.4 mililitros, 46.8 milimoles). Después de que se termina la adición (indicado por un cambio de color hasta rojo), el solvente se evapora, el resto se tritura con éter, y el producto precipitado se filtra para dar el 27 como un sólido blanco: ^{1}H-RMN (400 MHz, CD_3OD) δ = 7.98 (d, J = 9.0 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.72 (s, 1H), 3.83 (s, 3H), 3.75 (s, 3H). MS calculada para $C_{16}H_{15}O_3$ ($M-Br^+$) 255.1, encontrada 255.4.

Paso B: La 2-bromo-1,2-bis-(4-metoxi-fenil)-etanona 27 (3.0 gramos, 8.9 milimoles), y ditiocarbamato de amonio (1.5 gramos, 13.4 milimoles), se disuelven en EtOH (50 mililitros), y se calientan a 60°C durante 3 horas. Luego se remueve parcialmente el solvente, el precipitado se filtra y se recristaliza a partir de EtOH, para dar el 28 como un sólido blanco: ^{1}H-

RMN (400 MHz, CD_3OD) δ = 7.26 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 3.77 (s, 3H). MS calculada para $C_{17}H_{16}NO_2S_2$ ($M+H^+$) 330.1, encontrada 330.2.



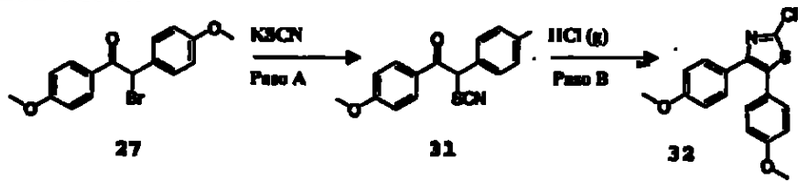
27 29 30

Intermediario 30. [4,5-bis-4-(4-metoxi-fenil)-tiazol-2-il]-metanol.

Paso A: Una solución de 2-bromo-1,2-bis-(4-metoxi-fenil)-etanona 27 (3.0 gramos, 9.0 mililitros), y tio-oxamato de etilo (1.2 gramos, 9.0 mililitros) en EtOH anhidro (20 mililitros), se calienta a reflujo durante 12 horas. El solvente se remueve al vacío, y el resto se purifica mediante cromatografía (sílice, gradiente de DCM/MeOH), para proporcionar el 29 como un semi-sólido incoloro: ^{1}H-RMN (400 MHz, CD_3OD) δ = 7.39 (d, J = 8.9 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.45 (q, J = 7.1, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H). MS calculada para $C_{20}H_{20}NO_4S$ ($M+H^+$) 370.1, encontrada 370.4.

Paso B: El etil-éster del ácido 4,5-bis-(4-metoxi-fenil)-tiazol-2-carboxílico 29 (1.0 gramos, 2.7 milimoles), se disuelve en tetrahidrofurano seco (20 mililitros), y se enfría a 0°C. Se agrega por goteo una solución de hidruro de litio y aluminio 1M en tetrahidrofurano (4 mililitros, 4.1 milimoles) por medio de una cánula, y la mezcla se agita a 0°C durante 1 hora. Se agrega lentamente decahidrato de sulfato de sodio (1.3 gramos, 4.1 milimoles), y la mezcla se agita durante 1 hora adicional a temperatura ambiente. Luego la suspensión se filtra sobre Celite ($MgSO_4$), y se

concentra. El concentrado se purifica mediante cromatografía (sílice, gradiente de DCM/MeOH), para dar el 30 como un aceite amarillo: ^{1}H-RMN (400 MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 3.96 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H). MS calculada para $C_{18}H_{18}NO_3S$ ($M+H^+$) 328.1, encontrada 328.4.



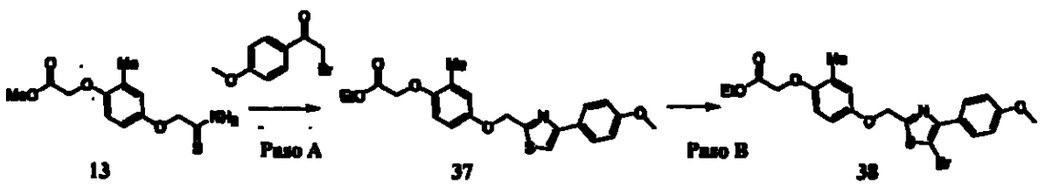
27 31 32

Intermediario 32: 2-cloro-4,5-bis-(4-metoxi-fenil)-tiazol.

Paso A: La 2-bromo-1,2-bis-(4-metoxi-fenil)-etanona 27 (500 miligramos, 1.49 milimoles), y rodanida de potasio (145 miligramos, 1.49 milimóles) se calientan a reflujo en acetona (20 mililitros) durante 8 horas. La mezcla se enfría, se diluye con agua (50 mililitros), se extrae con EtOAc (50 mililitros, 3 veces), y se lava con salmuera (30 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar la 1,2-bis-(4-metoxi-fenil)-2-tiocianato-etanona 31 cruda, la cual se utiliza sin mayor purificación en el Paso B.

Paso B: La 1,2-bis-(4-metoxi-fenil)-2-tiocianato-etanona 31 cruda(440 miligramos, 1.40 milimoles) se disuelve en EtOAc (100 mililitros), y luego se burbujea gas de HCl a través de la solución durante 2 horas. La mezcla se neutraliza con NaOH acuoso hasta un pH de 6, luego se extrae con EtOAc (50 mililitros, 3 veces), y se lava en secuencia con agua (30 mililitros) y salmuera (30 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, se concentra, y se purifica sobre sílice (gradiente de

EtOAc/hexano), para proporcionar el compuesto del título 32 como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.42 (d, J = 9.0 Hz, 2H), 7.25 (d, J = 9.3 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 9.3 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 3H). MS calculada para $C_{17}H_{16}ClNO_4S$ ($M+H^+$) 332.0, encontrada 332.3.



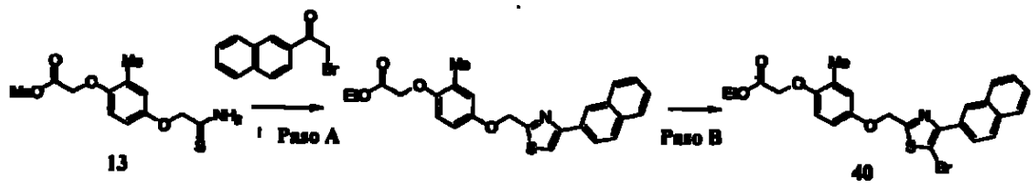
13 37 38

Intermediario 38: Etil-éster del ácido {4-[5-bromo-4-(4-metoxi-fenil)-tiazol-2-ilmetoxi]-metil-fenoxi}-acético.

Paso A: El intermediario 13 (200 miligramos, 0.743 milimoles), y 2-bromo-4'-metoxi-acetofenona (186 miligramos, 0.817 milimoles), se calientan a reflujo en EtOH (4 mililitros) durante 2 horas. La mezcla se enfría, se filtra, y se lava con metanol, para proporcionar el etil-éster del ácido {4-[4-(4-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético 37 como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.77 (d, J = 6.8 Hz, 1H), 7.75 (d, J = 6.8 Hz, 1H), 7.32 (s, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 3.0 Hz, 1H), 6.73 (dd, J = 3.0, 8.9 Hz, 1H), 6.65 (d, J = 8.8 Hz, 1H), 5.29 (s, 2H), 4.51 (s, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 2.22 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H). MS calculada para $C_{22}H_{24}NO_5S$ ($M+H^+$) 414.1, encontrada 414.4.

Paso B: El intermediario 37 (184.6 miligramos, 0.45 milimoles) se disuelve en diclorometano (2 mililitros), luego se agrega bromo (39 microlitros, 0.76 milimoles) en ácido acético (100 microlitros), y la mezcla

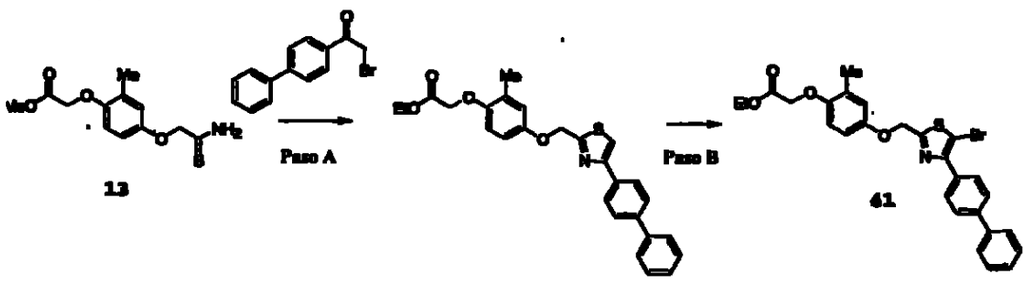
se agita a temperatura ambiente durante 1 hora. La mezcla se diluye con $NaHCO_3$ saturado, se extrae con diclorometano, y se lava con salmuera (10 millilitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar el Intermediario 38 como una sustancia vidriada blanca: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.80 (d, J = 6.8 Hz, 1H), 7.79 (d, J = 6.8 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 3.0 Hz, 1H), 6.67 (dd, J = 3.0, 8.9 Hz, 1H), 6.59 (d, J = 8.8 Hz, 1H), 5.20 (s, 2H), 4.51 (s, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 2.22 (s, 3H), 1.20 (t, J = 7.2 Hz, 3HJ). MS calculada para $C_{22}H_{23}BrNO_5S$ ($M+H^+$) 492.0, encontrada 492.2.



13 40

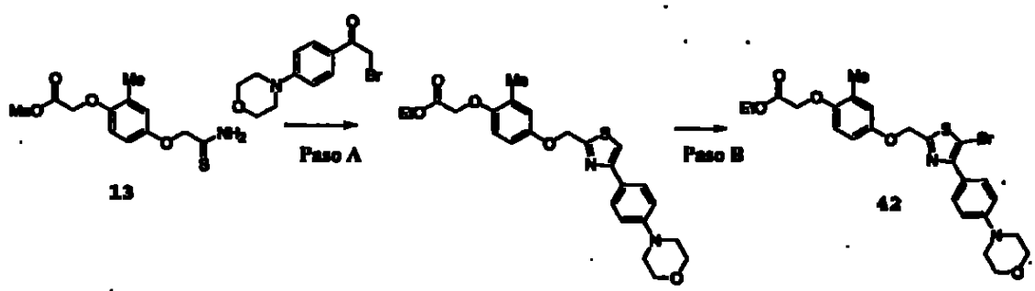
Intermediario 40: Etil-éster del ácido [4-(5-bromo-4-naftalen-2-il-tiazol-2-ilmetoxi)-2-metil-fenoxi]-acético.

Siguiendo el procedimiento del Intermediario 38, excepto que utilizando 2-bromo-1-naftalen-2-il-etanona para sustituir a la 2-bromo-4'-metoxi-acetofenona del Paso A, se purifica el compuesto del título sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 8.42 (s, 1H), 8.03 (dd, J = 1.6, 8.4 Hz, 1H), 7.92 (d, J = 8.8 Hz, 2H), 7.88 (m, 1H), 7.52 (m, 2H), 6.89 (d, J = 3.2 Hz, 1H), 6.77 (dd, J = 3.2, 8.8 Hz, 1H), 6.68 (d, J = 8.8 Hz, 1H)=, 5.33 (s, 2H), 4.60 (s, 2H), 4.26 (q, J = 7.2, Hz, 2H), 2.30 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H). MS calculada para $C_{26}H_{23}BrNO_4S$ ($M+H^+$) 512.1, encontrada 511,5.



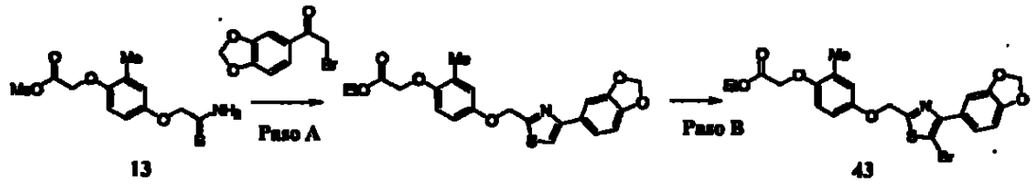
Intermediario 41: Etil-éster del ácido [4-(4-bifenil-4-il-5-bromo-tiazol-2-ilmetoxi)-2-metil-fenoxi]-acético.

Siguiendo el procedimiento del Intermediario 38, excepto que utilizando 1-bifenil-4-il-2-bromo-etanona para sustituir a la 2-bromo-4'-metoxi-acetofenona del Paso A, se purifica el compuesto del título sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.99 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 7.6 Hz, 2H), 7.43 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.72 (dd, J = 2.8, 8.8 Hz, 1H), 6.64 (d, J = 8.8 Hz, 1H), 5.26 (s, 2H), 4.56 (s, 2H), 4.22 (q, J = 7.2 Hz, 2H), 2.27 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H). MS calculada para $C_{27}H_{28}BrNO_4S$ ($M+H^+$) 538.1, encontrada 538.0.



Intermediario 42: Etil-éster del ácido {4-[5-bromo-4-(4-morfolin-4-il-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.

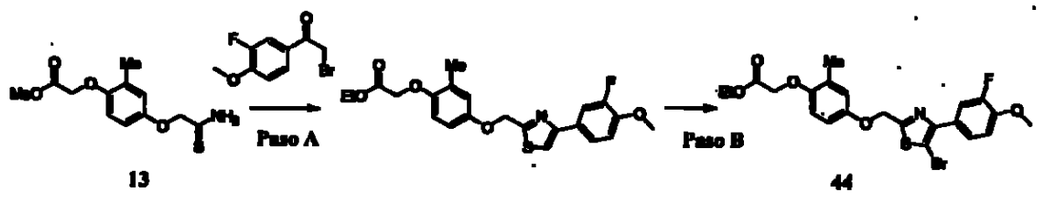
Siguiendo el procedimiento del Intermediario 38, excepto que utilizando la 2-bromo-1-(4-morfolin-4-il-fenil)-etanona para sustituir a la 2-bromo-4'-metoxi-acetofenona del Paso A, se prepara el compuesto del título como un sólido amarillo: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.99 (d, J = 9.2 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.74 (dd, J = 2.8 Hz, 8.8 Hz, 1H), 6.66 (d, J = 8.8 Hz, 1H), 5.27 (s, 2H), 4.59 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 4.04 (m, 4H), 3.45 (m, 4H), 2.29 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H). MS calculada para $C_{25}H_{28}BrN_2O_5S$ ($M+H^+$) 547.1, encontrada 547.3.



13 43

Intermediario 43: Etil-éster del ácido [4-(4-benzo[1,3]dioxol-5-il-5-bromo-tiazol-2-ilmetoxi)-2-metil-fenoxi]-acético.

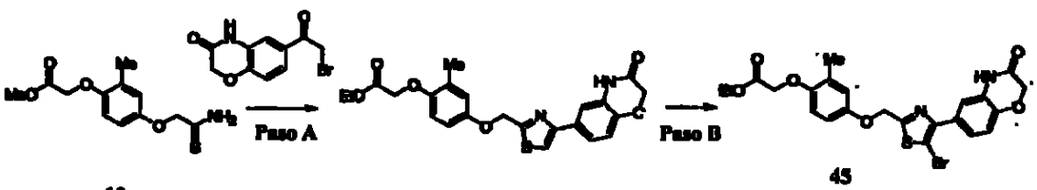
Siguiendo el procedimiento del Intermediario 38, excepto que utilizando la 1-benzo[1,3]dioxol-5-il-2-bromo-etanona para sustituir a la 2-bromo-4'-metoxi-acetofenona del Paso A, se prepara el compuesto del título como un sólido amarillo: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.43 (dd, J = 1.6, 8.0 Hz, 1H), 7.41 (d, J = 1.6 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 2.8 Hz, 1H)=, 6.74 (dd, J = 2.8, 8.8 Hz, 1H), 6.66 (d, J = 8.8 Hz, 1H), 6.02 (s, 2H), 5.27 (s, 2H), 4.59 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 2.27 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H). MS calculada para $C_{22}H_{21}BrNO_6S$ ($M+H^+$) 506.0, encontrada 506.2.



13 44

Intermediario 44: Etil-éster del ácido {4-[5-bromo-4-(3-fluoro-4-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.

Siguiendo el procedimiento del Intermediario 38, excepto que utilizando la 2-bromo-1-(3-fluoro-4-metoxi-fenil)-etanona para sustituir a la 2-bromo-4'-metoxiacetofenona del Paso A, se prepara el compuesto del título como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.70 (m, 2H), 7.07 (t, J = 8.4 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 6.71 (dd, J = 2.4, 8.8 Hz, 1H), 6.64 (d, J = 8.8 Hz, 1H), 5.24 (s, 2H), 4.56 (s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 3.92 (s, 3H), 2.26 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H). MS calculada para $C_{22}H_{22}BrFNO_6S$ ($M+H^+$) 510.0, encontrada 510.3.

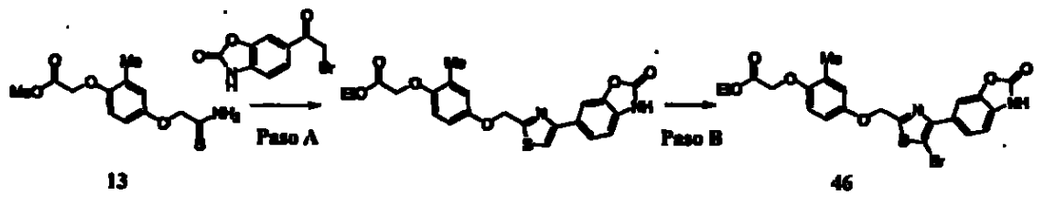


13 45

Intermediario 45: Etil-éster del ácido {4-[5-bromo-4-(3-oxo-3,4-dihidro-2H-benzo[1,4]oxazin-6-il)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.

Siguiendo el procedimiento del Intermediario 38, excepto que utilizando la 6-(2-bromo-acetil)-4H-benzo[1,4]oxazin-3-ona para sustituir a la 2-bromo-4'-metoxi-acetofenona del Paso A, se prepara el compuesto del título como un sólido amarillo: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.76 (s, 1H),

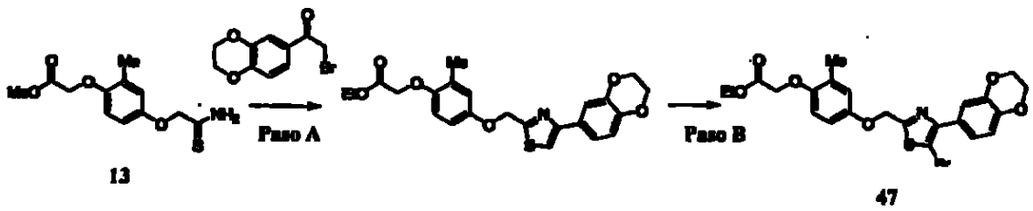
7.65 (dd, J = 2.0, 8.4 Hz, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 2.8 Hz, 1H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.31 (s, 2H), 4.71 (s, 2H), 4.64 (s, 2H), 4.31 (q, J = 7.2 Hz, 2H), 2.33 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H). MS calculada para $C_{23}H_{22}BrN_2O_6S$ ($M+H^+$) 533.0, encontrada 533.0.



13 46

Intermediario 46: Etil-éster del ácido {4-[5-bromo-4-(2-oxo-2,3-dihidro-benzo-oxazol-6-il)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.

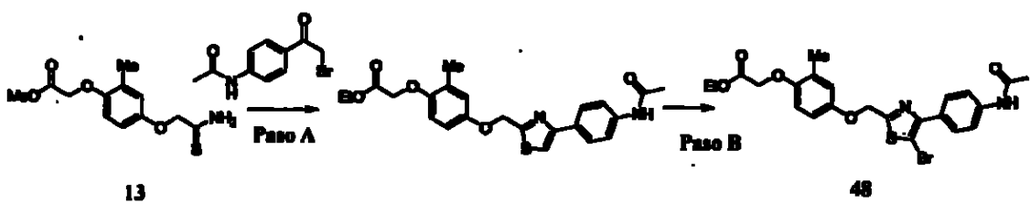
Siguiendo el procedimiento del Intermediario 38, excepto que utilizando la 6-(2-bromo-acetil)-3H-benzo-oxazol-2-ona para sustituir a la 2-bromo-4'-metoxi-acetofenona del Paso A, se prepara el compuesto del título como un sólido amarillo: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 8.07 (s, 1H), 7.82 (s, 1H), 7.78 (dd, J = 1.6, 8.4 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 6.74 (dd, J = 2.8, 8.8 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 5.28 (s, 2H), 4.60 (s, 2H), 4.26 (q, J = 7.2 Hz, 2H), 2.29 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H). MS calculada para $C_{22}H_{20}BrN_2O_6S$ ($M+H^+$) 519.0, encontrada 519.0.



13 47

Intermediario 47: Etil-éster del ácido {4-[5-bromo-4-(2,3-dihidro-benzo[1,4]dioxin-6-il)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.

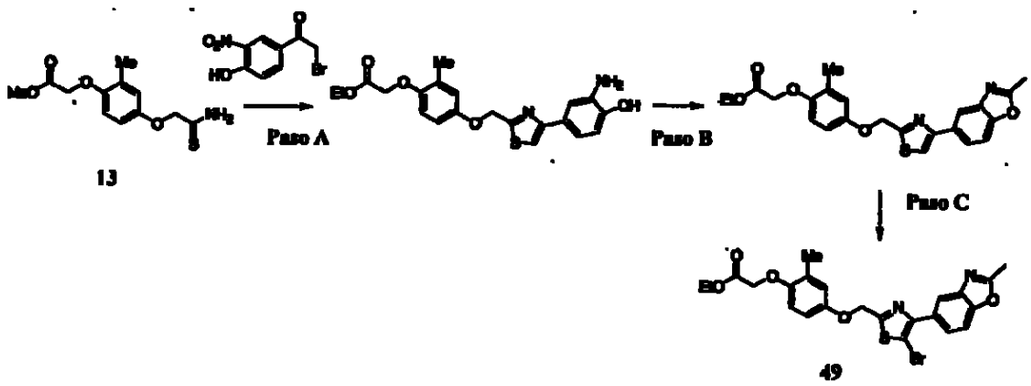
Siguiendo el procedimiento del Intermediario 38, excepto que utilizando 2-bromo-(2,3-dihidro-benzo[1,4]-dioxin-6-il)-etanona para sustituir a la 2-bromo-4'-metoxi-acetofenona del Paso A, se utiliza el compuesto del título sin purificación en el siguiente paso. MS calculada para $C_{23}H_{23}BrNO_6S$ ($M+H^+$) 520.0, encontrada 520.0.



13 48

Intermediario 48: Etil-éster del ácido {4-4-(4-acetil-amino-fenil)-5-bromo-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.

Siguiendo el procedimiento del Intermediario 38, excepto que utilizando la N-[4-(2-bromo-acetil)-fenil]-acetamida para sustituir a la 2-bromo-4'-metoxi-acetofenona del Paso A, se prepara el compuesto del título como un sólido amarillo: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.91 (d, J = 8.4 Hz, 2HJ), 7.60 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 2.8 Hz, 1H), 6.74 (dd, J = 2.8, 8.8 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.59 (s, 2H), 4.26 (q, J = 7.2 Hz, 2H), 2.29 (s, 3H), 2.21 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H). MS calculada para $C_{23}H_{24}BrN_2O_6S$ ($M+H^+$) 519.0, encontrada 519.1.



13

49

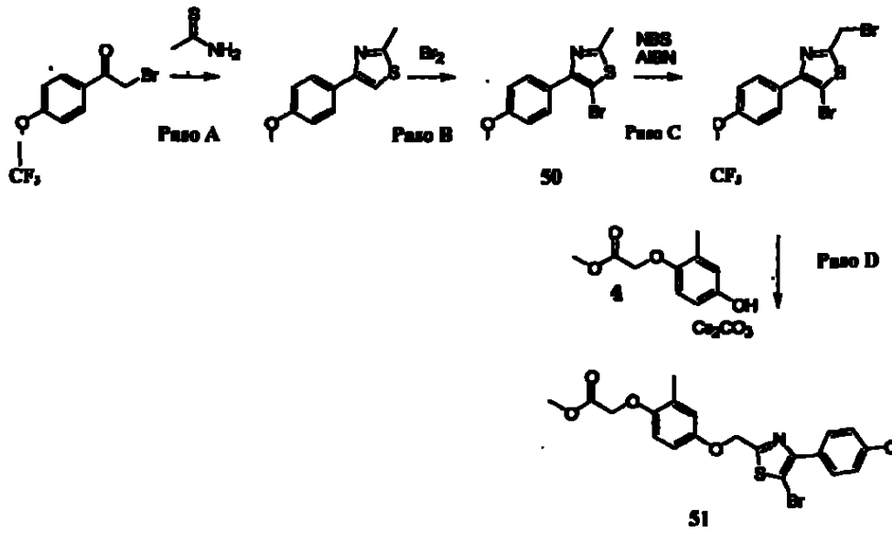
Intermediario 49: Etil-éster del ácido {4-[5-bromo-4-(2-metil-benzo-oxazol-5-il)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.

Paso A: El intermediario 13 (2.1 gramos, 7.79 milimoles), y 2-bromo-1-(4-hidroxi-3-nitro-fenil)-etanona (2.0 gramos, 7.79 milimoles), se calientan a reflujo en EtOH (40 mililitros) durante 4 horas. Se agrega cloruro de estaño (II) (4.4 gramos, 23 milimoles), y la mezcla se calienta a reflujo durante 2 horas adicionales. Luego la mezcla se extrae con acetato de etilo, se lava con una solución saturada de bicarbonato de sodio, y se filtra a través de Celite. La capa orgánica se seca ($MgSO_4$), se filtra, se concentra, y se purifica sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar el etil-éster del ácido {4-[4-(3-amino-4-hidroxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético: MS calculada $C_{21}H_{23}N_2O_6S$ ($M^{\cdot}+H^{+}$) 415.1, encontrada 415.4.

Paso B: El etil-éster del ácido {4-[4-(3-amino-4-hidroxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético (245 miligramos, 0.59 milimoles), se disuelve en tolueno (20 mililitros). Se agrega anhídrido acético (59 microlitros, 0.62 milimoles), y la mezcla se calienta a reflujo durante 2 horas. Luego se agrega ácido p-toluensulfónico (169 miligramos, 0.88 milimoles), y la mezcla se calienta a reflujo durante otras 2 horas

utilizando una trampa Dean-Stark para remover el agua. La mezcla se diluye con $NaHCO_3$ saturado, se extrae con EtOAc, y se lava con salmuera (10 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar el etil-éster del ácido {2-metil-4-[4-(2-metil-benzo-oxazol-5-il)-tiazol-2-ilmetoxi]-fenoxi}-acético como un sólido amarillo pálido, el cual se utiliza sin mayor purificación en el Paso C.

Paso C: El etil-éster del ácido {2-metil-4-[4-(2-metil-benzo-oxazol-5-il)-tiazol-2-ilmetoxi]-fenoxi}-acético crudo (208 miligramos, 0.47 milimoles), se disuelve en diclorometano (10 mililitros) y piridina (2 gotas); luego se agrega bromo (27 microlitros, 0.52 milimoles), y la mezcla se agita a temperatura ambiente durante 1 hora. La mezcla se diluye con $NaHCO_3$ saturado, se extrae en diclorometano, y se lava con salmuera (10 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar el intermediario 49 como un polvo blanco: MS calculada para $C_{23}H_{22}BrN_2O_5S$ ($M+H^+$) 517.0, encontrada 517.0.



Intermediario 50: Metil-éster del ácido {4-[5-bromo-4-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.

Paso A: La 2-bromo-1-(4-trifluoro-metoxi-fenil)-etanona (500 miligramos, 1.76 milimoles) y tioacetamida (146 miligramos, 1.94 milimoles) se disuelven en etanol, y se calientan a reflujo durante 2 horas. El solvente se remueve al vacío para proporcionar el 2-metil-4-(4-trifluoro-metoxi-fenil)-tiazol crudo, el cual se utiliza sin mayor purificación en el Paso B.

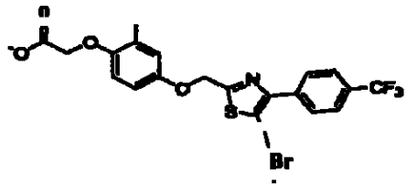
Paso B: El 2-metil-4-(4-trifluoro-metoxi-fenil)-tiazol 81.76 milimoles) se disuelve en diclorometano (5 mililitros) conteniendo ácido acético (1 mililitro). Se agrega bromo (0.20 mililitros, 3.9 milimoles), y la mezcla se calienta a 40°C durante 2 horas. La mezcla se diluye con $NaHCO_3$ saturado, se extrae en diclorometano, y se lava con salmuera (10 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar el 5-bromo-2-metil-4-(4-trifluoro-metoxi-fenil)-tiazol 50 como un aceite amarillo. ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.95 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H), 2.71 (s, 3H). MS calculada para $C_{11}H_8BrF_3NOS$ ($M+H^+$) 337.9, encontrada 337.9.

Paso C: El 5-bromo-2-metil-4-(4-trifluoro-metoxi-fenil)-tiazol 50 (548 miligramos, 1.62 milimoles), y N-bromosuccinimida (317 miligramos, 1.78 milimoles), se disuelven en tetracloruro de carbono (40 mililitros), y se calientan a 50°C. El azo-bis-isobutironitrilo (20 miligramos) se disuelve previamente en tetracloruro de carbono (10 mililitros), y se agrega por goteo a la mezcla, y luego la mezcla se calienta a 50°C durante 96 horas. La mezcla se diluye con $NaHCO_3$ saturado, se extrae en diclorometano, y

se lava con salmuera (10 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar el 5-bromo-2-bromo-metil-4-(4-trifluoro-metoxi-fenil)-tiazol crudo, el cual se utiliza sin mayor purificación en el Paso D.

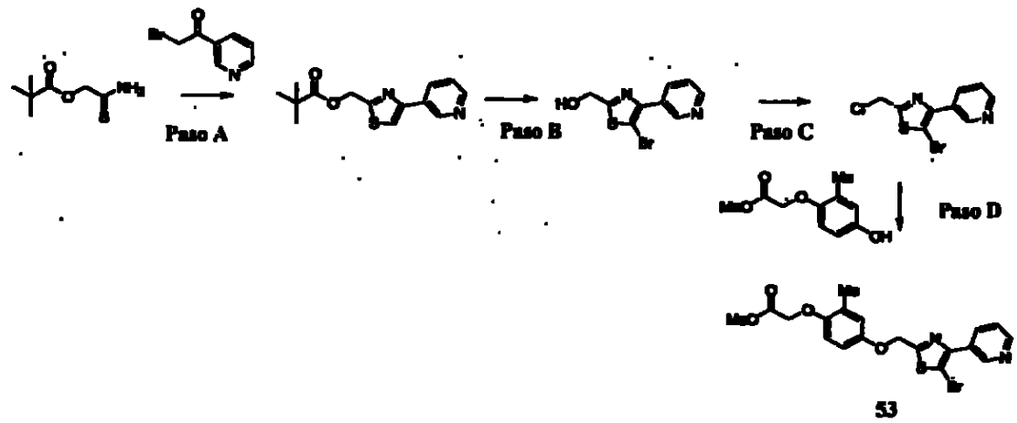
Paso D: El 5-bromo-2-bromo-metil-4-(4-trifluoro-metoxi-fenil)-tiazol (1.62 milimoles), Intermediario 4 (222 miligramos, 1.13 milimoles), y carbonato de cesio (736 miligramos, 2.26 milimoles), se forman en una pasta en acetonitrilo a temperatura ambiente durante 1 hora. La mezcla se filtra, el solvente se evapora, y el resto se purifica mediante cromatografía por evaporación utilizando una mezcla de hexano y acetato de etilo (5:1), para proporcionar el 51 como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.97 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 2.8 Hz, 6.74 (dd, J = 2.8, 8.8 Hz, 1H), 6.66 (d, J = 8.8 Hz, 1H), 5.27 (s, 2H), 4.61 (s, 2H), 3.80 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{21}H_{18}BrF_3NO_3S$ ($M+H^+$) 532.0, encontrada 532.0.

Intermediario 52: Metil-éster del ácido {4-[5-bromo-4-(4-trifluoro-metil-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.



Siguiendo el procedimiento del Intermediario 51, excepto que utilizando la 2-bromo-1-(4-trifluoro-metil-fenil)-etanona para sustituir a la 2-bromo-1-(4-trifluoro-metoxi-fenil)-etanona del Paso A, se prepara el compuesto del título como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 8.08 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 2.8 Hz, 1H),

6.75 (dd, J = 2.8, 8.8 Hz, 1H), 6.66 (d, J = 8.8 Hz, 1H), 5.28 (s, 2H), 4.61 (s, 2H), 3.80 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{21}H_{18}BrF_3NO_4S$ ($M+H^+$) 516.0, encontrada 516.3.



53

Intermediario 53: Metil-éster del ácido [4-(5-bromo-4-piridin-3-il-tiazol-2-ilmetoxi)-2-metil-fenoxi]-acético.

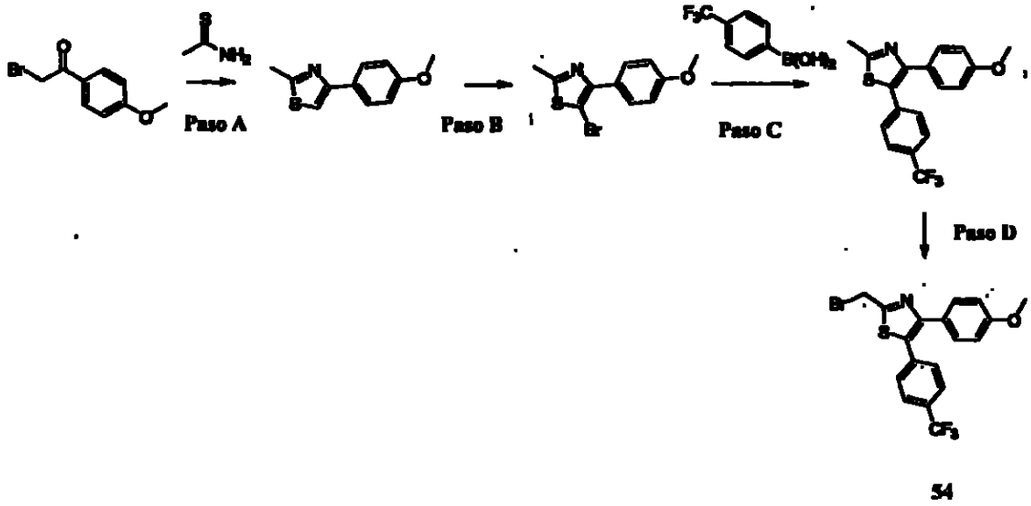
Paso A: La 2-bromo-1-piridin-3-il-etanona (200 miligramos, 0.71 milimoles), y pivalato de 2-amino-2-tioxoetilo (131 miligramos, 0.75 miligramos) se disuelven en etanol, y se calientan a reflujo durante 1 hora. La mezcla se diluye con $NaHCO_3$ saturado, se extrae en diclorometano, y se lava con salmuera (10 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar el 4-piridin-3-il-tiazol-2-ilmetil-éster del ácido 2,2-dimetil-propiónico, el cual se utiliza sin mayor purificación en el Paso B.

Paso B: El 4-piridin-3-il-tiazol-2-ilmetil-éster del ácido 2,2-dimetil-propiónico crudo (0.71 milimoles) se disuelve en diclorometano (10 mililitros) conteniendo piridina (2 gotas), luego se agrega bromo (47 microlitros, 0.93 milimoles), y la mezcla se agita durante 16 horas a

temperatura ambiente. La mezcla se diluye con $NaHCO_3$ saturado, se extrae en diclorometano, y se lava con salmuera (10 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra. El residuo se disuelve inmediatamente en tetrahidrofurano (5 mililitros), luego se agrega hidróxido de litio (1.0 N, 2 mililitros), y la mezcla se agita durante 1 hora. La mezcla se diluye con $NaHCO_3$ saturado, se extrae en acetato de etilo (2 veces), y se lava con salmuera (10 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar el (5-bromo-4-piridin-3-il-tiazol-2-il)-metanol, el cual se utiliza sin mayor purificación en el Paso C.

Paso C: El (5-bromo-4-piridin-3-il-tiazol-2-il)-metanol crudo (0.71 milimoles) se disuelve en tetrahidrofurano seco, luego se agrega cloruro de tionilo (0.30 mililitros, 4.1 milimoles); y la mezcla se agita durante 1 hora. La mezcla se diluye con $NaHCO_3$ saturado, se extrae en diclorometano, y se lava con salmuera (10 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar la 3-(5-bromo-2-clorometil-tiazol-4-il)-piridina, la cual se utiliza sin mayor purificación en el Paso D.

Paso D: La 3-(5-bromo-2-clorometil-tiazol-4-il)-piridina cruda (0.71 milimoles), el Intermediario 4 (139 miligramos, 0.71 milimoles), y carbonato de cesio (464 miligramos, 1.42 milimoles) se suspenden en acetonitrilo seco, y se agitan durante 2 horas. Luego la mezcla se filtra, el solvente se evapora, y el resto se purifica sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar el Intermediario 53 como el principal componente de una mezcla de compuestos (mediante ^1H RMN). Esta mezcla se utiliza directamente en el siguiente paso sin mayor purificación.



54

Intermediario 54: 2-bromo-metil-4-(4-metoxi-fenil)-5-(4-trifluoro-metil-fenil)-tiazol.

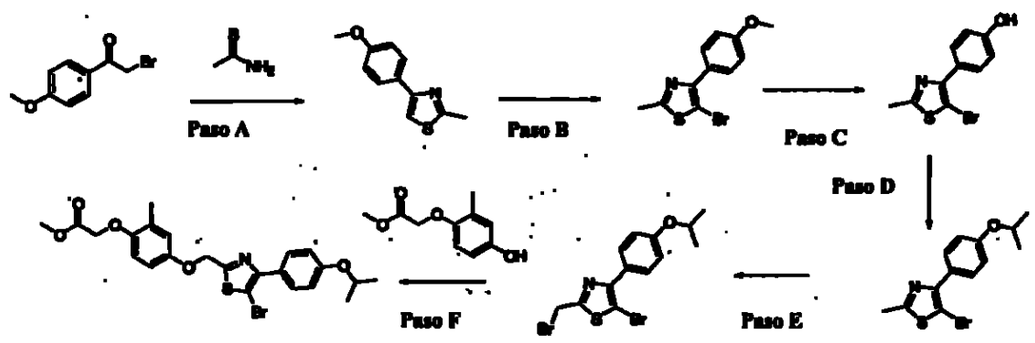
Paso A: La 2-bromo-1-(4-metoxi-fenil)-etanona (25.0 gramos, 109 milimoles), y tioacetamida (9.0 gramos, 120 milimoles), se disuelven en etanol (60 mililitros), y se calientan a reflujo durante 2 horas. El solvente se remueve al vacío para proporcionar el 4-(4-metoxi-fenil)-2-metil-tiazol crudo, el cual se utiliza sin mayor purificación en el Paso B.

Paso B: El 4-(4-metoxi-fenil)-2-metil-tiazol (109 milimoles) se disuelve en diclorometano (300 mililitros). Se agrega bromo (6.20 mililitros, 120 milimoles), y se mezcla se calienta a 40°C durante 3 horas. La mezcla se diluye con $NaHCO_3$ saturado, se extrae en diclorometano, y se lava con salmuera (50 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar el 5-bromo-4-(4-metoxi-fenil)-2-metil-tiazol. MS calculada para $C_{11}H_{11}BrNOS$ ($M+H^+$) 284.0, encontrada 284.1.

Paso C El 5-bromo-4-(4-metoxi-fenil)-2-metil-tiazol (4 gramos, 14.1 milimoles), ácido 4-trifluoro-metil-fenil-borónico (3.2 gramos, 16.9

milimoles), y carbonato de sodio (4.5 gramos, 42.3 milimoles), se disuelven en H_2O (12.6 mililitros), etanol (9.3 mililitros), y 1,2-dimetoxietano (37.8 mililitros), y la mezcla se desgasifica burbujeando argón a través de la solución durante 10 minutos. Se agrega $Pd(PPh_3)_4$ (490 miligramos, 0.42 milimoles), y la mezcla se calienta a 170°C mediante microondas en un tubo sellado durante 10 minutos. La mezcla se diluye con agua (50 mililitros), se extrae en EtOAc (200 mililitros), y se lava con salmuera (50 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, se concentra, y se purifica sobre una columna de gel de sílice, utilizando una mezcla de hexano y acetato de etilo, para proporcionar el 4-(4-metoxi-fenil)-2-metil-5-(4-trifluoro-metil-fenil)-tiazol: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.54 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 2.77 (s, 3H). MS calculada para $C_{18}H_{15}F_3NOS$ $(M+H^+)$ 350.1, encontrada 350.0.

Paso D: El 4-(4-metoxi-fenil)-2-metil-5-(4-trifluoro-metil-fenil)-tiazol (3.66 gramos, 10.5 milimoles), y N-bromo-succinimida (2.05 gramos, 11.5 milimoles), se disuelven en tetracloruro de carbono (60 mililitros), y se calientan a 50°C. El azo-bis-isobutironitrilo (172 miligramos) se disuelve previamente en tetracloruro de carbono (10 mililitros), y se agrega por goteo a la mezcla, y luego la mezcla se calienta a 60°C durante 16 horas. La mezcla se diluye con $NaHCO_3$ saturado, se extrae en diclorometano, y se lava con salmuera (50 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, se concentra, y se purifica mediante cromatografía por evaporación utilizando una mezcla de hexano y acetato de etilo, para proporcionar el Intermediario 54. MS calculada para $C_{18}H_{14}BrF_3NOS$ $(M+H^+)$ 428.0, encontrada 428.0.



Intermediario 55: Metil-éster del ácido {4-[5-bromo-4-(4-isopropoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.

Paso A: La tioacetamida (9.0 gramos, 120 milimoles), y 2-bromo-1-(4-metoxi-fenil)-etanona (25 gramos, 109 milimoles), se disuelven en etanol (60 mililitros), y se calientan a reflujo durante 2 horas. El etanol se remueve al vacío, y se utiliza el 4-(4-metoxi-fenil)-2-metil-tiazol crudo en el Paso B sin mayor purificación.

Paso B: El 4-(4-metoxi-fenil)-2-metil-tiazol (109 milimoles) se disuelve en diclorometano (300 mililitros). Se agrega bromo (6.2 mililitros, 120 milimoles), y la mezcla se calienta a reflujo durante 3 horas. La mezcla se apaga con $NaHCO_3$ (acuoso) saturado, se extrae en diclorometano, se lava con NaHCO (acuoso) saturado, se seca sobre sulfato de magnesio, se filtra, y se evapora, para dar el 5-bromo-4-(4-metoxi-fenil)-2-metil-tiazol como un polvo beige pálido: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.85 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 2.69 (s, 3H). MS calculada para $C_{11}H_{11}BrNOS$ ($M+H^+$) 284.0, encontrada 284.1.

Paso C: El 5-bromo-4-(4-metoxi-fenil)-2-metil-tiazol (15.0 gramos, 52.8 milimoles) se disuelve en diclorometano (200 mililitros). Se agrega

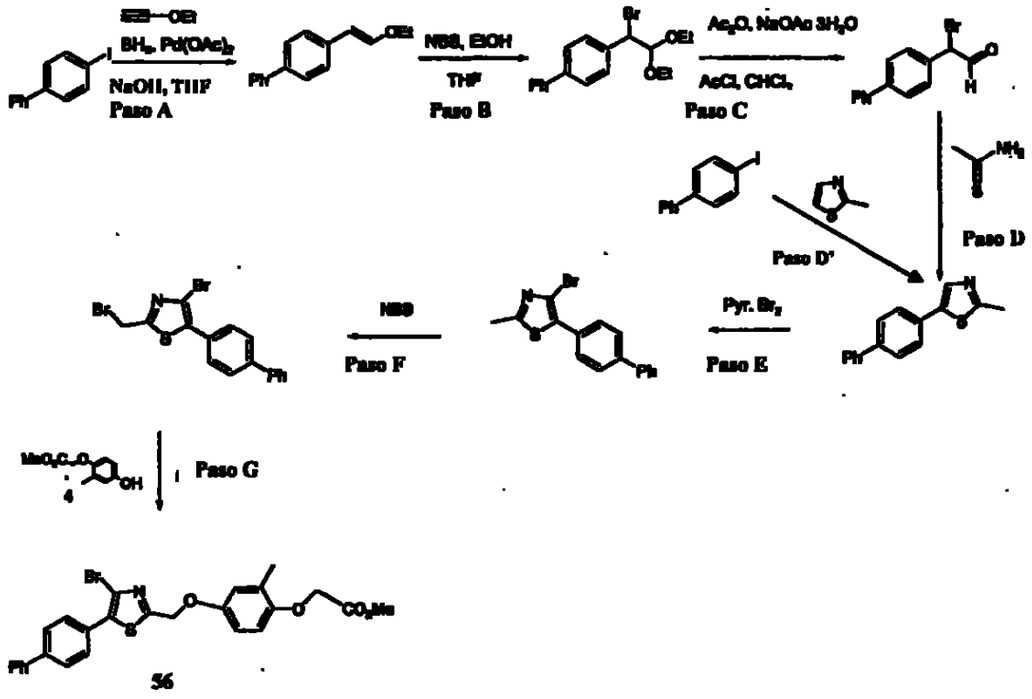
tribromuro de boro (15 mililitros, 158.3 milimoles), y la mezcla se agita a temperatura ambiente durante 1 hora. La mezcla se apaga con $NaHCO_3$ (acuoso) saturado, se extrae en diclorometano, se lava con $NaHCO_3$ (acuoso) saturado, se seca sobre sulfato de magnesio, se filtra, y se evapora, para dar el 4-(5-bromo-2-metil-tiazol-4-il)-fenol crudo (15.4 gramos), el cual se utiliza sin purificación en el Paso D: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.79 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 3.16 (s, 1H), 2.70 (s, 3H). MS calculada para $C_{10}H_9BrNOS$ ($M+H^+$) 270.0, encontrada 270.2.

Paso D: El 4-(5-bromo-2-metil-tiazol-4-il)-fenol (38.3 milimoles) se disuelve en acetona (100 mililitros). Se agrega K_2CO_3 (10.6 gramos, 76.6 milimoles), seguido por 2-yodopropano (7.7 mililitros, 76.6 milimoles), y la mezcla resultante se calienta a reflujo durante 18 horas. El solvente se evapora al vacío, y el residuo se purifica mediante cromatografía por evaporación utilizando una mezcla de hexano y acetato de etilo, para proporcionar el 5-bromo-4-(4-isopropoxi-fenil)-2-metil-tiazol. MS calculada para $C_{13}H_{15}BrNOS$ ($M+H^+$) 312.0, encontrada 312.0.

Paso E: El 5-bromo-4-(4-isopropoxi-fenil)-2-metil-tiazol (3.4 gramos, 10.89 milimoles), se disuelve en tetracloruro de carbono (100 mililitros). Se agrega N-bromosuccinimida (2.52 gramos, 14.16 milimoles), y la mezcla se calienta a 50°C, y luego se agrega AIBN (179 miligramos, 1.09 milimoles). La mezcla se calienta a 70°C durante 5 horas. Se agrega bromo adicional (0.5 gramos) y AIBN (60 miligramos), y se continúa la agitación a 70°C durante otras 12 horas. Luego la mezcla se enfría, se apaga con agua, se extrae en diclorometano, se seca sobre $MgSO_4$, se filtra, y se evapora, para dar el 5-bromo-2-bromometil-4-(4-isopropoxi-fenil)-tiazol crudo, el

cual se utiliza directamente en el Paso F.

Paso F: El 5-bromo-2-bromo-metil-4-(4-isopropoxi-fenil)-tiazol (10.89 milimoles) y el intermediario 4 (2.13 gramos, 10.89 milimoles), se disuelven en acetonitrilo (100 mililitros). Se agrega carbonato de cesio (7.1 gramos, 21.78 milimoles), y la mezcla se agita a temperatura ambiente durante 2 horas. La mezcla se filtra, se evapora, y se purifica mediante cromatografía por evaporación utilizando una mezcla de hexano y acetato de etilo, para proporcionar el intermediario 55: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.92 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 2.8 Hz, 1H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H), 4.67 (s, 2H), 3.86 (s, 3H), 2.36 (s, 3H), 2.12 (s, 1H), 1.44 (s, 6H). MS calculada para $C_{23}H_{25}BrNO_5S$ ($M+H^+$) 506.1, encontrada 506.1.



Intermediario 56: Metil-éster del ácido [4-(5-bifenil-4-il-4-bromo-tiazol-2-ilmetoxi)-2-metil-fenoxi]-acético.

Paso A: A una solución de etil-etinil-éter (6.0 gramos, 95.6 milimoles) en tetrahidrofurano (100 mililitros) a 0°C, se le agrega un complejo de borano-tetrahidrofurano (1.0 moles en tetrahidrofurano, 28.53 mililitros, 28.53 milimoles). La mezcla se calienta a temperatura ambiente, y se agita durante 2 horas. La solución resultante se agrega a una mezcla de 4-yodobifenilo (20.0 gramos, 71.33 milimoles), trifenil-fosfina (598 miligramos, 2.28 milimoles), acetato de paladio (II) (128 miligramos, 0.571 milimoles), e hidróxido de sodio (8.5 gramos, 214.0 milimoles) en tetrahidrofurano (200 mililitros). La mezcla se calienta a reflujo durante 15 horas, luego se enfría, se diluye con EtOAc (1000 mililitros), se lava con Na_2CO_3 saturado, salmuera, y agua. La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar el producto crudo, el cual se purifica mediante cromatografía en gel de sílice (gradiente de éter/hexano), para dar el 4-(2-etoxi-vinil)-bifenilo como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.52-7.19 (m, 9H), 6.97 (d, J = 12.8 Hz, 1H), 5.81 (d, J = 12.8 Hz, 1H), 3.87 (m, 2H), 1.29 (t, 3H). MS calculada para $C_{16}H_{17}O$ ($M+H^+$) 225.1, encontrada 225.1.

Paso B: El 4-(2-etoxi-vinil)-bifenilo (7.60 gramos, 33.88 milimoles) se disuelve en una mezcla de EtOH/THF (120 mililitros/30 mililitros), y luego se agrega NBS (6.03 gramos, 33.88 milimoles). La mezcla se agita a temperatura ambiente durante 2 horas, luego se concentra y se purifica mediante cromatografía en gel de sílice (gradiente de EtOAc/hexano), para dar el 4-(1-bromo-2,2-dietoxi-etil)-bifenilo como un sólido blanco: ^{1}H-RMN

(400 MHz, $CDCl_3$) δ = 7.33-7.63 (m, 9H), 4.98 (d, J = 6.4 Hz, 1H), 4.88 (d, J = 6.4 Hz, 1H), 3.81 (m, 1H), 3.64 (m, 2H), 3.45 9(m, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.07 (t, J = 7.2 Hz, 3H). MS calculada para $C_{18}H_{21}BrO_2$ (M^+) 349.3, encontrada 270.1 $(M-Br)^+$.

Paso C: El 4-(1-bromo-2,2-dietoxi-etil)-bifenilo (750 miligramos, 2.15 milimoles) se disuelve en cloroformo (3 mililitros), luego se agregan sucesivamente Ac_2O (220 miligramos, 2.15 milimoles), $NaOAc \cdot 3H_2O$ (175.4 miligramos, 1.29 milimoles), y AcCl (118 miligramos, 1.51 milimoles), y la mezcla se agita a 55°C durante 5 horas. La mezcla se diluye con CH_2Cl_2 (50 mililitros), y se lava con $NaHCO_3$ saturado, y salmuera. La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar el bifenil-4-il-bromo-acetaldehído 50 crudo como un aceite espeso, el cual se utiliza en el siguiente paso sin mayor purificación. MS calculada para $C_{14}H_{11}BrO$ (M^+) 275.2, encontrada 195.1 $(M-Br)^+$.

Paso D: El aldehído 50 (0.57 gramos, 2.07 milimoles) se disuelve en EtOH (8 mililitros), luego se agrega tioacetamida (156 miligramos, 2.07 milimoles), y la mezcla se agita a 90°C durante 15 horas. La solución se diluye con EtOAc (50 mililitros), y se lava con $NaHCO_3$ saturado (30 mililitros) y salmuera (10 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar el producto crudo, el cual se purifica mediante cromatografía en gel de sílice con EtOAc/hexano (gradiente), para dar el 5-bifenil-4-il-2-metil-tiazol como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.78 (s, 1H), 7.51-7.56 (m, 5H), 4.28-7.41 (m, 4H), 2.69 (s, 3H). MS calculada para $C_{16}H_{14}NS$ ($M+H^+$) 252.1, encontrada 252.0.

Paso D': Una reacción de acoplamiento alternativa de un paso para

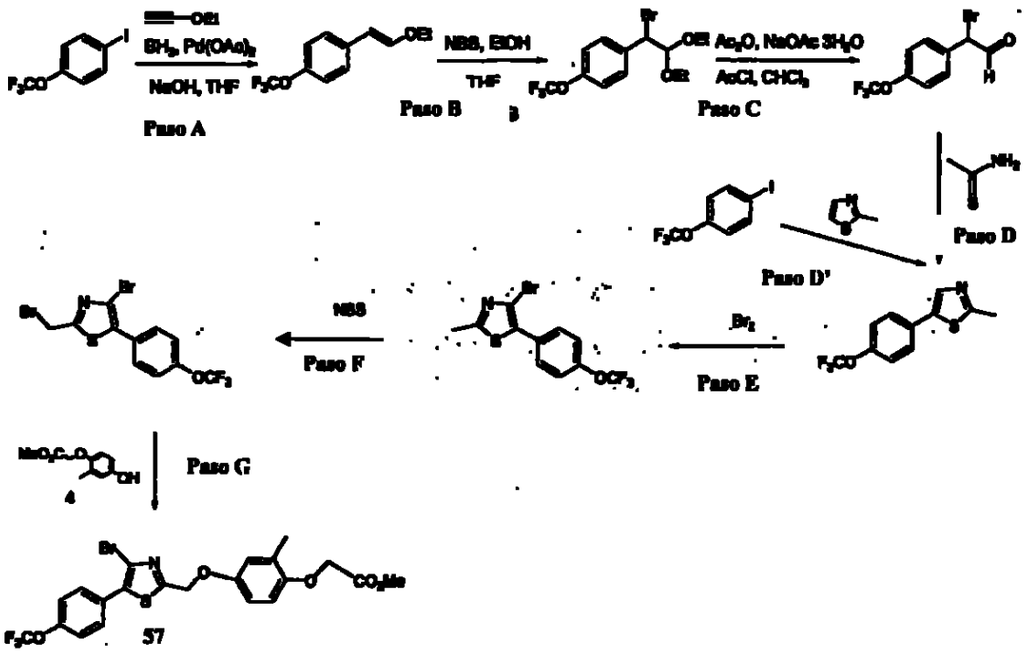
preparar el 5-bifenil-4-il-2-metil-tiazol.

El 4-yodobifenilo (40.0 gramos, 171.6 milimoles) se disuelve en dimetilformamida (800 mililitros), luego se agregan 2-metil-tiazol (8.50 gramos, 85.5 milimoles), trifenil-fosfina (3.6 gramos, 13.73 milimoles), carbonato de cesio (55.9 gramos, 171.6 milimoles), acetato de paladio (II) (3.01 gramos, 13.7 milimoles), y la mezcla se agita a 140°C durante 24 horas. La mezcla de reacción se filtra subsecuentemente a través de Celite 545, y se lava con K_2CO_3 saturado y EtOAc. El filtrado se diluye con EtOAc, y se lava con $NaHCO_3$ saturado, salmuera, y agua. La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar el producto crudo, el cual se purifica mediante cromatografía en gel de sílice (gradiente de éter/hexano), para dar el 5-bifenil-4-il-2-metil-tiazol.

Paso E: El 5-bifenil-4-il-2-metil-tiazol (1.0 gramos, 3.98 milimoles) se disuelve en cloroformo (100 mililitros), luego se agrega bromo (245 microlitros, 4.77 milimoles), y la mezcla se agita a temperatura ambiente durante 15 horas. Se agrega piridina (354.1 microlitros, 4.38 milimoles), y la solución se agita durante 4 horas a temperatura ambiente. La solución se diluye con CH_2Cl_2 (100 mililitros), y se lava con $NaHCO_3$ saturado (50 mililitros) y salmuera (30 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra para el producto crudo, el cual se purifica mediante cromatografía en gel de sílice con éter/hexano (gradiente), para dar el 5-bifenil-4-il-4-bromo-2-metil-tiazol como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.55-7.64 (m, 5H), 4.29-7.42 (m, 4H), 2.68 (s, 3H). MS calculada para $C_{16}H_{12}BrNS$ ($M+H^+$) 330.0, encontrada 330.0.

Paso F: La N-bromo-succinimida (504 miligramos, 2.83 milimoles) se agrega a una solución de 5-bifenil-4-il-4-bromo-2-metil-tiazol (850 miligramos, 2.57 milimoles) en tetracloruro de carbono (50 mililitros). La solución anterior se agita a 75°C durante 18 horas. La solución se diluye con CH_2Cl_2 (50 mililitros), y se lava con $NaHCO_3$ saturado (50 mililitros) y salmuera (30 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar el producto crudo, el cual se purifica mediante cromatografía en gel de sílice con hexano/éter (gradiente), para dar el 5-bifenil-4-il-4-bromo-2-bromo-metil-tiazol como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.55-7.66 (m, 5H), 4.30-7.45 (m, 4H), 4.65 (s, 2H). MS calculada para $C_{16}H_{12}Br_2NS$ ($M+H^+$) 410.1, encontrada 410.9.

Paso G: El intermediario 4 (169 miligramos, 0.86 milimoles), y Cs_2CO_3 (308 miligramos, 0.94 milimoles) se agregan a una solución de 5-bifenil-4-il-4-bromo--metil-tiazol (336 miligramos, 0.82 milimoles) en MeCN (30 mililitros). La mezcla se agita durante 3 horas a temperatura ambiente. Después, la mezcla se filtra, la solución orgánica se concentra y se purifica mediante cromatografía en gel de sílice con hexano/éter (gradiente), para dar el metil-éster del ácido [4-(5-bifenil-4-il-4-bromo-tiazol-2-ilmetoxi)-2-metil-fenoxi]-acético (56) como un sólido blanco. ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.60-7.72 (m, 5H), 7.35-7.47 (m, 4H), 6.85 (d, J = 2.8 Hz, 1H), 6.74 (dd, J = 2.8 Hz, J = 8.8 Hz, 1H), 6.65 (d, J = 8.8 Hz, 1H), 5.28 (s, 2H), 4.60 (s, 2H), 3.78 (s, 3H), 2.27 (s, 3H). MS calculada para $C_{26}H_{23}BrNO_4S$ ($M+H^+$) 525.0, encontrada 525.0.



Intermediario 57: Metil-éster del ácido {4-[4-bromo-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.

Paso A: Siguiendo el procedimiento del Intermediario 56, excepto que se utiliza 1-yodo-4-trifluoro-metoxi-benceno para sustituir al 4-yodo-bifenilo del Paso A, se prepara el 1-(2-etoxi-vinil)-4-trifluoro-metoxi-benceno como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.38 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 12.8 Hz, 1H), 5.98 (d, J = 13.2 Hz, 1H), 4.08 (q, J = 7.0 Hz, 2H), 1.50 (t, J = 7.0 Hz, 3H). MS calculada para $C_{11}H_{12}F_3O_2$ ($M+H^+$) 233.1, encontrada 233.1.

Paso B: Siguiendo el procedimiento del Intermediario 56, excepto que se utiliza 1-(2-etoxi-vinil)-4-trifluorometoxi-benceno para sustituir al 4-(2-etoxi-vinil)-bifenilo en el Paso B, se prepara el 1-(1-bromo-2,2-dietoxi-

etil)-4-trifluoro-metoxi-benceno como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.52 (d, J =8.8 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 4.95 (d, J = 6.4 Hz, 1H), 4.83 (d, J = 6.0 Hz, 1H), 3.84-3.77 (m, 1H), 3.71-3.61 (m, 2H), 3.50-3.43 (m, 1H), 1.29 (t, J = 7.0 Hz, 3H), 1.09 (t, J = 7.0 Hz, 3H). MS calculada para $C_{13}H_{16}BrF_3O_3$ (M^+) 356.0, encontrada 277.0 $(M-Br)^+$.

Paso C: Siguiendo el procedimiento del Intermediario 56, excepto que se utiliza 1-(1-bromo-2,2-dietoxi-etil)-trifluoro-metoxi-benceno para sustituir al 4-(1-bromo-2,2-dietoxi-etil)-bifenilo en el Paso C, se prepara el bromo-(4-trifluoro-metoxi-fenil)-acetaldehído como un sólido blanco sin purificación. MS calculada para $C_9H_6BrF_3O_2$ (M^+) 283.1, encontrada 203.1 $(M-Br)^+$.

Paso D: Siguiendo el procedimiento del Intermediario 56, excepto que se utiliza bromo-(4-trifluoro-metoxi-fenil)-acetaldehído para sustituir al bifenil-4-il-bromo-acetaldehído en el Paso D, se prepara el 2-metil-5-(4-trifluoro-metoxi-fenil)-tiazol como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.71 (s, 1H), 7.46 (m, 2H), 7.18 (m, 2H), 2.68 (s, 3H). MS calculada para $C_{11}H_8F_3NOS$ ($M+H^+$) 260.0, encontrada 260.0.

Paso D': Una reacción de acoplamiento alternativa de un paso para preparar el 2-metil-5-(4-trifluoro-metoxi-fenil)-tiazol.

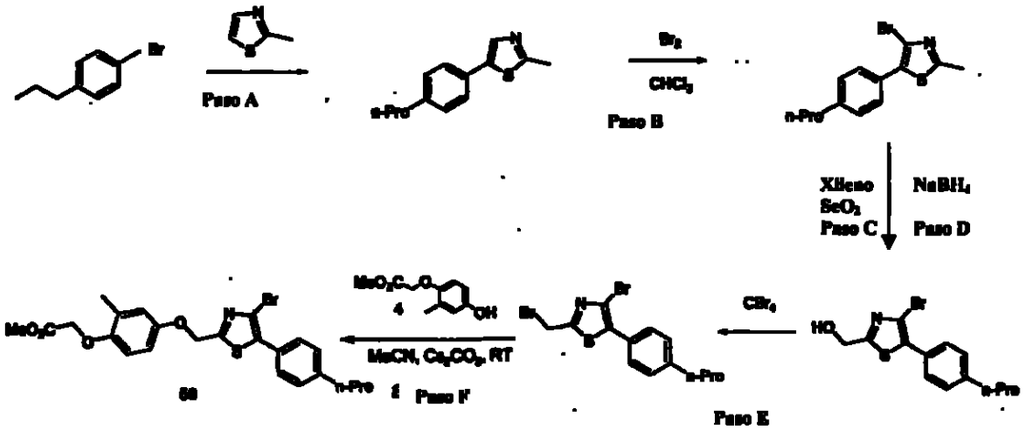
Siguiendo el procedimiento del Intermediario 56, excepto que se utiliza 1-yodo-4-trifluoro-metoxi-benceno para sustituir al 4-yodo-bifenilo en el Paso D', se obtiene el 2-metil-5-(4-trifluoro-metoxi-fenil)-tiazol.

Paso E: Siguiendo el procedimiento del Intermediario 56, excepto que se utiliza D-metil-5-(4-trifluoro-metoxi-fenil)-tiazol para sustituir al 5-bifenil-4-il-2-metil-tiazol, y sin agregar piridina en el Paso E, se prepara el

4-bromo-2-metil-5-(4-trifluoro-metoxi-fenil)-tiazol como un aceite incoloro: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.56 (m, 2H), 7.21 (m, 2H), 2.67 (s, 2H). MS calculada para $C_{11}H_8BrF_3NOS$ $(M+H^+)$ 337.9, encontrada 337.9.

Paso F: Siguiendo el procedimiento del Intermediario 56, excepto que se utiliza 4-bromo-2-metil-5-(4-trifluoro-metoxi-fenil)-tiazol para sustituir al 5-bifenil-4-il-4-bromo-2-metil-tiazol en el Paso F, se prepara el 4-bromo-2-bromometil-5-(4-trifluoro-metoxi-fenil)-tiazol como un aceite amarillo: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.59 (m, 2H), 7.23 (m, 2H), 4.63 (s, 2H). MS calculada para $C_{11}H_7Br_2F_3NOS$ $(M+2H)^+$ 416.9, encontrada 416.8.

Paso G: Siguiendo el procedimiento del Intermediario 56, excepto que se utiliza 4-bromo-2-bromo-metil-5-(4-trifluoro-metoxi-fenil)-tiazol para sustituir al 5-bromo-2-bromo-metil-4-(4-metoxi-fenil)-oxazol en el Paso G, se prepara el metil-éster del ácido {4-[4-bromo-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético (57) como un sólido blanco. ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.66 (m, 2H), 7.28 (m, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.74 (dd, J = 3.2 Hz, J = 8.8 Hz, 1H), 6.67 (d, J = 8.8 Hz, 2H), 5.28 (s, 2H), 4.61 (s, 2H), 3.80 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{21}H_{18}BrF_3NO_3S$ $(M+H^+)$ 532.0, encontrada 532.0.



Intermediario 58: Metil-éster del ácido {4-[4-bromo-5-(4-propil-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.

Paso A: El romo-4-propil-benceno (50.0 gramos, 251.1 milimoles) se disuelve en dimetilformamida (800 mililitros), luego se agregan 2-metil-tiazol (12.45 gramos, 125.6 milimoles), trifenil-fosfina (3.2 gramos, 12.56 milimoles), carbonato de cesio (81.2 gramos, 251.14 milimoles), acetato de paladio (II) (4.5 gramos, 20.09 milimoles), y la mezcla se agita a 140°C durante 24 horas. La mezcla de reacción se filtra a través de Celite 545, se lava con K_2CO_3 saturado y EtOAc. La solución se diluye con EtOAc, y se lava con $NaHCO_3$ saturado, salmuera, y agua. La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra para dar el producto crudo, el cual se purifica mediante cromatografía en gel de sílice con éter/hexano (gradiente), para dar el 2-metil-5-(4-propil-fenil)-tiazol como un aceite: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.83 (s, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 2.80 (s, 3H), 2.66 (t, J = 7.6 Hz, 2H), 1.71 (m, 2H), 1.02 (t, J = 7.2 Hz, 3H). MS calculada para $C_{13}H_{16}NS$ ($M+H^+$) 218.1, encontrada 218.1.

Paso B: El 2-metil-5-(4-propil-fenil)-tiazol (2.0 gramos, 9.20 milimoles) se disuelve en cloroformo (25 mililitros), luego se agrega bromo (0.52 mililitros, 10.12 milimoles), y la mezcla se agita a temperatura ambiente durante 2 horas. La solución se diluye con CH_2Cl_2, y se lava con $NaHCO_3$ saturado y salmuera (100 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar el producto crudo, el cual se purifica mediante cromatografía en gel de sílice con éter/hexano (gradiente), para dar el 4-bromo-2-metil-5-(4-propil-fenil)-tiazol como un aceite: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.52 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 2.71 (s, 3H), 2.62 (t, J = 7.4 Hz, 2H), 1.67 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H). MS calculada para $C_{13}H_{14}BrNS$ ($M+H^+$) 296.0, encontrada 296.0.

Pasos C y D: Se agrega dióxido de selenio (4.5 gramos, 40.51 milimoles) a una solución de 4-bromo-2-metil-5-(4-propil-fenil)-tiazol (6.0 gramos, 20.25 milimoles) en xileno (150 mililitros). La mezcla se agita a 150°C durante 30 horas. Después de 15 horas, se agregan 1.2 gramos adicionales de SeO_2 a la mezcla de reacción. Luego la solución se diluye con EtOAc, y se lava con Na_2CO_3 saturado y salmuera. La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar el 4-bromo-5-(4-propil-fenil)-tiazol-2-carbaldehído como un producto crudo, el cual se utiliza para la siguiente reacción.

Se agrega $NaBH_4$ (604 miligramos, 16.0 milimoles) a una solución del 4-bromo-5-(4-propil-fenil)-tiazol-2-carbaldehído crudo en MeOH (100 mililitros), y la mezcla se agita durante 10 minutos. La solución se concentra, se diluye con EtOAc, se lava con Na_2CO_3 saturado, y salmuera.

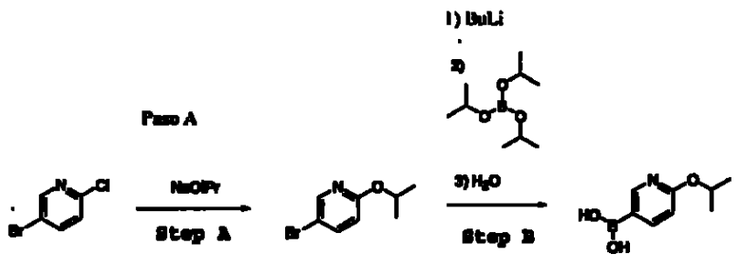
La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar una mezcla cruda, la cual se purifica mediante cromatografía en gel de sílice con hexano/EtOAc (gradiente), para dar el [4-bromo-5-(4-propil-fenil)-tiazol-2-il]-metanol como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.37 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 4.79 (s, 2H), 2.47 (t, J = 8.0 Hz, 2H), 2.17 (s, bro. 1H), 1.51 (m, 2H), 0.81 (t, J = 6.4 Hz, 3H). MS calculada para $C_{13}H_{16}BrNOS$ ($M+H^+$) 312.0, encontrada 312.0.

Paso E: Se agrega $P(Ph)_3$ (2.22 gramos, 8.46 milimoles) a la solución de [4-bromo-5-(4-propil-fenil)-tiazol-2-il]-metanol en CH_2Cl_2 (40 mililitros), y se agita durante 10 minutos a 0°C. Luego se agrega CBr_4 (2.81 gramos, 8.46 milimoles) disuelto en CH_2Cl_2 (20 mililitros) a la mezcla de reacción. La mezcla se calienta a temperatura ambiente y se agita durante la noche. La solución se concentra para dar una mezcla cruda, la cual se purifica mediante cromatografía en gel de sílice con hexano/éter (gradiente), para dar el 4-bromo-2-bromo-metil-5-(4-propil-fenil)-tiazol como un aceite incoloro: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.37 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 4.52 (s, 2H), 2.46 (t, J = 8.0 Hz, 2H), 1.49 (m, 2H), 0.80 (T, J = 8.0 Hz, 3H). MS calculada para $C_{13}H_{14}Br_2NO$ ($M+H^+$) 373.9, encontrada 373.9.

Paso F: Una mezcla del 4-bromo-2-bromo-metil-5-(4-propil-fenil)-tiazol (910 miligramos, 2.43 milimoles), metil-éster del ácido (4-hidroxi-2-metil-fenoxi)-acético (4) (524 miligramos, 2.67 milimoles), y Cs_2CO_3 (911 miligramos, 2.79 milimoles) en MeCN (15 mililitros), se agita a temperatura ambiente durante 4 horas. La mezcla se filtra, luego se concentra para dar el producto crudo, el cual se purifica mediante cromatografía en gel de

silice con EtOAc/hexano (gradiente), para dar el metil-éster del ácido {4-[4-bromo-5-(4-propil-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético (58) como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.54 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.74 (m, 1H), 6.65 (m, 1H), 5.27 (s, 2H), 4.61 (s, 2H), 3.80 (s, 3H), 2.65 (t, J=8.0 Hz, 3H), 2.29 (s, 3H), 1.67 (m, 2H), 0.97 (t, J = 8.0 Hz, 3H). MS calculada para $C_{23}H_{26}BrNO_4S$ ($M+H^+$) 490.1, encontrada 490.1.

Intermediario 59: Ácido 2-isopropoxi-5-piridin-borónico.

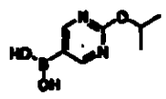


Paso A: Se suspende NaH (5.2 gramos, 130 milimoles) en isopropanol (50 mililitros). La mezcla se agita durante 30 minutos a 60°C. Después de que cesa el desprendimiento de gas, se agrega 2-cloro-5-bromo-piridina (10.0 gramos, 52 milimoles) disuelta en isopropanol (100 mililitros), y la mezcla se calienta a reflujo durante 24 horas. El solvente se remueve al vacío, y el resto se recupera en H_2O, y se extrae con EtOAc. La capa orgánica se separa y se seca sobre $MgSO_4$, se filtra, y se concentra, para proporcionar la 2-isopropoxi-5-bromo-piridina como un aceite castaño claro: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 8.10 (d, J = 2.5 Hz, 1H), 7.54 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.52 (d, J = 8.8 Hz, 1H), 5.17 (m, 1H), 1.26 (d, J = 6.2 Hz, 6H). MS calculada para $C_8H_{11}BrNO$ ($M+H^+$)

216.0, encontrada 215.9.

Paso B: La 2-isopropoxi-5-bromo-piridina (0.65 gramos, 3 milimoles) se disuelve en éter seco (10 mililitros), y se enfría a -78°C bajo argón. Se agrega por goteo butil-litio (1.6 M en hexano, 2.81 mililitros, 4.5 milimoles), y la mezcla se agita a -78°C durante 2 horas. Luego se agrega rápidamente borato de tri-isopropilo (1.72 mililitros, 7.5 milimoles), y la mezcla se agita durante otras 2 horas a -78°C. La mezcla se deja calentar a temperatura ambiente, se apaga con H_2O (20 mililitros), y se agita durante la noche a temperatura ambiente. El éter se remueve al vacío, la capa acuosa se ajusta a un pH de 10 (con NaOH 2M), y se lava con éter. Luego se ajusta la capa acuosa a un pH de 3 (con HBr acuoso al 48 por ciento), y se extrae con EtOAc tres veces. La capa orgánica se separa y se seca sobre $MgSO_4$, se filtra, y se concentra, para proporcionar el ácido 2-isopropoxi-5-piridin-borónico 59 como un cristal incoloro: MS calculada para $C_8H_{13}BNO_3$ ($M+H^+$) 182.1, encontrada 182.1.

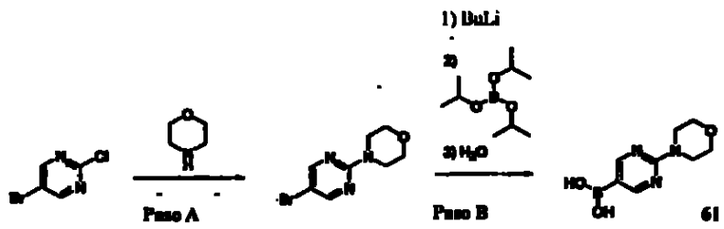
Intermediario 60. Ácido 2-isopropoxi-5-pirimidin-borónico.



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Siguiendo el procedimiento del Intermediario 59, excepto que se utiliza 2-cloro-5-bromo-pirimidina para sustituir a la 2-cloro-5-bromo-piridina del Paso A, se prepara el compuesto del título como un sólido blanco: MS calculada para $C_7H_{12}BN_2O_3$ ($M+H^+$) 183.1, encontrada 183.1.

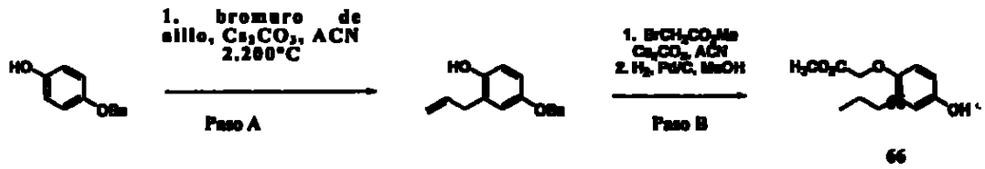
Intermediario 61: Ácido 2-morfolino-5-pirimidin-borónico.



Paso A: Se disuelve morfolina (5.4 mililitros, 62.4 milimoles) en MeCN (250 mililitros). Se agrega K_2CO_3 (8.6 gramos, 62.4 milimoles), y la mezcla se agita a temperatura ambiente durante 1 hora. Luego se agrega 2-cloro-5-bromo-pirimidina (2.0 gramos, 52 milimoles), y la mezcla se calienta a reflujo durante 5 horas. El solvente se mueve parcialmente al vacío, y el resto se recupera en H_2O, y se extrae con EtOAc. La capa orgánica se separa y se seca sobre $MgSO_4$, se filtra, y se concentra, para proporcionar la 2-isopropoxi-5-bromo-pirimidina como un aceite castaño claro: : ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 8.24 (s, 2H), 3.69 (m, 8H). MS calculada para $C_8H_{11}BrN_3O$ ($M+H^+$) 244.0, encontrado 243.9.

Paso B: Siguiendo el procedimiento del Intermediario 59, Paso B, excepto que se utiliza la 2-isopropoxi-5-bromo-pirimidina para sustituir a la 2-isopropoxi-5-bromo-piridina, se prepara el compuesto del título como un sólido blanco: MS calculada para $C_8H_{13}BN_3O_3$ ($M+H^+$) 210.1, encontrada 210.1.

Intermediario 66: Metil-éster del ácido (4-hidroxi-2-propil-fenoxi)-acético.



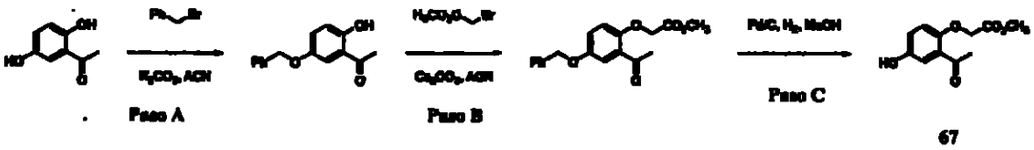
Paso A: Se disuelve 4-benciloxi-fenol (5.0 gramos, 25 milimoles) en

acetonitrilo (70 mililitros). Se agrega carbonato de cesio en polvo (10.50 gramos, 32.2 milimoles) con agitación, seguido por bromuro de alilo (2.25 mililitros, 26.6 milimoles). La mezcla se agita vigorosamente durante la noche. La filtración a través de un tapón de Celite 545, y lavado de los sólidos con más acetonitrilo, el secado de la solución sobre Na_2SO_4, y la concentración, produjeron el alil-éter como un sólido blanco. El éter (1.83 gramos, 7.62 milimoles) se calienta bajo nitrógeno en un frasco sellado, a 200°C. Después de aproximadamente 4.5 horas, la mezcla se enfría para dar un aceite castaño claro: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.42 (m, 2H), 7.38 (m, 2H), 7.32 (m, 1H), 6.78 (s, 1H), 6.75 (s, 2H), 6.00 (dddd, 1H), 5.18 (m, 1H), 5.14 (m, 1H), 5.00 (s, 1H), 4.62 (br. s, 1H), 3.38 (d, J = 6.0 Hz, 2H).

Paso B: El 2-alil-4-benciloxi-fenol (0.30 gramos, 1.25 milimoles) se disuelve en acetonitrilo seco (3 mililitros). Se agrega carbonato de cesio en polvo (0.68 gramos, 2.1 milimoles) con agitación vigorosa, seguido por bromoacetato de metilo (0.15 mililitros, 1.6 milimoles). La suspensión se agita a temperatura ambiente durante la noche. La dilución con HCl acuoso 1N, la extracción con acetato de etilo, el secado sobre $MgSO_4$, y la concentración, producen un aceite. Una porción de este producto (0.075 gramos, 0.24 milimoles) se disuelve en metanol (5 mililitros) y acetato de etilo (30 mililitros). Se agrega negro de paladio sobre carbono (5 por ciento, 10 miligramos, 2 por ciento molar). La mezcla se desgasifica y se agita vigorosamente bajo una atmósfera de hidrógeno durante la noche. La filtración y la concentración producen el fenol 66: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 6.66 (d, J = 2.8 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 6.57 (dd, J =

2.8, 8.4 Hz, 1H), 4.58 (s, 2H), 4.48 (s, 1H), 3.79 (s, 3H), 2.60 (t, J = 7.6 Hz, 2H), 1.61 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H). MS calculada para $C_{12}H_{17}O_4$ ($M+H^+$) 225.1, encontrada 225.1.

Intermediario 67: Metil-éster del ácido (2-acetil-4-hidroxi-fenoxi)-acético.



Paso A Paso B Paso C 67

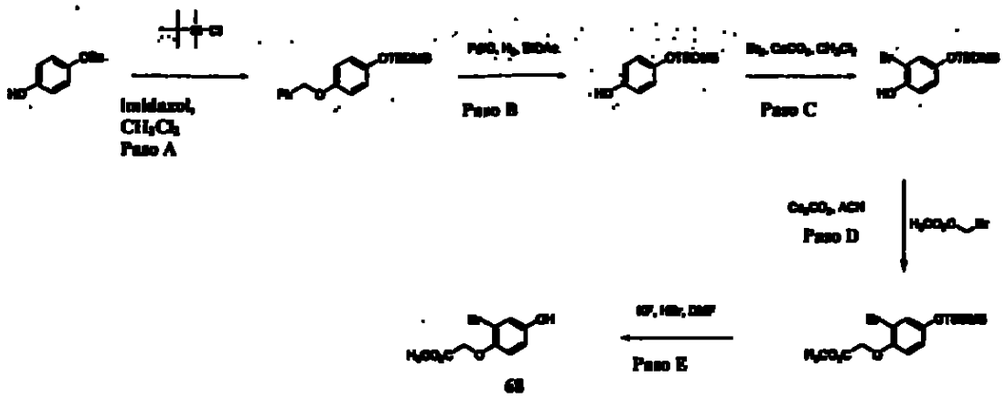
Paso A: Se disuelve 1-(2,5-dihidroxi-fenil)-etanona (5.0 gramos, 33 milimoles) en 30 mililitros de acetonitrilo. Se agrega carbonato de potasio en polvo (7.10 gramos, 51.4 milimoles) con agitación, seguido por la adición por goteo de bromuro de bencilo (4.0 mililitros, 33.4 milimoles). La suspensión resultante se agita a temperatura ambiente bajo nitrógeno durante la noche, luego se filtra a través de un tapón de Celite 545, y se concentra, para dar un aceite castaño claro. La cromatografía en gel de sílice (hexano hasta acetato de etilo al 30 por ciento en hexano) produjo el bencil-éter puro como un aceite casi incoloro: ^{1}H-RMN (400 MHz, DMSO-d_6) δ = 11.50 (s, 1H), 7.35 (m, 6H), 7.25 (dd, J = 3.1, 9.0 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 5.10 (s, 2H), 2.63 (s, 3H); MS calculada para $C_{15}H_{15}O_3$ ($M+H^+$) 243.2, encontrada 243.1.

Paso B: La 1-(5-benciloxi-2-hidroxi-fenil)-etanona (7.27 gramos, 29.4 milimoles) se disuelve en acetonitrilo (100 mililitros). Se agrega carbonato de cesio en polvo (14.36 gramos, 44.1 milimoles) con agitación, seguido por bromoacetato de metilo (3.5 mililitros, 38 milimoles). La suspensión resultante se agita a 80°C bajo nitrógeno durante 3 horas. Se filtra a través

de un tapón de Celite 454, y se concentra, para dar el metil-éster del ácido (2-acetil-4-benciloxi-fenoxi)-acético como un aceite casi incoloro que se solidifica lentamente: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.36 (m, 6H), 7.25 (dd, J = 3.2, 9.0 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 5.04 (s, 2H), 4.69 (s, 2H), 3.80 (s, 3H), 2.71 (s, 3H), MS calculada para $C_{18}H_{19}O_5$ ($M+H^+$) 315.2, encontrada 315.1.

Paso C: El metil-éster del ácido (2-acetil-4-benciloxi-fenoxi)-acético (9.17 gramos, 29.2 milimoles) se disuelve en metanol (50 mililitros) y acetato de etilo (50 mililitros). Se agrega negro de paladio sobre carbono (5 por ciento, 1.53 gramos, 2.4 por ciento molar). La mezcla se desgasifica y se agita vigorosamente bajo una atmósfera de hidrógeno durante la noche. La filtración y la concentración producen el fenol 67: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.32 (d, J = 3.2 Hz, 1H), 6.97 (dd, J = 3.2, 8.9 Hz, 1H), 6.74 (d, J = 8.9 Hz, 1H), 4.68 (s, 2H), 3.81 (s, 3H), 2.71 (s, 3H). MS calculada para $C_{11}H_{13}O_5$ ($M+H^+$) 225.1, encontrada 225.1.

Intermediario 68: Metil-éster del ácido (2-bromo-4-hidroxi-fenoxi)-acético.



Paso A: El 4-benciloxi-fenol (5.01 gramos, 25.0 milimoles) se

suspende en 65 mililitros de diclorometano. Se agrega imidazol sólido (4.05 gramos, 26.9 milimoles), y la agitación se continúa hasta que la mezcla se hace homogénea. Se agrega terbutil-cloro-dimetil-silano (2.49 gramos, 36.6 milimoles) en porciones, y se empieza a formar un precipitado blanco. La suspensión se agita a temperatura ambiente durante la noche. Luego se filtra y se concentra para dar el (4-benciloxi-fenoxi)-terbutil-dimetil-silano como un polvo blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.43 (m, 2H), 7.38 (m, 2H), 7.32 (m, 1H), 6.85 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 9.,0 Hz, 2H), 0.98 (s, 9H), 0.17 (s, 6H); MS calculada para $C_{19}H_{27}O_2Si$ ($M+H^+$) 315.2, encontrada 315.1.

Paso B: El (4-benciloxi-fenoxi)-terbutil-dimetil-silano (7.73 gramos, 24.6 milimoles) se disuelve en metanol (10 mililitros) y acetato de etilo (80 mililitros). Se agrega negro de paladio sobre carbón (5 por ciento, 0.6 gramos, 1 por ciento molar), y la mezcla se agita vigorosamente bajo hidrógeno a temperatura ambiente 48 horas. La filtración y la concentración produjeron el 4-(terbutil-dimetil-silaniloxi)-fenol: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 6.70 (s, 4H), 3.90 (br. s, 1H), 0.97 (s, 9H), 0.16 (s, 6H). MS calculada para $C_{12}H_{12}O_2Si$ ($M+H^+$) 225.1, encontrada 225.0.

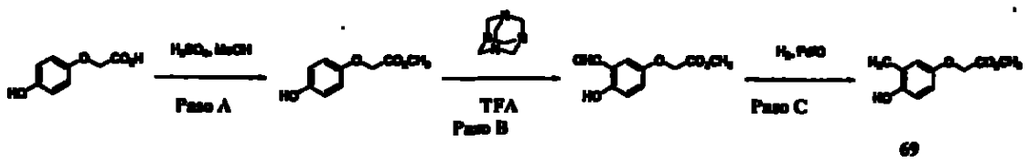
Paso C: El 4-(terbutil-dimetil-silaniloxi)-fenol (4.66 gramos, 20.8 milimoles) se disuelve en diclorometano (100 mililitros). Se suspende carbonato de calcio en polvo (4.61 gramos, 46.7 milimoles) en la solución, y la mezcla se agita vigorosamente a 0°C. Se agrega por goteo bromo (1.10 millilitros, 21.4 milimoles) con agitación vigorosa. Después de 1.5 horas a 0°C, la mezcla se calienta a temperatura ambiente, se trata con $MgSO_4$ anhidro, se filtra, y se concentra, para dar el 2-bromo-4-(terbutil-

dimetil-silaniloxi)-fenol como un aceite que se solidifica lentamente: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 6.96 (d, J = 2.8 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.71 (dd, J = 2.8, 8.8 Hz, 1H), 5.14 (br. s, 1H), 0.97 (s, 9H), 0.17 (s, 6H). MS calculada para $C_{12}H_{20}BrO_2Si$ (M+H$^+$) 303.1, encontrada 303.0.

Paso D: El 2-bromo-4-(terbutil-dimetil-silaniloxi)-fenol (5.19 gramos, 17 milimoles) se disuelve en acetonitrilo (100 mililitros). Se agrega carbonato de cesio (14.10 gramos, 43 milimoles), seguido por bromoacetato de metilo (1.60 mililitros, 17.4 milimoles); la mezcla se agita durante la noche a temperatura ambiente. La filtración y la concentración producen el metil-éster del ácido [2-bromo-4-(terbutil-dimetil-silaniloxi)-fenoxi]-acético como un aceite: MS calculada paras $C_{15}H_{24}BrO_4Si$ (M+H$^+$) 375.2, encontrada 375.1.

Paso E: El metil-éster del ácido [2-bromo-4-(terbutil-dimetil-silaniloxi)-fenoxi]-acético (6.19 gramos, 16.5 milimoles) se disuelve en dimetil-formamida (80 mililitros). Se agrega fluoruro de potasio en polvo (2.10 gramos, 36 milimoles), seguido por una solución acuosa concentrada de bromuro de hidrógeno (48 por ciento, 1.0 mililitros, 5.9 milimoles). La mezcla se agita durante la noche a temperatura ambiente. La dilución con agua, la extracción con diclorometano (100 mililitros, 4 veces), seguida por secado sobre Na_2so_4, la filtración y la concentración, producen un aceite; el secado durante la noche a baja presión produce el metil-éster del ácido (2-bromo-4-hidroxi-fenoxi)-acético 68 como un sólido: MS calculada para $C_9H_{10}BrO_4$ (M+H$^+$) 261.0, encontrada 260.9.

Intermediario 69: Metil-éster del ácido (4-hidroxi-3-metil-fenoxi)-acético.



69

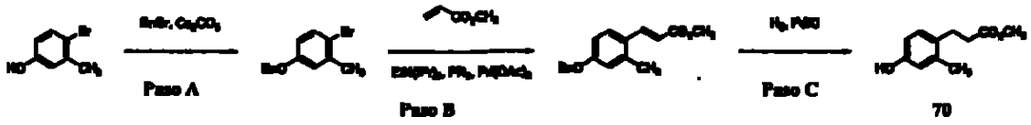
Paso A: El ácido (4-hidroxi-fenoxi)-acético (14.96 gramos, 89 milimoles) se suspende en metanol (35 mililitros). Se agrega ácido sulfúrico concentrado (0.25 mililitros, cat.), y la mezcla se pone a reflujo durante la noche. El enfriamiento a temperatura ambiente y la concentración a sequedad producen el metil-éster del ácido (4-hidroxi-fenoxi)-acético como un sólido (16 gramos, cuantitativo). ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 6.78 (m, 4H), 4.81 (s, 1H), 4.58 (s, 2H), 3.80 (s, 3H).

Paso B: El metil-éster del ácido (4-hidroxi-fenoxi)-acético (4.25 gramos, 23.3 milimoles) se disuelve en ácido trifluoro-acético (25 mililitros). Se agrega hexametilen-tetramina (5.11 gramos, 36.5 milimoles). La mezcla homogénea resultante se agita a 70°C durante 3 horas. El enfriamiento a temperatura ambiente y la concentración a sequedad producen una pasta. La cromatografía en gel de sílice (10 por ciento a 60 por ciento de acetato de etilo en hexanos) producen el metil-éster del ácido (3-formil-4-hidroxi-fenoxi)-acético: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 10.70 (s, 1H), 9.84 (s, 1H), 7.20 (dd, J = 3.2, 9.2 Hz, 1H), 7.03 (d, J = 3.2 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 4.64 (s, 2H), 3.82 (s, 3H); MS calculada para $C_9H_{10}BrO_4$ ($M+H^+$) 261.0, encontrada 260.9.

Paso C: Metil-éster del ácido (3-formil-4-hidroxi-fenoxi)-acético (0.26 gramos, 1.24 milimoles) se disuelve en metanol (15 mililitros). Se agrega negro de paladio sobre carbón (10 miligramos, 0.4 por ciento molar), y la

mezcla se agita durante la noche bajo hidrógeno (1 atmósfera). La purificación en HPLC de fase inversa produce el metil-éster del ácido (4-hidroxi-3-metil-fenoxi)-acético 69 como un aceite: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 6.8 (m, 3H), 4.93 (s, 1H), 4.69 (s, 2H), 3.93 (s, 3H), 2.35 (s, 3H).

Intermediario 70: Metil-éster del ácido 3-(4-hidroxi-2-metil-fenil)-propiónico.



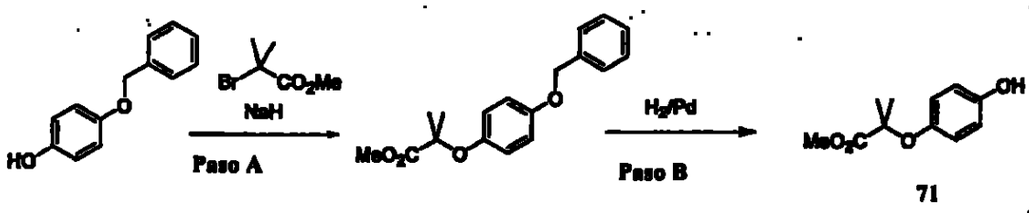
Paso A: El 4-bromo-3-metil-fenol (13.71 gramos, 73.3 milimoles) se disuelve en acetonitrilo (100 mililitros). Se agregan carbonato de cesio (30.46 gramos, 93.5 milimoles) y bromuro de bencilo (10 mililitros, 84.2 milimoles), y la mezcla se agita durante la noche a temperatura ambiente. La filtración y la concentración a sequedad producen el 4-benciloxi-1-bromo-2-metil-benceno como un sólido (23.5 gramos, cuantitativo). ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.4 (m, 6H), 6.87 (d, J = 3.2 Hz, 1H), 6.68 (dd, J = 3.2, 8.8 Hz, 1H), 5.03 (s, 2H), 2.36 (s, 3H); no se pudo obtener el espectro de masas.

Paso B: El 4-benciloxi-1-bromo-2-metil-benceno (9.29 gramos, 33.5 milimoles) se disuelve en propionitrilo (80 mililitros). Se agregan etil-di-isopropil-amina (12 mililitros, 72.6 milimoles), y acrilato de metilo (12 mililitros, 133 milimoles). La mezcla se desgasifica con argón, y se agregan tri-orto-tolil-fosfina (4.11 gramos, 20.1 milimoles) y acetato de paladio (1.53 gramos, 6.8 milimoles). La mezcla se calienta a 100°C durante la noche. El enfriamiento a temperatura ambiente y la

concentración a sequedad producen una pasta. El residuo se recupera en acetato de etilo, y se lava con agua y salmuera, se seca sobre $MgSO_4$, y se concentra. La cromatografía en gel de sílice (0 por ciento a 60 por ciento de acetato de etilo en hexanos), produce el metil-éster del ácido 3-(4-benciloxi-2-metil-fenil)-acrílico: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.92 (d, J = 15.6 Hz, 1H), 7.52 (d, J = 9.6 Hz, 1H), 7.4 (m, 5H), 7.68 (m, 2H), 6.26 (d, J = 5.6 Hz, 1H), 5.08 (s, 2H), 3.80 (s, 3H), 2.42 (s, 3H); MS calculada para $C_{18}H_{18}O_3$ ($M+H^+$) 283.1, encontrada 283.1.

Paso C: El metil-éster del ácido 3-(4-benciloxi-2-metil-fenil)-acrílico (4.83 gramos, 17 milimoles) se disuelve en metanol (85 mililitros), y acetato de etilo (25 mililitros). Se agrega negro de paladio sobre carbón (5 por ciento, 0.51 gramos, 1.4 por ciento molar), y la mezcla se agita bajo hidrógeno durante 36 horas. La concentración produce el metil-éster del ácido 3-(4-hidroxi-2-metil-fenil)-propiónico 70 como un aceite: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 6.98 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 2.8 Hz, 1H), 6.60 (dd, J = 2.8, 8.4 Hz, 1H), 3.68 (s, 3H), 2.87 (t, J = 7.6 Hz, 2H), 2.55 (t, J = 7.6 Hz, 2H), 2.26 (s, 3H).

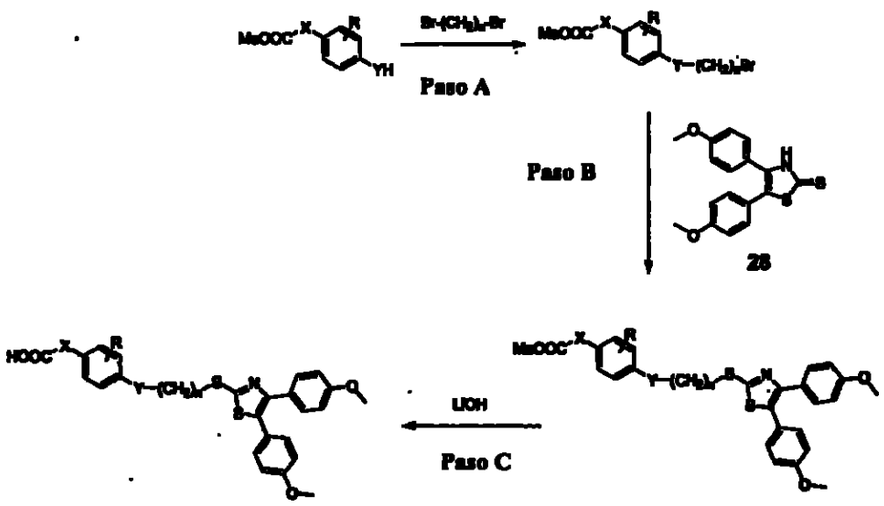
Intermediario 71: Metil-éster del ácido 2-(4-hidroxi-fenoxi)-2-metil-propiónico.



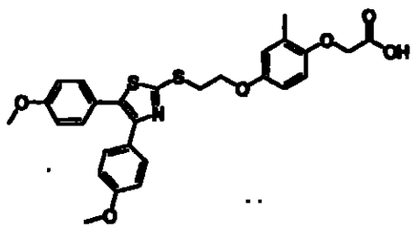
Paso A: El 4-(benciloxi)-fenol (5.0 gramos, 25 milimoles) se disuelve

en dimetil-formamida (40 mililitros). A la solución se le agrega NaH (dispersión al 60 por ciento, 1.1 gramos, 27.5 milimoles) en porciones, mientras que la temperatura se mantiene a la temperatura ambiente. Después de agitar la suspensión durante 30 minutos a temperatura ambiente, se agrega por goteo α-bromo-isobutirato de metilo (9.05 gramos, 50 milimoles). La mezcla se agita a 50°C durante 3 horas, luego se concentra. El resto se diluye con agua (200 mililitros), y se extrae con EtOAc (150 mililitros, 3 veces). La capa orgánica se separa y se seca sobre $MgSO_4$, se filtra, y se concentra. El producto crudo se purifica mediante cromatografía por evaporación (sílice, gradiente de Hex/EtOAc), para proporcionar el metil-éster del ácido 2-(4-benciloxi-fenoxi)-2-metil-propiónico como un aceite transparente: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.44-7.33 (m, 5H), 6.85 (m, 4H), 5.01 (s, 2H), 3.78 (s, 3H), 1.55 (s, 6H). MS calculada para $C_{18}H_{21}O_4$ ($M+H^+$) 301.1, encontrada 301.4.

Paso B: El metil-éster del ácido 2-(4-benciloxi-fenoxi)-2-metil-propiónico (0.5 gramos, 1.7 milimoles) se disuelve en EtOH (15 mililitros). Después de la adición de una cantidad catalítica de paladio (0) sobre carbón, la mezcla se somete a una atmósfera de hidrógeno, y se agita durante 5 horas a temperatura ambiente. Luego la mezcla se filtra a través de Celite, el solvente se remueve, y el resto se seca a un alto vacío, para dar el metil-éster del ácido 2-(4-hidroxi-fenoxi)-2-metil-propiónico 71 como un aceite castaño: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 6.76 (d, J = 9.0 Hz, 9H), 6.69 (d, J = 9.0 Hz, 2H), 3.78 (s, 3H), 1.53 (s, 6H). MS calculada para $C_{11}H_{15}O_4$ ($M+H^+$) 211.1, encontrada 211.3.



Ejemplo A1. Ácido (4-{2-[4,5-bis-(4-metoxi-fenil)-tiazol-2-ilsulfanil]-etoxi}-2-metil-fenoxi)-acético.

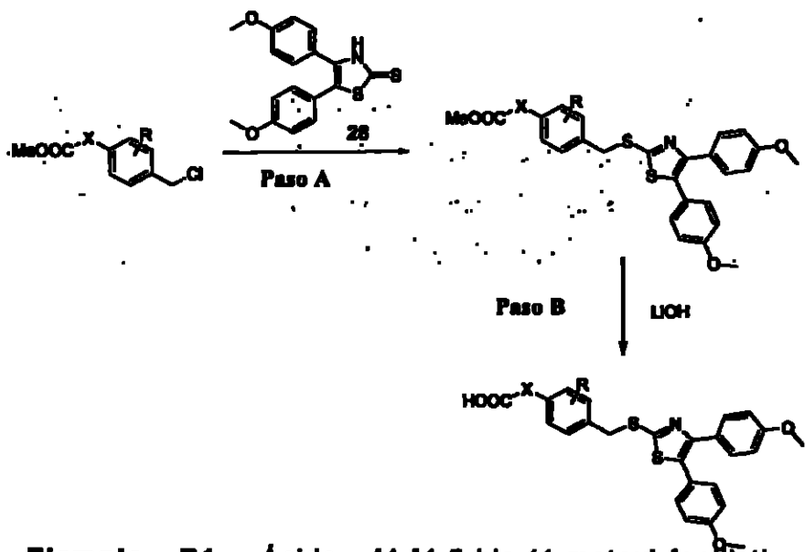


Paso A: El Intermediario 4 (0.5 gramos, 2.8 milimoles), 1,2-dibromoetano (2.4 mililitros, 27.7 milimoles), y Cs_2CO_3 (4.5 gramos, 13.9 milimoles), se suspenden en acetona seca. La mezcla se calienta a reflujo durante la noche. La mezcla de reacción se enfría a temperatura ambiente, se filtra, y el solvente se remueve al vacío. El resto se purifica mediante cromatografía (sílice, gradiente de DCM/MeOH), para proporcionar el metil-éster del ácido [4-(2-bromo-etoxi)-2-metil-fenoxi]-acético como un

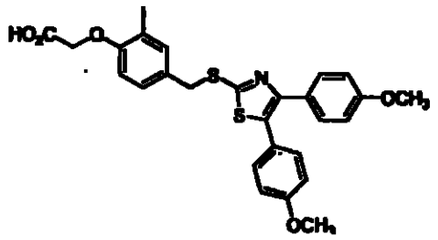
sólido blanco: MS calculada para $C_{11}H_{14}BrO_4$ ($M+H^+$) 303.0, encontrada 303.2.

Paso B: El metil-éster del ácido [4-(2-bromo-etoxi)-2-metil-fenoxi]-acético (91 miligramos, 0.30 milimoles) se agrega por goteo a una solución de NaOMe (23 miligramos, 0.33 milimoles) y el intermediario 28 en EtOH (5 mililitros). Después de agitar a temperatura ambiente durante 24 horas, el solvente se remueve para proporcionar el metil-éster del ácido (4-{2-[4,5-bis-(4-metoxi-fenil)-tiazol-2-ilsulfanil]-etoxi}-2-metil-fenoxi)-acético crudo.

Paso C: El metil-éster del ácido (4-{2-[4,5-bis-(4-metoxi-fenil)-tiazol-2-ilsulfanil]-etoxi}-2-metil-fenoxi)-acético crudo se disuelve en tetrahidrofurano (3 mililitros), se agrega una solución de LiOH 1M en H_2O (0.6 mililitros), y la mezcla se agita durante la noche a temperatura ambiente. La mezcla se acidifica con HCl 1M, se agrega EtOAc (10 mililitros), y la capa orgánica se lava con H_2O (5 mililitros, 3 veces). La capa orgánica se seca ($MgSO_4$), se filtra, se concentra, y se purifica sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar el compuesto del título A1 como un sólido blanco: ^{1}H-RMN (400 MHz, CD_3OD) δ = 7.34 (d, J = 8.9 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.73-6.64 (m, 3H), 4.56 (s, 2H), 4.29 (t, J = 6.4 Hz), 3.79 (s, 3H), 3.78 (s, 3H), 3.57 (t, J = 6.4 Hz, 2H), 2.18 (s, 3H). MS calculada para $C_{28}H_{28}NO_6S_2$ ($M+H^+$) 538.1, encontrada 538.4.



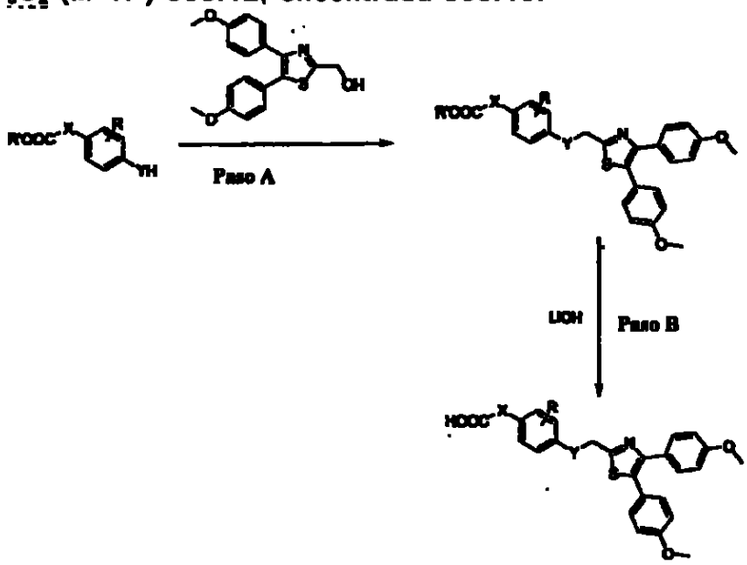
Ejemplo B1. Ácido {4-[4,5-bis-(4-metoxi-fenil)-tiazol-2-ilsulfanil-metil]-2-metil-fenoxi}-acético.



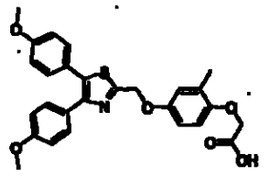
Paso A: Se disuelve NaOEt (23 miligramos, 0.33 milimoles) en EtOH absoluto (5 mililitros). Se agregan sucesivamente 4,5-bis-(4-metoxi-fenil)-3H-tiazol-2-tiona 28 (73 miligramos, 0.30 milimoles) y etil-éster del ácido (4-cloro-metil-2-metil-fenoxi)-acético (Intermediario 11) (100 miligramos, 0.30 milimoles). La reacción se agita durante 12 horas a temperatura ambiente para proporcionar el producto crudo.

Paso B: Se agrega LiOH 2N (3.0 mililitros) a la mezcla de reacción del Paso A, y se agita durante 3 horas a 60°C. La reacción se enfría a temperatura ambiente, y se acidifica a un pH de 2 a 3 con HCl 2N. Luego se extrae con CH_2Cl_2. La capa orgánica se separa, se seca ($MgSO_4$), y se

concentra. El producto se recristaliza en acetato de etilo y hexano, para proporcionar el compuesto del título B1 como un sólido ligeramente amarillo: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.44 (d, J = 8.8 Hz, 2H), 7.24-7.18 (m, 4H), 6.86-6.80 (m, 4H), 6.66 (d, J = 8.4 Hz, 1H), 5.30 (s, 2H), 4.67 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 2.27 (s, 3H). MS calculada para $C_{27}H_{26}NO_5S_2$ ($M+H^+$) 508.12, encontrada 508.10.



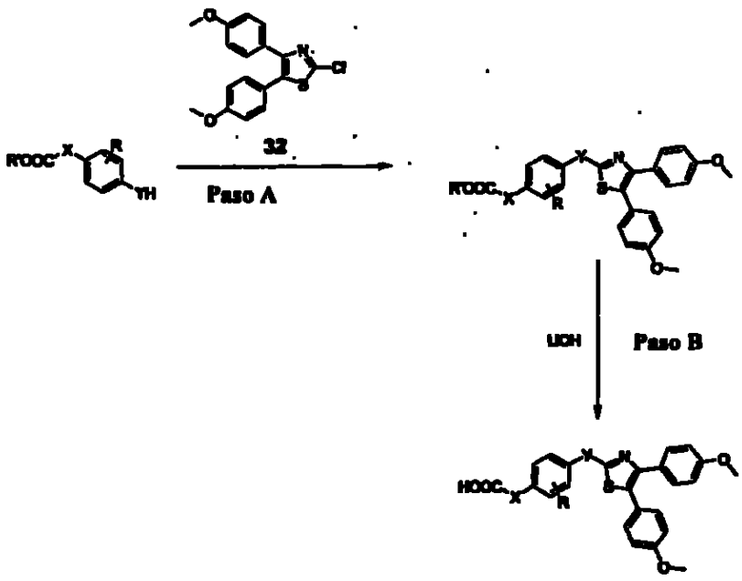
Ejemplo C1. Ácido {4-[4,5-bis-(4-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.



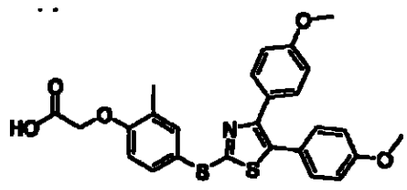
Paso A: El intermediario 30 (25 miligramos, 0.08 milimoles), el intermediario 4 (18 miligramos, 0.09 milimoles), y trifenil-fosfina (30 miligramos, 0.11 milimoles) se disuelven en DCM seco (1 mililitro), y se enfrían a 0°C. Después de la adición lenta de azodicarboxilato de dietilo (24 microlitros, 0.15 milimoles), la solución se agita a temperatura

ambiente durante la noche. El solvente se remueve para proporcionar el metil-éster del ácido {4-[4,5-bis-(4-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético crudo, el cual se utiliza sin mayor purificación en el Paso B.

Paso B: El metil-éster del ácido {4-[4,5-bis-(4-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético crudo, se disuelve en tetrahidrofurano (1 mililitros), se agrega una solución de LIOH en H_2O (0.2 mililitros), y la mezcla se agita durante la noche a temperatura ambiente. La mezcla se acidifica con HCl 1M (0.25 mililitros), se agrega EtOAc (10 mililitros), y la capa orgánica se lava con H_2O (5 mililitros, 3 veces). La capa orgánica ($MgSO_4$), se filtra, se concentra, y se purifica sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar el compuesto del título C1 como un cristal incoloro: ^{1}H-RMN (400 MHz, CD_3OD) δ = 7.36 (d, J = 8.9 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 6.91-6.75 (m, 7H), 5.30 (s, 2H), 4.62 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 2.25 (s, 3H). MS calculada para $C_{27}H_{26}NO_6S$ ($M+H^+$) 492.1, encontrada 492.4.

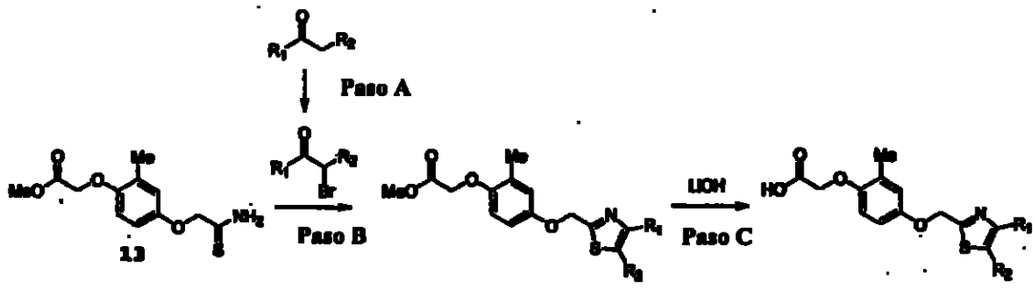


Ejemplo D1: Ácido {4-[4,5-bis-(4-metoxi-fenil)-tiazol-2-ilsulfanil]-2-metil-fenoxi}-acético.

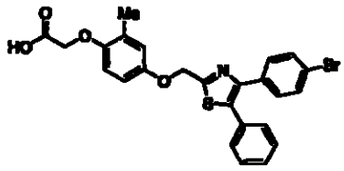


Paso A: El Intermediario 10 (28 miligramos, 0.131 milimoles), el Intermediario 32 (40 miligramos, 0.131 milimoles), y NaOEt (18 miligramos, 0.262 milimoles) se disuelven en EtOH (1 mililitros), y se calientan a reflujo durante 6 horas. La mezcla se acidifica con HCl 1N acuoso (1 mililitro), y se extrae con EtOAc (4 mililitros, 2 veces). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para proporcionar el etil-éster del ácido {4-[4,5-bis-(4-metoxi-fenil)-tiazol-2-ilsulfanil]-2-metil-fenoxi}-acético.

Paso B: El etil-éster del ácido {4-[4,5-bis-(4-metoxi-fenil)-tiazol-2-ilsulfanil]-2-metil-fenoxi}-acético se disuelve entonces en tetrahidrofurano (1 mililitros), y se trata con LiOH 1N (200 microlitros), y se agita a temperatura ambiente durante 2 horas. La mezcla se acidifica con HCl acuoso (1N, 300 microlitros), se extrae con EtOH (4 mililitros, 2 veces), se seca ($MgSO_4$), se filtra, se concentra, y se purifica sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar el compuesto del título D1 como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.45 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.33 (d, 8.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 6.70 (m, 5H), 4.65 (s, 2H), 3.71 (s, 3H), 3.69 (s, 3H), 2.22 (s, 3H). MS calculada para $C_{26}H_{24}NO_5S_2$ ($M+H^+$) 494.1, encontrada 494.4.



Ejemplo E1. Ácido {4-[4-(4-bromo-fenil)-5-fenil-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.



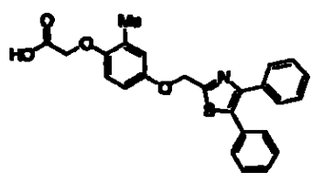
Paso A: La 1-(4-bromo-fenil)-2-fenil-etanona (0.24 gramos, 0.87 milimoles) se disuelve en ácido acético glacial (3 mililitros). Se agrega bromo (50 microlitros, 0.97 milimoles), y la mezcla se agita durante 30 minutos a temperatura ambiente. La dilución con agua (40 mililitros) produce un sólido blanco. La filtración, el lavado con agua, y el secado, producen la 2-bromo-1-(4-bromo-fenil)-2-fenil-etanona como un polvo blanco: 0.30 gramos, ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.85 (d, J = 6.8 Hz, 2H), 7.59 (d, J = 6.8 Hz, 2H), 7.50 (dd, J = 2.0, 8.4 Hz, 2H), 7.36 (m, 3H), 6.30 (s, 1H). MS calculada para $C_{11}H_{11}Br_2O$ ($M+H^+$) 354.9, encontrada 355.1.

Paso B: El metil-éster del ácido (2-metil-4-tiocarbamoil-metoxi-fenoxi)-acético (Intermediario 13) (46 miligramos, 0.17 milimoles), y la 2-bromo-1-(4-bromo-fenil)-2-fenil-etanona, se suspenden en etanol, y se calientan a 75°C durante 18 horas. El enfriamiento a temperatura ambiente, la concentración, y la purificación mediante cromatografía

(sílice, gradiente del 10 por ciento a 40 por ciento de acetato de acetilo en hexano) proporciona el etil-éster del ácido {4-[4-(4-bromo-fenil)-5-fenil-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.28 (m, 4H), 7.21 (m, 5H), 6.77 (d, J = 2.8 Hz, 1H), 6.66 (dd, J = 2.8, 8.8 Hz, 1H), 6.55 (d, J = 8.8 Hz, 1H), 5.23 (s, 2H), 4.47 (s, 2H), 4.13 (q, J = 7.2 Hz, 2H), 2.17 (s, 3H), 1.17 (q, J = 7.2 Hz, 3H).

Paso C: El etil-éster del ácido {4-[4-(4-bromo-fenil)-5-fenil-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético (55.2 miligramos, 0.11 milimoles) se disuelve en dioxano. Se agrega monohidrato de dióxido de litio (13.0 miligramos, 0.31 milimoles) disuelto en agua (0.5 mililitros). Después de 40 minutos, la mezcla se hace homogénea. La concentración hasta un jarabe, la dilución con acetato de etilo, el lavado con una solución de ácido cítrico al 10 por ciento, agua, cloruro de amonio acuoso saturado, y salmuera, el secado sobre Na_2SO_4, y la concentración, producen el compuesto del título de ácido {4-[4-(4-bromo-fenil)-5-fenil-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético E1 como un sólido blanco: la purificación con HPLC de fase inversa da el ácido puro: ^{1}H-RMN (400 MHz, DMSO-d_6) δ = 12.87 (s, 1H), 7.53 (m, 2H), 7.41-7.34 (m, 7H), 6.95 (d, J = 2.9 Hz, 1H), 6.85 (dd, J = 2.9, 8.9 Hz, 1H), 6.77 (d, J = 8.9 Hz, 1H), 5.39 (s, 2H), 4.61 (s, 2H), 2.18 (s, 3H). MS calculada para $C_{25}H_{21}BrNO_4S$ ($M+H^+$) 512.0, encontrada 512.3.

Ejemplo E2: Ácido [4-(4,5-difenil-tiazol-2-ilmetoxi)-2-metil-fenoxi]-acético.

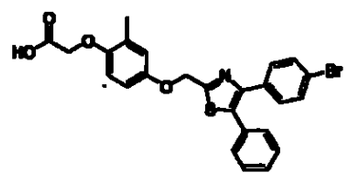


Paso A: Para el compuesto del título, se adquiere el intermediario de bromuro, y se utiliza directamente en el Paso B.

Paso B: El Intermediario 13 (20 miligramos, 0.076 milimoles), y bromuro de desilo (23 miligramos, 0.084 milimoles) se disuelven en EtOH (2 mililitros), y se calientan a reflujo durante 2 horas. El solvente se remueve mediante evaporación para proporcionar el metil-éster del ácido [4-(4,5-difenil-tiazol-2-ilmetoxi)-2-metil-fenoxi]-acético, el cual se utiliza sin mayor purificación en el Paso C.

Paso C: El metil-éster del ácido [4-(4,5-difenil-tiazol-2-ilmetoxi)-2-metil-fenoxi]-acético crudo se disuelve en tetrahidrofurano (1 mililitros), se agrega una solución de LiOH 1M en H_2O (0.2 mililitros), y la mezcla se agita durante 1 hora a temperatura ambiente. La mezcla se acidifica con HCl 1M (0.25 mililitros), se agrega EtOAc (10 mililitros), y la capa orgánica se lava con salmuera (5 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, se concentra, y se purifica sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar el compuesto del título E2 como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.40 (m, 2H), 7.23 (m, 8H), 6.82 (d, J = 2.9 Hz, 1H), 6.69 (dd, J = 3.0, 8.9 Hz, 1H), 6.61 (d, J = 8.9 Hz, 1H), 5.26 (s, 2H), 4.53 (s, 2H), 2.20 (s, 3H). MS calculada para $C_{25}H_{22}NO_4S$ ($M+H^+$) 432.1, encontrada 432.4.

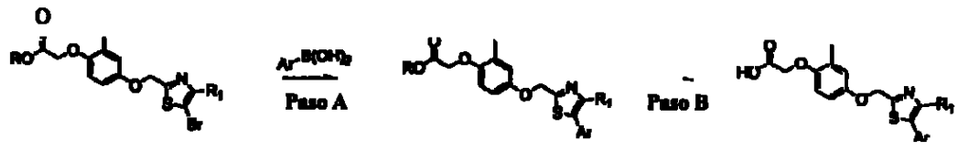
Ejemplo E3: Ácido {4-[4-(4-bromo-fenil)-5-fenil-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.



Paso A: La 1-(4-bromo-fenil)-2-fenil-etanona (275 miligramos, 1.00 milimoles) se disuelve en DCM (2 mililitros). Se agrega tribromuro de piridinio (352 miligramos, 1.1 milimoles), y la mezcla se agita a temperatura ambiente durante 2 horas. Luego la mezcla se diluye con DCM (1 mililitros), y se lava con H_2O (2 mililitros). La capa orgánica se concentra al vacío para proporcionar la 1-(4-bromo-fenil)-2-bromo-2-fenil-etanona cruda como un sólido amarillo, y se utiliza en el Paso B sin mayor purificación.

Paso B: Una mezcla de 1-(4-bromo-fenil)-2-bromo-2-fenil-etanona (43 miligramos, 0.12 milimoles), y metil-éster del ácido (2-metil-4-tiocarbamoil-metoxi-fenoxi)-acético (Intermediario 13, 32 miligramos, 0.12 milimoles) en EtOH (1 mililitros), se calienta a 180°C durante 5 minutos en un aparato de microondas. La solución resultante se utiliza directamente en el siguiente paso.

Paso C: Se agregan tetrahidrofurano (2 mililitros) y LiOH 1N (0.5 mililitros) a la solución derivada del Paso B. La mezcla se agita durante la noche a temperatura ambiente, y luego se acidifica con HCl 1N (1 mililitros). La mezcla de reacción se extrae con EtOAc (3 mililitros), la capa orgánica se separa y se concentra al vacío. El resto se recupera en sulfóxido de dimetilo (1 mililitros), y se purifica sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar el compuesto del título E59 como un sólido blanco: ^{1}H-RMN (600 MHz, $(CD_3)_2SO$) δ = 7.54-7.31 (m, 9H), 6.96 (d, J = 3.0 Hz, 1H), 6.87 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.40 (s, 2H), 4.63 (s, 2H), 2.19 (s, 3H). MS calculada para $C_{25}H_{21}BrNO_4S$ ($M+H^+$) 510.0, encontrada 510.3.



38 R1 = 4-metoxifenilo

40 R1 = 2-naftilo

41 R1 = 4-bifenilo

42 R1 = 4-morfolino-fenilo

43 R1 = benzo[3,4]-dioxol

44 R1 = 3-fluoro-4-metoxi-fenilo

45 R1 = benzo[3,4]-oxazin-3-ona

46 R1 = benzo[3,4]-oxazol-2-ona

47 R1 = benzo[3,4]-dioxina

48 R1 = 4-acetilamino-fenilo

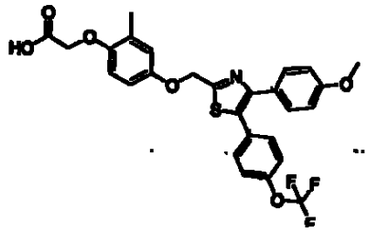
49 R1 = 2'-metilbenzo[3,4]-oxazol

51 R1 = 4-(trifluorometoxi)-fenilo

52 R1 = 4-trifluorometilfenilo

53 R1 = 3-piridilo.

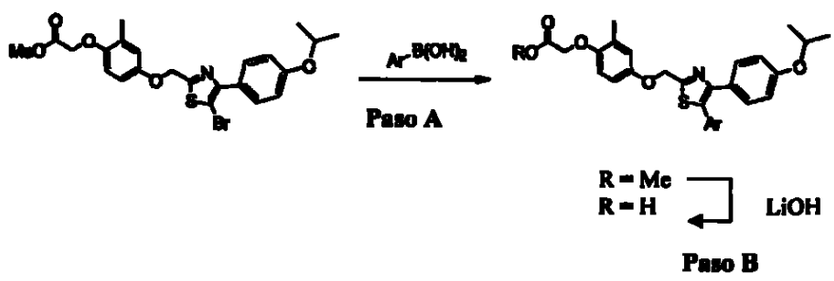
Ejemplo F1: Ácido {4-[4-(4-metoxi-fenil)-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.



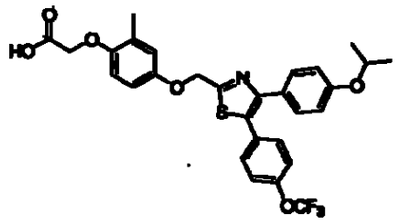
Paso A: El intermediario 38 (21 miligramos, 0.042 milimoles), ácido 4-trifluoro-metoxi-fenil-borónico (10.3 miligramos, 0.050 milimoles), y

carbonato de sodio (13 miligramos, 0.126 milimoles), se disuelven en agua (120 microlitros), etanol (90 microlitros), y 1,2-dimetoxietano (360 microlitros), y la mezcla se desgasifica con burbujeo de argón durante 2 minutos. Se agrega $Pd(PPh_3)_4$ (10 por ciento molar), y la mezcla se somete a microondas (180°C) durante 5 minutos en un tubo sellado. La mezcla se diluye con agua saturada (5 mililitros), se extrae en EtOAc (10 mililitros), y se lava con salmuera (5 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra para dar el metil-éster del ácido {4-[4-(4-metoxi-fenil)-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético crudo, el cual se utiliza sin mayor purificación en el Paso B.

Paso B: El metil-éster del ácido {4-[4-(4-metoxi-fenil)-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético se disuelve en tetrahidrofurano (1 mililitros), se agrega una solución de LiOH 1M en H_2O (0.2 mililitros), y la mezcla se agita durante 1 hora a temperatura ambiente. La mezcla se acidifica con HCl 1M (0.25 mililitros), se agrega EtOAc (10 mililitros), y la capa orgánica se lava con salmuera (5 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, se concentra, y se purifica sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar el compuesto del título F1 como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.32 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.1 Hz, 2H), 6.82 (d, J = 2.9 Hz, 1H), 6.76 (d, J = 8.8 Hz, 2H), 6.71 (dd, J = 2.8, 8.8 Hz, 1H), 6.63 (d, J = 8.9 Hz, 1H), 5.25 (s, 2H), 4.56 (s, 2H), 3.75 (s, 3H), 2.21 (s, 3H). MS calculada para $C_{27}H_{23}F_3NO_6S$ ($M+H^+$) 546.1, encontrada 546.3.



Ejemplo G1: Ácido {4-[4-(4-isopropoxi-fenil)-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.

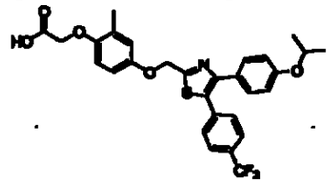


Paso A: El intermediario 55 (21 miligramos, 0.041 milimoles), ácido 4-trifluoro-metoxi-fenil-borónico (10.3 miligramos, 0.050 milimoles), y carbonato de sodio (13 miligramos, 0.126 milimoles), se disuelven en agua (120 microlitros), etanol (90 microlitros), y 1,2-dimetoxi-etano (360 microlitros). La mezcla se desgasifica con argón durante 2 minutos. Se agrega $Pd(PPh_3)_4$ (10 por ciento molar), y la mezcla se somete a microondas (170°C) durante 5 minutos. La mezcla se diluye con agua (5 mililitros), se extrae en EtOAc (10 mililitros), y se lava con salmuera (5 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra, para dar el metil-éster del ácido {4-[4-(4-isopropoxi-fenil)-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético crudo, el cual se utiliza sin mayor purificación en el Paso B.

Paso B: El metil-éster del ácido {4-[4-(4-isopropoxi-fenil)-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético crudo se

disuelve en tetrahidrofurano (1 mililitro), se agrega una solución de LiOH 1M en H_2O (0.2 mililitros), y la mezcla se agita durante 1 hora a temperatura ambiente. La mezcla se acidifica con HCl 1M (0.25 mililitros), se agrega EtOAc (10 mililitros), y la capa orgánica se lava con salmuera (5 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, se concentra, y se purifica sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar el compuesto del título G1 como un sólido blanco: ^{1}H-RMN (400 MHz, MeOD) δ = 8.4 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.77 (d, J = 8.4 Hz, 2H), 6.75 (dd, J = 2.8, 8.8 Hz, 1H), 6.68 (d, J = 8.8 Hz, 1H), 5.25 (s, 2H), 4.53 (m, 3H), 2.17 (s, 3H), 1.23 (s, 3H), 1.21 (s, 3H). MS calculada para $C_{28}H_{27}F_3NO_6S$ ($M+H^+$) 574.1, encontrada 574.1.

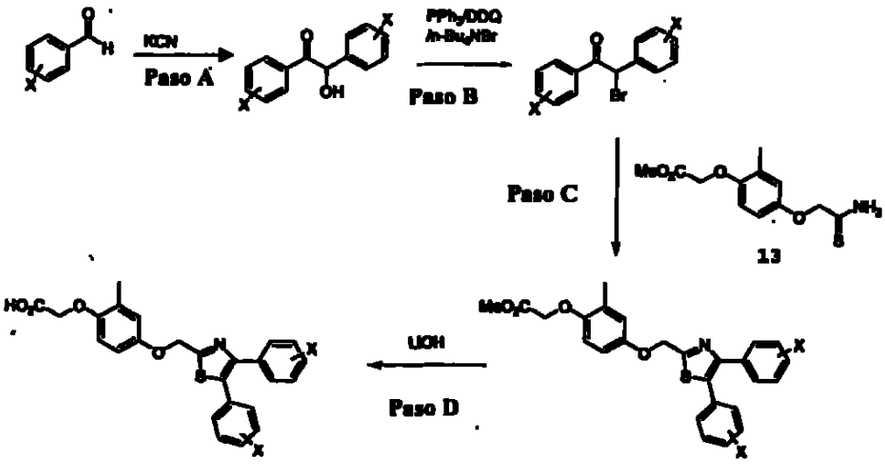
Ejemplo G2: Ácido {4-[4-(4-isopropoxi-fenil)-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.



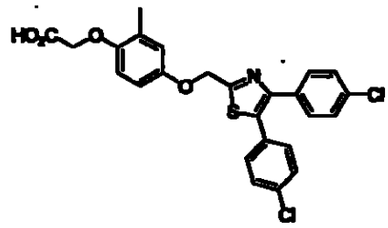
Paso A: El Intermediario 55 (21 miligramos, 0.04 milimoles), ácido 4-trifluoro-metil-fenil-borónico (9.,5 miligramos, 0.05 milimoles), y carbonato de sodio (13 miligramos, 0.13 milimoles), se disuelven en agua (120 microlitros), etanol (90 microlitros), y 1,2-dimetoxietano (360 microlitros). La mezcla se desgasifica con argón durante 2 minutos. Se agrega $Pd(PPh_3)_4$ (10 por ciento molar), y la mezcla se somete a microondas (170°C) durante 5 minutos. La mezcla se diluye con agua (5 mililitros), se extrae en EtOAc (10 mililitros), y se lava con salmuera (5 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra para dar el metil-

éster del ácido {4-[4-(4-isopropoxi-fenil)-5-(4-trifluoro-metil-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético crudo, el cual se utiliza sin mayor purificación en el Paso B.

Paso B: El metil-éster del ácido {4-[4-(4-isopropoxi-fenil)-5-(4-trifluoro-metil-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético crudo se disuelve en tetrahidrofurano (1 mililitros), se agrega una solución de LiOH 1M en H_2O (0.2 mililitros), y la mezcla se agita durante 1 hora a temperatura ambiente. La mezcla se acidifica con HCl 1M (0.25 mililitros), se agrega EtOAc (10 mililitros), y la capa orgánica se lava con salmuera (5 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, se concentra, y se purifica sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar el compuesto del título G2 que se prepara como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.70 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 2.8 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.90 (dd, J = 2.8, 8.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 5.41 (s, 2H), 4.67 (m, 3H), 2.32 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H). MS calculada para $C_{29}H_{27}F_3NO_5S$ ($M+H^+$) 558.1, encontrada 558.2.



Ejemplo H1. Ácido {4-[4,5-bis-(4-cloro-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.



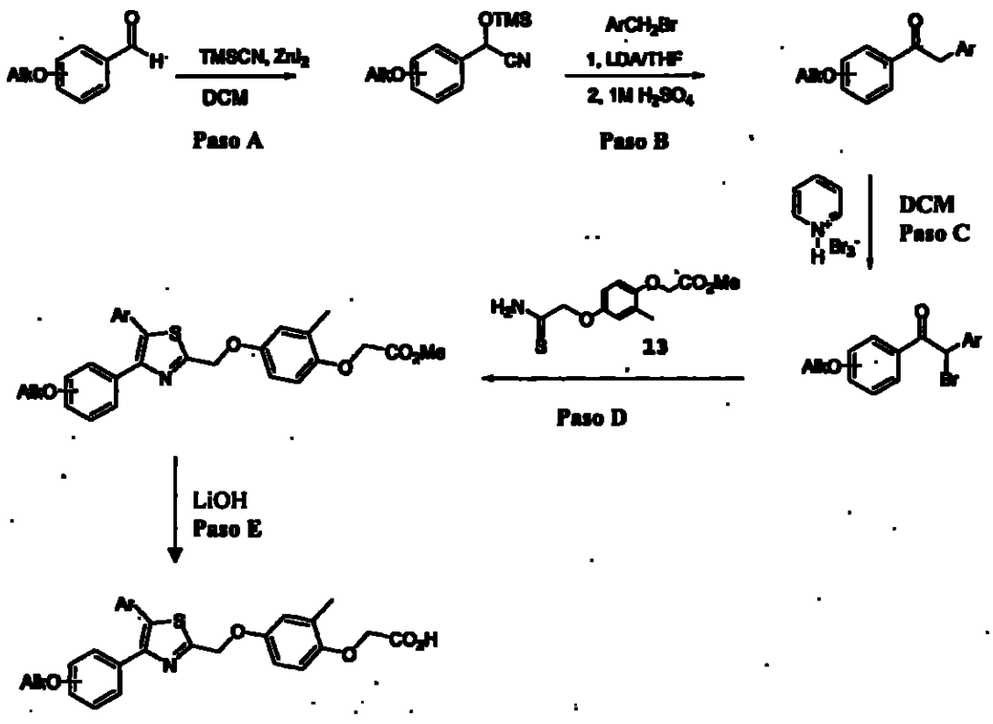
Paso A: A una solución de 4-cloro-benzaldehído (0.57 gramos, 2.04 milimoles) en EtOH (8 mililitros), se le agrega KCN (18.0 miligramos, 0.27 milimoles) disuelto en agua (4 mililitros). La mezcla se calienta a reflujo durante 7 horas, luego se enfría a temperatura ambiente, y se extrae con acetato de etilo (100 mililitros). La capa orgánica se seca ($MgSO_4$), se filtra, y se concentra. El residuo se purifica mediante cromatografía por evaporación con éter al 40 por ciento/hexano, para dar un sólido: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.83 (m, 2H), 7.39 (m, 2H), 7.31 (m, 2H), 7.25 (m, 2H), 5.88 (s, 1H), 4.50 (bro. 1H). MS calculada para $C_{14}H_9OCl_2$ ($M\text{-}OH^-$) 263.0, encontrada 262.9.

Paso B: A una solución de 2,3-dicloro-5,6-diciano-benzoquinona (242 miligramos, 1.07 milimoles), y trifenil-fosfina (280 miligramos, 1.07 milimoles) en CH_2Cl_2 seco (5 mililitros), se le agrega subsecuentemente bromuro de tetrabutil-amonio (344 miligramos, 1.07 milimoles) y 1,2-bis-(4-cloro-fenil)-2-hidroxi-etanona (200 miligramos, 0.71 milimoles). La suspensión se mantiene agitándose durante 1.5 horas a temperatura ambiente. La solución castaña resultante se concentra al vacío y se purifica mediante cromatografía por evaporación (hexano/acetato de etilo,

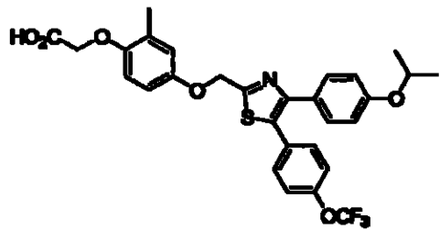
5:1), para proporcionar la 2-bromo-1,2-bis-(4-cloro-fenil)-etanona como un aceite incoloro: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.86 (d, J = 8.8 Hz, 2H), 7.40-7.35 (m, 4H), 7.29 (d, J = 8.4 Hz, 2H), 6.17 (s, 1H). MS calculada para $C_{14}H_8OCl_2$ ($M-Br^-$) 263.0, encontrada 262.9.

Paso C: Una mezcla de 2-bromo-1,2-bis-(4-cloro-fenil)-etanona (44.0 gramos, 0.13 milimoles), metil-éster del ácido (2-metil-4-tiocarbamoil-metoxi-fenoxi)-acético 13 (34.0 miligramos, 0.13 milimoles), y EtOH (1 mililitros), se somete a microondas (180°C) durante 5 minutos. La solución resultante se utiliza directamente en el siguiente paso.

Paso D: El metil-éster del ácido {4-[4,5-bis-(4-cloro-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético crudo del Paso C, se disuelve en tetrahidrofurano (1 mililitros) y H_2O (0.5 mililitros). Se agrega $LiOH \cdot H_2O$ (53.7 miligramos, 0.64 milimoles). La mezcla se agita durante 2 horas a temperatura ambiente, luego se acidifica con HCl 1N. Se agrega EtOAc (20 mililitros), y se extrae el producto. La capa orgánica se seca ($MgSO_4$), se filtra, se concentra, y se purifica sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar el compuesto del título H1 como un sólido blanco: ^{1}H-RMN (400 MHz, CD_3OD) δ = 7.45 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.34-7.30 (m, 4H), 6.91 (d, J = 2.8 Hz, 1H), 6.85-6.76 (m, 2H), 5.34 (s, 2H), 4.62 (s, 2H), 2.26 (s, 3H). MS calculada para $C_{25}H_{20}Cl_2NO_4S$ ($M+H^+$) 500.04, encontrada 501.00.



Ejemplo J1: Ácido {4-[4-(4-isopropoxi-fenil)-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.



Paso A: El 4-isopropoxi-benzaldehído (5.0 gramos, 30.45 milimoles) y cianuro de trimetil-sililo (3.02 gramos, 30.45 milimoles) se disuelven en DCM seco (50 mililitros). La solución se enfría a 0°C, y luego se agrega yoduro de zinc (42.76 miligramos, 1.13 milimoles). Luego la mezcla de reacción se calienta a temperatura ambiente, y se mantiene agitándose durante la noche. La mezcla se concentra, se vuelve a disolver en éter, y

se filtra a través de carbón activado. El filtrado se seca ($MgSO_4$), y se concentra, para dar el (4-isopropoxi-fenil)-trimetil-silaniloxi-acetonitrilo como un aceite incoloro: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.16 (d, J = 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.22 (s, 1H), 4.38-4.32 (m, 1H), 1.13 (d, J = 4.0 Hz, 6H), 0.00 (s, 9H). MS calculada para $C_{14}N_{21}NO_2Si$, (M^+) 263.1, encontrada 237.1 (M-CN).

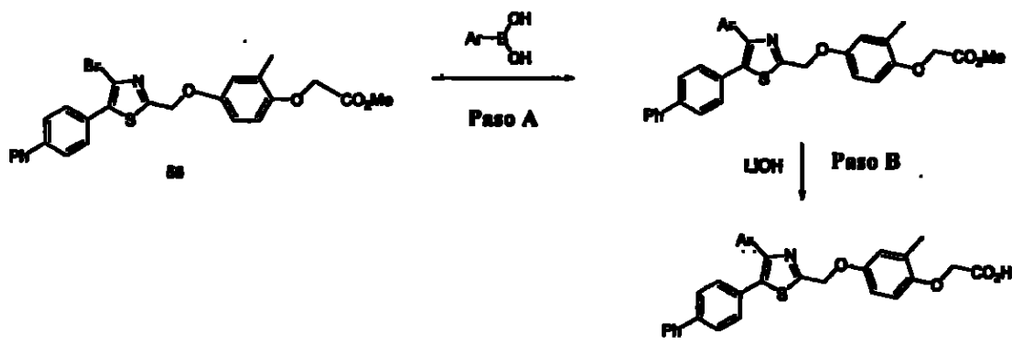
Paso B: El (4-isopropoxi-fenil)-trimetil-silaniloxi-acetonitrilo (1.0 gramos, 3.78 milimoles), se disuelve en tetrahidrofurano seco (8 mililitros). La solución se agrega por goteo a una solución de LDA (2M en tetrahidrofurano, 1.89 mililitros) en tetrahidrofurano (4 mililitros) a -78°C. La mezcla de reacción se agita durante 0.5 horas, seguido por la adición de una solución de bromuro de 4-(trifluoro-metoxi)-bencilo (0.97 gramos, 3.78 milimoles) en tetrahidrofurano (2 mililitros). La mezcla de reacción se deja calentar a temperatura ambiente, y se mantiene agitándose durante 18 horas. La mezcla de reacción se vierte en H_2O (10 mililitros), y se extrae con EtOAc 3 veces. Las capas orgánicas se combinan y se lavan con salmuera, se secan ($MgSO_4$), y se concentran. El residuo se vuelve a disolver en MeOH (10 mililitros), y luego se agrega H_2SO_4 (1M, 4 mililitros). Después de agitar a temperatura ambiente durante la noche, la mezcla de reacción se ajusta a un pH de 10 mediante la adición de NaOH 1N, y luego se extrae con EtOAc tres veces. Las capas orgánicas se combinan y se lavan con H_2O y salmuera, se secan y se concentran para dar la 1-(4-isopropoxi-fenil)-2-(4-trifluorometoxi-fenil)-etanona cruda, la cual se utiliza directamente en el siguiente paso sin purificación. MS calculada para $C_{18}H_{18}F_3O_3$, ($M+H^+$) 339.1, encontrada 339.4.

Paso C: La 1-(4-isopropoxi-fenil)-2-(4-trifluoro-metoxi-fenil)-etanona cruda (100 miligramos) se disuelve en DCM (2 mililitros). Se agrega tribromuro de piridinio (94.5 miligramos, 0.30 milimoles). La mezcla de reacción se agita durante 2 horas a temperatura ambiente. El solvente se remueve para dar la 2-bromo-1-(4-isopropoxi-fenil)-2-(4-trifluoro-metoxi-fenil)-etanona cruda, la cual se utiliza directamente en el siguiente paso sin purificación. MS calculada para $C_{18}H_{17}BrF_3O_3$, $(M+H^+)$ 417.0, encontrada 417.3.

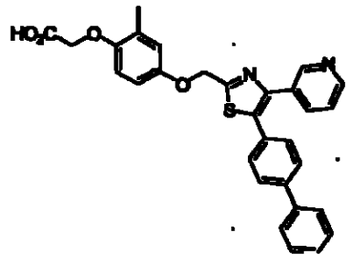
Paso D: La 2-bromo-1-(4-isopropoxi-fenil)-2-(4-trifluoro-metoxi-fenil)-etanona cruda se disuelve en EtOH (1.0 mililitros) en un recipiente de reacción de microondas de 5 mililitros. Se agrega el metil-éster del ácido (2-metil-4-tiocarbamoil-metoxi-fenoxi)-acético (13) (79.6 miligramos, 0.30 milimoles), y se sella el recipiente. Se obtiene el metil-éster del ácido {4-[4-(4-isopropoxi-fenil)-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético crudo después de someterse a microondas (5 minutos a 180°C), y se utiliza directamente en el siguiente paso sin purificación. MS calculada para $C_{30}H_{29}F_3NO_6S$ $(M+H^+)$ 588.2, encontrada 588.1.

Paso E: Se agregan tetrahidrofurano (0.8 mililitros), H_2O (0.5 mililitros), y $LiOH \cdot H_2O$ (62 miligramos, 1.48 milimoles) a la mezcla de reacción del Paso D. La mezcla de reacción se agita durante 1 hora a temperatura ambiente, y luego se purifica sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar el compuesto del título J1 como un sólido blanco: ^{1}H-RMN (400 MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 2.8 Hz, 1H), 6.78-6.67 (m, 4H), 5.24 (s, 2H), 4.53 (s, 2H), 4.51 (m, 1H), 2.16 (s,

3H), 1.22 (s, 3H), 1.20 (s, 3H). MS calculada para $C_{28}H_{27}F_3NO_6S$ ($M+H^+$) 574.1, encontrada 574.2.



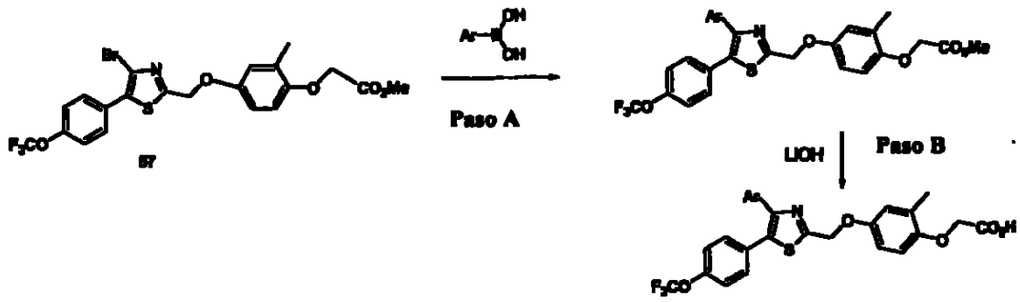
Ejemplo K1: Ácido [4-(5-bifenil-4-il-4-piridin-3-il-tiazol-2-ilmetoxi)-2-metil-fenoxi]-acético.



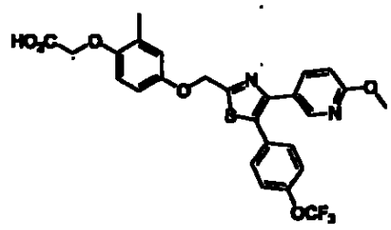
Paso A: Una mezcla del metil-éster del ácido [4-(5-bifenil-4-il-4-bromo-tiazol-2-ilmetoxi)-2-metil-fenoxi]-acético (56) (10.0 miligramos, 0.019 milimoles), ácido 3-piridin-borónico (3.7 miligramos, 0.023 milimoles), tetraquis-(trifenil-fosfina)-paladio (2.2 miligramos, 0.0019 milimoles), carbonato de potasio (10.5 miligramos, 76.0 milimoles), 1,4-dioxano (1 mililitros), EtOH (0.3 mililitros), y H_2O (0.2 mililitros) en un frasco sellado, se calienta a 120°C, y se agita a esta temperatura durante la noche. La mezcla de reacción se enfría a temperatura ambiente, y se utiliza en el siguiente paso sin mayor purificación. MS calculada para $C_{30}H_{26}N_2O_4S$ ($M+H^+$) 523.2, encontrada 523.2.

Paso B: Se agrega $LiOH \cdot H_2O$ (4.0 miligramos, 0.095 milimoles) a la

mezcla de reacción del paso anterior. La mezcla se agita a temperatura ambiente durante 2 horas, y luego se filtra. El filtrado se purifica sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar el compuesto del título K1 como un sólido blanco: ^{1}H-RMN (400 MHz, CD_3OD) δ = 8.77 (bs, 1H), 8.55 (bs, 1H), 8.33 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 6.4 Hz, 1H), 7.64-7.42 (m, 4H), 7.41-7.35 (m, 4H), 7.30-7.26 (m, 1H), 6.84 (d, J = 2.8 Hz, 1H), 6.78-6.68 (m, 2H), 5.31 (s, 2H), 4.54 (s, 2H), 2.17 (s, 3H). MS calculada para $C_{30}H_{25}N_2O_4S$ ($M+H^+$) 509.2, encontrada 509.1.



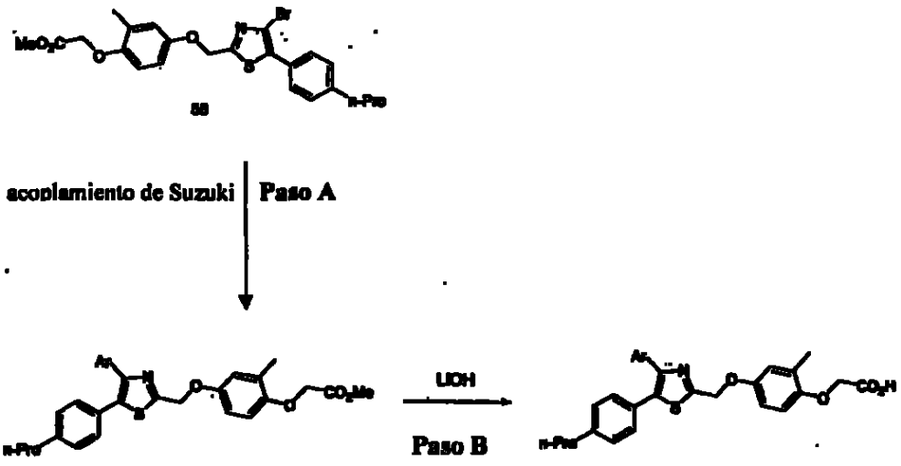
Ejemplo L1: Ácido {4-[4-(6-metoxi-piridin-3-il)-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.



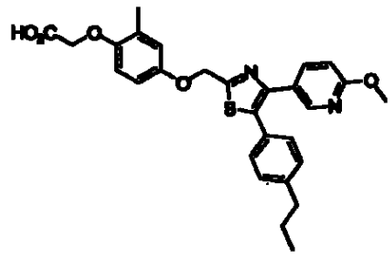
Paso A: Una mezcla del metil-éster del ácido {4-[4-bromo-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético (400 miligramos, 0.75 milimoles), ácido 2-metoxi-5-piridin-borónico (229.7 miligramos, 1.50 milimoles), tetraquis-(trifenil-fosfina)-paladio (86.9 miligramos, 0.075 milimoles), carbonato de potasio (1.0 N, 3.0 mililitros,

3.0 milimoles), 1,4-dioxano (10.0 mililitros), y EtOH (6.0 mililitros) en un frasco sellado, se calienta a 120°C durante la noche. La mezcla de reacción se enfría a temperatura ambiente, y se utiliza en el siguiente paso sin mayor purificación.

Paso B: Se agrega $LiOH \cdot H_2O$ (158 miligramos, 3.75 milimoles) a la mezcla de reacción del paso anterior. La mezcla se agita a temperatura ambiente durante 2 horas, y luego se filtra. El filtrado se purifica sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar el compuesto del título L1 como un sólido blanco: ^{1}H-RMN (400 MHz, CD_3OD) δ = 8.13 (d, J = 2.0 Hz, 1H), 7.72 (dd, J = 2.4 Hz, J = 8.4 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 3H), 5.27 (s, 2H), 4.54 (s, 2H), 3.83 (s, 3H), 2.17 (s, 3H). MS calculada para $C_{28}H_{22}F_3N_2O_6S$ ($M+H^+$) 547.1, encontrada 547.1.



Ejemplo M1: Ácido {4-[4-(6-metoxi-piridin-3-il)-5-(4-propil-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.

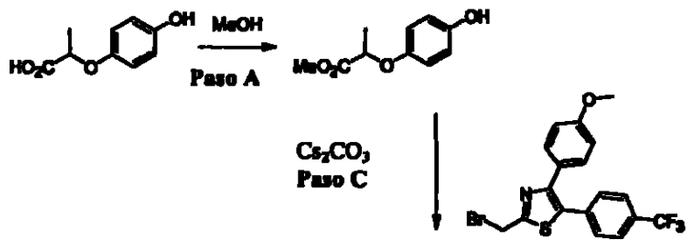


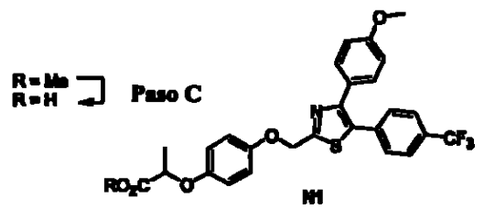
Paso A: Una mezcla del metil-éster del ácido {4-[4-bromo-5-(4-propil-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético 58 (20 miligramos, 0.041 milimoles), ácido 2-metoxi-5-piridin-borónico (12.5 miligramos, 0.082 milimoles), tetraquis-(trifenil-fosfina)-paladio (4.7 miligramos, 0.0041 milimoles), carbonato de potasio (1.0N, 0.16 mililitros, 0.16 milimoles), 1,4-dioxano (0.6 mililitros), y EtOHA (0.3 mililitros) en un frasco sellado, se somete a microondas (5 minutos a 170°C). Se obtiene el metil-éster del ácido {4-[4-(6-metoxi-piridin-3-il)-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético crudo, y se utiliza directamente en el siguiente paso sin purificación. MS calculada para $C_{27}H_{24}F_3N_2O_7$ ($M+H^+$) 519.2, encontrada 519.2.

Paso B: Se agregan $LiOH \cdot H_2O$ (17.0 miligramos, 0.41 milimoles), MeOH (0.4 mililitros), tetrahidrofurano (0.3 mililitros), y H_2O (0.2 mililitros) a la mezcla de reacción del Paso G. La mezcla se agita a temperatura ambiente durante 2 horas, y luego se filtra. El filtrado se purifica sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar el compuesto del título M1 como un sólido blanco: ^{1}H-RMN (400 MHz, CD_3OD) δ = 8.12 (s, 1H), 7.71 (dd, J = 2.4 Hz, J = 8.8 Hz, 1H), 7.17-7.11 (m, 4H), 6.82 (d, J = 2.8 Hz, 1H), 6.73-6.66 (m, 3H), 5.24 (s, 2H), 4.53 (s,

2H), 3.82 (s, 3H), 2.51 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.61-1.51 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H). MS calculada para $C_{28}H_{28}N_2O_5S$ ($M+H^+$) 505.2, encontrada 505.2.

Ejemplo N1: Ácido 2-{4-[4-(4-metoxi-fenil)-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-fenoxi}-propiónico.





H1

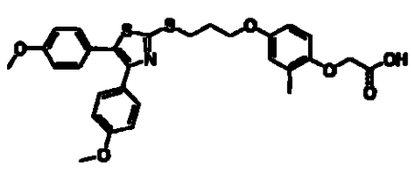
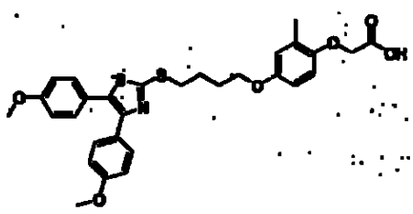
Paso A: El ácido 2-(4-hidroxi-fenoxi)-propiónico (25 miligramos, 0.14 milimoles) se disuelve en MeOH (20 mililitros). Se agrega cloruro de tionilo (5 microlitros, 0.06 milimoles), y la solución se agita a 60°C durante 2 horas. El solvente se remueve al vacío para proporcionar el metil-éster del ácido 2-(4-hidroxi-fenoxi)-propiónico crudo como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 6.77 (d, J = 9.2 Hz, 2H), 6.72 (d, J = 9.2 Hz, 1H), 4.66 (q, J = 6.8 Hz, 1H), 3.75 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H). MS calculada para $C_{10}H_{13}O_4$ ($M+H^+$) 197.1, encontrada 197.4.

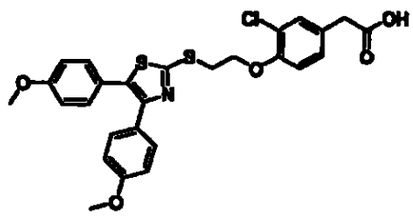
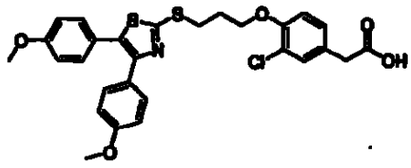
Paso B: Se agregan el metil-éster del ácido 2-(4-hidroxi-fenoxi)-propiónico (27 miligramos, 0.14 milimoles) y Cs_2CO_3 (137 miligramos, 0.42 milimoles) a una solución del intermediario 64 (60 miligramos, 0.14

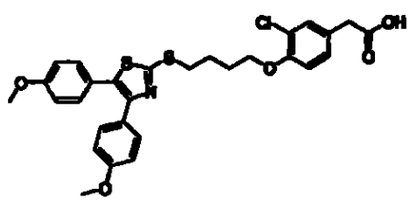
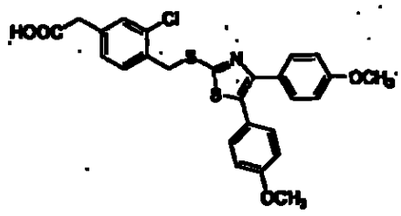
milimoles) en MeCN (5 mililitros). La mezcla se agita durante 3 horas a temperatura ambiente. Después de que se filtra, la mezcla, la solución orgánica se concentra para proporcionar el metil-éster del ácido 2-{4-[4-(4-metoxi-fenil)-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-fenoxi}-propiónico crudo, el cual se utiliza en el siguiente paso sin mayor purificación.

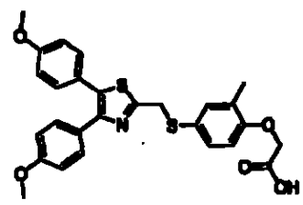
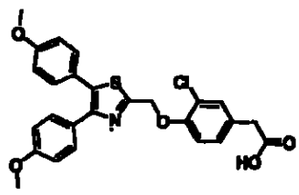
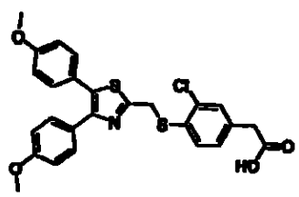
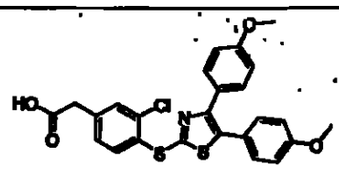
Paso C: Se agregan tetrahidrofurano (2 mililitros) y LiOH 1N (0.5 mililitros) al producto crudo del Paso B. La mezcla se agita durante la noche a temperatura ambiente, y luego se acidifica con HCl 1N (1 mililitros). La mezcla de reacción se extrae con EtOAc (3 mililitros), la capa orgánica se separa y se concentra al vacío. El resto se recupera en sulfóxido de dimetilo (1 mililitros), y se purifica sobre HPLC de fase inversa (gradiente de H_2O/MeCN), para proporcionar el compuesto del título N1 como un sólido blanco: ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 7.55 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 6.95-6.83 (m, 6H), 5.31 (s, 2H), 4.69 (q, J = 6.8 Hz, 1H), 3.81 (s, 3H), 1.60 (d, J = 6.8 Hz, 3H). MS calculada para $C_{27}H_{23}F_3NO_6S$ ($M+H^+$) 530.1, encontrada 530.4.

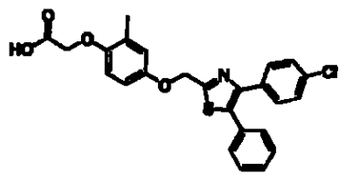
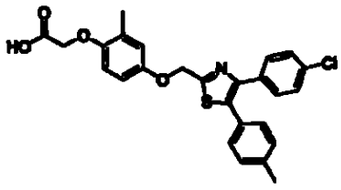
Mediante la repetición de los procedimientos descritos en los ejemplos anteriores, utilizando los materiales de partida apropiados, se obtienen los siguientes compuestos de la Fórmula I, como se identifican en la Tabla 1.

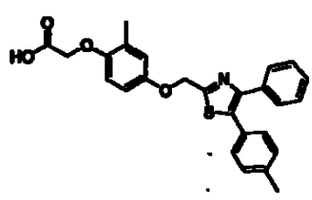
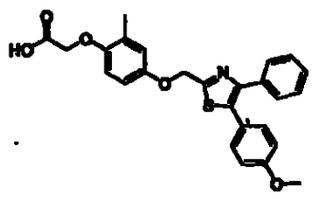
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
A2		^{1}H-RMN (400MHz, CD_3OD) δ =7.34 (d, J=8.9 Hz, 2H), 7.14 (d, J=8.9 Hz, 2H), 6.87 (d, J=8.9 Hz, 2H), 6.82 (d, J=8.9 Hz, 2H), 6.73-6.63 (m, 3H), 4.55 (s, 2H), 4.06 (t, J=5.9 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.42 (t, J=7.0 Hz, 2H), 2.23 (m, 2H), 2.18 (s,3H). MS calculada para $C_{29}H_{30}NO_6S_2$ ($M+H^+$) 552.1, encontrada 552.4.
A3		^{1}H-RMN (400MHz, CD_3OD) δ = 7.34 (d, J=8.9 Hz, 2H), 7.16 (d, J=8.9 Hz, 2H), 6.87(d, J=8.9 Hz, 2H), 6.80 (d, J=8.9 Hz, 2H), 6.72-6.61 (m, 3H), 4.56 (s, 2H), 3.95 (t, J=6.0 Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.31 (t, J=7.2 Hz, 2H), 2.19 (s,

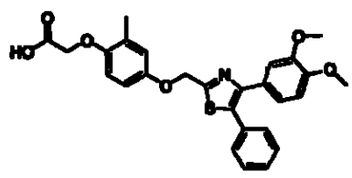
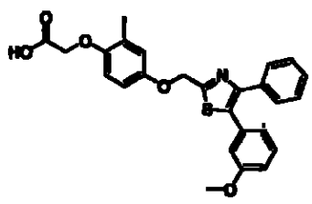
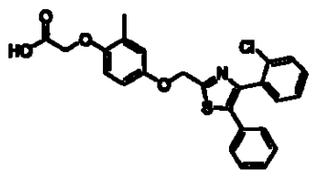
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		3H), 2.01-1.89 (m, 4H). MS calculada para $C_{30}H_{32}NO_6S_2$ ($M+H^+$) 566.2, encontrada 566.4.
A4		^{1}H-RMN (400MHz, CD_3OD) δ = 7.37-6.82 (m, 11H), 4.42 (t, J=6.4 Hz, 2HJ), 3.79 (s, 3H), 3.78 (s, 3H), 3.66 (t, J=6.4 Hz, 2H), 3.50 (s, 2H). MS calculada para $C_{27}H_{25}ClNO_5S_2$ ($M+H^+$) 542.1, encontrada 542.3.
A5		^{1}H-RMN (400MHz, CD_3OD) δ = 7.35-6.80 (m, 11H), 4.19 (t, J=5.8 Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.55 (s, 2H), 3.47 (t, J=7.0 Hz, 2H), 2.30 (m, 2H). MS calculada para $C_{28}H_{27}ClNO_5S_2$ ($M+H^+$) 556.1, encontrada 556.4.

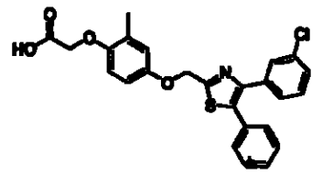
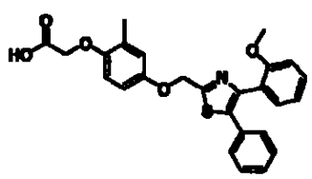
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
A6		^{1}H-RMN (400MHz, CD_3OD) δ = 7.36-6.80 (m, 11H), 4.10 (t, J=5.7 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.51 (s, 2H), 3.36 (t, J=7.1 Hz, 2H), 2.08-1.98 (m, 4H). MS calculada para $C_{29}H_{29}ClNO_3S_2$ ($M+H^+$) 570.1, encontrada 570.4.
B2		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.51-7.45 (m, 3H), 7.35 (d, J=1.2 Hz, 1H), 7.22 (m, 1H), 7.20 (s,1H), 7.13 (dd, J=1.2 Hz, J=8.0 Hz, 1H), 4.57 (s, 2H), 3.802 (s,3H), 3.809 (s, 3H), 3.62 (s, 2H). MS calculada para $C_{28}H_{23}ClNO_4S_2$ ($M+H^+$) 512.0, encontrada 512.00.
C2		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.74-6.63 (m, 1H), 4.62 (s,

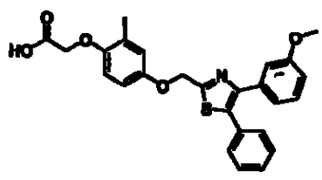
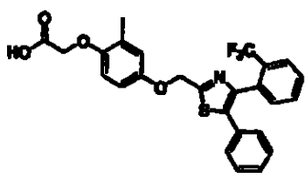
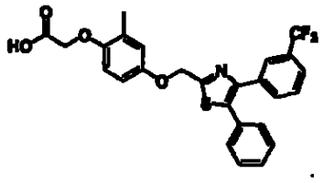
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2H), 4.35 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.23 (s, 3H). MS calculada para $C_{27}H_{26}NO_5S_2$ ($M+H^+$) 501.1, encontrada 508.4.
C3		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.74-6.80 (m, 11H), 5.43 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.57 (s, 2H). MS calculada para $C_{26}H_{23}ClNO_5S$ ($M+H^+$) 496.1, encontrada 496.3.
C4		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.74-6.78 (m, 11H), 4.51 (s, 2H), 3.79 (s, 3H), 3.79 (s, 3H), 3.58 (s, 2H). MS calculada para $C_{26}H_{23}ClNO_4S_2$ ($M+H^+$) 512.1, encontrada 512.3.
D2		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.59 (d, J=8.0 Hz, 1H), 7.44 (s, 1H), 7.37 (d, 8.8 Hz, 2H),

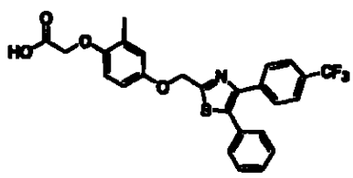
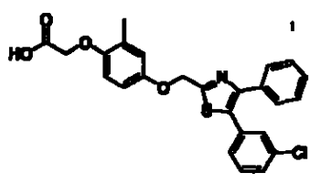
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		7.21 (d, J=8.4 Hz, 1H), 7.15 (d, J=8.8 Hz, 2H), 6.80 (d, J=8.4 Hz, 4H), 3.77 (s, 6H), 3.64 (s, 2H). MS calculada para $C_{26}H_{24}NO_6S_2$ ($M+H^+$) 498.0, encontrada 498.3.
E48		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.46-7.31 (m, 9H), 6.96 (d, J=3.0 Hz, 1H), 6.87 (dd, J=3.0 Hz, J=8.9 Hz, 1H), 6.79 (d, J=8.9 Hz, 1H), 5.40 (s, 2H), 4.63 (s, 2H), 2.19 (s, 3H). MS calculada para $C_{26}H_{21}ClNO_4S$ ($M+H^+$) 466.1, encontrada 466.3.
E49		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.46-7.08 (m, 8H), 6.96 (d, J=3.0 Hz, 1H), 6.86 (dd, J=3.0 Hz, J=8.9 Hz, 1H), 6.78 (d, J=8.9 Hz, 1H), 5.39 (s, 2H),

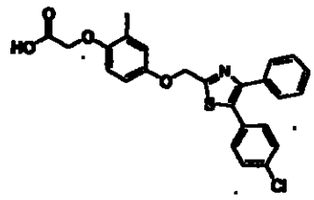
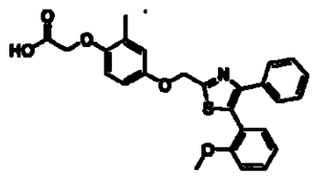
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		4.63 (s, 2H), 2.69 (m, 3H), 2.19 (s, 3H). MS calculada para $C_{26}H_{23}ClNO_4S$ ($M+H^+$) 480.1, encontrada 480.3.
E60		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.46-7.19 (m, 9H), 6.96 (d, J=2.9 Hz, 1H), 6.87 (dd, J=3.0 Hz, J=8.9 Hz, 1H), 6.79 (d, J=8.9 Hz, 1H), 5.39 (s, 2H), 4.63 (s, 2H), 2.32 (s, 3H), 2.19 (s, 3H). MS calculada para $C_{26}H_{24}NO_4S$ ($M+H^+$) 446.1, encontrada 446.4.
E61		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.47-7.26 (m, 7H), 6.95 (m, 3H), 6.87 (dd, J=3.0 Hz, J=8.9 Hz, 1H), 6.79 (d, J=8.9 Hz, 1H), 5.38 (s, 2H), 4.63 (s, 2H), 3.77 (s, 3H), 2.19 (s, 3H). MS calculada para $C_{26}H_{24}NO_5S$

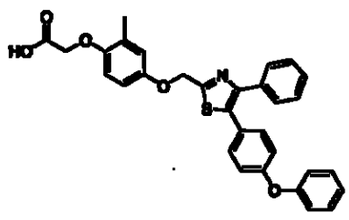
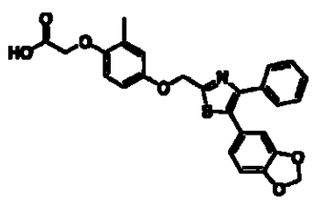
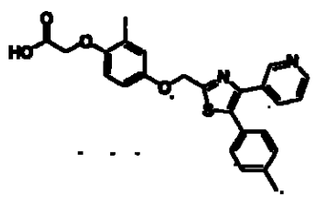
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		($M+H^+$) 462.1, encontrada 462.4.
E62		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.50-7.44 (m, 5H), 7.09-6.85 (m, 6H), 5.46 (s, 2H), 4.70 (s, 2H), 3.81 (s, 3H), 3.59 (s, 3H), 2.26 (s, 3H). MS calculada para $C_{27}H_{26}NO_6S$ ($M+H^+$) 492.1, encontrada 492.4.
E63		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.45-7.26 (m, 6H), 6.94-6.76 (m, 6H), 5.37 (s, 2H), 4.61 (s, 2H), 3.64 (s, 3H), 2.17 (s, 3H). MS calculada para $C_{26}H_{24}NO_5S$ ($M+H^+$) 462.1, encontrada 462.4.
E64		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.54-7.19 (m, 9H), 6.96 (d, J=3.0 Hz, 1H), 6.88 (d, J=3.0 Hz, J=8.9 Hz, 1H), 6.79 (d,

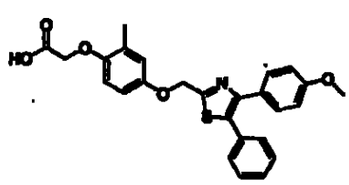
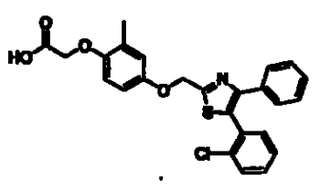
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		J=8.9 Hz, 1H), 5.39 (s, 2H), 4.64 (s, 2H), 2.19 (s, 3H). MS calculada para $C_{26}H_{21}ClNO_4S$ ($M+H^+$) 466.1, encontrada 466.3.
E65		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.46-7.27 (m, 9H), 6.94 (d, J=3.0 Hz, 6.84 (dd, J=3.0 Hz, J=8.9 Hz, 1H), 6.76 (d, J=8.9 Hz, 1H), 5.38 (s, 2H), 4.61 (s, 2H), 2.17 (s, 3H). MS calculada para $C_{26}H_{21}ClNO_4S$ ($M+H^+$) 466.1, encontrada 466.3.
E66		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.39-7.19 (m, 7H), 7.01-6.96 (m, 3H), 6.87 (dd, J=3.0 Hz, J=8.9 Hz, 1H), 6.79 (d, J=8.9 Hz, 1H), 5.36 (s, 2H), 4.63 (s, 2H), 3.39 (s, 3H), 2.20 (s, 3H).

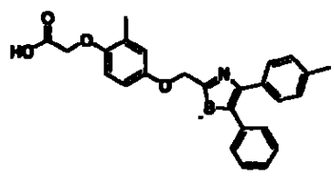
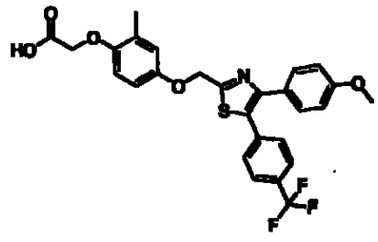
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		MS calculada para $C_{28}H_{24}NO_6S$ (M+H$^+$) 462.1, encontrada 462.4.
E67		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.41-7.22 (m, 7H), 7.03-6.97 (m, 3H), 6.88 (dd, J=3.0 Hz, J=8.9 Hz, 1H), 6.79 (d, J=8.9 Hz, 1H), 5.40 (s, 2H), 4.63 (s, 2H), 3.62 (s, 3H), 2.19 (s, 3H). MS calculada para $C_{28}H_{24}NO_6S$ (M+H$^+$) 462.1, encontrada 462.4.
E68		MS calculada para $C_{28}H_{21}F_3NO_4S$ (M+H$^+$) 500.1, encontrada 500.4.
E69		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.75-7.34 (m, 9H), 6.98 (d, J=3 Hz, 1H), 6.88 (dd, J=3.0 Hz, J=8.9 Hz, 1H), 6.79 (d,

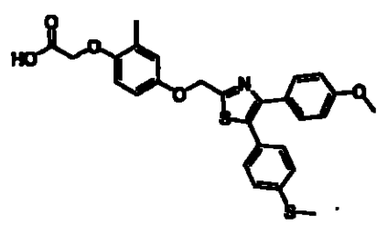
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		J=8.9 Hz, 1H), 5.43 (s, 2H), 4.64 (s, 2H), 2.20 (s, 3H). MS calculada para $C_{28}H_{21}F_3NO_4S$ ($M+H^+$) 5001., encontrada 500.3.
E70		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.71-7.63 (m, 4H), 7.44-7.33 (m, 5H), 6.97 (d, J=3 Hz, 1H), 6.88 (dd, J=3.0 Hz, J=8.9 Hz, 1H), 6.79 (d, J=8.9 Hz, 1H), 5.42 (s, 2H), 4.64 (s, 2H), 2.19 (s, 3H). MS calculada para $C_{28}H_{21}F_3NO_4S$ ($M+H^+$) 500.1, encontrada 500.4.
E71		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.46-7.26 (m, 9H), 6.97 (d, J=3.0 Hz, 1H), 6.88 (dd, J=3.0 Hz, J=8.9 Hz, 1H), 6.79 (d, J=8.9 Hz, 1H), 5.41 (s, 2H), 4.64 (s, 2H), 2.19 (s, 3H). MS

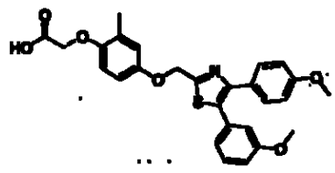
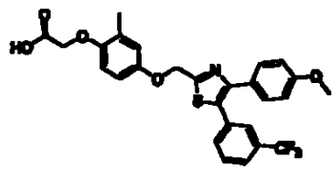
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		calculada para $C_{25}H_{21}ClNO_4S$ ($M+H^+$) 466.1, encontrada 466.3.
E72		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.47-7.30 (m, 9H), 6.96 (d, J=3.0 Hz, 1H), 6.87 (dd, J=3.0 Hz, J=8.9 Hz, 1H), 6.79 (d, J=8.9 Hz, 1H), 5.40 (s, 2H), 4.64 (s, 2H), 2.19 (s, 3H). MS calculada para $C_{25}H_{21}ClNO_4S$ ($M+H^+$) 466.1, encontrada 466.3.
E73		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.43-7.12 (m, 8H), 6.97-6.79 (m, 4H), 5.39 (s, 2H), 4.64 (s, 2H), 3.64 (s, 3H), 2.19 (s, 3H). MS calculada para $C_{26}H_{24}NO_5S$ ($M+H^+$) 462.1, encontrada 462.4.
E74		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ

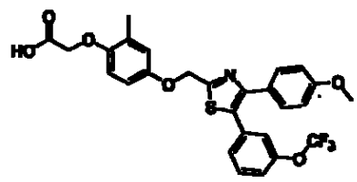
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		=7.45-7.31 (m, 8H), 7.17-6.78 (m, 9H), 5.38 (s, 2H), 4.63 (s, 2H), 2.19 (s, 3H). MS calculada para $C_{31}H_{28}NO_5S$ ($M+H^+$) 524.2, encontrada 524.4.
E75		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.48-7.30 (m, 5H), 6.96-6.78 (m, 6H), 6.06 (s, 2H), 5.37 (s, 2H), 4.63 (s, 2H), 2.19 (s, 3H). MS calculada para $C_{28}H_{22}NO_6S$ ($M+H^+$) 476.1, encontrada 476.4.
E76		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 8.64 (d, J=1.7 Hz, 1H), 8.54 (dd, J=1.4 Hz, J=4.8 Hz, 1H), 7.91 (d, J=8.0 Hz), 7.47 (dd, J=5.0 Hz, J=7.9 Hz, 1H), 7.27 (d, J=8.1 Hz, 2H), 7.24 (d, J=8.1 Hz, 2H), 6.97 (d, J=3.0

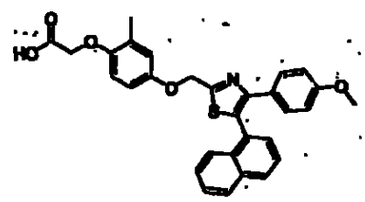
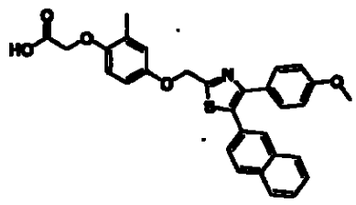
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		Hz, 1H), 6.87 (dd, J=3.0 Hz, J=8.9 Hz, 1H), 6.79 (d, J=8.9 Hz, 1H), 5.41 (s,2H), 4.64 (s, 2H), 2.34 (s, 3H), 2.19 (s, 3H). MS calculada para $C_{25}H_{23}N_2O_4S$ ($M+H^+$) 447.1, encontrada 447.4.
E87		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.40-7.34 (m, 7H), 6.96 (d, J=3.0 Hz, 1H), 6.87 (m, 3H), 6.78 (d, J=8.9 Hz, 1H), 5.38 (s, 2H), 4.63 (s, 2H), 3.74 (s, 3H), 2.19 (s, 3H). MS calculada para $C_{26}H_{24}NO_5S$ ($M+H^+$) 462.1, encontrada 462.4.
E90		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.62-7.25 (m, 9H), 6.98 (d, J=3.0 Hz, 1H), 6.89 (dd, J=3.0 Hz, J=8.9 Hz, 1H), 6.80 (d,

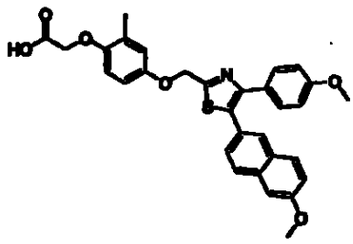
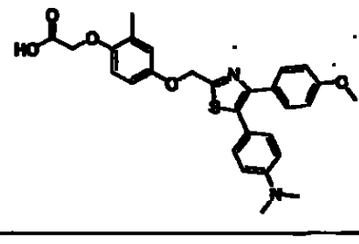
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		J=8.9 Hz, 1H), 5.44 (s, 2H), 4.64 (s, 2H), 2.20 (s, 3H). MS calculada para $C_{26}H_{21}ClNO_4S$ $(M+H^+)$ 466.1, encontrada 466.3.
E91		^{1}H-RMN (600MHz, $CD_3)_2SO$) δ = 7.40-7.33 (m, 7H), 7.13 (d, J=8.0 Hz, 2H), 6.96 (d, J=3.0 Hz, 1H), 6.87 (dd, J=3.0 Hz, J=8.9 Hz, 1H), 6.79 (d, J=8.9 Hz, 1H), 5.39 (s, 2H), 4.63 (s, 2H), 2.29 (s, 3H), 2.19 (s, 3H). MS calculada para $C_{26}H_{24}NO_4S$ $(M+H^+)$ 446.1, encontrada 446.4.
F2		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.48 (d, J=8.2 Hz, 2H), 7.36 (d, J=8.2 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 6.83 (d, J=3.0 Hz, 1H), 6.77 (d, J=8.8 Hz,

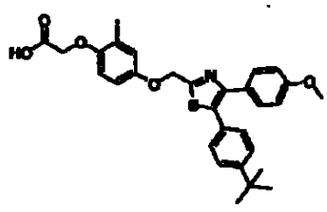
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2H), 6.71 (dd, J=3.0, 8.9 Hz, 1H), 6.64 (d, J=8.8 Hz, 1H), 5.26 (s, 2H), 4.56 (s, 2H), 3.74 (s, 3H), 2.21 (s, 3H). MS calculada para $C_{27}H_{23}F_3NO_6S$ ($M+H^+$) 530.1, encontrada 530.3.
F3		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.35 (d, J=8.8 Hz, 2H), 7.15 (d, J=8.3 Hz, 2H), 7.09 (d, J=8.4 Hz, 2H), 6.82 (d, J=2.8 Hz, 1H), 6.76 (d, J=8.8 Hz, 2H), 6.71 (dd, J=3.1, 8.9 Hz, 1H), 6.63 (d, J=8.8 Hz, 1H), 5.26 (s, 2H), 4.55 (s, 2H), 3.74 (s, 3H), 2.41 (s, 3H), 2.21 (s, 3H). MS calculada para $C_{27}H_{26}NO_5S_2$ ($M+H^+$) 508.1, encontrada 508.3.
F4		^{1}H-RMN (400MHz, $CDCl_3$) δ =

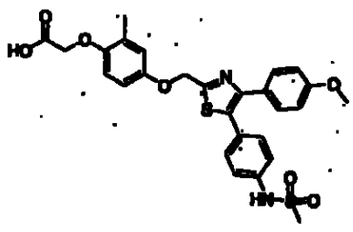
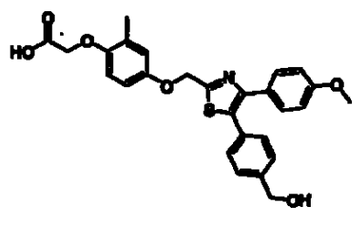
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		7.42 (d, J=8.8 Hz, 2H), 7.22 (t, J=7.5 Hz, 1H), 6.90 (m, 2H), 6.86 (m, 4H), 6.77 (dd, J=3.1, 8.8 Hz, 1H), 6.70 (d, J=8.8 Hz, 1H), 5.35 (s, 2H), 4.63 (s, 2H), 3.81 (s, 3H), 3.70 (s, 3H), 2.28 (s, 3H). MS calculada para $C_{27}H_{28}NO_6S$ ($M+H^+$) 492.1, encontrada 492.4.
F5		^{1}H-RMN (400MHz, $CDCl_3$) δ =7.61 (s, 1H), 7.56 (d, J=7.6 Hz, 1H), 7.47 (d, J=8.0 Hz, 1H), 7.43 (d, J=7.6 Hz, 1H), 7.38 (d, J=8.8 Hz, 2H), 6.90 (d, J=2.8 Hz, 1H), 6.85 (d, J=8.8 Hz, 2H), 6.78 (dd, J=3.2, 8.8 Hz, 1H), 6.71 (d, J=8.8 Hz, 1H), 5.37 (s, 2H), 4.64 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS

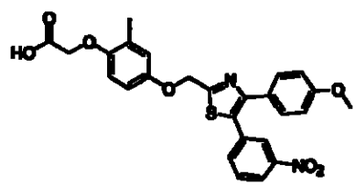
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		calculada para $C_{27}H_{23}F_3NO_6S$ ($M+H^+$) 530.1, encontrada 530.4.
F6		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.39 (d, J=8.8 Hz, 2H), 7.34 (t, J=7.2 Hz, 1H), 7.27 (d, J=7.2 Hz, 1H), 7.15 (m, 2H), 6.90 (d, J=2.8 Hz, 1H), 6.85 (d, J=8.8 Hz, 2H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J=8.8 Hz, 1H), 5.35 (s, 2H), 4.64 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{27}H_{23}F_3NO_6S$ ($M+H^+$) 546.1, encontrada 546.0.
F7		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.91 (m, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.48 (m, 3H), 7.40 (m, 1H), 7.33 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 2.8 Hz, 1H),

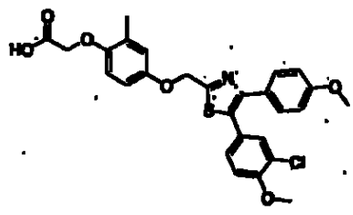
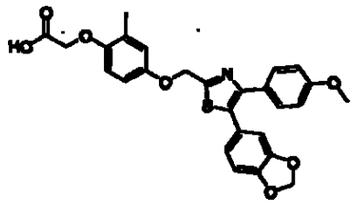
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		6.82 (dd, J = 2.8, 8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 6.64 (d, J = 8.9 Hz, 2H), 5.42 (s, 2H), 4.65 (s, 2H), 3.69 (s, 3H), 2.30 (s, 3H). MS calculada para $C_{30}H_{26}NO_5S$ ($M+H^+$) 512.2, encontrada 512.1.
F8		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.88 (s, 1H), 7.76 (m, 3H), 7.49 (m, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.34 (dd, J = 1.6, 8.4 Hz, 1H), 6.92 (d, J = 2.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.39 (s, 2H), 4.64 (s, 2H), 3.80 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{30}H_{26}NO_5S$ ($M+H^+$) 512.2, encontrada 512.1.

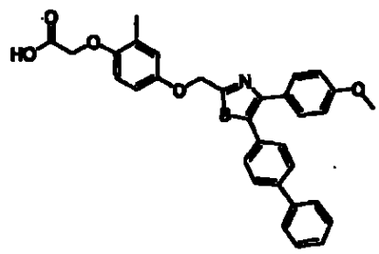
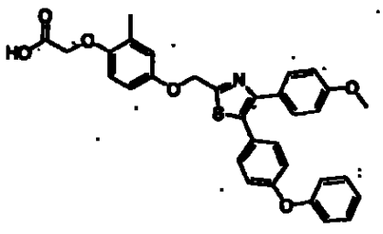
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
F9		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.78 (s, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.43 (d, J = 8.8 Hz, 2H), 7.29 (dd, J = 2.0, 8.4 Hz, 1H), 7.16 (dd, J = 2.4, 8.8 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 6.91 (d, J = 2.8 Hz, 1H), 6.81 (d, J = 9.2 Hz, 2H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.39 (s, 2H), 4.64 (s, 2H), 3.95 (s, 3H), 3.80 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{31}H_{29}NO_6S$ ($M+H^+$) 542.2, encontrada 542.4.
F10		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.50 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 2.8

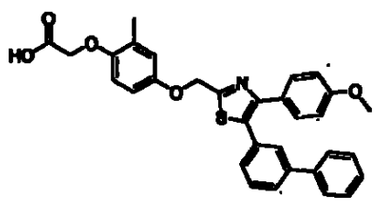
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 6.88 (dd, J = 2.8, 8.8 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 5.46 (s, 2H), 4.73 (s, 2H), 3.93 (s, 3H), 3.22 (s, 6H), 2.39 (s, 3H). MS calculada para $C_{28}H_{28}NO_5S$ ($M+H^+$) 505.2, encontrada 505.4.
F11		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.40 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 2.4 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.44 (s, 2H), 4.63 (s, 2H), 3.83 (s, 3H), 2.28 (s, 3H), 1.31 (s, 9H). MS calculada para $C_{30}H_{32}NO_5S$ ($M+H^+$) 518.2, encontrada 518.4.

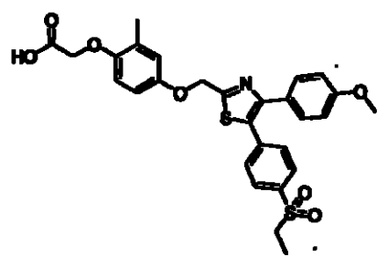
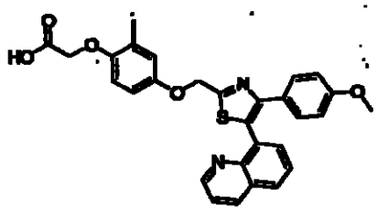
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
F12		^{1}H-RMN (400MHz, DMSO-d_6) δ = 9.98 (s, 1H), 7.40 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 2.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 6.86 (dd, J = 2.8, 8.8 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.63 (s, 2H), 3.76 (s, 3H), 2.51 (s, 3H), 2.20 (s, 3H). MS calculada para $C_{27}H_{27}N_2O_7S_2$ ($M+H^+$) 555.1, encontrada 555.3.
F13		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.39 (d, J = 8.8 Hz, 2H), 7.30 (s, 4H), 6.88 (d, J = 2.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.76 (dd, J = 2.8, 9.2 Hz, 1H), 6.68 (d, J = 9.2 Hz, 1H), 5.33 (s, 2H), 4.69 (s, 2H), 4.61 (s,

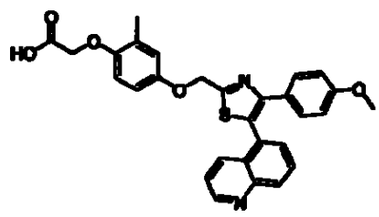
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2H), 3.79 (s, 3H), 2.26 (s, 3H). MS calculada para $C_{27}H_{26}NO_6S$ ($M+H^+$) 492.1, encontrada 492.4.
F14		^{1}H-RMN (400MHz, DMSO-d_6) δ = 8.21 (d, J = 7.2 Hz, 1H), 8.14 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 8.0 Hz, 1H), 7.39 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 2.8 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 6.85 (dd, J = 2.8, 8.8 Hz, 1H), 6.79 (d, J = 9.2 Hz, 1H), 5.42 (s, 2H), 4.63 (s, 2H), 3.76 (s, 3H), 2.20 (s, 3H). MS calculada para $C_{26}H_{23}N_2O_7S$ ($M+H^+$) 507.1, encontrada 507.4.
F15		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.41 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 2.4 Hz, 1H), 7.15 (dd, J

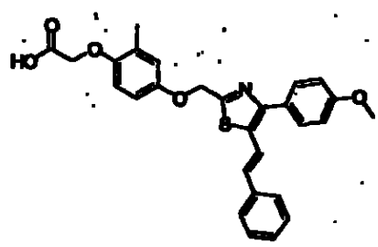
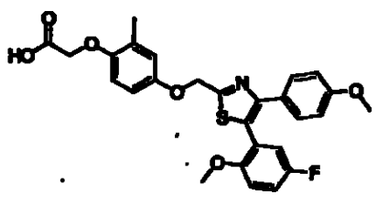
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		= 2.0, 8.4 Hz, 1H), 6.89 (d, J = 2.8 Hz, 1H), 6.84 (m, 3H), 6.76 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.32 (s, 2H), 4.63 (s, 2H), 3.94 (s, 3H), 3.82 (s, 3H), 2.28 (s, 3H). MS calculada para $C_{27}H_{26}ClNO_6S$ ($M+H^+$) 526.1, encontrada 526.3.
F16		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.40 (d, J = 8.8 Hz, 2H), 6.96 (s, 1H), 6.94 (s, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.86 (m, 3H), 6.78 (d, J = 9.2 Hz, 1H), 6.10 (s, 2H), 5.37 (s, 2H), 4.63 (s, 2H), 3.76 (s, 3H), 2.19 (s, 3H). MS calculada para $C_{27}H_{24}NO_7S$ ($M+H^+$) 506.1, encontrada 506.4.
F17		^{1}H-RMN (400MHz, $CDCl_3$) δ =

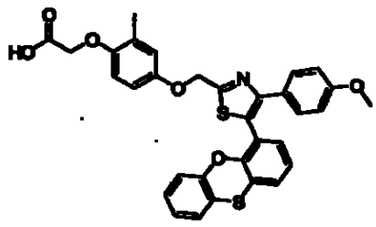
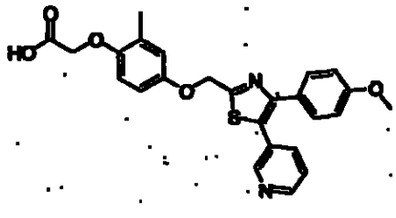
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		7.60 (d, J = 7.6 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.41 (m, 7H), 6.91 (d, J = 2.8 Hz, 1H), 6.85 (d, J = 8.4 Hz, 2H), 6.79 (dd, J = 2.4, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.64 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{32}H_{28}NO_5S$ ($M+H^+$) 538.2, encontrada 538.4.
F18		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.43 (d, J = 8.4 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.14 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 7.6 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 2.4, 8.4 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.63

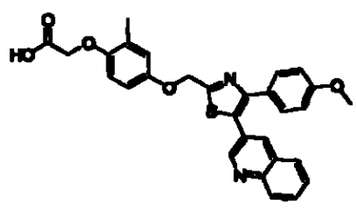
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{32}H_{28}NO_6S$ ($M+H^+$) 554.2, encontrada 554.4.
F19		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.56 (t, J = 1.6 Hz, 1H), 7.53 (dt, J = 1.6, 8.0 Hz, 1H), 7.47 (d, J = 8.8 Hz, 4H), 7.40 (m, 3H), 7.32 (m, 2H), 6.91 (d, J = 3.2 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.63 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{32}H_{28}NO_5S$ ($M+H^+$) 538.2, encontrada 538.1.
F20		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.83 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.8 Hz, 1H), 7.37 (d, J

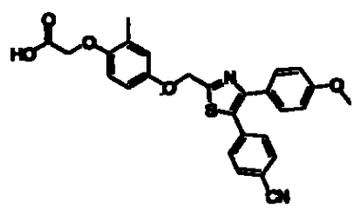
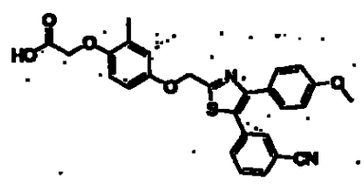
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		= 8.8 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 6.79 (dd, J = 2.4, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.64 (s, 2H), 3.85 (s, 3H), 3.13 (q, J = 7.2 Hz, 2H), 2.29 (s, 3H), 1.30 (t, J = 7.6 Hz, 3H). MS calculada para $C_{28}H_{28}NO_7S_2$ ($M+H^+$) 554.1, encontrada 554.0.
F21		^{1}H-RMN (400MHz, $CDCl_3$) δ = 9.10 (dd, J = 1.6, 4.8 Hz, 1H), 8.55 (dd, J = 1.6, 8.4 Hz, 1H), 8.03 (dd, J = 1.2, 8.4 Hz, 1H), 7.94 (dd, J = 1.6, 7.2 Hz, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.70 (dd, J = 4.8, 8.0 Hz, 1H), 7.25 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 2.4 Hz, 1H), 6.79 (dd, J = 2.4, 8.8 Hz, 1H), 6.67 (m, 3H),

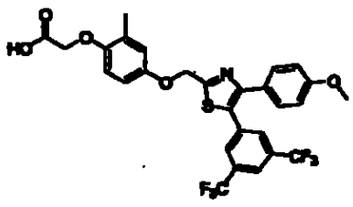
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6). y/o MS (m/z)
		5.44 (s, 2H), 4.61 (s, 2H), 3.73 (s, 3H), 2.26 (s, 3H). MS calculada para $C_{28}H_{25}N_2O_6S$ ($M+H^+$) 513.1, encontrada 513.0.
F22		^{1}H-RMN (400MHz, $CDCl_3$) δ = 9.19 (d, J = 4.8 Hz, 1H), 8.57 (d, J = 8.4 Hz, 1H), 8.51 (d, J = 8.8 Hz, 1H), 8.03 (t, J = 7.6 Hz, 1H), 7.91 (d, J = 7.2 Hz, 1H), 7.63 (m, 2H), 7.50 (m, 1H), 7.22 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 2.8 Hz, 1H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 6.66 (d, J = 8.8 Hz, 2H), 5.42 (s, 2H), 4.65 (s, 2H), 3.70 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{28}H_{25}N_2O_6S$ ($M+H^+$) 513.1, encontrada 513.4.

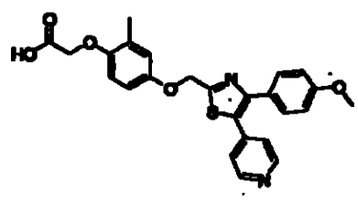
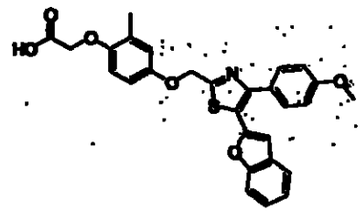
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
F23		^{1}H-RMN (400MHz, DMSO-d_6) δ = 7.54 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 7.6 Hz, 2H), 7.24 (m, 2H), 7.20 (m, 2H), 7.02 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 16.0 Hz, 1H), 6.88 (d, J = 2.8 Hz, 1H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.31 (s, 2H), 4.56 (s, 2H), 3.76 (s, 3H), 2.12 (s, 3H). MS calculada para $C_{28}H_{26}NO_5S$ ($M+H^+$) 488.1, encontrada 488.4.
F24		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.84 (d, J = 8.8 Hz, 0.7H), 7.38 (d, J = 8.8 Hz, 1.3H), 6.70-7.02 (m, 8H), 5.36 (s, 1.3H), 5.27 (s, 0.7H), 4.63 (s, 2H), 3.86 (s, 1.1H), 3.80 (s,

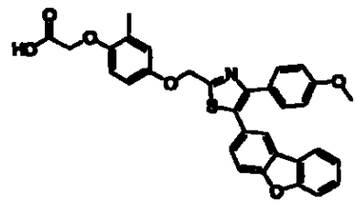
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1.9H), 3.66 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{27}H_{25}FNO_6S$ ($M+H^+$) 510.1, encontrada 510.0
F25		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.43 (d, J = 8.8 Hz, 2H), 7.12 (dd, J = 1.6, 7.6 Hz, 1H), 7.09 (dd, J = 2.0, 9.2 Hz, 1H), 7.00 (m, 5H), 6.80 (m, 3H), 6.72 (d, J = 8.8 Hz, 1H), 6.63 (dd, J = 2.0, 7.6 Hz, 1H), 5.47 (s, 2H), 4.65 (s, 2H), 3.76 (s, 3H), 2.30 (s, 3H). MS calculada para $C_{32}H_{28}NO_6S$ ($M+H^+$) 584.1, encontrada 584.0.
F26		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.74 (d, J = 2.0 Hz, 1H), 8.66 (dd, J = 1.6, 5.2, Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.54 (m, 1H), 7.36 (d, J = 8.8 Hz, 2H),

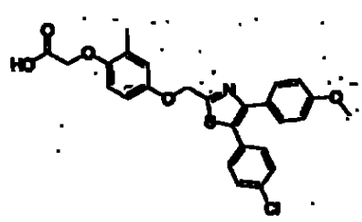
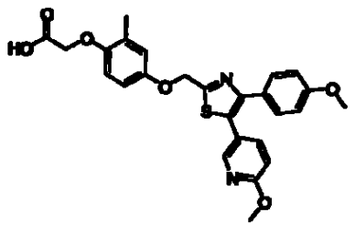
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		6.88 (m, 3H), 6.77 (dd, J = 2.8, 8.4 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.38 (s, 2H), 4.67 (s, 2H), 3.83 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{28}H_{23}N_2O_5S$ ($M+H^+$) 463.1, encontrada 463.0.
F27		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.86 (d, J = 2.0 Hz, 1H), 8.24 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.77 (m, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.63 (s, 2H), 3.77 (s, 3H), 2.27 (s, 3H). MS calculada para $C_{28}H_{25}N_2O_5S$ ($M+H^+$) 513.1, encontrada

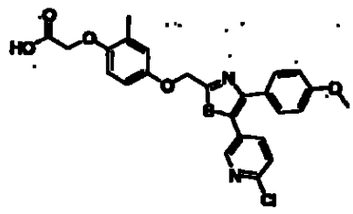
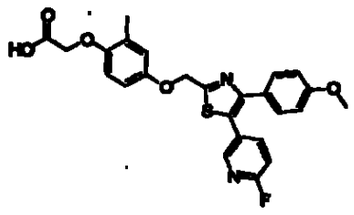
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		513.0.
F28		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.59 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 3.2, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 3.83 (s, 3H), 2.29 (s, 3H).
F29		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.55 (d, J = 1.2 Hz, 1H), 7.51 (dd, J = 1.2, 7.6 Hz, 1H), 7.48 (dd, J = 1.2, 8.0 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.78 (d, J = 8.8 Hz, 2H), 6.71 (dd, J = 2.4, 8.8 Hz, 1H), 6.63 (d, J= 8.8 Hz, 1H), 5.28 (s, 2H), 4.57 (s, 2H), 3.75

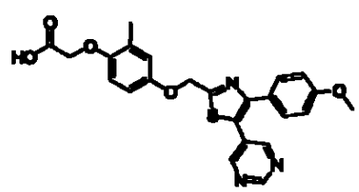
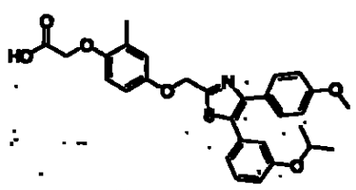
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(s, 3H), 2.22 (s, 3H). MS calculada para $C_{27}H_{23}N_2O_6S$ ($M+H^+$) 487.1, encontrada 487.4.
F30		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.78 (s, 1H), 7.76 (s, 2H), 7.37 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{28}H_{22}F_6NO_5S$ ($M+H^+$) 598.1, encontrada 598.3.
F31		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.60 (d, J = 5.6 Hz, 2H), 7.62 (d, J = 5.6 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4

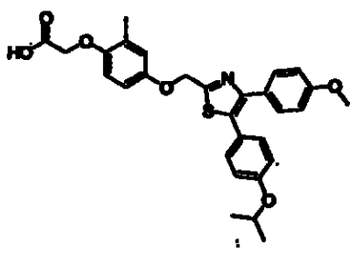
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.71 (dd, J = 2.8, 8.8 Hz, 1H), 6.65 (d, J = 8.8 Hz, 1H), 5.30 (s, 2H), 4.59 (s, 2H), 3.80 (s, 3H), 2.23 (s, 3H). MS calculada para $C_{25}H_{23}N_2O_5S$ ($M+H^+$) 463.1, encontrada 463.1.
F32		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.48 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 7.6 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 3.2 Hz, 1H), 6.73 (dd, J = 3.2, 8.8 Hz, 1H), 6.72 (s, 1H), 6.64 (d, J = 8.8 Hz, 1H), 5.28 (s, 2H), 4.48 (s, 2H), 3.71 (s, 3H), 2.10 (s, 3H). MS calculada para $C_{26}H_{24}NO_6S$

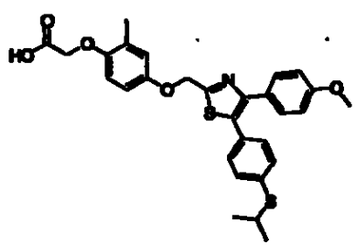
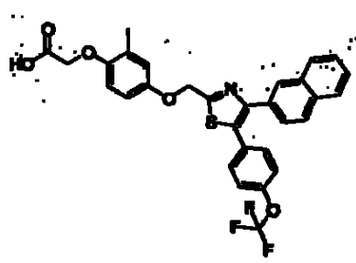
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(M+H$^+$) 502.1, encontrada 502.3.
F33		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.85 (d, J = 8.0 Hz, 1H), 7.82 (dd, J = 1.2, 7.6 Hz, 1H), 7.34 (m, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.24 (m, 2H), 7.17 (d, J = 7.6 Hz, 1H), 6.83 (d, J = 2.8 Hz, 1H), 6.72 (dd, J = 2.8, 8.8 Hz, 1H), 6.64 (d, J = 8.8 Hz, 2H), 6.62 (d, J = 8.8 Hz, 1H), 5.32 (s, 2H), 4.53 (s, 2H), 3.65 (s, 3H), 2.19 (s, 3H). MS calculada para $C_{32}H_{29}NO_6S$ (M+H$^+$) 552.1, encontrada 552.4.
F34		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.40 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 2.8

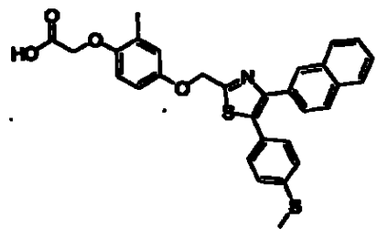
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 3.2, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H), 4.63 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{26}H_{23}ClNO_6S$ ($M+H^+$) 496.1, encontrada 496.3.
F35		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.18 (d, J = 2.0 Hz, 1H), 7.47 (dd, J = 2.0, 8.8 Hz, 1H), 7.40 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.76 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 5.33 (s, 2H), 4.63 (s, 2H), 3.95 (s, 3H), 3.81 (s, 3H), 2.28 (s, 3H). MS calculada par $C_{26}H_{26}N_2O_6S$ ($M+H^+$) 493.1,

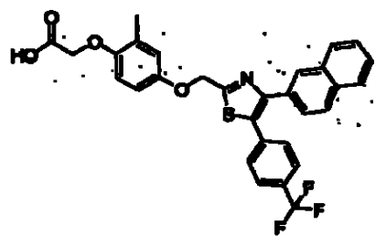
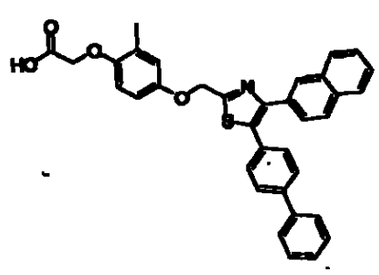
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		encontrada 493.1.
F36		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.40 (d, J = 2.4 Hz, 1H), 7.57 (dd, J = 2.4, 8.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 2.8 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{25}H_{22}ClN_2O_6S$ ($M+H^+$) 497.1, encontrada 497.0.
F37		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.22 (d, J = 2.0 Hz, 1H), 7.69 (dt, J = 2.4, 8.4 Hz, 1H), 7.37 (d, J = 8.8 Hz, 2H), 6.88 (m, 2H), 6.85 (d, J = 8.8 Hz, 2H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H),

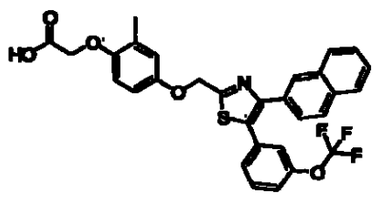
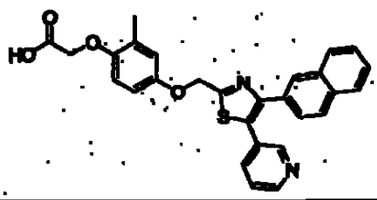
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		8.70 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.64 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{25}H_{22}FN_2O_5S$ $(M+H^+)$ 481.1, encontrada 481.0.
F38		^{1}H-RMN (400MHz, $CDCl_3$) δ = 9.14 (s, 1H), 8.71 (s, 2H), 7.37 (d, J = 8.8 Hz, 2H), 6.87 (m, 3H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.64 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{24}H_{22}N_3O_5S$ $(M+H^+)$ 464.1, encontrada 464.1.
F39		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.42 (d, J = 8.8 Hz, 2H), 7.20 (t, J = 8.0 Hz, 1H), 6.85 (m, 6H), 6.76 (dd, J = 2.8, 8.8 Hz,

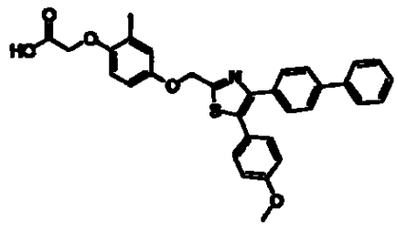
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1H), 6.69 (d, J = 9.2 Hz, 1H), 5.35 (s, 2H), 4.63 (s, 2H), 4.39 (m, 1H), 3.80 (s, 3H), 2.28 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H). MS calculada para $C_{28}H_{30}NO_6S$ ($M+H^+$) 520.2, encontrada 520.1.
F40		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.41 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.83 (d, J = 9.2 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.76 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 9.2 Hz, 1H), 5.35 (s, 2H), 4.62 (s, 2H), 4.55 (m, 1H), 3.81 (s, 3H), 2.28 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H). MS calculada para $C_{28}H_{30}NO_6S$ ($M+H^+$) 520.2, encontrada 520.1.

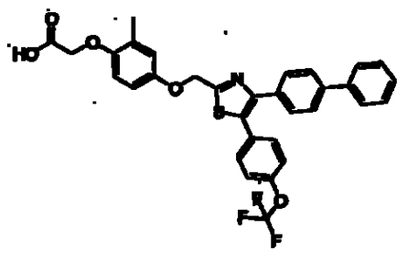
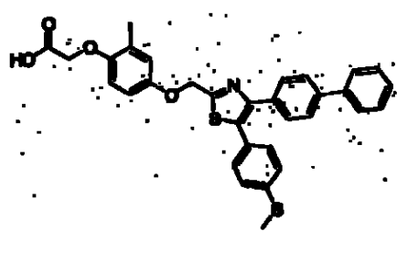
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
F41		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.40 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.63 (s, 2H), 3.81 (s, 3H), 3.42 (m, 1H), 2.28 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H). MS calculada para $C_{29}H_{30}NO_5S_2$ (M+H$^+$) 536.2, encontrada 536.1.
F42		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.05 (s, 1H), 7.81 (dd, J = 2.4, 6.8 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.48 (m, 3H), 7.37 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 2.8 Hz, 1H), 6.81 (dd, J = 2.8, 8.8

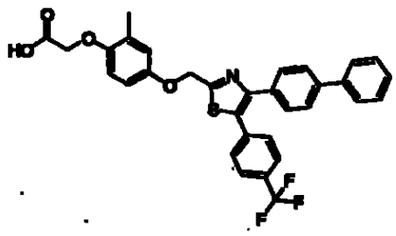
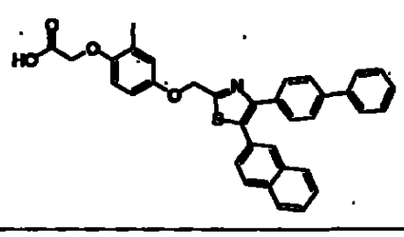
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.38 (s, 2H), 4.64 (s, 2H), 2.29 (s, 3H). MS calculada para $C_{30}H_{23}F_3NO_5S$ ($M+H^+$) 566.2, encontrada 566.1.
F43		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.09 (s, 1H), 7.80 (m, 2H), 7.74 (d, J = 8.4 Hz, 1H), 7.51 (dd, J = 1.6, 8.4 Hz, 1H), 7.47 (m, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 2.8 Hz, 1H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.38 (s, 2H), 4.64 (s, 2H), 2.47 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{30}H_{28}NO_4S_2$ ($M+H^+$) 528.1, encontrada 528.1.
F44		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.05 (s, 1H), 7.82 (dd, J = 2.0,

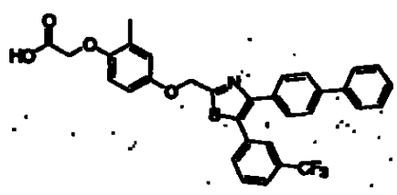
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		7.2 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.48 (m, 5H), 6.92 (d, J = 2.8 Hz, 1H), 6.82 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.41 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{30}H_{23}F_3NO_4S$ ($M+H^+$) 550.1, encontrada 550.1.
F45		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.14 (s, 1H), 7.80 (m, 2H), 7.76 (d, J = 8.8 Hz, 1H), 7.56 (m, 5H), 7.46 (m, 6H), 7.37 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 2.8 Hz, 1H), 6.83 (dd, J = 3.2, 8.8 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 5.41 (s, 2H), 4.65 (s, 2H), 2.31 (s, 3H). MS calculada para $C_{36}H_{28}NO_4S$

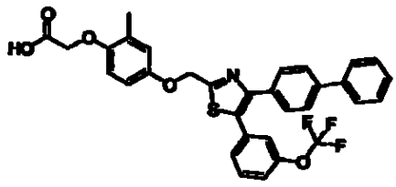
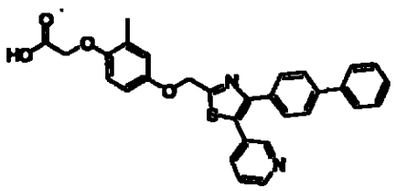
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(M+H$^+$) 558.2, encontrada 558.1.
F46		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.07 (s, 1H), 7.81 (dd, J = 2.0, 8.8 Hz, 1H), 7.75 (m, 2H), 7.47 (m, 3H), 7.31 (m, 2H), 7.23 (s, 1H), 7.17 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 2.8 Hz, 1H), 6.81 (dd, J = 2.8, 8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 5.39 (s, 2H), 4.64 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{30}H_{23}F_3NO_5S$ (M+H$^+$) 566.1, encontrada 566.1.
F47		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.88 (d, J = 1.6 Hz, 1H), 8.72 (d, J = 5.6 Hz, 1H), 8.01 (m, 2H), 7.84 (t, J = 8.0 Hz, 2H), 7.78 (d, J = 7.2 Hz, 1H), 7.54

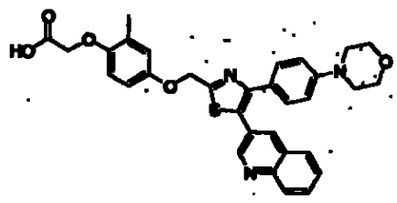
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(m, 3H), 7.43 (dd, J = 1.6, 8.4 Hz, 1H), 6.92 (d, J = 2.8 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 5.44 (s, 2H), 4.69 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{28}H_{23}N_2O_4S$ ($M+H^+$) 483.1, encontrada 483.1.
F48		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.54 (m, 5H), 7.40 (t, J = 7.2 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 2.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 6.75 (dd, J = 2.8, 8.8 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 5.31 (s, 2H), 4.60 (s, 2H), 3.79 (s, 3H), 2.26 (s, 3H). MS calculada para $C_{32}H_{28}NO_5S$ ($M+H^+$) 538.2, encontrada 538.4.

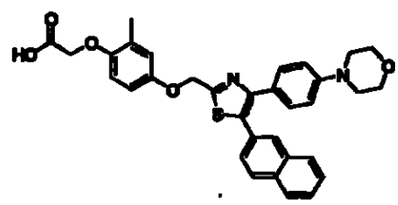
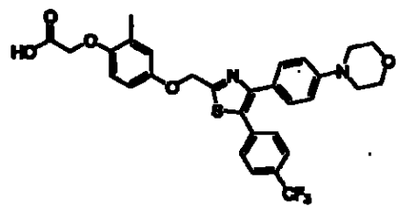
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
F49		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.61 (d, J = 7.2 Hz, 2H), 7.56 (s, 4H), 7.44 (t, J = 7.2 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 2.8 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.64 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{32}H_{25}F_3NO_6S$ ($M+H^+$) 592.1, encontrada 592.4.
F50		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.54 (m, 6H), 7.41 (t, J = 7.2 Hz, 2H), 7.32 (t, J = 7.2 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J =

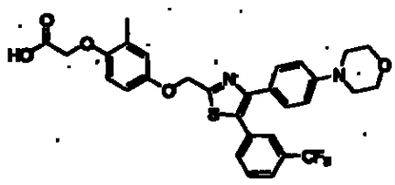
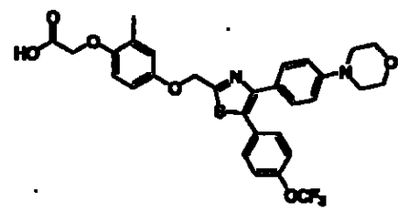
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		8.8 Hz, 1H), 5.33 (s, 2H), 4.61 (s, 2H), 2.47 (s, 3H), 2.27 (s, 3H). MS calculada para $C_{32}H_{28}NO_4S$ (M+H$^+$) 554.1, encontrada 554.3.
F51		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.58 (m, 8H), 7.49 (d, J = 8.4 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.35 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 2.8 Hz, 1H), 6.81 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{32}H_{25}F_3NO_4S$ (M+H$^+$) 576.1, encontrada 576.4.
F52		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.92 (s, 1H), 7.81 (m, 3H), 7.58 (m, 4H), 7.51 (m, 4H), 7.41 (m, 3H), 7.33 (t, J = 7.2

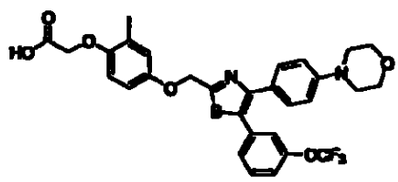
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		Hz, 1H), 6.94 (d, J = 2.8, 1H), 6.82 (dd, J = 2.8, 8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 5.40 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{35}H_{28}NO_4S$ ($M+H^+$) 558.2, encontrada 558.4.
F53		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.66 (s, 1H), 7.58 (m, 3H), 7.54 (m, 5H), 7.44 (t, J = 7.2 Hz, 3H), 7.35 (t, J = 7.2 Hz, 1H), 6.92 (d, J = 3.2 Hz, 1H), 6.81 (dd, J = 3.2, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.38 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{32}H_{25}F_3NO_4S$ ($M+H^+$) 576.1, encontrada 576.3.

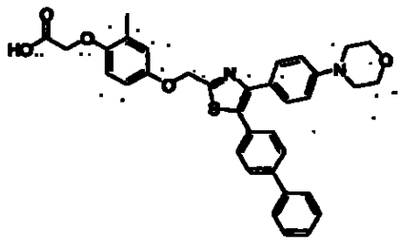
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
F54		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.60 (d, J = 7.2 Hz, 2H), 7.56 (s, 4HJ), 7.44 (t, J = 7.2 Hz, 2H), 7.35 (m, 3H), 7.23 (s, 1H), 7.18 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 2.8 Hz, 1H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{32}H_{25}F_3NO_5S$ ($M+H^+$) 592.1, encontrada 592.4.
F55		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.59 (m, 2H), 7.85 (dt, J = 2.0, 8.0 Hz, 1H), 7.69 (m, 4H), 7.53 (d, J = 8.4 Hz, 2H), 7.47 (t, J = 7.2 Hz, 2H), 7.37 (t, J = 7.6 Hz, 1H), 6.98 (d, J = 2.8 Hz, 1H), 6.89 (dd, J = 2.8, 8.8 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H),

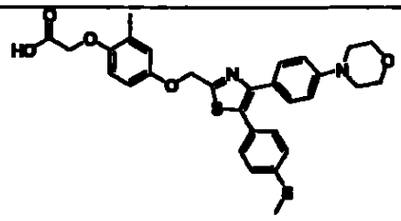
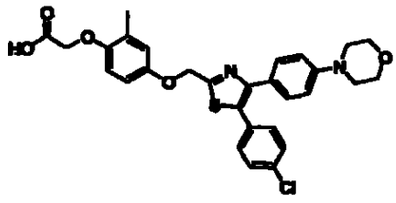
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		5.45 (s, 2H), 4.65 (s, 2H), 2.20 (s, 3H). MS calculada para $C_{30}H_{28}N_2O_4S$ (M+H$^+$) 509.2, encontrada 509.4.
F56		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.97 (d, J = 1.6 Hz, 1H), 8.47 (d, J = 1.6 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 7.90 (m, 2H), 7.74 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 8.8 Hz, 2H), 6.89 (m, 3H), 6.75 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.63 (s, 2H), 3.87 (m, 4H), 3.21 (m, 4H), 2.27 (s, 3H). MS calculada para $C_{32}H_{30}N_3O_5S$ (M+H$^+$) 568.2, encontrada 568.2.
F57		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.88 (s, 1H), 7.81 (m, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.52

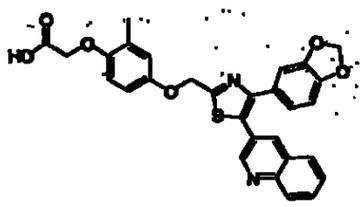
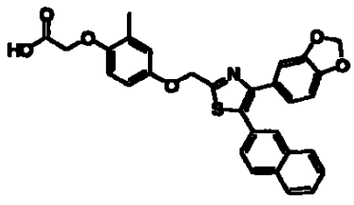
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(m, 5H), 7.32 (dd, J = 1.2, 8.4 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.75 (dd, J = 2.8 Hz, 1H), 6.75 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.38 (s, 2H), 4.64 (s, 2H), 3.99 (m, 4H), 3.37 (m, 4H), 2.28 (s, 3H). MS calculada para $C_{33}H_{31}N_2O_5S$ ($M+H^+$) 567.2, encontrada 567.2.
F58		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.57 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.63 (s, 2H), 3.92 (m, 4H), 3.27 (m, 4H), 2.28 (s,

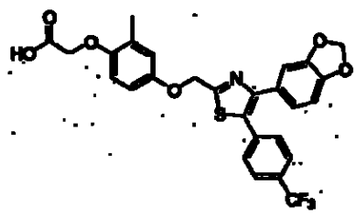
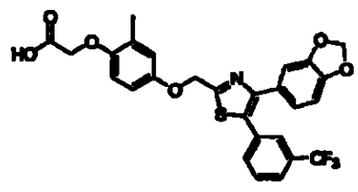
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		3H). MS calculada para $C_{30}H_{28}F_3N_2O_6S$ ($M+H^+$) 585.2, encontrada 585.2.
F59		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.60 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.43 (m, 3H), 7.03 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.63 (s, 2H), 3.94 (m, 4H), 3.29 (m, 4H), 2.28 (s, 3H). MS calculada para $C_{30}H_{28}F_3N_2O_6S$ ($M+H^+$) 585.2, encontrada 585.1.
F60		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.42 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 2.8 Hz,

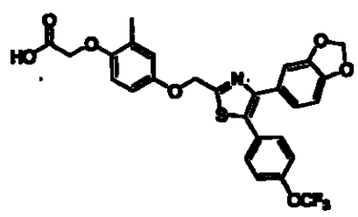
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H), 4.63 (s, 2H), 3.93 (m, 4H), 3.27 (m, 4H), 2.28 (s, 3H). MS calculada para $C_{30}H_{28}F_3N_2O_6S$ ($M+H^+$) 601.2, encontrada 601.2.
F61		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.45 (d, J = 8.8 Hz, 2H), 7.36 (t, J = 8.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.63 (s, 2H), 3.96 (m, 4H), 3.30 (m, 4H), 2.28 (s, 3H). MS calculada para $C_{30}H_{28}F_3N_2O_6S$ ($M+H^+$) 601.2, encontrada 601.2.

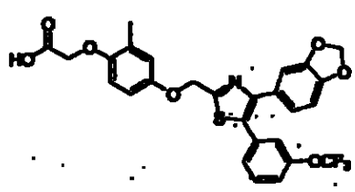
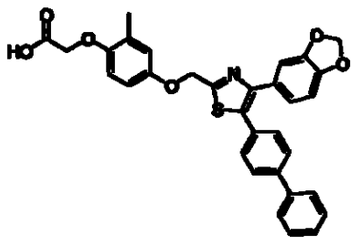
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
F62		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.52 (d, J = 8.4 Hz, 2H), 7.47 (t, J = 8.4 Hz, 4H), 7.37 (t, J = 7.6 Hz, 2H), 7.30 (m, 3H), 7.04 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 2.8 Hz, 1H), 6.70 (dd, J = 2.8, 8.8 Hz, 1H), 6.61 (d, J = 8.8 Hz, 1H), 5.27 (s, 2H), 4.55 (s, 2H), 3.90 (m, 4H), 3.26 (m, 4H), 2.20 (s, 3H). MS calculada para $C_{25}H_{33}N_2O_6S$ ($M+H^+$) 593.2, encontrada 593.2.
F63		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.54 (d, J = 8.8 Hz, 2H), 7.21 (m, 6H), 6.88 (d, J = 2.8 Hz, 1H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H), 4.63 (s, 2H), 4.03

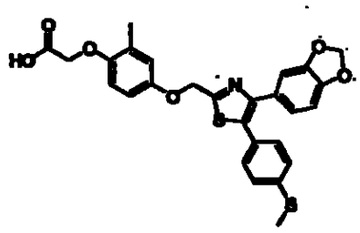
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(m, 4H), 3.40 (m, 4H), 2.49 (s, 3H), 2.28 (s, 3H). MS calculada para $C_{30}H_{33}N_2O_6S_2$ ($M+H^+$) 563.2, encontrada 563.2.
F64		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.48 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 2.8 Hz, 1H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H), 4.63 (s, 2H), 4.00 (m, 4H), 3.36 (m, 4H), 2.28 (s, 3H), 2.28 (s, 3H). MS calculada para $C_{29}H_{28}ClN_2O_6S$ ($M+H^+$) 551.1, encontrada 551.2.
F65		^{1}H-RMN (400MHz, $CDCl_3$) δ =

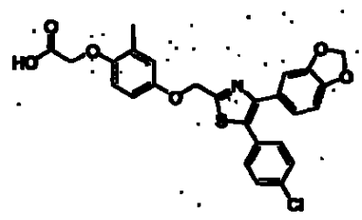
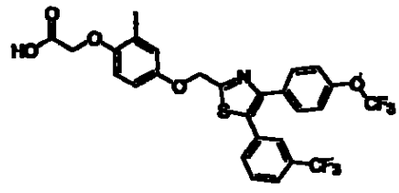
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		8.92 (d, J = 1.6 Hz, 1H), 8.36 (s, 1H), 8.29 (d, J = 8.8 Hz, 1H), 7.84 (m, 2H), 7.68 (t, J = 8.0 Hz, 1H), 6.97 (d, J = 1.2 Hz, 1H), 6.91 (m, 2H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.97 (s, 2H), 5.37 (s, 2H), 4.65 (s, 2H), 2.28 (s, 3H). MS calculada para $C_{29}H_{23}N_2O_6S$ ($M+H^+$) 527.1, encontrada 527.3.
F66		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.87 (s, 1H), 7.81 (m, 2H), 7.76 (d, J = 8.8 Hz, 1H), 7.51 (m, 2H), 7.33 (dd, J = 2.0, 8.8 Hz, 1H), 6.99 (m, 2H), 6.92 (d, J = 2.8 Hz, 1H), 6.81 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.0 Hz, 2H), 5.95 (s, 2H), 5.40

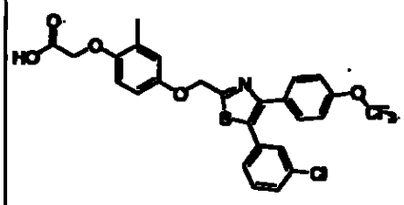
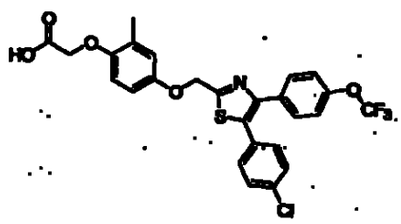
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{30}H_{24}NO_6S$ ($M+H^+$) 526.1, encontrada 526.3.
F67		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.57 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 6.94 (m, 2H), 6.90 (d, J = 3.2, Hz, 1H), 6.77 (m, 2H), 6.70 (d, J = 8.8 Hz, 1H), 5.98 (s, 2H), 5.33 (s, 2H), 4.64 (s, 2H), 2.29 (s, 3H). MS calculada para $C_{27}H_{21}F_3NO_6S$ ($M+H^+$) 544.1, encontrada 544.3.
F68		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.60 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 6.93 (m, 2H), 6.90 (d, J = 3.2 Hz, 1H), 6.78 (dd, J = 3.2, 8.8

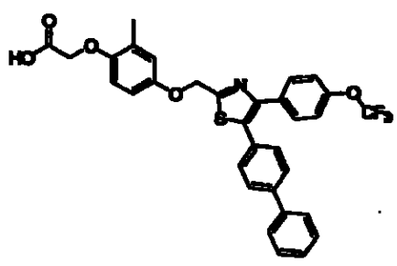
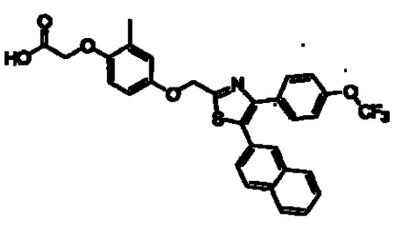
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.97 (s, 2H), 5.35 (s, 2H), 4.65 (s, 2H), 2.29 (s, 3H). MS calculada para $C_{27}H_{21}F_3NO_6S$ ($M+H^+$) 544.1, encontrada 544.3.
F69		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.35 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.94 (m, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.77 (m, 2H), 6.70 (d, J = 8.8 Hz, 1H), 5.97 (s, 2H), 5.33 (s, 2H), 4.64 (s, 2H), 2.29 (s, 3H). MS calculada para $C_{27}H_{21}F_3NO_7S$ ($M+H^+$) 560.1, encontrada 560.3.
F70		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.36 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.16 (m,

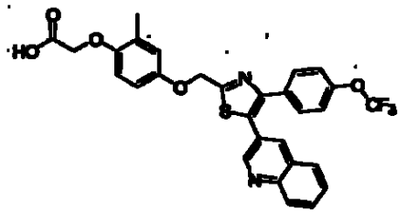
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2H), 6.95 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 1.2 Hz, 1H), 6.90 (d, J = 2.0 Hz, 1H), 6.77 (m, 2H), 6.70 (d, J = 8.8 Hz, 1H), 5.97 (s, 2H), 5.33 (s, 2H), 4.64 (s, 2H), 2.29 (s, 3H). MS calculada para $C_{27}H_{21}F_3NO_7S$ (M+H$^+$) 560.1, encontrada 560.3.
F71		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.58 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.37 (m, 3H), 7.02 (dd, J = 1.6, 8.0 Hz, 1H), 6.98 (d, J = 1.6 Hz, 1H), 6.90 (d, J = 2.4 Hz, 1H), 6.79 (dd, J =2.8, 8.8 Hz, 1H), 6.76 (d, J =8.0 Hz, 1H), 6.71 (d, J =8.8 Hz, 1H), 5.96 (s, 2H), 5.36 (s, 2H), 4.63 (s, 2H), 2.28 (s, 3H).

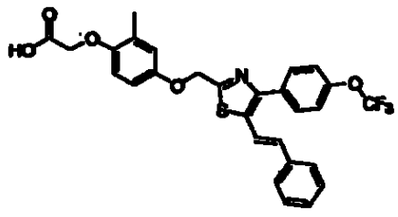
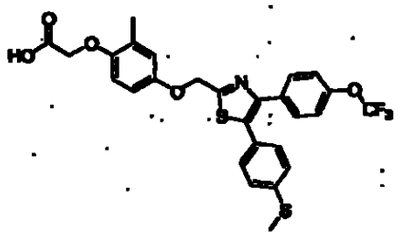
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		MS calculada para $C_{32}H_{28}NO_6S$ (M+H$^+$) 552.1, encontrada 552.4.
F72		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.25 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.69 (dd, J = 1.6, 8.0 Hz, 1H), 6.97 (d, J = 1.6 Hz, 1H), 6.90 (d, J = 3.2 Hz, 1H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.75 (d, J =8.4 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.96 (s, 2H), 5.33 (s, 2H), 4.63 (s, 2H), 2.49 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{27}H_{24}NO_6S_2$ (M+H$^+$) 522.1, encontrada 522.3.
F73		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.30 (d, J = 8.4 Hz, 2H), 7.26

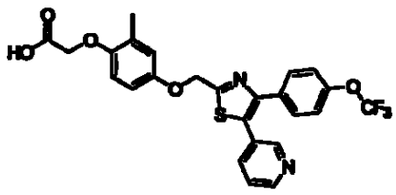
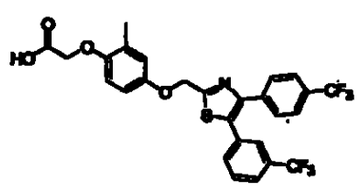
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(d, J = 8.8 Hz, 2H), 6.95 (dd, J = 1.6, 8.0 Hz, 1H), 6.93 (d, J = 1.6 Hz, 1H), 6.89 (d, J = 2.8 Hz, 1H), 6.78 (m, 2H), 6.70 (d, J = 8.8 Hz, 1H), 5.97 (s, 2H), 5.33 (s, 2H), 4.64 (s, 2H), 2.29 (s, 3H). MS calculada para $C_{26}H_{21}ClNO_6S$ ($M+H^+$) 510.1, encontrada 510.2.
F74		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.59 (d, J = 8.8 Hz, 2H), 7.48 (m, 4H), 7.16 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 2.8 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.65 (s, 2H), 2.29 (s, 3H). MS calculada para $C_{27}H_{20}F_6NO_5S$ ($M+H^+$) 584.1, encontrada 584.3.

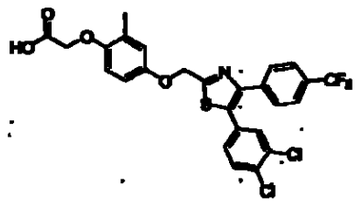
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
F75		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.52 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.26 (t, J = 8.0 Hz, 1H), 7.17 (t, J = 8.4 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.65 (s, 2H), 2.29 (s, 3H). MS calculada para $C_{26}H_{20}ClF_3NO_6S$ ($M+H^+$) 550.1, encontrada 550.3.
F76		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.49 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 2.8 Hz, 1H), 6.76 (dd, J = 2.8, 8.8 Hz, 1H), 6.68 (d, J = 8.8 Hz, 1H), 5.30 (s, 2H), 4.62 (s, 2H), 2.26 (s, 3H). MS calculada para

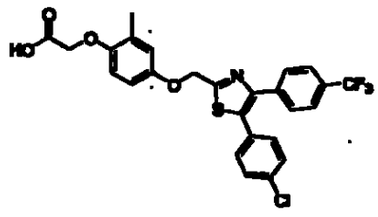
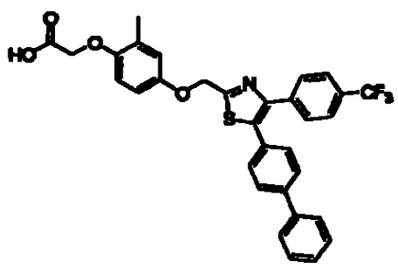
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		$C_{26}H_{20}ClF_3NO_6S$ ($M+H^+$) 550.1, encontrada 550.3.
F77		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.57 (m, 6H), 7.43 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 7.6 Hz, 3H), 7.13 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.75 (dd, J = 2.8, 8.8 Hz, 1H), 6.68 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H), 4.62 (s, 2H), 2.27 (s, 3H). MS calculada para $C_{32}H_{25}F_3NO_6S$ ($M+H^+$) 592.1, encontrada 592.4.
F78		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.87 (s, 1H), 7.83 (m, 1H), 7.78 (d, J=8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.51 (t, J =8.0 Hz, 2H), 7.34 (dd, J=1.6, 8.4 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 6.92 (d, J=2.8 Hz,

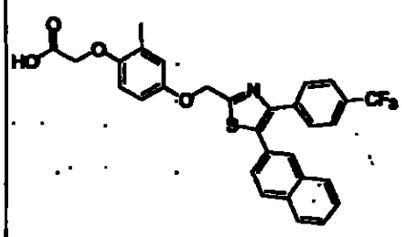
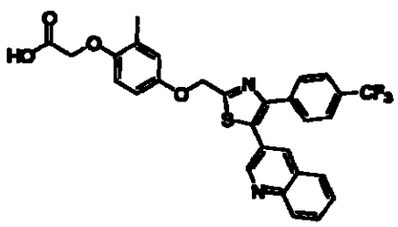
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1H), 6.81 (dd, J=2.8, 8.8 Hz, 1H), 6.72 (d, J=8.8 Hz, 1H), 5.37 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{30}H_{23}F_3NO_5S$ (M+H$^+$) 566.1, encontrada 566.3.
F79		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.90 (d, J = 2.0 Hz, 1H), 8.23 (m, 2H), 7.80 (m, 2H), 7.65 (t, J = 7.2 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 3.2 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 5.39 (s, 2H), 4.66 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{29}H_{22}F_3N_2O_5S$ (M+H$^+$) 567.1, encontrada 567.3.
F80		^{1}H-RMN (400MHz, DMSO-d_6) δ = 8.10 (s, 1H), 7.66 (d, J = 8.8

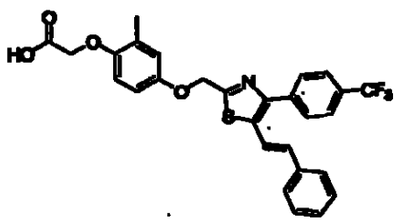
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		Hz, 2H), 7.40 (d, J = 7.2 Hz, 2H), 7.32 (d, J = 7.2 Hz, 2H), 7.17 (m, 4H), 6.92 (d, J = 16.4 Hz, 1H), 6.78 (d, J = 2.8 Hz, 1H), 6.69 (dd, J = 2.8, 8.8 Hz, 1H), 6.62 (d, J = 8.8 Hz, 1H), 5.22 (s, 2H), 4.46 (s, 2H), 2.07 (s, 3H). MS calculada para $C_{28}H_{23}F_3NO_6S$ ($M+H^+$) 542.1, encontrada 542.3.
F81		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.54 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.64 (s, 2H), 2.50 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{27}H_{23}F_3NO_6S_2$

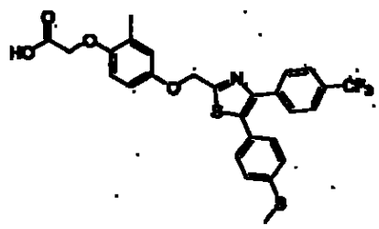
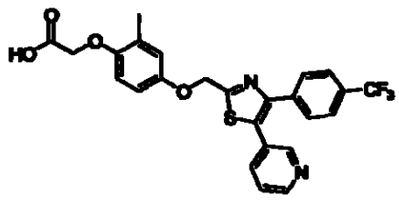
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		($M+H^+$) 562.1, encontrada 562.3.
F82		^{1}H-RMN (400MHz, DMSO-d_6) δ = 8.58 (dd, J = 1.6, 8.8 Hz, 1H), 8.54 (d, J = 2.0 Hz, 1H), 8.24 (s, 1H), 7.80 (dt, J = 2.0, 8.0 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.44 (dd, J = 5.2, 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 2.8 Hz, 1H), 6.85 (dd, J = 3.2, 8.8 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 5.40 (s, 2H), 4.60 (s, 2H), 2.20 (s, 3H). MS calculada para $C_{25}H_{20}F_3N_2O_6S$ ($M+H^+$) 517.1, encontrada 517.3.
F83		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.61 (d, J = 2.8 Hz, 2H), 7.57 (m, 4H), 7.47 (s, 1H), 7.46 (d, J = 3.2 Hz, 1H), 6.91 (d, J =

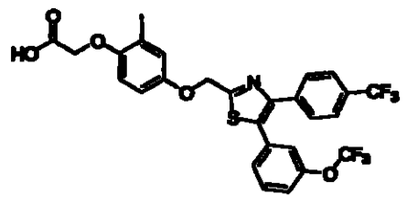
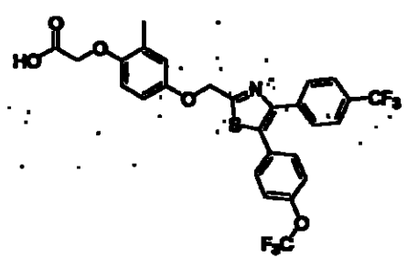
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2.8 Hz, 1H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{27}H_{20}F_6NO_4S$ ($M+H^+$) 568.1, encontrada 567.9.
F84		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.56 (m, 4H), 7.42 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.07 (dd, J = 2.0, 8.4 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 6.75 (dd, J = 2.8, 8.8 Hz, 1H), 6.68 (d, J = 8.8 Hz, 1H), 5.30 (s, 2H), 4.61 (s, 2H), 2.26 (s, 3H). MS calculada para $C_{26}H_{19}Cl_2F_3NO_4S$ ($M+H^+$) 568.0, encontrada 567.9.
F85		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.61 (d, J = 8.0 Hz, 2H), 7.56

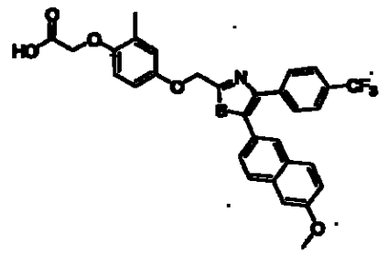
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 3.2 Hz, 1H), 6.79 (dd, J = 3.2, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{26}H_{20}ClF_3NO_4S$ (M+H$^+$) 534.1, encontrada 534.0.
F86		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.67 (d, J = 8.4 Hz, 2H), 7.58 (m, 6H), 7.45 (t, J = 7.2 Hz, 2H), 7.39 (m, 3H), 6.92 (d, J = 2.8 Hz, 1H), 6.81 (dd, J = 2.8, 8,8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{32}H_{25}F_3NO_4S$ (M+H$^+$) 576.1, encontrada 576.0.

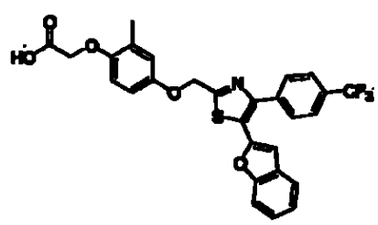
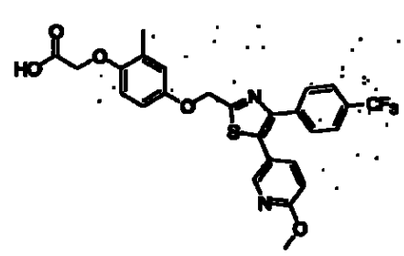
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
F87		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.88 (s, 1H), 7.85 (m, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 7.52 (,m, 4H), 7.32 (dd, J = 1.2, 8.4 Hz, 1H), 6.93 (d, J = 2.8 Hz, 1H), 6.82 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.38 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{30}H_{23}F_3NO_4S$ ($M+H^+$) 550.1, encontrada 550.0.
F88		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.89 (d, J = 2.0 Hz, 1H), 8.25 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.82 (m, 2H), 7.66 (d, J = 7.2 Hz, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 2.8 Hz, 1H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H),

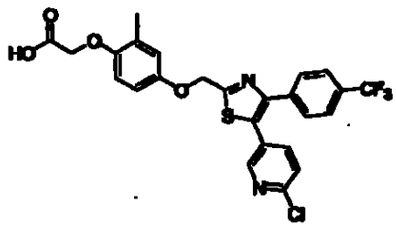
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		6.73 (d, J = 8.8 Hz, 1H), 5.40 (s, 2H), 4.66 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{28}H_{22}F_3N_2O_4S$ ($M+H^+$) 551.1, encontrada 551.0.
F89		^{1}H-RMN (400MHz, DMSO-d_6) δ = 8.30 (t, J = 2.0 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.37 (m, 3H), 7.30 (d, J = 7.2 Hz, 1H), 7.13 (d, J = 15.6 Hz, 1H), 6.95 (d, J = 2.8 Hz, 1H), 6.86 (dd, J = 2.8, 8.8 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 5.40 (s, 2H), 4.62 (s, 2H), 2.20 (s, 3H). MS calculada para $C_{28}H_{23}F_3NO_4S$ ($M+H^+$) 526.1, encontrada 526.0.
F90		^{1}H-RMN (400MHz, $CDCl_3$) δ =

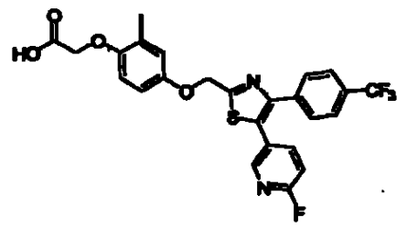
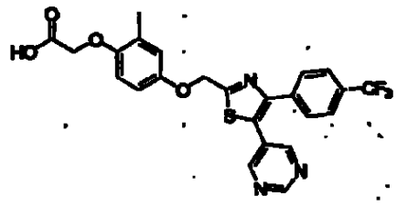
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		7.63 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.21 (m, 4H), 6.90 (d, J = 2.8 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.64 (s, 2H), 2.50 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{27}H_{23}F_3NO_4S_2$ ($M+H^+$) 546.1, encontrada 546.0.
F91		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.36 (d, J = 2.4 Hz, 1H), 8.31 (dd, J = 1.2, 8.8 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.26 (s, 4H), 7.08 (dd, J = 4.8, 8.0 Hz, 1H), 6.57 (d, J = 2.8 Hz, 1H), 6.58 (dd, J = 2.8, 8.8 Hz, 1H), 6.40 (d, J = 8.8 Hz, 1H), 5.05 (s, 2H), 4.33 (s, 2H), 1.97 (s, 3H). MS calculada para

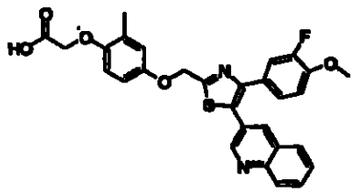
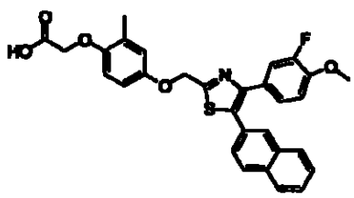
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		$C_{26}H_{18}F_3N_2O_4S$ ($M+H^+$) 501.1, encontrada 501.0.
F92		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.60 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.40 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 8.4 HZ, 1h), 7.15 (S, 1h), 6.91 (d, J = 3.2 Hz, 1H), 6.79 (dd, J = 3.2, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{27}H_{20}F_6NO_6S$ ($M+H^+$) 584.1, encontrada 584.0.
F93		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.60 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 3.2 Hz,

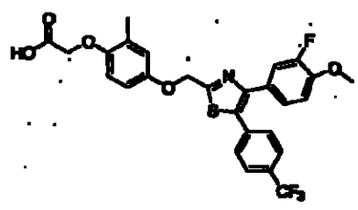
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1H), 6.79 (dd, J = 3.2, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{27}H_{20}F_6NO_5S$ ($M+H^+$) 584.1, encontrada 584.0.
F94		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.79 (s, 1H), 7.69 (s, J = 2.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 3H), 7.51 (d, J = 8.0 Hz, 2H), 7.29 (dd, J = 1.6, 8.4 Hz, 1H), 7.18 (dd, J = 2.4, 8.8 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 3.2 Hz, 1H), 6.82 (dd, J = 3.2, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.65 (s, 2H), 3.94 (s, 3H), 2.30 (s, 3H). MS calculada para $C_{31}H_{25}F_3NO_5S$ ($M+H^+$) 580.1, encontrada 580.0.

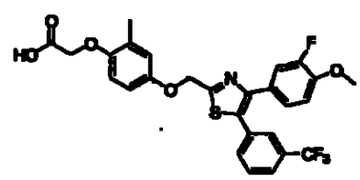
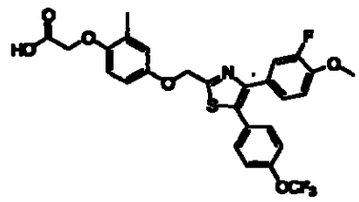
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
F95		^{1}H-RMN (400MHz, DMSO-d_6) δ = 8.33 (s, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 6.8 Hz, 1H), 7.29 (t, J = 7.2 Hz, 1H), 7.06 (s, 1H), 7.01 (d, J = 3.2 Hz, 1H), 6.91 (dd, J = 3.2, 8.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 5.49 (s, 2H), 4.66 (s, 2H), 2.23 (s, 3H). MS calculada para $C_{28}H_{21}F_3NO_6S$ ($M+H^+$) 540.1, encontrada 540.0.
F96		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.17 (d, J = 2.0 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.47 (dd, J = 2.8, 8.4 Hz, 1H), 6.91 (d, J = 2.8 Hz, 1H), 6.80 (dd, J = 2.8,

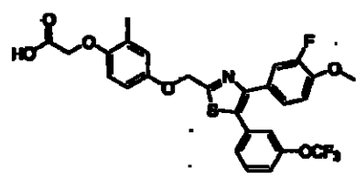
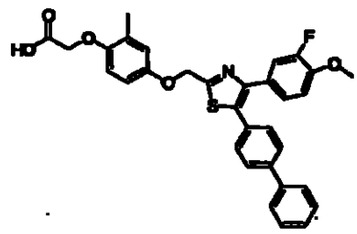
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 2H), 5.34 (s, 2H), 4.65 (s, 2H), 3.96 (s, 3H), 2.30 (s, 3H). MS calculada para $C_{28}H_{21}F_3N_2O_6S$ (M+H$^+$) 531.1, encontrada 531.0.
F97		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.35 (d, J = 2.4 Hz, 1H), 7.56 (m, 4H), 7.53 (dd, J = 2.4, 8.4 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 2.8 Hz, 1H), 6.76 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (s, J = 8.8 Hz, 1H), 5.32 (s, 2H), 4.62 (s, 2H), 2.26 (s, 3H). MS calculada para $C_{26}H_{19}ClF_3N_2O_4S$ (M+H$^+$) 535.1, encontrada 535.0.
F98		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.23 (d, J = 2.4 Hz, 1H), 7.70 (dt, J = 2.8, 8.4 Hz, 1H), 7.58

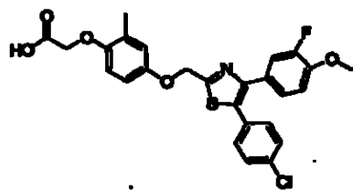
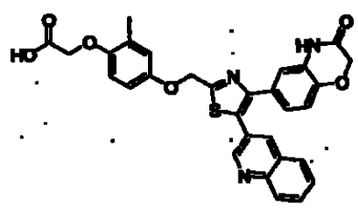
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(m, 4H), 7.53 (dd, J = 2.4, 8.4 Hz, 1H), 6.95 (dd, J = 2.0, 8.4 Hz, 1H), 6.90 (d, J = 2.8 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 2.29 (s, 3H). MS calculada para $C_{26}H_{19}F_4N_2O_4S$ ($M+H^+$) 519.1, encontrada 519.0.
F99		^{1}H-RMN (400MHz, DMSO-d_6) δ = 9.21 (s, 1H), 8.82 (s, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 2.8 Hz, 1H), 6.88 (dd, J = 2.8, 8.8 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 5.47 (s, 2H), 4.63 (s, 2H), 2.20 (s, 3H). MS calculada para $C_{24}H_{18}F_3N_3O_4S$ ($M+H^+$) 502.1, encontrada 502.0.

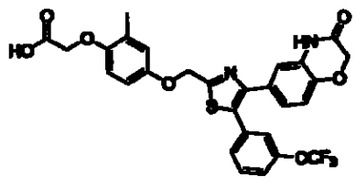
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
F100		^{1}H-RMN (400MHz, $CDCl_3$) δ = 9.06 (d, J = 1.6 Hz, 1H), 8.56 (s, 1H), 8.46 (d, J = 8.8 Hz, 1H), 7.80 (t, J = 7.2 Hz, 1H), 7.95 (d, J= 8.0 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.28 (m, 1H), 7.12 (d, J = 8.4 Hz, 1H), 6.89 (m, 2H), 6.76 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.39 (s, 2H), 4.66 (s, 2H), 3.89 (s, 3H), 2.28 (s, 3H). MS calculada para $C_{28}H_{24}FN_2O_5S$ ($M+H^+$) 531.1, encontrada 531.3.
F101		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.88 (s, 1H), 7.80 (m, 3H), 7.51 (m, 2H), 7.34 (dd, J = 2.0, 8.8 Hz, 1H), 7.30 (dd, J = 2.0, 12.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 2.8

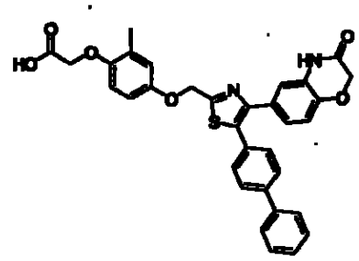
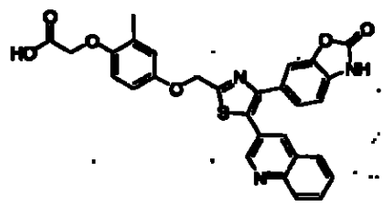
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		Hz, 1H), 6.84 (t, J = 8.4 Hz, 1H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.65 (s, 2H), 3.87 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{30}H_{26}FNO_6S$ ($M+H^+$) 530.1, encontrada 530.3.
F102		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.59 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.24 (dd, J = 1.6, 12 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 6.89 (m, 2H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 3.90 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{27}H_{22}F_4NO_5S$ ($M+H^+$) 548.1, encontrada 548.4.
F103		^{1}H-RMN (400MHz, $CDCl_3$) δ =

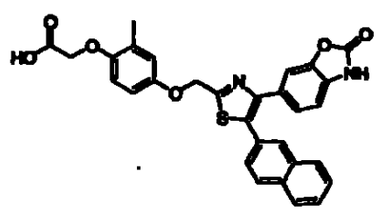
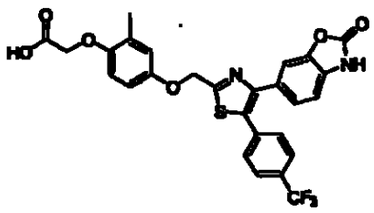
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		7.59 (m, 2H), 7.47 (m, 2H), 7.22 (dd, J = 2.0, 12.4 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 7.90 (d, J = 2.8 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 3.90 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{27}H_{22}F_4NO_6S$ ($M+H^+$) 548.1, encontrada 548.4.
F104		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.35 (d, J = 8.4 Hz, 2H), 7.21 (m, 3H), 6.89 (m, 2H), 6.78 (dd, J = 2.8, 8.,8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.65 (s, 2H), 3.90 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{27}H_{22}F_4NO_6S$ ($M+H^+$) 564.1, encontrada 564.3.

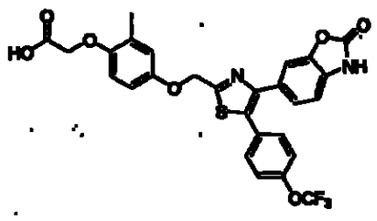
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
F105		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.53 (t, J = 7.6 Hz, 1H), 7.41 (m, 2H), 7.35 (m, 3H), 7.04 (m, 2H), 6.93 (dd, J = 2.8, 8.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 5.49 (s, 2H), 4.80 (s, 2H), 4.05 (s, 3H), 2.44 (s, 3H). MS calculada para $C_{27}H_{22}F_4NO_6S$ ($M+H^+$) 564.1, encontrada 564.3.
F106		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.40 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.25 (m, 2H), 7.18 (m, 3H), 7.10 (dd, J 0 1.2, 12.4 Hz, 1H), 7.06 (m, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 6.59 (dd, J = 2.8, 8.8 Hz, 1H), 6.50 (d, J = 8.8 Hz, 1H), 5.14 (s, 2H), 4.44 (s, 2H), 3.69 (s, 3H),

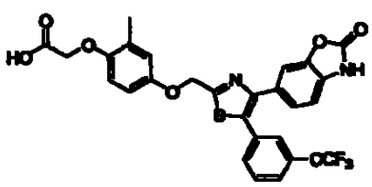
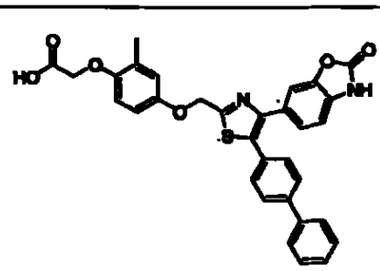
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2.09 (s, 3H). MS calculada para $C_{32}H_{27}FNO_3S$ ($M+H^+$) 556.2, encontrada 556.2.
F107		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.26 (d, J = 8.8 Hz, 2H), 7.20 (m, 3H), 7.11 (d, J = 8.4 Hz, 1H), 6.83 (m, 2H), 6.72 (dd, J = 2.8, 8.,8 Hz, 1H), 6.65 (d, J = 8.8 Hz, 1H), 5.28 (s, 2H), 4.58 (s, 2H), 3.83 (s, 3H), 2.29 (s, 3H). MS calculada para $C_{28}H_{22}ClFNO_5S$ ($M+H^+$) 514.1, encontrada 514.2.
F108		^{1}H-RMN (400MHz, DMSO-d_6) δ = 10.61 (s, 1H), 8.60 (d, J = 2.0 Hz, 1H), 8.41 (s, 1H), 7.91 (d, J = 8.8 Hz, 2H), 7.70 (t, J = 7.6 Hz, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.04 (d, J = 1.6 Hz, 1H), 6.83 (m, 2H), 6.76 (m,

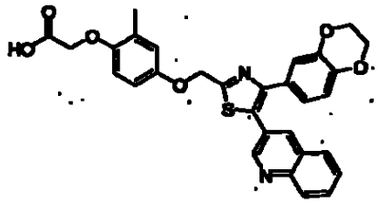
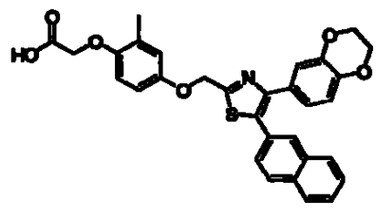
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2H), 6.68 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H), 4.52 (s, 2H), 4.48 (s, 2H), 2.09 (s, 3H). MS calculada para $C_{30}H_{24}N_3O_6S$ ($M+H^+$) 554.1, encontrada 554.1.
F109		^{1}H-RMN (400MHz, DMSO-d_6) δ = 10.66 (s, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.17 (s, 1H), 7.05 (d, J = 2.4 Hz, 1H)=, 6.85 (d, J = 2.8 Hz, 1H), 6.77 (m, 3H), 6.68 (d, J = 8.8 Hz, 1H), 5.29 (s, 2H), 4.53 (s, 2H), 4.48 (s, 2H), 2.11 (s, 3H). MS calculada para $C_{28}H_{22}F_3N_2O_2S$ ($M+H^+$) 587.1, encontrada 587.1.
F110		^{1}H-RMN (400MHz, DMSO-d_6) δ = 10.73 (s, 1H), 7.66 (d, J =

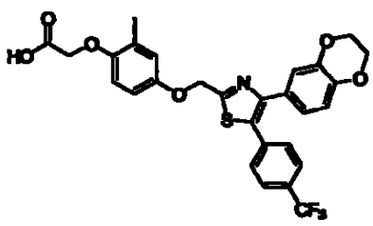
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		8.0 Hz, 4H), 7.44 (m, 4H), 7.35 (t, J = 7.6 Hz, 1H), 7.21 (d, J = 1.6 Hz, 1H), 6.93 (m, 2H), 6.75 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.59 (s, 2H), 4.55 (s, 2H), 2.21 (s, 3H). MS calculada para $C_{33}H_{27}N_2O_6S$ ($M+H^+$) 579.2, encontrada 579.1.
F111		^{1}H-RMN (400MHz, DMSO-d_6) δ = 11.60 (s, 1H), 8.75 (d, J 0 2.4 Hz, 1H), 8.44 (s, 1H), 7.96 (d, J = 7.2 Hz, 1H), 7.81 (t, J = 7.2 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 2.8 Hz, 1H), 6.86 (dd, J = 2.8, 8.4 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 5.42 (s, 2H), 4.59 (s, 2H), 2.27 (s, 3H). MS calculada para $C_{29}H_{22}N_3O_6S$ ($M+H^+$) 540.1, encontrada 540.1.

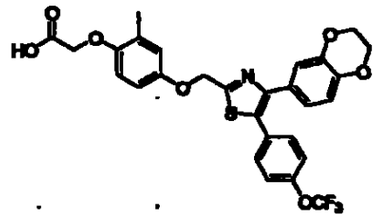
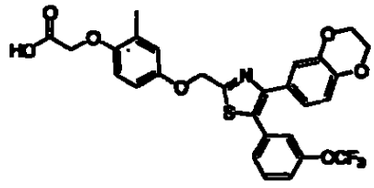
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
F112		^{1}H-RMN (400MHz, DMSO-d_6) δ = 11.55 (s, 1H), 7.93 (s, 1H), 7.84 (m, 3H), 7.50 (m, 2H), 7.32 (dd, J = 2.0, 8.8 Hz, 1H), 7.29 (s, 1H), 7.22 (d, J = 9.6 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.56 (s, 2H), 2.21 (s, 3H). MS calculada para $C_{30}H_{23}N_2O_6S$ (M+H$^+$) 539.1, encontrada 539.1.
F113		^{1}H-RMN (400MHz, DMSO-d_6) δ = 11.62 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 7.6 Hz, 2H), 7.31 (s, 1H), 7.20 (d, J = 7.6 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.92 (s, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.75 (d, J

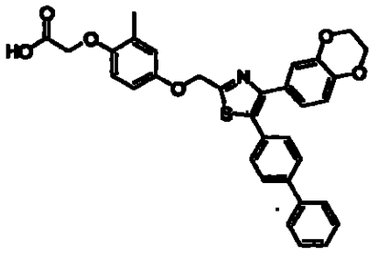
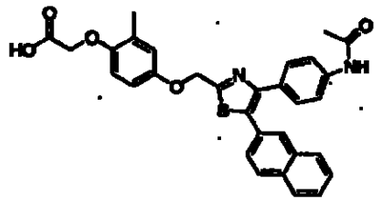
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		= 8.4 Hz, 1H), 5.38 (s, 2H), 4.59 (s, 2H), 2.25 (s, 3H). MS calculada para $C_{27}H_{20}F_3N_2O_6S$ ($M+H^+$) 557.1, encontrada 557.3.
F114		^{1}H-RMN (400MHz, DMSO-d_6) δ = 11.64 (s, 1H), 8.13 (m, 2H), 7.49 (m, 2H), 7.33 (br s, 3H), 7.26 (d, J = 8.4 Hz, 1H), 7.03 (dd, J = 4.0, 8.0 Hz, 1H), 6.95 (s, 1H), 6.88 (m, 1H), 6.79 (dd, J = 3.2, 8.8 Hz, 1H), 5.41 (s, 2H), 4.63 (s, 2H), 2.30 (s, 3H). MS calculada para $C_{27}H_{20}F_3N_2O_7S$ ($M+H^+$) 573.1, encontrada 573.2.
F115		^{1}H-RMN (400MHz, DMSO-d_6) δ = 11.35 (s, 1H), 7.88 (m, 2H), 7.24 (t, J = 8.0 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 7.03 (d, J

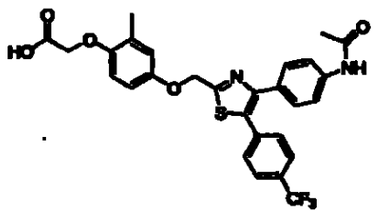
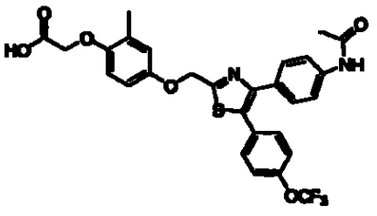
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		= 9.6 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.72 (d, J = 8.0 Hz, 1H), 6.65 (s, 1H), 6.58 (dd, J = 2.4, 8.8 Hz, 1H), 6.49 (d, J = 8.8 Hz, 1H), 5.10 (s, 2H), 4.32 (s, 2H), 1.97 (s, 3H). MS calculada para $C_{27}H_{20}F_3N_2O_7S$ ($M+H^+$) 573.1, encontrada 573.2.
F116		^{1}H-RMN (400MHz, DMSO-d_6) δ = 11.68 (s, 1H), 8.23 (m, 2H), 7.67 (d, J = 8.0 Hz, 4H), 7.44 (m, 4H), 7.37 (d, J = 6.8 Hz, 1H), 7.33 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.93 (s, 1H), 6.85 (dd, J = 2.4, 8.8 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.60 (s, 2H), 2.21 (s, 3H). MS calculada para

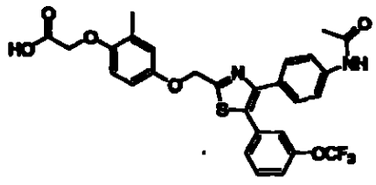
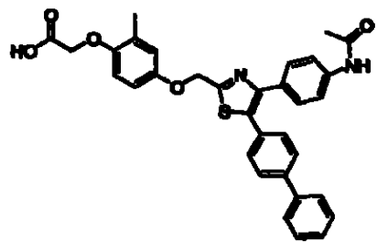
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		$C_{32}H_{28}N_2O_6S$ ($M+H^+$) 565.1, encontrada 565.1.
F117		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.87 (s, 1H), 8.27 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.79 (m, 2H), 7.63 (t, J = 7.6 Hz, 1H), 7.05 (s, 1H), 6.89 (s, 2H), 6.78 (m, 2H), 6.71 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.64 (s, 2H), 4.23 (m, 4H), 2.28 (s, 3H). MS calculada para $C_{30}H_{25}N_2O_6S$ ($M+H^+$) 541.1, encontrada 541.1.
F118		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.88 (s, 1H), 7.80 (m, 2H), 7.75 (d, J = 8.8 Hz, 1H), 7.49 (m, 2H), 7.36 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 1.2 Hz, 1H), 6.94 (m, 2H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.73 (t, J =

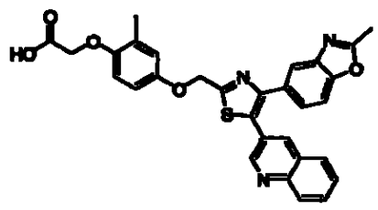
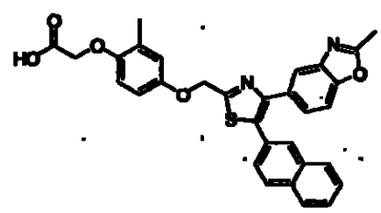
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		8.8 Hz, 2H), 5.37 (s, 2H), 4.64 (s, 2H), 4.23 (m, 4H), 2.01 (s, 3H),. MS calculada para $C_{31}H_{28}NO_6S$. (M+H$^+$) 540.1, encontrada 540.2.
F119		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.56 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 2.0 Hz, 1H), 6.89 (m, 2H), 6.77 (m, 2H), 6.70 (d, J = 8.8 Hz, 1H), 5.32 (s, 2H), 4.63 (s, 2H), 4.26 (m, 4H), 2.28 (s, 3H). MS calculada para $C_{28}H_{23}F_3NO_6S$ (M+H$^+$) 558.1, encontrada 558.1.
F120		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.37 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 2.0 Hz, 1H), 6.90 (m, 2H),

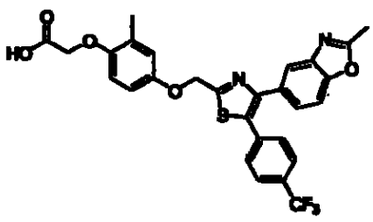
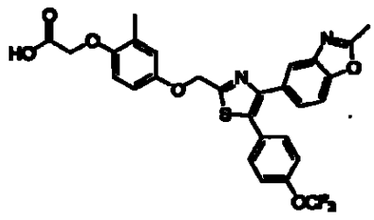
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		6.77 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 8.8 Hz, 1H), 5.31 (s, 2H), 4.63 (s, 2H), 4.26 (m, 4H), 2.28 (s, 3H). MS calculada para $C_{28}H_{23}F_3NO_7S$ ($M+H^+$) 574.1, encontrada 574.1.
F121		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.35 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 2.0 Hz, 1H), 6.92 (dd, J = 2.0, 8.4 Hz, 1H), 6.89 (d, J = 2.8 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.32 (s, 2H), 4.63 (s, 2H), 4.25 (m, 4H), 2.28 (s, 3H). MS calculada para $C_{28}H_{23}F_3NO_7S$ ($M+H^+$) 574.1, encontrada

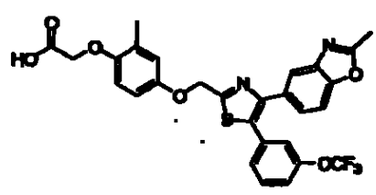
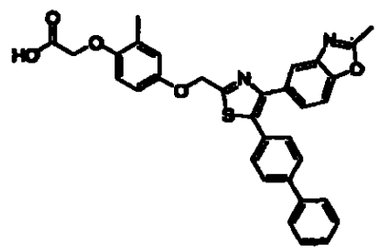
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		574.1.
F122		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.60 (d, J = 7.2 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.42 (m, 5H), 7.08 (d, J = 2.4 Hz, 1H), 6.97 (dd, J = 2.0, 8.4 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.64 (s, 2H), 4.25 (m, 4H), 2.29 (s, 3H). MS calculada para $C_{33}H_{28}NO_6S$ ($M+H^+$) 566.2, encontrada 566.2.
F123		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.05 (s, 1H), 8.00 (m, 1H), 7.94 (m, 2H), 7.66 (m, 4H), 7.59 (m, 2H), 7.50 (d, J = 9.2 Hz, 1H), 7.10 (s, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 5.56 (s, 2H), 4.82

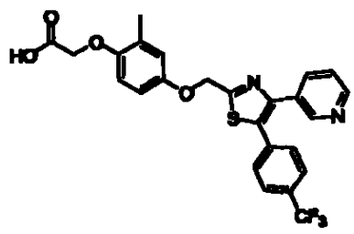
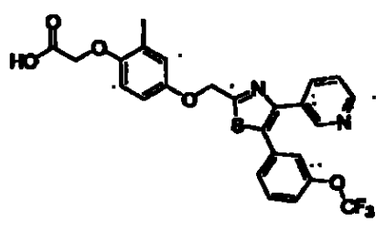
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(s, 2H), 2.48 (s, 3H), 2.37 (s, 3H). MS calculada para $C_{31}H_{27}N_2O_6S$ ($M+H^+$) 539.2, encontrada 539.2.
F124		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.43 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.31 (m, 3H), 7.13 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 2.4 Hz, 1H), 6.76 (dd, J = 2.4, 8.8 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.61 (s, 2H), 2.25 (s, 3H), 2.19 (s, 3H). MS calculada para $C_{28}H_{24}F_3N_2O_6S$ ($M+H^+$) 557.1, encontrada 557.1.
F125		MS calculada para $C_{28}H_{24}F_3N_2O_6S$ ($M+H^+$) 573.1, encontrada 573.1.
F126		^{1}H-RMN (400MHz, $CDCl_3$) δ =

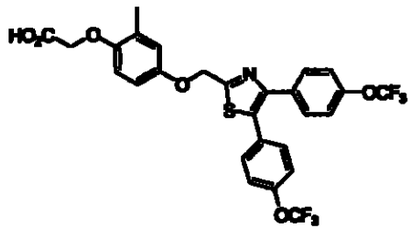
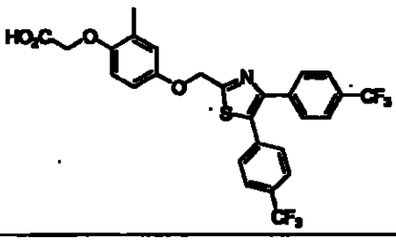
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		7.45 (m, 4H), 7.35 (t, J = 8.8 Hz, 1H), 7.22 (s, 1H), 7.18 (m, 2H), 6.90 (d, J = 3.2 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.64 (s, 2H), 2.29 (s, 3H), 2.19 (s, 3H). MS calculada para $C_{28}H_{24}F_3N_2O_6S$ ($M+H^+$) 573.1, encontrada 573.1.
F127		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.62 (d, J = 7.6 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.50 (m, 6H), 7.40 (m, 3H), 7.34 (s, 1H), 6.94 (d, J = 2.8 Hz, 1H), 6.83 (dd, J = 2.8, 8.8 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 5.40 (s, 2H), 4.67 (s, 2H), 2.32 (s, 3H), 2.23 (s, 3H). MS calculada para $C_{33}H_{28}N_2O_6S$

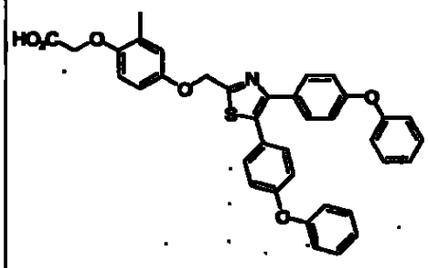
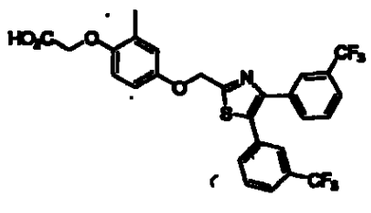
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(M+H$^+$) 565.2, encontrada 565.1.
F128		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.76 (s, 1H), 8.19 (s, 1H), 8.13 (m, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.70 (s, 1H), 6.59 (t, J = 8.0 Hz, 1H), 7.35 (s, 2H), 6.91 (s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 5.40 (s, 2H), 4.69 (s, 2H), 2.64 (s, 3H), 2.31 (s, 3H). MS calculada para $C_{30}H_{24}N_3O_6S$ (M+H$^+$) 538.1, encontrada 538.0.
F129		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.86 (s, 1H), 7.79 (m, 2H), 7.73 (m, 2H), 7.48 (m, 2H), 7.39 (dd, J = 1.6, 8.4 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.30 (dd, J = 1.6, 6.8 Hz, 1H), 6.92 (d, J = 2.8 Hz, 1H), 6.85 (dd, J = 2.8, 8.8 Hz, 1H), 6.76 (d, J =

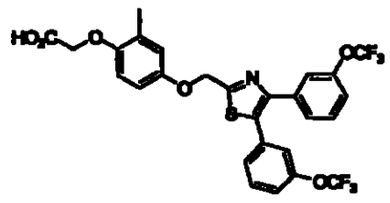
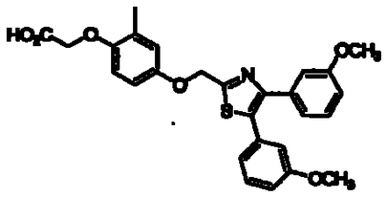
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		8.8 HZ, 1h), 5.39 (S, 2h), 4.67 (s, 2H), 2.65 (s, 3H), 2.30 (s, 3H). MS calculada para $C_{31}H_{28}N_2O_6S$ (M+H$^+$) 537.1, encontrada 537.0.
F130		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.79 (s, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.47 (m, 4H), 6.90 (d, J = 2.4 Hz, 1H), 6.90 (dd, J = 2.8, 8.8 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 5.44 (s, 2H), 4.74 (s, 2H), 2.75 (s, 3H), 2.37 (s, 3H). MS calculada para $C_{28}H_{22}F_3N_2O_6S$ (M+H$^+$) 555.1, encontrada 555.0.
F131		MS calculada para $C_{28}H_{22}F_3N_2O_6S$ (M+H$^+$) 571.1, encontrada 571.0.

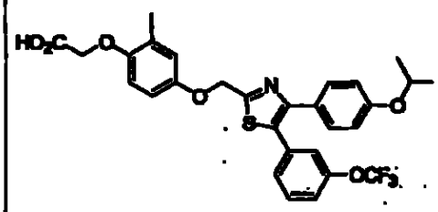
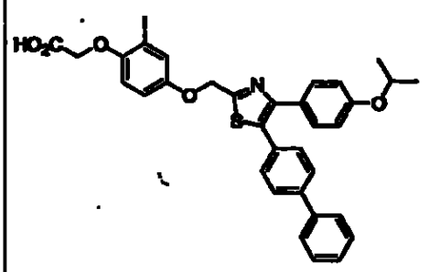
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
F132		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.71 (s, 1H), 7.36 (m, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.25 (m, 1H), 7.15 (m, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.82 (dd, J = 2.8, 8.8 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 5.35 (s, 2H), 4.67 (s, 2H), 2.66 (s, 3H), 2.30 (s, 3H). MS calculada para $C_{28}H_{22}F_3N_2O_6S$ ($M+H^+$) 571.1, encontrada 571.0.
F133		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.75 (d, J = 1.2 Hz, 1H), 7.58 (d, J = 7.2 Hz, 2H), 7.45 (m, 6H), 6.90 (m, 4H), 6.85 (dd, J = 2.8, 8.8 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.67 (s, 2H)=, 2.65 (s, 3H), 2.30 (s, 3H). MS calculada para $C_{33}H_{27}N_2O_6S$ ($M+H^+$) 563.2,

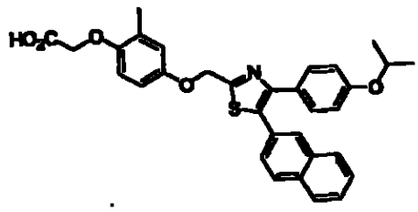
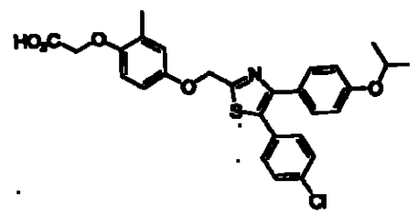
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		encontrada 563.0.
F134		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.86 (s, 1H), 8.77 (d, J = 4.4 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.55 (m, 1H), 7.47 (d, J = 8.0 Hz, 2H), 6.89 (dd, J = 2.4, 8.8 Hz, 1H), 6.80 (d, J = 2.4 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.72 (s, 2H), 2.25 (s, 3H). MS calculada para $C_{26}H_{20}F_3N_2O_4S$ ($M+H^+$) 501.1, encontrada 501.1.
F135		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.83 (s, 1H), 8.59 (d, J = 4.4 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.34 (m, 2H), 7.23 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.12 (s, 1H), 6.83 (d, J = 2.8 Hz, 1H), 6.75 (dd, J =

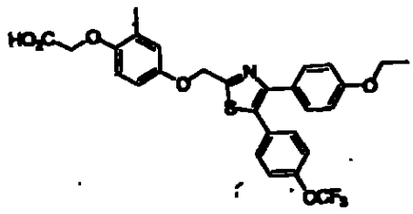
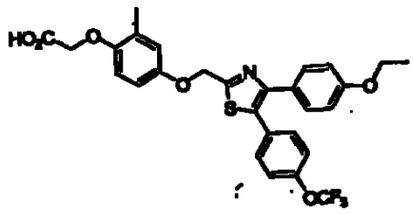
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2.8, 8.8 Hz, 1H), 6.68 (d, J = 8.8 Hz, 1H), 5.30 (s, 2H), 4.61 (s, 2H), 2.25 (s, 3H). MS calculada para $C_{26}H_{20}F_3N_2O_6S$ ($M+H^+$) 517.1, encontrada 517.1.
H2		^{1}H-RMN (400MHz, CD_3OD) δ = 7.57 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 2.8 Hz, 1H), 6.85-6.76 (m, 2H), 5.35 (s, 2H), 4.62 (s, 2H), 2.26 (s, 3H). MS calculada para $C_{27}H_{20}F_6NO_6S$ ($M+H^+$) 600.08, encontrada 600.00.
H3		^{1}H-RMN (400MHz, CD_3OD) δ = 7.71 (d, J = 8.4 Hz, 2H), 7.65 (s, 4H), 7.56 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 2.8 Hz, 1H),

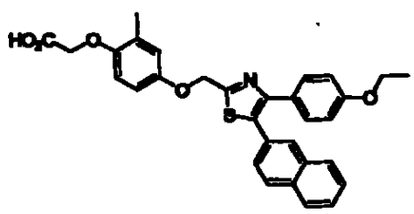
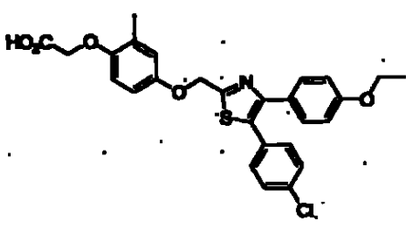
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		6.87-6.77 (m, 2H), 5.39 (s, 2H), 4.63 (s, 2H), 2.27 (s, 3H). MS calculada para $C_{27}H_{20}F_6NO_4S$ (M+H$^+$) 560.09, encontrada 568.00.
H4		^{1}H-RMN (400MHz, CD_3OD) δ =7.46 (d, J = 6.8 Hz, 2H), 7.40-7.34 (m, 4H), 7.33 (d, J = 8.8 Hz, 2H), 7.17-7.12 (m, 2H), 7.04-7.00 (m, 4H), 6.96-6.91 (m, 5H), 6.85-6.76 (m, 2H), 5.33 (s, 2H), 4.62 (s, 2H), 2.26 (s, 3H). MS calculada para $C_{37}H_{30}NO_6S$ (M+H$^+$) 616.17, encontrada 616.00.
H5		^{1}H-RMN (400MHz, CD_3OD) δ = 7.73-7.69 (m, 3H), 7.64-7.58 (m, 4H), 7.54-7.50 (m, 1H), 6.94 (d, J = 2.8 Hz, 1H), 6.87-6.77 (m, 2H), 5.39 (s, 2H),

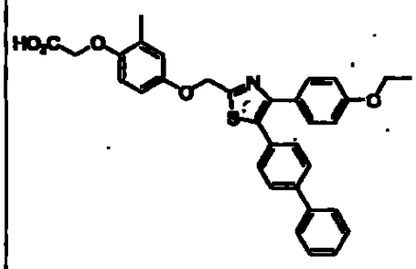
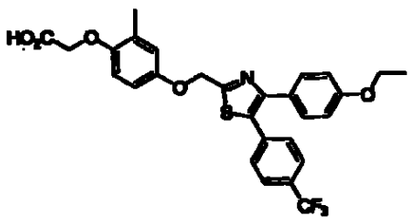
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		4.62 (s, 2H), 2.26 (s, 3H). MS calculada para $C_{27}H_{20}F_6NO_4S$ ($M+H^+$) 568.09, encontrada 568.00.
H6		^{1}H-RMN (400MHz, CD_3OD) δ = 7.53-7.37 (m, 4H), 7.32-7.30 (m, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.19 (s, 1H), 6.93 (d, J = 2.8 Hz, 1H), 6.86-6.77 (m, 2H), 5.38 (s, 2H), 4.63 (s, 2H), 2.26 (s, 3H). MS calculada para $C_{27}H_{20}F_6NO_6S$ ($M+H^+$) 600.08, encontrada 600.00.
H7		^{1}H-RMN (400MHz, CD_3OD) δ = 7.25 (t, J = 8.0 Hz, 2H), 7.18 (t, J = 8.0 Hz, 2H), 6.97-6.79 (m, 8H), 6.73-6.71 (m, 1H), 5.33 (s, 2H), 4.57 (s, 2H), 3.62 (s, 3H), 3.58 (s, 3H), 2.12 (s, 3H). MS calculada para

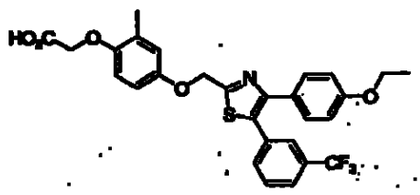
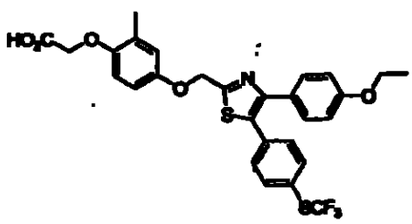
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		$C_{27}H_{26}NO_6S$ ($M+H^+$) 492.14, encontrada 492.00.
J2		^{1}H-RMN (400MHz, CD_3OD) δ = 7.47 (t, J = 8.0 Hz, 1H), 7.39-7.34 (m, 3H), 7.26-7.24 (m, 1H), 7.17 (s, 1H), 6.94 (d, J = 3.2 Hz, 1H), 6.89-6.78 (m, 4H), 5.35 (s, 2H), 4.64 (s, 2H), 4.62 (m, 1H), 2.27 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H). MS calculada para $C_{28}H_{27}F_3NO_6S$ ($M+H^+$) 574.1, encontrada 574.2.
J3		^{1}H-RMN (400MHz, CD_3OD) δ = 7.61-7.57 (m, 4H), 7.40-7.35 (m, 6H), 7.29 (t, J = 6.8 Hz, 1H), 6.88 (d, J = 2.8 Hz, 1H), 6.80-6.71 (m, 4H), 5.28 (s, 2H), 4.56 (s, 2H), 4.53 (m, 1H), 2.17 (s, 3H), 1.22 (s, 3H),

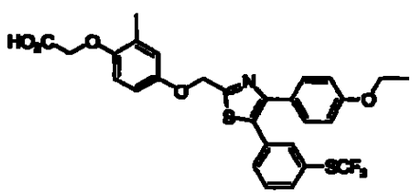
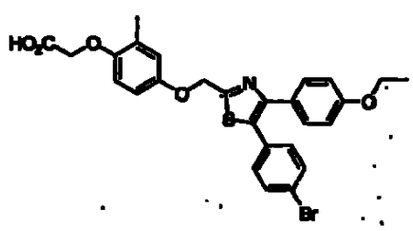
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1.21 (s, 3H). MS calculada para $C_{28}H_{27}F_3NO_6S$ ($M+H^+$) 566.2, encontrada 566.2.
J4		^{1}H-RMN (400MHz, CD_3OD) δ = 7.79-7.68 (m, 4H), 7.42-7.37 (m, 2H), 7.30-7.23 (m, 3H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 4H), 5.26 (s, 2H), 4.53 (s, 2H), 4.48 (m, 1H), 2.17 (s, 3H), 1.20 (s, 3H), 1.18 (s, 3H). MS calculada para $C_{28}H_{27}F_3NO_6S$ ($M+H^+$) 540.2, encontrada 540.2.
J5		^{1}H-RMN (400MHz, CD_3OD) δ = 7.29-7.22 (m, 6H), 6.83 (d, J = 2.4 Hz, 1H), 6.77-6.68 (m, 4H), 5.25 (s, 2H), 4.54 (s, 2H), 4.51 (m, 1H), 2.16 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H). MS calculada para $C_{28}H_{27}ClNO_6S$

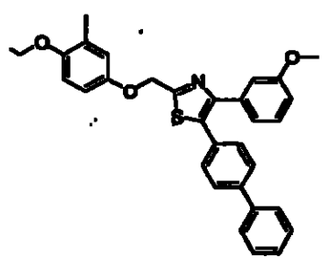
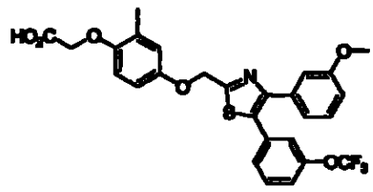
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(M+H$^+$) 524.1, encontrada 524.1.
J6		^{1}H-RMN (400MHz, CD_3OD) δ = 7.36-7.16 (m, 6H), 6.85 (d, J = 2.8 Hz, 1H), 6.79-6.68 (m, 4H), 5.26 (s, 2H), 4.54 (s, 2H), 3.97-3.91 (m, 2H), 2.16 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H). MS calculada para $C_{28}H_{25}F_3NO_6S$ (M+H$^+$) 560.1, encontrada 560.2.
J7		^{1}H-RMN (400MHz, CD_3OD) δ = 7.36-7.00 (m, 6H), 6.80 (d, J = 2.8 Hz, 1H), 6.76-6.64 (m, 4H), 5.22 (s, 2H), 4.49 (s, 2H), 3.95-3.89 (m, 2H), 2.14 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H). MS calculada para $C_{28}H_{25}F_3NO_6S$ (M+H$^+$) 560.1, encontrada 560.2.

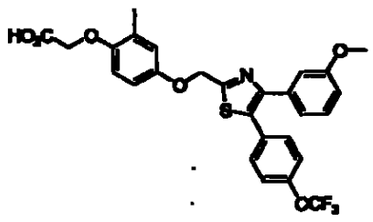
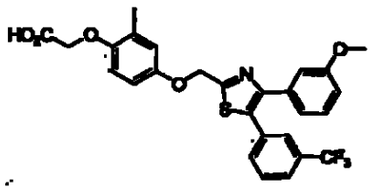
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
J8		^{1}H-RMN (400MHz, CD_3OD) δ = 7.80 (s, 1H), 7.77-7.69 (m, 3H), 7.43-7.40 (m, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.26 (dd, J 0 1.8 Hz, J = 8.4 Hz, 1H), 6.85 (d, J = 2.8 Hz, 1H), 6.78-6.68 (m, 4H), 5.27 (s, 2H), 4.53 (s, 2H), 3.95-3.89 (m, 2H), 2.18 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H). MS calculada para $C_{31}H_{28}NO_5S$ (M+H$^+$) 526.2, encontrada 526.2.
J9		^{1}H-RMN (400MHz, CD_3OD) δ = 7.27-7.19 (m, 6H), 6.82 (d, J = 2.8 Hz, 1H), 6.78-6.67 (m, 4H), 5.23 (s, 2H), 4.53 (s, 2H), 3.96-3.91 (m, 2H), 2.16 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H). MS calculada para $C_{27}H_{26}ClNO_5S$ (M+H$^+$) 510.1,

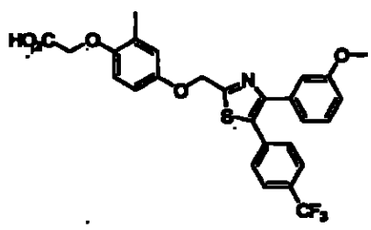
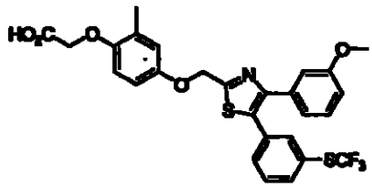
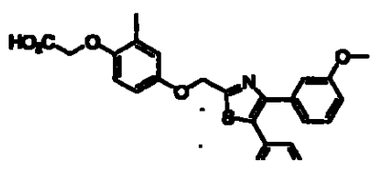
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		encontrada 510.1.
J10		^{1}H-RMN (400MHz, CD_3OD) δ = 7.54-7.49 (m, 4H), 7.34-7.23 (m, 7H), 6.82 (d, J = 2.8 Hz, 1H), 6.76-6.65 (m, 4H), 5.22 (s, 2H), 4.50 (s, 2H), 3.92-3.87 (m, 2H), 2.12 (s, 3H), 1.23 (t, J = 7.0 Hz, 3H). MS calculada para $C_{33}H_{30}NO_5S$ ($M+H^+$) 552.2, encontrada 552.2.
J11		^{1}H-RMN (400MHz, CD_3OD) δ = 7.55 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.80-6.67 (m, 4H), 5.25 (s, 2H), 4.53 (s, 2H), 3.96-3.91 (m, 2H), 2.16 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H). MS calculada para $C_{28}H_{25}F_3NO_5S$ ($M+H^+$) 544.1,

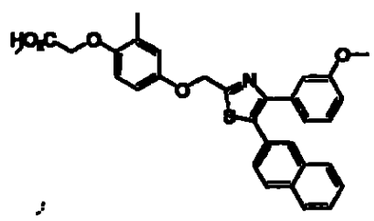
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		encontrada 544.1.
J12		^{1}H-RMN (400MHz, CD_3OD) δ = 7.54-7.42 (m, 4H), 7.25 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.79-6.67 (m, 4H), 5.25 (s, 2H), 4.53 (s, 2H), 3.96-3.91 (m, 2H), 2.16 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H). MS calculada para $C_{28}H_{25}F_3NO_5S$ ($M+H^+$) 544.1, encontrada 544.1.
J13		^{1}H-RMN (400MHz, CD_3OD) δ = 7.60 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.80-6.69 (m, 4H), 5.27 (s, 2H), 4.54 (s, 2H), 3.98-3.93 (m, 2H), 2.17 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H). MS calculada para

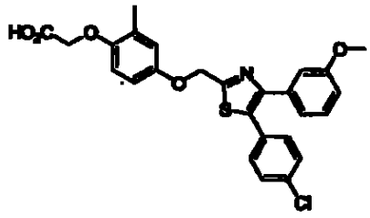
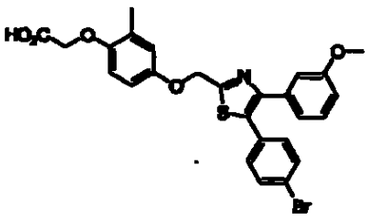
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		$C_{28}H_{26}F_3NO_5S_2$ ($M+H^+$) 576.1, encontrada 576.1.
J14		^{1}H-RMN (400MHz, CD_3OD) δ = 7.58-7.45 (m, 4H), 7.27 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.81-6.68 (m, 4H), 5.25 (s, 2H), 4.53 (s, 2H), 3.96-3.91 (m, 2H), 2.16 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H). MS calculada para $C_{28}H_{26}F_3NO_5S_2$ ($M+H^+$) 576.1, encontrada 576.1.
J15		^{1}H-RMN (400MHz, CD_3OD) δ = 7.45 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.80-6.69 (m, 4H), 5.26 (s, 2H), 4.54 (s, 2H), 3.97-3.92 (m, 2H), 2.16 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H).

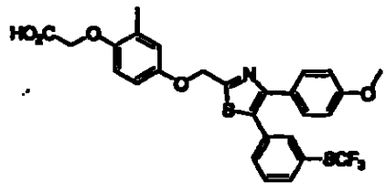
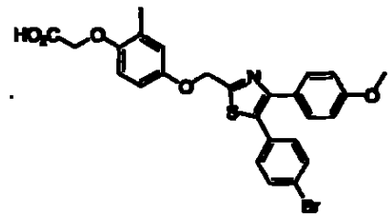
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		MS calculada para $C_{27}H_{26}BrNO_5S$ ($M+H^+$) 554.1, encontrada 554.1.
J16		^{1}H-RMN (400MHz, CD_3OD) δ = 7.56-7.51 (m, 5H), 7.37-7.26 (m, 6H), 7.14 (t, J = 7.6 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.81-6.68 (m, 3H), 5.27 (s, 2H), 4.54 (s, 2H), 3.59 (s, 3H), 2.18 (s, 3H). MS calculada para $C_{32}H_{28}NO_5S$ ($M+H^+$) 538.2, encontrada 538.2.
J17		^{1}H-RMN (400MHz, CD_3OD) δ = 7.38 (t, J = 8.0 Hz, 1H), 7.29-7.27 (m, 1H), 7.18-7.12 (m, 2H), 7.07 (s, 1H), 7.92-6.79 (m, 4H), 6.74-6.67 (m, 2H), 5.26 (s, 2H), 4.53 (s, 2H), 3.59 (s, 3H), 2.17 (s, 3H). MS calculada para $C_{27}H_{23}F_3NO_6S$

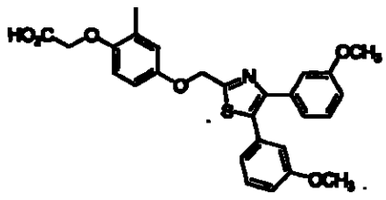
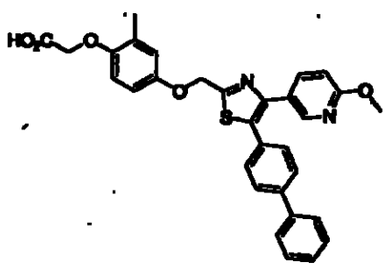
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(M+H$^+$) 546.1, encontrada 546.1.
J18		^{1}H-RMN (400MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.18-7.11 (m, 3H), 6.93-6.88 (m, 2H), 6.82 (d, J = 2.8 Hz, 1H), 6.80-6.66 (m, 3H), 5.25 (s, 2H), 4.52 (s, 2H), 3.57 (s, 3H), 2.16 (s, 3H). MS calculada para $C_{27}H_{23}F_3NO_6S$ (M+H$^+$) 546.1, encontrada 546.1.
J19		^{1}H-RMN (400MHz, CD_3OD) δ = 7.55 (t, J = 8.0 Hz, 2H), 7.44-7.38 (m, 2H), 7.16-7.11 (m, 1H), 6.91-6.67 (m, 6H), 5.27 (s, 2H), 4.53 (s, 2H), 3.59 (s, 3H), 2.16 (s, 3H). MS calculada para $C_{27}H_{23}F_3NO_6S$ (M+H$^+$) 530.1, encontrada 530.1.

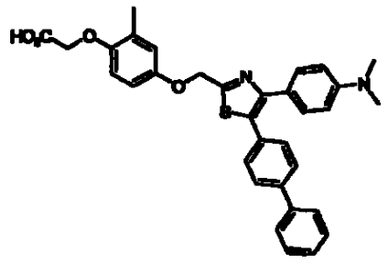
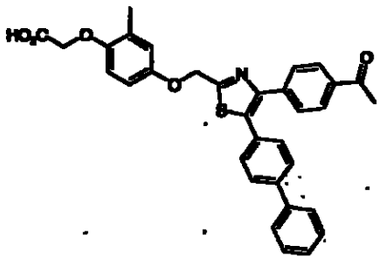
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
J20		^{1}H-RMN (400MHz, CD_3OD) δ = 7.56-7.45 (m, 4H), 7.12 (t, J = 8.4 Hz, 1H), 6.89-6.66 (m, 6H), 5.26 (s, 2H), 4.52 (s, 2H), 3.57 (s, 3H), 2.15 (s, 3H). MS calculada para $C_{27}H_{23}F_3NO_6S$ ($M+H^+$) 530.1, encontrada 530.1.
J21		^{1}H-RMN (400MHz, CD_3OD) δ = 7.59 (t, J = 8.0 Hz, 1H), 7.51 (s, 1H), 7.48-7.41 (m, 2H), 7.13 (t, J = 8.0 Hz, 1H), 6.91-6.87 (m, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.81-6.67 (m, 3H), 5.27 (s, 2H), 4.52 (s, 2H), 3.58 (s, 3H), 2.17 (s, 3H). MS calculada para $C_{27}H_{23}F_3NO_6S_2$ ($M+H^+$) 562.1, encontrada 562.0.
J22		^{1}H-RMN (400MHz, CD_3OD) δ =

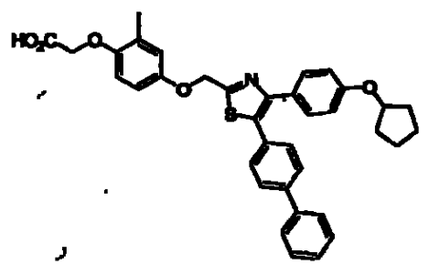
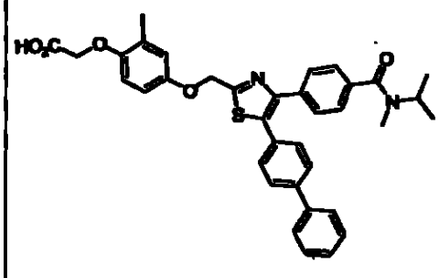
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		7.59 (t, J = 8.0 Hz, 2H), 7.38 (t, J = 8.4 Hz, 2H), 7.14 (t, J = 8.0 Hz, 1H), 6.95-6.87 (m, 2H), 6.83 (d, J = 3.2 Hz, 1H), 6.81-6.67 (m, 3H), 5.27 (s, 2H), 4.53 (s, 2H), 3.56 (s, 3H), 2.17 (s, 3H). MS calculada para $C_{27}H_{23}F_3NO_5S_2$ (M+H$^+$) 562.1, encontrada 562.0.
J23		^{1}H-RMN (400MHz, CD_3OD) δ = 7.80 (s, 1H), 7.77-7.68 (m, 4H), 7.42-7.38 (m, 2H), 7.26 (dd, J = 1.6 Hz, J = 8.4 Hz, 1H), 7.08 (t, J = 8.0 Hz, 1H), 6.95-6.93 (m, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.78-6.68 (m, 2H), 5.27 (s, 2H), 4.53 (s, 2H), 3.50 (s, 3H), 2.17 (s, 3H). MS calculada para $C_{30}H_{26}NO_5S$ (M+H$^+$) 512.1, encontrada

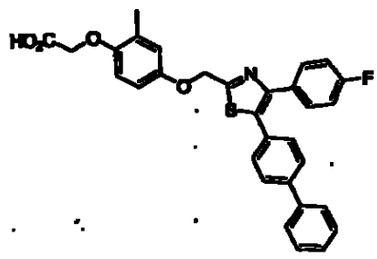
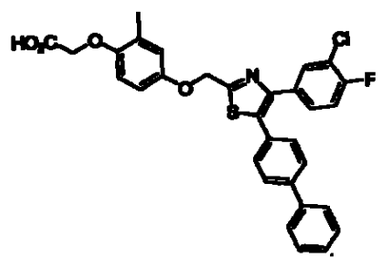
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		512.1.
J24		^{1}H-RMN (400MHz, CD_3OD) δ = 7.33-7.25 (m, 4H), 7.15 (t, J = 8.0 Hz, 1H), 6.94-6.92 (m, 2H), 6.96 (d, J = 2.8 Hz, 1H), 6.82-6.69 (m, 3H), 5.28 (s, 2H), 4.55 (s, 2H), 3.61 (s, 3H), 2.17 (s, 3H). MS calculada para $C_{26}H_{23}ClNO_5S$ ($M+H^+$) 496.1, encontrada 496.0.
J25		^{1}H-RMN (400MHz, CD_3OD) δ = 7.48 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.16 (t, J = 8.2 Hz, 1H), 6.94-6.92 (m, 2H), 6.87 (d, J = 3.2 Hz, 1H), 6.83-6.70 (m, 3H), 5.29 (s, 2H), 4.55 (s, 2H), 3.62 (s, 3H), 2.17 (s, 3H). MS calculada para $C_{26}H_{23}BrNO_5S$ ($M+H^+$) 540.0, encontrada 540.1.

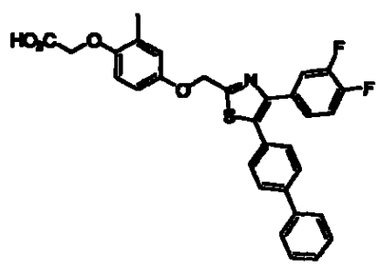
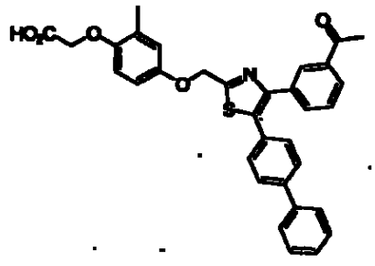
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
J26		^{1}H-RMN (400MHz, CD_3OD) δ = 7.57 (d, J = 8.0 Hz, 1H), 7.50 (s, 1H), 7.47-7.37 (m, 2H), 7.27 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.79 (d, J = 8.8 Hz, 2H), 6.76-6.67 (m, 2H), 5.25 (s, 2H), 4.53 (s, 2H), 3.70 (s, 3H), 2.17 (s, 3H). MS calculada para $C_{27}H_{23}F_3NO_6S_2$ ($M+H^+$) 562.1, encontrada 562.0.
J27		^{1}H-RMN (400MHz, CD_3OD) δ = 7.48 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.80-6.70 (m, 2H), 5.28 (s, 2H), 4.56 (s, 2H), 3.71 (s, 3H), 2.16 (s, 3H). MS calculada para $C_{26}H_{23}BrNO_6S$

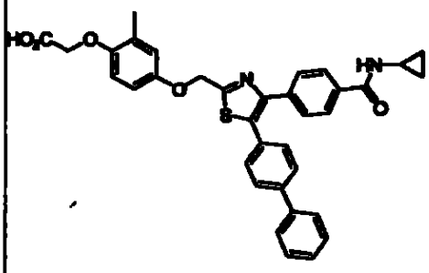
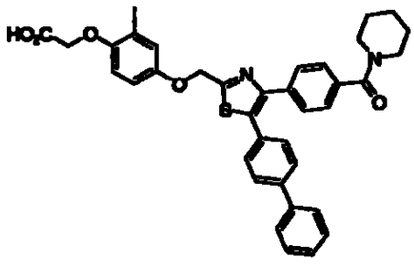
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(M+H$^+$) 540.0, encontrada 540.0.
J28		^{1}H-RMN (400MHz, CD_3OD) δ = 7.25 (t, J = 8.0 Hz, 2H), 7.18 (t, J = 8.0 Hz, 2H), 6.97-6.79 (m, 8H), 6.73-6.71 (m, 1H), 5.33 (s, 2H), 4.57 (s, 2H), 3.62 (s, 3H), 3.58 (s, 3H), 2.12 (s, 3H). MS calculada para $C_{27}H_{28}NO_6S$ (M+H$^+$) 492.14, encontrada 492.00.
K2		^{1}H-RMN (400MHz, CD_3OD) δ = 8.16 (d, J = 2.0 Hz, 1H), 7.75 (dd, J = 2.4 Hz, J = 8.8 Hz, 1H), 7.57-7.54 (m, 4H), 7.37-7.30 (m, 4H), 7.28-7.24 (m, 1H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 3H), 5.27 (s, 2H), 4.53 (s, 2H), 3.81 (s, 3H), 2.17 (s, 3H). MS calculada

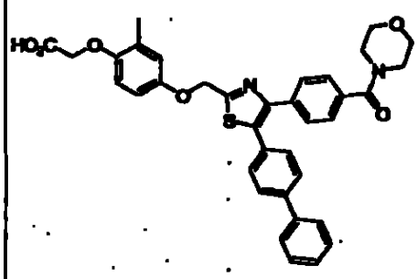
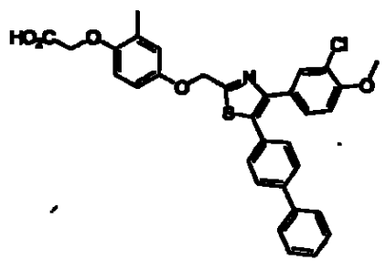
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		para $C_{31}H_{27}N_2O_5S$ ($M+H^+$) 539.2, encontrada 539.1.
K3		^{1}H-RMN (400MHz, CD_3OD) δ = 7.58-7.55 (m, 4H), 7.41-7.34 (m, 4H), 7.29-7.26 (m, 1H), 6.91 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 2.8 Hz, 1H), 6.79-6.69 (m, 2H), 5.27 (s, 2H), 4.55 (s, 2H), 2.96 (s, 6H), 2.17 (s, 3H). MS calculada para $C_{33}H_{31}N_2O_4S$ ($M+H^+$) 551.2, encontrada 551.2.
K4		^{1}H-RMN (400MHz, CD_3OD) δ = 7.88 (d, J = 8.4 Hz, 4H), 7.58-7.55 (m, 6H), 7.37-7.32 (m, 4H), 7.28-7.25 (m, 1H), 6.85 (d, J = 2.8 Hz, 1H), 6.78-6.68 (m, 2H), 5.29 (s, 2H), 4.53 (s, 2H), 2.50 (s, 3H), 2.18 (s, 3H). MS calculada para $C_{33}H_{28}NO_6S$

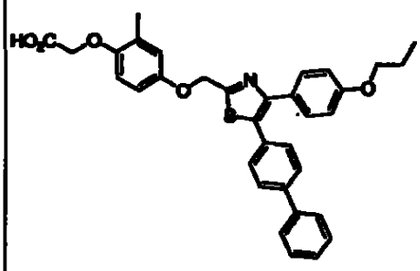
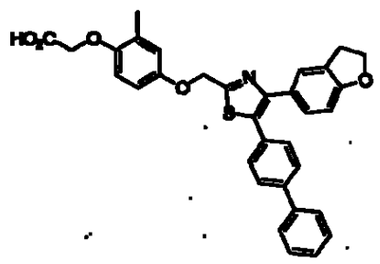
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(M+H$^+$) 550.2, encontrada 550.2.
K5		^{1}H-RMN (400MHz, CD_3OD) δ = 7.59-7.55 (m, 4H), 7.37-7.33 (m, 6H), 7.29-7.26 (m, 1H), 6.86 (d, J = 2.8 Hz, 1H), 6.78-6.68 (m, 2H), 5.27 (s, 2H), 4.55 (s, 2H), 4.72 (m, 1H), 2.50 (s, 3H), 2.18 (s, 3H), 1.90-1.52 (m, 8H). MS calculada para $C_{36}H_{34}NO_6S$ (M+H$^+$) 592.2, encontrada 592.2.
K6		^{1}H-RMN (400MHz, CD_3OD) δ = 7.54-7.51 (m, 6H), 7.36-7.31 (m, 4H), 7.28-7.24 (m, 3H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 2H), 5.27 (s, 2H), 4.53 (s, 2H), 3.92-3.66 (m, 1H), 2.83-2.74 (m, 3H), 2.17

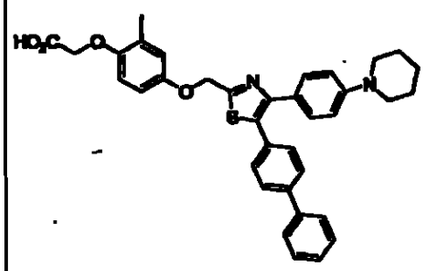
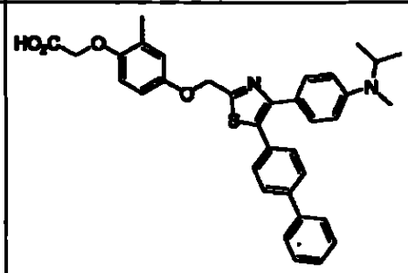
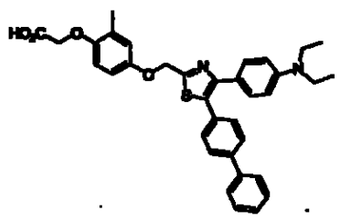
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(s, 3H), 1.14-1.07 (m, 6H). MS calculada para $C_{36}H_{36}N_2O_6S$ ($M+H^+$) 607.2, encontrada 607.3.
K7		^{1}H-RMN (400MHz, CD_3OD) δ = 7.59-7.56 (m, 5H), 7.38-7.25 (m, 7H), 7.10 (t, J = 8.8 Hz, 1H), 6.85 (d, J = 2.8 Hz, 1H), 6.78-6.69 (m, 2H), 5.27 (s, 2H), 4.54 (s, 2H), 2.18 (s, 3H). MS calculada para $C_{31}H_{26}FNO_4S$ ($M+H^+$) 526.1, encontrada 526.1.
K8		^{1}H-RMN (400MHz, CD_3OD) δ = 7.62 (d, J = 8.4 Hz, 4H), 7.49-7.30 (m, 7H), 7.07-7.02 (m, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.82-6.71 (m, 2H), 5.30 (s, 2H), 4.56 (s, 2H), 2.17 (s, 3H). MS calculada para

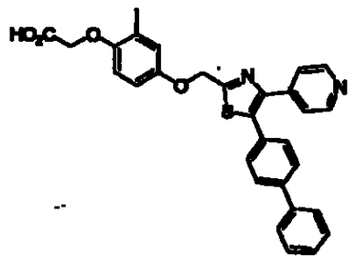
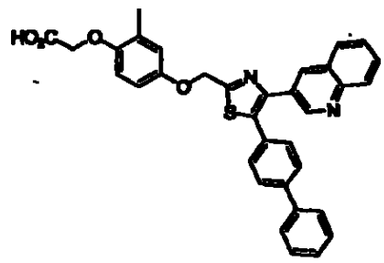
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		$C_{31}H_{24}ClFNO_4S$ ($M+H^+$) 560.1, encontrada 560.1.
K9		^{1}H-RMN (400MHz, CD_3OD) δ = 7.63-7.60 (m, 4H), 7.41-7.15 (m, 8H), 6.87 (d, J = 2.8 Hz, 1H), 6.80-6.70 (m, 2H), 5.30 (s, 2H), 4.54 (s, 2H), 2.17 (s, 3H). MS calculada para $C_{31}H_{24}F_2NO_4S$ ($M+H^+$) 544.1, encontrada 544.1.
K10		^{1}H-RMN (400MHz, CD_3OD) δ = 8.06 (s, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.58-7.54 (m, 4H), 7.40-7.25 (m, 6H), 6.86 (d, J = 2.4 Hz, 1H), 6.79-6.69 (m, 2H), 5.30 (s, 2H), 4.54 (s, 2H), 2.37 (s, 3H), 2.18 (s, 3H). MS calculada para $C_{33}H_{28}NO_5S$ ($M+H^+$) 550.2, encontrada

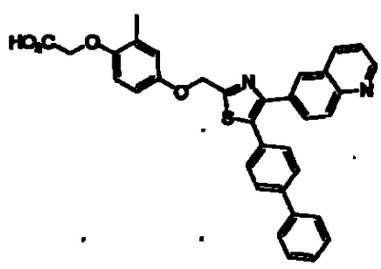
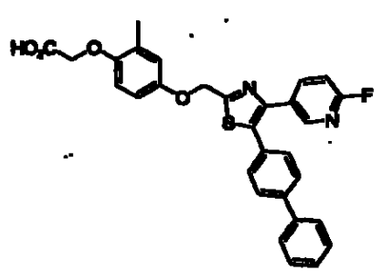
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		550.2.
K11		^{1}H-RMN (400MHz, CD_3OD) δ = 7.67 (d, J = 8.4 Hz, 2H), 7.54-7.48 (m, 5H), 7.36-7.24 (m, 6H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 2H), 5.26 (s, 2H), 4.53 (s, 2H), 2.80-2.72 (m, 1H), 2.17 (s, 3H), 0.70-0.53 (m, 4H). MS calculada para $C_{35}H_{31}N_2O_5S$ ($M+H^+$) 591.2, encontrada 591.2.
K12		^{1}H-RMN (400MHz, CD_3OD) δ = 7.55-7.51 (m, 7H), 7.37-7.26 (m, 6H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 2H), 5.28 (s, 2H), 4.54 (s, 2H), 3.64-3.23 (m, 4H), 2.18 (s, 3H), 1.72-1.40 (m, 6H). MS calculada para $C_{37}H_{35}N_2O_5S$ ($M+H^+$) 619.2, encontrada 619.2.

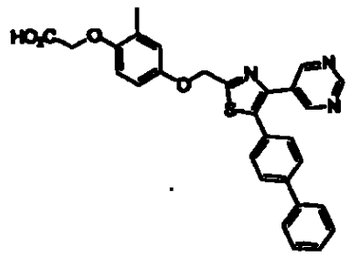
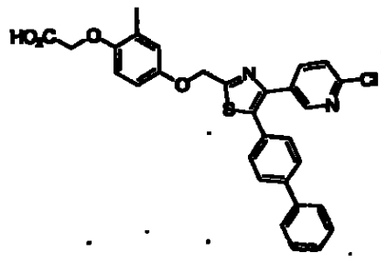
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
K13		^{1}H-RMN (400MHz, CD_3OD) δ = 7.59-7.53 (m, 6H), 7.39-7.26 (m, 7H), 6.87 (d, J = 2.4 Hz, 1H), 6.80-6.69 (m, 2H), 5.29 (s, 2H), 4.55 (s, 2H), 3.70-3.25 (m, 8H), 2.17 (s, 3H). MS calculada para $C_{36}H_{33}N_2O_6S$ ($M+H^+$) 621.2, encontrada 612.2.
K14		^{1}H-RMN (400MHz, CD_3OD) δ = 7.56 (d, J = 8.0 Hz, 4H), 7.48 (d, J = 1.6 Hz, 1H), 7.37-7.25 (m, 6H), 6.93 (d, J = 8.4 Hz, 4H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 2H), 5.26 (s, 2H), 4.54 (s, 2H), 3.79 (s, 3H), 2.18 (s, 3H). MS calculada para $C_{32}H_{27}ClNO_6S$ ($M+H^+$) 572.1, encontrada 572.1.
K15		^{1}H-RMN (400MHz, CD_3OD) δ =

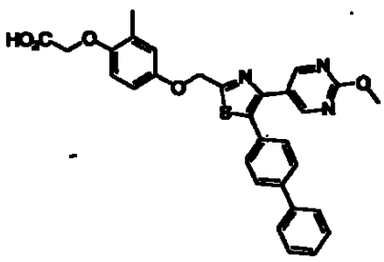
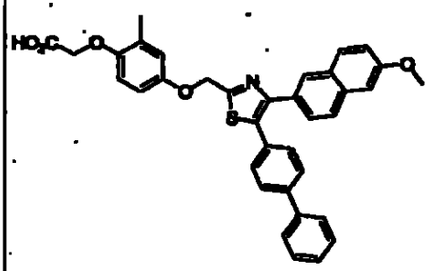
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		7.65-7.57 (m, 4H), 7.40-7.29 (m, 7H), 6.87 (d, J = 2.4 Hz, 1H), 6.82-6.70 (m, 4H), 5.28 (s, 2H), 4.54 (s, 2H), 3.85 (t, J = 6.6 Hz, 2H), 2.17 (s, 3H), 1.71-1.66 (m, 2H), 0.94 (t, J = 7.0 Hz, 3H). MS calculada para $C_{34}H_{32}NO_6S$ ($M+H^+$) 566.2, encontrada 566.1.
K16		^{1}H-RMN (400MHz, CD_3OD) δ = 7.58-7.54 (m, 4H), 7.39-7.26 (m, 6H), 7.15 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 6.79-6.60 (m, 3H), 5.27 (s, 2H), 4.55 (s, 2H), 4.47 (t, J = 8.8 Hz, 2H), 3.10 (t, J = 8.4 Hz, 2H), 2.17 (s, 3H). MS calculada para $C_{33}H_{28}NO_5S$ ($M+H^+$) 550.2, encontrada 550.1.

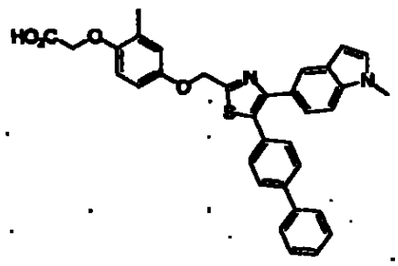
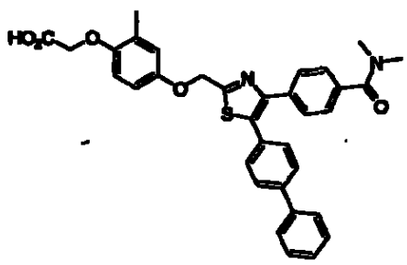
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
K17		^{1}H-RMN (400MHz, CD_3OD) δ = 7.58-7.54 (m, 6H), 7.38-7.25 (m, 7H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 2H), 5.27 (m, 2H), 4.54 (s, 2H), 3.43 (t, J = 5.4 Hz, 4H), 2.17 (s, 3H), 1.88-1.83 (m, 4H), 1.68-1.64 (m, 2H). MS calculada para $C_{38}H_{38}N_2O_4S$ ($M+H^+$) 591.2, encontrada 591.2.
K18		MS calculada para $C_{38}H_{38}N_2O_4S$ ($M+H^+$) 579.2, encontrada 579.2.
K19		MS calculada para $C_{38}H_{38}N_2O_4S$ ($M+H^+$) 579.2, encontrada 579.2.

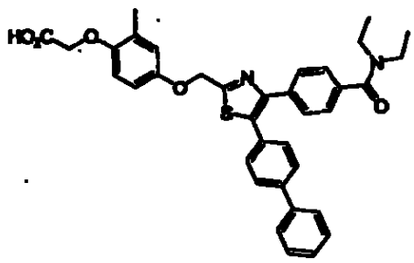
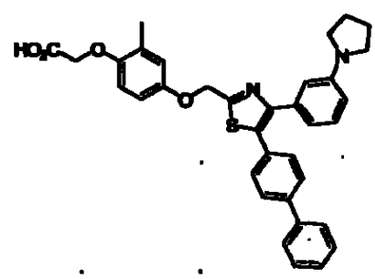
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
K20		^{1}H-RMN (400MHz, CD_3OD) δ = 8.62 (d, J = 6.8 Hz, 1H), 8.07 (d, J = 6.4 Hz, 1H), 7.70-7.28 (m, 11H), 6.85 (d, J = 2.8 Hz, 1H), 6.78-6.68 (m, 2H), 5.33 (s, 2H), 4.54 (s, 2H), 2.17 (s, 3H). MS calculada para $C_{30}H_{25}N_2O_4S$ ($M+H^+$) 509.2, encontrada 509.1.
K21		^{1}H-RMN (400MHz, CD_3OD) δ = 9.08 (s, 1H), 8.80 (s, 1H), 8.16-8.08 (m, 2H), 7.96 (t, J = 7.6 Hz, 1H), 7.83-7.77 (m, 4H), 7.69-7.46 (m, 4H), 7.08 (d, J = 2.4 Hz, 1H), 7.02-6.89 (m, 2H), 5.55 (s, 2H), 4.74 (s, 2H), 2.34 (s, 3H). MS calculada para $C_{34}H_{27}N_2O_4S$ ($M+H^+$) 559.2, encontrada

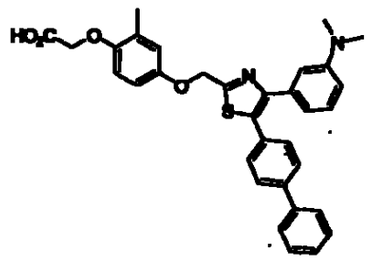
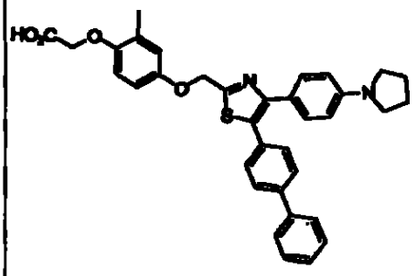
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		559.2.
K22		^{1}H-RMN (400MHz, CD_3OD) δ = 9.00 (d, J = 4.0 Hz, 1H), 8.82-8.79 (m, 1H), 8.36 (s, 1H), 8.09-8.00 (m, 2H), 7.85-7.81 (m, 1H), 7.58-7.25 (m, 9H), 6.86 (d, J = 3.2 Hz, 1H), 6.79-6.69 (m, 2H), 5.32 (s, 2H), 4.54 (s, 2H), 2.18 (s, 3H). MS calculada para $C_{34}H_{27}N_2O_4S$ ($M+H^+$) 559.2, encontrada 559.1.
K23		^{1}H-RMN (400MHz, CD_3OD) δ = 8.26 (s, 1H), 8.05-8.00 (m, 1H), 7.64-7.28 (m, 9H), 7.03 (dd, J = 2.4 Hz, J = 8.8 Hz, 1H), 6.88 (d, J = 2.8 Hz, 1H), 6.81-6.70 (m, 2H), 5.32 (s, 2H), 4.54 (s, 2H), 2.17 (s, 3H). MS calculada para

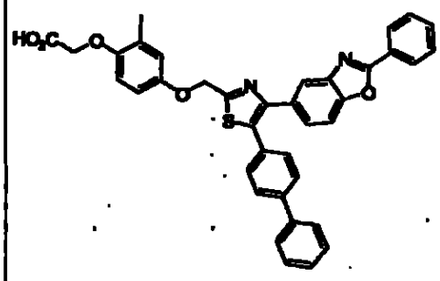
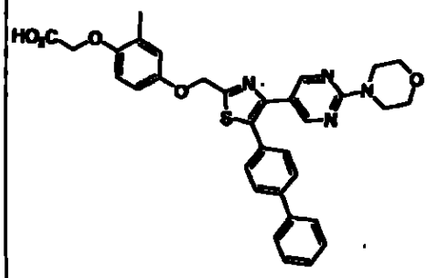
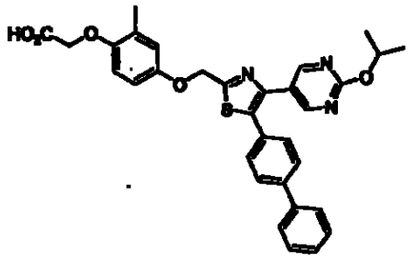
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		$C_{30}H_{24}FN_2O_4S$ ($M+H^+$) 527.1, encontrada 527.1.
K24		^{1}H-RMN (400MHz, CD_3OD) δ = 9.01 (s, 1H), 8.81 (s, 2H), 7.68-7.61 (m, 4H), 7.44-7.30 (m, 5H), 6.89 (d, J = 2.4 Hz, 1H), 6.82-6.71 (m, 2H), 5.35 (s, 2H), 4.55 (s, 2H), 2.17 (s, 3H). MS calculada para $C_{29}H_{24}N_3O_4S$ ($M+H^+$) 510.1, encontrada 510.1.
K25		^{1}H-RMN (400MHz, CD_3OD) δ = 8.40 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 2.6 Hz, J = 8.2 Hz, 1H), 7.61-7.55 (m, 4H), 7.37-7.25 (m, 6H), 6.83 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 2H), 5.29 (s, 2H), 4.48 (s, 2H), 2.17 (s, 3H). MS calculada para $C_{30}H_{24}ClN_2O_4S$ ($M+H^+$) 543.1,

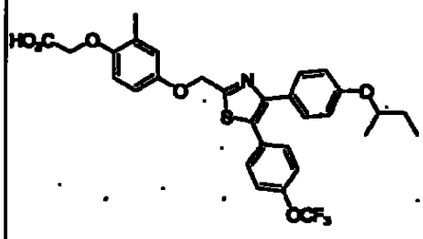
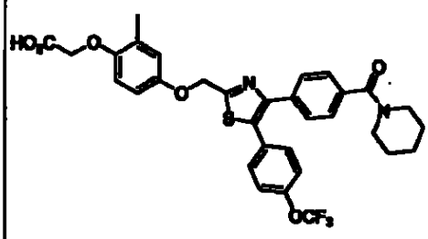
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		encontrada 543.1.
K26		^{1}H-RMN (400MHz, CD_3OD) δ = 8.40 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 2.6 Hz, J = 8.2 Hz, 1H), 7.61-7.55 (m, 4H), 7.37-7.25 (m, 6H), 6.83 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 2H), 5.29 (s, 2H), 4.48 (s, 2H), 2.17 (s, 3H). MS calculada para $C_{30}H_{26}N_3O_5S$ ($M+H^+$) 540.2, encontrada 540.1.
K27		^{1}H-RMN (400MHz, CD_3OD) δ = 7.88 (s, 1H), 7.63-7.50 (m, 6H), 7.42-7.24 (m, 6H), 7.13 (d, J = 2.8 Hz, 1H), 7.03 (dd, J = 2.6 Hz, J = 9.0 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 6.77-6.69 (m, 2H), 5.29 (s, 2H), 4.54 (s, 2H), 3.81 (s, 3H), 2.18 (s, 3H). MS calculada para $C_{36}H_{30}NO_5S$

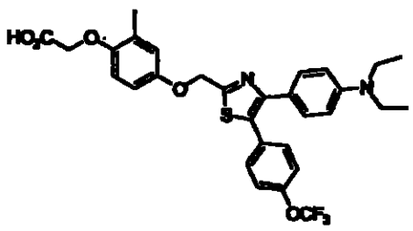
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(M+H$^+$) 588.2, encontrada 588.2.
K28		^{1}H-RMN (400MHz, CD_3OD) δ = 7.67 (s, 1H), 7.58-7.53 (m, 4H), 7.39-7.21 (m, 7H), 7.15 (s, 1H), 6.89 (d, J = 2.4 Hz, 1H), 6.82-6.71 (m, 2H), 5.30 (s, 2H), 4.56 (s, 2H), 3.72 (s, 3H), 2.18 (s, 3H). MS calculada para $C_{34}H_{28}N_2O_4S$ (M+H$^+$) 561.2, encontrada 561.2.
K29		^{1}H-RMN (400MHz, CD_3OD) δ = 7.54-7.51 (m, 6H), 7.36-7.23 (m, 7H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 2H), 5.27 (s, 2H), 4.53 (s, 2H), 3.00 (s, 3H), 2.92 (s, 3H), 2.17 (s, 3H). MS calculada para $C_{34}H_{31}N_2O_5S$ (M+H$^+$) 579.2,

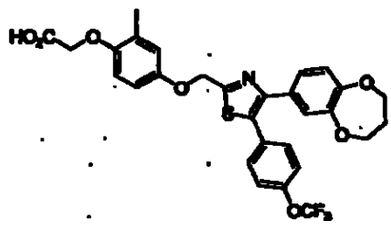
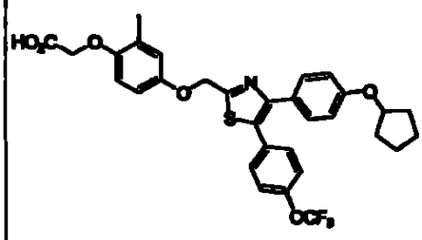
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		encontrada 579.2.
K30		^{1}H-RMN (400MHz, CD_3OD) δ = 7.54-7.51 (m, 6H), 7.36-7.24 (m, 7H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 2H), 5.27 (s, 2H), 4.53 (s, 2H), 3.47-3.36 (m, 4H), 2.17 (s, 3H), 1.10-0.99 (m, 6H). MS calculada para $C_{34}H_{31}N_2O_5S$ ($M+H^+$) 607.2, encontrada 607.2.
K31		^{1}H-RMN (400MHz, CD_3OD) δ = 7.56 (d, J = 8.0 Hz, 4H), 7.38-7.25 (m, 5H), 7.12 (t, J = 8.0 Hz, 1H), 6.67-6.61 (m, 6H), 5.27 (s, 2H), 4.54 (s, 2H), 3.14-3.11 (m, 4H), 2.17 (s, 3H), 1.89-1.86 (m, 4H). MS calculada para $C_{35}H_{33}N_2O_4S$ ($M+H^+$) 577.2, encontrada 577.2.

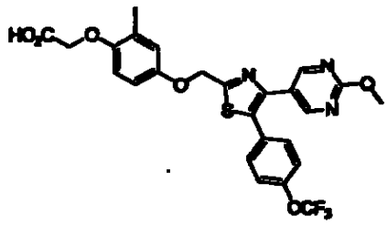
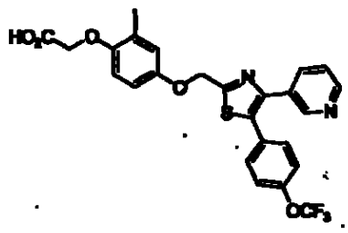
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
K32		^{1}H-RMN (400MHz, CD_3OD) δ = 7.58-7.53 (m, 4H), 7.37-7.17 (m, 9H), 6.84 (d, J = 2.8 Hz, 1H), 6.78-6.68 (m, 2H), 5.28 (s, 2H), 4.54 (s, 2H), 2.99 (s, 6H), 2.17 (s, 3H). MS calculada para $C_{33}H_{31}N_2O_4S$ ($M+H^+$) 551.2, encontrada 551.2.
K33		^{1}H-RMN (400MHz, CD_3OD) δ = 7.54-7.49 (m, 4H), 7.36-7.23 (m, 7H), 6.83 (d, J = 3.2 Hz, 1H), 6.77-6.68 (m, 2H), 6.50 (d, J = 8.4 Hz, 2H), 5.24 (s, 2H), 4.53 (2H), 3.21-3.18 (m, 4H), 2.17 (s, 3H), 1.98-1.92 (m, 4H). MS calculada para $C_{35}H_{33}N_2O_4S$ ($M+H^+$) 577.2, encontrada 577.2.
K34		^{1}H-RMN (400MHz, CD_3OD) δ =

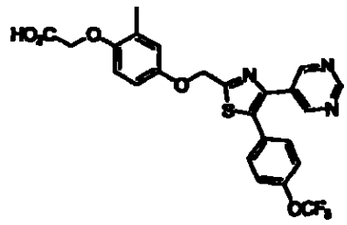
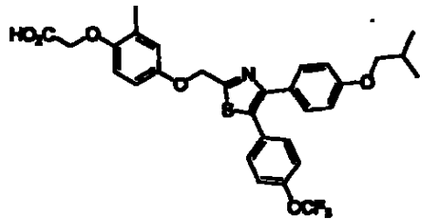
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		8.15 (d, J = 7.2 Hz, 7.2 Hz, 4H), 7.78-7.27 (m, 13H), 6.90-6.72 (m, 3H), 5.34 (s, 2H), 4.57 (s, 2H), 2.18 (s, 3H). MS calculada para $C_{38}H_{29}N_2O_6S$ ($M+H^+$) 625.2, encontrada 625.2.
K35		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.51 (s, 2H), 7.61-7.37 (m, 9H), 6.92-6.71 (m, 3H), 5.33 (s, 2H), 4.64 (s, 2H), 3.82 (m, 4H), 3.77 (m, 4H), 2.29 (s, 3H). MS calculada para $C_{33}H_{31}N_4O_6S$ ($M+H^+$) 595.2, encontrada 595.2.
K36		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.69 (s, 2H), 7.71-7.38 (m, 9H), 6.91-6.71 (m, 3H), 5.34 (s, 2H), 5.27 (m, 1H), 4.64 (s, 2H), 2.29 (s, 3H), 1.39 (d, J =

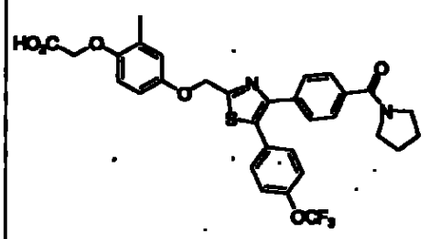
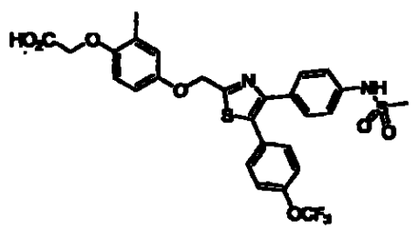
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		6.2 HZ, 6H). MS calculada para $C_{32}H_{30}N_3O_5S$ ($M+H^+$) 568.2, encontrada 568.2.
L2		^{1}H-RMN (400MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 4H), 5.24 (s, 2H), 4.52 (s, 2H), 4.30-4.25 (m, 1H), 2.16 (s, 3H), 1.62-1.52 (m, 2H), 1.18 (d, J = 6.0 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H). MS calculada para $C_{30}H_{28}F_3NO_6S$ ($M+H^+$) 588.2, encontrada 588.1.
L3		^{1}H-RMN (400MHz, CD_3OD) δ = 7.57 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 2.8 Hz,

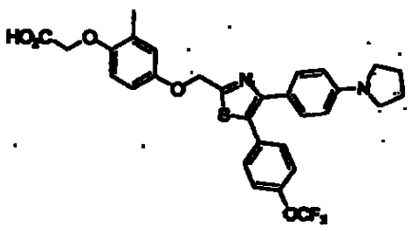
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		1H), 6.86-6.77 (m, 2H), 5.37 (s, 2H), 4.63 (s, 2H), 3.70 (bs, 2H), 3.39 (bs, 2H), 2.26 (s, 3H), 1.72-1.54 (m, 6H). MS calculada para $C_{32}H_{30}F_3N_2O_6S$ ($M+H^+$) 627.2, encontrada 627.1.
L4		^{1}H-RMN (400MHz, CD_3OD) δ = 7.50 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.14 (bs 4H), 6.83 (d, J = 2.8 Hz, 1H), 6.76-6.67 (m, 2H), 5.26 (s, 2H), 4.53 (s, 2H), 3.51 (q, J = 7.2 Hz, 4H), 2.16 (s, 3H), 1.05 (t, J = 7.0 Hz, 6H). MS calculada para $C_{30}H_{30}F_3N_2O_6S$ ($M+H^+$) 587.2, encontrada 587.2.
L5		^{1}H-RMN (400MHz, CD_3OD) δ = 7.34 (d, J = 7.34 (d, J = 8.8

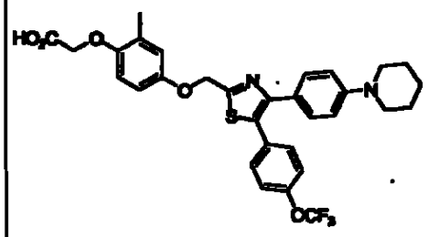
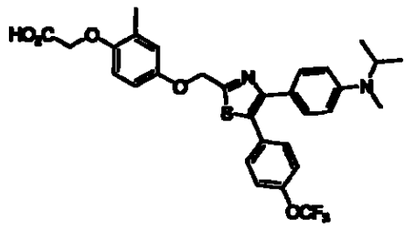
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 8.97 (d, J = 2.0 Hz, 2H), 6.90-6.77 (m, 3H), 6.75-6.67 (m, 2H), 5.24 (s, 2H), 4.53 (s, 2H), 4.09-4.02 (q, 4H), 2.16 (s, 3H), 2.08-2.03 (m, 3H). MS calculada para $C_{29}H_{25}F_3NO_7S$ (M+H$^+$) 588.1, encontrada 588.1.
L6		^{1}H-RMN (400MHz, CD_3OD) δ = 7.38 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 2.8 Hz, 1H), 6.79-6.69 (m, 4H), 5.27 (s, 2H), 4.73 (m, 1H), 4.54 (s, 2H), 2.16 (s, 3H), 1.86-1.54 (m, 8H). MS calculada para $C_{31}H_{29}F_3NO_6S$ (M+H$^+$) 600.2, encontrada 600.1.

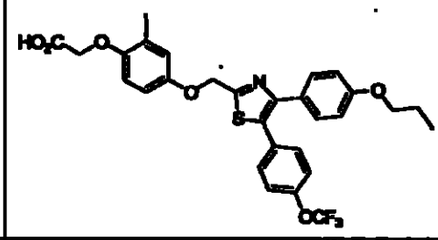
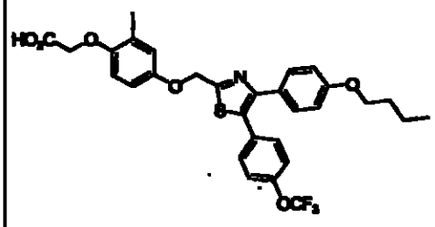
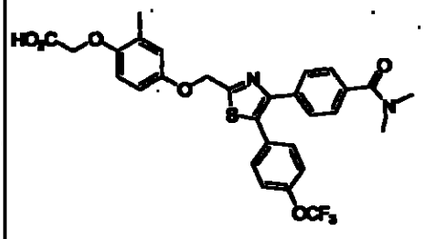
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
L7		^{1}H-RMN (400MHz, CD_3OD) δ = 8.53 (s, 2H), 7.44 (d, J = 8.8 Hz, 2H), 7.28 (d, JJ = 8.8 Hz, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 2H), 5.29 (s, 2H), 4.54 (s, 2H), 3.93 (s, 3H), 2.17 (s, 3H). MS calculada para $C_{26}H_{21}F_3N_3O_6S$ ($M+H^+$) 548.1, encontrada 548.1.
L8		^{1}H-RMN (400MHz, CD_3OD) δ = 8.68 (s, 1H), 8.55 (d, J = 5.2 Hz, 1H), 8.11 (dd, J = 1.8 Hz, J = 8.2 Hz, 1H), 7.60-7.56 (m, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 2.8 Hz, 1H), 6.81-6.70 (m, 2H), 5.34 (s, 2H), 4.56 (s, 2H), 2.16 (s, 3H). MS calculada para $C_{26}H_{20}F_3N_2O_6S$

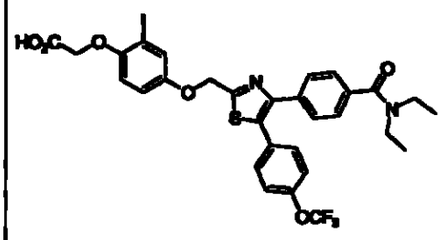
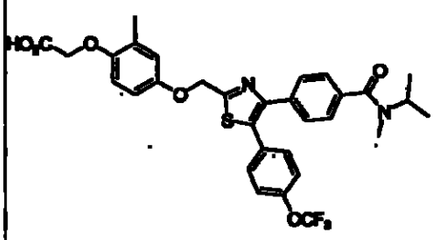
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(M+H$^+$) 517.1, encontrada 516.9.
L9		^{1}H-RMN (400MHz, CD_3OD) δ = 9.24 (s, 1H), 8.98 (s, 2H), 7.71 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 2.8 Hz, 1H), 7.02-6.90 (m, 2H), 5.56 (s, 2H), 4.67 (s, 2H), 2.39 (s, 3H). MS calculada para $C_{24}H_{18}F_3O_5S$ (M+H$^+$) 518.1, encontrada 518.1.
L10		^{1}H-RMN (400MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 2.8 Hz, 1H), 6.80-6.66 (m, 4H), 5.24 (s, 2H), 4.49 (s, 2H), 3.66 (d, J = 6.4 Hz, 2H), 2.19 (s, 3H), 2.01-1.91 (m, 1H), 0.94 (s, 3H), 0.93 (s, 3H). MS

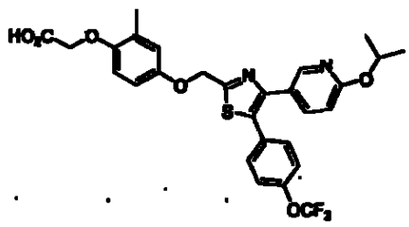
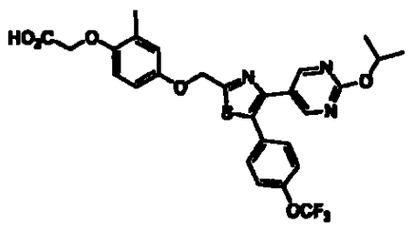
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		calculada para $C_{30}H_{28}F_3NO_6S$ ($M+H^+$) 588.2, encontrada 588.1.
L11		^{1}H-RMN (400MHz, CD_3OD) δ = 7.47-7.40 (m, 4H), 7.37 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 2H), 5.28 (s, 2H), 4.54 (s, 2H), 3.49 (t, J = 7.0 Hz, 2H), 3.38 (t, J = 6.4 Hz, 2H), 2.17 (s, 3H), 1.93-1.78 (m, 4H). MS calculada para $C_{31}H_{28}F_3N_2O_6S$ ($M+H^+$) 613.2, encontrada 613.1.
L12		^{1}H-RMN (400MHz, CD_3OD) δ = 7.36-7.32 (m, 4H), 7.20 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.76-6.67 (m, 2H), 5.25 (s, 2H), 4.52 (s, 2H), 2.89 (s,

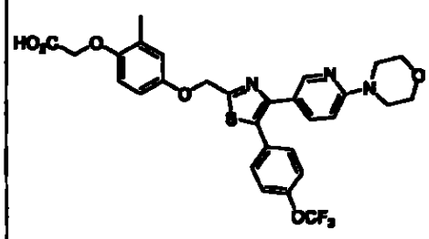
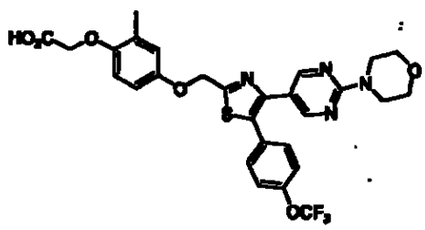
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		3H), 2.16 (s, 3H). MS calculada para $C_{27}H_{24}F_3N_2O_7S_2$ ($M+H^+$) 609.1, encontrada 609.1.
L13		^{1}H-RMN (400MHz, CD_3OD) δ = 7.51 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.76-6.67 (m, 2H), 5.27 (s, 2H), 4.54 (s, 2H), 3.42 (t, J = 5.4 Hz, 4H), 2.17 (s, 3H), 1.87-1.82 (m, 4H), 1.68-1.64 (m, 2H). MS calculada para $C_{31}H_{30}F_3N_2O_6S$ ($M+H^+$) 599.2, encontrada C599.2.
L14		^{1}H-RMN (400MHz, CD_3OD) δ = 7.33 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 7.15 (d, J

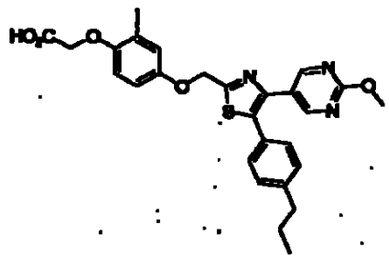
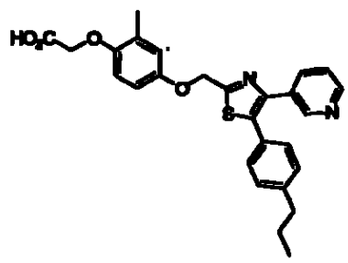
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		0 8.0 Hz, 2H), 6.81 (d, J = 2.8 Hz, 1H), 6.74-6.65 (m, 2H), 6.50 (d, J = 8.8 Hz, 2H), 5.21 (s, 2H), 4.52 (s, 2H), 3.21 (t, J = 5.4 Hz, 4H), 2.15 (s, 3H), 1.95-1.90 (m, 4H). MS calculada para $C_{30}H_{28}F_3N_2O_6S$ $(M+H^+)$ 585.2, encontrada 585.2.
L15		^{1}H-RMN (400MHz, CD_3OD) δ = 7.39-7.36 (m, 4H), 6.86-6.82 (m, 5H), 6.77-6.67 (m, 2H), 5.04 (s, 2H), 4.50 (s, 2H), 4.00-3.94 (m, 1H), 3.01 (s, 3H), 2.16 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H). MS calculada para $C_{30}H_{30}F_3N_2O_6S$ $(M+H^+)$ 587.2, encontrada 587.2.
L16		MS calculada para

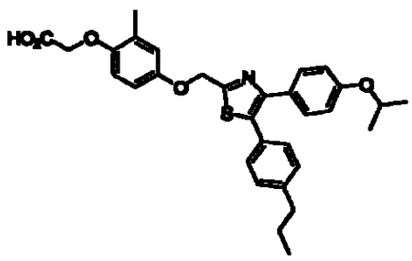
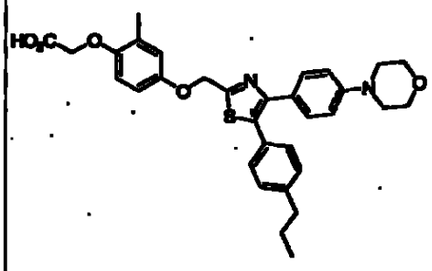
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		$C_{29}H_{27}F_3NO_6S$ ($M+H^+$) 573.1, encontrada 573.1.
L17		MS calculada para $C_{30}H_{29}F_3NO_6S$ ($M+H^+$) 588.2, encontrada 588.1.
L18		^{1}H-RMN (400MHz, CD_3OD) δ = 7.48 (d, J = 8.4 Hz, 2H), 7.37-7.30 (m, 4H), 7.20 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.77-6.68 (m, 2H), 5.28 (s, 2H), 4.53 (s, 2H), 3.01 (s, 3H), 2.92 (s, 3H), 2.17 (s, 3H). MS calculada para $C_{29}H_{28}F_3N_2O_6S$ ($M+H^+$) 587.1,

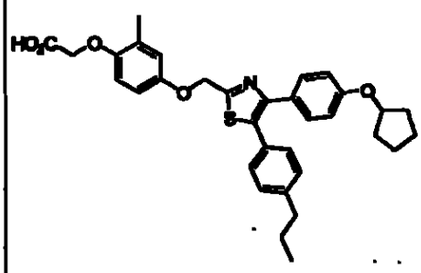
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		encontrada 587.1.
L19		^{1}H-RMN (400MHz, CD_3OD) δ = 7.56 (d, J = 8.0 Hz, 2H), 7.45-7.34 (m, 4H), 7.28 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 2.8 Hz, 1H), 6.86-6.77 (m, 2H), 5.37 (s, 2H), 4.62 (s, 2H), 3.59-3.25 (m, 4H), 2.26 (s, 3H), 1.39-1.10 (m, 6H). MS calculada para $C_{31}H_{30}F_3N_2O_6S$ ($M+H^+$) 615.2, encontrada 615.2.
L20		^{1}H-RMN (400MHz, CD_3OD) δ = 7.52 (d, J = 8.0 Hz, 2H), 7.41-7.28 (m, 4H), 7.24 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 3.2 Hz, 1H), 6.82-6.73 (m, 2H), 5.32 (s, 2H), 4.58 (s, 2H), 3.95-3.86 (m, 1H), 2.89-2.88 (m, 3H), 2.22 (s, 3H), 1.25-1.12 (m, 6H). MS calculada para

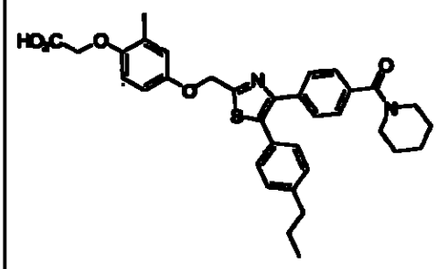
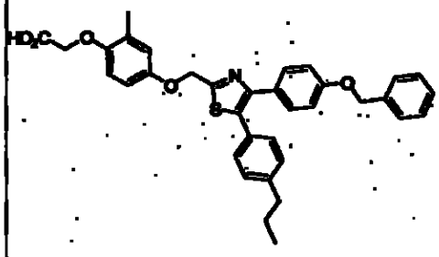
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		$C_{31}H_{30}F_3N_2O_6S$ ($M+H^+$) 615.2, encontrada 615.2.
L21		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.48 (m, 1H), 7.77 (m, 1H), 7.32-7.16 (m, 5H), 6.80-6.64 (m, 3H), 5.31 (m, 2H), 5.25 (s, 2H), 4.58 (s, 2H), 3.77 (m, 4H), 2.21 (s, 3H), 1.38 (d, J = 6.1 Hz, 6H). MS calculada para $C_{28}H_{26}F_3N_2O_6S$ ($M+H^+$) 575.1, encontrada 575.1.
L22		MS calculada para $C_{27}H_{25}F_3N_3O_6S$ ($M+H^+$) 576.1, encontrada 576.1.
L23		^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.39 (d, J = 2.1 Hz, 1H), 7.83 (m, 1H), 7.51-7.35 (m, 4H),

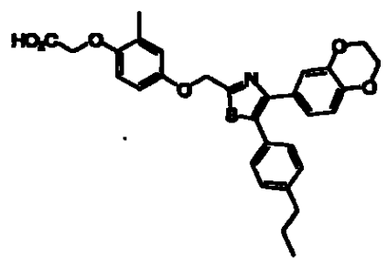
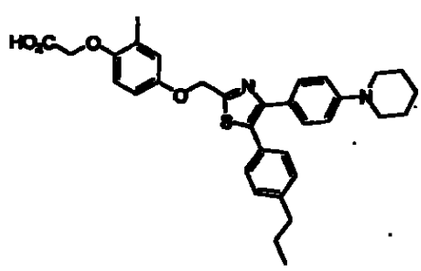
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		6.99-6.82 (m, 4H), 5.41 (s, 2H), 4.77 (s, 2H), 3.98 (m, 4H), 3.79 (m, 4H), 2.40 (s, 3H). MS calculada para $C_{28}H_{26}F_3N_3O_6S$ (M+H$^+$) 602.2, encontrada 602.2.
L24		^{1}H-RMN (400MHz, $CDCl_3$) δ =^{1}H-RMN (400MHz, $CDCl_3$) δ = 8.48 (s, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.89 (s, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.71 (d, J = 7.3 Hz, 1H), 5.32 (s, 2H), 4.64 (s, 2H), 3.82 (m, 4H), 3.78 (m, 4H), 2.29 (s, 3H). MS calculada para $C_{28}H_{26}F_3N_4O_6S$ (M+H$^+$) 603.1, encontrada 603.3.
M2		^{1}H-RMN (400MHz, CD_3OD) δ = 8.52 (s, 2H), 7.23-7.16 (m,

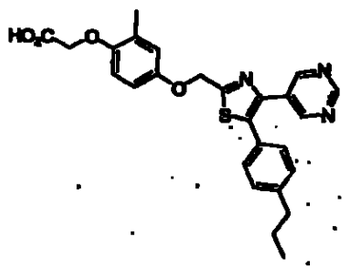
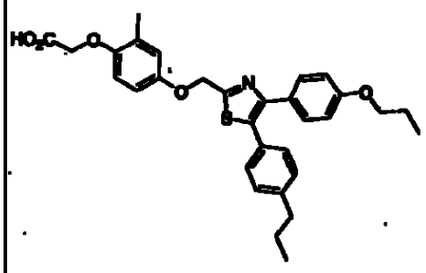
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		4H), 6.84 (d, J = 2.8 Hz, 1H), 6.78-6.68 (m, 2H), 5.27 (s, 2H), 4.54 (s, 2H), 3.90 (s, 3H), 2.52 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.60-1.54 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H). MS calculada para $C_{27}H_{28}N_3O_5S$ (M+H$^+$) 506.2, encontrada 506.2.
M3		^{1}H-RMN (400MHz, CD_3OD) δ = 8.69 (bs, 1H), 8.51 (bs, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.62 (bs, 1H), 7.23-7.16 (m, 4H), 6.83 (d, J = 2.8 Hz, 1H), 6.76-6.67 (m, 2H), 5.28 (s, 2H), 4.53 (s, 2H), 2.54 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.62-1.52 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H). MS calculada para $C_{27}H_{27}N_2O_4S$ (M+H$^+$) 475.2

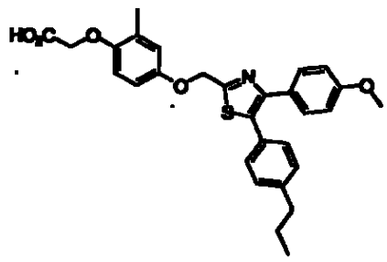
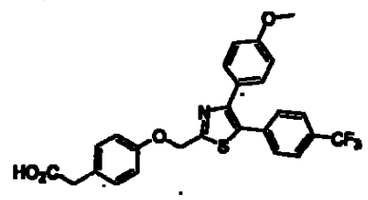
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		encontrada 475.2.
M4		^{1}H-RMN (400MHz, CD_3OD) δ = 7.26 (d, J = 8.8 Hz, 2H), 7.13-7.04 (m, 4HJ), 6.81 (d, J = 2.8 Hz, 1H), 6.74-6.66 (m, 2H), 5.21 (s, 2H), 4.52 (s, 2H), 4.51-4.46 (m, 1H), 2.49 (t, J = 7.6 Hz, 2H), 2.16 (s, 3HJ), 1.57-1.51 (m, 2H), 1.21 (d, J = 6.0 Hz, 6H), 0.85 (t, J = 7.4 Hz, 3H). MS calculada para $C_{31}H_{34}NO_5S$ ($M+H^+$) 532.2, encontrada 532.2.
M5		^{1}H-RMN (400MHz, CD_3OD) δ = 7.32 (d, J = 8.8 Hz, 2H), 7.13-7.05 (m, 4H), 6.91 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 2.8 Hz, 1H), 6.74-6.66 (m, 2H), 5.21 (s, 2H), 4.52 (s, 2H), 3.75 (t, J

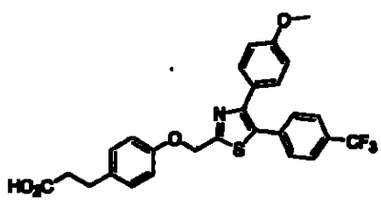
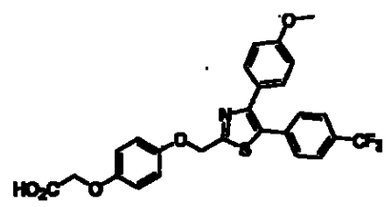
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		= 4.6 Hz, 4H), 3.14 (bs, 4H), 2.49 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.57-1.50 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H). MS calculada para $C_{32}H_{35}N_2O_5S$ ($M+H^+$) 559.2, encontrada 559.2.
M6		^{1}H-RMN (400MHz, CD_3OD) δ = 7.27 (d, J = 8.4 Hz, 2H), 7.15-7.06 (m, 4H), 6.83 (d, J = 2.4 Hz, 1H), 6.76-6.67 (m, 4H), 5.23 (s, 2H), 4.73-4.69 (m, 1H), 4.53 (s, 2H), 2.50 (t, J = 7.6 Hz, 2H), 2.17 (s, 3H), 1.88-1.51 (m, 10H), 0.86 (t, J = 7.4 Hz, 3H). MS calculada para $C_{33}H_{38}NO_5S$ ($M+H^+$) 558.2, encontrada 558.2.
M7		^{1}H-RMN (400MHz, CD_3OD) δ = 7.48 (d, J = 8.0 Hz, 2H), 7.26

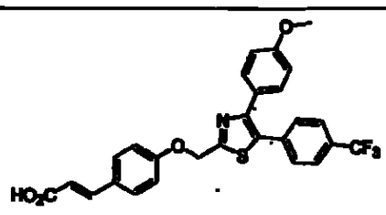
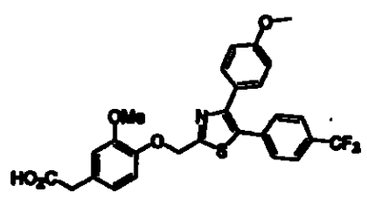
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(d, J = 8.4 Hz, 2H), 7.16-7.08 (m, 4H), 6.83 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 2H), 5.25 (s, 2H), 4.53 (s, 2H), 3.61 (bs, 2H), 3.30 (bs, 2H), 2.51 (t, J = 7.6 Hz, 2H), 2.17 (s, 3H), 1.63-1.43 (m, 8H), 0.86 (t, J = 7.4 Hz, 3H). MS calculada para $C_{34}H_{37}N_2O_5S$ ($M+H^+$) 585.2, encontrada 585.2.
M8		^{1}H-RMN (400MHz, CD_3OD) δ = 7.34-7.20 (m, 7H), 7.13-7.04 (m, 4H), 6.85-6.81 (m, 3H), 6.75-6.66 (m, 2H), 5.21 (s, 2H), 4.97 (s, 2H), 4.52 (s, 2H), 2.49 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.57-1.52 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H). MS calculada para $C_{35}H_{34}NO_5S$ ($M+H^+$) 580.2; encontrada

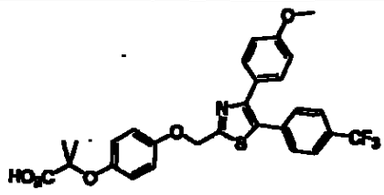
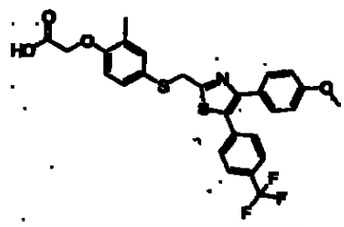
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		580.2.
M9		^{1}H-RMN (400MHz, CD_3OD) δ = 7.14-7.06 (m, 4H), 6.84-6.62 (m, 6H), 5.21 (s, 2H), 4.51 (s, 2H), 4.14-4.11 (m, 4H), 2.51 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.58-1.53 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H). MS calculada para $C_{30}H_{30}NO_6S$ ($M+H^+$) 532.1, encontrada 532.1.
M10		^{1}H-RMN (400MHz, CD_3OD) δ = 7.50 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.16-7.09 (m, 4H), 6.83 (d, J = 2.4 Hz, 1H), 6.77-6.77 (m, 2H), 5.25 (s, 2H), 4.53 (s, 2H), 3.41-3.38 (m, 4H), 2.52 (t, J = 7.6 Hz, 2H), 2.17 (s, 3H), 1.84-1.52 (m, 10H), 0.86 (t, J = 7.2 Hz,

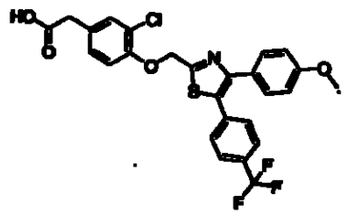
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		3H). MS calculada $C_{33}H_{37}N_2O_4S$ ($M+H^+$) 557.2, encontrada 557.2.
M11		^{1}H-RMN (400MHz, CD_3OD) δ = 8.94 (s, 1H), 8.75 (s, 2H), 7.23-7.17 (m, 4H), 6.83 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 2H), 5.28 (s, 2H), 4.53 (s, 2H), 2.53 (t, J = 7.6 Hz, 2H), 2.17 (s, 3H), 1.63-1.55 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H). MS calculada para $C_{26}H_{26}N_3O_4S$ ($M+H^+$) 476.1, encontrada 476.1.
M12		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.52-6.62 (m, 1H), 5.85 (s, 2H), 4.62 (s, 2H), 3.91 (t, J = 6.5 Hz, 2H), 2.58 (m, 2H), 2.27 (s, 3H), 1.78 (m, 2H), 1.63 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H),

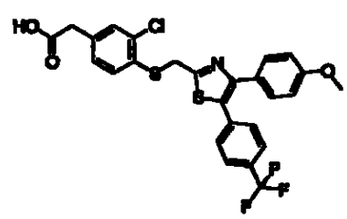
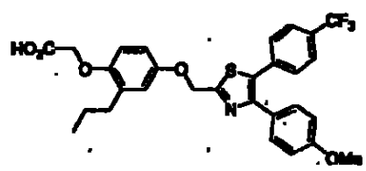
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		0.93 (t, J = 7.3 Hz, 3H). MS calculada para $C_{31}H_{34}NO_6S$ ($M+H^+$) 532.2, encontrada 532.2.
M13		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.28 (m, 6H), 6.82 (d, J = 2.8 Hz, 1H), 6.77-6.66 (m, 4H), 5.22 (s, 2HJ), 4.52 (s, 2H), 3.69 (s, 3H), 2.49 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.58-1.52 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H). MS calculada para $C_{29}H_{30}NO_5S$ ($M+H^+$) 504.2, encontrada 504.2.
N2		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.56 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H) 7.25 (d, J = 10.0 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H),

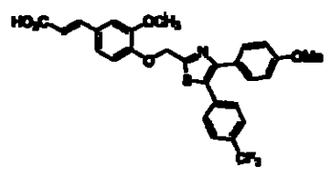
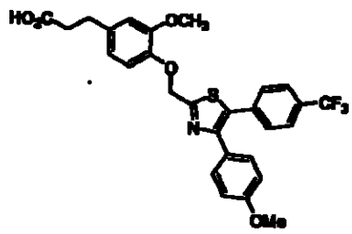
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		5.40 (s, 2H), 3.82 (s, 3H), 3.62 (s, 2H). MS calculada para $C_{26}H_{21}F_3NO_4S$ (M+H$^+$) 500.1, encontrada 500.3.
N3		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.57 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H), 6.97 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.44 (s, 2H), 3.83 (s, 3H), 2.93 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H). MS calculada para $C_{27}H_{23}F_3NO_4S$ (M+H$^+$) 514.1, encontrada 514.3.
N4		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.56 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 9.1 Hz, 2H), 6.89 (d, J = 9.1 Hz,

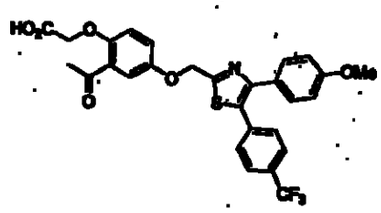
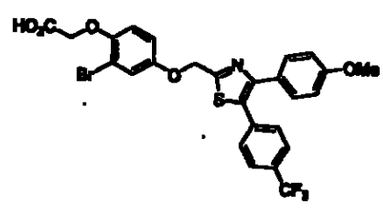
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		2H), 6.85 (d, J = 8.8 Hz, 2H), 5.35 (s, 2H), 4.62 (s, 2H), 3.83 (s, 3H). MS calculada para $C_{28}H_{21}F_3NO_5S$ (M+H$^+$) 515.1, encontrada 515.3.
N5		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.74 (d, J = 15.9 Hz, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 7.47-7.40 (m, 4H), 7.07 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.35 (d, J = 15.9 Hz, 1H), 5.45 (s, 2H), 3.83 (s, 3H). MS calculada para $C_{27}H_{21}F_3NO_4S$ (M+H$^+$) 512.1, encontrada 512.3.
N6		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.56 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 7.00 (d, J = 8.1

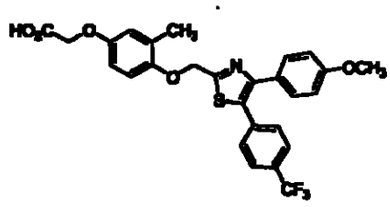
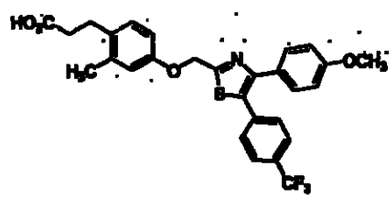
No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		Hz, 1H), 6.87-6.81 (m, 4H), 5.46 (s, 2H), 3.91 (s, 3H), 3.83 (s, 3H), 3.62 (s, 2H). MS calculada para $C_{27}H_{23}F_3NO_6S$ ($M+H^+$) 530.1, encontrada 530.3.
N7		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.55 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 6.92 (s, 4H), 6.84 (d, J = 8.8 Hz, 2H), 5.34 (s, 2H), 3.81 (s, 3H), 1.52 (s, 6H). MS calculada para $C_{28}H_{26}F_3NO_5S$ ($M+H^+$) 544.1, encontrada 544.4.
N13		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.30 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.05 (m, 4H), 6.58 (d, j = 8.8 Hz, 2H),

No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		6.41 (d, J = 8.4 Hz, 1H), 4.41 (s, 2H), 4.16 (s, 2H), 3.56 (s, 3H), 2.01 (s, 3H). MS calculada para $C_{27}H_{23}F_3NO_4S_2$ (M+H$^+$) 546.1, encontrada 546.3.
N14		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.56 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 2.0 Hz, 1H), 7.16 (dd, J = 2.0, 8.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 5.46 (s, 2H), 3.82 (s, 3H), 3.59 (s, 2H). MS calculada para $C_{28}H_{20}ClF_3NO_4S$ (M+H$^+$) 534.1, encontrada 534.1.
N15		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.46 (d, J = 8.0 Hz, 2H), 7.29 (m, 6H), 7.06 (dd, J = 1.6, 8.0

No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		Hz, 1H), 6.76 (d, J = 8.8 Hz, 2H), 4.44 (s, 2H), 3.73 (s, 3H), 3.52 (s, 2H). MS calculada para $C_{28}H_{20}ClF_3NO_3S_2$ ($M+H^+$) 550.0, encontrada 550.3.
N20		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.56 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.37 (d, j = 8.4 Hz, 2H), 6.89 (d, j = 3.0 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 6.79 (dd, J = 3.0, 9.0 Hz, 1H), 6.71 (d, J = 9.0 Hz, 1H), 5.37 (s, 2H), 4.63 (s, 2H), 3.82 (s, 3H), 2.63 (t, J = 7.6 Hz, 2H), 1.63 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H): ^{19}F-RMN (376.5 MHz, $CDCl_3$) δ = -62.7. MS calculada para $C_{29}H_{27}F_3NO_6S$ ($M+H^+$) 558.2, encontrada 558.2.

No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
N21		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.70 (d, J = 15.6 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.10 (m, 3H), 6.85 (d, J = 8.8 Hz, 2H), 6.32 (d, J = 16.0 Hz, 1H), 5.50 (s, 2H), 3.95 (s, 3H), 3.82 (s, 3H); ^{19}F-RMN (376.5 MHz, $CDCl_3$) δ = 62.7. MS calculada para $C_{28}H_{23}F_3NO_5S$ ($M+H^+$) 542.1, encontrada 542.1.
N22		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.42 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 8.8 Hz, 2H), 6.67 (d, J = 2.0 Hz;1H), 6.62 (dd, J = 2.0, 8.0 Hz, 1H),

No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		5.31 (s, 2H), 3.78 (s, 3H), 3.69 (s, 3H), 2.79 (t, J = 7.8 Hz, 2H), 2.54 (t, J = 7.8 Hz, 2H); ^{19}F-RMN (376.5 MHz, $CDCl_3$) δ = -62.65. MS calculada para $C_{28}H_{23}F_3NO_5S$ (M+H$^+$) 544.1, encontrada 544.1.
N23		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.55 (d, J = 8.4 Hz, 2H), 7.2 (m, 5H), 7.20 (m, 1H), 6.90 (m, 3H), 5.50 (s, 2H), 4.72 (s, 2H), 3.80 (s, 3H), 2.65 (s, 3H); ^{19}F-RMN (376.5 MHz, $CDCl_3$) δ = -62.8. MS calculada para $C_{28}H_{23}F_3NO_6S$ (M+H$^+$) 558.1, encontrada 558.0.
N24		^{19}F-RMN (376.5MHz, $CDCl_3$) δ = -62.7. MS calculada para $C_{28}H_{19}BrF_3NO_5S$ (M+H$^+$) 594.1, encontrada 594.0.

No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
N25		^{1}H-RMN (400MHz, $CDCl_3$) δ = 7.57 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.84 (m, 2H), 6.71 (dd, J = 3.2, 8.8 Hz, 1H), 5.36 (s, 2H), 4.63 (s, 2H), 3.82 (s, 3H), 2.31 (s, 3H); ^{19}FF-RMN (376.5 MHz, $CDCl_3$) δ = -62.7. MS calculada para $C_{27}H_{23}F_3NO_5S$ ($M+H^+$) 530.1, encontrada 530.1.
N26		^{1}H-RMN (400MHz, CD_3CN) δ = 7.64 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 2.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 6.83 (dd, J = 2.8, 8.4 Hz, 1H), 5.36 (s, 2H), 3.78 (s, 3H), 2.83

No. de Com-puesto	Estructura del Compuesto	Datos Físicos ^{1}H RMN 400 MHz (DMSO-d_6) y/o MS (m/z)
		(t, J = 7.2 Hz, 2H), 2.52 (t, J = 7.2 Hz, 2H), 2.29 (s, 3H); ^{19}F-RMN (376.5 MHz, $CDCl_3$) δ = 63.16. MS calculada para $C_{28}H_{26}F_3NO_4S$ (M+H$^+$) 528.1, encontrada 528.2.

Mediante la repetición de los procedimientos descritos en los ejemplos anteriores, utilizando los materiales de partida apropiados, se obtienen los siguientes compuestos de la Fórmula I, como se identifican en la Tabla 1.

Ensayo de Transcripción

Se emplean ensayos de transfección para evaluar la capacidad de los compuestos de la invención para modular la actividad de transcripción de los PPARs. Dicho de una manera breve, los vectores de expresión para proteínas quiméricas que contengan el dominio de enlace de ADN de GAL4 de levadura fusionado con el dominio de enlace de ligando (LBD) de cualquiera de PPARδ, PPARα, ó PPARγ, se introducen mediante transfección transitoria en células de mamífero, junto con un plásmido reportero en donde el gen de luciferasa esté bajo el control de un sitio de

enlace de GAL4. Al exponerse a un modulador de PPAR, varía la actividad de transcripción de PPAR, y esto se puede monitorear por los cambios en los niveles de luciferasa. Si las células transfectadas se exponen a un agonista de PPAR, aumenta la actividad de transcripción dependiente del PPAR y se elevan los niveles de luciferasa.

Se siembran células de riñón embriónicas humanas 293T ($8x10^6$) en un matraz de 175 cm^2 un día antes del inicio del experimento, en FBS al 10 por ciento, Penicilina al 1por ciento/Estreptomicina/Fungizoma, Medio DMEM. Las células se cosechan lavando con PBS (30 mililitros), y luego se disocian utilizando tripsina (0.05 por ciento; 3 mililitros). La tripsina se inactiva mediante la adición del medio de ensayo (DMEM, suero bovino fetal con CA-dextrano (5 por ciento)). Las células se centrifugan y se vuelven a suspender hasta 170,000 células/mililitro). Se prepara una mezcla de transfección del plásmido de expresión del dominio de enlace de ligando GAL4-PPAR (1 microgramo), el plásmido reportero de luciferasa-UAS (1 microgramo), fugeno (proporción de 3:1; 6 microlitros), y medio exento de suero (200 microlitros), y se incuba durante 15 a 40 minutos a temperatura ambiente. Las mezclas de transfección se agregan a las células para dar 0.16 M de células/mililitro, y luego las células (50 microlitros/pozo) se aplican en 384 placas blancas, de fondo sólido, tratadas con TC. Las células se incuban adicionalmente a 37°C, con CO_2 al 5.0 por ciento, durante 5 a 7 horas. Se prepara una serie de diluciones de 12 puntos (diluciones seriales triplicadas) para cada compuesto de prueba en sulfóxido de dimetilo, con una concentración del compuesto de partida de 10 µM. Se agrega el compuesto de prueba (500 nanolitros) a cada pozo

de las células de la placa de ensayo, y las células se incuban a 37°C, con CO_2 al 5.0 por ciento, durante 18 a 24 horas. Se agrega a cada pozo el regulador de lisis celular/luciferasa, Bright-Glo^{MR} (25 por ciento; 25 microlitros; Promega). Después de una incubación adicional durante 5 minutos a temperatura ambiente, se mide la actividad de luciferasa.

Los valores de luminiscencia brutos se normalizan dividiéndolos entre el valor del control de sulfóxido de dimetilo presente en cada placa. Los datos normalizados se analizan, y se ajustan las curvas de respuesta a la dosis utilizando el programa de ajuste de gráfica Prizm. La EC50 se define como la concentración a la cual el compuesto provoca una respuesta que está a la mitad del camino entre los valores máximo y mínimo. La eficacia relativa (o el porcentaje de eficacia) se calcula mediante una comparación de la respuesta provocada por el compuesto, con el máximo valor obtenido para el modulador de PPAR de referencia.

Los compuestos de la Fórmula I, en forma libre o en forma de sal farmacéuticamente aceptable, exhiben valiosas propiedades farmacológicas, por ejemplo, como se indica por las pruebas *in vitro* descritas en esta solicitud. Los compuestos de la invención de preferencia tienen una EC50 para PPARδ menor a 1μM, más preferiblemente menor a 500 nM, de una manera más preferible menor a 100 nM. Los compuestos de la invención son cuando menos 100 veces selectivos para PPARδ sobre PPARγ.

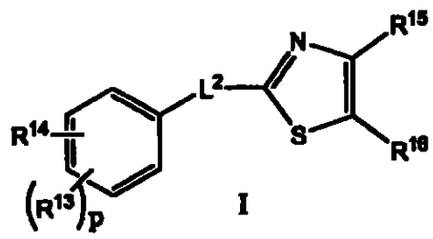
Se entiende que los ejemplos y modalidades descritos en la presente son solamente para propósitos ilustrativos, y que las personas expertas en la técnica podrán ver diferentes modificaciones o cambios a la luz de los

mismos, y se deben incluir dentro del espíritu y panorama de esta solicitud, y del alcance de las reivindicaciones adjuntas.

Todas las publicaciones, patentes, y solicitudes de patente citadas en la presente, se incorporan a la presente como referencia para todos los propósitos.

REIVINDICACIONES

.1. Un compuesto de la Fórmula I:



I

en donde:

p es un entero seleccionado de 0 a 3;

L^2 se selecciona a partir de -XOX-, $-XS(O)_{0-2}X-$ y $-XS(O)_{0-2}XO-$; en donde X se selecciona independientemente a partir de un enlace y alquileno de 1 a 4 átomos de carbono; en donde cualquier alquileno de L^2 pude estar opcionalmente sustituido por 1 a 3 radicales seleccionados a partir de halógeno, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, y alcoxi de 1 a 6 átomos de carbono sustituido por halógeno;

R^{13} se selecciona a partir de halógeno, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, hidroxi-alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxi de 1 a 6 átomos de carbono sustituido por halógeno, arilo de 6 a 10 átomos de carbono, heteroarilo de 5 a 10 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, y heterocicloalquilo de 3 a 8 átomos de carbono; en donde cualquier arilo, heteroarilo, cicloalquilo, y heterocicloalquilo de R^{13} está opcionalmente sustituido con 1 a 3 radicales

independientemente seleccionados a partir de halógeno, nitro, ciano, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, hidroxi-alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, y alcoxi de 1 a 6 átomos de carbono sustituido por halógeno;

R^{14} se selecciona a partir de -XOXC(O)OR^{17} y -XC(O)OR^{17}; en donde X es un enlace o alquileno de 1 a 4 átomos de carbono; y R^{17} se selecciona a partir de hidrógeno y alquilo de 1 a 6 átomos de carbono;

R^{15} y R^{16} se seleccionan independientemente a partir de -R^{16} y -YR^{16}; en donde Y se selecciona a partir de alquileno de 1 a 6 átomos de carbono, alquenileno de 2 a 6 átomos de carbono, alquinileno de 2 a 6 átomos de carbono, -C(O)NR^{17}- y -OX-; X es un enlace o alquileno de 1 a 4 átomos de carbono; R^{17} se selecciona a partir de hidrógeno y alquilo de 1 a 6 átomos de carbono; y R^{16} se selecciona a partir de cicloalquilo de 3 a 12 átomos de carbono, hetero-ciclo-alquilo de 3 a 8 átomos de carbono, arilo de 6 a 10 átomos de carbono, y hetero-arilo de 5 a 13 átomos de carbono; o R^{15} y R^{16}, junto con los átomos con los que están unidos R^{15} y R^{16}, forman un heteroarilo de 5 a 14 átomos de carbono biciclico o triciclico fusionado;

en donde cualquier arilo, hetero-arilo, cicloalquilo, y hetero-ciclo-alquilo de R^{16}, o la combinación de R^{15} y R^{16}, está opcionalmente sustituido con 1 a 3 radicales independientemente seleccionados a partir de halógeno, nitro, ciano, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, tioalquilo de 1 a 6 átomos de carbono, hidroxi-alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono

sustituido por halógeno, alcoxi de 1 a 6 átomos de carbono sustituido por halógeno, ciclo-alquilo de 3 a 12 átomos de carbono, hetero-ciclo-alquilo de 3 a 8 átomos de carbono, arilo de 6 a 10 átomos de carbono, hetero-arilo de 5 a 13 átomos de carbono, $-XS(O)_{0-2}R^{17}$, $-XS(O)_{0-2}XR^{18}$, $XNR^{17}R^{17}$, $-XNR^{17}S(O)_{0-2}R^{17}$, $-XNR^{17}C(O)R^{17}$, $XC(O)NR^{17}R^{17}$, $-XNR^{17}C(O)R^{18}$, $-XC(O)NR^{17}R^{18}$, $-XC(O)R^{19}$, $-XNR^{17}XR^{19}$, y $XOXR^{19}$; en donde cualquier sustituyente de arilo, heteroarilo, cicloalquilo, o heterocicloalquilo está además sustituido opcionalmente con 1 a 3 radicales independientemente a partir de halógeno, nitro, ciano, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, tioalquilo de 1 a 6 átomos de carbono, hidroxi-alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, y alcoxi de 1 a 6 átomos de carbono, sustituido por halógeno; en donde X es un enlace o alquileno de 1 a 4 átomos de carbono, R^{17} se selecciona a partir de hidrógeno y alquilo de 1 a 4 átomos de carbono, y R^{18} se selecciona a partir de cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 8 átomos de carbono, arilo de 6 a 10 átomos de carbono, y heteroarilo de 5 a 10 átomos de carbono; en donde cualquier arilo, heteroarilo, cicloalquilo, o heterocicloalquilo de R^{19} está opcionalmente sustituido con 1 a 3 radicales independientemente seleccionados a partir de halógeno, nitro, ciano, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, y alcoxi de 1 a 6 átomos de carbono sustituido por halógeno; y las sales farmacéuticamente aceptables, hidratos, solvatos, isómeros, y profármacos del mismo.

2. El compuesto de la reivindicación 1, en donde:

p es un entero seleccionado de 0 a 3;

L^2 se selecciona de -XOX-, -XS(O)$_{0-2}$X-, y -XS(O)$_{0-2}$XO-; en donde X se selecciona independientemente a partir de un enlace y alquileno de 1 a 4 átomos de carbono; en donde cualquier alquileno de L^2 puede estar opcionalmente sustituido por 1 a 3 radicales seleccionados a partir de halógeno, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, y alcoxi de 1 a 6 átomos de carbono sustituido por halógeno;

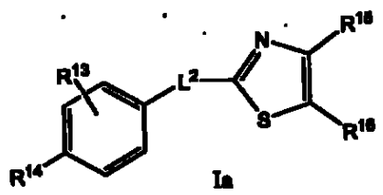
R^{13} es alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, y halógeno; y

R^{14} se selecciona a partir de -XOXC(O)OR^{17} y -XC(O)OR^{17}; en donde X es un enlace o alquileno de 1 a 4 átomos de carbono; y R^{17} se selecciona a partir de hidrógeno y alquilo de 1 a 6 átomos de carbono;

R^{15} y R^{16} se seleccionan independientemente a partir de -R^{18} e -YR^{18}; en donde Y se selecciona a partir de alquileno de 1 a 6 átomos de carbono, alquenileno de 2 a 6 átomos de carbono, -C(O)NR^{17}-, y -OX-; X es un enlace o alquileno de 1 a 4 átomos de carbono; R^{17} se selecciona a partir de hidrógeno y alquilo de 1 a 6 átomos de carbono; y R^{18} se selecciona a partir de arilo de 6 a 10 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, y heteroarilo de 5 a 13 átomos de carbono; o R^{15} y R^{16}, junto con los átomos con los que están unidos R^{15} y R^{16}, forman un heteroarilo de 5 a 14 átomos de carbono bicíclico o tricíclico fusionado; en donde cualquier arilo, heteroarilo, y cicloalquilo de R^{18}, o la combinación de R^{15} y R^{16}, está opcionalmente sustituido con 1 a 3 radicales independientemente seleccionados a partir de halógeno, nitro, ciano,

alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, tioalquilo de 1 a 6 átomos de carbono, hidroxi-alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxi de 1 a 6 átomos de carbono sustituido por halógeno, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 8 átomos de carbono, arilo de 6 a 10 átomos de carbono opcionalmente sustituido con alcoxi de 1 a 6 átomos de carbono, heteroarilo de 5 a 13 átomos de carbono, $-XS(O)_{0-2}R^{17}$, $-XS(O)_{0-2}XR^{18}$, $-XNR^{17}R^{17}$, $-XNR^{17}S(O)_{0-2}R^{17}$, $-XNR^{17}C(O)R^{17}$, $-XC(O)NR^{17}R^{17}$, $-XNR^{17}C(O)R^{18}$, $-XC(O)NR^{17}R^{18}$, $-XC(O)R^{18}$, $-XNR^{17}XR^{18}$, y $-XOXR^{18}$; en donde X es un enlace o alquileno de 1 a 4 átomos de carbono; R^{17} se selecciona a partir de hidrógeno y alquilo de 1 a 6 átomos de carbono; y R^{18} se selecciona a partir de arilo de 6 a 10 átomos de carbono, heteroarilo de 5 a 10 átomos de carbono, heterocicloalquilo de 3 a 8 átomos de carbono, y cicloalquilo de 3 a 12 átomos de carbono, en donde cualquier arilo, heteroarilo, cicloalquilo, o heterocicloalquilo de R^{18} está opcionalmente sustituido con 1 a 3 radicales independientemente seleccionados a partir de halógeno, nitro, ciano, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, y alcoxi de 1 a 6 átomos de carbono sustituido por halógeno.

3. El compuesto de la reivindicación 1, de Fórmula Ia:



Ia

L^2 se selecciona a partir de $-S(O)_{0-2}(CH_2)_{1-4}O-$, $-O(CH_2)_{1-4}S(O)_{0-2}-$, $-CH_2S(O)_{0-2}-$, $-S(O)_{0-2}CH_2-$, $-S(O)_{0-2}-$, $-CH_2O-$, y $-OCH_2-$;

R^{13} se selecciona a partir de alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, y halógeno;

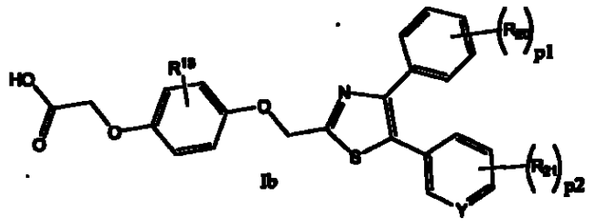
R^{14} se selecciona a partir de $-OCH_2C(O)OH$, y $-CH_2C(O)OH$;

R^{15} y R^{16} se seleccionan independientemente a partir de $-R^{18}$ e $-YR^{18}$; en donde Y se selecciona a partir de alquileno de 1 a 6 átomos de carbono, alquenileno de 2 a 6 átomos de carbono, -C(O)NH-, y $-O(CH_2)_{1-3}-$; y R^{18} se selecciona a partir de fenilo, bifenilo, ciclohexilo, naftilo, benzo[1,3]dioxol-5-ilo, benzo[b]furanilo, piridinilo, pirimidinilo, dibenzofuran-2-ilo, furanilo, benzo[b]tiofeno, tiofenilo, fenoxantiin-4-ilo, benzoxazolilo, 3-oxo-3,4-dihidro-2H-benzo[1,4]oxazin-6-ilo, 2-oxo-2,3-dihidro-benzo-oxazol-6-ilo, 2,3-dihidro-benzo[1,4]dioxin-6-ilo, benzoxazolilo, 3,4-dihidro-2H-benzo[b][1,4]dioxepin-7-ilo, y quinolinilo; o R^{15} y R^{16} junto con los átomos con los que están unidos R^{15} y R^{16}, forman 4,5-dihidro-nafto[1,2-d]tiazol-2-ilo, 4H-cromeno[4,3-d]tiazol-2-ilo, 5,6-dihidro-4H-3-tia-1-aza-benzo[e]-azulen-2-ilo, benzotiazolilo, benzoxazolilo, y 1-oxa-3-aza-ciclopenta-[a]naftalen-2-ilo;

en donde cualquier arilo, heteroarilo, cicloalquilo y heterocicloalquilo de R^{15} y R^{16} la combinación de R^{15} y R^{16}, está opcionalmente sustituido con 1 a 3 radicales independientemente seleccionados a partir de halógeno, ciano, nitro, metilo, isopropilo, isopropil-sulfanilo, isopropiloxi, hidroxi-metilo, metil-sulfanilo, metoxi, etoxilo, pentafluoro-etoxilo, trifluoro-metilo, trifluoro-metoxi, trifluoro-metil-sulfonilo, morfolino, fenoxilo, benzoxilo, etil-sulfonilo, dimetil-amino, metil-sulfonil-amino, etil-sulfonilo,

propilo, vinilo, propiloxi, butoxilo secundario, trifluoro-metil-sulfanilo, dimetil-amino-carbonilo, dietil-amino-carbonilo, metil-carbonil-amino, metil-carbonilo, ciclopentil-oxilo, isopropil-metil-amino-carbonilo, ciclopropil-amino-carbonilo, ciclohexilo, morfolino, piperidinilo, indolilo, pirrolidinilo, pirrolidinil-carbonilo, 2,3-dihidro-benzofuran-5-ilo, piperidinil-carbonilo, morfolino-carbonilo, isopropil-metil-amino, isopropil-metil-amino-carbonilo, dietil-amino, y fenilo opcionalmente sustituido con metoxi.

4. El compuesto de la reivindicación 3, de la Fórmula Ib:



Ib

en donde p1 y p2 se seleccionan independientemente de 0, 1, y 2;

Y se selecciona a partir de N y CH;

R^{13} se selecciona a partir de alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, y halógeno;

R^{20} se selecciona a partir de trifluorometilo y trifluorometoxi; y

R^{21} se selecciona a partir de isopropiloxi y metoxi.

5. El compuesto de la reivindicación 4, seleccionado a partir de ácido {4-[4-(4-isopropoxi-fenil)-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético; ácido {4-[4-(4-isopropoxi-fenil)-5-(4-trifluoro-metil-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético; y ácido {4-[4-(6-metoxi-piridin-3-il)-5-(4-trifluoro-metoxi-fenil)-tiazol-2-ilmetoxi]-2-metil-fenoxi}-acético.

6. Un método para tratar una enfermedad o desorden en un

animal en donde la modulación de la actividad de PPARδ pueda prevenir, inhibir, o reducir la patología y/o sintomatología de la enfermedad, cuyo método comprende administrar al animal una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1.

7. El método de la reivindicación 6, en donde la enfermedad o desorden se selecciona a partir del tratamiento o la profilaxis de dislipidemia, hiperlipidemia, hipercolesteremia, ateroesclerosis, aterogénesis, hipertrigliceridemia, insuficiencia cardiaca, infarto de miocardio, enfermedad vasculares, enfermedades cardiovasculares, hipertensión, obesidad, caquexia, inflamación, artritis, cáncer, anorexia, anorexia nerviosa, bulimia, enfermedad de Alzheimer, trastornos de la piel, enfermedades respiratorias, trastornos oftálmicos, enfermedades de intestino irritable, colitis ulcerativa, enfermedad de Crohn, diabetes tipo I, diabetes tipo II, y síndrome X.

8. El método de la reivindicación 6, en donde la enfermedad o desorden se selecciona a partir de síndrome de desecho por VIH, enfermedad crítica de largo plazo, masa muscular y/o fuerza muscular reducidas, masa corporal magra reducida, mantenimiento de fuerza y función muscular en los ancianos, duración muscular y función muscular disminuidas, y fragilidad en los ancianos.

9. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5, en la fabricación de un medicamento para el tratamiento de una enfermedad en un animal en donde la actividad de PPARδ contribuya a la patología y/o sintomatología de la enfermedad.

10. Una composición farmacéutica, la cual comprende una

cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1 a 5, en combinación con uno o más excipientes farmacéuticamente aceptables.

11. Una combinación farmacéutica, en especial una composición farmacéutica, la cual comprende:

1) un compuesto de cualquiera de las reivindicaciones 1 a 5, o una sal farmacéuticamente aceptable del mismo, y

2) cuando menos un ingrediente activo seleccionado a partir del grupo que consiste en:

a) agentes antidiabéticos tales como insulina, derivados de insulina y miméticos; secretagogos de insulina tales como las sulfonil-ureas, por ejemplo Glipizida, gliburida, y Amarilo; ligandos de receptores de sulfonilurea insulinotrópica tales como meglitinidas, por ejemplo nateglinida y repaglinida; sensibilizantes a insulina, tales como inhibidores de fosfatasa de proteína tirosina-1B (PTP-1B), tales como PTP-112; inhibidores de GSK3 (quinasa de sintasa de glicógeno-3), tales como SB-517955, SB-4195052, SB-216763, NN-57-05441, y NN-57-05445; ligandos RXR, tales como GW-0791 y AGN-194204; inhibidores del co-transportador de glucosa dependiente de sodio, tales como T-1095; inhibidores de fosforilasa de glicógeno A, tales como BAY R3401; biguanidas, tales como metformina; inhibidores de alfa-glucosidasa, tales como acarbosa; GLP-1 (péptido tipo glucagon-1), análogos de GLP-1 tales como Exendin-4 y miméticos de GLP-1; inhibidores de dipeptidil-peptidasa IV tales como DPPT728, vildagliptina, MK-0431, saxagliptina, GSK23A; un rompedor de AGE; un derivado de tiazolidona (glitazona) tal como pioglitazona,

rosiglitazona, o ácido (R)-1-{4-[5-metil-2-(4-trifluoro-metil-fenil)-oxazol-4-ilmetoxi]-bencen-sulfonil}-2,3-dihidro-1H-indol-2-carboxílico, un agonista de PPARδ que no es tipo glitazona, por ejemplo GI-262570;

b) agentes hipolipidémicos, tales como inhibidores de reductasa de 3-hidroxi-3-metil-glutaril-coenzima A (HMG-CoA), por ejemplo lovastatina, pitavastatina, simvastatina, pravastatina, cerivastatina, mevastatina, velostatina, fluvastatina, dalvastatina, atorvastatina, rosuvastatina, y rivastatina; inhibidores de sintasa de escualeno; ligandos FXR (receptor farnesoide X) y LXR (receptor de hígado X); colestiramina; fibratos; ácido nicotínico y aspirina;

c) un agente contra la obesidad o un agente regulador del apetito, tal como fentermina, leptina, bromocriptina, dexanfetamina, anfetamina, fenfluramina, dexfenfluramina, sibutramina, orlistato, dexfenfluramina, mazindol, fentermina, fendimetrazina, dietilpropión, fluoxetina, bupropión, topiramato, dietilpropión, benzofetamina, fenilpropanolamina, o ecopipam, efedrina, pseudo-efedrina, o antagonistas del receptor canabinoide;

d) agentes anti-hipertensivos, por ejemplo diuréticos de ciclo tales como ácido etacrínico, furosemida, y torsemida diuréticos tales como derivados de tiazida, clortiazida, hidroclorotiazida, amilorida; inhibidores de la enzima convertidora de angiotensina (ACE), tales como benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril, y trandolapril; inhibidores de la bomba de membrana de Na-K-ATPasa, tales como digoxina; inhibidores de neutralendopeptidasa (NEP), por ejemplo tiorfán, terteo-tiorfán, SQ29072; inhibidores de ECE, por

ejemplo SV306; inhibidores de ACE/EP, tales como omapatrilato, sampatrilato, y fasidotril; antagonistas de angiotensina II, tales como candesartan, eprosartan, irbesartan, losartan, telmisartan, y valsartan, en particular valsartan; inhibidores de renina, tales como alisquireno, terlaquireno, ditequireno, ditequireno, RO 66-1132, RO-66-1168; bloqueadores del receptor β-adrenérgico, tales como acebutolol, atenolol, betaxolol, bisoprolol, metaprolol, nadolol, propranolol, sotalol, y timolol; agentes inotrópicos tales como digoxina, dobutamina, y milrinona; bloqueadores del canal de calcio, tales como amlodipina, bepridil, diltiazem, felodipina, nicardipina, nimodipina, nifedipida, nisoldipina, y verapamil; antagonistas del receptor de aldosterona; e inhibidores de sintasa de aldosterona;

e) un compuesto incrementador de lipoproteínas de alta densidad (HDL),

f) modulador de absorción de colesterol, tal como Zetia® y KT6-971,

g) análogos y miméticos de Apo-A1,

h) inhibidores de trombina, tales como Ximelagatran,

i) inhibidores de aldosterona, tales como anastrazol, fadrazol, eplerenona,

j) inhibidores de la acumulación de plaquetas, tales como aspirina, bisulfato de clopidogrel,

k) estrógeno, testosterona, un modulador del receptor de estrógeno selectivo, un modulador de receptor de andrógeno selectivo;

l) un agente quimioterapéutico, tal como los inhibidores de

aromatasa, por ejemplo femara, anti-estrógenos, inhibidores de topoisomerasa I, inhibidores de topoisomerasa II, agentes activos en microtúbulos, agentes alquilantes, antimetabolitos antineoplásticos, compuestos de platina, compuestos que reducen la actividad de la quinasa de proteína tales como el inhibidor de quinasa de tirosina receptora de PDGF, de preferencia imatinib, ó 4-metil-N-[3-(4-metil-imidazol-1-il)-5-trifluoro-metil-fenil]-3-(4-piridin-3-il-pirimidin-2-ilamino)-benzamida; y

m) un agente que interactúe con un receptor 5-HT_3 y/o un agente que interactúe con un receptor 5-HT_4, tal como tegaserod, maleato ácido de tegaserod, cisaprida, cilansetron;

o en cada caso una sal farmacéuticamente aceptable de los mismos;

y opcionalmente un vehículo farmacéuticamente aceptable.

12. Una composición farmacéutica de acuerdo con la reivindicación 10, o una combinación farmacéutica de acuerdo con la reivindicación 11, para el tratamiento o la prevención de dislipidemia, hiperlipidemia, hipercolesteremia, ateroesclerosis, hipertrigliceridemia, insuficiencia cardíaca, infarto de miocardio, enfermedades vasculares, enfermedades cardiovasculares, hipertensión, obesidad, inflamación, artritis, cáncer, enfermedad de Alzheimer, trastornos de la piel, enfermedades respiratorias, trastornos oftálmicos, enfermedades inflamatorias de intestino, IBDs (enfermedad de intestino irritable), colitis ulcerativa, enfermedad de Crohn, condiciones en las que estén implicadas la intolerancia a la glucosa, hiperglicemia, y resistencia a la insulina, tales como diabetes tipo 1 y tipo 2, Metabolismo Deteriorado de Glucosa (IGM), Intolerancia a la Glucosa (IGT), Glucosa Deteriorada en Ayunas (IFG), y

Síndrome X.

13. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5, o una composición farmacéutica de acuerdo con la reivindicación 10, o una combinación farmacéutica de acuerdo con la reivindicación 11, para utilizarse como un medicamento.

14. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5, o una composición farmacéutica de acuerdo con la reivindicación 10, o una combinación farmacéutica de acuerdo con la reivindicación 11, para la fabricación de un medicamento para el tratamiento o la prevención de dislipidemia, hiperlipidemia, hipercolesteremia, ateroesclerosis, hipertrigliceridemia, insuficiencia cardiaca, infarto de miocardio, enfermedades vasculares, enfermedades cardiovasculares, hipertensión, obesidad, inflamación, artritis, cáncer, enfermedad de Alzheimer, trastornos de la piel, enfermedades respiratorias, trastornos oftálmicos, enfermedades inflamatorias de intestino, IBDs (enfermedad de intestino irritable), colitis ulcerativa, enfermedad de Crohn, condiciones en las que estén implicadas la intolerancia a la glucosa, hiperglicemia, y resistencia a la insulina, tales como diabetes tipo 1 y tipo 2, Metabolismo Deteriorado de Glucosa (IGM), Intolerancia a la Glucosa (IGT), Glucosa Deteriorada en Ayunas (IFG), y Síndrome X.

RESUMEN

La invención proporciona compuestos, composiciones farmacéuticas que comprenden estos compuestos, y métodos para utilizar tales compuestos con el fin de tratar o prevenir enfermedades o trastornos asociados con la actividad de las familias del Receptor Activado por Proliferador de Peroxisoma (PPAR), en particular la actividad de PPAR.

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TRATADO DE COOPERACION EN MATERIA DE PATENTES

De la
AUTORIDAD EXAMINADORA PRELIMINAR INTERNACIONAL

Para:

SCOTT W. REID
GENOMICS INSTITUTE OF THE
NOVARTIS RESEARCH FOUNDATION
10675 JOHN J. HOPKINS DRIVE
SAN DIEGO, CA 92121

PCT

NOTIFICACION DE TRANSMISION DEL REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

(Regla 71.1 del PCT)

Fecha de envío (día/mes/año)	18 de abril de 2006
Referencia de archivo del solicitante o agente P1153PC21	**NOTIFICACIÓN IMPORTANTE**

No. de solicitud internacional	Fecha de presentación internacional (día/mes/año)	Fecha de prioridad (día/mes/año)
PCT/US05/18167	24 de mayo de 2005 (24.05.2005)	24 de mayo de 2004 (24.05.2004)

Solicitante
IRM LLC

1. Mediante la presente se notifica al solicitante que esta Autoridad Examinadora Preliminar Internacional transmite con la presente el reporte de examen preliminar internacional y sus anexos, si los hay, establecido en la solicitud internacional.

2. Una copia del reporte y sus anexos, si los hay, se transmite a la Oficina Internacional para su comunicación a todas las Oficinas elegidas.

3. En donde se requiera por las Oficinas elegidas, la Oficina Internacional preparará una traducción al inglés del reporte (pero no de ningún anexo) y transmitirá tal traducción a aquellas Oficinas.

4. **RECORDATORIO**

El solicitante debe entrar a la fase nacional ante cada Oficina electa al llevar a cabo ciertos actos (presentación de traducciones y pago de cuotas nacionales) en el transcurso de 30 días desde la fecha de prioridad (o después en algunas Oficinas) (Artículo 39(1) (véase también el recordatorio enviado por la Oficina Internacional con la Forma PCT/IB/301).

En donde una traducción de la solicitud internacional se deba proporcionar a una Oficina elegida, aquella traducción debe contener una traducción de algunos anexos al reporte de examen preliminar internacional. Es la responsabilidad del solicitante preparar y proporcionar tal traducción directamente a cada Oficina electa concerniente.

Para más detalles en cuanto a los límites de tiempo y requerimientos aplicables de las Oficinas electas, véase el Volumen II de la Guía del Solicitante del PCT.

Nombre y dirección de correspondencia de la IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patentes P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsímil No. (703) 305-3230	Oficial autorizado Patricia L. Morris (SELLO) Teléfono No. (571) 272-1600

Forma PCT/IPEA/416 (julio de 1992)

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

PCT

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

(Artículo 36 y Regla 70 del PCT)

Referencia de archivo del solicitante o agente P1153PC21	PARA ACCIÓN ADICIONAL	Véase la Notificación de transmisión del reporte de examen preliminar internacional (Forma PCT/IPEA/416)
No. de solicitud internacional PCT/US05/18167	Fecha de presentación internacional (día/mes/año) 24 de mayo de 2005 (24.05.2005)	Fecha de prioridad (día/mes/año) 24 de mayo de 2004 (24.05.2004)
Clasificación de Patente Internacional (IPC) o clasificación nacional e IPC IPC(7): C07D 277/24 (20006.01) USPC: 548/205		
Solicitante IRM LLC		

1. Este reporte de examen preliminar internacional ha sido preparado por esta Autoridad Examinadora Preliminar Internacional y se transmite al solicitante de acuerdo al Artículo 36.

2. Este REPORTE consiste de un total de __5__ hojas que incluyen esta portada.

☐ Este reporte también está acompañado de ANEXOS, esto es, hojas de la descripción, reivindicaciones y/o dibujos los cuales han sido enmendados y son la base de este reporte y/u hojas que contienen rectificaciones hechas ante esta Autoridad. (véase Regla 70.16 y Sección 607 de las Instrucciones Administrativas bajo el PCT).
Estos anexos consisten de un total de _____ Hojas.

3. Este reporte contiene indicaciones y páginas correspondientes que se relacionan con los siguientes ítems:

I [X] Base del reporte

II [ ] Prioridad

III [X] No se establece opinión con respecto a novedad, paso o etapa inventiva y aplicabilidad industrial

IV [ ] Carencia de unidad de la invención

V [X] Declaración justificada bajo el Artículo 35(2) con respecto a novedad, etapa o paso inventivo o aplicabilidad industrial; citas y explicaciones que apoyan tal declaración.

VI [ ] Ciertos documentos citados

VII [ ] Ciertos defectos en la solicitud internacional

VIII [ ] Ciertas observaciones en la solicitud internacional

Fecha de presentación de la demanda 14 de diciembre de 2005 (14.12.2005)	Fecha de consumación de este reporte 03 de abril de 2006 (03.04.2006)
Nombre y dirección de correspondencia de la IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patentes P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsímile No. (703) 305-3230	Oficial autorizado Patricia L. Morris (SELLO) Teléfono No. (571) 272-1600

Forma PCT/IPEA/409 (portada) (julio de 1998)

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REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud internacional No. PCT/US05/18167

I. Base del Reporte

1. Con respecto a los elementos de la solicitud internacional:*
   - ☒ la solicitud internacional como se presentó originalmente
   - ☒ la descripción:
     - páginas 1-175, como se presentó originalmente
     - páginas NINGUNA, presentadas con la demanda
     - páginas NINGUNA, con la carta del _____
   - ☒ las reivindicaciones:
     - páginas 176-183, como se presentaron originalmente
     - páginas NINGUNA, como se enmendaron (junto con cualquier declaración bajo el Artículo 19
     - páginas NINGUNA, presentadas con la demanda
     - páginas NINGUNA, con la carta del _____
   - ☐ los dibujos:
     - páginas NINGUNA, como se presentaron originalmente
     - páginas NINGUNA, presentadas con la demanda
     - páginas NINGUNA, presentadas con la carta del _____
   - ☐ la secuencia que lista parte de la descripción:
     - páginas NINGUNA, como se presentaron originalmente
     - páginas NINGUNA, presentadas con la demanda
     - páginas NINGUNA, presentadas con la carta del _____

2. Con respecto al **idioma**, todos los elementos marcados anteriormente están disponibles o proporcionados a esta Autoridad en el idioma en el que la solicitud internacional fue presentada, a menos que por otra parte se indique bajo en este artículo.
   Estos elementos están disponibles o proporcionados a esta Autoridad en el idioma siguiente _____el cual es:
   - ☐ el idioma de una traducción proporcionado para los propósitos de búsqueda internacional (bajo la Regla 23.1 (b)).
   - ☐ el idioma de publicación de la solicitud internacional (bajo la Regla 48.3(b)).
   - ☐ el idioma de la traducción proporcionado para los propósitos del examen preliminar internacional (bajo la Regla 55.2 y/o 55.3).

3. Con respecto a cualquier **nucleótido y/o secuencia de aminoácido** descrita en la solicitud internacional, el examen preliminar internacional se llevó a cabo en base al listado de secuencias:
   - ☐ contenida en la solicitud internacional en forma escrita.
   - ☐ presentada junto con la solicitud internacional en forma leíble por computadora.
   - ☐ proporcionada seguidamente a esta Autoridad en forma escrita.
   - ☐ proporcionada seguidamente a esta Autoridad en forma leíble por computadora.
   - ☐ Se ha proporcionado la declaración que listó las secuencias escrito presentada subsecuentemente que no va más allá de la descripción en la solicitud internacional como se presentó.
   - ☐ Se ha proporcionado la declaración que registró la información en la forma leíble por computadora que es idéntica al listado de secuencias escrito.

4. ☐ Las enmiendas han producido la cancelación de:
   - ☐ la descripción, páginas NINGUNA.
   - ☐ las reivindicaciones, Nos. NINGUNA.
   - ☐ los dibujos, hojas/fig. NINGUNA.

5. ☐ Este reporte se ha establecido como si (algunas de) las enmiendas no se habían hechos, ya que se ha considerado que ellas van más allá de la descripción como se presentó, indicadas en el Cuadro Complementario (Regla 70.2(c)).**

* Hojas de reemplazo que se han proporcionado para la Oficina receptora en respuesta a una invitación bajo el Artículo 14 se envían en este reporte como "se presentaron originalmente". y no se anexa a este reporte ya que ellas no contienen las enmiendas (Regla 70.16 y 71.17).

** *Cualquier hoja de reemplazo que contenga tales enmiendas debe enviarse bajo el artículo 1 y anexarse a este reporte.*

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

No. de solicitud internacional
PCT/US05/18167

III. Sin establecimiento del reporte con respecto a la novedad, etapa inventiva o aplicabilidad industrial.

1. La novedad, etapa inventiva o aplicabilidad industrial descritas en las reivindicaciones no serán examinadas con respecto de:

☐ la solicitud internacional completa

☒ las reivindicaciones Nos. 1-4 y 6-14 .

debido:

☐ La solicitud internacional, o las reivindicaciones Nos._____ se relacionan a la siguiente materia que no requiere un examen preliminar internacional (*especificar*):

☒ Una opinión no puede citarse debido a que no es clara de la descripción, reivindicaciones o dibujos (indicados a continuación) o las reivindicaciones Nos. 1-4 y 6-14 (especificar):

Favor de Ver Hoja de Continuación

☐ Una opinión apropiada no se puede proporcionarse debido a que todas las reivindicaciones, o las reivindicaciones Nos. _____ se soportan inadecuadamente por la descripción.

☒ No se ha establecido ningún reporte de búsqueda internacional para las reivindicaciones Nos. 18, 19, 24 .

2. Un examen preliminar internacional apropiado no puede llevarse a cabo debido a la falla del listado de frecuencias de nucleótidos y/o aminoácidos para cumplir con el estándar proporcionado que son definidas en el Anexo C de las Instrucciones Administrativas bajo el PCT:

☐ El listado de frecuencias en forma escrita no ha sido proporcionado o no cumple con los estándares.

☐ El listado de frecuencias en forma leíble en computadora no se ha proporcionado o no cumple ciertos estándares.

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Cuadro Complementario
(Para ser usado cuando el espacio en cualquiera de los cuadros precedentes no es suficiente)

Sección III. Sin establecimiento del reporte (descripción/reivindicaciones/dibujos confusos)
En estas reivindicaciones, variables numerosas y sus significados voluminosos, complejos y sus permutaciones y combinaciones aparentemente sin fin, hacen virtualmente imposible determinar el alcance completo y significado completo de la materia objeto reivindicada. Los compuestos definidos en las reivindicaciones carecen de un elemento estructural significativo que califique como característica técnica especial que defina una contribución sobre la técnica anterior. Los sustitutos en la estructura varían extensivamente y cuando se toman como un total resulta en compuestos sumamente diversos. Según lo presentado, la materia objeto reivindicada no se puede considerar como una descripción clara y concisa para la cual se busca la protección y debido a que las reivindicaciones mencionadas no cumplen con los requisitos del Artículo 6 PCT. Así, es imposible realizar una búsqueda significativa de las mismas. Se hará una búsqueda en la primera invención discutida de la reivindicación 5, es decir, el primer compuesto citado en la misma.

GNF Legal Department
RECEIVED

W-37
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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
SCOTT W. REID
GENOMICS INSTITUTE OF THE NOVARTIS RESEARCH FOUNDATION
10675 JOHN JAY HOPKINS DRIVE
SAN DIEGO, CA 92121

BY:

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing (day/month/year)	18 APR 2006
Applicant's or agent's file reference P1153PC21	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US05/18167	24 May 2005 (24.05.2005)	24 May 2004 (24.05.2004)

Applicant

IRM LLC

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.

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. (571) 273-3201	Authorized officer Patricia L. Morris Telephone No. (571) 272-1600

Form PCT/IPEA/416 (July 1992)

GNF Legal Department
RECEIVED

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P1153PC21	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US05/18167	International filing date (day/month/year) 24 May 2005 (24.05.2005)	Priority date (day/month/year) 24 May 2004 (24.05.2004)
International Patent Classification (IPC) or national classification and IPC IPC: C07D 277/24(2006.01) USPC: 548/205		
Applicant IRM LLC		

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 5 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 ---- 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 14 December 2005 (14.12.2005)	Date of completion of this report 03 April 2006 (03.04.2006)
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. (571) 273-3201	Authorized officer Patricia L. Morris Telephone No. (571) 272-1600

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US95/18167

I. Basis of the report

1. With regard to the elements of the international application:*

- [x] the international application as originally filed.
- [x] the description:
  pages 1-175 as originally filed
  pages NONE, filed with the demand
  pages NONE, filed with the letter of _____,
- [x] the claims:
  pages 176-183 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/US05/18167

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-4 and 6-14

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-4 and 6-14 are so unclear that no meaningful opinion could be formed *(specify)*:

Please See Continuation Sheet

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. _____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US05/18167

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 5	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 5	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 5	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Claim 5 meets the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the instant compound.

NEW CITATIONS

International application No.
PCT/US05/18167

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Section III. Non-establishment of report (descriptions/claims/drawings unclear)
In these claims, the numerous variables and their voluminous, complex meanings and their seemingly endless permutations and combinations, makes it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. The compounds defined in the claims lack a significant structural element qualifying as the special technical feature that defines a contribution over the prior art. The substituents on the structure vary extensively and when taken as a whole result in vastly different compounds. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT Article 6. Thus, it is impossible to carry out a meaningful search on same. A search will be made on the first discernable invention of claim 5, i.e., the first compound recited therein.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/18167

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 277/24
US CL : 548/204
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. : 548/204

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,356,185 A (CAVALLA) 26 October 1982 (26.10.1982), see entire document.	5

☐ 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
16 August 2005 (16.08.2005)	14 SEP 2005
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Patricia L. Morris Telephone No. (571) 272-1600

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATI NAL SEARCH REPORT

International application No.
PCT/US05/18167

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-4 and 6-14
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/18167

Continuation of Box II Reason 2:
In these claims, the numerous variables and their voluminous, complex meanings and their seemingly endless permutations and combinations, make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. The compounds defined in the claims lack a significant structural element qualifying as the special technical feature that defines a contribution over the prior art. The substituents on the structure vary extensively and when taken as a whole result in vastly different compounds. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT Article 6. Thus, it is impossible to carry out a meaningful search on same. A search will be made on the first discernable invention of claim 5, i.e., the first compound recited therein.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 08-117272- -00000-0000
Fec: 2008-11-20 17:28:22 Usu: 2550 NUEVOS ALTAMIRA
Fol: 11 PATENTES
Exp: 3/0 PATENTES
Act 411 PRESENTACION Folios: 3/0
SUPERINTENDENCIA

380
490

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [✓] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [✓]
- Datos de identificación del solicitante o de la persona que 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 y 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 se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha_____

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491/38+
06/228

OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-117272- -00000-0000
Fec: 2006-11-28 17:28:22 Usu: ZULU NUEVENUEVE
Tra: 11 PATENTES
Eve: 3/U PASE NACIONAL
Act 411 PRESENTACION Hora: 3/U

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL 24/12/06
SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[ ] Capítulo I. [X] Capítulo II.

(2) **SOLICITANTE (71)**

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IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número _____

REPRESENTANTE APODERADO

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Cual _____
Número 79782747Bta
TP 74.295

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(5) **PCT (86)**

Solicitud Internacional No. PCT/US2005/018167 Fecha Mayo 24, 2005

Publicación Internacional No. WO 2005/116000 Fecha Diciembre 24, 2005

(6) **Título (54)** **COMPUESTOS Y COMPOSICIONES COMO MODULADORES DEL RECEPTOR ACTIVADO POR PROLIFERADOR DE PEROXISOMA (PPAR)**

Clasificación Internacional (51) **C07D 277/24.**

Prioridad
SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Mayo 24, 2004	60/574.137
US	Enero 31, 2005	60/648.985

(9) **Comprobante de pago No.** 06 – 88.387 **Fecha** Noviembre 15, 2006

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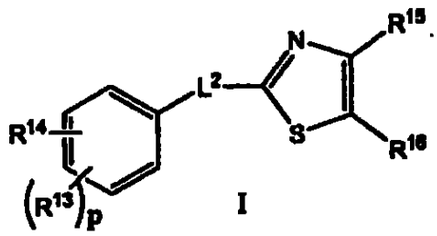
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REIVINDICACIONES

1. Un compuesto de la Fórmula I:



I

en donde:

p es un entero seleccionado de 0 a 3;

L^2 se selecciona a partir de -XOX-, $-XS(O)_{0-2}X-$ y $-XS(O)_{0-2}XO-$; en donde X se selecciona independientemente a partir de un enlace y alquileno de 1 a 4 átomos de carbono; en donde cualquier alquileno de L^2 pude estar opcionalmente sustituido por 1 a 3 radicales seleccionados a partir de halógeno, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, y alcoxi de 1 a 6 átomos de carbono sustituido por halógeno;

R^{13} se selecciona a partir de halógeno, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, hidroxi-alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, alcoxi de 1 a 6 átomos de carbono sustituido por halógeno, arilo de 6 a 10 átomos de carbono, heteroarilo de 5 a 10 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, y heterocicloalquilo de 3 a 8 átomos de carbono; en donde cualquier arilo, heteroarilo, cicloalquilo, y heterocicloalquilo de R^{13} está opcionalmente sustituido con 1 a 3 radicales

independientemente seleccionados a partir de halógeno, nitro, ciano, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, hidroxi-alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono sustituido por halógeno, y alcoxi de 1 a 6 átomos de carbono sustituido por halógeno;

R^{14} se selecciona a partir de -XOXC(O)OR^{17} y -XC(O)OR^{17}; en donde X es un enlace o alquileno de 1 a 4 átomos de carbono; y R^{17} se selecciona a partir de hidrógeno y alquilo de 1 a 6 átomos de carbono;

R^{15} y R^{16} se seleccionan independientemente a partir de -R^{18} y -YR^{18}; en donde Y se selecciona a partir de alquileno de 1 a 6 átomos de carbono, alquenileno de 2 a 6 átomos de carbono, alquinileno de 2 a 6 átomos de carbono, -C(O)NR^{17}- y -OX-; X es un enlace o alquileno de 1 a 4 átomos de carbono; R^{17} se selecciona a partir de hidrógeno y alquilo de 1 a 6 átomos de carbono; y R^{18} se selecciona a partir de cicloalquilo de 3 a 12 átomos de carbono, hetero-ciclo-alquilo de 3 a 8 átomos de carbono, arilo de 6 a 10 átomos de carbono, y hetero-arilo de 5 a 13 átomos de carbono; o R^{15} y R^{16}, junto con los átomos con los que están unidos R^{15} y R^{16}, forman un heteroarilo de 5 a 14 átomos de carbono bicíclico o tricíclico fusionado;

en donde cualquier arilo, hetero-arilo, cicloalquilo, y hetero-ciclo-alquilo de R^{18}, o la combinación de R^{15} y R^{16}, está opcionalmente sustituido con 1 a 3 radicales independientemente seleccionados a partir de halógeno, nitro, ciano, alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, tioalquilo de 1 a 6 átomos de carbono, hidroxi-alquilo de 1 a 6 átomos de carbono, alquilo de 1 a 6 átomos de carbono

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495

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCI

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO

REFERENCIA	Radicación No.	6 117272
	Solicitud internacional	PCT/US2005/018167
	Fecha inicio fase nacional	24/12/2006
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	14885

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:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

2. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

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 Unica No.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
aalvarado 29 DIC. 2006