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PCT

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PATENTE DE INVENCIÓN

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54. **TÍTULO** *ANTAGONISTAS DEL RECEPTOR 2 DE CITOCINA QUIMIOATRATENTE DE SALES CUATERNARIAS*

51. **CLASIFICACIÓN INTERNACIONAL** C07D 309/14; A61K 31/165; A61P 29/00.

71. **SOLICITANTE** *JANSSEN PHARMACEUTICA N.V.*

DOMICILIO *BEERSE, BELGICA*

74. **APODERADO** *JIMENA ESCOBAR URIBE*

22. **BOGOTÁ, D. C.,** 27-12-2006

(FORMA P-10)

55

PETITOR

Industria y Comercio
SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1) SOLICITUD DE:

☒ Patente de invención ☐ Patente de Modelo de Utilidad

☒ Capitulo I. ☐ Capitulo II.

2) SOLICITANTE (71)	**Nombre: 7TM PHARMA A/S** **Dirección: Fremtidsvej 3, DK-2970 Hoersholm, Alemania** **Nacionalidad o domicilio: Hoersholm, Alemania** DK **Lugar de constitución: Alemania** **Teléfono: Fax:** **E. Mail:**	**IDENTIFICACIÓN** **C.C.** ☐ **NIT:** ☒ **C.E.** ☐ **OTRO** ☐ **Cual** _____ **NÚMERO** _____
3) REPRESENTANTE APODERADO	Nombre: DILIA MARÍA RODRÍGUEZ D´ALEMAN Dirección: Carrera 11 N°. 86-53 Piso 6 Bogotá D.C. Teléfono: 6181088 Fax: 6350824 E. Mail: info@clarkemodet.com.co	**IDENTIFICACIÓN** **C.C.** ☒ **NIT:** ☐ **C.E.** ☐ **OTRO** ☐ **NÚMERO:** 41.654.882 **TP:** 20824 CSJ
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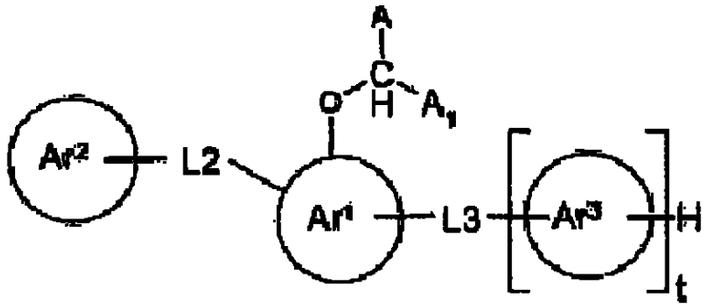
Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta pagina

10) ANEXOS

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [ ] Comprobante de pago por reivindicación de prioridad
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- [ ] Poderes, si fuera el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- [ ] Copia del examen preliminar efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12 y 6 x 6 cm
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- [ ] Otros:

11) FIGURA CARACTERÍSTICA:



12) Solicitud concesión de la patente,

NOMBRE: DILIA RODRÍGUEZ D'ALEMAN

FIRMA: _____

C.C. 41.654.882 de Bogota TP 20824 CSJ

Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta pagina

p-882

P882

3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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C O N C E P T O

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(72) Inventors; and

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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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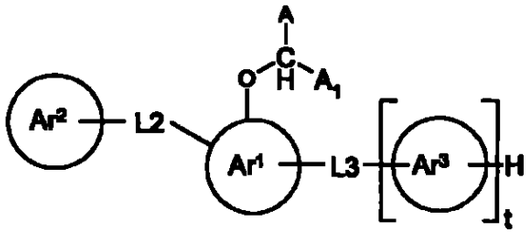
(54) Title: CRTH2 RECEPTOR LIGANDS FOR MEDICINAL USES



(I)

(57) Abstract: Compounds of formula (I) are useful for the treatment of disease responsive to modulation of CRTH2 receptor activity, such as asthma, rhinitis, allergic airway syndrome, and allergic rhinobronchitis, wherein A represents a carboxyl group -COOH, or a carboxyl bioisostere; A_1, is hydrogen or methyl; ring Ar^1 is an optionally substituted phenyl ring 5-or 6-membered monocyclic heteroaryl ring, in which AA_1CHO- and L2 are linked to adjacent ring atoms; rings Are^2, Ar^3 each independently represent a phenyl or 5- or 6-membered monocyclic heteroaryl ring, or a bicyclic ring system consisting of a 5- or 6-membered carbocyclic or heterocyclic ring which is benz-fused or fused to a 5- or 6-membered monocyclic heteroaryl ring, said ring or ring system being optionally substituted; t is 0 or 1; L2 and L3 are linker radicals as defined in the description.

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CRTH2 RECEPTOR LIGANDS FOR MEDICINAL USES

This invention relates to the use of a class of compounds which are ligands of the CRTH2 receptor (Chemoattractant Receptor-homologous molecule expressed on T Helper cells type 2), in the treatment of diseases responsive to modulation of CRTH2 receptor activity, principally diseases having a significant inflammatory component. The invention also relates to novel members of that class of ligands and pharmaceutical compositions containing them.

Many classes of antiinflammatory agents are known, including the non-steroidal antiinflammatory compounds known as NSAIDs and the inhibitors of cyclooxygenase (COX-1 and COX-2). Benzoylphenylacetic acid and some benzophenone derivatives with carboxymethoxy substituents in one of the rings have been identified as antiinflammatory agents (see, for example, Khanum et. al. Bioorganic Chemistry Vol 32, No. 4, 2004, pages 211-222 and the references cited therein). Some o-phenyl carbamoyl-phenoxyacetic acids and o-benzamido-phenoxymethyl tetrazoles have been reported as potential antiinflammatory agent, see for example Drain et. al. J. Pharm. Pharmac., 1971, 23, 857-864, and ibid 1970, 22, 684-693. WO 99/15520 discloses a few benzophenone derivatives with carboxymethoxy or tetrazolylmethoxy substituents in one of the rings, synthesised as members of a group of compounds said to have activity as inhibitors of peroxisome proliferator-activated receptor (PPAR), and utility in a variety of disease states including diabetes, cardiac disease, and circulatory disease.

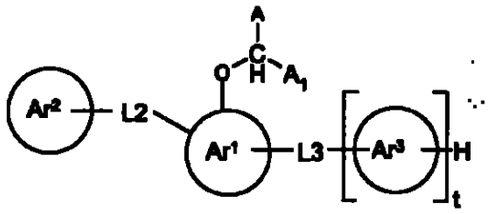
The natural ligand of the G-protein coupled receptor CRTH2 is prostaglandin D2. As its name implies, CRTH2 is expressed on T helper cells type 2 (Th2 cells) but it is also known to be expressed on eosinophils and basophil cells. Cell activation as a result of binding of PGD2 to the CRTH2 receptor results in a complex biological response, including release of inflammatory mediators. Elevated levels of PGD2 are therefore associated with many diseases which have a strong inflammatory component, such as asthma, rhinitis and allergies. Blocking binding of PGD2 to the CRTH2 receptor is therefore a useful therapeutic strategy for treatment of such diseases.

Some small molecule ligands of CRTH2, apparently acting as antagonists of PGD2, are known, for example as proposed in the following patent publications: WO

03/097042, WO 03/097598, WO 03/066046, WO 03/066047, WO 03/101961, WO 03/101981, GB 2388540, WO 04/089885 and WO 05/018529.

The structures of PGD2 antagonist compounds referred to in some of the foregoing publications have a bicyclic or tricyclic core ring system related to the indole core of indomethacin, a known anti-inflammatory agent, now known to bind to CRTH2. The present invention arises from the identification of a class of compounds having a monocyclic core whose substituent moieties are selected and orientated by the monocyclic core to interact with and bind to CRTH2. The class of compounds with which this invention is concerned are thus capable of modulating CRTH2 activity, and are useful in the treatment of diseases which benefit from such modulation, for example asthma, allergy and rhinitis.

According to the present invention, there is provided the use of a compound of formula (I) or a salt, hydrate or solvate thereof in the manufacture of a composition for the treatment of disease responsive to modulation of CRTH2 receptor activity:



(I)

wherein

A represents a carboxyl group –COOH, or a carboxyl bioisostere;

A_1 is hydrogen or methyl;

ring Ar^1 is an optionally substituted phenyl ring or 5- or 6-membered monocyclic heteroaryl ring, in which AA_1CHO- and L2 are linked to adjacent ring atoms;

rings Ar^2, Ar^3 each independently represent a phenyl or 5- or 6-membered monocyclic heteroaryl ring, or a bicyclic ring system consisting of a 5- or 6-membered carbocyclic or heterocyclic ring which is benz-fused or fused to a 5- or 6-membered monocyclic heteroaryl ring, said ring or ring system being optionally substituted;

t is 0 or 1;

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L2 and L3 each independently represents a divalent radical of formula $-(Alk^1)_m-(Z)_n-(Alk^2)_p$ wherein

m, n and p are independently 0 or 1,

Alk^1 and Alk^2 are independently optionally substituted straight or branched chain C_1-C_3 alkylene or C_2-C_3 alkenylene radicals which may contain a compatible –O-, -S- or –NR- link wherein R is hydrogen or C_1-C_3 alkyl, and

Z is –O-; -S-; -C(=O)-; $-SO_2$-; -SO-; -NR-, $-NRSO_2$-, $-SO_2NR$-, -C(=O)NR-, -NRC(=O)-, -NRCONH-, -NHCONR-, -NRC(=NR)NH-, -NHC(=NR)NR-, –C(R)=N-NR-, or –NR-N=C(R)- wherein R is hydrogen or C_1-C_3 alkyl; or a divalent 5- or 6-membered monocyclic carbocyclic or heterocyclic radical,

PROVIDED THAT

(A) the total length of L2 and L3 does not exceed that of an unbranched saturated chain of 10 carbon atoms; and

(B) L2 is not –C(=O)-, -C(=O)NR-, or -NRC(=O)- when Ar^2 is optionally substituted phenyl; and

(C) (a) L2 is not a bond and (b) p in L2 is not 0 when n is 1 and Z is aryl or heteroaryl, and

(D) (a) L2 is not –O-, $-SO_2$-, -NR-, $-CHR^XR^Y$- or $-CH(R^X)(OR^Y)$-, wherein R^X and R^Y are independently hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_3-C_7 cycloalkyl, or join to form a ring, and (b) when p is 1 and n is 1 and Z is aryl or heteroaryl then Alk^2 is not $-CHR^XR^Y$- or $-CH(R^X)(OR^Y)$-, wherein R^X and R^Y are independently hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_3-C_7 cycloalkyl, or join to form a ring.

In one aspect of the invention, in compounds (I), the length of each of L2 and L3 does not exceed that of an unbranched saturated chain of 5 carbon atoms and (ii) the total length of L2 and L3 does not exceed that of an unbranched saturated chain of 7 carbon atoms, and (iii) neither of L2 and L3 includes more than two R substituents different from hydrogen.

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In a narrower aspect of the invention, compounds (I) as defined above wherein A_1 is hydrogen and Z is –O-; -S-; -C(=O)-; -SO_2-; -SO-; -NR-, -$NRSO_2$-, -C(=O)NR-, -NRCONH-, -NRC(=NR)NH-, or –C(R)=N-NR-, wherein R is hydrogen or C_1-C_3 alkyl; or a divalent 5- or 6-membered monocyclic carbocyclic or heterocyclic radical, may be used

In another narrower aspect of the invention, compounds (I) as defined above wherein L2 is -N=CR-, -OCR_2C(=O)NR-N=CR-, -C(=O)NR-, -N=CR-, -C(=O)-, -CH=CHC(=O)-, -$(CH_2)_{0-3}$NRC(=O)-, -NRC(=O)$(CH_2)_{0-3}$-, –O-N=CH-, -CH_2NRCH_2-, -$NR(CH_2)_{1-3}$-, -$(CH_2)_{1-3}$NR-, -S-, -CH_2OCH_2-, -$O(CH_2)_{1-3}$-, -$(CH_2)_{1-3}$O-, -CH_2SCH_2-, -$S(CH_2)_{0-3}$-, -$(CH_2)_{0-3}$S-, a divalent (C_2-C_8)alkylene radical, a divalent (C_2-C_8)alkenylene radical, or a divalent (C_2-C_8)alkynylene radical, wherein R is hydrogen or C_1-C_3 alkyl, may be used

In further narrower aspects of the invention, compounds (I) as defined above wherein L2 is –NRN=CH-, -ON=CH-, or -N=CH-; or L2 is –C(=O)-; or L2 is –NHC(=O)- or –C(=O)NH-, may be used.

An independent aspect of the invention is the use of a compound of formula (I) set out above or a salt, hydrate or solvate thereof in the manufacture of a composition for the treatment of disease responsive to modulation of CRTH2 receptor activity, in which compound (I):

A represents a carboxyl group –COOH, or a carboxyl bioisostere;

A_1 is hydrogen or methyl;

ring Ar^1 is an optionally substituted phenyl ring or 5- or 6-membered monocyclic heteroaryl ring, in which AA_1CHO- and L2 are linked to adjacent ring atoms;

rings Ar^2, Ar^3 each independently represent a phenyl or 5- or 6-membered monocyclic heteroaryl ring, or a bicyclic ring system consisting of a 5- or 6-membered carbocyclic or heterocyclic ring which is benz-fused or fused to a 5- or 6-membered monocyclic heteroaryl ring, said ring or ring system being optionally substituted;

t is 0 or 1;

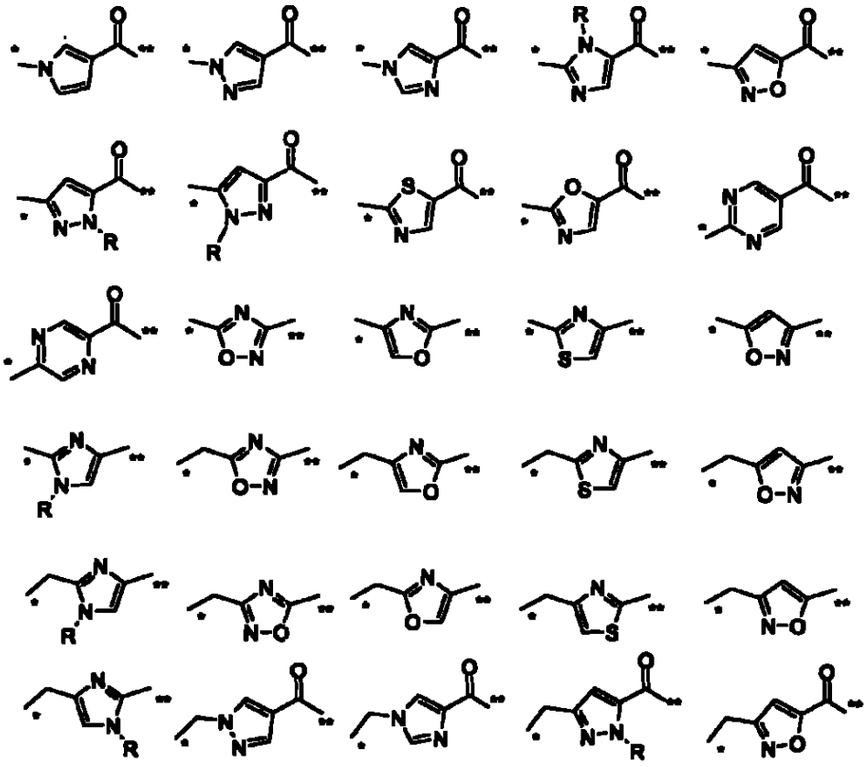
L3 represents a divalent radical of formula $-(Alk^1)_m-(Z)_n-(Alk^2)_p$ wherein

m, n and p are independently 0 or 1,

Alk^1 and Alk^2 are independently optionally substituted straight or branched chain C_1-C_3 alkylene or C_2-C_3 alkenylene radicals which may contain a compatible –O-, -S- or –NR- link wherein R is hydrogen or C_1-C_3 alkyl, and

Z is –O-; -S-; -C(=O)-; $-SO_2-$; -SO-; -NR-, $-NRSO_2-$, $-SO_2NR-$, -C(=O)NR-, -NRC(=O)-, -NRCONH-, -NHCONR-, -NRC(=NR)NH-, -NHC(=NR)NR-, –C(R)=N-NR-, or –NR-N=C(R)- wherein R is hydrogen or C_1-C_3 alkyl; or a divalent 5- or 6-membered monocyclic carbocyclic or heterocyclic radical;

L2 represents a divalent radical selected from one of the following formulae (sometimes called "L2 set A" herein), wherein either (i) the bond marked * is attached to Ar^2 while the bond marked ** is attached to Ar^1, or (ii) the bond marked * is attached to Ar^1 while the bond marked ** is attached to Ar^2:



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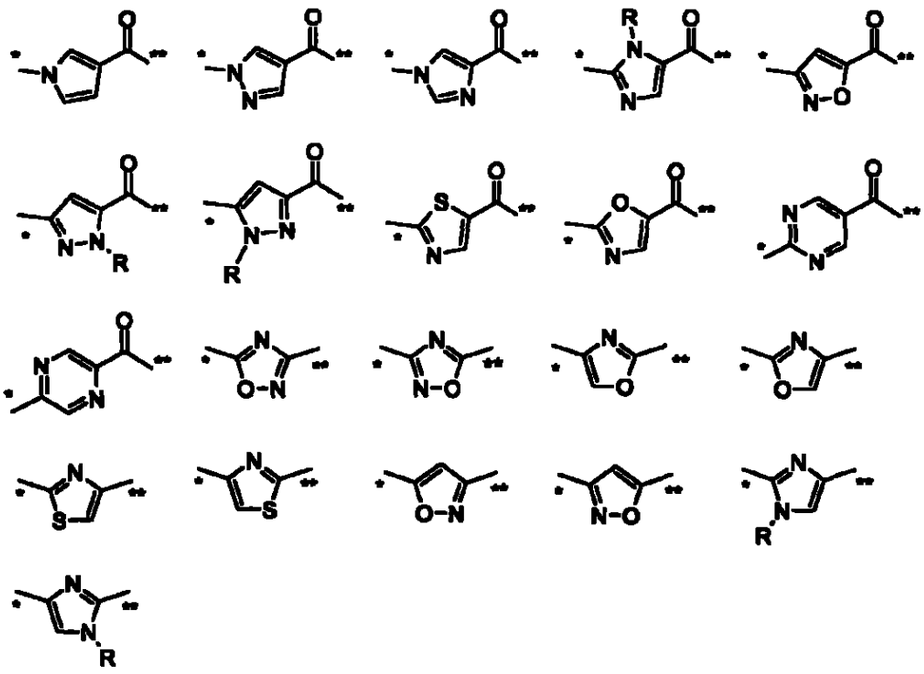
wherein R is hydrogen or C_1-C_3 alkyl; and

the total length of L2 and L3 does not exceed that of an unbranched saturated chain of 10 carbon atoms.

In a narrower definition of this aspect of the invention, in the compounds (I), (i) the length of L3 does not exceed that of an unbranched saturated chain of 5 carbon atoms and (ii) the total length of L2 and L3 does not exceed that of an unbranched saturated chain of 7 carbon atoms, and (iii) L3 does not include more than two R substituents different from hydrogen.

In the two immediately foregoing aspects of the invention, in the compounds (I), A1 may be hydrogen and L2 may be one of the following formulae (sometimes called "L2 set B" herein) wherein the bond marked * is attached to Ar^2 while the bond marked ** is attached to Ar^1:



wherein R is hydrogen or C_1-C_3 alkyl.

The compounds with which the invention is concerned are defined by reference to formula (I) as a result of studies towards elucidation of the ligand binding site of

CRTH2. Such studies led to the overall conclusion that a general pharmacophore comprising one negatively charged moiety, represented by AA_1CHO-, and two aromatic and/or hydrophobic moieties, represented by Ar^2L2 and either $H(Ar^3)_1L3\text{-}Ar^1$ or only Ar^1, oriented in an approximate triangle, would form an arrangement for interaction with the receptor binding site. It was concluded that the substituent groupings AA_1CHO- and Ar^2L2- should be on adjacent ring atoms of Ar^1. The linkers L2 and L3 provide some flexibility to the molecule to facilitate optimum binding. The restrictions on the lengths of, and substitutions in, the linkers L2 and L3 are in order to restrict the total molecular size and complexity of structures for use in accordance with the invention. For the avoidance of doubt, the total length of L2 and L3 is, for the purposes of this description and claims, the sum n2+n3, where n2 is the number of connected atoms in the shortest chain of atoms from terminal atom to terminal atom of linker L2, and n3 is the number of connected atoms in the shortest chain of atoms from terminal atom to terminal atom of linker L2. Preferably the compounds with which the invention is concerned should have a molecular weight of no more than 600. Optional substituents in any element of the compounds (I) are permitted as in the definition of compounds (I). Such substituents can modulate pharmacokinetic and solubility properties, as well as picking up additional binding interactions with the receptor.

In another aspect, the invention provides a method of treatment of a subject suffering from a disease responsive to modulation of CRTH2 receptor activity, which comprised administering to the subject an amount of a compound (I) as defined and described above effective to ameliorate the disease.

In particular, compounds with which the invention is concerned are useful in the treatment of disease associated with elevated levels of prostaglandin D2 (PGD2) or one or more active metabolites thereof.

Examples of such diseases include asthma, rhinitis, allergic airway syndrome, allergic rhinobronchitis, bronchitis, chronic obstructive pulmonary disease (COPD), nasal polyposis, sarcoidosis, farmer's lung, fibroid lung, cystic fibrosis, chronic cough, conjunctivitis, atopic dermatitis, Alzheimer's disease, amyotrophic lateral sclerosis, AIDS dementia complex, Huntington's disease, frontotemporal dementia, Lewy body dementia, vascular dementia, Guillain-Barre syndrome, chronic demyelinating polyradiculoneurophathy, multifocal motor neuropathy, plexopathy, multiple sclerosis, encephalomyelitis, panencephalitis, cerebellar degeneration and

encephalomyelitis, CNS trauma, migraine, stroke, rheumatoid arthritis, ankylosing spondylitis, Behçet's Disease, bursitis, carpal tunnel syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, dermatomyositis, Ehlers-Danlos Syndrome (EDS), fibromyalgia, myofascial pain, osteoarthritis (OA), osteonecrosis, psoriatic arthritis, Reiter's syndrome (reactive arthritis), sarcoidosis, scleroderma, Sjogren's Syndrome, soft tissue disease, Still's Disease, tendinitis, polyarteritis Nodossa, Wegener's Granulomatosis, myositis (polymyositis dermatomyositis), gout, atherosclerosis, lupus erythematosus, systemic lupus erythematosus (SLE), type I diabetes, nephritic syndrome, glomerulonephritis, acute and chronic renal failure, eosinophilia fasciitis, hyper IgE syndrome, sepsis, septic shock, ischemic reperfusion injury in the heart, allograft rejection after transplantations, and graft versus host disease.

However, the compounds with which the invention is concerned are primarily of value for the treatment asthma, rhinitis, allergic airway syndrome, and allergic rhinobronchitis.

Many compounds of formula (I) above are novel in their own right, and the invention includes such novel compounds *per se*.

As used herein, the term "(C_a-C_b)alkyl" wherein a and b are integers refers to a straight or branched chain alkyl radical having from a to b carbon atoms. Thus when a is 1 and b is 6, for example, the term includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein the term "divalent (C_a-C_b)alkylene radical" wherein a and b are integers refers to a saturated hydrocarbon chain having from a to b carbon atoms and two unsatisfied valences.

As used herein the term "(C_a-C_b)alkenyl" wherein a and b are integers refers to a straight or branched chain alkenyl moiety having from a to b carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. The term includes, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "divalent (C_a-C_b)alkenylene radical" means a hydrocarbon chain having from a to a carbon atoms, at least one double bond, and two unsatisfied valences.

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As used herein the term "C_a-C_b alkynyl" wherein a and b are integers refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1- and 2-propynyl, 1-, 2- and 3-butynyl, 1, 2-, 3- and 4-pentynyl, 1-, 2-, 3-, 4- and 5-hexynyl, 3-methyl-1-butynyl, 1-methyl-2-pentynyl.

As used herein the term "divalent (C_a-C_b)alkynylene radical" wherein a and b are integers refers to a divalent hydrocarbon chain having from 2 to 6 carbon atoms, at least one triple bond, and two unsatisfied valences.

As used herein the term "carbocyclic" refers to a mono-, bi- or tricyclic radical having up to 16 ring atoms, all of which are carbon, and includes aryl and cycloalkyl.

As used herein the term "cycloalkyl" refers to a monocyclic saturated carbocyclic radical having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

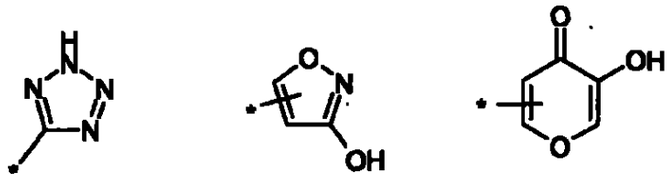
As used herein the unqualified term "aryl" refers to a mono-, bi- or tri-cyclic carbocyclic aromatic radical, and includes radicals having two monocyclic carbocyclic aromatic rings which are directly linked by a covalent bond. Illustrative of such radicals are phenyl, biphenyl and napthyl.

As used herein the unqualified term "heteroaryl" refers to a mono-, bi- or tri-cyclic aromatic radical containing one or more heteroatoms selected from S, N and O, and includes radicals having two such monocyclic rings, or one such monocyclic ring and one monocyclic aryl ring, which are directly linked by a covalent bond. Illustrative of such radicals are thienyl, benzthienyl, furyl, benzfuryl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, isothiazolyl, benzisothiazolyl, pyrazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, triazolyl, benztriazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyridazinyl, triazinyl, indolyl and indazolyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in addition means a mono-, bi- or tri-cyclic non-aromatic radical containing one or more heteroatoms selected from S, N and O, and to groups consisting of a monocyclic non-aromatic radical containing one or more

such heteroatoms which is covalently linked to another such radical or to a monocyclic carbocyclic radical. Illustrative of such radicals are pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, morpholinyl, benzfuranyl, pyranyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, maleimido and succinimido groups.

The term "carboxyl bioisostere" is a term familiar to medicinal chemists (see for example "The Organic Chemistry of Drug Design and Drug Action", by Richard B. Silverman, pub. Academic Press, 1992), and refers to a group which has similar acid-base characteristics to those of a carboxyl group. Well known carboxyl bioisosteres include $-SO_2NHR$ or $-P(=O)(OH)(OR)$ wherein R is, for example, hydrogen methyl or ethyl, $-SO_2OH$, $-P(=O)(OH)(NH_2)$, $-C(=O)NHCN$ and groups of formulae:



Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four compatible substituents, each of which independently may be, for example, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy, hydroxy(C_1-C_6)alkyl, mercapto, mercapto(C_1-C_6)alkyl, (C_1-C_6)alkylthio, halo (including fluoro, bromo and chloro), fully or partially fluorinated (C_1-C_3)alkyl, (C_1-C_3)alkoxy or (C_1-C_3)alkylthio such as trifluoromethyl, trifluoromethoxy, and trifluoromethylthio, nitro, nitrile (-CN), oxo, phenyl, phenoxy, , $-COOR^A$, $-COR^A$, $-OCOR^A$, $-SO_2R^A$, $-CONR^AR^B$, $-SO_2NR^AR^B$, $-NR^AR^B$, $-OCONR^AR^B$, $-NR^BCOR^A$, $-NR^BCOOR^A$, $-NR^BSO_2OR^A$ or $-NR^ACONR^AR^B$ wherein R^A and R^B are independently hydrogen or a (C_1-C_6)alkyl group or, in the case where R^A and R^B are linked to the same N atom, R^A and R^B taken together with that nitrogen may form a cyclic amino ring. Where the substituent is phenyl or phenoxy, the phenyl ring thereof may itself be substituted by any of the above substituents except phenyl or phenoxy. An "optional substituent" may be one of the foregoing substituent groups.

As used herein the term "salt" includes base addition, acid addition and quaternary salts. Compounds of the invention which are acidic can form salts, including pharmaceutically acceptable salts, with bases such as alkali metal hydroxides, e.g.

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sodium and potassium hydroxides; alkaline earth metal hydroxides e.g. calcium, barium and magnesium hydroxides; with organic bases e.g. N-methyl-D-glucamine, choline tris(hydroxymethyl)amino-methane, L-arginine, L-lysine, N-ethyl piperidine, dibenzylamine and the like. Those compounds (I) which are basic can form salts, including pharmaceutically acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, nitric acid or phosphoric acid and the like, and with organic acids e.g. with acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic, p-toluenesulphonic, benzoic, benzenesunfonic, glutamic, lactic, and mandelic acids and the like.

Compounds with which the invention is concerned which may exist in one or more stereoisomeric form, because of the presence of asymmetric atoms or rotational restrictions, can exist as a number of stereoisomers with R or S stereochemistry at each chiral centre or as atropisomeres with R or S stereochemistry at each chiral axis. The invention includes all such enantiomers and diastereoisomers and mixtures thereof.

Use of prodrugs, such as esters, of compounds (I) with which the invention is concerned is also part of the invention.

For use in accordance with the above aspects of the invention the following structural characteristics may be present, in any compatible combination, in the compounds (I):

L2 may be a member of L2 set A above (and of course L2 set A includes L2 set B);

L2 may be -N=CR-, $-OCR_2C(=O)NR-N=CR-$, -C(=O)NR-, -N=CR-, -C(=O)-, -CH=CHC(=O)-, $-(CH_2)_{0-3}NRC(=O)-$, $-NRC(=O)(CH_2)_{0-3}-$, -O-N=CH-, $-CH_2NRCH_2-$, $-NR(CH_2)_{1-3}-$, $-(CH_2)_{1-3}NR-$, -S-, $-CH_2OCH_2-$, $-O(CH_2)_{1-3}-$, $-(CH_2)_{1-3}O-$, $-CH_2SCH_2-$, $-S(CH_2)_{0-3}-$, $-(CH_2)_{0-3}S-$, a divalent (C_2-C_6)alkylene radical, a divalent (C_2-C_6)alkenylene radical, or a divalent (C_2-C_6)alkynylene radical, wherein R is hydrogen or C_1-C_3 alkyl;

L2 may be -NRN=CH-, -ON=CH-, -N=CH-, -C(=O)-, -NHC(=O)- or -C(=O)NH-;

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Ar^2 may be an optionally substituted phenyl or 5- or 6-membered nitrogen-containing heteroaryl ring, for example pyridyl, pyrimidyl, diazolyl, thiazolyl, oxazolyl, triazinyl, quinolinyl, pyrrolyl, furanyl, thiazolyl;

Optional substituents in Ar^2 may be selected from fluoro, chloro, bromo, (C_1-C_3)alkyl, trifluoromethyl, (C_1-C_3)alkoxy, trifluoromethoxy, trifluoromethylthio, dimethylamino, cyano, (C_1-C_3alkyl)SO_2-, NH_2SO_2-, (C_1-C_3alkyl)$NHSO_2$-, (C_1-C_3alkyl)$_2NSO_2$-, and nitro;

Ar^1 may be an optionally substituted 5- or 6-membered nitrogen-containing heteroaryl ring, for example pyridyl, pyrimidyl, diazolyl, thiazolyl, oxazolyl, triazinyl, quinolinyl, pyrrolyl, furanyl, thiazolyl, and wherein L3 may be linked to a ring carbon in (for a 6-membered ring) the 4 position thereof relative to the $ACHA_1O$- radical or (for a 5-membered ring) the 4 position thereof counting the $ACHA_1O$- radical as in position 1 and the Ar^2L2- radical as in position 2 thereof;

Ar^1 may be an optionally substituted phenyl ring wherein L3 is linked to the 4 position thereof relative to the $ACHA_1O$- radical;

when t is 1, Ar^3 may be an optionally substituted phenyl ring, or an optionally substituted 5- or 6-membered heteroaryl ring, for example pyridyl, pyrimidyl, diazolyl, thiazolyl, oxazolyl, triazinyl, quinolinyl, pyrrolyl, furanyl, or thiazolyl;

optional substituents in ring Ar^1 or Ar^3 may be selected from fluoro, chloro, bromo, iodo, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, (C_1-C_3alkyl)SO_2-, NH_2SO_2-, (C_1-C_3alkyl)$NHSO_2$-, (C_1-C_3alkyl)$_2NSO_2$-, C_1-C_6 alkyl, C_1-C_6 alkoxy, cycloalkyl, aryl, aryloxy, aryl(C_1-C_6)- or aryl(C_1-C_6 alkoxy)-;

when t is 0, L3 may be a bond;

A may be –COOH or a carboxyl bioisostere selected from $-SO_2NHR$ and $-P(=O)(OH)(OR)$ wherein R is hydrogen methyl or ethyl, $-SO_2OH$, $-P(=O)(OH)(NH_2)$, $-C(=O)NHCN$ and groups of formulae:

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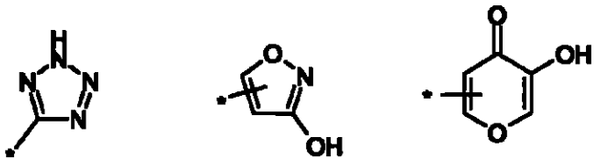
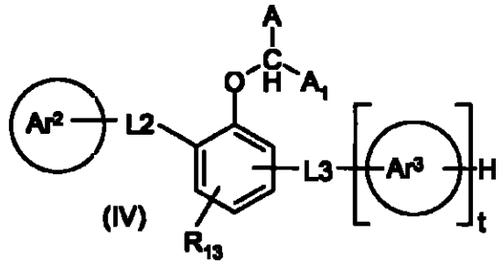


It is currently preferred that A be carboxyl;

A_1 may be hydrogen or methyl.

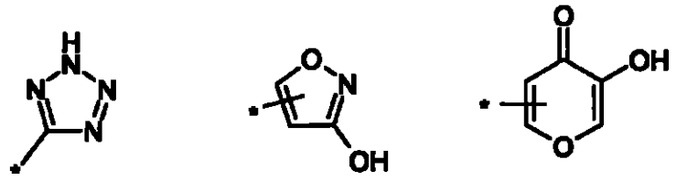
Compounds (I) for use in accordance with the invention include those of formula (IV) and salts, hydrates or solvates thereof, which are believed novel *per se*, and which form another aspect of the invention:



wherein A, A1, L3, Ar^3, Ar^2, and t are as defined and discussed above in relation to formula (I), R13 represents hydrogen or one or more optional substituents, and L2 is a member of the L2 set A, as defined above. This includes the case where A_1 is hydrogen and L2 is a member of the L2 set B as defined above.

The following structural characteristics may be present in compounds (IV), in any compatible combination:

A may be –COOH, or a carboxyl bioisostere selected from $-SO_2NHR$ and $-P(=O)(OH)(OR)$ wherein R is hydrogen methyl or ethyl, $-SO_2OH$, $-P(=O)(OH)(NH_2)$, –C(=O)NHCN and groups of formulae:



Currently it is preferred that A be carboxyl.

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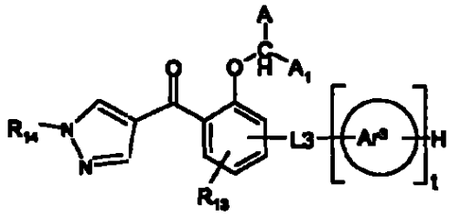
R_{13} may represent one or more substituents selected from fluoro, chloro, bromo, iodo, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, (C_1-C_3alkyl)SO_2-, NH_2SO_2-, (C_1-C_3alkyl)$NHSO_2$-, (C_1-C_3alkyl)$_2NSO_2$-, C_1-C_6 alkyl, C_1-C_6 alkoxy, cycloalkyl, aryl, aryloxy, aryl(C_1-C_6)- or aryl(C_1-C_6 alkoxy)-.

A_1 may be methyl or A_1 may be hydrogen.

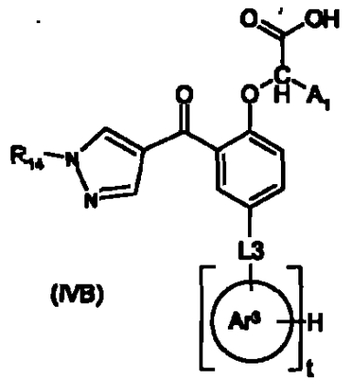
One preferred subset of the compounds (IV) has formula (IVA)



(IVA)

wherein A, A_1 L3, t, Ar^3, R_{13} are as defined and discussed above in relation to compounds of formula (I) and (IV) and R_{14} is optionally substituted phenyl or 5- or 6-membered heteroaryl.

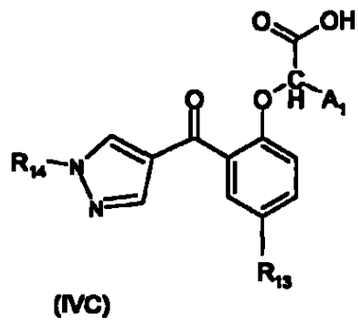
Another preferred subset of the compounds (IV) has formula (IVB):



(IVB)

wherein A_1, L3, t, and Ar^3 are as defined and discussed above in relation to formulae (I), (IV) and (IVA), and R_{14} is optionally substituted phenyl or 5- or 6- membered heteroaryl

Another preferred subset of the compounds (IV) has formula (IVC):



(IVC)

wherein R_{13} represents a substituent selected from fluoro, chloro, bromo, iodo, (C_1-C_6)alkyl, trifluoromethyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylmercapto, trifluoromethoxy, trifluoromethylthio, dimethylamino, cyano, (C_1-C_3alkyl)SO_2-, NH_2SO_2-, (C_1-C_3alkyl)$NHSO_2$-, (C_1-C_3alkyl)$_2NSO_2$-, and nitro, and R_{14} is optionally substituted phenyl or 5- or 6- membered heteroaryl. In this subset, R_{14} may be a 2-substituted, 2,4-disubstituted, 2,6-disubstituted or 2,4,6-trisubstituted phenyl ring where the substituents are selected from fluoro, chloro, bromo, iodo, (C_1-C_6)alkyl, trifluoromethyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylmercapto, trifluoromethoxy, trifluoromethylthio, dimethylamino, (C_1-C_3alkyl)SO_2-, NH_2SO_2-, (C_1-C_3alkyl)$NHSO_2$-, (C_1-C_3alkyl)$_2NSO_2$-, and cyano. This subset specifically includes compounds wherein A_1 is hydrogen.

In any compound (I), (IV) (IVA), (IVB) or IVC) defined and discussed above, wherein A1 is methyl, the carbon atom to which it is attached preferrably has the S stereochemical configuration.

Specific novel compounds of the invention are the following:
4-chloro-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxyacetic acid,
4-bromo-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxyacetic acid,
[4-bromo-2-(1-pyridin-2-yl-1H-pyrazole-4-carbonyl)phenoxy]acetic acid,
{4-bromo-2-[1-(2-chlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(3-chlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(4-bromophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(4-chlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(2-ethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(2-bromophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(2-fluorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,

{4-bromo-2-[1-(3-bromophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(2,4-dichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{2-[1-(2-chlorophenyl)-1H-pyrazole-4-carbonyl]-4-nitrophenoxy}acetic acid,
{4-bromo-2-[1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{2-[1-(2-bromophenyl)-1H-pyrazole-4-carbonyl]-4-ethylphenoxy}acetic acid,
{4-bromo-2-[1-(2,4-dibromophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(4-bromo-2-chlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
2-[4-bromo-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxy]propionic acid,
(S)-2-[4-bromo-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxy]propionic acid,
2-{4-Bromo-2-[1-(2-chlorophenyl)-1-H-pyrazole-4-carbonyl]phenoxy}propionic acid,
(S)-2-{4-Bromo-2-[1-(2-chlorophenyl)-1-H-pyrazole-4-carbonyl]phenoxy}-propionic acid,
2-{4-Bromo-2-[1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,
(S)-2-{4-Bromo-2-[1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,
{4-Bromo-2-[1-(2-ethoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[1-(4-bromo-2-ethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[1-(2-phenoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[1-(2-methylthiophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[1-(2-bromo-4-methylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
2-{4-Bromo-2-[1-(4-bromo-2-ethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,
2-{4-Bromo-2-[1-(2-phenoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,
(S)-2-{4-Bromo-2-[1-(2-phenoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,
2-{4-Bromo-2-[1-(2-methylthio)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,
(S)-2-{4-Bromo-2-[1-(2-methylthio)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,
{4-Bromo-2-[1-(2,4-dimethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[1-(4-chloro-2-methylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[1-(2,5-dichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
2-{4-Bromo-2-[1-(4-chloro-2-methylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,

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2-{4-Bromo-2-[1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,
{4-Bromo-2-[1-(2,6-diethyl-phenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[1-(2,6-dimethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid
{4-Bromo-2-[1-(2-ethyl-6-methylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[1-(2-chloro-6-methylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[1-(3,5-dichloropyridin-4-yl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
[4-Bromo-2-(1-naphthalen-1-yl-1H-pyrazole-4-carbonyl)phenoxy]acetic acid,
{4-Bromo-2-[2-(4-chlorobenzyl)thiazol-4-yl]phenoxy}acetic acid,
{4-Bromo-2-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid,
{4-Bromo-2-[3-(4-methoxy-phenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid,
{4-Bromo-2-[3-(4-chlorophenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid,
{4-Bromo-2-[3-(4-fluoro-benzyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid,
{4-Bromo-2-[3-(2,6-dichloro-benzyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid,
{4-Bromo-2-[3-(2-trifluoromethylbenzyl)-[1,2,4]oxadiazol-5-yl]phenoxy}-acetic acid,
4-Bromo-2-[3-(2,6-dichloro-phenyl)isoxazole-5-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[3-(1-phenylcyclopropyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid,
{4-Bromo-2-[3-(2,4-dichlorophenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid,

and salts, hydrates and solvates thereof.

The invention also includes pharmaceutical compositions comprising a compound belonging to the above described compounds of formula (IV), (IVA), (IVB) or (IVC), together with a pharmaceutically acceptable carrier.

Compositions

As mentioned above, the compounds with which the invention is concerned are capable of modulating CRTH2 activity, and are useful in the treatment of diseases which benefit from such modulation. Examples of such diseases are referred to above, and include asthma, allergy and rhinitis.

It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular

disease undergoing treatment. Optimum dose levels and frequency of dosing will be determined by clinical trial, as is required in the pharmaceutical art.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. The orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

For topical application to the eye, the drug may be made up into a solution or suspension in a suitable sterile aqueous or non aqueous vehicle. Additives, for instance buffers such as sodium metabisulphite or disodium edeate; preservatives including bactericidal and fungicidal agents such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorhexidine, and thickening agents such as hypromellose may also be included.

The drug may also be formulated for inhalation, for example as a nasal spray, or dry powder or aerosol inhalers.

The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

The compounds with which the invention is concerned may be administered alone, or as part of a combination therapy with other drugs used for treatment of diseases with a major inflammatory component. In the case of asthma, rhinitis, and allergic airway syndrome such drugs include corticosteroids, long-acting inhaled beta agonists, cromolyn, nedocromil, theophylline, leukotriene receptor antagonists, antihistamines, and anticholinergics (e.g. ipratropium), and are often administered as nasal sprays, dry powder or aerosol inhalers.

In the case of arthritis and related inflammatory diseases other known drugs include glucocorticoids, NSAIDs (Non Steroidal Anti-Inflammatory Drugs – conventional prostaglandin synthesis inhibitors, COX-2 inhibitors, salicylates), and DMARDs (disease-modifying anti-rheumatic drugs such as methotrexate, sulfasalazine, gold, cyclosporine).

Synthetic Routes

There are multiple synthetic strategies for the synthesis of the compounds (I) with which the present invention is concerned, but all rely on known chemistry, known to the synthetic organic chemist. Thus, compounds according to Formula I can be synthesised according to procedures described in the standard literature and are well-known to the one skilled in the art. Typical literature sources are "*Advanced organic chemistry*", 4th Edition (Wiley), J March, "*Comprehensive Organic Transformation*", 2nd Edition (Wiley), R.C. Larock , "*Handbook of Heterocyclic Chemistry*", 2nd Edition (Pergamon), A.R. Katritzky), review articles such as found in "*Synthesis*", "*Acc. Chem. Res.*" , "*Chem. Rev*", or primary literature sources identified by standard literature searches online or from secondary sources such as "*Chemical Abstracts*" or "*Beilstein*".

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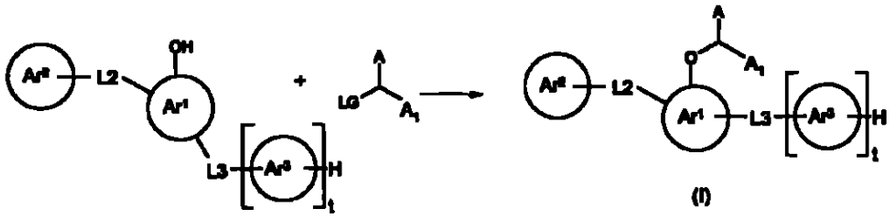
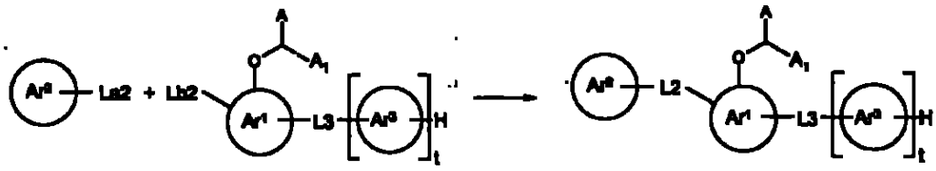
In the discussion which follows,A represents a carboxylic acid, a carboxyl bioisostere, or a protected carboxylic acid or bioisostere, or a precursor of these. In the latter case, a deprotection step is implied. A_1 represents hydrogen or methyl.

Many compounds claimed in this invention may be synthesized by reacting a phenol precursor with LG-CH(A_1)-A, where LG is a leaving group and A is a carboxylic acid or a protected analog or precursor, or a bioisostere or a protected analog of this.



(I)

The linker L2 can be formed by joining two appropriately functionalised and, if needed, suitably protected fragments containing La2 and Lb2 as reactive moieties as outlined below. La2 and Lb2 are defined as any moieties that can react by e.g. a nucleophilic substitution, addition to multiple bonds or cyclisation reaction to form a given L2 linker as exemplified below.



(I)

For example, the linker -L2- being $-Alk^1-Z-(Alk^2)_p-$ can be formed by reacting Ar^2–Alk^1-"leaving group" with a nucleophilic derivative H-Z-$(Alk^2)_p$-Ar^1(L1A)L3Ar^3H wherein Z could be O, S or NR and Alk^1 could be an alkyl group. The reactions can also be made by reversing the functionalisation of La2 and Lb2 to make the connection between Z and Alk^2. The linkers wherein Z is SO or SO_2 can be obtained by oxidations of the corresponding $-(Alk^1)_m-S-(Alk^2)_p-$ derivatives during appropriate conditions.

Further representative examples, –L2- being $-Alk^1-Z-(Alk^2)_p-$ wherein Z is NH(CO) or $NHSO_2$ can be formed by reacting Ar^2–(Alk^1)-NH_2 with an acylating derivative "leaving group"-CO-$(Alk^2)_p$-Ar^1(L1A)L3Ar^3H or "leaving group"-SO_2-$(Alk^2)_p$-Ar^1(L1A)L3Ar^3H, respectively. Alternatively, the conversion can be made directly with the acids HO-

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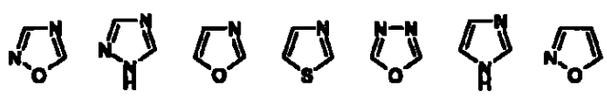
$CO\text{-}(Alk^2)_p\text{-}Ar^1(L1A)L3Ar^3H$ and $HO\text{-}SO_2\text{-}(Alk^2)_p\text{-}Ar^1(L1A)L3Ar^3H$, respectively, using suitable coupling reagents such as dicyclohexylcarbodiimide (DCC), and promoters such as 1-hydroxybenzotriazole. Analogously, –L2- being $–Alk^1\text{-}Z\text{-}(Alk^2)_p$- wherein Z being NH(CO)NH can be formed by reacting $Ar^2–(Alk^1)\text{-}NH_2$ with an isocyanate derivative $OCN\text{-}(Alk^2)_p\text{-}Ar^1(L1A)L3Ar^3H$ using suitable acid or base catalysis. The reactions can also be made by reversing the functionalisation of La2 and Lb2 to provide the "retro-bonds" in the case of NH(CO) or $NHSO_2$. Analogously, the connections can be made between Z and Alk^2.

A metal catalyzed coupling reaction like the Stille coupling reaction, the Suzuki coupling reaction, the Heck reaction and the Sonogashira reaction are useful in the synthesis of examples with L2 being an divalent alkylene radical, a divalent alkenylene radical or a divalent alkynylene radical.

Compounds with L2 being a hydrazone are usually conveniently formed by a condensation reaction between the corresponding hydrazines and aldehydes in ethanol or without solvent.

Likewise, L2 being $–(Alk^1)_m\text{-}Z\text{-}(Alk^2)_p$- wherein Z is a 5-membered heterocyclic system exemplified by, for example,



can be made according to standard cyclisation procedures using appropriate solvents, catalysts and temperatures. For example, formation of 1,2,4-triazole can be made with La2 being acylhydrazide and Lb2 being amide or thioamide or the reverse orientation of La2 and Lb2. 1,2,4-Oxadiazole can be formed from La2 being amidoxime and Lb2 being carboxylic ester or the reverse orientation of La2 and Lb2. 1,3,4-Oxadiazole can be formed from La2 being acylhydrazide and Lb2 being carboxylic ester or the reverse orientation of La2 and Lb2. The thiazole can be made from La2 being thioamide and Lb2 being an α-haloketone or the reverse orientation of La2 and Lb2. The isoxazole can be made from La2 being alkyne and Lb2 being nitriloxide or the reverse orientation in a cycloaddition reaction.

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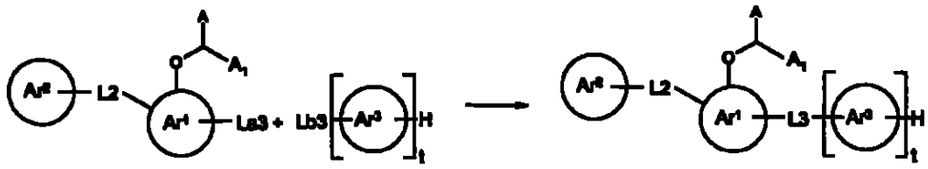
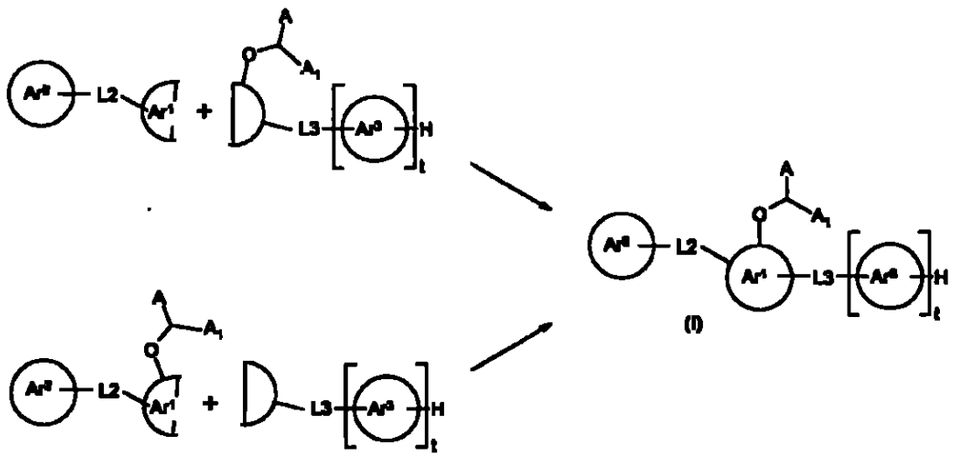
In an analogous manner the compounds of formula I can be made by forming the linker L3, according to procedures outlined for L2, as depicted below. Thus, La and Lb are defined as any moieties that can react by e.g. a nucleophilic substitution, addition to multiple bonds or cyclisation reaction to form a given linker as exemplified below.



(I)

The Ar^1 moiety can also be the central scaffold that is used in connecting the L2 and L3 parts in a stepwise fashion. This can be done via aromatic substitutions of the Ar^1 core to attach L2 and/or L3, which then can be further functionalised to give the final Formula I compounds.

Furthermore, the Ar^1 moiety can also be assembled via ring cyclisation reactions with reactants containing the L2 and L3 units either containing the full appendices as outlined below:



(I)

or in forms that can be further functionalised into the final Formula I structures as described previously. One such illustration is given below

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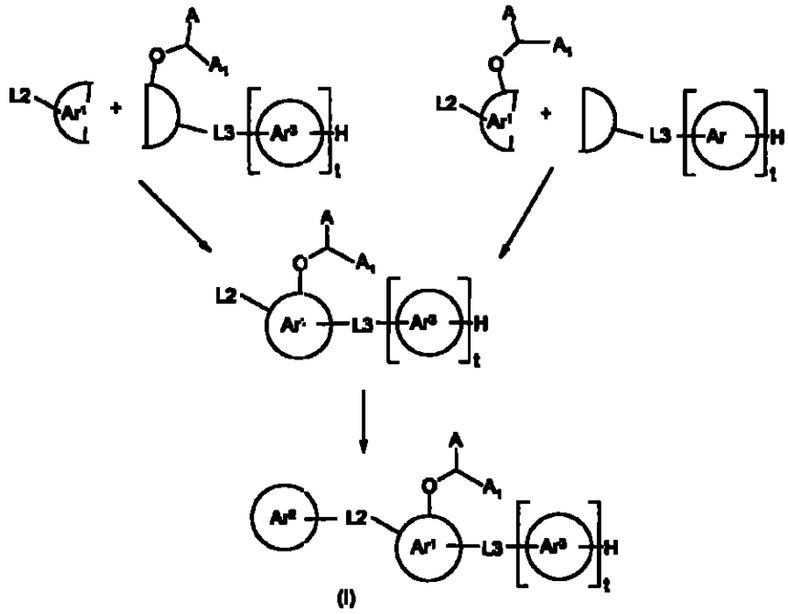

(I)

For example, 1,2,4-triazoles can be made from acylhydrazides and amides or thioamides; 1,2,4-Oxadiazoles from amidoximes and carboxylic esters; 1,3,4-Oxadiazoles from acylhydrazides and carboxylic esters; Thiazoles from thioamides and α-haloketones; Pyridines via various cycloaddition reactions.

The building blocks used in the reactions are either commercially available or made according to standard procedures well-know to one skilled in the art as described in "*Advanced organic chemistry*", 4th Edition (Wiley), J March, "*Comprehensive Organic Transformation*", 2nd Edition (Wiley), R.C. Larock, "*Handbook of Heterocyclic Chemistry*", 2nd Edition (Pergamon), A.R. Katritzky or other suitable literature sources. The Examples herein describe specific strategies for the synthesis of compounds wherein Ar^1 is phenyl. Analogous compounds are accessible by variation of the intermediates used in the Examples.

The following Examples illustrate the preparation of compounds with which this invention is concerned. Some compounds were synthesised, and some were acquired from commercial sources. In the Examples:

General comments:

Microwave chemistry was performed in a Personal Chemistry Emrys Optimizer. NMR spectra were obtained on a Bruker Avance AMX 300 MHz instrument. LC/MS was performed on an Agilent 1100-series instrument. LC/MS methods are as follows:

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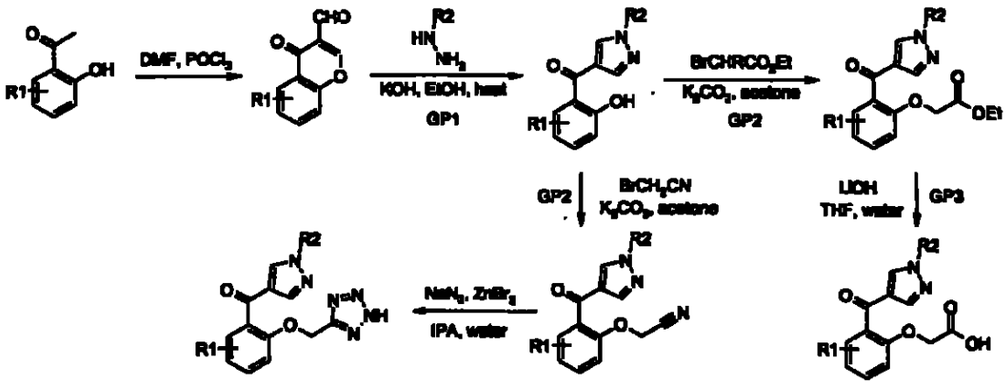
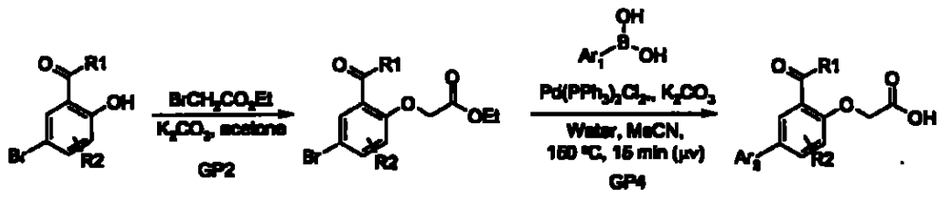
An10p8: Column: XTerra MS C18; Flow: 1.0 mL/min; Gradient: 0-5 min: 15-100% MeCN in water, 5-7½ min: 100% MeCN; Modifier: 5 mM ammonium formate; MS-ionisation mode: API-ES (pos.). An10n8: Column: XTerra MS C18; Flow: 1.0 mL/min; Gradient: 0-5 min: 15-100% MeCN in water, 5-7½ min: 100% MeCN; Modifier: 5 mM ammonium formate; MS-ionisation mode: API-ES (neg.).

General synthetic route I



General synthetic route II



General procedure 1 (GP1):

Condensation of 3-formylchromone with arylhydrazine

The 3-formylchromone (1.0 mmol) and the arylhydrazine (1.0 mmol) in ethanol (3.0 mL) in a reaction tube was added 4.0 M aq. KOH (1.0 mL, 4.0 mmol). The tube was sealed and heated by microwaves to 120 °C for 7 min (420 s). The reaction mixture was added 3% HCl until pH <1 and left to precipitated. The precipitate was filtered off and washed with a small amount of ethanol. The product was used directly or purified by recrystallisation from ethanol or by flash chromatography.

General procedure 2 (GP2):

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Alkylation of phenol

The phenol (0.5 mmol) in acetone (1 mL) was added ethyl bromoacetate (85 mg, 0.5 mmol) or ethyl 2-bromopropionate (91 mg, 0.5 mmol) and K_2CO_3 (75 mg, 0.54 mmol), and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then concentrated in vacuo and the residue was partitioned between water and ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated. The product was used directly or purified by recrystallization from MeOH or by flash chromatography.

General procedure 3 (GP3):

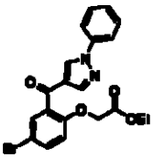
Hydrolysis of ester

The ester (0.10 mmol) in THF (0.5 mL) was added $LiOH \cdot H_2O$ (6.3 mg, 0.15 mmol) in water (0.5 mL). The reaction was stirred at room temperature for >2 h, 3% HCl was added until pH <1, and the mixture was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated to give the product.

General procedure 4 (GP4):

Suzuki coupling/ester hydrolysis

Aryl bromide (0.20 mmol), aryl boronic acid (0.21 mmol) and $Pd(PPh_3)_2Cl_2$ (9 mg, 0.01 mmol) was added MeCN (0.4 mL, degassed) and 1.0 M Na_2CO_3 (0.4 mL, degassed). The reaction mixture was degassed by letting argon through for ½ min and heated by microwaves (150 °C, 300 s), then added 3% HCl until pH <1 and extracted with CH_2Cl_2. The extract was filtered through celite and concentrated, and the residue was purified by solid-phase extraction (pre-packed 1 g SAX columns), or by flash chromatography.



Intermediate-1 **Ethyl 4-bromo-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxyacetate.** Prepared from (5-bromo-2-hydroxy-phenyl)-(1-phenyl-1H-pyrazol-4-yl)ketone and ethyl bromoacetate according to GP2 to give 215 mg (100%) white crystals. The product was used without further purification: LC/MS (an10p8): Rt 6.15 min, *m/z* 429 [M + H]$^+$; ^{1}H NMR ($CDCl_3$): δ 1.26 (t, *J* = 7.1 Hz, 3H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.64 (s, 2H), 6.72 (d, *J* = 8.9 Hz, 1H), 7.34 (m, 1H), 7.46 (m, 2H), 7.53 (dd, *J* = 8.9, 2.5 Hz, 1H),

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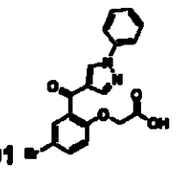
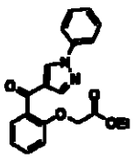
7.59 (d, J = 2.5 Hz, 1H), 7.73-7.78 (m, 2H), 8.17 (s, 1H), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.3, 61.9, 65.5, 114.0, 114.5, 119.8, 125.3, 127.7, 129.8, 131.8, 132.3, 132.7, 134.6, 139.6, 142.7, 154.1, 168.5, 186.9.



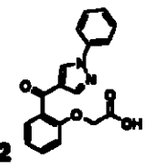
D1

4-Bromo-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxyacetic acid. Prepared from ethyl 4-bromo-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxyacetate (31 mg, 0.072 mmol) according to GP3 to give 28.4 mg (99%) white solid: LC/MS (an10p8): Rt 3.14 min, m/z 401; ^{1}H NMR ($CDCl_3$): δ 3.51 (s, 1H), 4.80 (s, 1H), 6.97 (d, J = 8.7 Hz, 1H), 7.38-7.44 (m, 1H), 7.49-7.55 (m, 2H), 7.64-7.69 (m, 1H), 7.72-7.77 (m, 3H), 8.19 (s, 1H), 8.52 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 67.2, 115.1, 116.6, 120.1, 124.5, 128.4, 130.0, 131.9, 133.3, 136.2, 139.2, 143.3, 155.2, 169.9, 187.6.



Intermediate-2

Ethyl 2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxyacetate. Prepared from (2-hydroxyphenyl)-(1-phenyl-1H-pyrazol-4-yl)ketone (264 mg, 1.0 mmol) and ethyl bromoacetate according to GP2 to give 235 mg (67%) of the title compound as white solid: ^{1}H NMR ($CDCl_3$): δ 1.26 (t, J = 7.1 Hz, 3H), 4.24 (q, J = 7.1 Hz, 2H), 4.67 (s, 2H), 6.84 (d, J = 8.3 Hz, 1H), 7.10 (ts, J = 7.4, 0.8 Hz, 1Hz), 7.29-7.38 (m, 1H), 7.41-7.53 (m, 4H), 7.72-7.78 (m, 2H), 8.18 (s, 1H), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.3, 61.7, 65.4, 112.2, 118.8, 119.3, 119.7, 120.0, 122.1, 125.8, 127.6, 129.7, 129.9, 130.1, 130.6, 131.8, 132.1, 136.3, 139.7, 142.8, 155.0, 168.9, 188.7.



D2

2-(1-Phenyl-1H-pyrazole-4-carbonyl)phenoxyacetic acid. Prepared from ethyl 2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxyacetate according to GP3 and purified by column chromatography (SiO_2, EtOAc:heptane, 1:1) to give 15 mg (56%) of the title

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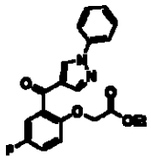
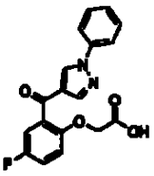
compound as white solid: LC/MS (an10n8): Rt 2.90 min, *m/z* 321.0 [M-H]⁻; ^{1}H NMR ($CDCl_3$): δ 4.83 (s, 2H), 7.10 (d, *J* = 8.3 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.35-7.42 (m, 1H), 7.46-7.53 (m, 2H), 7.54-7.61 (m, 1H), 7.66 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.70-7.75 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 67.7, 115.5, 120.1, 122.6, 124.7, 128.3, 128.6, 129.9, 131.0, 131.9, 134.0, 139.3, 143.5, 156.6, 170.4, 189.3.



Intermediate-3

Ethyl 4-fluoro-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxyacetate. Prepared from 4-fluoro-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenol (282 mg) and ethyl bromoacetate according to GP2 to give 335 mg (91%) yellow solid: LC/MS (an10n8): Rt 3.16, *m/z* 339.0 [M-H]⁻; ^{1}H NMR ($CDCl_3$): δ 1.26 (t, *J* = 7.0 Hz, 3H), 4.23 (t, *J* = 7.1 Hz, 2H), 4.63 (s, 2H), 6.81 (dd, *J* = 9.0, 4.0 Hz, 1H), 7.13 (ddd, *J* = 8.9, 4.5, 3.0 Hz, 1H), 7.21 (dd, *J* = 8.1, 3.2 Hz, 1H), 7.31-7.37 (m, 1H), 7.24-7.50 (m, 2H), 7.72-7.78 (m, 2H), 8.18 (s, 1H), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.3, 61.8, 66.1, 114.0 (d, J_{CF} = 7.6 Hz), 116.8 (d, J_{CF} = 24.5 Hz), 118.3 (d, J_{CF} = 23.5 Hz), 119.7, 125.2, 127.7, 129.7, 131.8, 139.6, 142.8, 151.1 (d, J_{CF} = 2.2 Hz), 157.6 (d, J_{CF} = 241.1 Hz), 168.7, 187.1.



D3

4-Fluoro-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxyacetic acid. Prepared from ethyl 4-fluoro-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxyacetate (31 mg) according to GP3 to give 30 mg (100%) of a pale yellow solid: LC/MS (an10n8): Rt 3.16, *m/z* 339.0 [M-H]⁻; ^{1}H NMR ($CDCl_3$): δ 4.60 (s, 2H), 6.90 (dd, *J* = 9.2 Hz, 1H), 7.08-7.17 (m, 1H), 7.21 (dd, *J* = 7.9, 3.0 Hz, 1H), 7.28-7.35 (m, 1H), 7.38-7.48 (m, 2H), 7.85 (d, *J* = 7.5 Hz, 2H), 8.06 (s, 1H), 8.44 (s, 1H).

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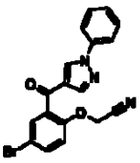
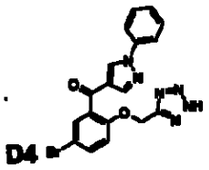


Intermediate-4

4-Bromo-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxyacetonitrile. (5-Bromo-2-hydroxy-phenyl)-(1-phenyl-1H-pyrazol-4-yl)ketone (342 mg) was added bromoacetonitrile (122 mg), acetone (2 mL) and K_2CO_3 (140 mg), and the reaction was stirred for 24 h. The reaction mixture was concentrated and the residue was partitioned between water and EtOAc. The organic phase was washed with brine, dried (MgSO4) and concentrated to give 383 mg (100%) yellow solid, that was used directly in the next step: LC/MS (an10p8): Rt 4.39 min, *m/z* 381.5 $[M + 1]^+$; ^1H NMR ($CDCl_3$): δ 4.80 (s, 2H), 7.07 (d, *J* = 8.7 Hz, 1H), 7.35-7.42 (m, 1H), 7.45-7.54 (m, 2H), 7.60-7.69 (m, 2H), 7.69-7.75 (m, 2H), 8.03 (s, 1H), 8.31 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 55.2, 114.7, 116.6, 116.7, 120.1, 125.1, 128.2, 129.9, 131.0, 132.6, 133.2, 135.0, 139.3, 142.7, 153.0, 186.0.



D4

[5-Bromo-2-(2H-tetrazol-5-ylmethoxy)phenyl](1-phenyl-1H-pyrazol-4-yl)ketone. [4-Bromo-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxy]-acetonitrile (38 mg) was added NaN3 (66 mg), $ZnBr_2$ (59 mg), isopropanol (1.3 mL) and water (1.6 mL), and the reaction mixture was heated to reflux for 1 h. The mixture was added 3% HCl (1 mL) and EtOAc (4 mL) and stirred until two clear phases appeared. The aqueous phase was added 3% HCl until pH <1 and extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated to give 47 mg white foam: LC/MS (an10n8): Rt 2.93, *m/z* 243.0 $[M - H]^-$; ^1H NMR ($CDCl_3$): δ 5.69 (s, 2H), 7.13 (d, *J* = 8.6 Hz, 1H), 7.39-7.45 (m, 1H), 7.49-7.56 (m, 2H), 7.62-7.71 (m, 2H), 7.71-7.79 (m, 1H), 8.13 (s, 1H), 8.45 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 63.3, 115.6, 117.7, 120.3, 124.5, 128.6, 130.0, 131.2, 132.0, 132.9, 136.3, 139.1, 143.5, 154.7, 188.4.

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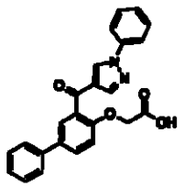
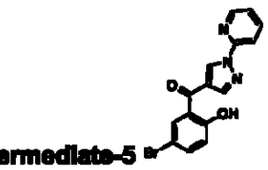


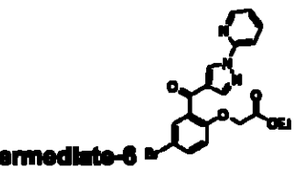
D5

3-(1-Phenyl-1H-pyrazole-4-carbonyl)biphenyl-4-yloxyacetic acid. Prepared from ethyl [4-bromo-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxy]acetate and phenylboronic acid according to GP4: LC/MS (an10p8): Rt 1.05 min, *m/z* 398.6 $[M-H]^-$; ^1H NMR ($CDCl_3$): δ 4.86 (s, 2H), 7.17 (d, *J* = 8.6 Hz, 1H), 7.35-7.57 (m, 8H), 7.70-7.75 (m, 2H), 7.78 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.84 (d, *J* = 2.3 Hz, 1H), 8.20 (s, 1H), 8.54 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 67.7, 115.8, 120.1, 124.8, 127.1, 128.0, 128.3, 129.1, 129.3, 129.4, 129.9, 132.3, 136.2, 139.3, 139.3, 143.5, 155.8, 170.4, 189.3.



Intermediate-5

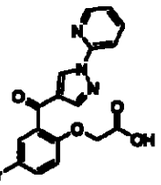
(5-Bromo-2-hydroxyphenyl)-(1-pyridin-2-yl-1H-pyrazol-4-yl)ketone. To a suspension of 6-bromo-3-formylchromone (253 mg) in isopropanol (3 mL) and CH_2Cl_2 (2 mL) was added 2-hydrazinopyridine (109 mg), and the mixture was stirred for 15 min to form a yellow slurry. The slurry was added KOH (0.25 g) in water (0.25 mL), and the reaction was heated to reflux for 1 h. The reaction mixture was diluted with water, added 3% HCl until pH <1 and extracted with CH_2Cl_2 (2x). The extract was washed with water and brine, dried ($MgSO_4$) and concentrated to give 342 mg orange foam, which was purified by flash chromatography (SiO_2, EA:Hep, 1:1) to give 53 mg (15%) yellow solid: LC/MS (an10p8): Rt 5.0 min, *m/z* 343.5 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 6.98 (d, *J* = 8.9 Hz, 1H), 7.31 (ddd, *J* = 7.3, 4.9, 0.9 Hz, 1H), 7.60 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.87-7.93 (m, 1H), 8.03 (d, *J* = 2.4 Hz, 1H), 8.04-8.09 (m, 1H), 8.02 (s, 1H), 8.47-8.51 (m, 1H), 9.13 (s, 1H), 11.94 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 110.9, 113.3, 120.8, 121.6, 122.8, 123.1, 130.5, 133.5, 138.9, 139.3, 143.3, 148.7, 161.9, 191.4.



Intermediate-6

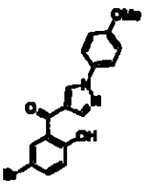
34

Ethyl 4-bromo-2-(1-pyridin-2-yl-1H-pyrazole-4-carbonyl)phenoxyacetate. Prepared from (5-bromo-2-hydroxyphenyl)-(1-pyridin-2-yl-1H-pyrazol-4-yl)ketone (43 mg) according to GP2 and purified by flash chromatography (SiO_2, EtOAc:heptane, 1:2) to give 34 mg (63%) of a pale yellow solid: LC/MS (an10p8): Rt 4.9 min, *m/z* 429.5 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 1. 23 (t, *J* = 7.2 Hz, 3H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.62 (s, 2H), 6.76 (d, *J* = 8.6 Hz, 1H), 7.23-7.28 (m, 1H), 7.53 (ddd, *J* = 8.9, 2.6, 1.0 Hz, 1H), 7.58 (d, *J* = 2.5 Hz, 1H), 7.82-7.99 (m, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 8.19 (s, 1H), 8.40-8.44 (m, 1H), 8.99 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.3, 61.8, 66.1, 114.5, 114.7, 131.6, 132.3, 132.4, 134.6, 139.1, 148.5, 154.4, 168.3, 187.1.



D8

4-Bromo-2-(1-pyridin-2-yl-1H-pyrazole-4-carbonyl)phenoxyacetic acid. Prepared from ethyl [4-bromo-2-(1-pyridin-2-yl-1H-pyrazole-4-carbonyl)phenoxy]-acetate (21 mg) according to GP3 to give 20 mg white foam: LC/MS (an10n8): Rt 2.8 min, *m/z* . 401.9 $[M - H]^-$; ^1H NMR ($CDCl_3$): δ 4.79 (s, 2H), 6.98 (d, *J* = 8.9 Hz, 1H), 7.28-7.34 (m, 1H), 7.67 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.75 (d, *J* = 2.5 Hz, 1H), 7.86-7.94 (m, 1H), 8.02-8.08 (m, 1H), 8.22 (s, 1H), 8. 43-8.48 (m, 1H), 9.04 (s, 1H).



Intermediate-7

(5-Bromo-2-hydroxy-phenyl)-[1-(4-methoxyphenyl)-1H-pyrazol-4-yl]ketone. To a suspension of 6-bromo-3-formylcromone (253 mg, 1.0 mmol) in ethanol (5 mL) was added 4-methoxyphenylhydrazine (175 mg, 1.0 mmol), and the mixture was stirred under argon for 12 h an orange slurry. The slurry was added KOH (280 mg) in water (0.25 mL), and the reaction was heated to reflux for 1½ h. The reaction mixture was added 3% HCl until pH <1 and left on ice to precipitate. The precipitate was filtered off and washed with a small amount of cold ethanol to give 256 mg (69%) beige solid that was used without further purification: LC/MS (an10p8): Rt 5.0 min, *m/z* 372.5 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 3.88 (s, 3H), 6.98 (d, *J* = 8.9 Hz, 1H), 7.03 (d, *J* = 9.1 Hz, 2H), 7.59 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.66 (d, *J* = 9.1 Hz, 2H), 8.02 (d, *J* = 2.4 Hz, 1H),

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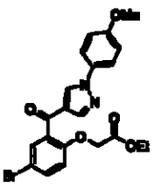
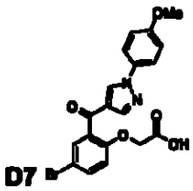
8.15 s, 1H), 8.39 (s, 1H), 11.92 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 55.9, 110.9, 115.0, 120.8, 121.6, 121.8, 122.9, 130.7, 133.5, 138.8, 142.3, 159.7, 161.6.



Intermediate-8

Ethyl 4-bromo-2-[1-(4-methoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxyacetate. Prepared from (5-bromo-2-hydroxyphenyl)-[1-(4-methoxyphenyl)-1H-pyrazol-4-yl]ketone and ethyl bromoacetate according to GP2: LC/MS (an10p8): Rt 4.59 min, *m/z* 458.4/460.4 $[M + H]^+$; ^{1}H NMR ($CDCl_3$): δ 1.26 (t, *J* = 7.1 Hz, 3H), 3.84 (s, 3H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.62 (s, 2H), 6.72 (d, *J* = 8.9 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 7.52 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.58 (d, *J* = 2.5 Hz, 1H), 7.64 (d, *J* = 8.9 Hz, 2H), 8.13 (s, 1H), 8.46 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.3, 55.8, 61.9, 65.6, 114.1, 114.4, 114.8, 121.4, 125.0, 131.6, 132.4, 132.6, 133.2, 134.5, 142.5, 154.1, 159.2, 168.5, 186.9.



D7

4-Bromo-2-[1-(4-methoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from ethyl 4-bromo-2-[1-(4-methoxy-phenyl)-1H-pyrazole-4-carbonyl]phenoxyacetate (23 mg) according to GP3 to give 21 mg (97%) white foam: LC/MS (an10n8): Rt 5.76 min, *m/z* 428.9 $[M - H]^-$; ^{1}H NMR ($CDCl_3$): δ 3.86 (s, 3H), 4.77 (s, 2H), 6.94 (d, *J* = 8.9 Hz, 1H), 6.99 (d, *J* = 9.2 Hz, 2H), 7.59-7.66 (m, 3H), 7.71 (d, *J* = 2.4 Hz, 1H), 8.14 (d, *J* = 0.6 Hz, 1H), 8.40 (d, *J* = 0.6 Hz, 1H) ^{13}C NMR ($CDCl_3$): δ 55.9, 67.2, 115.0, 115.1, 116.6, 121.8, 124.2, 130.7, 131.8, 132.7, 133.2, 136.1, 143.2, 155.2, 159.7, 169.9, 187.6.

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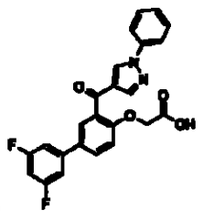
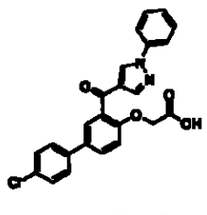


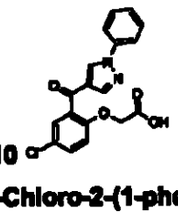
D8

[3',5'-Difluoro-3-(1-phenyl-1H-pyrazole-4-carbonyl)biphenyl-4-yloxy]acetic acid. Prepared ethyl [4-bromo-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxy]acetate and 3,5-difluorophenylboronic acid according to GP4: LC/MS (an10n8): Rt 3.03 min, *m/z* 434.5 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.85 (s, 2H), 6.81 (td, *J* = 8.9, 2.3 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.9 Hz, 1H), 7.41 (d, *J* = 6.6 Hz, 1H), 7.48 (s, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.66-7.78 (m, 4H), 8.23 (s, 1H), 8.57 (s, 1H)



D9

[4'-Chloro-3-(1-phenyl-1H-pyrazole-4-carbonyl)biphenyl-4-yloxy]acetic acid. Prepared from ethyl [4-bromo-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxy]acetate and 4-chlorophenylboronic acid according to GP4: LC/MS (an10n8): Rt 3.08 min, *m/z* 432.5 $[M - H]^-$.



D10

[4-Chloro-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxy]acetic acid. Prepared from (2-hydroxy-5-chlorophenyl)-(1-phenyl-1H-pyrazol-4-yl)-methanone and ethyl bromoacetate according to GP2 and GP3: LC/MS (an10p8): Rt 3.08 min, *m/z* 356.6 $[M + 1]^+$; ^1H NMR ($CDCl_3$): δ 4.75 (s, 2H), 6.95 (d, *J* = 8.9 Hz, 1H), 7.33-7.41 (m, 1H), 7.44-7.52 (m, 3H), 7.55 (d, *J* = 2.6 Hz, 1H), 7.69-7.75 (m, 2H), 8.18 (s, 1H), 8.52 (s, 1H).

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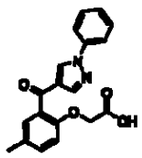
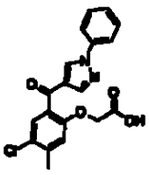


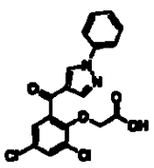
D11

[4-Methyl-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxy]acetic acid. Prepared from (2-hydroxy-5-methylphenyl)-(1-phenyl-1H-pyrazol-4-yl)-methanone and ethyl bromoacetate according to GP2 and GP3: LC/MS (an10p8): Rt 3.08 min, *m/z* 356.6 $[M + 1]^+$; ^1H NMR ($CDCl_3$): δ 2.37 (s, 3H), 4.78 (s, 2H), 6.97 (d, *J* = 9.0 Hz, 1H), 7.33-7.51 (m, 5H), 7.73 (d, *J* = 6 Hz, 2H), 8.16 (s, 1H), 8.51 (s, 1H), 11.21 (br s, 1H)



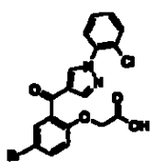
D12

[4-Chloro-3-methyl-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxy]acetic acid. Prepared from (3-chloro-6-hydroxy-2-methyl-phenyl)-(1-phenyl-1H-pyrazol-4-yl)methanone and ethyl bromoacetate according to GP2 and GP3: LC/MS (an10p8): Rt 3.34 min, *m/z* 370.6 $[M + 1]^+$; ^1H NMR ($CDCl_3$): δ 2.44 (s, 3H), 4.77 (s, 2H), 6.92 (s, 1H), 7.39 (d, *J* = 9.0 Hz, 1H), 7.46-7.51 (m, 2H), 7.59 (s, 1H), 7.72 (d, *J* = 9.0 Hz, 2H), 8.19 (s, 1H), 8.52 (s, 1H), 10.39 (br s, 1H)



D13

[2,4-Dichloro-6-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxy]acetic acid. Prepared from (3,5-dichloro-2-hydroxyphenyl)-(1-phenyl-1H-pyrazol-4-yl)methanone and ethyl bromoacetate according to GP2 and GP3: LC/MS (an10p8): Rt 3.27 min, *m/z* 390.5 $[M + 1]^+$; ^1H NMR ($CDCl_3$): δ 4.72 (s, 2H), 7.38-7.51 (m, 4H), 7.57-7.58 (m, 1H), 7.70 (d, *J* = 8.1 Hz, 2H), 8.06 (s, 1H), 8.36 (s, 1H), 9.23 (br s, 1H).



D14

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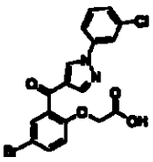
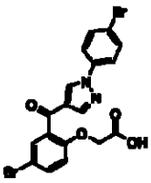
4-Bromo-2-[1-(2-chloro-phenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-bromo-3-formylchromone, 2-chlorophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8) Rt 3.02 min, *m/z* 436.4 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.76 (s, 2H), 6.94 (d, *J* = 8.9 Hz, 1H), 7.39-7.47 (m, 2H), 7.53-7.67 (m, 3H), 7.74 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.21 (s, 1H), 8.40 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 67.2, 115.0, 116.7, 123.9, 127.9, 128.2, 128.7, 130.55, 130.59, 131.1, 133.3, 136.2, 136.6, 137.1, 143.1, 155.2, 170.0, 187.5.



D15

4-Bromo-2-[1-(3-chloro-phenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-bromo-3-formylchromone and 3-chlorophenylhydrazine according to: LC/MS (an10p8) Rt 3.57 min, *m/z* 436.4 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.76 (s, 2H), 6.90 (d, *J* = 8.9 Hz, 1H), 7.34 (dm, *J* = 8.8 Hz, 1H), 7.41 (t, *J* = 8.3 Hz, 1H), 7.58-7.66 (m, 2H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.78 (m, 1H), 8.17 (s, 1H), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 66.8, 115.1, 116.2, 117.9, 120.4, 124.9, 128.3, 130.7, 131.0, 132.0, 133.2, 135.8, 136.1, 140.2, 143.4, 155.0, 170.1, 187.4.



D16

4-Bromo-2-[1-(4-bromophenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-bromo-3-formylchromone, 4-bromophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8) Rt 3.75 min, *m/z* 480.3 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.75 (s, 2H), 6.89 (d, *J* = 8.9 Hz, 1H), 7.59-7.65 (m, 5H), 7.66-7.69 (m, 1H), 8.16 (s, 1H), 8.50 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 66.5, 115.0, 115.9, 121.5, 121.8, 124.9, 130.8, 131.8, 133.0, 133.1, 135.9, 138.2, 143.4, 154.8, 170.6, 187.4.

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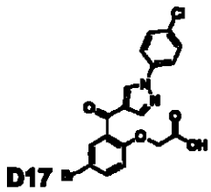
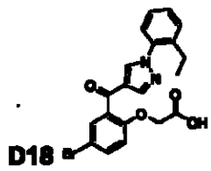


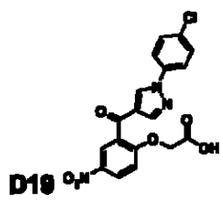
D17

4-Bromo-2-[1-(4-chlorophenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-bromo-3-formylchromone, 4-chlorophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 3.53 min, *m/z* 436.4 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.74 (s, 2H), 6.88 (d, *J* = 8.9 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.61 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.63-7.70 (m, 3H), 8.17 (s, 1H), 8.49 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 66.4, 114.9, 115.7, 121.2, 124.9, 130.0, 130.9, 131.9, 133.1, 133.9, 135.9, 137.7, 143.3, 154.7, 170.8, 187.4.



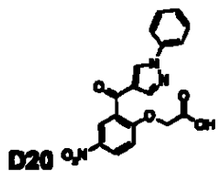
D18

4-Bromo-2-[1-(2-ethylphenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-bromo-3-formylchromone, 2-ethylphenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.58 min, 427.0 *m/z* $[M - H]^+$; ^1H NMR ($CDCl_3$): δ 1.14 (t, *J* = 7.5 Hz, 3H), 2.58 (q, *J* = 7.5, 2H), 4.76 (s, 2H), 6.93 (d, *J* = 8.9 Hz, 1H), 7.28-7.34 (m, 2H), 7.37-7.48 (m, 2H), 7.62 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.72 (d, *J* = 2.5 Hz, 1H), 8.15 (s, 1H), 8.18 (s, 1H).



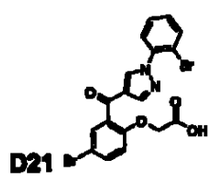
D19

4-Nitro-2-[1-(4-chlorophenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-nitro-3-formylchromone, 4-chlorophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 2.44 min, *m/z* 401.7 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.84 (d, 2H), 7.1 (d, *J* = 9.6 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 2H), 8.22 (s, 1H), 8.36 (d, *J* = 9.2 Hz, 1H), 8.41 (s, 1H), 8.53 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 65.6, 112.9, 121.3, 124.9, 126.2, 126.2, 130.0, 130.1, 131.9, 134.1, 137.6, 142.4, 143.3, 159.7, 169.9, 186.2.



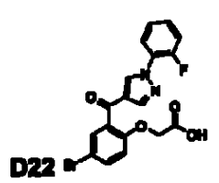
D20

4-Nitro-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxyacetic acid. Prepared from 6-nitro-3-formylchromone, 2-ethylphenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8) Rt 2.05 min, *m/z* 367.8 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.83 (s, 2H), 7.01 (d, *J* = 9.0 Hz, 1H), 7.34-7.42 (m, 1H), 7.44-7.53 (m, 1H), 7.65-7.72 (m, 1H), 8.26 (s, 1H), 8.34 (dd, *J* = 9.0, 2.6 Hz, 1H), 8.41 (d, *J* = 2.6 Hz, 1H), 8.53 (s, 1H).



D21

4-Bromo-2-[1-(2-bromophenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-bromo-3-formylchromone, 2-bromophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 3.38 min, *m/z* 480.6 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.75 (s, 2H), 6.91 (d, *J* = 9.0 Hz, 1H), 7.34-7.64 (m, 6H), 7.73-7.74 (m, 2H), 8.22 (s, 1H), 8.36 (s, 1H).



D22

4-Bromo-2-[1-(2-fluorophenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-bromo-3-formylchromone, 2-fluorophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 3.36 min, *m/z* 418.7 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.75 (s, 2H), 6.91 (d, *J* = 8.9 Hz, 1H), 7.21-7.42 (m, 3H), 7.62 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.70 (d, *J* = 2.5 Hz, 1H), 7.85-7.92 (m, 1H), 8.20 (s, 1H), 8.51 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 66.9, 115.0, 116.3, 117.1, 117.4, 124.62, 124.63, 125.0, 125.39, 125.44, 127.4, 127.5, 129.6, 129.7, 130.8, 133.2, 135.8, 136.8, 143.0, 152.3, 155.0, 155.6, 170.5, 187.4.

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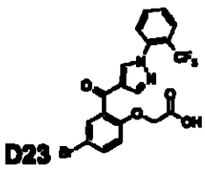
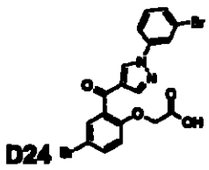


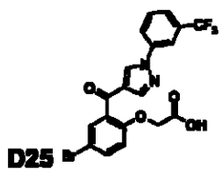
D23

4-Bromo-2-[1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-bromo-3-formylchromone, 2-trifluoromethylphenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 3.44 min, *m/z* 468.7 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.72 (s, 2H), 6.89 (d, *J* = 8.9 Hz, 1H), 7.53-7.75 (m, 5H), 7.84 (d, *J* = 7.9 Hz, 1H), 8.20 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 66.8, 114.9, 116.2, 124.3, 126.3, 126.7, 127.58, 127.64, 129.2, 130.3. 130.7, 133.2, 136.0, 136.9, 143.1, 155.0, 170.3, 187.4.



D24

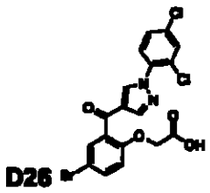
4-Bromo-2-[1-(3-bromophenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-bromo-3-formylchromone, 3-bromophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 4.29 min, *m/z* 480.5 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.79 (s, 2H), 6.95 (d, *J* = 9.0 Hz, 1H), 7.28-7.40 (m, 1H), 7.53 (d, *J* = 9 Hz, 1H), 7.65 -7.73 (m, 3H), 7.96 (s, 1H), 8.18 (s, 1H); 8.51 (s, 1H).



D25

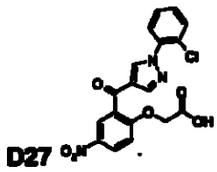
4-Bromo-2-[1-(3-trifluoromethylphenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-bromo-3-formylchromone, 3-trifluoromethylphenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 4.54 min, *m/z* 468.7 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.76 (s, 2H), 6.89 (d, *J* = 8.9 Hz, 1H), 7.57-7.66 (m, 3H), 7.68 (d, *J* = 2.4 Hz, 1H), 7.89-7.96 (m, 1H), 8.04 (s, 1H), 8.20 (s, 1H), 8.59 (s, 1H), 9.15 (br s, 1H).

42



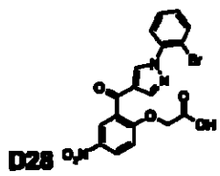
D26

4-Bromo-2-[1-(2,4-dichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-bromo-3-formylchromone, 2,4-dichlorophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 4.35 min, *m/z* 468.6 $[M + H]^+$; ^1H NMR (DMSO-d_6): δ 4.76 (s, 2H), 7.03 (d, *J* = 9.0 Hz, 1H), 7.52 (m, 1H), 7.57-7.69 (m, 3H), 7.89 (m, 1H), 8.19 (s, 1H), 8.69 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 55.8, 103.6, 106.2, 115.2, 119.5, 120.6, 120.7, 121.1, 122.4, 125.5, 125.6, 127.1, 128.3, 133.4, 145.1, 160.9, 177.4.



D27

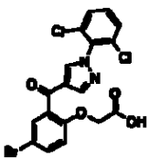
4-Nitro-2-[1-(2-chlorophenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-nitro-3-formylchromone 2-chlorophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 2.42 min, *m/z* 401.8 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.83 (s, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 7.42-7.48 (m, 2H), 7.56-7.63 (m, 2H), 8.34-8.40 (m, 2H), 8.5 (s, 2H).



D28

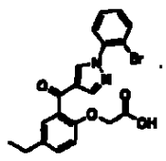
4-Nitro-2-[1-(2-bromophenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-nitro-3-formylchromone, 2-bromophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 2.33 min, *m/z* 445.9 $[M - H]^+$; ^1H NMR ($CDCl_3$): δ 4.85 (s, 2H), 7.04 (d, *J* = 9 Hz, 1H), 7.37-7.81 (m, 4H), 8.32-8.44 (m, 3H), 8.50 (s, 1H).

43



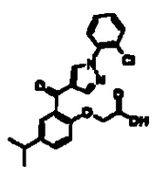
D29

4-Bromo-2-[1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-bromo-3-formylchromone, 2,6-dichlorophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 2.56 min, *m/z* 468.8 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.72, 6.88 (d, *J* = 8.9 Hz, 1H), 7.37-7.44 (m, 1H), 7.45-7.52 (m, 2H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.70 (m, 1H), 8.14 (s, 1H), 8.26 (s, 1H).



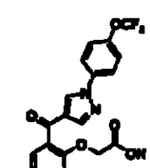
D30

4-Ethyl-2-[1-(2-bromophenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-ethyl-3-formylchromone, 2-bromophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 2.88 min, *m/z* 428.8 $[M + H]^+$.



D31

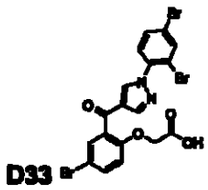
2-[1-(2-Chlorophenyl)-1H-pyrazole-4-carbonyl]-4-isopropylphenoxyacetic acid. Prepared from 6-isopropyl-3-formylchromone, 2-chlorophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 2.83 min, *m/z* 398.8 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 1.28 (d, *J* = 7.0 Hz, 6H), 2.93 (septet, *J* = 6.9 Hz, 1H), 4.82 (s, 2H), 7.04 (d, *J* = 8.5 Hz, 1H), 7.40-7.65 (m, 6H), 8.28 (s, 1H), 8.40 (s, 1H).



D32

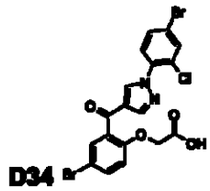
44

{4-Bromo-2-[1-(4-trifluoromethoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxy-acetic acid. Prepared from 6-bromo-3-formylchromone, 4-trifluoromethoxy-phenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 3.24 min, *m/z* 484.6 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.75 (s, 2H), 6.89 (d, *J* = 8.9 Hz, 1H), 7.34 (d, *J* = 9.0 Hz, 2H), 7.61 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.67 (m, 1H), 7.72-7.80 (m, 2H), 8.17 (s, 1H), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 66.5, 115.0, 115.8, 121.4, 122.5, 125.0, 130.8, 132.0, 133.1, 136.0, 137.6, 143.4, 148.6, 148.7, 154.8, 170.8, 187.4.



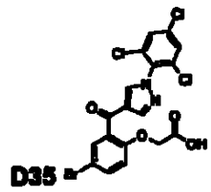
D33

4-Bromo-2-[1-(2,4-dibromophenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-bromo-3-formylchromone, 2,4-dibromophenylhydrazine according and ethyl bromoacetate to GP1, GP2 and GP3: LC/MS (an10p8): Rt 3.41 min, *m/z* 556.4 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.75 (s, 2H), 6.92 (d, *J* = 9.0 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.63 (m, 2H), 7.73 (d, *J* = 2.5 Hz, 1H), 7.92 (d, *J* = 2.1 Hz, 1H), 8.22 (s, 1H), 8.37 (s, 1H).



D34

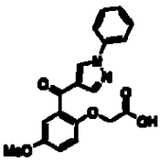
4-Bromo-2-[1-(4-bromo-2-chlorophenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-bromo-3-formylchromone, 4-bromo-2-chlorophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 3.34 min, *m/z* 512.5 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.78 (s, 2H), 6.95 (d, *J* = 8.6 Hz, 1H), 7.51-7.78 (m, 5H), 8.21 (s, 1H), 8.42 (s, 1H).



D35

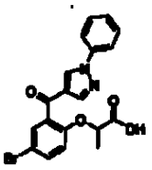
45

4-Bromo-2-[1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-bromo-3-formylchromone, 2,4,6-trichlorophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 3.35 min, *m/z* 502.6 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.91 (s, 2H), 7.05 (d, *J* = 8.9 Hz, 1H), 7.68 (s, 2H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.88 (s, 1H), 8.31 (s, 1H), 8.43 (s, 1H), 9.03 (br s, 1H).



D38

4-Methoxy-2-[1-phenyl-1H-pyrazole-4-carbonyl]phenoxyacetic acid. Prepared from 6-bromo-3-formylchromone, 2,4-dichlorophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.46 min, *m/z* 350.9 $[M - H]^+$; ^1H NMR ($CDCl_3$): δ 3.81 (s, 3H), 4.77 (s, 2H), 7.02-7.16 (m, 3H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 8.17 (s, 1H), 8.52 (s, 1H).

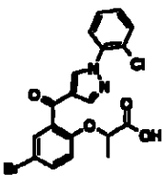


D37

2-[4-Bromo-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxy]propionic acid. Prepared from (5-bromo-2-hydroxyphenyl)-(1-phenyl-1H-pyrazol-4-yl)ketone and ethyl 2-bromopropionate according to GP2 and GP3: LC/MS (an10p8) Rt 2.51 min, *m/z* 415 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 1.65 (d, *J* = 6.8 Hz, 3H), 4.93 (q, *J* = 6.8 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 1H), 7.35-7.43 (m, 1H), 7.46-7.53 (m, 2H), 7.62 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.70-7.76 (m, 3H), 8.17 (s, 1H), 8.52 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 18.8, 75.2, 114.8, 116.7, 120.1, 124.4, 128.3, 130.0, 133.3, 136.2, 139.2, 143.3, 155.0, 173.1, 187.8.

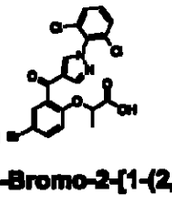
2(*S*)-[4-Bromo-2-(1-phenyl-1H-pyrazole-4-carbonyl)-phenoxy]-propionic acid. (5-Bromo-2-hydroxyphenyl)-(1-phenyl-1H-pyrazol-4-yl)ketone (100 mg, 0.29 mmol), (R)-(+)-bromoacetic acid (44 mg, 0.29 mmol) ethyl 2-bromopropionate and K2CO3 (80 mg, 0.58 mmol) in acetone was stirred at room temperature for 16 h. The reaction mixture was concentrated and the residue was partitioned between EtOAc and dilute HCl (pH ~1). The organic phase was dried (Na_2SO_4) and concentrated, and the

residue was purified by flash chromatography (EtOAc:heptane, 1:1) to yield 55 mg (46%) of the title compound: Chiral HPLC (Column: Ciracel OD (0.46 cm x 24 cm); Eluent: isocratic, 85% hexane + 15% 2-propanol + 0.1% TFA; Flow 0.5 mL/min) Rt 15.7 min, >90% e.e. (Racemic material eluates with baseline separation of enantiomeres: Rt 15.7 and 16.7 min.) MS and NMR spectra correspond to racemic material.



D38

2-{4-Bromo-2-[1-(2-chlorophenyl)-1-H-pyrazole-4-carbonyl]phenoxy}propionic acid. Prepared from 6-bromo-3-formylchromone, 2-chlorophenylhydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.56 min, 448.9 *m/z* $[M - H]^+$; ^1H NMR ($CDCl_3$): δ 1.65 (d, *J* = 7.0 Hz, 3H), 4.93 (q, *J* = 7.0 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 1H), 7.41-7.47 (m, 2H), 7.55-7.64 (m, 3H), 7.74 (s, 1H), 8.23 (s, 1H), 8.42 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 18.9, 75.4, 115.0, 117.0, 124.1, 128.1, 128.4, 128.9, 130.7, 131.3, 133.6,136.4,136.8,137.3, 143.3, 155.2, 173.5, 188.0.



D39

2-{4-Bromo-2-[1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}-propionic acid. Prepared from 6-bromo-3-formylchromone, 2,6-dichlorophenyl-hydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.55 min, 482.9 *m/z* $[M - H]^+$; ^1H NMR ($CDCl_3$): δ 1.65 (d, *J* = 6.8 Hz, 3H), 4.91 (q, *J* = 6.8 Hz, 1H), 6.93 (d, *J* = 8.9 Hz, 1H), 7.41-7.53 (m, 3H), 7.62 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.74 (d, *J* = 2.4, 1H), 8.17 (s, 1H), 8.28 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 18.9, 75.1, 114.9, 116.8, 124.2, 129.3, 130.7, 132.0,133.6, 134.5,135.6, 136.4, 137.6, 143.6, 155.1, 173.6, 187.8.

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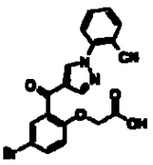
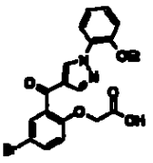


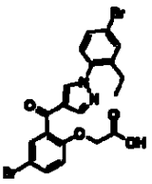
D40

{4-Bromo-2-[1-(2-cyano-phenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid. Prepared from 6-bromo-3-formylchromone, 2-hydrazinobenzonitril (prepared according to van der Mey, et al. *J. Med. Chem.* 2003, 2008-2016) and ethyl bromoacetate according to GP1, GP2 and GP3: ^{1}H NMR (DMSO-d_6): δ 4.72 (s, 2H), 7.17 (d, J = 8.9 Hz, 1H), 7.36 (t, *J* = 15.1, 7.3 Hz, 1 H), 7.8 (m, 4H), 8.29 (d, *J* = 8.3 Hz, 1 H), 9.03 (s, 1 H), 9.66 (s, 1H), 13.04 (br s, 1H).



D41

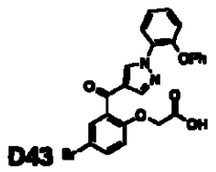
{4-Bromo-2-[1-(2-ethoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid. Prepared from 6-bromo-3-formylchromone, 2-ethoxyphenylhydrazine and ethyl 2-bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 2.33 min, *m/z* 446.7 [M + H]$^+$; ^{1}H NMR ($CDCl_3$): δ 1.47 (t, *J* = 7.0 Hz, 3H), 4.18 (q, *J* = 7.0 Hz, 2H), 4.78 (s, 2H), 6.97 (d, *J* = 8.9 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 2H), 7.36 (td, *J* = 7.9, 1.8 Hz, 1H), 7.64 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.79 (d, *J* = 2.5 Hz, 1H), 7.80 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.22 (s, 1H), 8.65 (s, 1H).



D42

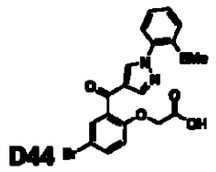
{4-Bromo-2-[1-(4-bromo-2-ethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid. Prepared from 6-bromo-3-formylchromone, 4-bromo-2-ethylphenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.78 min, *m/z* 506.6 [M – H]$^-$; ^{1}H NMR ($CDCl_3$): δ 1.16 (td, *J* = 7.8, 2.4 Hz, 3H), 2.58 (qd, *J* = 7.8, 1.8 Hz, 2H), 4.77 (s, 2H), 6.94 (d, *J* = 9.0 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.56 (s, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.72 (s,1H), 8.15 (s, 1H), 8.19 (s, 1H).

48



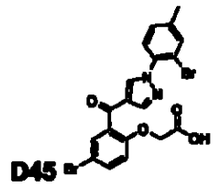
D43

{4-Bromo-2-[1-(2-phenoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid. Prepared from 6-bromo-3-formylchromone, 4-bromo-2-ethylphenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.77 min, *m/z* 492.7 [M – H]⁻; ^{1}H NMR ($CDCl_3$): δ 4.75 (s, 2H), 6.85 (d, *J* = 8.6 Hz, 1H), 7.00-7.09 (m, 3H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.29-7.40 (m, 4H), 7.62-7.68 (m, 2H), 7.90 (d, *J* = 9.0 Hz, 1H), 8.17 (s, 1H), 8.60 (s, 1H).



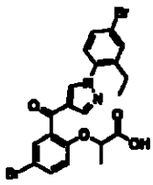
D44

{4-Bromo-2-[1-(2-methylthiophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid. Prepared from 6-bromo-3-formylchromone, 2-methylthiophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.26 min, *m/z* 446.7 [M – H]⁻; ^{1}H NMR ($CDCl_3$): δ 2.46 (s, 3H), 4.77 (s, 2H), 6.93 (d, *J* = 8.9 Hz, 1H), 7.28-7.32 (m, 1H), 7.39-7.49 (m, 3H); 7.62 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.76 (s, 1H), 8.23 (s, 1H), 8.31 (s, 1H).



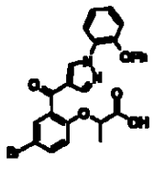
D45

{4-Bromo-2-[1-(2-bromo-4-methylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}-acetic acid. Prepared from 6-bromo-3-formylchromone, 2-bromo-4-methylphenyl-hydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.47 min, *m/z* 492.6 [M – H]⁻; ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H), 4.80 (s, 2H), 6.99 (d, *J* = 8.9 Hz, 1H), 7.27-7.30 (m, 1H), 7.48 (d, *J* = 8.1 Hz , 1H), 7.58 (s, 1H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.80 (s, 1H), 8.20 (s, 1H), 8.33 (s, 1H).



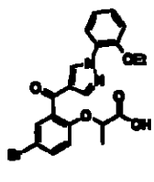
D46

2-{4-Bromo-2-[1-(4-bromo-2-ethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}-propionic acid. Prepared from 6-bromo-3-formylchromone, 4-bromo-2-ethylphenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 2.72 min, *m/z* 522.6 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 1.16 (t, *J* = 7.7 Hz, 3H), 1.67 (d, *J* = 6.8 Hz, 3H), 2.59 (q, *J* = 7.5 Hz, 2H), 4.95 (q, *J* = 7.0 Hz,1H), 6.96 (d, *J* = 9.0 Hz, 1H), 7.21 (d, *J* = 8.3 Hz, 1H), 7.47 (d, *J* = 8.7 Hz , 1H), 7.55 (s, 1H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.73 (s, 1H), 8.17 (s, 1H), 8.18 (s, 1H).



D47

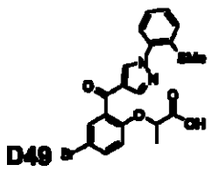
2-{4-Bromo-2-[1-(2-phenoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid. Prepared from 6-bromo-3-formylchromone, 2-phenoxyphenylhydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 2.68 min, *m/z* 508.7 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 1.65 (d, *J* = 6.8 Hz, 3H), 4.92 (q, *J* = 7.3 Hz,1H), 6.96-7.18 (m, 5H), 7.26-7.39 (m, 4H), 7.62 (d, *J* = 8.6 Hz , 1H), 7.67 (s, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 8.17 (s, 1H), 8.61 (s, 1H).



D48

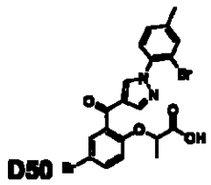
2-{4-Bromo-2-[1-(2-ethoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid. Prepared from 6-bromo-3-formylchromone, 2-ethoxyphenylhydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3:
LC/MS (an10p8): Rt 2.39 min, *m/z* 458.7 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 1.49 (t, *J* = 7.1 Hz, 3H), 1.66 (d, *J* = 7.1 Hz, 3H), 4.19 (m,2H), 4.98 (q, *J* = 6.9 Hz, 1H), 7.02-7.12 (m,3H), 7.37 (t, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 8.9 Hz , 1H), 7.78 (s, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 8.20 (s, 1H), 8.67 (s, 1H).

50



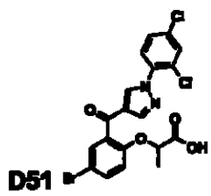
D49

2-{4-Bromo-2-[1-(2-methylthio)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid. Prepared from 6-bromo-3-formylchromone, 2-ethoxyphenylhydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.56 min, 480.9 *m/z* [M - H]$^+$; ^{1}H NMR ($CDCl_3$): δ 1.71 (d, *J* = 6.8 Hz, 3H), 2.46 (s, 3H), 4.96 (q, *J* = 7.0 Hz , 1H), 7.00 (d, *J* = 8.9 Hz, 1H), 7.29-7.34 (m, 1H), 7.40-7.50 (m , 3H), 7.64 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.80 (s, 1H), 8.22 (s, 1H), 8.32 (s, 1H).



D50

2-{4-Bromo-2-[1-(2-bromo-4-methylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid. Prepared from 6-bromo-3-formylchromone, 2-bromo-4-methylphenylhydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.74 min, 506.8 *m/z* [M - H]$^+$; ^{1}H NMR ($CDCl_3$): δ 1.72 (d, *J* = 7.0 Hz, 3H), 2.45 (s, 3H), 4.98 (q, *J* = 7.0 Hz , 1H), 7.03 (d, *J* = 8.9 Hz, 1H), 7.28-7.30 (m, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.59 (s, 1H), 7.67 (dd, *J* = 8.9,2.43 Hz, 1H), 7.81 (d, *J* = 2.6 Hz, 1H), 8.19 (s, 1H), 8.34 (s, 1H).



D51

2-{4-Bromo-2-[1-(2,4-dichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}-propionic acid. Prepared from 6-bromo-3-formylchromone, 2,4-dichlorophenyl-hydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.83 min, 482.8 *m/z* [M - H]$^+$; ^{1}H NMR ($CDCl_3$): δ 1.50 (d, *J* = 6.0 Hz, 3H), 4.75 (q, *J* = 4.5 Hz , 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 7.40 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.54-7.57 (m, 2H), 7.61 (s, 1H), 8.16 (s, 1H), 8.32 (s, 1H).

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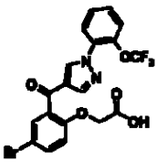
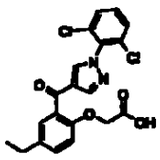


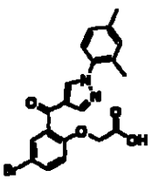
D52

{4-Bromo-2-[1-(2-trifluoromethoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid. Prepared from 6-bromo-3-formylchromone, 2-trifluoromethoxyphenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.43 min, *m/z* 482.7 $[M - H]^-$; ^1H NMR ($CDCl_3$): δ 4.77 (s, 2H), 6.95 (d, *J* = 8.8 Hz, 1H), 7.45-7.50 (m, 3H), 7.65 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.82 (s, 1H), 8.23 (s, 1H), 8.40 (s, 1H).



D53

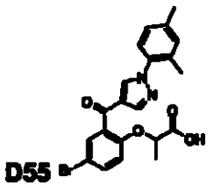
{2-[1-(2,6-Dichlorophenyl)-1H-pyrazole-4-carbonyl]-4-ethylphenoxy}acetic acid. Prepared from 6-ethyl-3-formylchromone, 2,6-dichlorophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.25 min, *m/z* 416.8 $[M - H]^-$; ^1H NMR ($CDCl_3$): δ 1.26 (t, *J* = 7.5 Hz, 3H), 2.69 (q, *J* = 7.7 Hz, 2H), 4.82 (s, 2H), 7.04 (d, *J* = 8.7 Hz, 1H), 7.39-7.44 (m, 1H), 7.46-7.54 (m, 4H), 8.14 (s, 1H), 8.25 (s, 1H).



D54

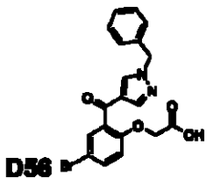
{4-Bromo-2-[1-(2,4-dimethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid. Prepared from 6-bromo-3-formylchromone, 2,4-dimethylphenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.41 min, *m/z* 428.7 $[M - H]^-$; ^1H NMR ($CDCl_3$): δ 2.26 (s, 3H), 2.40 (s, 3H), 4.75 (s, 2H), 6.91 (d, *J* = 8.9 Hz, 1H), 7.11 (d, *J* = 8.1 Hz , 1H), 7.17 (s, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.60 (dd, *J* = 8.9, 2.46 Hz, 1H), 7.71 (s, 1H), 8.15 (s, 1H), 8.22 (s, 1H).

52



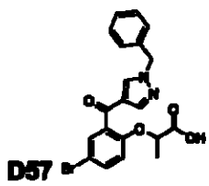
D55

2-(4-Bromo-2-[1-(2,4-dimethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy)-propionic acid. Prepared from 6-bromo-3-formylchromon, 2,4-dimethylphenyl-hydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.40 min, *m/z* 442.7 [M – H]⁻; ^{1}H NMR ($CDCl_3$): δ 1.67 (d, *J* = 6.9 Hz, 3H), 2.25 (s, 3H), 2.40 (s, 3H), 4.93 (q, *J* = 6.8 Hz, 1H), 6.97 (d, *J* = 8.9 Hz, 1H), 7.12 (d, *J* = 8.1 Hz , 1H), 7.17 (s, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.62 (dd, *J* = 8.7, 1.52 Hz, 1H), 7.73 (s, 1H), 8.15-8.16 (m, 2H).



D56

[2-(1-Benzyl-1H-pyrazole-4-carbonyl)-4-bromophenoxy]acetic acid. Prepared from 6-bromo-3-formylchromone, benzylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.14 min, *m/z* 414.7 [M – H]⁻; ^{1}H NMR ($CDCl_3$): δ 4.70 (s, 2H), 5.36 (s, 2H), 6.88 (d, *J* = 8.7 Hz, 1H), 7.28-7.30 (m , 2H), 7.40-7.46 (m, 3H), 7.57 (d, *J* = 8.9 Hz, 1H), 7.63 (s, 1H), 8.01 (s, 1H), 8.04 (s, 1H).



D57

2-[2-(1-Benzyl-1H-pyrazole-4-carbonyl)-4-bromophenoxy]propionic acid. Prepared from 6-bromo-3-formylchromone, benzylhydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.16 min, *m/z* 428.8 [M – H]⁻; ^{1}H NMR ($CDCl_3$): δ 1.59 (d, *J* = 6.8 Hz, 3H), 4.88 (q, *J* = 7.1 Hz, 1H), 5.35 (s, 2H), 6.91 (d, *J* = 8.9 Hz, 1H), 7.30-7.42 (m , 5H), 7.53-7.71 (m, 2H), 8.01 (s, 2H).

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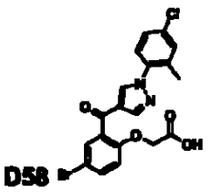
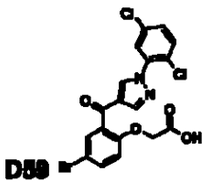


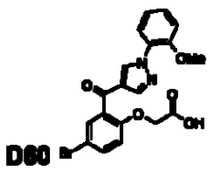
D58

{4-Bromo-2-[1-(4-chloro-2-methylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}-acetic acid. Prepared from 6-bromo-3-formylchromone, 4-chloro-2-methylphenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.49 min, *m/z* 448.7 $[M-H]^-$; ^1H NMR ($CDCl_3$): δ 2.27 (s, 3H), 4.75 (s, 2H), 6.91 (d, *J* = 8.9 Hz, 1H), 7.31 (s , 2H), 7.36 (s, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.70 (s, 1H), 8.17 (s, 1H), 8.21 (s, 1H).



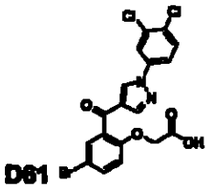
D59

{4-Bromo-2-[1-(2,5-dichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid. Prepared from 6-bromo-3-formylchromone, 2,5-dichlorophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.46 min, *m/z* 468.6 $[M-H]^-$; ^1H NMR ($CDCl_3$): δ 4.78 (s, 2H), 6.92 (d, *J* = 8.9 Hz, 1H), 7.39 (dd, *J* = 8.7, 2.44 Hz , 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.61 (dd, *J* = 8.9, 2.53 Hz, 1H), 7.70 (dd, *J* = 8.1, 2.36 Hz, 2H), 8.22 (s, 1H), 8.45 (s, 1H).



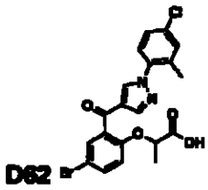
D60

{4-Bromo-2-[1-(2-methoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid. Prepared from 6-bromo-3-formylchromone, 2-methylphenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.20 min, *m/z* 430.7 $[M-H]^-$; ^1H NMR ($CDCl_3$): δ 3.96 (s,3H), 4.79 (s, 2H), 6.96 (d, *J* = 8.9 Hz, 1H), 7.11 (t, *J* = 8.2 Hz , 2H), 7.40 (td, *J* = 8.1, 1.5 Hz, 1H), 7.65 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.76 (d, *J* = 2.5 Hz, 2H), 8.18 (s, 1H), 8.60 (s, 1H).



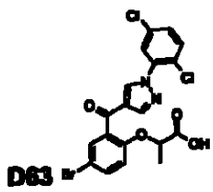
D61

{4-Bromo-2-[1-(3,4-dichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid. Prepared from 6-bromo-3-formylchromone, 3,4-chlorophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.77 min, *m/z* 468.6 $[M-H]^-$; ^1H NMR ($CDCl_3$): δ 4.78 (s, 2H), 6.90 (d, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 8.1 Hz , 1H), 7.64 (d, *J* = 8.9 Hz, 1H), 7.69 (d, *J* = 2.43 Hz, 2H), 7.91 (d, *J* = 2.46 Hz, 1H), 8.18 (s, 1H), 8.53 (s, 1H).



D62

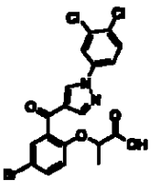
2-{4-Bromo-2-[1-(4-chloro-2-methylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}-propionic acid. Prepared from 6-bromo-3-formylchromone, 4-chloro-2-methylphenylhydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.55 min, *m/z* 462.7 $[M-H]^-$; ^1H NMR ($CDCl_3$): δ 1.65 (d, *J* = 6.9 Hz, 3H), 2.28 (s, 3H), 4.92 (d, *J* = 6.8 Hz, 1H), 6.95 (d, *J* = 8.9 Hz, 1H), 7.30 (s , 2H), 7.37 (s, 1H), 7.63 (d, *J* = 8.9 Hz, 1H), 7.72 (s, 1H), 8.19 (s, 2H).



D63

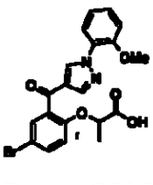
2-{4-Bromo-2-[1-(2,5-dichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}-propionic acid. Prepared from 6-bromo-3-formylchromone, 2,5-dichlorophenyl-hydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.51 min, *m/z* 482.6 $[M-H]^-$; ^1H NMR ($CDCl_3$): δ 1.70 (d, *J* = 6.8 Hz, 3H), 4.90 (q, *J* = 6.9 Hz, 1H), 6.93 (d, *J* = 9.1 Hz, 1H), 7.40 (dd, *J* = 8.7, 2.5 Hz , 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.62 (dd, *J* = 8.9, 2.5 Hz , 1H), 7.68 (d, *J* = 2.3 Hz, 1H), 7.71 (d, *J* = 2.4 Hz, 1H), 8.22 (s, 1H) 8.45 (s, 1H).

55



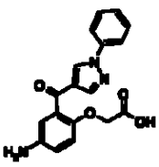
D84

2-{4-Bromo-2-[1-(3,4-dichloro-phenyl)-1H-pyrazole-4-carbonyl]phenoxy}-propionic acid. Prepared from 6-bromo-3-formylchromon, 3,4-dichlorophenyl-hydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.83 min, *m/z* 482.6 $[M - H]^-$; ^1H NMR ($CDCl_3$): δ 1.63 (d, *J* = 6.8 Hz, 3H), 4.93 (q, *J* = 6.9 Hz, 1H), 6.92 (d, *J* = 9.03 Hz, 1H), 7.55-7.65 (m, 3H), 7.70 (s,1H), 7.93 (d, *J* = 2.25 Hz, 1H), 8.20 (s, 1H), 8.57 (s, 1H).



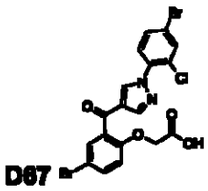
D85

2-{4-Bromo-2-[1-(2-methoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid. Prepared from 6-ethyl-3-formylchromone, 2,6-dichlorophenylhydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.23 min, *m/z* 444.7 $[M - H]^-$; ^1H NMR ($CDCl_3$): δ 1.68 (d, *J* = 7.0 Hz, 3H), 3.95 (s, 3H), 4.95 (d, *J* =7.0 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 7.10 (d, *J* = 8.5 Hz , 1H), 7.14 (s, 1H), 7.37-7.43 (m,1H), 7.63 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.77 (s, 1H), 7.79 (s,1H), 8.19 (s, 1H), 8.62 (s, 1H).



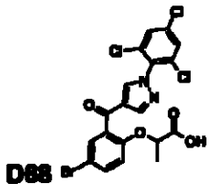
D86

[4-Amino-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxy]acetic acid. A mixture of ethyl 4-nitro-2-(phenyl-1H-pyrazole-4-carbonyl)phenoxyacetate (190 mg, 0.48 mmol) and 10% Pd/C (100 mg) in MeOH (50 mL) was stirred under an atmosphere of hydrogen of 12 h, then filtered through a pad of celite and concentrated, and the product was hydrolyzed according to GP3 to give the title compound.



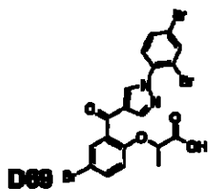
D67

{4-Bromo-2-[1-(4-bromo-2-chlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}-acetic acid. Prepared from 6-bromo-3-formylchromone, 4-bromo-2-chlorophenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.57 min, *m/z* 526.6 [M – H]$^-$; ^{1}H NMR (DMSO): δ 1.31 (d, *J* = 6.8 Hz, 3H), 4.94 (q, *J* = 6.8 Hz, 1H), 6.92 (d, *J* = 8.9 Hz, 1H), 7.53 (d, *J* = 2.5 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.66 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.76 (dd, *J* = 8.5, 2.3 Hz, 1H), 8.04 (d, *J* = 2.1 Hz, 1H), 8.22 (s, 1H), 8.77 (s, 1H).



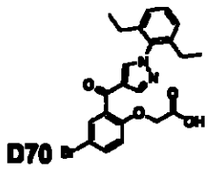
D68

2-{4-Bromo-2-[1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}-propionic acid. Prepared from 6-bromo-3-formylchromone, 2,4,6-trichlorophenylhydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.61 min, *m/z* 516.6 [M - H]$^+$; ^{1}H NMR (DMSO): δ 1.33 (d, *J* = 6.8 Hz, 3H), 4.94 (q, *J* = 7.0 Hz, 1H), 6.92 (d, *J* = 9.2 Hz, 1H), 7.54 (d, *J* = 2.4 Hz, 1H), 7.66 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.99 (s, 2H), 8.26 (s, 1H), 8.72 (s, 1H).



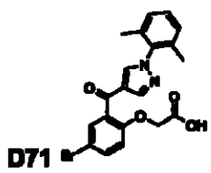
D69

2-{4-Bromo-2-[1-(2,4-dibromophenyl)-1H-pyrazole-4-carbonyl]phenoxy}-propionic acid. Prepared from 6-bromo-3-formylchromone, 2,4-dibromophenylhydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 2.67 min, *m/z* 572.7 [M + H]$^+$; ^{1}H NMR (DMSO): δ 1.32 (d, *J* = 6.8 Hz, 3H), 4.93 (q, *J* = 6.8 Hz,1H), 6.91 (d, *J* = 8.9 Hz, 1H), 7.54 (dd, *J* = 8.3, 2.3 Hz, 2H), 7.66 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.78 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.15 (d, *J* = 2.1 Hz, 1H), 8.21 (s, 1H), 8.72 (s, 1H).



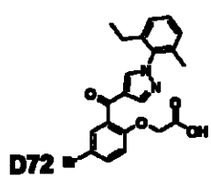
D70

{4-Bromo-2-[1-(2,6-diethyl-phenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid. Prepared from 6-bromo-3-formylchromone, 2,6-diethylphenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.54 min, *m/z* 457.0 $[M - H]^+$; ^1H NMR ($CDCl_3$): δ 1.27 (t, *J* = 7.3 Hz, 6H), 2.35 (q, *J* = 7.3 Hz, 4H), 4.82 (s, 2H), 6.99 (d, *J* = 8.9 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.48 (m, 1H), 7.67 (m, 1H), 7.79 (s, 1H), 8.11 (s, 1H), 8.27 (s, 1H), 8.87 (br s, 1H).



D71

{4-Bromo-2-[1-(2,6-dimethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid. Prepared from 6-bromo-3-formylchromone, 2,6-diethylphenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.27 min, *m/z* 428.9 $[M - H]^+$; ^1H NMR ($CDCl_3$): δ 2.07 (s, 6H), 4.74 (s, 2H), 6.91 (d, *J* = 8.7 Hz, 1H), 7.19 (d, *J* = 7.3 Hz, 2H), 7.25-7.35 (m, 1H), 7.55-7.66 (m, 1H), 7.71 (s, 1H), 8.06 (s, 1H), 8.23 (s, 1H), 8.91 (br s, 1H).



D72

{4-Bromo-2-[1-(2-ethyl-6-methylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid. Prepared from 6-bromo-3-formylchromone, 2-ethyl-6-methylphenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.43 min, *m/z* 443.0 $[M - H]^+$; ^1H NMR ($CDCl_3$): δ 1.12 (t, *J* = 7.8 Hz, 3H), 2.05 (s, 3H), 2.33 (q, *J* = 7.8 Hz, 2H), 4.76 (s, 2H), 6.94 (d, *J* = 8.7 Hz, 1H), 7.14-7.25 (m, 2H), 7.31-7.41 (m, 1H), 7.56-66 (m, 1H), 7.72 (s, 1H), 8.06 (s, 1H), 8.22 (s, 1H), 8.93 (br s, 1H).

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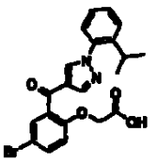
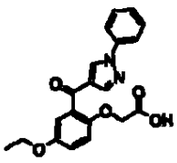


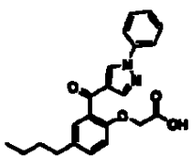
D73

{4-Bromo-2-[1-(2-isopropylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid. Prepared from 6-bromo-3-formylchromone, 2-ethyl-6-methylphenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 2.76 min, *m/z* 444.9 $[M + H]^+$; ^1H NMR (CDCl3-d): δ 1.22 (d, *J* = 6.5 Hz, 6H), 2.89 (septet, *J* = 6.1 Hz, 1H), 4.76 (s, 2H), 6.92 (d, *J* = 8.7 Hz, 1H), 7.30 (s, 2H), 7.49 (s, 2H), 7.62(d, 1H), 7.72 (s, 1H), 8.15 (s, 1H), 8.20 (s, 1H), 8.92 (br s, 1H).



D74

[4-Ethoxy-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxy]acetic acid. Prepared from 6-ethoxy-3-formylchromone, phenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 1.97 min, *m/z* 367.1 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 1.43 (t, *J* = 6.8 Hz, 3H), 4.03 (q, *J* = 6.9 Hz, 2H), 4.78 (s, 2H), 7.01-7.13 (m, 2H), 7.15 (s, 1H), 7.36-7.43 (m, 1H), 7.46-7.57 (m, 2H), 7.71-7.75 (m, 2H), 8.16 (s, 1H), 8.50 (s, 1H).

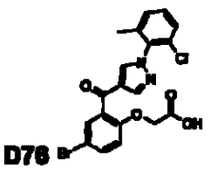


D75

[4-Butyl-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxy]acetic acid. A solution of ethyl [4-bromo-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxy]acetate (472 mg, 1.1 mmol), 1-butylboronic acid (102 mg, 1.0 mmol) and Pd $(dppf)Cl_2$ (72 mg, 0.05 mmol) in THF (10 mL) and water (1 mL) under argon was refluxed for 24 h. The reaction mixture was extracted with CH_2Cl_2, the organic phase was filtered through celite and concentrated, and the residue was purified by flash chromatography (SiO2, EtOAc:heptane, 1:10 to 1:1). The purest fraction was concentrated (~10 mg), and the residue was hydrolysed according to GP3: LC/MS (an10p8): Rt 2.59 min, *m/z* 379.1 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 0.88 (t, *J* = 7.5 Hz, 3H), 1.29 (m, 2 H), 1.49 (m, 2 H),

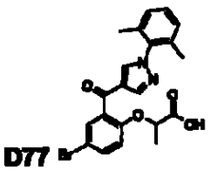
59

2.48 (m, 2 H), 4.51 (s, 2 H), 6.84 (m, 1 H), 7.14 (m, 1 H), 7.30 (m, 2H), 7.42 (m, 2H), 7.65 (m, 2H), 7.97 (s, 1H), 8.46 (s, 1H).



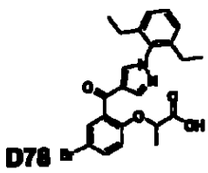
D76

{4-Bromo-2-[1-(2-chloro-6-methylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}-acetic acid. Prepared from 6-bromo-3-formylchromone, 2-chloro-6-methyl-phenylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 2.49 min, *m/z* 450.9 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 2.16 (s, 3H), 4.80 (s, 2H), 6.98 (d, *J* = 9.1 Hz, 1H), 7.30 (m, 1H), 7.34-7.40 (m, 2H), 7.66 (d, 1H), 7.77 (m, 1H), 8.13 (s, 1H); 8.24 (s, 1H).



D77

2-{4-Bromo-2-[1-(2,6-dimethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}-propionic acid. Prepared from 6-bromo-3-formylchromone, 2,6-dimethyl-phenylhydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.55 min, *m/z* 440.9 $[M - H]^+$; ^1H NMR ($CDCl_3$): δ 1.68(d, *J* = 6.8 Hz, 3H), 2.11 (s, 6H), 4.94 (q, *J* = 7.0 Hz 1H), 6.97 (d, *J* = 8.9 Hz, 1H), 7.19 (d, *J* = 7.5 Hz 2H), 7.28-7.32 (m, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.75 (m, 1H), 8.05 (s, 1H), 8.22 (s, 1H).

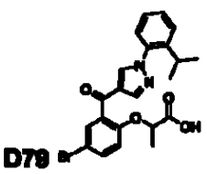


D78

2-{4-Bromo-2-[1-(2,6-diethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid. Prepared from 6-bromo-3-formylchromone, 2,6-diethylphenylhydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.85 min, *m/z* 469.0 $[M - H]^+$; ^1H NMR ($CDCl_3$): δ 1.08-1.21 (m, 6H), 1.69-1.76 (m, 3H), 2.18-2.48 (m, 4H), 2.67 (s,1H), 4.97 (q, *J* = 6.8 Hz 1H), 6.84 (d, *J* = 9.0 Hz, 1H), 7.00

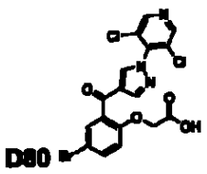
60

(d, J = 9.0 Hz, 1H), 7.24 (d, J = 7.7 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.77 (s, 1H), 7.86 (s, 1H), 8.06 (s, 1H), 8.22 (s, 1H).



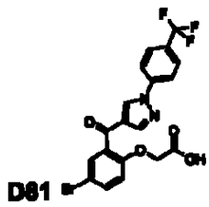
D79

2-{4-Bromo-2-[1-(2-isopropylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}-propionic acid. Prepared from 6-bromo-3-formylchromone, 2,6-diethyl-phenylhydrazine and ethyl 2-bromopropionate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 2.54 min, *m/z* 459.0 $[M + H]^+$; ^{1}H NMR ($CDCl_3$): δ 1.19-1.27 (m, 7H), 1.67 (d, J = 7.0 Hz, 2H), 4.92 (q, J = 6.8 Hz, 1H), 6.96 (d, J = 8.9 Hz, 1H), 7.27-7.53 (m,,4H), 7.58-7.67 (m, 1H), 7.73 (s, 1H), 8.17 (s, 1H), 8.20 (s,1H).



D80

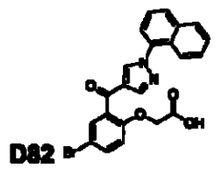
{4-Bromo-2-[1-(3,5-dichloropyridin-4-yl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid. Prepared from 6-bromo-3-formylchromone, 2,6-dichloropyridine-4hydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.08 min, *m/z* 469.8 $[M - H]^-$; ^{1}H NMR (DMSO-d_6): δ 4.75 (s, 2H), 7.05 (d, J = 9.1 Hz, 1H), 7.56 (s, 1H), 7.64 (d, J = 9.1 Hz, 1H), 8.32 (s, 1H), 8.77 (s, 1H), 8.93 (s, 2H).



D81

{4-Bromo-2-[1-(4-trifluoromethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}-acetic acid. Prepared from 6-bromo-3-formylchromone, 4-trifluoromethylphenyl-hydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10n8): Rt 2.88 min, *m/z* 468.9 $[M - H]^-$; ^{1}H NMR ($CDCl_3$): δ 4.78 (s, 2H), 6.92 (d, J = 8.9 Hz, 1H), 7.65 (d, J = 8.9 Hz, 1H), 7.71 (s, 1H), 7.79 (d, J = 8.9 Hz, 2H), 7.91 (d, J = 8.9 Hz, 2H), 8.23 (s, 1H), 8.65 (s, 1H).

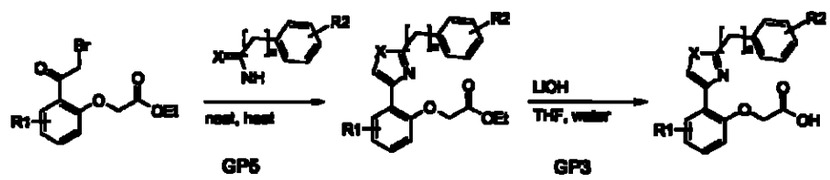
61



D82

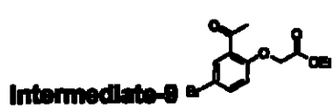
[4-Bromo-2-(1-naphthalen-1-yl-1H-pyrazole-4-carbonyl)phenoxy]acetic acid. Prepared from 6-bromo-3-formylchromone, 1-naphtylhydrazine and ethyl bromoacetate according to GP1, GP2 and GP3: LC/MS (an10p8): Rt 2.649 min, *m/z* 451.0 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 4.78 (s, 2H), 6.93 (d, *J* = 8.85 Hz, 1H), 7.52-7.68 (m, 6H), 7.73-7.82 (m , 2H), 7.93-8.05 (m, 2H), 8.33 (s, 1H), 8.38 (s, 1H).

General synthetic route IV



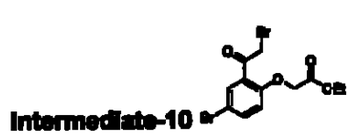
General procedure 5 (GP5):

A mixture of ethyl 2-(2-bromoacetyl)phenoxyacetate (0.1 mmol) and amide (X = O) or thioamide (X = S) (2.5 mmol) was heated neat in the microwave for 3 hours at 140 °C. After cooling, the solid residue was partitioned between EtOAc and saturated aq. $NaHCO_3$. The phases were separated and the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The crude solid was purified by flash chromatography to give the corresponding oxazole or thiazole derivative.



Intermediate-9

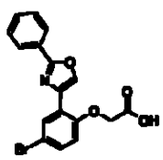
(2-Acetyl-4-bromophenoxy)acetic acid ethyl ester Prepared from 5'-bromo-2'-hydroxyacetophenone (2 g, 9.3 mmol) and ethyl bromoacetate (1.03 mL, 9.3 mmol) according to GP2 to give the title compound as a white solid (2.64 g, 8.7 mmol, 94%): LC/MS (an10p8) Rt 3.3 min, *m/z* 301 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 1.32 (t, 3H), 2.71 (s, 3H), 4.30 (q, 2H), 4.72 (s, 2H), 6.76 (d, 1H), 7.55 (dd, 1H), 7.88 (s, 1H).



Intermediate-10

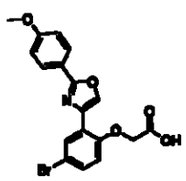
62

[4-Bromo-2-(2-bromoacetyl)phenoxy]acetic acid ethyl ester. To a cooled (0 °C) solution of (2-acetyl-4-bromophenoxy)acetic acid ethyl ester (2.5 g, 8.3 mmol) in $CHCl_3$ (25 mL) was slowly added bromine (425 uL, 8.3 mmol). After completion the reaction mixture was allowed to stir at room temperature for 1 hour. The mixture was partitioned between CH_2Cl_2 and brine. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a white solid (2.97 g, 7.8 mmol, 94%): ^1H NMR ($CDCl_3$): δ 1.35 (t, 3H), 4.32 (q, 2H), 4.75 (s, 2H), 4.76 (s, 2H), 6.77 (d, 1H), 7.60 (dd, 1H), 7.97 (s, 1H)



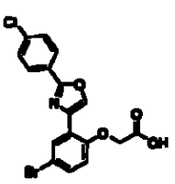
D83

[4-Bromo-2-(2-phenyloxazol-4-yl)phenoxy]acetic acid. Title compound was prepared from [4-bromo-2-(2-bromoacetyl)phenoxy]acetic acid ethyl ester and benzamide according to GP5 and GP3: LC/MS (an10p8) Rt 2.6 min, *m/z* 374/376 $[M + H]^+$.



D84

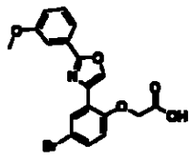
{4-Bromo-2-[2-(4-methoxyphenyl)oxazol-4-yl]phenoxy}acetic acid. Title compound was prepared from [4-bromo-2-(2-bromoacetyl)phenoxy]acetic acid ethyl ester and 4-methoxybenzamide according to GP5 and GP3: LC/MS (an10p8) Rt 2.61 min, *m/z* 404 $[M + H]^+$.



D85

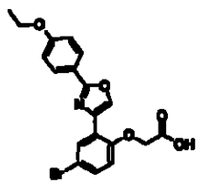
{4-Bromo-2-[2-(4-chlorophenyl)oxazol-4-yl]phenoxy}acetic acid. Title compound was prepared from [4-bromo-2-(2-bromoacetyl)phenoxy]acetic acid ethyl ester and 4-chlorobenzamide according to GP5 and GP3: LC/MS (an10p8) Rt 2.90 min, *m/z*

407.7 [M + H]$^+$; ^{1}H NMR ($CDCl_3$): δ 4.89 (s, 2H), 7.09 (d, 1H), 7.48 (d, 1H), 7.64 (d, 2H), 8.08 (d, 2H), 8.20 (s, 1H), 8.89 (s, 1H), 13.2 (br s, 1H).



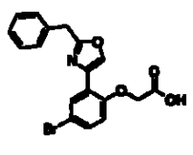
D86

{4-Bromo-2-[2-(3-methoxyphenyl)oxazol-4-yl]phenoxy}acetic acid. Title compound was prepared from [4-bromo-2-(2-bromoacetyl)phenoxy]acetic acid ethyl ester and 3-methoxybenzamide according to GP5 and GP3: LC/MS (an10p8) Rt 2.68 min, *m/z* 404 [M + H]$^+$; ^{1}H NMR ($CDCl_3$): δ 3.87 (s, 1H), 4.89 (s, 2H), 7.09 (m, 2H), 7.4-7.7 (m, 4H), 8.22 (s, 1H), 8.89 (s, 1H), 13.3 (br s, 1H).



D87

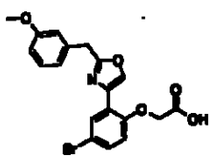
{4-Bromo-2-[2-(4-ethoxyphenyl)oxazol-4-yl]phenoxy}acetic acid. Title compound was prepared from [4-bromo-2-(2-bromoacetyl)phenoxy]acetic acid ethyl ester and 4-ethylbenzamide according to GP5 and GP3: LC/MS (an10p8) Rt 2.80 min, *m/z* 418/420 [M + H]$^+$; ^{1}H NMR ($CDCl_3$): δ 1.36 (t, 3H), 4.10 (q, 2H), 4.88 (s, 2H), 7.07 (m, 3H), 7.47 (d, 1H), 8.00 (d, 2H), 8.20 (s, 1H), 8.82 (s, 1H), 13.4 (br s, 1H).



D88

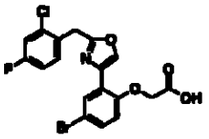
[2-(2-Benzyloxazol-4-yl)-4-bromophenoxy]acetic acid. Title compound was prepared from [4-bromo-2-(2-bromoacetyl)phenoxy]acetic acid ethyl ester and 2-phenylacetamide according to GP5 and GP3: LC/MS (an10p8) Rt 2.47 min, *m/z* 388 [M + H]$^+$; ^{1}H NMR ($CDCl_3$): δ 4.22 (s, 2H), 4.84 (s, 2H), 7.04 (d, 1H), 7.25 (m, 5H), 7.43 (d, 1H), 8.06 (s, 1H), 8.69 (s, 1H), 13 (br s, 1H).

64



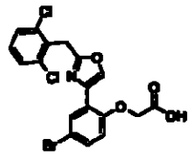
D89

{4-Bromo-2-[2-(3-methoxybenzyl)oxazol-4-yl]phenoxy}acetic acid. Title compound was prepared from [4-bromo-2-(2-bromoacetyl)phenoxy]acetic acid ethyl ester and 2-(3-methoxyphenyl)acetamide according to GP5 and GP3: LC/MS (an10p8) Rt 2.45 min, *m/z* 418 $[M + H]^+$.



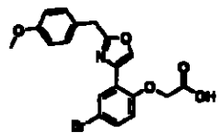
D90

{4-Bromo-2-[2-(2-chloro-4-fluorobenzyl)oxazol-4-yl]phenoxy}acetic acid. Title compound was prepared from [4-bromo-2-(2-bromoacetyl)phenoxy]acetic acid ethyl ester and 2-(2-chloro-4-fluorophenyl)acetamide according to GP5 and GP3: LC/MS (an10p8) Rt 2.75 min, *m/z* 440 $[M + H]^+$.



D91

{4-Bromo-2-[2-(2,6-dichlorobenzyl)oxazol-4-yl]phenoxy}acetic acid. Title compound was prepared from [4-bromo-2-(2-bromoacetyl)phenoxy]acetic acid ethyl ester and 2-(2,6-dichlorophenyl)acetamide according to GP5 and GP3: LC/MS (an10p8) Rt 2.75 min, *m/z* 456/458/460 $[M + H]^+$.



D92

{4-Bromo-2-[2-(4-methoxybenzyl)oxazol-4-yl]phenoxy}acetic acid. Title compound was prepared from [4-bromo-2-(2-bromoacetyl)phenoxy]acetic acid ethyl ester and 2-(4-methoxyphenyl)acetamide according to GP5 and GP3: LC/MS (an10p8) Rt 2.40 min, *m/z* 418 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 3.72 (s, 3H), 4.14 (s, 1H), 4.85 (s, 1H), 6.92 (m, 2H), 7.02 (d, 1H), 7.2 (d, 1H), 7.23 (d, 1H), 7.44 (d, 1H), 8.05 (s, 1H), 8.67 (s, 1H), 13.2 (br s, 1H).

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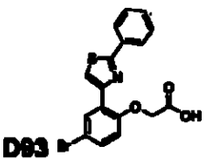
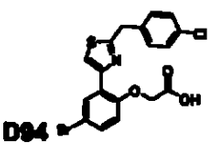


D93

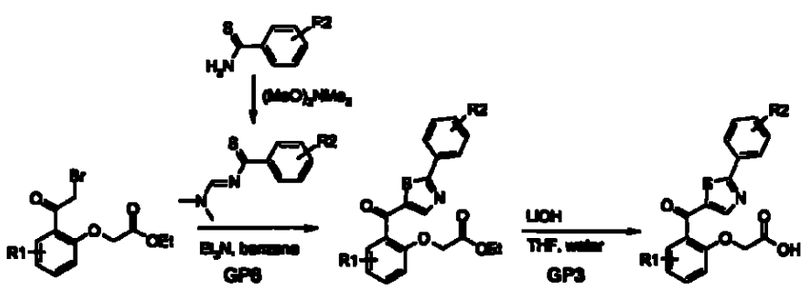
[4-Bromo-2-(2-phenylthiazol-4-yl)phenoxy]acetic acid. Title compound was prepared from [4-bromo-2-(2-bromoacetyl)phenoxy]acetic acid ethyl ester and thiobenzamide according to GP5 and GP3: LC/MS (an10p8) Rt 2.69 min, *m/z* 390 [M + H]$^+$.



D94

{4-Bromo-2-[2-(4-chlorobenzyl)thiazol-4-yl]phenoxy}acetic acid Title compound was prepared from [4-bromo-2-(2-bromoacetyl)phenoxy]acetic acid ethyl ester and 2-(4-chlorophenyl)thioacetamide according to GP5 and GP3: LC/MS (an10p8) Rt 2.69 min, *m/z* 390 [M + H]$^+$; ^{1}H NMR ($CDCl_3$): δ 4.42 (s, 2H), 4.86 (s, 2H), 7.06 (d, 1H), 7.45 (m, 5H), 8.33 (s, 1H), 8.41 (s, 1H), 13.2 (br s, 1H).

General synthetic route V



General procedure 6 (GP6)

Synthesis of carbonylthiazoles

A mixture of the thioamide (1.0 mmol) and N,N-dimethylformamide dimethylacetal (1.2 mmol) was stirred for 1 hour at room temperature under argon. The volatile materials were removed under reduced pressure without heating to give the corresponding N'-thioaroylformamidine which was used without further purification in the next step.

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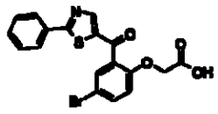
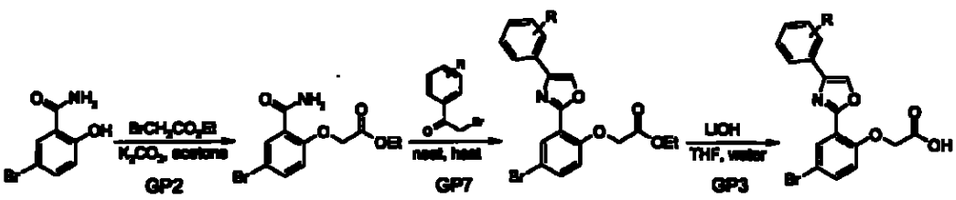
To a solution of the ethyl 2-(2-bromoacetyl)phenoxyacetate (1 mmol) and the N'-thioaroylformamidine (1 mmol) in benzene (2.6 mL) was added an excess of triethylamine (5 mmol). After stirring overnight at room temperature, solvent was removed *in vacuo*. The residue was partitioned between EtOAc and satureated aq. $NaHCO_3$. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography to give the thioamide.



D95

[4-Bromo-2-(2-phenylthiazole-5-carbonyl)phenoxy]acetic acid. Title compound was prepared from [4-bromo-2-(2-bromoacetyl)phenoxy]acetic acid ethyl ester and thiobenzamide according to GP6 and GP3: LC/MS (an10p8) Rt 2.44 min, *m/z* 418 $[M + H]^+$.

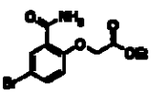
General synthetic route VI



General procedure 7 (GP7)

Synthesis of oxazole

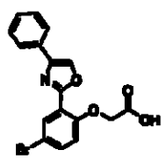
A mixture of benzamide (1.0 mmol) and 2-bromoacetophenone (0.5 mmol) was heated neat in an Emrys Optimizer microwave oven for 3 hours at 140 °C. After cooling EtOAc and CH_2Cl_2 were added and the formed precipitate was filtered off. The filtrate was concentrated *in vacuo* and purified by flash chromatography to give the corresponding oxazole.



Intermediate-11

(4-Bromo-2-carbamoylphenoxy)acetic acid ethyl ester. Prepared from bromosalicylamide and ethyl bromoacetate according GP2: ^1H NMR ($CDCl_3$): δ 1.35

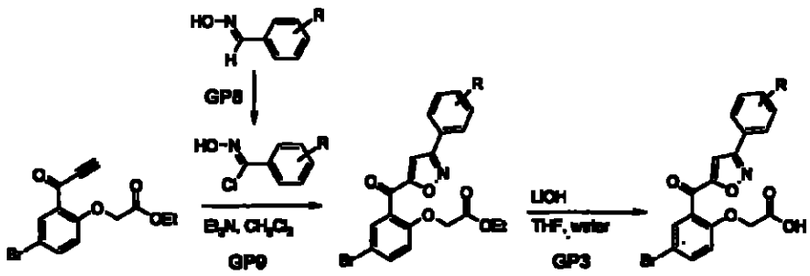
(t, 3H), 4.34 (q, 2H), 4.73 (s, 2H), 5.87 (br s, 1H), 6.76 (d, 1H), 7.56 (d, 1H), 8.33 (br s, 1H), 8.39 (s, 1H).



D96

[4-Bromo-2-(4-phenyl-oxazol-2-yl)-phenoxy]acetic acid. Title compound was prepared from (4-bromo-2-carbamoylphenoxy)acetic acid ethyl ester and 2-bromoacetophenone according to GP7: LC/MS (an10p8) Rt 2.32 min, *m/z* 374/376 $[M + H]^+$.

General synthetic route VII



General procedure 8 (GP8):

Synthesis of hydroximic acid chloride

To a solution of the aldoxime (1.0 mmol) in CH_2Cl_2 (1.7 mL) was added N-chlorosuccinimide (1.0 mmol) in one portion. The reaction mixture was stirred for 3 hours at room temperature under an argon atmosphere. Water was added. The phases were separated. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the corresponding hydroximic acid chloride derivative which was used without further purification.

General procedure 9 (GP9):

Synthesis of isoxazole

To a solution of the hydroximic acid chloride (1.0 mmol) and (4-bromo-2-propynoyl-phenoxy)acetic acid ethyl ester (1.0 mmol) in dry CH_2Cl_2 (3.7 mL) was slowly added a solution of Et_3N (1.0 mmol) in dry CH_2Cl_2 (0.8 mL) over a period of 4 hours (use of syringe-pump). After completion of the addition, the reaction mixture was washed

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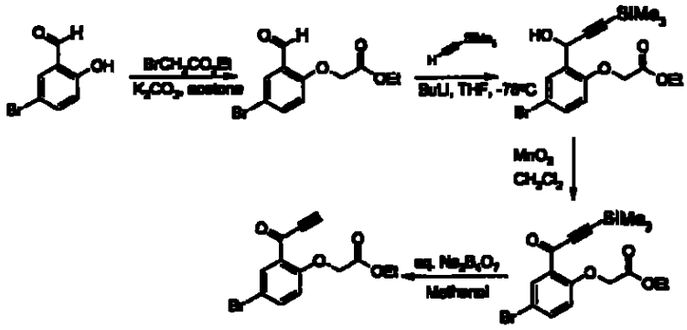
with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was purified by flash chromatography to give the corresponding isoxazol derivative.

Synthesis of Intermediate-12



(4-Bromo-2-formylphenoxy)acetic acid ethyl ester. Prepared from 5-bromo-2-hydroxybenzaldehyde according GP2: LC/MS (an10p8) Rt 3.45min, *m/z* 287 [M + H]$^+$; ^{1}H NMR ($CDCl_3$): δ 1.29 (t, 3H), 4.25 (q, 2H), 4.74 (s, 2H), 6.79 (d, 1H), 7.80 (d, 1H), 7.94 (s, 1H), 10.46 (s, 1H)

[4-Bromo-2-(1-hydroxy-3-trimethylsilanylprop-2-ynyl)phenoxy]acetic acid ethyl ester. To a cooled (-78 °C) solution of (trimethylsilyl)acetylene (3.93 g, 40.0 mmol) in dry THF (40 mL) was slowly added a 2.5 M solution of butyllithium in hexanes (14.54 mL, 36.36 mmol). After stirring for 30 minutes at -78 °C, the mixture was transferred to a cooled (-78 °C) solution of (4-bromo-2-formylphenoxy)acetic acid ethyl ester (10.44 g, 36.36 mmol) in dry THF (120 mL). Upon completion, the reaction mixture was stirred at -78 °C for 45 minutes. Saturated aq. NH_4Cl (40 mL) was slowly added to the reaction mixture followed by Et_2O (40 mL). The quenched reaction mixture was allowed to warm up to room temperature. The phases were separated and the aqueous phase was extracted with Et_2O (2x). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was purified by column chromatography (SiO_2), then was stirred for 90 min with polystyrene-supported trisamine (PS-Trisamine, 4.17 mmol/g, 8 g) in CH_2Cl_2 (160 mL). The resin was filtered off and the filtrate was concentrated *in vacuo* to give the title compound as pale yellow oil (7.6 g, 19.7 mmol, 54%). LC/MS (an10p8) Rt 4.30min, *m/z* 408 [M + Na]$^+$; ^{1}H NMR ($CDCl_3$): δ 0.24 (s, 9H), 1.31 (t, 3H), 4.27 (q, 2H), 4.71 (s, 2H), 5.79 (s, 1H), 6.74 (d, 1H), 7.39 (dd, 1H), 7.79 (d, 1H).

[4-Bromo-2-(3-trimethylsilanylpropynoyl)phenoxy]acetic acid ethyl ester. To a solution of [4-bromo-2-(1-hydroxy-3-trimethylsilanylprop-2-ynyl)phenoxy]acetic acid

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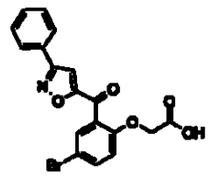
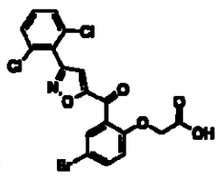
ethyl ester (0.95 g, 2.46 mmol) in CH_2Cl_2 (10 mL) was added activated MnO_2 in 2 portions (1.5 g + 1 g), and the reaction was stirred for 90 min. The solid was filtered off through a celite pad and the filtrate was concentrated *in vacuo* to give the title compound as yellow oil (0.83 g, 2.16 mmol, 87%). LC/MS (an10p8) Rt 4.70min, *m/z* 383 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 0.30 (s, 9H), 1.30 (t, 3H), 4.27 (q, 2H), 4.72 (s, 2H), 6.81 (d, 1H), 7.58 (dd, 1H), 8.10 (s, 1H).

(4-Bromo-2-propynoylphenoxy)acetic acid ethyl ester. To a solution of [4-bromo-2-(3-trimethylsilanylpropynoyl)phenoxy]acetic acid ethyl ester (0.83 g, 2.16 mmol) in methanol (20 mL) was added a 0.1M aqueous solution of $Na_2B_4O_7$ (10 mL). After stirring for 2 – 3 minutes at room temperature, Et_2O and 1N aq. HCl were added. The phases were separated, and the organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as yellow oil which crystallized upon standing (0.65 g, 2.09 mmol, 96%). LC/MS (an10p8) Rt 3.58min, *m/z* 311 $[M + H]^+$; ^1H NMR ($CDCl_3$): δ 1.31 (t, 3H), 3.45 (s, 1H), 4.27 (q, 2H), 4.74 (s, 2H), 6.83 (d, 1H), 7.61 (dd, 1H), 8.14 (d, 1H).



D97

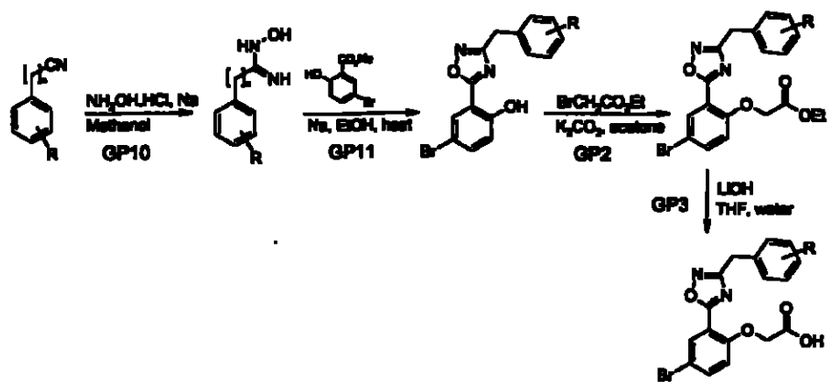
[4-Bromo-2-(3-phenylisoxazole-5-carbonyl)phenoxy]acetic acid Title compound was prepared from benzaldoxime and (4-bromo-2-propynoylphenoxy)acetic acid ethyl ester according to GP8 and GP9: LC/MS (an10n8) Rt 3.07 min, *m/z* 400 $[M - H]^-$; ^1H NMR (DMSO): δ 4.77 (s, 2H), 7.13 (d, 1H), 7.53 (m, 3H), 7.73-7.92 (m, 5H).



D98

{4-Bromo-2-[3-(2,6-dichloro-phenyl)isoxazole-5-carbonyl]phenoxy}acetic acid. Title compound was prepared from 2,6-dichlorobenzaldoxime and (4-bromo-2-propynoylphenoxy)acetic acid ethyl ester according to GP8 and GP9: LC/MS (an10n8) Rt 2.74 min, *m/z* 471.9 $[M + H]^+$.

General Synthetic Route VIII



General procedure 10 (GP10)

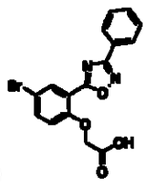
Synthesis of amidoximes

Sodium (1.25 mmol) was added to dry methanol (1ml) to give solution A. Hydroxylamine hydrochloride (1.2 mmol) was dissolved in dry methanol (1mL) to give solution B. Solution A and B were mixed, cooled in an ice-bath and filtered. To the filtrate was then added the nitrile (1 mmol) and the reaction mixture was stirred over night at room temperature. The solvent was removed *in vacuo* to give the corresponding amidoxime. The compound was purified over silica gel chromatography (EtOAc/Heptane: 1/2) or used without further purification.

General procedure 11 (GP11)

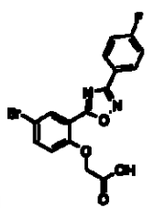
Synthesis of oxadiazoles

To a solution of sodium (3.3 mmol) in dry ethanol (10 mL) were successively added the amidoxime (1.15 mmol), molecular sieves (1g) and methyl benzoate (1 mmol). After stirring for 12 h under reflux, the reaction mixture was cooled and filtered through a celite pad. The celite pad was washed with methanol and CH_2Cl_2. The solvent was removed *in vacuo* and the residue was stirred with water. The precipitate was filtered off and dried to give the corresponding oxadiazole. The compound was purified over silica gel chromatography (EtOAc:Heptane, 1:2) or used without further purification in.



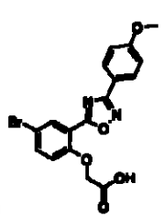
D99

[4-Bromo-2-(3-phenyl-[1,2,4]oxadiazol-5-yl)phenoxy]acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and benzonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8): Rt 2.41 min, *m/z* 373.4 $[M - H]^-$; ^1H NMR (DMSO-d_6): δ 4.97 (s, 2H), 7.2 (d, 1H), 7.62 (s, 3H), 7.82 (d, 2H), 8.10 (d, 1H), 8.2 (s, 1 H).



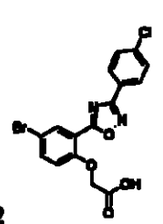
D100

{4-Bromo-2-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 4-fluorobenzonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.49, *m/z* 391.4 $[M - H]^-$.



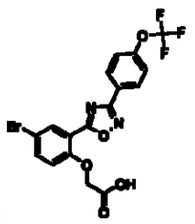
D101

{4-Bromo-2-[3-(4-methoxy-phenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 4-methoxybenzonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.44 min, *m/z* 403.4 $[M - H]^-$.



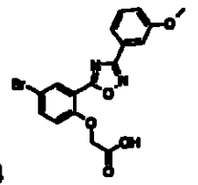
D102

{4-Bromo-2-[3-(4-chlorophenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 4-chlorobenzonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.68 min, *m/z* 407.4 $[M - H]^-$.



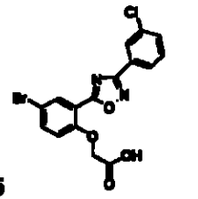
D103

{4-Bromo-2-[3-(4-trifluoromethoxyphenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 4-trifluoromethoxybenzonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.09 min, *m/z* 457.5 $[M - H]^-$; ^1H NMR (DMSO-d_6): δ 4.96 (s, 2H), 7.21 (d, 1H), 7.59 (d, 2H), 7.82 (d, 1H), 8.22 (d, 3H).



D104

{4-Bromo-2-[3-(3-methoxyphenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 3-methoxybenzonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.47 min, *m/z* 403.4 $[M - H]^-$; ^1H NMR (DMSO-d_6): δ 3.86 (s, 3H), 4.96 (s, 2H), 7.20 (d, 2H), 7.5 (t, 1H), 7.6 (s, 1H), 7.67 (d,1H), 7.8 (d, 1H), 8.2 (s, 1H).



D105

{4-Bromo-2-[3-(3-chlorophenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 3-chlorobenzonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.69

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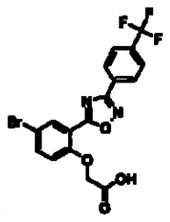
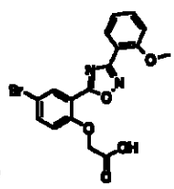
min, *m/z* 407.4 [M – H]⁻; ^{1}H NMR (DMSO): δ 4.97 (s, 2H), 7.2 (d, 1H), 7.6 (m, 2H), 7.7 (d, 1H), 7.8 (d 2 H), 8.2, (s, 1H).



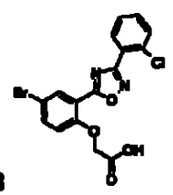
D106

{4-Bromo-2-[3-(4-trifluoromethyl-phenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 4-trifluoromethylbenzonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.83 min, *m/z* 441.4 [M - H]⁻; ^{1}H NMR (DMSO-d_6): δ 4.97 (s, 2H), 7.2 (d, 1H), 7.8 (dd, 1H), 7.9 (d, 2H), 8.2 (d, 1H), 8.3 (d, 2H).



D107

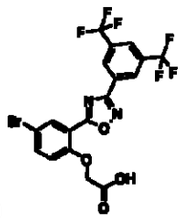
{4-Bromo-2-[3-(2-methoxyphenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 2-methoxybenzonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.31 min, *m/z* 403.4 [M - H]⁻; ^{1}H NMR (DMSO-d_6): δ 2.5 (s, 3H), 4.94 (s, 2H), 7.2 (m, 3H), 7.5 (t, 1H), 7.7 (d, 1H), 7.9 (d, 1H), 8.1 (s, 1H).



D108

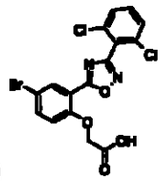
{4-Bromo-2-[3-(2-chlorophenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 2-chlorobenzonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.50 min, *m/z* 407.4 [M - H]⁻; ^{1}H NMR (DMSO-d_6): δ 4.94 (s, 2H), 7.2 (d, 1H), 7.5-7.7 (m, 3H), 7.8 (dd, 1H), 8.0 (d, 1H), 8.1 (s,1H).

74



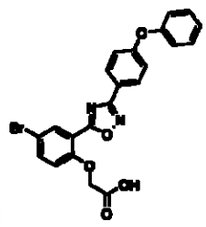
D109

{2-[3-(3,5-Bis-trifluoromethyl-phenyl)-[1,2,4]oxadiazol-5-yl]-4-bromo-phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 3,5-bistrifluoromethoxybenzonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 3,332 min, *m/z* 509.5 [M - H]$^-$; ^{1}H NMR (DMSO-d_6): δ 4.96 (s, 2H), 7.2 (d, 1H), 7.8 (d, 1H), 8.2 (s, 1H), 8.4 (s,1H), 8.5 (s, 1H), 8.6 (s, 1H).



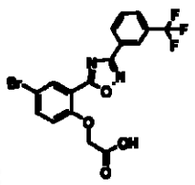
D110

{4-Bromo-2-[3-(2,6-dichlorophenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 2,6-Dicholoro-benzonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.59 min, *m/z* 441.4 [M - H]$^-$.



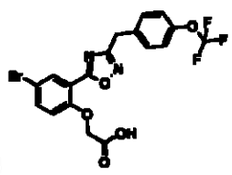
D111

{4-Bromo-2-[3-(4-phenoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 4-phenoxybenzonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 3.29 min, *m/z* 465.5 [M - H]$^-$; ^{1}H NMR (DMSO-d_6): δ 4.95 (s,2H), 7.2 (m, 6H), 7.4 (t, 2H), 7.8 (d, 1H), 8.0 (d, 2H), 8.1 (s, 1H).



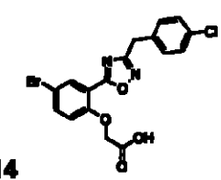
D112

{4-Bromo-2-[3-(3-trifluoromethylphenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 3-trifluoromethylbenzonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.96 min, *m/z* 441.4 [M - H]⁻; ^{1}H NMR (DMSO-d_6): δ 4.97 (s,2H), 7.2 (d, 1H), 7.8 (m, 2H), 8.0 (d, 1H), 8.2 (s, 1H), 8.3 (s, 1H), 8.4 (d, 1H).



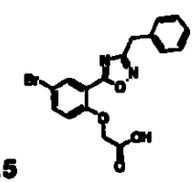
D113

{4-Bromo-2-[3-(4-trifluoromethoxy-benzyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and (4-trifluoromethoxyphenyl) acetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.76 min, *m/z* 4715 [M - H]⁻; ^{1}H NMR (DMSO-d_6): δ 4.2 (s, 2H), 4.9 (s, 2H), 7.1 (d, 1H), 7.3 (d, 2H), 7.5 (d, 2H), 7.7 (d, 1H), 8.0 (s, 1H).



D114

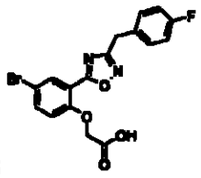
{4-Bromo-2-[3-(4-chloro-benzyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and (4-chlorophenyl)acetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt2.54 min, *m/z* 421.4 [M - H]⁻; ^{1}H NMR (DMSO-d_6): δ 4.2 (s, 2H), 4.9 (s, 2H), 7.1 (d, 1H), 7.4 (s, 4H), 7.8 (d, 1H), 8.0 (s, 1H).



D115

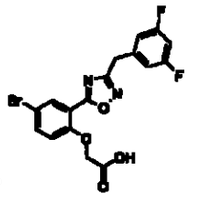
76

[2-(3-Benzyl-[1,2,4]oxadiazol-5-yl)-4-bromo-phenoxy]-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and phenylacetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.26 min, *m/z* 387.4 [M - H]$^-$; ^{1}H NMR (DMSO-d_6): δ 4.2 (s, 2H), 4.9 (s, 2H), 7.1 (d, 1H), 7.3 (m, 5H), 7.7 (d, 1H), 8.0 (s, 1H).



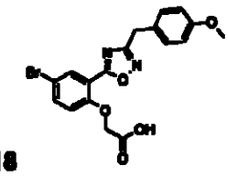
D116

{4-Bromo-2-[3-(4-fluoro-benzyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and (4-fluorophenyl)acetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.38 min, *m/z* 405.4 [M - H]$^-$.



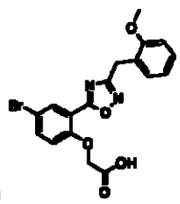
D117

{4-Bromo-2-[3-(3,5-difluoro-benzyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and (3,5-difluorophenyl)acetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.44 min, *m/z* 423.4 [M - H]$^-$.



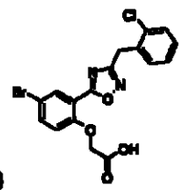
D118

{4-Bromo-2-[3-(4-methoxy-benzyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and (4-methoxyphenyl) acetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.25 min, *m/z* 417.4 [M –H]$^-$; ^{1}H NMR (DMSO-d_6): δ 4.1 (s, 2H), 4.9 (s, 2H), 6.9 (d, 2H), 7.1 (d, 1H), 7.2 (d, 2H), 7.7 (d, 1H), 8.0 (s, 1H).



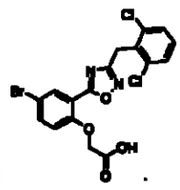
D119

{4-Bromo-2-[3-(2-methoxy-benzyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and (2-Methoxy-phenyl)-acetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.25 min, *m/z* 417.4 [M - H]⁻; ^{1}H NMR (DMSO-d_6): δ 3.7 (s, 3H), 4.1 (s, 2H), 4.9 (s, 2H), 6.9 (t, 1H), 7.0 (d, 1H), 7.1 (d, 1H), 7.2 (m, 2H), 7.7 (d, 1H), 8.0 (s, 1H).



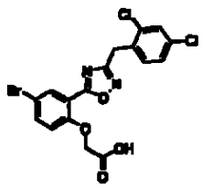
D120

{4-Bromo-2-[3-(2-chloro-benzyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and (2-chlorophenyl)acetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.48 min, *m/z* 421.4 [M - H]⁻; ^{1}H NMR (DMSO-d_6): δ 4.2 (s, 2H), 4.9 (s, 2H), 7.1 (d, 1H), 7.3 (m, 2H), 7.4 (m, 2H), 7.7 (dd, 1H), 8.0 (d, 1H).



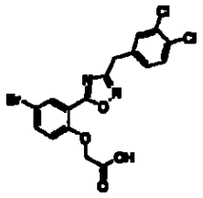
D121

{4-Bromo-2-[3-(2,6-dichloro-benzyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and (2,6-dichlorophenyl)acetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.58 min, *m/z* 455/457/459 [M - H]⁻; ^{1}H NMR (DMSO-d_6): δ 4.4 (s, 2H), 4.9 (s, 2H), 7.1 (d, 1H), 7.4 (t, 1H), 7.5 (d, 2H), 7.7-7.8 (dd, 1H), 8.0 (d, 1H).



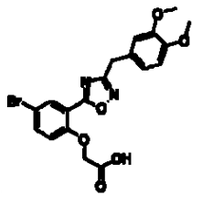
D122

{4-Bromo-2-[3-(2,4-dichloro-benzyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and (2,4-dichlorophenyl) acetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2,78 min, *m/z* 455/457/459 [M - H]⁻.



D123

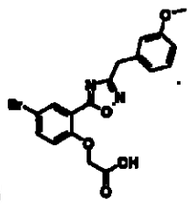
{4-Bromo-2-[3-(3,4-dichlorobenzyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and (3,4-dichlorophenyl)acetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.81 min, *m/z* 455/457/459 [M - H]⁻; ^{1}H NMR (DMSO-d_6): δ 4.3 (s, 2H), 4.8 (s, 2H), 7.1 (d, 1H), 7.3 (dd, 1H), 7.6 (d, 1H), 7.8 (d, 1H), 7.7 (dd, 1H), 8.0 (d, 1H).



D124

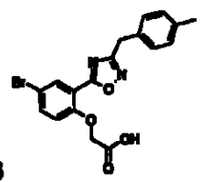
{4-Bromo-2-[3-(3,4-dimethoxybenzyl)-[1,2,4]oxadiazol-5-yl]phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and (3,4-bismethoxyphenyl)acetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.20 min, *m/z* 447,4 [M - H]⁻; ^{1}H NMR (DMSO-d_6): δ 3.72 (s, 3H), 3.74 (s, 3H), 4.1 (s, 2H), 4.9 (s, 2H), 6.8 (m, 2H), 6.9 (s, 1H), 7.1 (d, 1H), 7.7 (dd, 1H), 8.0 (d, 1H).

79



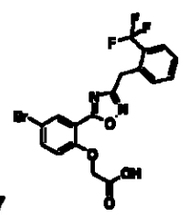
D125

{4-Bromo-2-[3-(3-methoxybenzyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and (3-methoxyphenyl)acetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.38 min, *m/z* 417.4 [M - H]$^-$; ^{1}H NMR (DMSO-d_6): δ 4.1 (s, 2H), 4.9 (s, 2H), 6.8 (d, 1H), 6.9 (m, 2H), 7.1 (d, 1H), 7.2 (t, 1H), 7:8 (m, 1H), 8.0 (d, 1H).



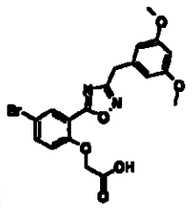
D126

{4-Bromo-2-[3-(4-methylbenzyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and (4-methylphenyl)acetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.72 min, *m/z* 401.4 [M - H]$^-$; ^{1}H NMR (DMSO-d_6): δ 3.3 (s, 3H), 4.1 (s, 2H), 4.9 (s, 2H), 7.1 (m, 3H), 7.2 (d, 2H), 7.7 (dd, 1H), 8.0 (d, 1H).



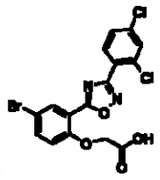
D127

{4-Bromo-2-[3-(2-trifluoromethylbenzyl)-[1,2,4]oxadiazol-5-yl]phenoxy}-acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and (2-trifluoromethylphenyl)acetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.77 min, *m/z* 455.5 [M - H]$^-$; ^{1}H NMR (DMSO-d_6): δ 4.3 (s, 2H), 4.9 (s, 2H), 7.1 (d, 1H), 7.5-7.6 (m, 2H), 7:6-7.7 (t, 1H), 7.7-7.8 (m, 2H), 8.0 (d, 1H).



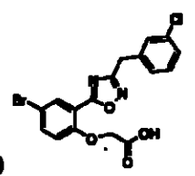
D128

{4-Bromo-2-[3-(3,5-dimethoxybenzyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and (3,5-bismethoxyphenyl)acetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.61 min, *m/z* 447.4 [M - H]$^-$; ^{1}H NMR (DMSO-d_6): δ 3.7 (s, 6H), 4.1 (s, 2H), 4.9 (s, 2H), 6.4 (d, 1H), 6.5 (d, 2H), 7.1 (d, 1H), 7.8 (dd, 1H), 8.0 (d, 1H).



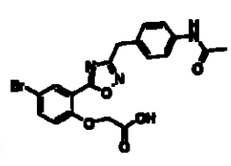
D129

{4-Bromo-2-[3-(2,4-dichlorophenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxy-benzoic acid methyl ester and 2,4-dichlorobenzonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.93 *m/z* 441/443/445 [M – H]$^-$; ^{1}H NMR (DMSO): δ 4.7 (s, 1H), 6.95-6.98 (d, 1H), 7.42-7.44 (d, 1H), 7.58-7.60 (d, 1H), 7.67 (s, 1H), 7.82-7.85 (d, 1H), 7.94-7.95 (s, 1H).



D130

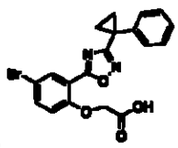
{4-Bromo-2-[3-(3-chlorobenzyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxy-benzoic acid methyl ester and 3-chlorophenylacetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.79 *m/z* 421.4 [M – H]$^-$; ^{1}H NMR (DMSO): δ 4.21 (s, 2H), 4.92 (s, 2H), 7.15-7.18(d, 1H), 7.32-7.39(m, 3H), 7.45 (s, 1H), 7.76-7.80 (dd, 1H), 8.03-8.04 (d, 1H).



D131

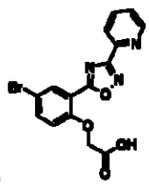
81

{2-[3-(4-Acetylaminobenzyl)-[1,2,4]oxadiazol-5-yl]-4-bromophenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and 4-acetamidophenylacetonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.15 *m/z* 444.4 $[M-H]^-$; ^1H NMR (DMSO): δ 2.02 (s, 3H), 4.10 (s, 2H), 4.92 (s, 2H), 7.14-7.17(d, 1H), 7.25-7.27(d, 2H), 7.52-7.54 (d, 2H), 7.76-7.78 (d, 1H), 8.03 (s, 1H).



D132

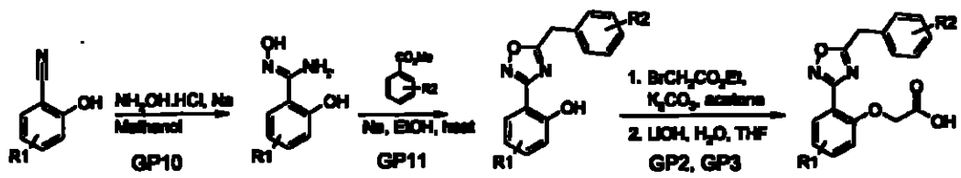
{4-Bromo-2-[3-(1-phenylcyclopropyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid. Title compound was prepared from 5-bromo-2-hydroxy-benzoic acid methyl ester and 1-phenyl-1-cyclopropanecarbonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt.2.756 *m/z* 413.4 $[M-H]^-$; ^1H NMR (DMSO-d_6): δ 0.92 (m, 2H), 1.11 (m, 2H), 4.38 (s, 2H), 6.63-6.66 (d, 1H), 6.79-6.88 (m, 3H), 6.93-6.95 (m, 2H), 7.25-7.29 (dd, 1H), 7.50-7.51 (d, 1H).

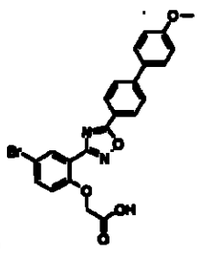


D133

[4-Bromo-2-(3-pyridin-2-yl-[1,2,4]oxadiazol-5-yl)phenoxy]acetic acid. Title compound was prepared from 5-bromo-2-hydroxybenzoic acid methyl ester and Pyridine-2-carbonitrile according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 1.89 min, *m/z* 374.4 $[M-H]^-$; ^1H NMR (DMSO-d_6): δ 4.9 (s, 2H), 7.2 (d, 1H), 7.6 (m, 1H), 7.8 (d, 1H), 8.0 (t, 1H), 8.2 (m, 2H), 8.8 (d, 1H).

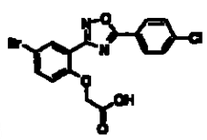
General Synthetic route IX





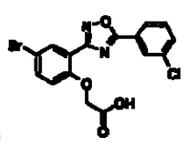
D134

{4-Bromo-2-[5-(4'-methoxybiphenyl-4-yl)-[1,2,4]oxadiazol-3-yl]phenoxy}acetic acid. Title compound was prepared from 2-hydroxy-5-bromo-benzonitrile and 4'-methoxy-biphenyl-4-carboxylic acid methyl ester according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.96 min, *m/z* 479.5 $[M - H]^-$.



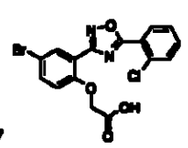
D135

{4-Bromo-2-[5-(4-chlorophenyl)-[1,2,4]oxadiazol-3-yl]phenoxy}acetic acid. Title compound was prepared from 2-hydroxy-5-bromo-benzonitrile and 4-chlorobenzoic acid methyl ester according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.61 min, *m/z* 407.4 $[M - H]^-$; ^{1}H NMR (DMSO-d_6): δ 4.3 (s, 2H), 6.9 (d, 1H), 7.6 (dd, 1H), 7.7 (d, 2H), 8.0 (d, 1H), 8.2 (d, 2H).



D136

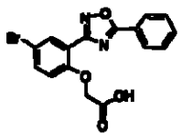
{4-Bromo-2-[5-(3-chlorophenyl)-[1,2,4]oxadiazol-3-yl]phenoxy}acetic acid. Title compound was prepared from 2-hydroxy-5-bromobenzonitrile and 3-chlorobenzoic acid methyl ester according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.61 min, *m/z* 407.4 $[M - H]^-$; ^{1}H NMR (DMSO-d_6): δ 4.4 (s, 2H), 6.9 (d, 1H), 7.6 (m, 2H), 7.8 (d, 1H), 8.0 (s, 1H), 8.2 (m, 2H).



D137

{4-Bromo-2-[5-(2-chlorophenyl)-[1,2,4]oxadiazol-3-yl]phenoxy}acetic acid. Title compound was prepared from 2-hydroxy-5-bromobenzonitrile and 2-chlorobenzoic acid methyl ester according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.45

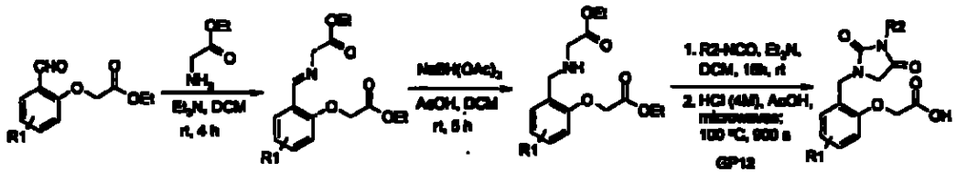
min, *m/z* 407.4 [M - H]$^-$; ^{1}H NMR (DMSO-d_6): δ 4.3 (s, 2H), 6.9 (d, 1H) 7.6-7.7 (m, 4H), 8.0 (s, 1H), 8.2 (d, 1H).

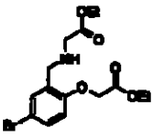


D138

[4-Bromo-2-(5-phenyl-[1,2,4]oxadiazol-3-yl)phenoxy]acetic acid. Title compound was prepared from 2-hydroxy-5-bromobenzonitrile and benzoic acid methyl ester according to GP10, GP11, GP2 and GP3: LC/MS (an10n8) Rt 2.33 min, *m/z* 373.4 [M - H]$^-$; ^{1}H NMR (DMSO-d_6): δ 4.8 (s, 2H), 7.1 (d, 1H), 7.6-7.7 (m, 4H), 8.0 (d, 1H), 8.2 (d, 2H).

General Synthetic Route X





Intermediate-13

4-Bromo-2-[(ethoxycarbonylmethylamino)methyl]phenoxyacetic acid ethyl ester. 4-Bromo-2-formylphenoxyacetic acid ethyl ester (1.44 g, 5 mmol) was dissolved in dichloromethane (50 mL) and glycine ethyl ester hydrochloride (1.39 g, 10 mmol) as well as Et_3N (1.4 mL, 10 mmol) was added. The mixture was stirred at room temperature for 4 h. Water and dichloromethane was added and the organic phase was passed through a phase separation filter and then evaporated to give {4-bromo-2-[(E)-ethoxycarbonylmethylaminomethyl]phenoxy}acetic acid ethyl ester, which was redissolved in dichloromethane (50 mL) and treated with $NaBH(OAc)_3$ (2.11 g, 10 mmol) and AcOH (1 mL), and then stirred at room temperature for 5 h. Saturated Na_2CO_3, water and dichloromethane was added, and the organic phase was passed through a phase separation filter and evaporated to give the title compound (1.56 g, 84% overall yield).

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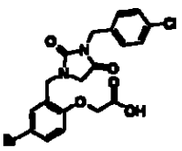
General procedure 12 (GP12)

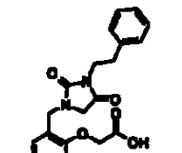
Reaction with isocyanates followed by ringclosure/hydrolysis

The aldehyde (0.6 mmol) was dissolved in dichloromethane (6 mL), and the isocyanate (1.2 mmol) and Et_3N (176 µL, 1.26 mmol) was added. The mixture was stirred at room temperature overnight. Then glycine (150 mg, 2 mmol) was added (as scavenger for excess isocyanate) and the mixture was stirred for additional 2 h. Finally water and dichloromethane was added and the organic phase was passed through a phase separation filter and then evaporated to give the urea, which was dissolved in acetic acid (3.5 mL) and placed in a sealed glass vial. Then 4 M HCl (3.5 mL) was added and the mixture heated by microwaves to 100 °C for 900s. After cooling to room temperature a white precipitate was formed, and the hydantoin was obtained after filtration and washing with water. In cases where the product did not precipitate after the hydrolysis, dichloromethane and water was added to the mixture, and the organic phase was passed through a phase separation filter. Evaporation of the organic phase gave the product, which in some cases was further purified on a 1 g SAX Acetate SPE column (equilibrated with 100% MeOH and then eluted with 10% AcOH in MeOH).



D139

4-Bromo-2-[3-(4-chlorobenzyl)-2,4-dioxoimidazolidin-1-ylmethyl]phenoxyacetic acid. Prepared from 4-bromo-2-[(ethoxycarbonylmethylamino)methyl]phenoxyacetic acid ethyl ester (235 mg, 0.63 mmol) and 4-chlorobenzylisocyanate (166 µL, 1.26 mmol) according to GP12 (yield: 183.4 mg, 62%): LC/MS (an10p8): Rt 2.3 min, *m/z* 465 [M - H]⁻; ^{1}H NMR (DMSO-d_6): δ 4.05 (s, 2H), 4.48 (s, 2H), 4.55 (s, 2H), 4.73 (s, 2H), 6.92 (d, *J* = 8.3 Hz, 1H), 7.25-7.45 (m, 6H), 13.11 (br. s, 1H).

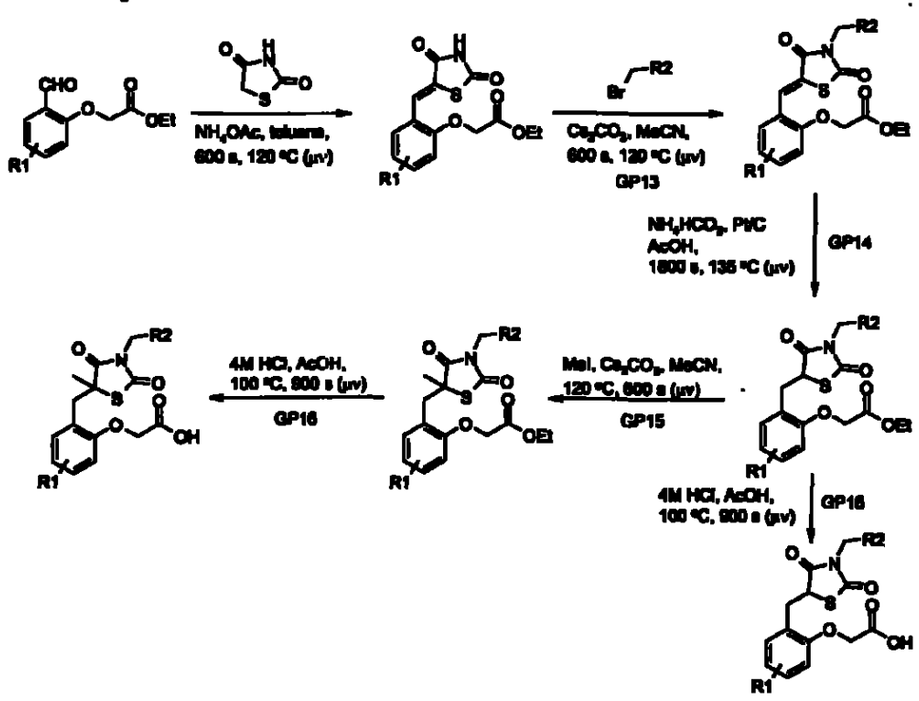


D140

4-Bromo-2-(2,4-dioxo-3-phenethylimidazolidin-1-ylmethyl)phenoxyacetic acid. Prepared from 4-bromo-2-[(ethoxycarbonylmethylamino)methyl]phenoxyacetic acid ethyl ester and phenethylisocyanateaccording to GP12: LC/MS (an10p8): Rt 2.2 min,

m/z 445 [M - H]$^-$; ^{1}H NMR (DMSO-d_6): δ 2.84 (t, *J* = 7.2 Hz, 2H), 3.59 (t, *J* = 7.2 Hz, 2H), 3.94 (s, 2H), 4.45 (s, 2H), 4.76 (s, 2H), 6.93 (d, *J* = 8.6 Hz, 1H), 7.17-7.46 (m, 7H), 12.45 (br. s, 1H).

General Synthetic Route XI



General procedure 13 (GP13)

N-Alkylation

The 2-[2,4-dioxothiazolidin-(5Z)-ylidenemethyl]phenoxyacetic acid ethyl ester (0.85 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and acetonitrile (10 mL) was mixed in a sealed glass vial. Then the alkylating agent (1.0 mmol) was added and the mixture heated by microwaves to 120 °C for 600 s. Water was added and the mixture was extracted with dichloromethane. The organic phase was passed through a phase separation filter and then evaporated. The product was used directly in the next step or purified by column chromatography (SiO_2).

General procedure 14 (GP14)

Hydrogenation

The 5-benzylidenylthiazolidine-2,4-dione (~0.8 mmol), ammonium formate (1.0 g, 16 mmol), Pt/C (5 wt%, 500 mg, 0.13 mmol), and acetic acid (12 mL) was mixed in a

sealed glass vial and heated by microwaves to 135 °C for 1800 s. Then methanol (15 mL) was added and the mixture was filtered through a 20 µm PE filter and then through a 1 g SAX Acetate SPE column, which was washed with additional methanol (10 mL). After evaporation of the methanol, dichloromethane and water was added, and the organic phase was passed through a phase separation filter and concentrated to give the product, which was used directly or purified by column chromatography on SiO_2.

General procedure 15 (GP15)

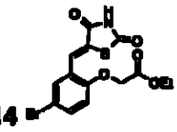
Alkylation of 5-position of thiazolidine-2,4-diones

3-Alkyl-5-arylmethylthiazolidine-2,4-dione (0.15 mmol), methyl iodide (28 µL, 0.45 mmol), Cs_2CO_3 (147 mg, 0.45 mmol), and acetonitrile (10 mL) was mixed in a sealed glass vial and heated by microwaves to 120 °C for 3600 s. Water and dichloromethane was added and the organic phase was passed through a phase separation filter and then evaporated to give the product, which was used directly for the hydrolysis.

General procedure 16 (GP16)

Acidic ester hydrolysis

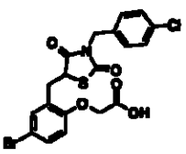
The ethyl phenoxyacetate (0.02-0.2 mmol) was dissolved in acetic acid (5 mL), 4M HCl (5 mL) was added and the mixture was heated by microwaves to 100 °C for 900 s. After cooling to room temperature a white precipitate was formed, which was filtered of, washed with water and dried to give the product. In cases where the product did not precipitate after the hydrolysis, dichloromethane was added, the organic phase was washed with water and concentrated, and the residue was purified on a 1 g SAX Acetate SPE column (equilibrated with 100% MeOH and then eluted with 10% AcOH in MeOH) to give the product.

Intermediate-14 

4-Bromo-2-[2,4-dioxothiazolidinylidenemethyl]phenoxyacetic acid ethyl ester.

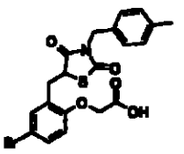
4-Bromo-2-formylphenoxyacetic acid ethyl ester (2.47 g, 8.7 mmol), 2,4-thiazolidinedione (1.13 g (90%), 8.7 mmol), and ammonium acetate (671 mg, 8.7 mmol) was mixed with toluene (9 mL) in a sealed vial and heated by microwaves to 120 °C for 600 s. After cooling to room temperature and scratching the inside of the

glass, the product precipitated out. The precipitate was filtered and washed with toluene to give the title compound as a yellow solid (2.38 g, 71%).



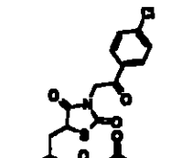
D141

4-Bromo-2-[3-(4-chlorobenzyl)-2,4-dioxothiazolidin-5-ylmethyl]phenoxyacetic acid. Prepared from 4-chlorobenzylbromide and 4-bromo-2-[2,4-dioxothiazolidin-(5Z)-ylidenemethyl]phenoxyacetic acid ethyl ester according to GP13, GP14 and GP16 to give 50.4 mg (21% overall yield) of the title compound: LC/MS (an10p8): Rt 2.6 min, *m/z* 482 [M - H]$^-$. ^{1}H NMR (DMSO-d_6): δ 3.05 (dd, *J* = 13.8, 9.7 Hz, 1H), 3.57 (dd, *J* = 13.8, 4.9 Hz, 1H), 5.11 (dd, *J* = 9.7, 4.9 Hz, 1H), 4.67 (s, 2H), 4.75 (s, 2H), 6.91 (d, *J* = 8.7, 1H), 7.25-7.28 (m, 2H), 7.37-7.42 (m, 4H), 13.15 (br. s, 1H).



D142

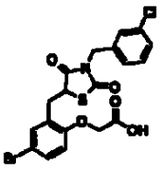
4-Bromo-2-[3-(4-methylbenzyl)-2,4-dioxothiazolidin-5-ylmethyl]phenoxyacetic acid. Prepared from 4-methylbenzylbromide and 4-bromo-2-[2,4-dioxothiazolidin-(5Z)-ylidenemethyl]phenoxyacetic acid ethyl ester according to GP13, GP14 and GP16 (yield: 14 mg, 21%): LC/MS (an10p8): Rt 2.5 min, *m/z* 462 [M - H]$^-$. ^{1}H NMR (DMSO-d_6): δ 2.98-3.07 (m, 1H), 3.53-3.59 (m, 1H), 4.63 (s, 2H), 4.74 (s, 2H), 5.07-5.13 (m, 1H), 6.89-6.91 (m, 1H), 7.11-7.16 (m, 4H), 7.38-7.43 (m, 2H), 13.11 (br s, 1H).



D143

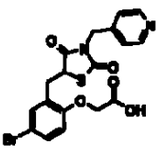
4-Bromo-2-[3-[2-(4-chlorophenyl)-2-oxoethyl]-2,4-dioxothiazolidin-5-ylmethyl]phenoxyacetic acid. Prepared from 2-bromo-1-(4-chlorophenyl)ethanone and 4-bromo-2-[2,4-dioxothiazolidin-(5Z)-ylidenemethyl]phenoxyacetic acid ethyl ester according to GP13, GP14 and GP16 (yield: 8.2 mg, 34%): LC/MS (an10p8): Rt

2.8 min, *m/z* 510 [M - H]$^-$. ^{1}H NMR (DMSO-*d6*): δ 3.01-3.09 (m, 1H), 3.57-3.63 (m, 1H), 4.79 (s, 2H), 5.17 (s, 2H), 5.21-5.24 (m, 1H), 6.91-6.95 (m, 1H), 7.44 (m, 2H), 7.66-7.69 (m, 2H), 8.07-8.09 (m, 2H).



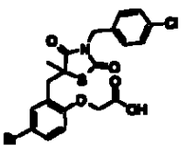
D144

4-Bromo-2-[3-(3-chlorobenzyl)-2,4-dioxothiazolidin-5-ylmethyl]phenoxyacetic acid (7d). Prepared from 3-chlorobenzyl bromide and 4-bromo-2-[2,4-dioxothiazolidin-(5Z)-ylidenemethyl]phenoxyacetic acid ethyl ester according to GP13, GP14 and GP16: LC/MS (an10p8): Rt 2.6 min, *m/z* 484 [M + H]$^+$. ^{1}H NMR (DMSO-*d6*): δ 3.02-3.10 (m, 1H), 3.54-3.60 (m, 1H), 4.69 (s, 2H), 4.75 (s, 2H), 5.09-5.14 (m, 1H), 6.89-6.92 (m, 1H), 7.18 (m, 1H), 7.33-7.43 (m, 5H), 13.01 (br s, 1H).



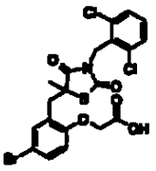
D145

4-Bromo-2-(2,4-dioxo-3-pyridin-4-ylmethylthiazolidin-5-ylmethyl)phenoxyacetic acid. Prepared from 4-bromomethylpyridine and 4-bromo-2-[2,4-dioxothiazolidin-(5Z)-ylidenemethyl]phenoxyacetic acid ethyl ester according to GP13, GP14 and GP16: LC/MS (an10p8): Rt 2.1 min, *m/z* 451 [M + H]$^+$.



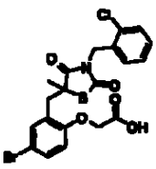
D148

4-Bromo-2-[3-(4-chlorobenzyl)-5-methyl-2,4-dioxothiazolidin-5-ylmethyl]-phenoxyacetic acid. Prepared from 4-bromomethylpyridine according to GP13, GP14, GP15 and GP16 (yield: 29 mg, 15%): LC/MS (an10p8): Rt 3.0 min, *m/z* 496 [M - H]$^-$; ^{1}H NMR (DMSO-*d6*): 1.71 (s, 3H), 3.24 (d, *J* = 13.8 Hz, 1H), 3.39 (d, *J* = 13.8 Hz, 1H), 4.63-4.68 (m, 4H), 6.86 (d, *J* = 8.6 Hz, 1H), 7.13-7.43 (m, 6H), 13.08 (br s, 1H).



D147

4-Bromo-2-[3-(2,6-dichlorobenzyl)-5-methyl-2,4-dioxothiazolidin-5-ylmethyl]phenoxyacetic acid. Prepared from 2,6-dichlorobenzylbromide according to GP13, GP14, GP15 and GP16 to give 21.1 mg of the title compound: LC/MS (an10n8): Rt 2.9 min, *m/z* 532 [M - H]$^-$; ^{1}H NMR (DMSO-d_6): δ 1.63 (s, 3H), 3.16 (d, *J* = 13.6 Hz, 1H), 3.40 (d, *J* = 13.6 Hz, 1H), 4.65 (s, 2H), 4.92 (s, 2H), 6.86 (d, *J* = 8.9 Hz, 1H), 7.21 (d, *J* = 2.5 Hz, 1H), 7.35-7.48 (m, 4H), 12.38 (br s, 1H).



D148

4-Bromo-2-[3-(2-chlorobenzyl)-5-methyl-2,4-dioxothiazolidin-5-ylmethyl]phenoxyacetic acid. Prepared from 2-chlorobenzylbromide according to GP13, GP14, GP15 and GP16 to give 22.0 mg of the title compound: LC/MS (an10n8): Rt 2.8 min, *m/z* 498 [M - H]$^-$; ^{1}H NMR (DMSO-d_6): δ 1.76 (s, 3H), 3.28 (d, *J* = 13.7 Hz, 1H), 3.43 (d, *J* = 13.7 Hz, 1H), 4.67 (d, *J* = 3.2 Hz, 2H), 4.73 (s, 2H), 6.81 (d, *J* = 8.9 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 1H), 7.24-7.36 (m, 3H), 7.43-7.50 (m, 2H), 12.18 (br s, 1H).

Biological Assays

Materials and Methods

Generation/origin of the cDNA Constructs. The coding sequence of the human CRTH2 receptor (genbank accession no NM_004778) was amplified by PCR from a human hippocampus cDNA library and inserted into the pcDNA3.1(+) expression vector (Invitrogen) via 5' Hind*III* and 3' EcoR*I*. To generate a CRTH2-Renilla luciferase (CRTH2-Rluc) fusion protein, the CRTH2 coding sequence without a STOP codon and Rluc were amplified, fused in frame by PCR and subcloned into the pcDNA3.1(+)Zeo expression vector (Invitrogen). Human β-arrestin2 (β-arr2) N-terminally tagged with GFP^2 (βarr2-GFP^2) and Renilla luciferase were purchased from BioSignal Packard Inc, (Montreal, Canada). The sequence identity of the

construct was verified by restriction endonuclease digests and sequencing in both directions on an ABI Prism (Applied Biosystems, Foster City, CA).

Sequence ID CRTH2 (protein sequence):

MSANATLKPLCPILEQMSRLQSHSNTSIRYIDHAAVLLEGLASLLGLVEN
GVILFVVGCRMRQTVVTTWVLHLALSDLLASASLPFFTYFLAVGHSWELG
TTFCKLESSIFFLNMFASGFLLSAISLDRCLQVVRPVWAQNHRTVAAAHK
VCLVLMALAVLNTVPYFVFRDTISRLDGRIMCYYNVLLLNPGPDRDATCN
SRQAALAVSKFLLAFLVPLAIIASSHAAVSLRLQHRGRRRPGRFVRLVAA
VVAAFALCWGPYHVFSLLEARAHANPGLRPLVWRGLPFVTSLAFFNSVAN
PVLYVLTCPDMLRKLRRSLRTVLESVLVDDSELGGAGSSRRRRTSSTARS
ASPLALCSRPEEPRGPARLLGWLLGSCAASPQTGPLNRALSSTSS

Sequence ID CRTH2 (nucleotide sequence):

atgtcggc
caacgccaca ctgaagccac tctgccccat cctggagcag atgagccgtc
tccagagcca
cagcaacacc agcatccgct acatcgacca cgcggccgtg ctgctgcacg
ggctggcctc
gctgctgggc ctggtggaga atggagtcat cctcttcgtg gtgggctgcc
gcatgcgcca
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gccgccgccg
cacctcctcc accgcccgct cggcctcccc tttagctctc tgcagccgcc
cggaggaacc
gcggggcccc gcgcgtctcc tcggctggct gctgggcagc tgcgcagcgt
ccccgcagac

91

gggccccctg aaccgggcgc tgagcagcac ctcgagttag

Cell Culture and Transfection. COS-7 cells were grown in Dulbecco's modified Eagle's medium (DMEM) 1885 supplemented with 10% fetal bovine serum, 100 units/ml penicillin, 1000 µg/ml streptomycin, and kept at 37°C in a 10% CO_2 atmosphere. HEK293 cells were maintained in Minimum Essential medium (MEM) supplemented with 10% (v/v) heat inactivated fetal calf serum (HIFCS), 2mM Glutamax™-I, 1% non essential amino acids (NEAA), 1% sodium pyruvate and 10 µg/ml gentamicin. For binding experiments, COS7 cells were transiently transfected with the CRTH2 receptor using a calcium phosphate-DNA coprecipitation method with the addition of chloroquine (as described by Holst et al., 2001+). To perform the functional Bioluminescence Resonance Energy Transfer (BRET) assays, a HEK293 cell clone stably expressing βarr2-GFP^2 and CRTH2-Rluc was generated (CRTH2-HEK293 cells).

Binding assay. 24h after transfection COS-7 cells were seeded into 96well plates at a density of 30.000 cells/well. Competition binding experiments on whole cells were then performed about 18-24 h later using 0.1 nM [^{3}H]PGD2 (NEN, 172 Ci/mmol) in a binding buffer consisting of HBSS (GIBCO) and 10 mM HEPES. Competing ligands were diluted in DMSO which was kept constant at 1% (v/v) of the final incubation volume. Total and nonspecific binding were determined in the absence and presence of 10 µM PGD2. Binding reactions were routinely conducted for 3 h at 4°C and terminated by 2 washes (100 µl each) with ice cold binding buffer. Radioactivity was determined by liquid scintillation counting in a TOPCOUNTER (Packard) following over night incubation in Microscint 20. Stable HEK293 cells were seeded at a density of 30.000 cells/well 18-24 h prior to the binding assay which was performed essentially as described for COS7 cells above. Determinations were made in duplicates.

BRET assay. Functional BRET assays were performed on HEK293 cells stably expressing human CRTH2-Rluc and GFP^2-β-arr2. Prior to their use in the BRET assay cells were detached and re-suspended in D-PBS with 1000 mg/L L-Glucose at a density of 2x10^6 cells/mL. DeepBlueC™ was diluted to 50 µM in D-PBS with 1000 mg/L L-Glucose (light sensitive). 100 µL of cell suspension was transferred to wells in a 96-well microplate (white OptiPlate) and placed in the Mithras LB 940 instrument (BERTHOLD TECHNOLOGIES, Bad Wildbad, Germany). 12 µL/well agonist was

then injected by injector 1 and 10 µL/well DeepBlueC™ was injected simultaneously by injector 2. Five seconds after the injections the light output from the well was measured sequentially at 400 nm and 515 nm, and the BRET signal (mBRET ratio) was calculated by the ratio of the fluorescence emitted by GFP^2-β-arr2 (515 nm) over the light emitted by the receptor-Rluc (400 nm). Antagonists were added before placing the microplates into the Mithras LB 940 and allowed to incubate for 15 minutes prior to the addition of agonist and DeepBlueC™. Compounds were dissolved in DMSO and the final DMSO concentration was kept constant at 1% in the assay.

Human eosinophil shape change assay. Blood was sampled from healthy volunteers according to a protocol approved by the Ethics Committee of the University of Graz and processed as described previously (Bohm et al., 2004). Preparations of polymorphonuclear leukocytes (containing eosinophils and neutrophils) were prepared by dextran sedimentation of citrated whole blood and Histopeque gradients. The resulting cells were washed and resuspended in assay buffer (comprising PBS with Ca^{2+}/Mg^{2+} supplemented with 0.1% BSA, 10 mM HEPES and 10 mM glucose, pH 7.4) at 5 x 10^6 cells/mL. Cells were incubated with the antagonists or vehicle (PBS or DMSO) for 10 min at 37°C and then stimulated with various concentration of the agonists (PGD2 or eotaxin) for 4 min at 37°C. To stop the reaction, samples were transferred to ice and fixed with 250 µL of fixative solution. Samples were immediately analyzed on a FACSCalibur flow cytometer (Becton Dickinson) and eosinophils were identified according to their autofluorescence in the FL-1 and FL-2 channels. Shape change responses were quantified as percentage of the maximal response to PGD2 or eotaxin in the absence of an antagonist.

Materials

Tissue culture media and reagents were purchased from the Gibco Invitrogen corporation (Breda, Netherlands). PGD2 was obtained from Cayman and [3H]PGD2 from NEN.

Data analysis

Curve analysis was performed with the GraphPadPrism software 3.0 (Graphpad Prism Inc., San Diego, USA) and IC_{50} values were calculated as a measure of the antagonistic potencies.

References

Holst B, Hastrup H, Raffetseder U, Martini L, Schwartz TW. Two active molecular phenotypes of the tachykinin NK1 receptor revealed by G-protein fusions and mutagenesis. J Biol Chem. 2001 Jun 8;276(23):19793-9. Epub 2001 Feb 22.

Biological data:

Compounds were tested in the receptor binding assay and the functional antagonist assay described below, and their IC_{50} values were assessed. The compounds are grouped in three classes:

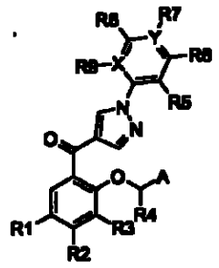
A: IC_{50} value lower than 0.5 µM

B: IC_{50} value between 0.5 µM and 5 µM

C: IC_{50} value higher than 5 µM

Tables 1 to 7 give the biological test results for the compounds synthesised above and for some additional compounds acquired from commercial sources. The ability of the compounds above to inhibit prostaglandin D2 induced eosinophil shape change is demonstrated by the examples in Figure 1.

Table 1

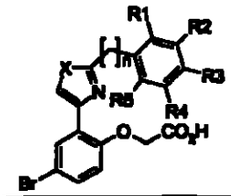


	A	R1	R2	R3	R4	R5	R6	R7	R8	R9	X	Y	Binding IC_{50}	Antag. IC_{50}
D1	COOH	Br	H	H	H	H	H	H	H	H	C	C	A	A
D2	COOH	H	H	H	H	H	H	H	H	H	C	C	A	B
D3	COOH	F	H	H	H	H	H	H	H	H	C	C	A	B
D4	Tetrazole	Br	H	H	H	H	H	H	H	H	C	C	A	C
D5	COOH	Ph	H	H	H	H	H	H	H	H	C	C	A	A
D6	COOH	Br	H	H	H	H	H	H	H	-	N	C	A	A
D7	COOH	Br	H	H	H	H	H	OMe	H	H	C	C	A	A
D8	COOH		H	H	H	H	H	H	H	H	C	C	A	B
D9	COOH		H	H	H	H	H	H	H	H	C	C	A	A
D10	COOH	Cl	H	H	H	H	H	H	H	H	C	C	A	B

D11	COOH	Me	H	H	H	H	H	H	H	H	C	C	A	B
D12	COOH	Cl	Me	H	H	H	H	H	H	H	C	C	B	C
D13	COOH	Cl	H	Cl	H	H	H	H	H	H	C	C	C	C
D14	COOH	Br	H	H	H	Cl	H	H	H	H	C	C	C	A
D15	COOH	Br	H	H	H	H	Cl	H	H	H	C	C	A	A
D16	COOH	Br	H	H	H	H	H	Br	H	H	C	C	A	A
D17	COOH	Br	H	H	H	H	H	Cl	H	H	C	C	A	A
D18	COOH	Br	H	H	H	Et	H	H	H	H	C	C	A	A
D19	COOH	NO_2	H	H	H	H	H	Cl	H	H	C	C	A	A
D20	COOH	NO_2	H	H	H	H	H	H	H	H	C	C	A	A
D21	COOH	Br	H	H	H	Br	H	H	H	H	C	C	A	A
D22	COOH	Br	H	H	H	F	H	H	H	H	C	C	A	A
D23	COOH	Br	H	H	H	CF_3	H	H	H	H	C	C	A	A
D24	COOH	Br	H	H	H	H	Br	H	H	H	C	C	A	A
D25	COOH	Br	H	H	H	H	CF_3	H	H	H	C	C	A	A
D26	COOH	Br	H	H	H	Cl	H	Cl	H	H	C	C	A	A
D27	COOH	NO_2	H	H	H	Cl	H	H	H	H	C	C	A	A
D28	COOH	NO_2	H	H	H	Br	H	H	H	H	C	C	A	A
D29	COOH	Br	H	H	H	Cl	H	H	H	Cl	C	C	A	A
D30	COOH	Et	H	H	H	Br	H	H	H	H	C	C	A	A
D31	COOH	i-Pr	H	H	H	Cl	H	H	H	H	C	C	A	A
D32	COOH	Br	H	H	H	H	H	OCF_3	H	H	C	C	A	A
D33	COOH	Br	H	H	H	Br	H	Br	H	H	C	C	A	A
D34	COOH	Br	H	H	H	Cl	H	Br	H	H	C	C	A	A
D35	COOH	Br	H	H	H	Cl	H	Cl	H	Cl	C	C	A	A
D36	COOH	OMe	H	H	H	H	H	H	H	H	C	C	A	B
D37	COOH	Br	H	H	Me	H	H	H	H	H	C	C	A	A
(S)-D37	COOH	Br	H	H	Me	H	H	H	H	H	C	C	A	A
D38	COOH	Br	H	H	Me	Cl	H	H	H	H	C	C	A	A
D39	COOH	Br	H	H	Me	Cl	H	H	H	Cl	C	C	A	A
D40	COOH	Br	H	H	H	CN	H	H	H	H	C	C	A	A
D41	COOH	Br	H	H	H	OEt	H	H	H	H	C	C	A	A
D42	COOH	Br	H	H	H	Et	H	Br	H	H	C	C	A	A
D43	COOH	Br	H	H	H	OPh	H	H	H	H	C	C	A	A
D44	COOH	Br	H	H	H	SMe	H	H	H	H	C	C	A	A
D45	COOH	Br	H	H	H	Br	H	Me	H	H	C	C	A	A
D46	COOH	Br	H	H	Me	Et	H	Br	H	H	C	C	A	A
D47	COOH	Br	H	H	Me	OPh	H	H	H	H	C	C	A	A
D48	COOH	Br	H	H	Me	OEt	H	H	H	H	C	C	A	A
D49	COOH	Br	H	H	Me	SMe	H	H	H	H	C	C	A	A
D50	COOH	Br	H	H	Me	Br	H	Me	H	H	C	C	A	A
D51	COOH	Br	H	H	Me	OPh	H	H	H	H	C	C	A	A

D52	COOH	Br	H	H	H	OCF_3	H	H	H	H	C	C	A	A
D53	COOH	Et	H	H	H	Me	H	H	H	Me	C	C	A	A
D54	COOH	Br	H	H	H	Me	H	Me	H	H	C	C	A	A
D55	COOH	Br	H	H	Me	Me	H	Me	H	H	C	C	A	A
D56	COOH	Br	H	H	H	Me	H	Cl	H	H	C	C	A	A
D59	COOH	Br	H	H	H	Cl	H	H	Cl	H	C	C	A	A
D60	COOH	Br	H	H	H	OMe	H	H	H	H	C	C	A	A
D61	COOH	Br	H	H	H	H	Cl	Cl	H	H	C	C	A	A
D62	COOH	Br	H	H	Me	Me	H	Cl	H	H	C	C	A	A
D63	COOH	Br	H	H	Me	Cl	H	Cl	H	H	C	C	A	A
D64	COOH	Br	H	H	Me	H	Cl	Cl	H	H	C	C	A	A
D65	COOH	Br	H	H	Me	OMe	H	H	H	H	C	C	A	A
D66	COOH	NH_2	H	H	H	H	H	H	H	H	C	C	B	A
D67	COOH	Br	H	H	Me	Cl	H	Br	H	H	C	C	A	A
D68	COOH	Br	H	H	Me	Cl	H	Cl	H	Cl	C	C	A	A
D69	COOH	Br	H	H	Me	Br	H	Br	H	H	C	C	A	A
D70	COOH	Br	H	H	H	Et	H	H	H	Et	C	C	A	A
D71	COOH	Br	H	H	H	Me	H	H	H	Me	C	C	A	A
D72	COOH	Br	H	H	H	Et	H	H	H	Me	C	C	A	A
D73	COOH	Br	H	H	H	i-Pr	H	H	H	H	C	C	A	A
D74	COOH	EtO	H	H	H	H	H	H	H	H	C	C	B	C
D75	COOH	n-Bu	H	H	H	H	H	H	H	H	C	C	A	C
D76	COOH	Br	H	H	H	Cl	H	H	H	Me	C	C	A	A
D77	COOH	Br	H	H	Me	Me	H	H	H	Me	C	C	A	A
D78	COOH	Br	H	H	Me	Et	H	H	H	Et	C	C	A	A
D79	COOH	Br	H	H	Me	i-Pr	H	H	H	H	C	C	A	A
D80	COOH	Br	H	H	H	Cl	H	H	H	Cl	C	N	A	A
D81	COOH	Br	H	H	H	H	H	CF_3	H	H	C	C	A	A

Table 2



	n	X	R1	R2	R3	R4	R5	Binding IC_{50}	Antag. IC_{50}
D83	0	O	H	H	H	H	H	A	C
D84	0	O	H	H	OMe	H	H	A	B
D85	0	O	H	H	Cl	H	H	A	C

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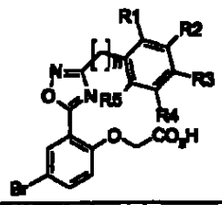
D86	0	O	H	OMe	H	H	H	A	A
D87	0	O	H	H	OEt	H	H	A	C
D88	1	O	H	H	H	H	H	A	A
D89	1	O	H	OMe	H	H	H	A	A
D90	1	O	Cl	H	F	H	H	A	A
D91	1	O	Cl	H	H	H	Cl	A	A

D92	1	O	H	H	OMe	H	H	A	A
D93	0	S	H	H	H	H	H	A	A
D94	1	S	H	H	Cl	H	H	A	A

Table 3

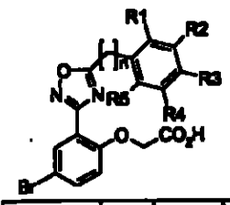


	n	R1	R2	R3	R4	R5	Binding IC_{50}	Antag. IC_{50}
D99	0	H	H	H	H	H	A	A

D100	0	H	H	F	H	H	A	A
D101	0	H	H	OMe	H	H	A	A
D102	0	H	H	Cl	H	H	A	A
D103	0	H	H	OCF_3	H	H	A	A
D104	0	H	OMe	H	H	H	A	A
D105	0	H	Cl	H	H	H	A	A
D106	0	H	H	CF_3	H	H	A	A
D107	0	OMe	H	H	H	H	A	A
D108	0	Cl	H	H	H	H	A	A
D109	0	H	CF_3	H	CF_3	H	A	C
D110	0	Cl	H	H	H	Cl	A	A
D111	0	H	H	OPh	H	H	A	A
D112	0	H	CF_3	H	H	H	A	A
D113	1	H	H	OCF_3	H	H	A	A
D114	1	H	H	Cl	H	H	A	A
D115	1	H	H	H	H	H	A	A

D116	1	H	H	F	H	H	A	A
D117	1	H	F	H	F	H	A	A
D118	1	H	H	OMe	H	H	A	A
D119	1	H	OMe	H	H	H	A	A
D120	1	Cl	H	H	H	H	A	A
D121	1	Cl	H	H	H	Cl	A	A
D122	1	Cl	H	Cl	H	H	A	A
D123	1	H	Cl	Cl	H	H	A	A
D124	1	H	OMe	OMe	H	H	A	A
D125	1	H	OMe	H	H	H	A	C
D126	1	H	H	Me	H	H	A	A
D127	1	CF_3	H	H	H	H	A	A
D128	1	H	OMe	H	OMe	H	A	B
D129	0	Cl	H	Cl	H	H	A	A
D130	1	H	Cl	H	H	H	A	A
D131	1	H	H	NHAc	H	H	A	A

Table 4



	n	R1	R2	R3	R4	R5	Activity	Binding IC_{50}	Antag. IC_{50}
D134	0	H	H	4-PhOMe	H	H	A	A	A
D135	0	H	H	Cl	H	H	A	A	A
D136	0	H	Cl	H	H	H	A	A	A
D137	0	Cl	H	H	H	H	A	A	A
D138	0	H	H	H	H	H	A	A	C

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Table 5

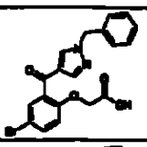
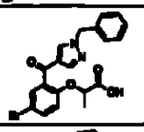
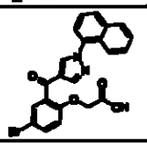
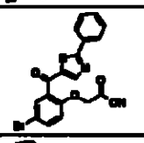
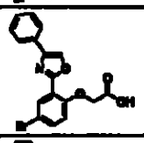
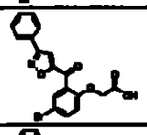
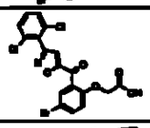
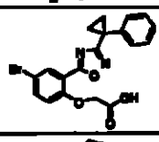
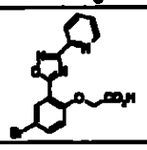
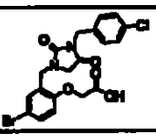
	Structure	Binding IC_{50}	Antag. IC_{50}
D56		A	A
D57		A	A
D82		A	A
D95		A	A
D96		A	B
D97		A	A
D98		A	
D132		A	A
D133		A	C

Table 6

	Structure	Binding IC_{50}	Antag. IC_{50}
D139		A	A

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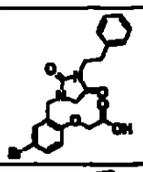
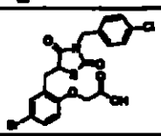
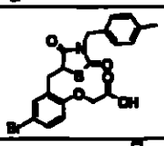
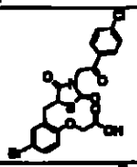
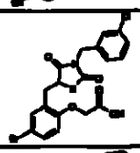
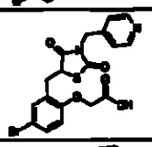
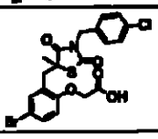
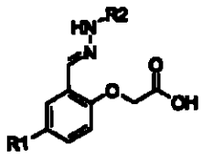
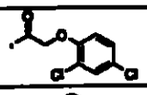
D140		A	B
D141		A	A
D142		A	A
D143		A	A
D144		A	A
D145		A	A
D146		A	A

Table 7



Cmp	R1	R2	Binding IC_{50}	Antag. IC_{50}
D149	H		A	A
D150	Br		A	C
D151	Br		A	C

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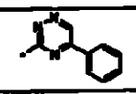
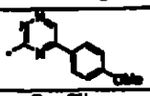
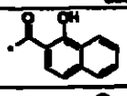
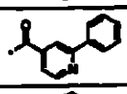
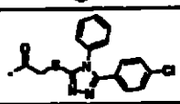
D152	Br		A	B
D153	H		B	C
D154	H		A	A
D155	H		A	B
D158	H		A	B

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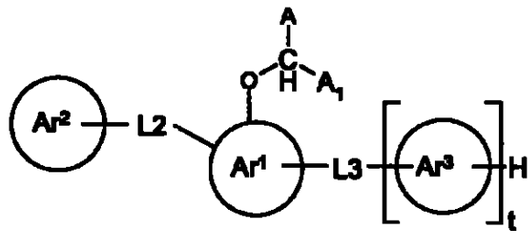
Claims:

1. Use of a compound of formula (I) or a salt, hydrate or solvate thereof in the manufacture of a composition for the treatment of disease responsive to modulation of CRTH2 receptor activity:



(I)

wherein

A represents a carboxyl group –COOH, or a carboxyl bioisostere;

A_1 is hydrogen or methyl;

ring Ar^1 is an optionally substituted phenyl ring or 5- or 6-membered monocyclic heteroaryl ring, in which AA_1CHO- and L2 are linked to adjacent ring atoms;

rings Ar^2, Ar^3 each independently represent a phenyl or 5- or 6-membered monocyclic heteroaryl ring, or a bicyclic ring system consisting of a 5- or 6-membered carbocyclic or heterocyclic ring which is benz-fused or fused to a 5- or 6-membered monocyclic heteroaryl ring, said ring or ring system being optionally substituted;

t is 0 or 1;

L2 and L3 each independently represent a divalent radical of formula $–(Alk^1)_m-(Z)_n-(Alk^2)_p$ wherein

m, n and p are independently 0 or 1,

Alk^1 and Alk^2 are independently optionally substituted straight or branched chain C_1-C_3 alkylene or C_2-C_3 alkenylene radicals which may contain a compatible –O-, -S- or –NR- link wherein R is hydrogen or C_1-C_3 alkyl, and

Z is –O-; -S-; -C(=O)-; $-SO_2-$; -SO-; -NR-, $-NRSO_2-$, $-SO_2NR-$,

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-C(=O)NR-, -NRC(=O)-, -NRCONH-, -NHCONR-, -NRC(=NR)NH-, -NHC(=NR)NR-, –C(R)=N-NR-, or –NR-N=C(R)- wherein R is hydrogen or C_1-C_3 alkyl; or a divalent 5- or 6-membered monocyclic carbocyclic or heterocyclic radical,

PROVIDED THAT

(A) the total length of L2 and L3 does not exceed that of an unbranched saturated chain of 10 carbon atoms; and

(B) L2 is not –C(=O)-, -C(=O)NR-, or -NRC(=O)- when Ar^2 is optionally substituted phenyl; and

(C) (a) L2 is not a bond and (b) p in L2 is not 0 when n is 1 and Z is aryl or heteroaryl, and

(D) (a) L2 is not –O-, -SO_2-, -NR-, -CHR^XR^Y- or –$CH(R^X)(OR^Y)$-, wherein R^X and R^Y are independently hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_3-C_7 cycloalkyl, or join to form a ring, and (b) when p is 1 and n is 1 and Z is aryl or heteroaryl then Alk^2 is not -CHR^XR^Y- or –$CH(R^X)(OR^Y)$-, wherein R^X and R^Y are independently hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_3-C_7 cycloalkyl, or join to form a ring.

2. A method of treatment of disease responsive to modulation of CRTH2 receptor activity comprising administering to a subvject suffering such disease and effective amount of a compound as defined in claim 1.

3. Use as claimed in claim 1 or a method as claimed in claim 2, wherein, in the compound (I), (i) the length of each of L2 and L3 does not exceed that of an unbranched saturated chain of 5 carbon atoms and (ii) the total length of L2 and L3 does not exceed that of an unbranched saturated chain of 7 carbon atoms, and (iii) neither of L2 and L3 includes more than two R substituents different from hydrogen,

4. Use or a method as claimed in any of the preceding claims wherein, in the compound (I), A_1 is hydrogen and Z is –O-; -S-; -C(=O)-; -SO_2-; -SO-; -NR-, -$NRSO_2$- -C(=O)NR-, -NRCONH-, -NRC(=NR)NH-, or –C(R)=N-NR-, wherein R is hydrogen or

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C_1-C_3 alkyl; or a divalent 5- or 6-membered monocyclic carbocyclic or heterocyclic radical.

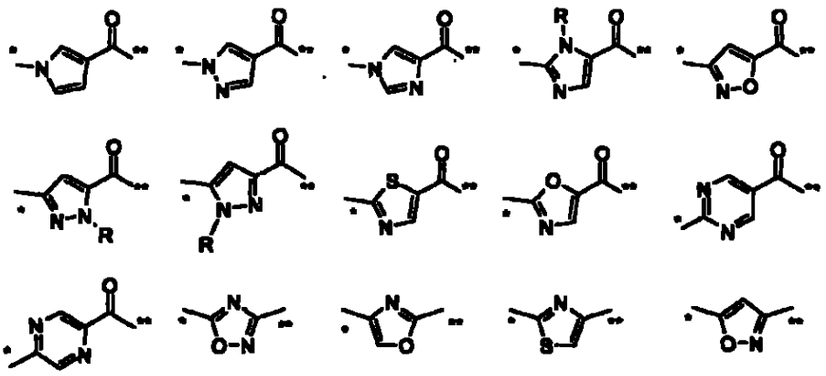
5. Use or a method as claimed in any of claims 1 to 4 wherein, in the compound (I), L2 is -N=CR-, -OCR_2C(=O)NR-N=CR-, -C(=O)NR-, -N=CR-, -C(=O)-, -CH=CHC(=O)-, -$(CH_2)_{0-3}$NRC(=O)-, -NRC(=O)$(CH_2)_{0-3}$-, –O-N=CH-, -CH_2NRCH_2-, -$NR(CH_2)_{1-3}$-, -$(CH_2)_{1-3}$NR-, -S-, -CH_2OCH_2-, -$O(CH_2)_{1-3}$-, -$(CH_2)_{1-3}$O-, -CH_2SCH_2-, -$S(CH_2)_{0-3}$-, -$(CH_2)_{0-3}$S-, a divalent (C_2-C_8)alkylene radical, a divalent (C_2-C_8)alkenylene radical, or a divalent (C_2-C_8)alkynylene radical, wherein R is hydrogen or C_1-C_3 alkyl.

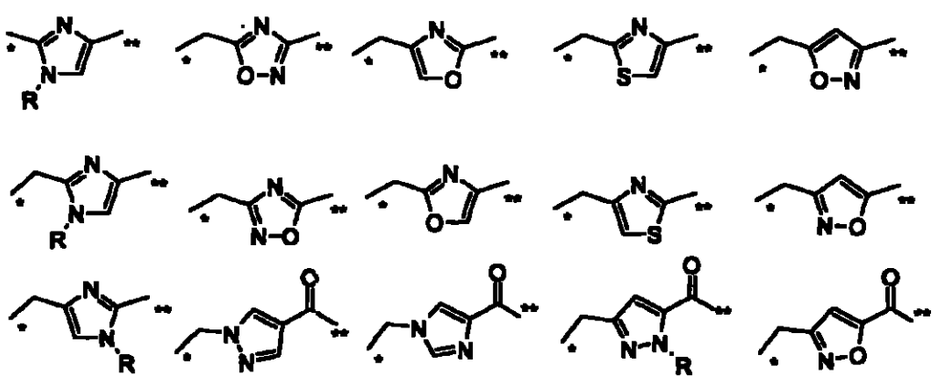
6. Use or a method as claimed in any of claims 1 to 4 wherein, in the compound (I), L2 is –NRN=CH-, -ON=CH-, or -N=CH-.

7. Use or a method as claimed in any of claims 1 to 4 wherein, in the compound (I), L2 is –C(=O)-.

8. Use or a method as claimed in any of claims 1 to 4 wherein, in the compound (I), L2 is –NHC(=O)- or –C(=O)NH-.

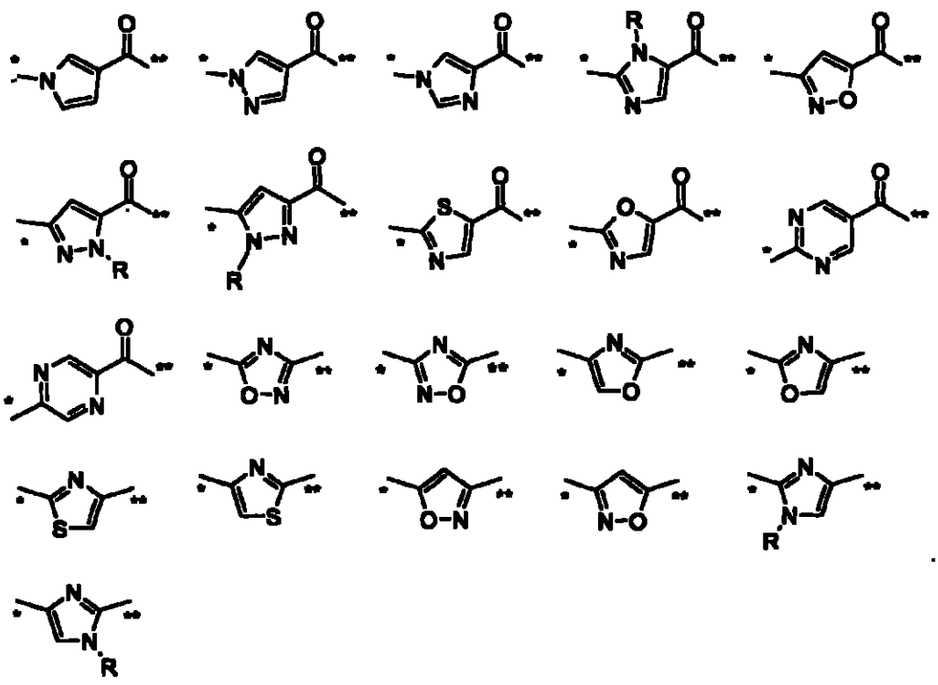
9. Use or a method as claimed in any of claims 1 to 4 wherein, in the compound (I), L2 is a divalent radical selected from one of the following formulae, wherein either (i) the bond marked * is attached to Ar^2 while the bond marked ** is attached to Ar^1, or (ii) the bond marked * is attached to Ar^1 while the bond marked ** is attached to Ar^2:





wherein R is hydrogen or C_1-C_3 alkyl.

10. Use or method as claimed in claim 9 wherein, in the compound (I), A1 is hydrogen and L2 has one of the following formulae wherein the bond marked * is attached to Ar^2 while the bond marked ** is attached to Ar^1:



wherein R is hydrogen or C_1-C_3 alkyl.

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11. Use or method as claimed in any of the preceding claims wherein the disease is one associated with elevated levels of prostaglandin D2 (PGD2) or one or more active metabolites thereof.

12. Use or method as claimed in any of claims 1 to 10 wherein the disease is an inflammatory, autoimmune, respiratory or allergy disease.

13. Use or method as claimed in any of claims 1 to 10 wherein the disease is selected from asthma, rhinitis, allergic airway syndrome, allergic rhinobronchitis, bronchitis, chronic obstructive pulmonary disease (COPD), nasal polyposis, sarcoidosis, farmer´s lung, fibroid lung, cystic fibrosis, chronic cough, conjunctivitis, atopic dermatitis, Alzheimer's disease, amyotrophic lateral sclerosis, AIDS dementia complex, Huntington's disease, frontotemporal dementia, Lewy body dementia, vascular dementia, Guillain-Barre syndrome, chronic demyelinating polyradiculoneurophathy, multifocal motor neuropathy, plexopathy, multiple sclerosis, encephalomyelitis, panencephalitis, cerebellar degeneration and encephalomyelitis, CNS trauma, migraine, stroke, rheumatoid arthritis, ankylosing spondylitis, Behçet's Disease, bursitis, carpal tunnel syndrome, inflammatory bowel disease, Crohn´s disease, ulcerative colitis, dermatomyositis, Ehlers-Danlos Syndrome (EDS), fibromyalgia, myofascial pain, osteoarthritis (OA), osteonecrosis, psoriatic arthritis, Reiter's syndrome (reactive arthritis), sarcoidosis, scleroderma, Sjogren's Syndrome, soft tissue disease, Still's Disease, tendinitis, polyarteritis Nodossa, Wegener's Granulomatosis, myositis (polymyositis dermatomyositis), gout, atherosclerosis, lupus erythematosus, systemic lupus erythematosus (SLE), type I diabetes, nephritic syndrome, glomerulonephritis, acute and chronic renal failure, eosinophilia fascitis, hyper IgE syndrome, sepsis, septic shock, ischemic reperfusion injury in the heart, allograft rejection after transplantations, and graft versus host disease.

14. Use or method as claimed in any of claims 1 to 10 wherein the disease is selected from asthma, rhinitis, allergic airway syndrome, and allergic rhinobronchitis,

15. Use or method as claimed in any of the preceding claims wherein, in the compound (I), ring Ar^2 is (i) an optionally substituted phenyl or naphthyl ring; (ii) a phenyl ring fused to a 5- or 6-membered nitrogen-containing heterocyclic ring, either or both of such rings being optionally substituted; (iii) an optionally substituted nitrogen-containing 5- or 6-membered heteroaryl ring; or (iv) a nitrogen-containing 5-

or 6-membered heterocyclic ring fused to a phenyl ring, either of which rings being optionally substituted.

16. Use or method as claimed in claim 15 wherein, in the compound (I), ring Ar^2 is optionally substituted phenyl, pyridyl, pyrimidyl, diazolyl, thiazolyl, oxazolyl, triazinyl, quinolinyl, pyrrollyl, furanyl, thiazolyl.

17. V as claimed in claim 15 or claim 16 wherein, in the compound (I), optional substituents in Ar^2 are selected from fluoro, chloro, bromo, (C_1-C_3)alkyl, trifluoromethyl, (C_1-C_3)alkoxy, trifluoromethoxy, trifluoromethylthio, dimethylamino, cyano, (C_1-C_3alkyl)SO_2-, NH_2SO_2-, (C_1-C_3alkyl)$NHSO_2$-, (C_1-C_3alkyl)$_2NSO_2$-, and nitro.

18. Use or method as claimed in any of the preceding claims wherein, in the compound (I), Ar^1 is a 5- or 6-membered nitrogen-containing heteroaryl ring, optionally substituted.

19. Use or method as claimed in any of claims 1 to 17 wherein in the compound (I), Ar^1 is a phenyl ring and L3 is linked to the 4-position thereof relative to the $ACHA_1O$- radical.

20. Use or method as claimed in any of the preceding claims wherein in compound (I), t is 1 and Ar^3 is a 5- or 6-membered heteroaryl ring, optionally substituted.

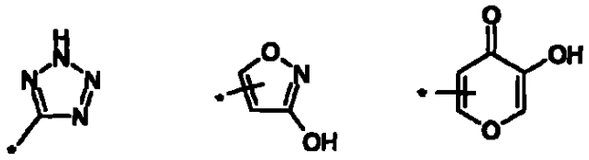
21. Use or method as claimed in any of the preceding claims wherein in compound (I), t is 1 and Ar^3 is a phenyl ring, optionally substituted.

22. Use or method as claimed in any of the preceding claims wherein in compound (I), any optional substituents in ring Ar^1 or Ar^3 are selected from fluoro, chloro, bromo, iodo, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, (C_1-C_3alkyl)SO_2-, NH_2SO_2-, (C_1-C_3alkyl)$NHSO_2$-, (C_1-C_3alkyl)$_2NSO_2$-, C_1-C_6 alkyl, C_1-C_6 alkoxy, cycloalkyl, aryl, aryloxy, aryl(C_1-C_6)- or aryl(C_1-C_6 alkoxy)-.

23. Use or method as claimed in any of claims 1 to 19 wherein in compound (I), t is 0 and L3 is a bond.

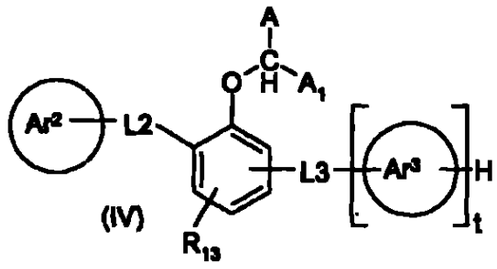
24. Use or method as claimed in any of the preceding claims wherein, in the compound (I), A is –COOH.

25. Use or method as claimed in any of claims 1 to 23 wherein, in the compound (I), A is a carboxyl bioisostere selected from $-SO_2NHR$ and $-P(=O)(OH)(OR)$ wherein R is hydrogen methyl or ethyl, $-SO_2OH$, $-P(=O)(OH)(NH_2)$, –C(=O)NHCN and groups of formulae:



26. Use or method as claimed in any of the preceding claims wherein, in the compound (I), A_1 is hydrogen.

27. A compound of formula (IV) or a salt, hydrate or solvate thereof

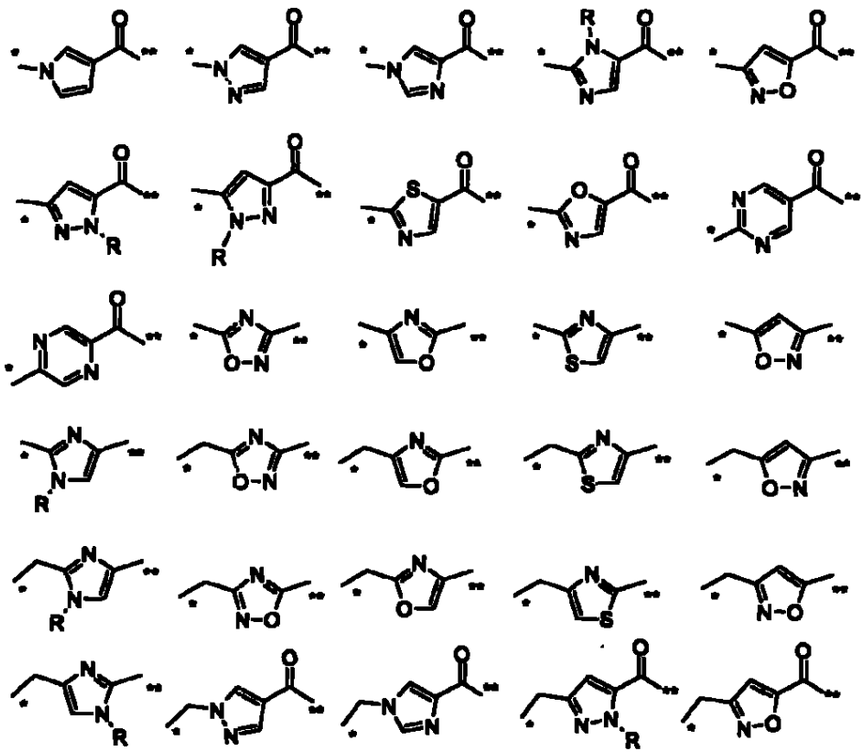


(IV)

wherein A, A_1, L3, Ar^3, Ar^2, and t are as defined in claim 1 or claim 2,

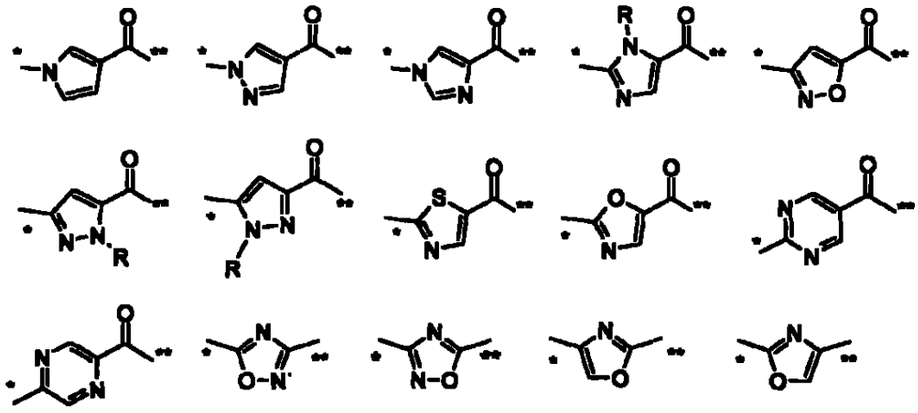
R_{13} represents hydrogen or one or more optional substituents,

L2 is a divalent radical selected from the following wherein either (i) the bond marked * is attached to Ar^2 while the bond marked ** is attached to Ar^1, or (ii) the bond marked * is attached to Ar^1 while the bond marked ** is attached to Ar^2:



wherein R is hydrogen or C_1-C_3 alkyl.

28. A compound as claimed in claim 26 wherein A_1 is hydrogen and L2 is selected from the following wherein the bond marked * is attached to Ar^2 while the bond marked ** is attached to Ar^1:



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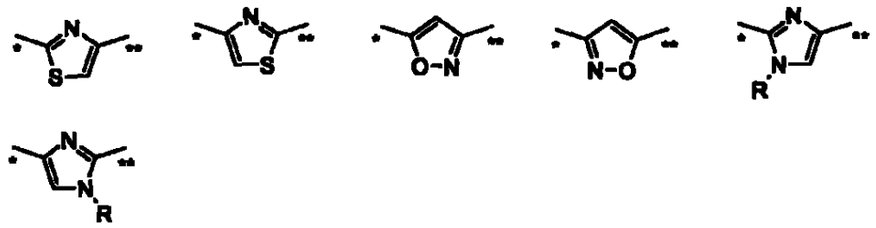
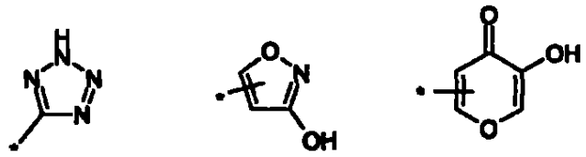


wherein R is hydrogen or C_1-C_3 alkyl.

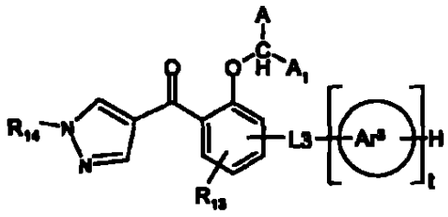
29. A compound as claimed in claim 27 or claim 28 wherein A is –COOH.

30. A compound as claimed in claim 27 or claim 28 wherein A is a carboxyl bioisostere selected from $-SO_2NHR$ and-P(=O)(OH)(OR) wherein R is hydrogen methyl or ethyl, $-SO_2OH$, $-P(=O)(OH)(NH_2)$, –C(=O)NHCN and groups of formulae:



31. A compound as claimed in any of claims 27 to 30 wherein R_{13} represents one or more substituents selected from fluoro, chloro, bromo, iodo, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, (C_1-C_3alkyl)SO_2-, NH_2SO_2-, (C_1-C_3alkyl)$NHSO_2$-, (C_1-C_3alkyl)$_2NSO_2$-, C_1-C_6 alkyl, C_1-C_6 alkoxy, cycloalkyl, aryl, aryloxy, aryl(C_1-C_6)- or aryl(C_1-C_6 alkoxy)-.

32. A compound of formula (IVA) or a salt, hydrate or solvate thereof



(IVA)

wherein A, L3, t, Ar^3, R_{13} are as defined in any of claims 28 to 30 and R_{14} is optionally substituted phenyl or 5- or 6- membered heteroaryl.

33. A compound of formula (IVB) or a salt hydrate or solvate thereof

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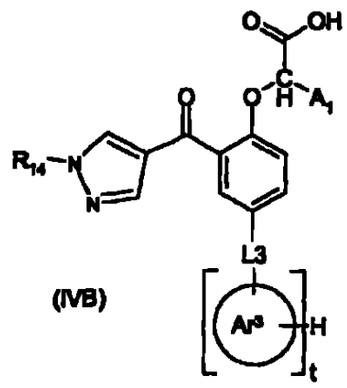
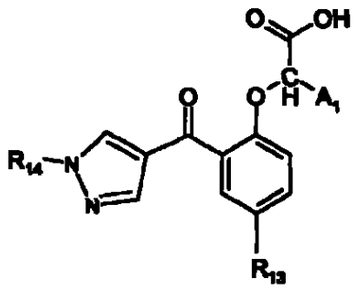


(IVB)

wherein L3, t, and Ar^3 are as defined in any of claims 26 to 30 and R_{14} is optionally substituted phenyl or 5- or 6- membered heteroaryl.

34. A compound of formula (IVC) or a salt hydrate or solvate thereof



(IVC)

wherein R_{13} represents a substituent selected from fluoro, chloro, bromo, iodo, (C_1-C_6)alkyl, trifluoromethyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylmercapto, trifluoromethoxy, trifluoromethylthio, dimethylamino, cyano, (C_1-C_3alkyl)SO_2-, NH_2SO_2-, (C_1-C_3alkyl)$NHSO_2$-, (C_1-C_3alkyl)$_2NSO_2$-, and nitro, and R_{14} is optionally substituted phenyl or 5- or 6- membered heteroaryl.

35. A compound as claimed in claim 34 wherein R_{14} is a 2-substituted, 2,4-disubstituted, 2,6-disubstituted or 2,4,6-trisubstituted phenyl ring where the substituents are selected from fluoro, chloro, bromo, iodo, (C_1-C_6)alkyl, trifluoromethyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylmercapto, trifluoromethoxy, trifluoromethylthio, dimethylamino, (C_1-C_3alkyl)SO_2-, NH_2SO_2-, (C_1-C_3alkyl)$NHSO_2$-, (C_1-C_3alkyl)$_2NSO_2$-, and cyano

36. A compound as claimed in claim 34 wherein R_{14} is a 2-substituted, 2,4-disubstituted, or 2,6-disubstituted phenyl ring where the substituents are selected

from fluoro, chloro, (C_1-C_3)alkyl, trifluoromethyl, (C_1-C_3)alkoxy, (C_1-C_3)alkylmercapto, trifluoromethoxy, trifluoromethylthio, and cyano.

37. A compound as claimed in claim 34 wherein R_{14} is a 2-substituted or 2,6-disubstituted pyridyl ring where the substituents are selected from fluoro, chloro, (C_1-C_3)alkyl, trifluoromethyl, (C_1-C_3)alkoxy, (C_1-C_3)alkylmercapto, trifluoromethoxy, trifluoromethylthio, and cyano.

38. A compound as claimed in claim 34 wherein R_{13} is selected from fluoro, chloro, bromo, iodo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, trifluoromethoxy and trifluoromethylthio, and R_{14} is optionally substituted phenyl or optionally substituted 5- or 6- membered heteroaryl.

39. A compound as claimed in any of claims 27 to 38 wherein A_1 is hydrogen.

40. An enantiomer of a compound as claimed in any of claims 27 to 38 wherein A_1 is methyl, and the carbon atom to which it is attached has the S stereochemical configuration.

41. A compound as claimed in claim 27 selected from the group consisting of:
4-chloro-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxyacetic acid,
4-bromo-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxyacetic acid,
[4-bromo-2-(1-pyridin-2-yl-1H-pyrazole-4-carbonyl)phenoxy]acetic acid,
{4-bromo-2-[1-(2-chlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(3-chlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(4-bromophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(4-chlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(2-ethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(2-bromophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(2-fluorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(3-bromophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(2,4-dichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{2-[1-(2-chlorophenyl)-1H-pyrazole-4-carbonyl]-4-nitrophenoxy}acetic acid,
{4-bromo-2-[1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{2-[1-(2-bromophenyl)-1H-pyrazole-4-carbonyl]-4-ethylphenoxy}acetic acid,
{4-bromo-2-[1-(2,4-dibromophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,

{4-bromo-2-[1-(4-bromo-2-chlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-bromo-2-[1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
2-{4-bromo-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxy}propionic acid,
(S)-2-{4-bromo-2-(1-phenyl-1H-pyrazole-4-carbonyl)phenoxy}propionic acid,
2-{4-Bromo-2-[1-(2-chlorophenyl)-1-H-pyrazole-4-carbonyl]phenoxy}propionic acid,
(S)-2-{4-Bromo-2-[1-(2-chlorophenyl)-1-H-pyrazole-4-carbonyl]phenoxy}-propionic acid,
2-{4-Bromo-2-[1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,
(S)-2-{4-Bromo-2-[1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,
{4-Bromo-2-[1-(2-ethoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[1-(4-bromo-2-ethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[1-(2-phenoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[1-(2-methylthiophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[1-(2-bromo-4-methylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
2-{4-Bromo-2-[1-(4-bromo-2-ethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,
2-{4-Bromo-2-[1-(2-phenoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,
(S)-2-{4-Bromo-2-[1-(2-phenoxyphenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,
2-{4-Bromo-2-[1-(2-methylthio)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,
(S)-2-{4-Bromo-2-[1-(2-methylthio)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,
{4-Bromo-2-[1-(2,4-dimethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[1-(4-chloro-2-methylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[1-(2,5-dichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
2-{4-Bromo-2-[1-(4-chloro-2-methylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,
2-{4-Bromo-2-[1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carbonyl]phenoxy}propionic acid,
{4-Bromo-2-[1-(2,6-diethyl-phenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[1-(2,6-dimethylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid
{4-Bromo-2-[1-(2-ethyl-6-methylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,

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{4-Bromo-2-[1-(2-chloro-6-methylphenyl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[1-(3,5-dichloropyridin-4-yl)-1H-pyrazole-4-carbonyl]phenoxy}acetic acid,
[4-Bromo-2-(1-naphthalen-1-yl-1H-pyrazole-4-carbonyl)phenoxy]acetic acid,
{4-Bromo-2-[2-(4-chlorobenzyl)thiazol-4-yl]phenoxy}acetic acid,
{4-Bromo-2-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid,
{4-Bromo-2-[3-(4-methoxy-phenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid,
{4-Bromo-2-[3-(4-chlorophenyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid,
{4-Bromo-2-[3-(4-fluoro-benzyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid,
{4-Bromo-2-[3-(2,6-dichloro-benzyl)-[1,2,4]oxadiazol-5-yl]-phenoxy}-acetic acid,
{4-Bromo-2-[3-(2-trifluoromethylbenzyl)-[1,2,4]oxadiazol-5-yl]phenoxy}-acetic acid,
4-Bromo-2-[3-(2,6-dichloro-phenyl)isoxazole-5-carbonyl]phenoxy}acetic acid,
{4-Bromo-2-[3-(1-phenylcyclopropyl)-[1,2,4]oxadiazol-5-yl]phenoxy}acetic acid,
{4-Bromo-2-[3-(2,4-dichlorophenyl)-[1,2,4]oxadiazol-5-yl[phenoxy}acetic acid,

and salts, hydrates and solvates thereof.

42. A pharmaceutical composition comprising a compound as claimed in any of claims 27 to 41, together with a pharmaceutically acceptable carrier.

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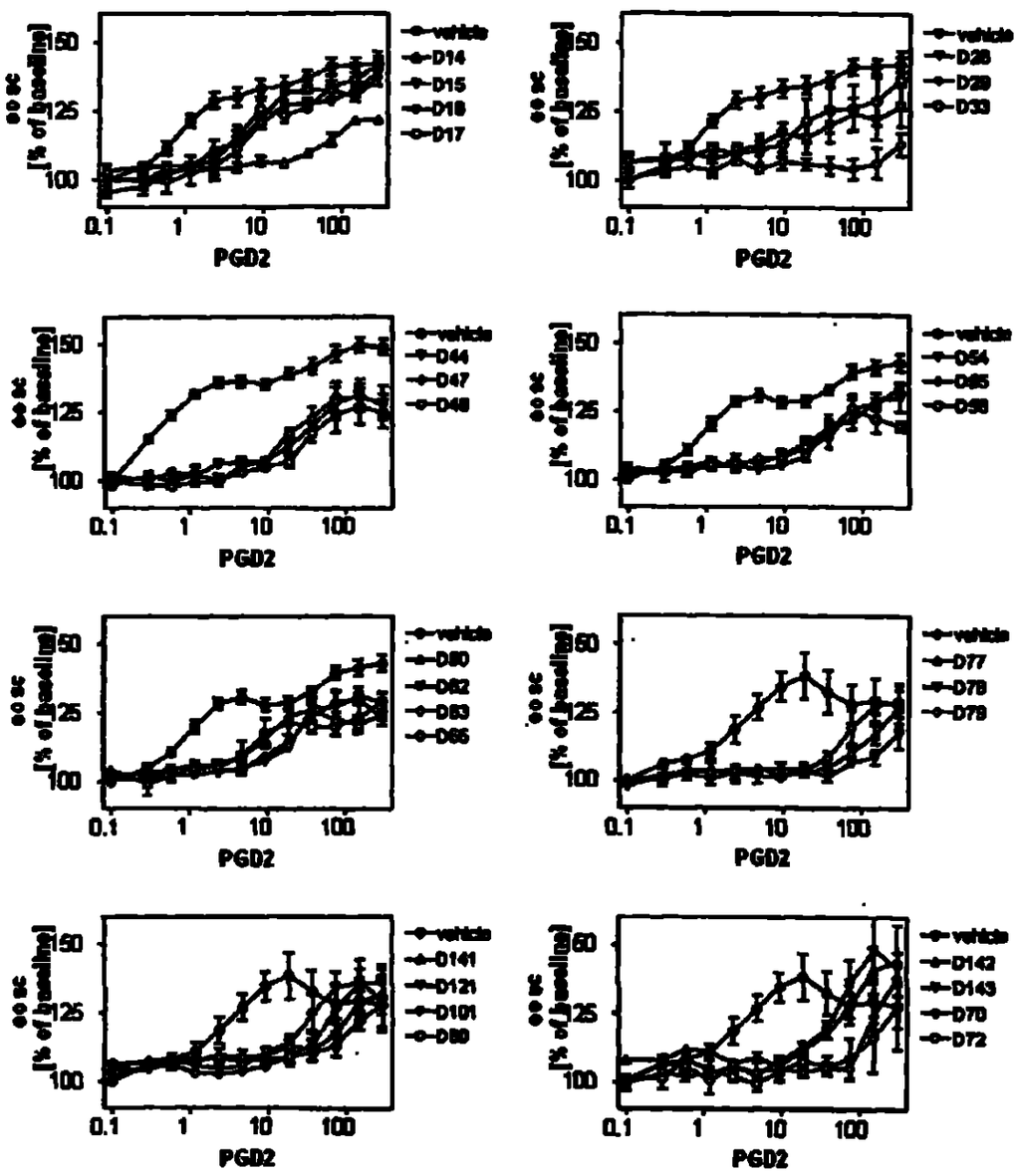
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Figure 1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/005884

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/415 A61K31/454 A61P29/00 A61P43/00

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)
IPC 7 A61K

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 practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/018529 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; BONNERT, ROGER, VICTOR; PATEL,) 3 March 2005 (2005-03-03) cited in the application abstract page 1, line 3 - line 5 page 14, line 24 - page 17, line 38 examples 1-68 claims 1-25 -/--	1-40,42

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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 document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 2005	18/10/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Taylor, G.M.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/005884

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/089885 A (ASTRAZENECA AB; BONNERT, ROGER; BROUGH, STEPHEN; DAVIES, ANDREW; LUKER) 21 October 2004 (2004-10-21) cited in the application abstract page 1, line 3 - line 5 page 11, line 11 - page 13, line 35 examples 1-170 claims 1-11	1-40,42
X	WO 01/21591 A (F. HOFFMANN-LA ROCHE AG) 29 March 2001 (2001-03-29) abstract page 41, line 3 - line 9 examples 1-34 claims 1-44	1-40,42
X	WO 99/57101 A (F. HOFFMANN-LA ROCHE AG) 11 November 1999 (1999-11-11) abstract page 52, line 14 - line 23 examples 1-30 claims 1-45	1-40,42
X	WO 94/13643 A (PFIZER INC; FARACI, WILLIAM, STEPHEN; WELCH, WILLARD, MCKOWAN, JR) 23 June 1994 (1994-06-23) abstract page 1, line 9 - line 20 page 4, line 18 - page 5, line 12 examples 1-18 claims 1-10	1-40,42
P,A	ULVEN T ET AL: "Minor Structural Modifications Convert the Dual TP/CRTH2 Antagonist Ramatroban into a Highly Selective and Potent CRTH2 Antagonist" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 48, no. 4, 24 February 2005 (2005-02-24), pages 897-900, XP002339598 ISSN: 0022-2623 the whole document	1-42

INTERNATIONAL SEARCH REPORT

International Application No
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USO MEDICINAL DE LIGANDOS DE RECEPTOR

Esta invención se relaciona con el uso de una clase de compuestos que son ligandos del receptor CRTH2 (molécula homóloga del receptor quimio-atrayente expresada sobre células colaboradoras T tipo 2), en el tratamiento de enfermedades que responden a la modulación de la actividad del receptor CRTH2, principalmente las enfermedades que tienen un componente inflamatorio significativo. La invención también se relaciona con miembros novedosos de la clase de ligandos y composiciones farmacéuticas que los contienen

Muchas clases de agentes antiinflamatorios son conocidos, incluyendo los compuestos antiinflamatorios no esteroides conocidos como los NSAID y los inhibidores de ciclooxigenasa (COX-1 y COX-2). El ácido benzolifenilacético y algunos derivados de benzofenona con sustituyentes carboximetoxi en uno de los anillos se han identificado como agentes antiinflamatorios (ver, por ejemplo, Khanum et. al. Bioorganic Chemistry Vol 32, No. 4, 2004, pages 211-222 y las referencias citadas aquí). Algunos ácidos o-fenil carbamoil-fenoxiacéticos y o-benzamido-fenoximetil tetrazoles se han reportado como agentes antiinflamatorios potenciales, ver por ejemplo Drain et. al J. Pharm. Pharmac., 1971, 23, 857-864, and ibid 1970, 22, 684-693. WO 99/15520 describen unos pocos derivados de benzofenona con sustituyentes carboximetoxi o tetrazolilmetoxi en uno de los anillos, sintetizados como miembros de un grupo de compuestos que se dice que tienen actividad como inhibidores del receptor activado proliferador de peroxisoma (PPAR), y la utilidad en una variedad de estados de enfermedad que incluyen la diabetes, la enfermedad cardiaca, y la enfermedad circulatoria.

El ligando natural del receptor acoplado a proteína G CRTH2 es la prostaglandina D2. Como su nombre lo indica, el CRTH2 se expresa sobre las células colaboradoras T tipo 2 (células Th2) pero también es conocido por expresarse sobre células eosinófilas y basófilas. La activación de la célula como resultado de la unión del PGD2 al receptor CRTH2 da como resultado una respuesta biológica compleja, que incluye la liberación de mediadores inflamatorios. Los niveles elevados de PGD2 están por lo tanto asociados con muchas enfermedades que tienen un fuerte componente inflamatorio, tal como el asma, la rinitis y las alergias. Bloquear la unión del PGD2 al receptor

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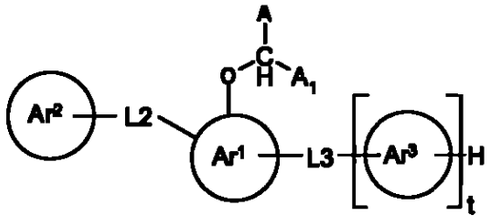
CRTH2 es por lo tanto una estrategia terapéutica útil para el tratamiento de tales enfermedades.

Algunos de los ligandos de molécula pequeña de CRTH2, aparentemente que actúan como antagonistas de PGD2, son conocidos, por ejemplo como se propone en las siguientes publicaciones de patente: WO 03/097042, WO 03/097598, WO 03/066046, WO 03/066047, WO 03/101961, WO 03/101981, GB 2388540, WO 04/089885 y WO 05/018529

Las estructuras de los compuestos antagonistas PGD2 referidas en algunas de las publicaciones anteriores tienen un sistema de anillo con núcleo bicíclico o tricíclico relacionado con el núcleo indol de la indometacina, un agente antiinflamatorio conocido, conocido ahora por unirse al CRTH2. La presente invención surge de la identificación de una clase de compuestos que tienen un núcleo monocíclico cuyas porciones sustituyentes se seleccionan y se orientan por el núcleo monocíclico para interactuar con y unirse al CRTH2. La clase de compuestos con los cuales esta invención está relacionada son así capaces de modular la actividad del CRTH2, y son útiles para el tratamiento de enfermedades que se benefician de tal modulación, por ejemplo asma, alergia y rinitis.

De acuerdo con la presente invención, se provee el uso de un compuesto de formula (I) o una sal, hidrato o solvato de éste en la elaboración de una composición para el tratamiento de enfermedad que responde a la modulación de la actividad receptora CRTH2:



(I)

en donde

A representa un grupo carboxilo –COOH, o un carboxil bioisostere;

A_1 es hidrógeno o metilo;

El anillo Ar^1 es un anillo de fenilo opcionalmente sustituido o un anillo heteroarilo monocíclico de 5 o 6 miembros, en el cual AA_1CHO- y L2 están ligados a átomos de anillo adyacente;

Los anillos Ar^2, Ar^3 cada uno representan independientemente un anillo fenilo o un anillo heteroarilo monocíclico de 5 o 6 miembros, o un sistema de anillo bicíclico que consiste de un anillo carbocíclico o heterocíclico de 5 o 6 miembros que es benzo-fusionado o fusionado a un anillo heteroarilo monocíclico de 5 o 6 miembros, dicho anillo o sistema de anillo es opcionalmente sustituido;

t es 0 o 1;

L2 y L3 cada uno independientemente representan un radical divalente de fórmula $-(Alk^1)_m-(Z)_n-(Alk^2)_p$ en donde

m, n y p son independientemente 0 o 1,

Alk^1 y Alk^2 son independientemente radicales alquileno C_1-C_3 o alquenileno C_2-C_3 de cadena recta o ramificada opcionalmente sustituidos que pueden contener un enlace –O-, -S- o –NR- compatible en donde R es hidrógeno o alquilo C_1-C_3, y

Z es –O-; -S-; -C(=O)-; $-SO_2-$; -SO-; -NR-; $-NRSO_2-$, $-SO_2NR-$, -C(=O)NR-, -NRC(=O)-, -NRCONH-, -NHCONR-, -NRC(=NR)NH-, -NHC(=NR)NR-, -C(R)=N-NR-, o –NR-N=C(R)- en donde R es hidrógeno o alquilo C_1-C_3; o un radical carbocíclico o heterocíclico monocíclico de 5 o 6 miembros divalente

SIEMPRE Y CUANDO

(A) la longitud total de L2 y L3 no exceda a aquella de la cadena saturada no ramificada de 10 átomos de carbono; y

(B) L2 no es –C(=O)-, -C(=O)NR-, o –NRC(=O)- cuando Ar^2 sea fenilo opcionalmente sustituido; y

(C) (a) L2 no sea un enlace y (b) p en L2 no sea 0 cuando n es 1 y Z es arilo o heteroarilo, y

(D) (a) L2 no es –O-, -SO_2-, -NR-, -CHR^XR^Y- or –$CH(R^X)(OR^Y)$-, en donde R^X and R^Y sean independientemente hidrógeno, halógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, o cicloalquilo C_3-C_7, o se unen para formar un anillo, y (b) cuando p es 1 y n es 1 y Z es arilo o heteroarilo entonces Alk^2 no es -CHR^XR^Y- o –$CH(R^X)(OR^Y)$-, en donde R^X y R^Y son independientemente hidrógeno, halógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, o cicloalquilo C_3-C_7, o se unen para formar un anillo.

En un aspecto de la invención, en los compuestos (I), la longitud de cada uno de L2 y L3 no excede aquella de una cadena saturada no ramificada de 5 átomos de carbono y (ii) la longitud total de L2 y L3 no excede a aquella de la cadena saturada no ramificada de 7 átomos de carbono, y (iii) ni L2 ni L3 incluyen más de dos sustituyentes R diferentes de hidrógeno.

En un aspecto más restringido de la invención, los compuestos (I) como se definieron anteriormente en donde A_1 es hidrógeno y Z es –O-; -S-; -C(=O)-; -SO_2-; -SO-; -NR-, -$NRSO_2$-, -C(=O)NR-, -NRCONH-, -NRC(=NR)NH-, o –C(R)=N-NR-, en donde R es hidrógeno o alquilo C_1-C_3; o un radical carbocíclico o heterocíclico monocíclico de 5- o 6- miembros divalente, se puede utilizar

En otro aspecto restringido de la invención, los compuestos (I) como se definieron anteriormente en donde L2 es -N=CR-, -OCR_2C(=O)NR-N=CR-, -C(=O)NR-, -N=CR-, -C(=O)-, -CH=CHC(=O)–$(CH_2)_{0-3}$NRC(=O)-, -NRC(=O)$(CH_2)_{0-3}$-, –O-N=CH-, -CH_2NRCH_2-, -NR$(CH_2)_{1-3}$-, -$(CH_2)_{1-3}$NR-, -S-, -CH_2OCH_2-, -O$(CH_2)_{1-3}$-, -$(CH_2)_{1-3}$O-, -CH_2SCH_2-, -S$(CH_2)_{0-3}$-, -$(CH_2)_{0-3}$S-, un radical alquileno (C_2-C_8) divalente, un radical alquenileno (C_2-C_8) divalente, o un radical alquinileno (C_2-C_8) divalente, en donde R es hidrógeno o alquilo C_1-C_3, pueden ser utilizados.

En aspectos adicionales más restringidos de la invención, los compuestos (I) como se definieron anteriormente en donde L2 es –NRN=CH-, -ON=CH-, o -N=CH-; o L2 es –C(=O)-; o L2 es –NHC(=O)- o –C(=O)NH-, pueden ser utilizados.

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Un aspecto independiente de la invención es el uso de un compuesto de fórmula (I) establecido anteriormente o una sal, hidrato o solvato de éste en la elaboración de una composición para el tratamiento de enfermedad que responde a la modulación de la actividad del receptor CRTH2, en el cual el compuesto (I):

A representa un grupo carboxilo –COOH, o un carboxil bioisostere;

A_1 es hidrógeno o metilo;

El anillo Ar^1 es un anillo de fenilo opcionalmente sustituido o un anillo heteroarilo monocíclico de 5- o 6- miembros, en el cual AA_1CHO- y L2 están ligados a átomos de anillo adyacente;

Los anillos Ar^2, Ar^3 cada uno independientemente representan un anillo fenilo o heteroarilo monocíclico de 5- o 6- miembros, o un sistema de anillo bicíclico que consiste de un anillo carbocíclico o heterocíclico de 5- o 6- miembros que es benzo-fusionado o fusionado a un anillo heteroarilo monocíclico de 5- o 6- miembros, dicho anillo o sistema de anillo es opcionalmente sustituido;

t es 0 o 1;

L3 representa un radical divalente de fórmula $–(Alk^1)_m-(Z)_n-(Alk^2)_p$ en donde

m, n y p son independientemente 0 o 1,

Alk^1 y Alk^2 son independientemente radicales alquileno C_1-C_3 o alquenileno C_2-C_3 de cadena recta o ramificada opcionalmente sustituidos que pueden contener un enlace –O-, -S- o –NR- compatible en donde R es hidrógeno o alquilo C_1-C_3, y

Z es –O-; -S-; -C(=O)-; $-SO_2-$; -SO-; -NR-, $-NRSO_2-$, $-SO_2NR-$, -C(=O)NR-, -NRC(=O)-, -NRCONH-, -NHCONR-, -NRC(=NR)NH-, -NHC(=NR)NR-, –C(R)=N-NR-, or –NR-N=C(R)- en donde R es hidrógeno o alquilo C_1-C_3; o un radical carbocíclico o heterocíclico monocíclico de 5- o 6- miembros divalente;

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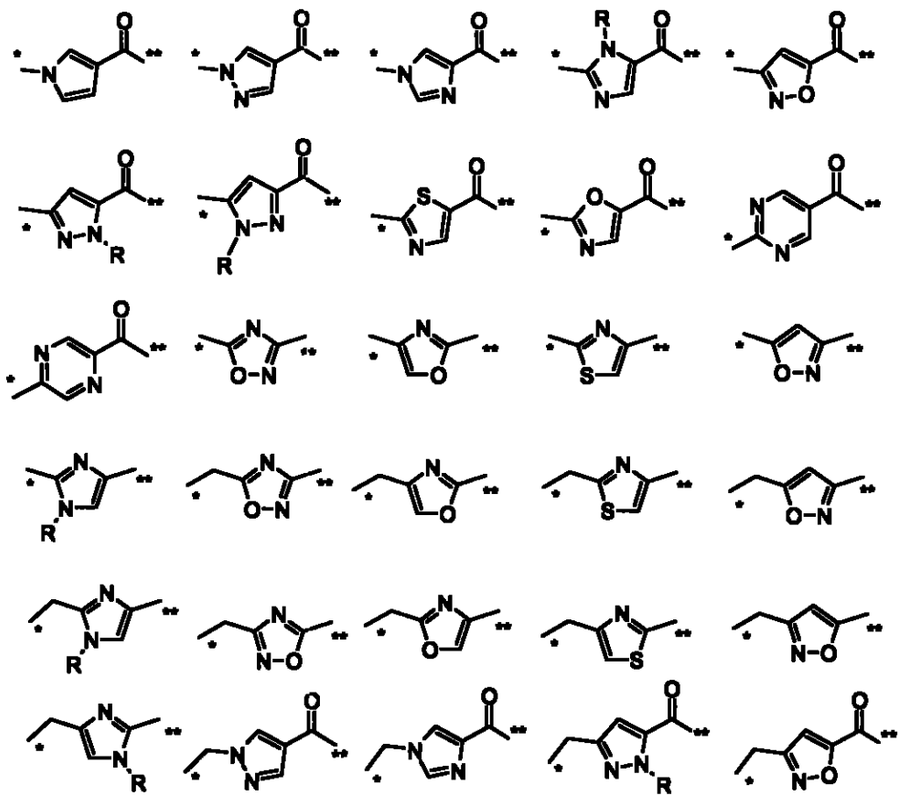
L2 representa un radical divalente seleccionado de una de las siguientes fórmulas (algunas veces denominada "L2 ajusta a A" aqui), en donde (i) el enlace marcado * esta unido a Ar^2 mientras que el enlace marcado ** esta unido a Ar^1, o (ii) el enlace marcado * esta unido a Ar^1 mientras que el enlace marcado ** esta unido a Ar^2:

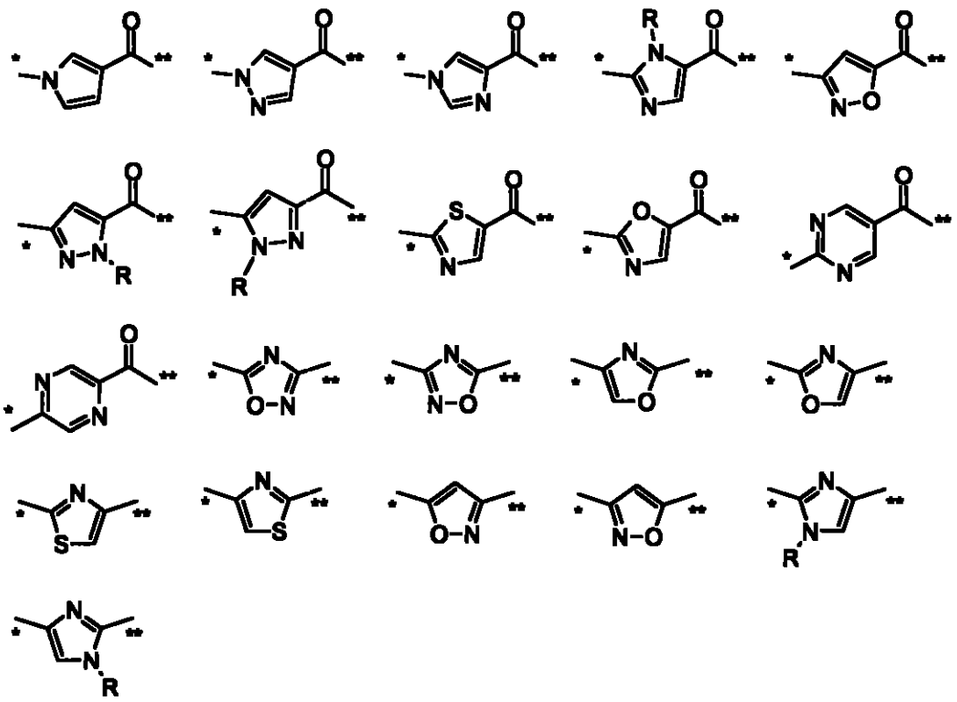


en donde R is hidrógeno o alquilo C_1-C_3; y

la longitud total de L2 y L3 no excede a aquella de una cadena saturada no ramificada de 10 átomos de carbono.

En una definición más restringida de este aspecto de la invención, en los compuestos (I), (i) la longitud de L3 no excede aquella de la cadena saturada no ramificada de 5 átomos de carbono y (ii) la longitud total de L2 y L3 no excede a aquella de la cadena saturada no ramificada de 7 átomos de carbono, y (iii) L3 no incluye más de dos sustituyentes R diferentes de hidrógeno.

En dos aspectos inmediatamente precedentes de la invención, en los compuestos (I), A1 puede ser hidrógeno y L2 puede ser una de las siguientes fórmulas (algunas veces denominada "L2 ajusta a B" aqui) en donde el enlace marcado * esta unido a Ar^2 mientras que el enlace marcado ** esta unido a Ar^1:



en donde R es hidrógeno o alquilo C_1-C_3.

Los compuestos con los cuales la invención esta relacionada se definen mediante referencia a la fórmula (I) como resultado de estudios hacia la elucidación del sitio que se une al ligando del CRTH2. Tales estudios conducen a la conclusión total de que un farmacóforo general que comprende una porción negativamente cargada, representada por AA_1CHO-, y dos porciones aromáticas y/o hidrófobas, representadas por Ar^2L2 y $H(Ar^3)L3$-Ar^1 o solamente Ar^1, orientado en un triangulo aproximado, formarían una disposición para la interacción con el sitio de unión del receptor. Se concluyó que las agrupaciones de sustituyentes a AA_1CHO- y Ar^2L2- deben estar sobre átomos de anillo adyacentes de Ar^1. Los ligadores L2 y L3 suministran alguna flexibilidad a la molécula para facilitar la unión óptima. Las restricciones sobre las longitudes de, y las sustituciones en, los ligadores L2 y L3 están con el fin de restringir

el tamaño y la complejidad molecular total de las estructuras para uso de acuerdo con la invención. Para evitar dudas, la longitud total de L2 y L3 es, para los propósitos de esta descripción y reivindicaciones, la suma n2+n3, en donde n2 es el número de átomos conectados en la cadena más corta de átomos del átomo terminal al átomo terminal del ligador L2, y n3 es el número de átomos conectados en la cadena más corta de átomos desde el átomo terminal al átomo terminal del ligador L2. Preferiblemente los compuestos con los cuales la invención esta relacionada deben tener un peso molecular de no más de 600. Los sustituyentes opcionales en cualquier elemento de los compuestos (I) se permiten como en la definición de los compuestos (I). Tales sustituyentes pueden modular propiedades farmacocinéticas y solubilidad, así como también recoger interacciones de unión adiciónales con el receptor.

En otro aspecto, la invención suministra un método para el tratamiento de un sujeto que sufre de una enfermedad que responde a la modulación de la actividad del receptor CRTH2, que comprende administrarle al sujeto una cantidad de un compuesto (I) como se definió y describió anteriormente efectivo para mejorar la enfermedad.

En particular, los compuestos con los cuales la invención esta relacionada son útiles en el tratamiento de enfermedad asociada con los niveles elevados de prostaglandina D2 (PGD2) o uno o más metabolitos activos de éste.

Ejemplos de tales enfermedades incluyen asma, rinitis, síndrome alérgico de vías aéreas, rinobronquitis alérgica, bronquitis, enfermedad pulmonar obstructiva crónica (COPD), poliposis nasal, sarcoidosis, enfermedad del campesino, pulmón fibroide, c fibrosis cística, tos crónica, conjuntivitis, dermatitis atópica, enfermedad de Alzheimer, esclerosis lateral amiotrófica, complejo de demencia de SIDA, enfermedad de Huntington, demencia frontotemporal, demencia de cuerpo Lewy, demencia vascular, síndrome Guillen-Barre, polirradiculoneuropatía desmielinizante crónica, neuropatía motora multifocal, plexopatía, esclerosis múltiple, encefalomielitis, panencefalitis, degeneración cerebelar y encefalomielitis, trauma del SNC, migraña, ataques, artritis reumatoide, espondilitis anquilosante, Enfermedad de Behçet, bursitis, síndrome de túnel carpiano, enfermedad inflamatoria del intestino, enfermedad de Crohn, colitis ulcerativa, dermatomiositis, Síndrome de Ehlers-Danlos (EDS), fibromialgia, dolor miofascial, osteoartritis (OA), osteonecrosis, artritis soriática, síndrome de Reiter

(artritis reactiva), sarcoidosis, esclerodema, Síndrome de Sjogren, enfermedad de tejido liso, Enfermedad de Still, tendinitis, poliarteritis Nodosa, Granulomatosis de Wegener, miositis (polimiositis dermatomiositis), gota, ateroesclerosis, lupus eritematoso, lupus sistémico eritematoso (SLE), diabetes tipo I, síndrome nefrítico, glomerulonefritis, falla renal aguda y crónica, fascitis eosinofilia, síndrome hiper IgE, sepsis, choque séptico, daño por repercusión isquémica en el corazón, rechazo por aloinjerto después de transplantes, y rechazo versus enfermedad de huésped.

Sin embargo, los compuestos con los cuales la invención esta relacionada son principalmente de valor para el tratamiento de asma, rinitis, síndrome alérgico de vías aéreas, y rinobronquitis alérgica.

Muchos compuestos de Fórmula (I) anteriores son novedosos por sí mismos, y la invención incluye tales compuestos novedosos *per se*.

Como se utiliza aquí, el término "alquilo(C_a-C_b)" en donde a y b son enteros se refieren a un radical alquilo de cadena recta o ramificada que tiene de a a b átomos de carbono. Así cuando a es 1 y b es 6, por ejemplo, el término incluye metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, sec-butilo, t-butilo, n-pentilo y n-hexilo.

Como se utiliza aquí el término " radical alquileno (C_a-C_b) divalente" en donde a y b son enteros se refieren a una cadena de hidrocarburo saturado que tiene de a a b átomos de carbono y dos valencias no satisfechas.

Como se utiliza aquí el término "alquenilo (C_a-C_b)" en donde a y b son enteros se refiere a una porción alquenilo de cadena recta o ramificada que tiene de a a b átomos de carbono que tienen al menos un doble enlace de la estereoquímica E o Z donde es aplicable. El término incluye, por ejemplo, vinilo, alilo, 1- y 2-butenilo y 2-metil-2-propenilo.

Como se utiliza aquí el término "radical alquenileno (C_a-C_b) divalente" significa una cadena de hidrocarburo que tiene desde a a a átomos de carbono, al menos un doble enlace, y dos valencias no satisfechas.

Como se utiliza aquí el termino "alquinilo C_a-C_b " en donde a y b son enteros se refiere a grupos de hidrocarburo de cadena recta o cadena ramificada que tienen de dos a seis átomos de carbono y que tienen además un triple enlace. Este término incluiría por ejemplo, etinilo, 1- y 2-propinilo, 1-, 2- y 3-butinilo, 1, 2-, 3- y 4-pentinilo, 1-, 2-, 3-, 4- y 5-hexinilo, 3-metil-1-butinilo, 1-metil-2-pentinilo.

Como se utiliza aquí el término " radical alquinileno (C_a-C_b) divalente" en donde a y b son enteros se refiere a una cadena de hidrocarburo divalente que tiene de 2 a 6 átomos de carbono, al menos un triple enlace, y dos valencias no satisfechas.

Como se utiliza aquí el término "carbocíclico" se refiere a un radical mono-, bi- o tricíclico que tiene hasta 16 átomos por anillo, todos los cuales son carbonos, e incluyen arilo y cicloalquilo.

Como se utiliza aquí el término "cicloalquilo" se refiere a un radical carbocíclico saturado monocíclico que tiene de 3-8 átomos de carbono e incluye, por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo y ciclooctilo.

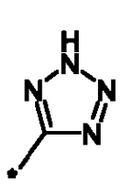
Como se utiliza aquí el término no calificado "arilo" se refiere a un radical aromático carbocíclico mono-, bi- o tri-cíclico, e incluye radicales que tienen dos anillos aromáticos carbocíclicos monocíclicos que están directamente ligados a un enlace covalente. Ilustrativos de tales radicales son fenilo, bifenilo y naftilo.

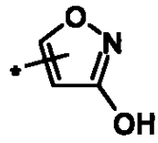
Como se utiliza aquí el término no calificado "heteroarilo" se refiere a un radical aromático mono-, bi- o tri-cíclico que contiene uno o más heteroátomos seleccionados de S, N y O, e incluye radicales que tienen dos de tales anillos monocíclicos, o uno de tales anillos monocíclicos y un anillo arilo monocíclico, que están directamente ligados a un enlace covalente. Ilustrativo de tales radicales son tienilo, benztienilo, furilo, benzfurilo, pirrolilo, imidazolilo, benzimidazolilo, tiazolilo, benztiazolilo, isotiazolilo, benzisotiazolilo, pirazolilo, oxazolilo, benzoxazolilo, isoxazolilo, benzisoxazolilo, isotiazolilo, triazolilo, benztriazolilo, tiadiazolilo, oxadiazolilo, piridinilo, piridazinilo, pirimidinilo, piridazinilo, triazinilo, indolilo e indazolilo.

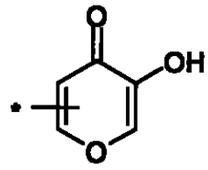
Como se utiliza aquí el término no calificado "heterociclilo" o "heterocíclico" incluyen "heteroarilo" como se definió anteriormente, y además significa un radical no aromático

mono-, bi- o tri-cíclico que contiene uno o más heteroátomos seleccionados de S, N y O, y con grupos que consisten de un radical no aromático monocíclico que contienen uno de tales heteroátomos que esta covalentemente ligado a otro de tal radical o a un radical carbocíclico monocíclico. Ilustrativo de tales radicales son grupos pirrolilo, furanilo, tienilo, piperidinilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, pirazolilo, piridinilo, pirrolidinilo, pirimidinilo, morfolinilo, piperazinilo, indolilo, morfolinilo, benzfuranilo, piranilo, isoxazolilo, benzimidazolilo, metilenodioxifenilo, etilenodioxifenilo, maleimido y los grupos succinimido.

El término "carboxilo bioisostere" es un término familiar con los químicos medicinales (ver por ejemplo "The Organic Chemistry of Drug Design and Drug Action", by Richard B. Silverman, pub. Academic Press, 1992), y se refiere a un grupo que tiene características ácido-base similares a aquellas del grupo carboxilo. Los bioisosteres carboxilo bien conocidos incluyen $-SO_2NHR$ o $-P(=O)(OH)(OR)$ en donde R es, por ejemplo, hidrogen metilo o etilo, $-SO_2OH$, $-P(=O)(OH)(NH_2)$, $-C(=O)NHCN$ y los grupos de fórmulas:







A menos que se especifique otra cosa en el contexto en el cual este ocurre, el término "sustituido" como se aplica a cualquier porción aquí significa sustituido con hasta cuatro sustituyentes compatibles, cada uno de los cuales independientemente puede ser, por ejemplo, alquilo (C_1-C_8), alcoxi (C_1-C_8), hidroxi, hidroxi-alquilo (C_1-C_8), mercapto, mercapto-alquilo (C_1-C_8), alquiltio (C_1-C_8), halo (que incluye flúor, bromo y cloro), alquilo (C_1-C_3) completa o parcialmente fluorinado , alcoxi (C_1-C_3) o alquiltio (C_1-C_3) tal como trifluorometilo, trifluorometoxi, y trifluorometiltio, nitro, nitrilo (-CN), oxo, fenilo, fenoxi, , $-COOR^A$, $-COR^A$, $-OCOR^A$, $-SO_2R^A$, $-CONR^AR^B$, $-SO_2NR^AR^B$, $-NR^AR^B$, $-OCONR^AR^B$, $-NR^BCOR^A$, $-NR^BCOOR^A$, $-NR^BSO_2OR^A$ o $-NR^ACONR^AR^B$ en donde R^A y R^B son independientemente hidrógeno o un grupo alquilo (C_1-C_8) o, en el caso donde R^A y R^B están ligados al mismo átomo N, R^A y R^B tomados juntos con ese nitrógeno pueden formar un anillo amino cíclico. Donde el sustituyente es fenilo o fenoxi, el anillo de fenilo de este puede en sí mismo ser sustituido por cualquiera de los sustituyentes

anteriores excepto fenilo o fenoxi. Un "sustituyente opcional" puede ser uno de los grupos sustituyentes precedentes.

Como se utiliza aquí el término "sal" incluye adición de base, adición de ácido y sales cuaternarias. Los compuestos de la invención que son ácidos pueden ser sales, incluyendo sales farmacéuticamente aceptables, con bases tales como hidróxidos de metal alcalino, por ejemplo, hidróxidos de sodio y potasio; hidróxidos de metal alcalino terreo por ejemplo, hidróxidos de calcio, bario y magnesio; con bases orgánicas, por ejemplo, N-metil-D-glucamina, colina tris(hidroximetil)amina-metano, L-arginina, L-lisina, N-etil piperidina, dibenzilamina y similares. Aquellos compuestos (I) que son básicos pueden formar sales, incluyendo sales farmacéuticamente aceptables con ácidos inorgánicos, por ejemplo, con ácidos hidrohálicos tales como ácidos clorhídrico o bromhídrico, ácido sulfúrico, ácido nítrico o ácido fosfórico y similares, y con ácidos orgánicos, por ejemplo, con ácido acético, tartárico, succínico, fumárico, maleico, málico, salicílico, cítrico, metanosulfónico, p-toluenosulfónico, benzoico, bencenosulfónico, glutámico, láctico, y mandélico y similares.

Los compuestos con los cuales la invención esta relacionada los cuales pueden existir en una o más formas estereoisoméricas, en razón de la presencia de átomos asimétricos o restricciones rotacionales, pueden existir como un número de estereoisómeros con estereoquímica R o S en cada centro quiral o como atropisómeros con estereoquímica R o S en cada eje quiral. La invención incluye todos los tales enantiómeros y diaestereoisómeros y mezclas de estos.

El uso de prodrogas, tales como ésteres, de los compuestos (I) con los cuales la invención esta relacionado también es parte de la invención.

Para uso de acuerdo con los aspectos anteriores de la invención pueden estar presentes las siguientes características estructurales, en cualquier combinación compatible, en los compuestos (I):

L2 puede ser un miembro de L2 ajustado a A anterior (y por su puesto L2 ajustado a A incluye L2 ajustado a B);

L2 puede ser -N=CR-, $-OCR_2C(=O)NR-N=CR-$, -C(=O)NR-, -N=CR-, -C(=O)-, -CH=CHC(=O)-, $-(CH_2)_{0-3}NRC(=O)-$, $-NRC(=O)(CH_2)_{0-3}-$, -O-N=CH-,

$-CH_2NRCH_2-$, $-NR(CH_2)_{1-3}-$, $-(CH_2)_{1-3}NR-$, -S-, $-CH_2OCH_2-$, $-O(CH_2)_{1-3}-$, $-(CH_2)_{1-3}O-$, $-CH_2SCH_2-$, $-S(CH_2)_{0-3}-$, $-(CH_2)_{0-3}S-$, un radical alquileno (C_2-C_8) divalente, un radical alquenileno (C_2-C_8) divalente, o un radical alquinileno (C_2-C_8) divalente, en donde R es hidrógeno o alquilo C_1-C_3;

L2 puede ser –NRN=CH-, -ON=CH-, -N=CH-, –C(=O)-, –NHC(=O)- o –C(=O)NH-;

Ar^2 puede ser un fenilo opcionalmente sustituido o un anillo heteroarilo que contiene nitrógeno de 5- o 6- miembros, por ejemplo piridilo, pirimidilo, diazolilo, tiazolilo, oxazolilo, triazinilo, quinolinilo, pirrolilo, furanilo, tiazolilo;

Los sustituyentes opcioales en Ar^2 se pueden seleccionar de flúor, cloro, bromo, alquilo (C_1-C_3), trifluorometilo, alcoxi (C_1-C_3), trifluorometoxi, trifluorometiltio, dimetilamino, ciano, (alquilo C_1-C_3)SO_2-, NH_2SO_2-, (alquilo C_1-C_3)$NHSO_2$-, (alquilo C_1-C_3)$_2NSO_2$-, y nitro;

Ar^1 puede ser un anillo heteroarilo que contiene nitrógeno de 5- o 6-miembros opcionalmente sustituidos, por ejemplo piridilo, pirimidilo, diazolilo, tiazolilo, oxazolilo, triazinilo, quinolinilo, pirrolilo, furanilo, tiazolilo, y en donde L3 puede estar ligado a un carbono del anillo en (para un anillo de 6- miembros) la posición 4 de éste con relación al radical $ACHA_1O$- o (para un anillo de 5-miembros) la posición 4 de éste que cuenta el radical $ACHA_1O$- como en la posición 1 y el radical Ar^2L2- como en la posición 2 de éste;

Ar^1 puede ser un anillo de fenilo opcionalmente sustituido en donde L3 esta ligado a la posición 4 de éste con relación al radical $ACHA_1O$-;

Cuando t es 1, Ar^3 puede ser un anillo de fenilo opcionalmente sustituido, o un anillo heteroarilo de 5- o 6- miembros opcionalmente sustituido, por ejemplo piridilo, pirimidilo, diazolilo, tiazolilo, oxazolilo, triazinilo, quinolinilo, pirrolilo, furanilo, o tiazolilo;

Los sustituyentes opcionales en el anillo Ar^1 o Ar^3 se pueden seleccionar de flúor, cloro, bromo, yodo, ciano, nitro, trifluorometilo, trifluorometoxi,

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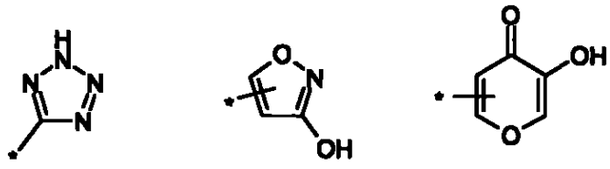
trifluorometilito, (alquilo C_1-C_3)SO_2-, NH_2SO_2-, (alquilo C_1-C_3)$NHSO_2$-, (alquilo C_1-C_3)$_2NSO_2$-, alquilo C_1-C_8, alcoxi C_1-C_8, cicloalquilo, arilo, ariloxi, aril (C_1-C_6)- o aril (alcoxi C_1-C_8)-;

Cuando t es 0, L3 puede ser un enlace;

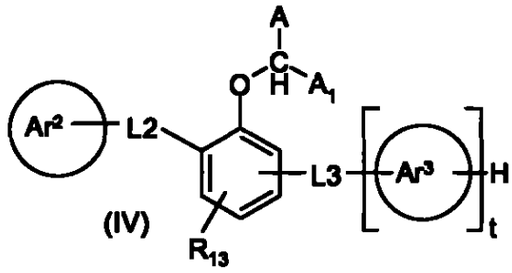
A puede ser –COOH o un carboxil biolsostere seleccionado de-SO_2NHR y -P(=O)(OH)(OR) en donde R es hidrogen metilo o etilo, -SO_2OH, -P(=O)(OH)(NH_2), –C(=O)NHCN y grupos de las fórmulas:



Es habitualmente preferido que A sea carboxilo;

A_1 puede ser hidrógeno o metilo.

Los compuestos (I) para uso de acuerdo con la invención incluyen aquellos de fórmula (IV) y sales, hidratos o solvatos de éstos, los cuales se creen son novedosos *per se*, y que forman otro aspecto de la invención:



(IV)

en donde A, A1, L3, Ar^3, Ar^2, y t son como se definió y se discutió anteriormente defienden relación con la fórmula (I), R13 representa hidrógeno o uno o más sustituyentes opcionales, y L2 es un miembro de L2 ajustado a A, como se definió anteriormente. Este incluye el caso donde A_1 es hidrógeno y L2 es un miembro de L2 ajustado a B como se definió anteriormente.

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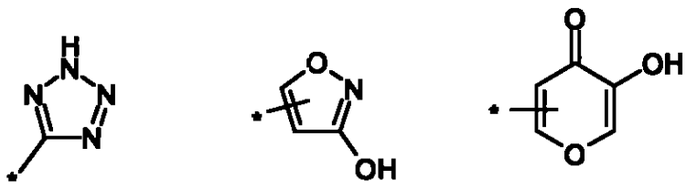
Las siguientes características estructurales pueden estar presentes en los compuestos (IV), en cualquier combinación compatible:

A puede ser –COOH, o un carboxil bioisostere seleccionado de $-SO_2NHR$ y $-P(=O)(OH)(OR)$ en donde R es hidrogen metilo o etilo, $-SO_2OH$, $-P(=O)(OH)(NH_2)$, $-C(=O)NHCN$ y los grupos de fórmulas:

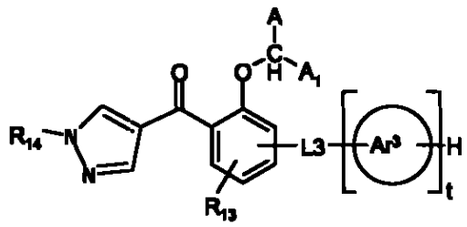


Habitualmente se prefiere que A sea carboxilo.

R_{13} puede representar uno o más sustituyentes seleccionados de flúor, cloro, bromo, yodo, ciano, nitro, trifluorometilo, trifluorometoxi, trifluorometiltio, (alquilo C_1-C_3)SO_2-, NH_2SO_2-, (alquilo C_1-C_3)$NHSO_2$-, (alquilo C_1-C_3)$_2NSO_2$-, alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo, arilo, ariloxi, arilo (C_1-C_6)- o arilo(alcoxi C_1-C_6)-.

A_1 puede ser metilo o A_1 puede ser hidrógeno.

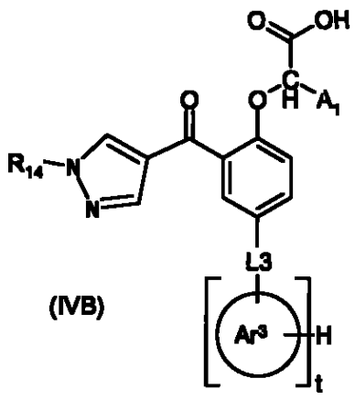
Un subconjunto preferido de los compuestos (IV) tiene la fórmula (IVA)



(IVA)

en donde A, A_1 L3, t, Ar^3, R_{13} son como se definió y discutió anteriormente en relación con los compuestos de fórmula (I) y (IV) y R_{14} es fenilo opcionalmente sustituido o un heteroarilo de 5- o 6- miembros.

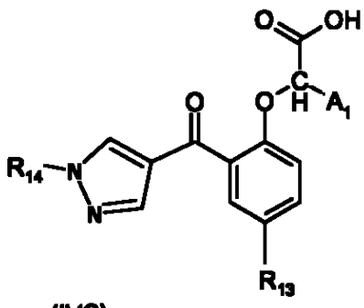
Otro subconjunto preferido de compuestos (IV) tienen la fórmula (IVB):



(IVB)

en donde A_1, L3, t, and Ar^3 son como se definió y se discutió anteriormente en relación con las fórmulas (I), (IV) y (IVA), y R_{14} es fenilo opcionalmente sustituido o un heteroarilo de 5- o 6- miembros.

Otro subconjunto preferido de los compuestos (IV) tienen la fórmula (IVC):



(IVC)

en donde R_{13} representa un sustituyente seleccionado de flúor, cloro, bromo, yodo, alquilo(C_1-C_6), trifluorometilo, alcoxi(C_1-C_6), alquilmercapto(C_1-C_6), trifluorometoxi, trifluorometiltio, dimetilamino, ciano, (alquiloC_1-C_3)SO_2-, NH_2SO_2-, (alquiloC_1-C_3)$NHSO_2$-, (alquiloC_1-C_3)$_2NSO_2$-, y nitro, y R_{14} es fenilo opcionalmente sustituido o heteroarilo de 5- o 6- miembros. En este subconjunto, R_{14} puede ser un anillo de fenilo 2-sustituido, 2,4-disustituido, 2,6-disustituido o 2,4,6-trisustituido donde los sustituyentes se seleccionan de flúor, cloro, bromo, yodo, alquilo(C_1-C_6), trifluorometilo, alcoxi(C_1-C_6), alquilmercapto(C_1-C_6), trifluorometoxi, trifluorometiltio, dimetilamino, (alquilC_1-C_3)SO_2-, NH_2SO_2-, (alquilC_1-C_3)$NHSO_2$-, (alquilC_1-C_3)$_2NSO_2$-, y ciano. Este subconjunto incluye específicamente los compuestos en donde A_1 es hidrógeno.

En cualquiera de los compuestos (I), (IV) (IVA), (IVB) o IVC) definidos y discutidos anteriormente, en donde A1 es metilo, el átomo de carbono al cual éste está unido tiene preferiblemente la configuración estereoquímica S.

Los compuestos específicos novedosos de la invención son los siguientes:
ácido 4-cloro-2-(1-fenil-1H-pirazol-4-carbonil)fenoxiacético,
ácodo 4-bromo-2-(1-fenil-1H-pirazol-4-carbonil)fenoxiacético,
ácido [4-bromo-2-(1-piridin-2-il-1H-pirazol-4-carbonil)fenoxi]acético,
ácido {4-bromo-2-[1-(2-clorofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-bromo-2-[1-(3-clorofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-bromo-2-[1-(4-bromofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-bromo-2-[1-(4-clorofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-bromo-2-[1-(2-etilfenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-bromo-2-[1-(2-bromofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-bromo-2-[1-(2-fluorofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-bromo-2-[1-(2-trifluorometilfenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-bromo-2-[1-(3-bromofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-bromo-2-[1-(2,4-diclorofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {2-[1-(2-clorofenil)-1H-pirazol-4-carbonil]-4-nitrofenoxi}acético,
ácido {4-bromo-2-[1-(2,6-diclorofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {2-[1-(2-bromofenil)-1H-pirazol-4-carbonil]-4-etilfenoxi}acético,
ácido {4-bromo-2-[1-(2,4-dibromofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-bromo-2-[1-(4-bromo-2-clorofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-bromo-2-[1-(2,4,6-triclorofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido 2-[4-bromo-2-(1-fenil-1H-pirazol-4-carbonil)fenoxi]propiónico,
ácido (S)-2-[4-bromo-2-(1-fenil-1H-pirazol-4-carbonil)fenoxi]propiónico,
ácido 2-{4-Bromo-2-[1-(2-clorofenil)-1-H-pirazol-4-carbonil]fenoxi}propiónico,
ácido (S)-2-{4-Bromo-2-[1-(2-clorofenil)-1-H-pirazol-4-carbonil]fenoxi}¬propiónico,
ácido 2-{4-Bromo-2-[1-(2,6-diclorofenil)-1H-pirazol-4-carbonil]fenoxi}propiónico,
ácido (S)-2-{4-Bromo-2-[1-(2,6-diclorofenil)-1H-pirazol-4-carbonil]fenoxi}propiónico,
ácido {4-Bromo-2-[1-(2-etoxifenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-Bromo-2-[1-(4-bromo-2-etilfenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-Bromo-2-[1-(2-fenoxifenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-Bromo-2-[1-(2-metiltiofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-Bromo-2-[1-(2-bromo-4-metilfenil)-1H-pirazol-4-carbonil]fenoxi}acético,

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ácido 2-{4-Bromo-2-[1-(4-bromo-2-etilfenil)-1H-pirazol-4-carbonil]fenoxi}propiónico,
ácido 2-{4-Bromo-2-[1-(2-fenoxifenil)-1H-pirazol-4-carbonil]fenoxi}propiónico,
ácido (S)-2-{4-Bromo-2-[1-(2-fenoxifenil)-1H-pirazole-4-carbonil]fenoxi}propiónico,
ácido 2-{4-Bromo-2-[1-(2-metiltio)-1H-pirazol-4-carbonil]fenoxi}propiónico,
ácido (S)-2-{4-Bromo-2-[1-(2-metiltio)-1H-pirazol-4-carbonil]fenoxi}propiónico,
ácido {4-Bromo-2-[1-(2,4-dimetilfenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-Bromo-2-[1-(4-chloro-2-metilfenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-Bromo-2-[1-(2,5-diclorofenil)-1H-pirazol-4-carbonil] fenoxi}acético,
ácido 2-{4-Bromo-2-[1-(4-cloro-2-metilfenil)-1H-pirazol-4-carbonil] fenoxi}propiónico,
ácido 2-{4-Bromo-2-[1-(2,4,6-triclorofenil)-1H-pirazol-4-carbonil] fenoxi}propiónico,
ácido {4-Bromo-2-[1-(2,6-dietil-fenil)-1H-pirazol-4-carbonil] fenoxi}acético,
ácido {4-Bromo-2-[1-(2,6-dimetilfenil)-1H-pirazol-4-carbonil] fenoxi}acético,
ácido {4-Bromo-2-[1-(2-etil-6-metilfenil)-1H-pirazol-4-carbonil] fenoxi}acético,
ácido {4-Bromo-2-[1-(2-cloro-6-metilfenil)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido {4-Bromo-2-[1-(3,5-dicloropiridin-4-yl)-1H-pirazol-4-carbonil]fenoxi}acético,
ácido [4-Bromo-2-(1-naftaleno-1-il-1H-pirazol-4-carbonil)fenoxi]acético,
ácido {4-Bromo-2-[2-(4-clorobencil)tiazol-4-il]fenoxi}acético,
ácido {4-Bromo-2-[3-(4-fluoro-fenil)-[1,2,4]oxadiazol-5-yl]fenoxi}acético,
ácido {4-Bromo-2-[3-(4-metoxi-fenil)-[1,2,4]oxadiazol-5-il]fenoxi}acético,
ácido {4-Bromo-2-[3-(4-clorofenil)-[1,2,4]oxadiazol-5-il]fenoxi}acético,
ácido {4-Bromo-2-[3-(4-fluoro-bencil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético,
ácido {4-Bromo-2-[3-(2,6-dicloro-bencil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético,
ácido {4-Bromo-2-[3-(2-trifluorometilbencil)-[1,2,4]oxadiazol-5-il]fenoxi}-acético,
ácido 4-Bromo-2-[3-(2,6-dicloro-fenil)isoxazol-5-carbonil]fenoxi}acético,
ácido {4-Bromo-2-[3-(1-fenilciclopropil)-[1,2,4]oxadiazol-5-il]fenoxi}acético,
ácido {4-Bromo-2-[3-(2,4-diclorofenil)-[1,2,4]oxadiazol-5-il]fenoxi}acético,

y sales, hidratos y solvatos de éstos.

La invención también incluye composiciones farmacéuticas que comprenden un compuesto que pertenece a los compuestos anteriormente descritos de fórmula (IV), (IVA), (IVB) or (IVC), junto con un vehículo farmacéuticamente aceptable.

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Composiciones

Como se mencionó anteriormente, los compuestos con los cuales la invención esta relacionado son capaces de modular actividad CRTH2, y son útiles para el tratamiento de enfermedades que se benefician de tal modulación. Ejemplos de tales enfermedades son referidas anteriormente, e incluyen asma, alergia y rinitis.

Se entenderá que el nivel de dosis específico para cualquier paciente particular dependerá de una variedad de factores que incluyen la actividad del compuesto específico empleado, la edad, el peso del cuerpo, la salud general, el sexo, la dieta, el tiempo de administración, la ruta de administración, la proporción de excreción, la combinación de droga y la severidad de la enfermedad particular que está en tratamiento. Los niveles de dosis óptimos y la frecuencia de dosificación se determinarán mediante ensayo clínico, como se requiere en la técnica farmacéutica.

Los compuestos con los cuales esta relacionada la invención se pueden preparar para la administración mediante cualquier ruta consistente con sus propiedades farmacocinéticas. Las composiciones oralmente administrables pueden estar en la forma de tabletas, cápsulas, polvos, gránulos, pastillas, preparaciones líquidas o de gel, tal como soluciones o suspensiones parenterales orales, tópicas, o estériles. Las tabletas y las cápsulas para la administración oral pueden estar en una forma de presentación de dosis unitaria, y pueden contener excipientes convencionales tales como agentes ligantes, por ejemplo melaza, acacia, gelatina, sorbitol, tragacanto, o polivinilpirrolidona; llenadores por ejemplo lactosa, azúcar, almidón de maíz, fosfato de calcio, sorbitol o glicina; lubricantes para fabricación de tabletas, por ejemplo estearato de magnesio, talco, polietilenglicol o sílice; desintegrantes por ejemplo almidón de papa, o agentes humectantes aceptables tales como laurilsulfato de sodio. Las tabletas pueden ser recubiertas de acuerdo con métodos bien conocidos en la práctica farmacéutica normal. Las preparaciones líquidas orales pueden estar en la forma de, por ejemplo, suspensiones acuosas o aceitosas, soluciones, emulsiones, melazas o elixires, o pueden estar presentes como un producto seco para la reconstitución con agua u otro vehículo adecuado antes de uso. Tales preparaciones líquidas pueden contener aditivos convencionales tales como agentes de suspensión, por ejemplo sorbitol, melaza, metil celulosa, melaza de glucosa, grasas comestibles hidrogenadas en gelatina; agentes emulsificantes, por ejemplo lecitina, monooleato sorbitán, o acacia; vehículos no acuosos (que pueden incluir aceites comestibles), por

ejemplo aceite de almendra, aceite de coco fraccionado, ésteres aceitosos tales como glicerina, propilenglicol, o etil alcohol; preservativos, por ejemplo metil o propil p-hidroxibenzoato o ácido sórbico, y si se desea agentes saborizantes o colorantes convencionales.

Para la aplicación tópica a la piel, la droga puede hacerse en crema, loción o ungüento. Las formulaciones de crema o ungüento que se pueden utilizar para la droga son formulaciones convencionales bien conocidas en la técnica, por ejemplo como se describió en los textos de libro estándar de farmacéuticos tales como la Farmacopeia Británica.

Para la aplicación tópica al ojo, la droga puede ser hecha en una solución o suspensión en un vehículo acuoso o no acuoso estéril adecuado. Los aditivos, por ejemplo amortiguadores tales como metabisulfito de sodio o edeato disodio; los preservativos que incluyen agentes bactericidas y fungicidas tal como acetato o nitrato mercúrico fenilo, cloruro de benzalconio o clorhexidina, y agentes espesantes tales como hipromelosa también pueden estar incluidos.

La droga también se puede formular para inhalación, por ejemplo como pulverizado nasal, o polvo seco o inhaladores en aerosol.

El ingrediente activo también se puede administrar parenteralmente en un medio estéril. Dependiendo del vehículo y la concentración utilizada, la droga puede ser suspendida o disuelta en el vehículo. De manera ventajosa, los adyuvantes tales como agentes anestésicos locales, preservativos y amortiguantes se pueden disolver en el vehículo.

Los compuestos con los cuales la invención esta relacionado se pueden administrar solos o como parte de una terapia de combinación con otras drogas utilizadas para el tratamiento de enfermedades con componente inflamatorio principal. En el caso de asma, rinitis, y síndrome alérgico de vías aéreas tales drogas incluyen corticosteroides, agonistas beta inhalados de larga acción, cromolina, nedocromilo, teofilina, antagonistas receptores de leucotrieno, antihistaminas, y anticolinérgicos (por ejemplo, ipratropio), y son a menudo administrados en pulverizados nasales, polvo seco o inhaladores en aerosol.

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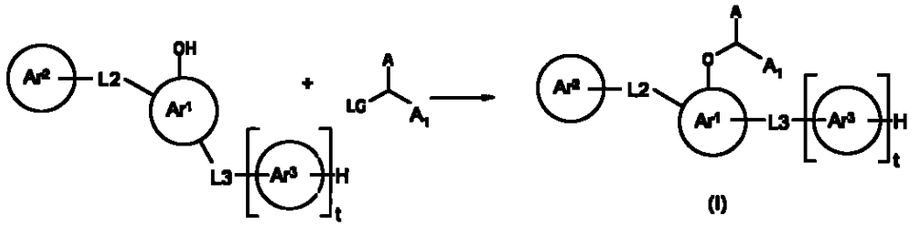
En el caso de la artritis y las enfermedades inflamatorias relacionadas otras drogas conocidas incluyen glucocorticoides, los NSAID (Drogas Anti-Inflamatorias No Esteroides – inhibidores de síntesis de prostaglandina convencionales, inhibidores COX-2, salicilatos), y los DMARD (drogas anti-reumáticas que modifican la enfermedad tales como metotrexato, sulfasalazina, oro, ciclosporina).

Rutas Sintéticas

Existen múltiples estrategias sintéticas para la síntesis de los compuestos (I) con los cuales la presente invención esta relacionada, pero todos confían en la química conocida, conocida en la química orgánica sintética. Así, los compuestos de acuerdo con la Fórmula I se pueden sintetizar de acuerdo con los procedimientos descritos en la literatura estándar y son bien conocidos por un experto en la técnica. Las fuentes de literatura típica son "*Advanced organic chemistry*", 4th Edition (Wiley), J March, "*Comprehensive Organic Transformation*", 2nd Edition (Wiley), R.C. Larock , "*Handbook of Heterocyclic Chemistry*", 2nd Edition (Pergamon), A.R. Katritzky), artículos revisados tales como los encontrados en "*Synthesis*", "*Acc. Chem. Res.*" , "*Chem. Rev*", o fuentes de literatura primaria identificadas mediante búsquedas de literatura estándar en línea o de fuentes secundarias tales como "*Chemical Abstracts*" o "*Beilstein*".

En la discusión que sigue, A representa un ácido carboxílico, un carboxil bioisostere, o un ácido carboxílico protegido o bioisostere, o un precursor de éstos. En un caso posterior, una etapa de desprotección esta implicada. A_1 representa hidrógeno o metilo.

Muchos compuestos reivindicados en esta invención pueden ser sintetizados al reaccionar un precursor de fenol con LG-CH(A_1)-A, donde LG es un grupo saliente y A es un ácido carboxílico o un análogo o precursor protegido, o un bioisostere o un análogo protegido de éste.



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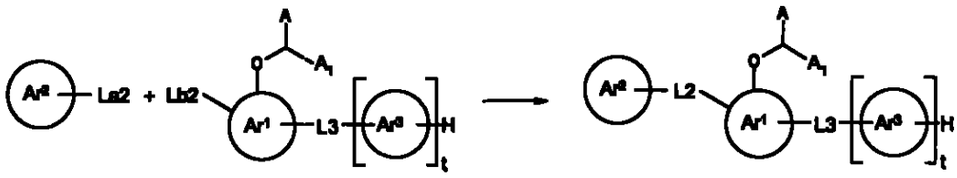
El ligador L2 se puede formar al unir dos fragmentos apropiadamente funcionalizados y, si se necesita, adecuadamente protegidos que contienen La2 y Lb2 como porciones reactivas como se subraya adelante. La2 y Lb2 se definen como cualesquiera porciones que pueden reaccionar mediante, por ejemplo, una sustitución nucleofílica, adición a múltiples enlaces o reacción de ciclización para formar un ligadore L2 dado como se ejemplifica adelante.



(I)

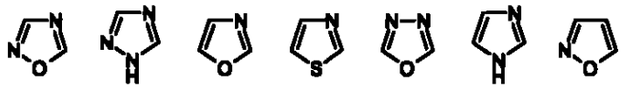
Por ejemplo, el ligador -L2- que es $-Alk^1-Z-(Alk^2)_p-$ se puede formar al reaccionar Ar^2-Alk^1-"grupo saliente" con un derivado nucleofílico $H-Z-(Alk^2)_p-Ar^1(L1A)L3Ar^3H$ en donde Z puede ser O, S o NR y Alk^1 puede ser un grupo alquilo. Las reacciones también pueden hacersen al reversar la funcionalización de La2 y Lb2 para hacer la conexión entre Z y Alk^2. Los ligadores en donde Z es SO o SO_2 se pueden obtener mediante oxidaciones de los derivados $-(Alk^1)_m-S-(Alk^2)_p-$ correspondientes durante condiciones apropiadas.

Ejemplos representativos adicionales, –L2- siendo $-Alk^1-Z-(Alk^2)_p-$ en donde Z es NH(CO) o $NHSO_2$ se pueden formar al hacer reaccionar $Ar^2-(Alk^1)-NH_2$ con un derivado acilante "grupo saliente"$-CO-(Alk^2)_p-Ar^1(L1A)L3Ar^3H$ o "grupo saliente"$-SO_2-(Alk^2)_p-Ar^1(L1A)L3Ar^3H$, respectivamente. Alternativamente, la conversión se puede hacer directamente con los ácidos $HO-CO-(Alk^2)_p-Ar^1(L1A)L3Ar^3H$ y $HO-SO_2-(Alk^2)_p-Ar^1(L1A)L3Ar^3H$, respectivamente, utilizando reactivos de acoplamiento adecuados tales como diciclohexilcarbodimida (DCC), y promotores tales como 1-hidroxibenzotriazol. De manera análoga, –L2- es $-Alk^1-Z-(Alk^2)_p-$ en donde Z es NH(CO)NH que se puede formar al hacer reaccionar $Ar^2-(Alk^1)-NH_2$ con un derivado de isocianato $OCN-(Alk^2)_p-Ar^1(L1A)L3Ar^3H$ utilizando catálisis de ácido o base adecuada. Las reacciones también se pueden hacer al reversar la funcionalización de La2 y Lb2 para suministrar los "retro-enlaces" en el caso de NH(CO) o $NHSO_2$. De manera análoga, las conexiones se pueden hacer entre Z y Alk^2.

Una reacción de acoplamiento catalizada con metal como la reacción de acoplamiento Stille, la reacción de acoplamiento Suzuki, la reacción Heck y la reacción Sonogashira son útiles en la síntesis de ejemplos con L2 siendo un radical alquileno divalente, un radical alquenileno divalente o un radical alquinileno divalente.

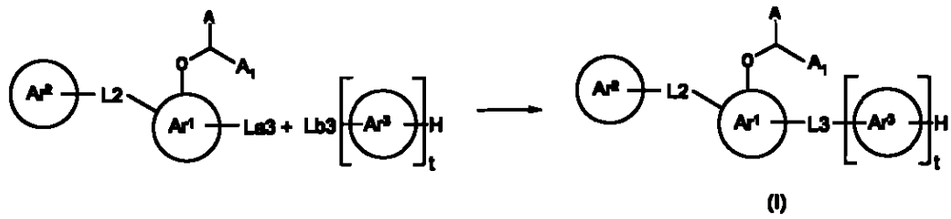
Los compuestos con L2 que son una hidrazona son usualmente convenientemente formados por una reacción de condensación entre las hidracinas y los aldehídos correspondientes en etanol o sin solvente.

De manera similar, L2 es $-(Alk^1)_m-Z-(Alk^2)_p-$ en donde Z es un sistema heterocíclico de 5 miembros ejemplificado por, por ejemplo,



Se puede hacer de acuerdo con procedimientos de ciclización estándar utilizando solventes apropiados, catalizadores y temperaturas. Por ejemplo, la formación de 1,2,4-triazol se puede hacer con La2 siendo acilhidrazida y Lb2 siendo amida o tioamida o la orientación inversa de La2 y Lb2. 1,2,4-Oxadiazol se puede formar de La2 siendo amidoxima y Lb2 siendo éster carboxílico o la orientación inversa de La2 y Lb2. 1,3,4-Oxadiazol se puede formar de La2 siendo acilhidrazida y Lb2 siendo éster carboxílico o la orientación inversa de La2 y Lb2. El tiazol se puede hacer de La2 que es tioamida y Lb2 que es una □-halocetona o la orientación inversa de La2 y Lb2. El isoxazol se puede hacer de La2 que es alquino y Lb2 que es nitriióxido o la orientación inversa en una reacción de cicloadición.

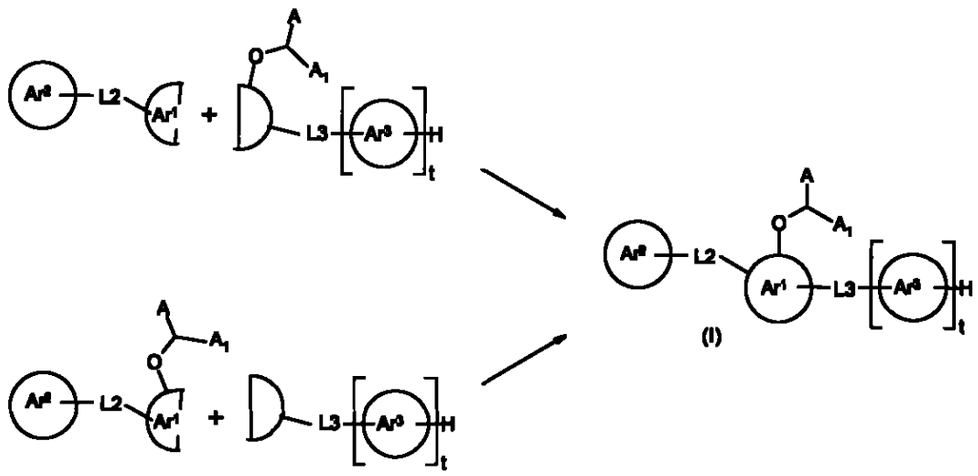
De manera análoga los compuestos de fórmula I se pueden hacer al formar el ligador L3, de acuerdo a procedimientos subrayados para L2, como se describe adelante. Así, La y Lb se definen como cualquiera porciones que pueden reaccionar mediante por ejemplo, una sustitución nucleofílica, adición a enlaces múltiples o reacción de ciclización para formar un ligador dado como se ejemplificó adelante.



(I)

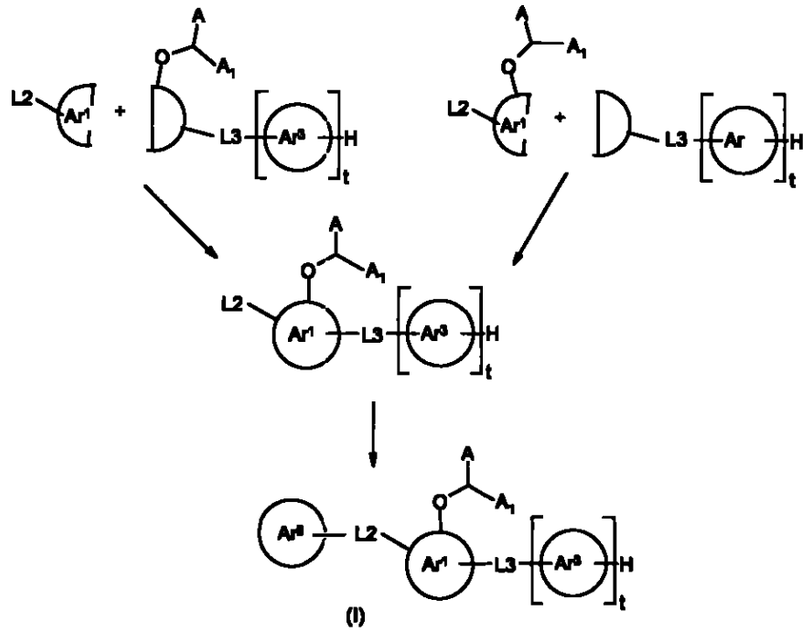
La porción Ar^1 también puede ser el andamio central que se utilice para conectar las partes L2 y L3 en forma de etapas. Esto se puede hacer por vía de sustituciones aromáticas del núcleo Ar^1 para unir L2 y/o L3, el cual entonces puede ser adicionalmente funcionalizado para dar los compuestos de fórmula I finales.

Adicionalmente, la porción Ar^1 también se puede ensamblar por vía de reacciones de ciclización de anillo con reactivos que contienen las unidades L2 y L3 o que contienen los apéndices completos como se subraya adelante:



(I)

O en formas que pueden ser adicionalmente funcionalizadas en las estructuras de Fórmula I finales como se describió previamente. Una de tales ilustraciones es dada adelante



(I)

Por ejemplo, 1,2,4-triazoles se pueden hacer de acilhidrazidas y amidas o tioamidas; 1,2,4-Oxadiazoles de amidoximas y ésteres carboxílicos; 1,3,4-Oxadiazoles de acilhidrazidas y ésteres carboxílicos; Tiazoles de tioamidas y □-halocetonas; Piridinas por vía de varias reacciones de cicloadición.

Los bloques de construcción utilizados en las reacciones están comercialmente disponibles o se hacen de acuerdo a procedimientos estándar bien conocidos por un experto en la técnica como se describió en "*Advanced organic chemistry*", 4th Edition (Wiley), J March, "*Comprahensive Organic Transformation*", 2nd Edition (Wiley), R.C. Larock, "*Handbook of Heterocyclic Chemistry*", 2nd Edition (Pergamon), A.R. Katritzky u otras fuentes de literatura adecuadas. Los ejemplos aquí descritos especifican estrategias para la síntesis de compuestos en donde Ar^1 es fenilo. Los compuestos análogos son accesibles mediante la variación de los intermedios utilizados en los Ejemplos.

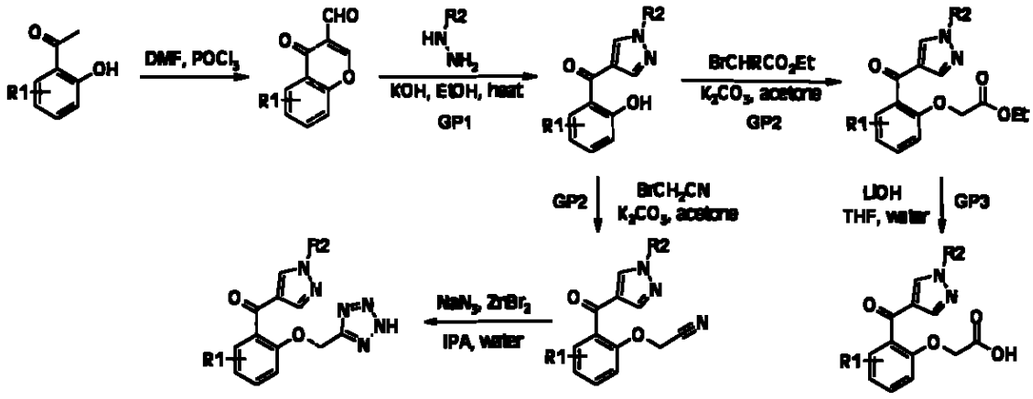
Los siguientes Ejemplos ilustran la preparación de compuestos con los cuales esta invención está relacionada. Algunos compuestos fueron sintetizados, y algunos fueron adquiridos de fuentes comerciales. En los Ejemplos:

Comentarios generales:

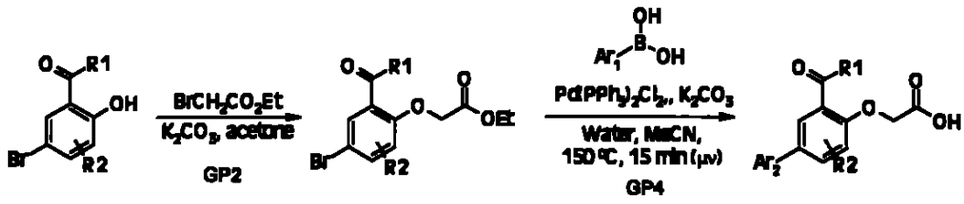
La química de microondas fue desarrollada en un "Personal Chemistry Emrys Optimizer". Los espectros NMR fueron obtenidos en un instrumento Bruker Avance

AMX de 300 MHz. El LC/MS se desarrolló en un instrumento Agilent 1100-series. Los métodos LC/MS son como sigue: An10p8: Columna: XTerra MS C18; Flujo: 1.0 mL/min; Gradiente: 0-5 min: 15-100% MeCN en agua, 5-7½ min: 100% MeCN; Modificador: 5 mM de formato de amonio; modo de ionización MS: API-ES (pos.). An10n8: Columna: XTerra MS C18; Flujo: 1.0 mL/min; Gradiente: 0-5 min: 15-100% MeCN en agua, 5-7½ min: 100% MeCN; Modificador: 5 mM de formato de amonio; modo de ionización MS: API-ES (neg.).

Ruta sintética general I



Ruta sintética general II



Procedimiento general 1 (GP1):

Condensación ode 3-formilcromona con arilhidracina

La 3-formilcromona (1.0 mmol) y la arilhidrazina (1.0 mmol) en etanol (3.0 mL) en un tubo de reacción se agregó 4.0 M de KOH a ac (1.0 mL, 4.0 mmol). El tubo se selló y se calentó mediante microondas a 120 °C durante 7 min (420 s). A la mezcla de reacción se agregó el 3% de HCl hasta un pH <1 y se dejó hasta que se precipitó. El precipitado se filtró y se lavó con una pequeña cantidad de etanol. El producto se utilizó directamente o se purificó mediante recristalización de etanol o mediante cromatografía flash.

Procedimiento general 2 (GP2):

Alquilación de fenol

Al fenol (0.5 mmol) en acetona (1 mL) se agregó etil bromoacetato (85 mg, 0.5 mmol) o etil 2-bromopropionato (91 mg, 0.5 mmol) y K_2CO_3 (75 mg, 0.54 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 12 h. La mezcla de reacción fue entonces concentrada in vacuo y el residuo se particionó entre agua y etil acetato. La fase orgánica se lavó con solución salina, se secó ($MgSO_4$) y se concentró. El producto se utilizó directamente o se purificó mediante recristalización de MeOH o mediante cromatografía flash.

Procedimiento general 3 (GP3):

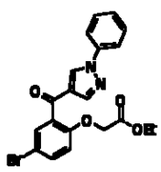
Hidrólisis de éster

Al éster (0.10 mmol) en THF (0.5 mL) se agregó $LiOH \cdot H_2O$ (6.3 mg, 0.15 mmol) en agua (0.5 mL). La reacción se agitó a temperatura ambiente durante >2 h, 3% HCl se agregó hasta pH <1, y la mezcla se extrajo con CH_2Cl_2. La fase orgánica se secó ($MgSO_4$) y se concentró para dar el producto.

Procedimiento general 4 (GP4):

Acoplamiento Suzuki/hidrólisis de éster

A aril bromuro (0.20 mmol), ácido aril borónico (0.21 mmol) y $Pd(PPh_3)_2Cl_2$ (9 mg, 0.01 mmol) se agregó MeCN (0.4 mL, desgasificado) y 1.0 M Na_2CO_3 (0.4 mL, desgasificado). La mezcla de reacción se desgasificó al dejar pasar argón durante ½ min y calentado en microondas (150 °C, 300 s), luego se agregó 3% de HCl hasta pH <1 y se extrajo con CH_2Cl_2. El extracto se filtró a través de celita y se concentró, y el residuo se purificó mediante extracción de fase sólida (pre-empacada columnas 1 g SAX), o mediante cromatografía flash.



Intermedio-1 **Etil 4-bromo-2-(1-fenil-1H-pirazol-4-carbonil)fenoxiacetato.** Preparado de (5-bromo-2-hidroxi-fenil)-(1-fenil-1H-pirazol-4-il)cetona y etil bromoacetato de acuerdo a GP2 para dar 215 mg (100%) cristales blancos. El producto se utilizó sin purificación

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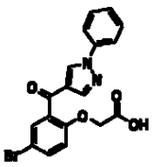
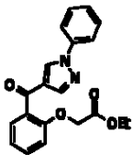
adicional: LC/MS (un10p8): Rt 6.15 min, *m/z* 429 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 1.26 (t, *J* = 7.1 Hz, 3H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.64 (s, 2H), 6.72 (d, *J* = 8.9 Hz, 1H), 7.34 (m, 1H), 7.46 (m, 2H), 7.53 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.59 (d, *J* = 2.5 Hz, 1H), 7.73-7.78 (m, 2H), 8.17 (s, 1H), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 14.3, 61.9, 65.5, 114.0, 114.5, 119.8, 125.3, 127.7, 129.8, 131.8, 132.3, 132.7, 134.6, 139.6, 142.7, 154.1, 168.5, 186.9.



D1

Ácido 4-Bromo-2-(1-fenil-1H-pirazol-4-carbonil)fenoxiacético. Preparado de etil 4-bromo-2-(1-fenil-1H-pirazol-4-carbonil)fenoxiacetato (31 mg, 0.072 mmol) de acuerdo a GP3 para dar 28.4 mg (99%) sólido blanco: LC/MS (un10p8): Rt 3.14 min, *m/z* 401; ^1H NMR ($CDCl_3$): □ 3.51 (s, 1H), 4.80 (s, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 7.38-7.44 (m, 1H), 7.49-7.55 (m, 2H), 7.64-7.69 (m, 1H), 7.72-7.77 (m, 3H), 8.19 (s, 1H), 8.52 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 67.2, 115.1, 116.6, 120.1, 124.5, 128.4, 130.0, 131.9, 133.3, 136.2, 139.2, 143.3, 155.2, 169.9, 187.6.



Intermedio-2

Etil 2-(1-fenil-1H-pirazol-4-carbonil)fenoxiacetato. Preparado de (2-hidroxifenil)-(1-fenil-1H-pirazol-4-il)cetona (264 mg, 1.0 mmol) y etil bromoacetato de acuerdo a GP2 para dar 235 mg (67%) del compuesto del título como un sólido blanco: ^1H NMR ($CDCl_3$): □ 1.26 (t, *J* = 7.1 Hz, 3H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.67 (s, 2H), 6.84 (d, *J* = 8.3 Hz, 1H), 7.10 (ts, *J* = 7.4, 0.8 Hz, 1Hz), 7.29-7.36 (m, 1H), 7.41-7.53 (m, 4H), 7.72-7.78 (m, 2H), 8.18 (s, 1H), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 14.3, 61.7, 65.4, 112.2, 118.8, 119.3, 119.7, 120.0, 122.1, 125.8, 127.6, 129.7, 129.9, 130.1, 130.6, 131.8, 132.1, 136.3, 139.7, 142.8, 155.0, 168.9, 188.7.

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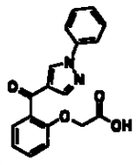
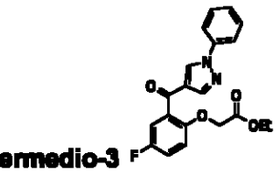


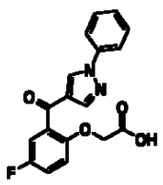
D2

Ácido 2-(1-Fenil-1H-pirazol-4-carbonil)fenoxiacético. Preparado de etil 2-(1-fenil-1H-pirazol-4-carbonil)fenoxiacetato de acuerdo a GP3 y purificado mediante cromatografía de columna (SiO_2, EtOAc:heptano, 1:1) para dar 15 mg (56%) del compuesto del título como un sólido blanco: LC/MS (un10n8): Rt 2.90 min, *m/z* 321.0 $[M-H]^-$; ^1H NMR ($CDCl_3$): □ 4.83 (s, 2H), 7.10 (d, *J* = 8.3 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.35-7.42 (m, 1H), 7.46-7.53 (m, 2H), 7.54-7.61 (m, 1H), 7.66 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.70-7.75 (m, 2H); ^{13}C NMR ($CDCl_3$): □ 67.7, 115.5, 120.1, 122.8, 124.7, 128.3, 128.6, 129.9, 131.0, 131.9, 134.0, 139.3, 143.5, 156.6, 170.4, 189.3.



Intermedio-3

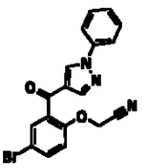
Etil 4-fluoro-2-(1-fenil-1H-pirazol-4-carbonil)fenoxiacetato. Preparado de 4-fluoro-2-(1-fenil-1H-pirazol-4-carbonil)fenol (282 mg) y etil bromoacetato de acuerdo a GP2 para dar 335 mg (91%) sólido amarillo: LC/MS (un10n8): Rt 3.16, *m/z* 339.0 $[M-H]^-$; ^1H NMR ($CDCl_3$): □ 1.26 (t, *J* = 7.0 Hz, 3H), 4.23 (t, *J* = 7.1 Hz, 2H), 4.83 (s, 2H), 6.81 (dd, *J* = 9.0, 4.0 Hz, 1H), 7.13 (ddd, *J* = 8.9, 4.5, 3.0 Hz, 1H), 7.21 (dd, *J* = 8.1, 3.2 Hz, 1H), 7.31-7.37 (m, 1H), 7.24-7.50 (m, 2H), 7.72-7.78 (m, 2H), 8.18 (s, 1H), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 14.3, 61.8, 66.1, 114.0 (d, J_{CF} = 7.6 Hz), 116.8 (d, J_{CF} = 24.5 Hz), 118.3 (d, J_{CF} = 23.5 Hz), 119.7, 125.2, 127.7, 129.7, 131.8, 139.6, 142.8, 151.1 (d, J_{CF} = 2.2 Hz), 157.6 (d, J_{CF} = 241.1 Hz), 168.7, 187.1.



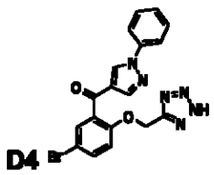
D3

Ácido 4-Fluoro-2-(1-fenil-1H-pirazol-4-carbonil)fenoxiacético. Preparado de etil 4-fluoro-2-(1-fenil-1H-pirazol-4-carbonil)fenoxiacetato (31 mg) de acuerdo a GP3 para dar 30 mg (100%) de un sólido amarillo pálido: LC/MS (un10n8): Rt 3.16, *m/z* 339.0

[M-H]; ^{1}H NMR ($CDCl_3$): □ 4.60 (s, 2H), 6.90 (dd, *J* = 9.2 Hz, 1H), 7.08-7.17 (m, 1H), 7.21 (dd, *J* = 7.9, 3.0 Hz, 1H), 7.28-7.35 (m, 1H), 7.38-7.46 (m, 2H), 7.65 (d, *J* = 7.5 Hz, 2H), 8.06 (s, 1H), 8.44 (s, 1H).



Intermedio-4 **4-Bromo-2-(1-fenil-1H-pirazol-4-carbonil)fenoxiacetonitrilo.** (5-Bromo-2-hidroxi-fenil)-(1-fenil-1H-pirazol-4-il)cetona (342 mg) se agregó bromoacetonitrilo (122 mg), acetona (2 mL) y K_2CO_3 (140 mg), y la reacción se agitó durante 24 h. La mezcla de reacción se concentró y el residuo se particionó entre agua y EtOAc. La fase orgánica se lavó con solución salina, se secó ($MgSO_4$) y se concentró para dar 383 mg (100%) sólido amarillo, que se utilizó directamente en la siguiente etapa: LC/MS (un10p8): Rt 4.39 min, *m/z* 381.5 [M + 1]$^+$; ^{1}H NMR ($CDCl_3$): □ 4.80 (s, 2H), 7.07 (d, *J* = 8.7 Hz, 1H), 7.35-7.42 (m, 1H), 7.45-7.54 (m, 2H), 7.60-7.69 (m, 2H), 7.69-7.75 (m, 2H), 8.03 (s, 1H), 8.31 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 55.2, 114.7, 116.6, 116.7, 120.1, 125.1, 128.2, 129.9, 131.0, 132.6, 133.2, 135.0, 139.3, 142.7, 153.0, 186.0.



D4 **[5-Bromo-2-(2H-tetrazol-5-ilmetoxi)fenil](1-fenil-1H-pirazol-4-il)cetona.** [4-Bromo-2-(1-fenil-1H-pirazol-4-carbonil)fenoxi]-acetonitrilo (38 mg) se agregó NaN3 (66 mg), $ZnBr_2$ (59 mg), isopropanol (1.3 mL) y agua (1.6 mL), y la mezcla de reacción se calentó hasta reflujo durante 1 h. A la mezcla se agregó 3% de HCl (1 mL) y EtOAc (4 mL) y se agitó hasta que aparecieron dos fases claras. A la fase acuosa se agregó 3% HCl hasta pH <1 y se extrajo con EtOAc. Las fases orgánicas combinadas se lavaron con solución salina, se secaron ($MgSO_4$) y se concentraron para dar 47 mg de espuma blanca: LC/MS (un10n8): Rt 2.93, *m/z* 243.0 [M - H]; ^{1}H NMR ($CDCl_3$): □ 5.69 (s, 2H), 7.13 (d, *J* = 8.6 Hz, 1H), 7.39-7.45 (m, 1H), 7.49-7.56 (m, 2H), 7.62-7.71 (m, 2H), 7.71-7.79 (m, 1H), 8.13 (s, 1H), 8.45 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 63.3, 115.6, 117.7, 120.3, 124.5, 128.6, 130.0, 131.2, 132.0, 132.9, 136.3, 139.1, 143.5, 154.7, 188.4.

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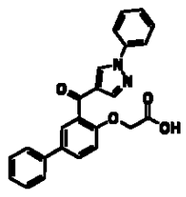
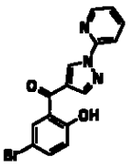


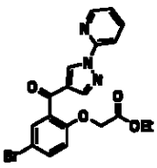
D5

Ácido 3-(1-Fenil-1H-pirazol-4-carbonil)bifenil-4-iloxiacético. Preparado de etil [4-bromo-2-(1-fenil-1H-pirazol-4-carbonil)fenoxi]acetato y ácido fenilborónico de acuerdo a GP4: LC/MS (un10p8): Rt 1.05 min, *m/z* 398.6 [M – H]$^-$; ^{1}H NMR ($CDCl_3$): □ 4.86 (s, 2H), 7.17 (d, *J* = 8.6 Hz, 1H), 7.35-7.57 (m, 8H), 7.70-7.75 (m, 2H), 7.78 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.84 (d, *J* = 2.3 Hz, 1H), 8.20 (s, 1H), 8.54 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 67.7, 115.8, 120.1, 124.8, 127.1, 128.0, 128.3, 129.1, 129.3, 129.4, 129.9, 132.3, 136.2, 139.3, 139.3, 143.5, 155.8, 170.4, 189.3.



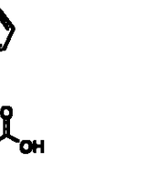
Intermedio-5

(5-Bromo-2-hidroxifenil)-(1-piridin-2-il-1H-pirazol-4-il)cetona. A una suspensión de 6-bromo-3-formilcromona (253 mg) en isopropanol (3 mL) y CH_2Cl_2 (2 mL) se agregó 2-hidrazinopiridina (109 mg), y la mezcla se agitó durante 15 min para formar una suspensión amarilla. A la suspensión se agregó KOH (0.25 g) en agua (0.25 mL), y la reacción se calentó hasta reflujo durante 1 h. La mezcla de reacción se diluyó con agua, se agregó 3% HCl hasta pH <1 y se extrajo con CH_2Cl_2 (2x). El extracto se lavó con agua y solución salina, se secó ($MgSO_4$) y se concentró para dar 342 mg de espuma naranja, que se purificó mediante cromatografía flash (SiO_2, EA:Hep, 1:1) para dar 53 mg (15%) sólido amarillo: LC/MS (un10p8): Rt 5.0 min, *m/z* 343.5 [M + H]$^+$; ^{1}H NMR ($CDCl_3$): □ 6.98 (d, *J* = 8.9 Hz, 1H), 7.31 (ddd, *J* = 7.3, 4.9, 0.9 Hz, 1H), 7.60 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.87-7.93 (m, 1H), 8.03 (d, *J* = 2.4 Hz, 1H), 8.04-8.09 (m, 1H), 8.02 (s, 1H), 8.47-8.51 (m, 1H), 9.13 (s, 1H), 11.94 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 110.9, 113.3, 120.8, 121.6, 122.8, 123.1, 130.5, 133.5, 138.9, 139.3, 143.3, 148.7, 161.9, 191.4.



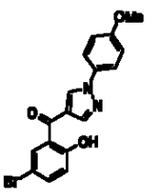
Intermedio-6

Etil 4-bromo-2-(1-piridin-2-il-1H-pirazol-4-carbonil)fenoxiacetato. Preparado de (5-bromo-2-hidroxifenil)-(1-piridin-2-il-1H-pirazol-4-il)cetona (43 mg) de acuerdo a GP2 y purificado mediante cromatografía flash (SiO_2, EtOAc:heptano, 1:2) para dar 34 mg (63%) de un sólido amarillo pálido: LC/MS (un10p8): Rt 4.9 min, *m/z* 429.5 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 1. 23 (t, *J* = 7.2 Hz, 3H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.62 (s, 2H), 6.76 (d, *J* = 8.6 Hz, 1H), 7.23-7.28 (m, 1H), 7.53 (ddd, *J* = 8.9, 2.6, 1.0 Hz, 1H), 7.58 (d, *J* = 2.5 Hz, 1H), 7.82-7.99 (m, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 8.19 (s, 1H), 8.40-8.44 (m, 1H), 8.99 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 14.3, 61.8, 66.1, 114.5, 114.7, 131.6, 132.3, 132.4, 134.6, 139.1, 148.5, 154.4, 168.3, 187.1.



D6

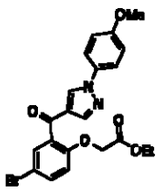
Ácido 4-Bromo-2-(1-piridin-2-il-1H-pirazol-4-carbonil)fenoxiacético. Preparado de etil [4-bromo-2-(1-piridin-2-il-1H-pirazol-4-carbonil)fenoxi]-acetato (21 mg) de acuerdo a GP3 para dar 20 mg de espuma blanca: LC/MS (un10n8): Rt 2.8 min, *m/z* 401.9 $[M - H]^-$; ^1H NMR ($CDCl_3$): □ 4.79 (s, 2H), 6.98 (d, *J* = 8.9 Hz, 1H), 7.28-7.34 (m, 1H), 7.67 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.75 (d, *J* = 2.5 Hz, 1H), 7.86-7.94 (m, 1H), 8.02-8.08 (m, 1H), 8.22 (s, 1H), 8. 43-8.48 (m, 1H), 9.04 (s, 1H).



Intermedio-7

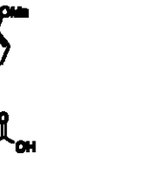
(5-Bromo-2-hidroxi-fenil)-[1-(4-metoxifenil)-1H-pirazol-4-il]cetona. A una suspensión de 6-bromo-3-formilcromona (253 mg, 1.0 mmol) en etanol (5 mL) se agregó 4-metoxifenilhidrazina (175 mg, 1.0 mmol), y la mezcla se agitó bajo argón durante 12 h una suspensión naranja. A la suspensión se agregó KOH (260 mg) en

agua (0.25 mL), y la reacción se calentó hasta reflujo durante 1½ h. A la mezcla de reacción se agregó 3% HCl hasta pH <1 y se dejó sobre hielo para precipitarse. El precipitado se filtró y se lavó con una pequeña cantidad de etanol frío para dar 256 mg (69%) sólido beige que se utilizó sin purificación adicional: LC/MS (un10p8): Rt 5.0 min, *m/z* 372.5 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 3.88 (s, 3H), 6.98 (d, *J* = 8.9 Hz, 1H), 7.03 (d, *J* = 9.1 Hz, 2H), 7.59 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.66 (d, *J* = 9.1 Hz, 2H), 8.02 (d, *J* = 2.4 Hz, 1H), 8.15 s, 1H), 8.39 (s, 1H), 11.92 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 55.9, 110.9, 115.0, 120.8, 121.6, 121.8, 122.9, 130.7, 133.5, 138.8, 142.3, 159.7, 161.8.



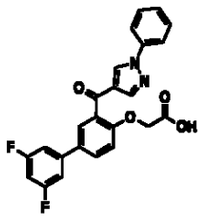
Intermedio-8

Etil 4-bromo-2-[1-(4-metoxifenil)-1H-pirazol-4-carbonil]fenoxiacetato. Preparado de (5-bromo-2-hidroxifenil)-[1-(4-metoxifenil)-1H-pirazol-4-il]cetona y etil bromoacetato de acuerdo a GP2: LC/MS (un10p8): Rt 4.59 min, *m/z* 458.4/460.4 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 1.26 (t, *J* = 7.1 Hz, 3H), 3.84 (s, 3H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.62 (s, 2H), 6.72 (d, *J* = 8.9 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 7.52 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.58 (d, *J* = 2.5 Hz, 1H), 7.64 (d, *J* = 8.9 Hz, 2H), 8.13 (s, 1H), 8.46 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 14.3, 55.8, 61.9, 65.6, 114.1, 114.4, 114.8, 121.4, 125.0, 131.6, 132.4, 132.6, 133.2, 134.5, 142.5, 154.1, 159.2, 168.5, 186.9.



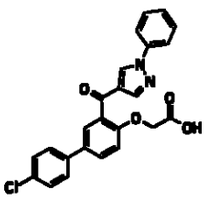
D7

Ácido 4-Bromo-2-[1-(4-metoxifenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de etil 4-bromo-2-[1-(4-metoxi-fenil)-1H-pirazol-4-carbonil]fenoxiacetato (23 mg) de acuerdo a GP3 para dar 21 mg (97%) de espuma blanca: LC/MS (un10n8): Rt 5.76 min, *m/z* 428.9 $[M - H]^-$; ^1H NMR ($CDCl_3$): □ 3.86 (s, 3H), 4.77 (s, 2H), 6.94 (d, *J* = 8.9 Hz, 1H), 6.99 (d, *J* = 9.2 Hz, 2H), 7.59-7.66 (m, 3H), 7.71 (d, *J* = 2.4 Hz, 1H), 8.14 (d, *J* = 0.6 Hz, 1H), 8.40 (d, *J* = 0.6 Hz, 1H) ^{13}C NMR ($CDCl_3$): □ 55.9, 67.2, 115.0, 115.1, 116.6, 121.8, 124.2, 130.7, 131.8, 132.7, 133.2, 136.1, 143.2, 155.2, 159.7, 169.9, 187.6.



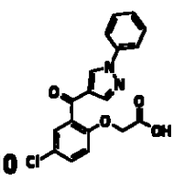
D8

Ácido [3',5'-Difluoro-3-(1-fenil-1H-pirazol-4-carbonil)bifenil-4-iloxi]acético. Preparado etil [4-bromo-2-(1-fenil-1H-pirazol-4-carbonil)fenoxi]acetato y ácido 3,5-difluorofenilborónico de acuerdo a GP4: LC/MS (un10n8): Rt 3.03 min, *m/z* 434.5 [M + H]$^+$; ^{1}H NMR ($CDCl_3$): □ 4.85 (s, 2H), 6.81 (td, *J* = 8.9, 2.3 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.9 Hz, 1H), 7.41 (d, *J* = 6.6 Hz, 1H), 7.48 (s, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.66-7.78 (m, 4H), 8.23 (s, 1H), 8.57 (s, 1H)



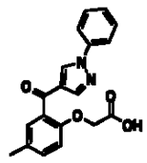
D9

Ácido [4'-Cloro-3-(1-fenil-1H-pirazol-4-carbonil)bifenil-4-iloxi]acético. Preparado de etil [4-bromo-2-(1-fenil-1H-pirazol-4-carbonil)fenoxi]acetato y ácido 4-clorofenilborónico de acuerdo a GP4: LC/MS (un10n8): Rt 3.08 min, *m/z* 432.5 [M – H]$^-$.



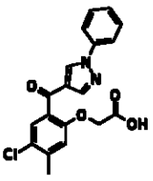
D10

Ácido [4-Cloro-2-(1-fenil-1H-pirazol-4-carbonil)fenoxi]acético. Preparado de (2-hidroxi-5-clorofenil)-(1-fenil-1H-pirazol-4-il)-metanona y etil bromoacetato de acuerdo a GP2 y GP3: LC/MS (un10p8): Rt 3.08 min, *m/z* 356.6 [M + 1]$^+$; ^{1}H NMR ($CDCl_3$): □ 4.75 (s, 2H), 6.95 (d, *J* = 8.9 Hz, 1H), 7.33-7.41 (m, 1H), 7.44-7.52 (m, 3H), 7.55 (d, *J* = 2.6 Hz, 1H), 7.69-7.75 (m, 2H), 8.18 (s, 1H), 8.52 (s, 1H).



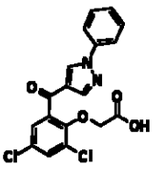
D11

Ácido [4-Metil-2-(1-fenil-1H-pirazol-4-carbonil)fenoxi]acético. Preparado de (2-hidroxi-5-metilfenil)-(1-fenil-1H-pirazol-4-il)-metanona y etil bromoacetato de acuerdo a GP2 y GP3: LC/MS (un10p8): Rt 3.08 min, *m/z* 356.6 $[M + 1]^+$; ^1H NMR ($CDCl_3$): □ 2.37 (s, 3H), 4.78 (s, 2H), 6.97 (d, *J* = 9.0 Hz, 1H), 7.33-7.51 (m, 5H), 7.73 (d, *J* = 6 Hz, 2H), 8.16 (s, 1H), 8.51 (s, 1H), 11.21 (br s, 1H)



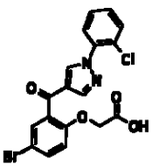
D12

Ácido [4-Cloro-3-metil-2-(1-fenil-1H-pirazol-4-carbonil)fenoxi]acético. Preparado de (3-cloro-6-hidroxi-2-metil-fenil)-(1-fenil-1H-pirazol-4-il)metanona y etil bromoacetato de acuerdo a GP2 y GP3: LC/MS (un10p8): Rt 3.34 min, *m/z* 370.6 $[M + 1]^+$; ^1H NMR ($CDCl_3$): □ 2.44 (s, 3H), 4.77 (s, 2H), 6.92 (s, 1H), 7.39 (d, *J* = 9.0 Hz, 1H), 7.46-7.51 (m, 2H), 7.59 (s, 1H), 7.72 (d, *J* = 9.0 Hz, 2H), 8.19 (s, 1H), 8.52 (s, 1H), 10.39 (br s, 1H)



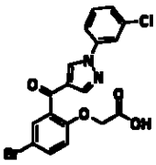
D13

Ácido [2,4-Dicloro-6-(1-fenil-1H-pirazol-4-carbonil)fenoxi]acético. Preparado de (3,5-dicloro-2-hidroxifenil)-(1-fenil-1H-pirazol-4-il)metanona y etil bromoacetato de acuerdo a GP2 y GP3: LC/MS (un10p8): Rt 3.27 min, *m/z* 390.5 $[M + 1]^+$; ^1H NMR ($CDCl_3$): □ 4.72 (s, 2H), 7.38-7.51 (m, 4H), 7.57-7.58 (m, 1H), 7.70 (d, *J* = 8.1 Hz, 2H), 8.06 (s, 1H), 8.36 (s, 1H), 9.23 (br s, 1H).



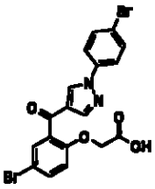
D14

Ácido 4-Bromo-2-[1-(2-cloro-fenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-bromo-3-formilcromona, 2-clorofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8) Rt 3.02 min, *m/z* 436.4 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 4.76 (s, 2H), 6.94 (d, *J* = 8.9 Hz, 1H), 7.39-7.47 (m, 2H), 7.53-7.67 (m, 3H), 7.74 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.21 (s, 1H), 8.40 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 67.2, 115.0, 116.7, 123.9, 127.9, 128.2, 128.7, 130.55, 130.59, 131.1, 133.3, 136.2, 136.6, 137.1, 143.1, 155.2, 170.0, 187.5.



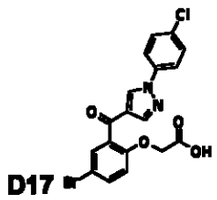
D15

ácido 4-Bromo-2-[1-(3-cloro-fenil)-1H-pirazole-4-carbonil]fenoxiacético. Preparado de 6-bromo-3-formilcromona y 3-clorofenilhidracina de acuerdo a: LC/MS (an10p8) Rt 3.57 min, *m/z* 436.4 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 4.76 (s, 2H), 6.90 (d, *J* = 8.9 Hz, 1H), 7.34 (dm, *J* = 6.8 Hz, 1H), 7.41 (t, *J* = 8.3 Hz, 1H), 7.58-7.66 (m, 2H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.78 (m, 1H), 8.17 (s, 1H), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 66.8, 115.1, 116.2, 117.9, 120.4, 124.9, 128.3, 130.7, 131.0, 132.0, 133.2, 135.8, 136.1, 140.2, 143.4, 155.0, 170.1, 187.4.



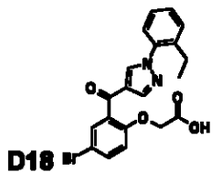
D16

Ácido 4-Bromo-2-[1-(4-bromofenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-bromo-3-formilcromona, 4-bromofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8) Rt 3.75 min, *m/z* 480.3 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 4.75 (s, 2H), 6.89 (d, *J* = 8.9 Hz, 1H), 7.59-7.65 (m, 5H), 7.66-7.69 (m, 1H), 8.16 (s, 1H), 8.50 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 66.5, 115.0, 115.9, 121.5, 121.8, 124.9, 130.8, 131.8, 133.0, 133.1, 135.9, 138.2, 143.4, 154.8, 170.6, 187.4.



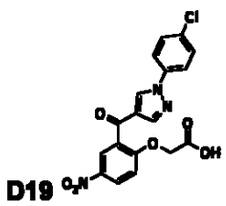
D17

Ácido 4-Bromo-2-[1-(4-clorofenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-bromo-3-formilcromona, 4-clorofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 3.53 min, *m/z* 436.4 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 4.74 (s, 2H), 6.88 (d, *J* = 8.9 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.61 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.63-7.70 (m, 3H), 8.17 (s, 1H), 8.49 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 66.4, 114.9, 115.7, 121.2, 124.9, 130.0, 130.9, 131.9, 133.1, 133.9, 135.9, 137.7, 143.3, 154.7, 170.8, 187.4.



D18

Ácido 4-Bromo-2-[1-(2-etilfenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-bromo-3-formilcromona, 2-etilfenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.58 min, 427.0 *m/z* $[M - H]^+$; ^1H NMR ($CDCl_3$): □ 1.14 (t, *J* = 7.5 Hz, 3H), 2.58 (q, *J* = 7.5, 2H), 4.76 (s, 2H), 6.93 (d, *J* = 8.9 Hz, 1H), 7.28-7.34 (m, 2H), 7.37-7.48 (m, 2H), 7.62 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.72 (d, *J* = 2.5 Hz, 1H), 8.15 (s, 1H), 8.18 (s, 1H).

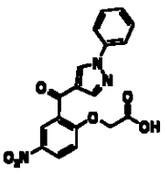


D19

Ácido 4-Nitro-2-[1-(4-clorofenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-nitro-3-formilcromona, 4-clorofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 2.44 min, *m/z* 401.7 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 4.84 (d, 2H), 7.1 (d, *J* = 9.6 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 2H), 8.22 (s, 1H), 8.36 (d, *J* = 9.2 Hz, 1H), 8.41 (s, 1H), 8.53 (s, 1H); ^{13}C NMR ($CDCl_3$): □

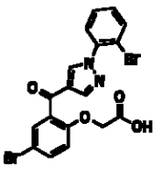
156

65.6, 112.9, 121.3, 124.9, 126.2, 128.2, 130.0, 130.1, 131.9, 134.1, 137.6, 142.4, 143.3, 159.7, 169.9, 186.2.



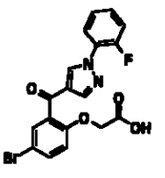
D20

Ácido 4-Nitro-2-(1-fenil-1H-pirazol-4-carbonil)fenoxiacético. Preparado de 6-nitro-3-formilcromona, 2-etilfenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8) Rt 2.05 min, *m/z* 367.8 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 4.83 (s, 2H), 7.01 (d, *J* = 9.0 Hz, 1H), 7.34-7.42 (m, 1H), 7.44-7.53 (m, 1H), 7.65-7.72 (m, 1H), 8.26 (s, 1H), 8.34 (dd, *J* = 9.0, 2.6 Hz, 1H), 8.41 (d, *J* = 2.6 Hz, 1H), 8.53 (s, 1H).



D21

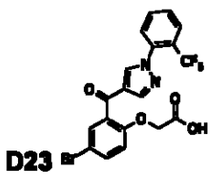
Ácido 4-Bromo-2-[1-(2-bromofenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-bromo-3-formilcromona, 2-bromofenilhidrazina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 3.38 min, *m/z* 480.6 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 4.75 (s, 2H), 6.91 (d, *J* = 9.0 Hz, 1H), 7.34-7.64 (m, 6H), 7.73-7.74 (m, 2H), 8.22 (s, 1H), 8.36 (s, 1H).



D22

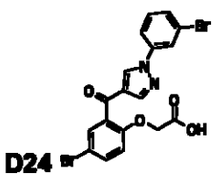
Ácido 4-Bromo-2-[1-(2-fluorofenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-bromo-3-formilcromona, 2-fluorofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 3.36 min, *m/z* 418.7 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 4.75 (s, 2H), 6.91 (d, *J* = 8.9 Hz, 1H), 7.21-7.42 (m, 3H), 7.62 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.70 (d, *J* = 2.5 Hz, 1H), 7.85-7.92 (m, 1H), 8.20 (s, 1H), 8.51 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): □ 66.9, 115.0, 116.3, 117.1, 117.4, 124.62, 124.63, 125.0, 125.39,

125.44, 127.4, 127.5, 129.6, 129.7, 130.8, 133.2, 135.8, 136.8, 143.0, 152.3, 155.0, 155.6, 170.5, 187.4.



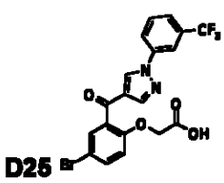
D23

Ácido 4-Bromo-2-[1-(2-trifluorometilfenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-bromo-3-formilcromona, 2-trifluorometilfenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 3.44 min, *m/z* 468.7 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 4.72 (s, 2H), 6.89 (d, *J* = 8.9 Hz, 1H), 7.53-7.75 (m, 5H), 7.84 (d, *J* = 7.9 Hz, 1H), 8.20 (s, 2H); ^{13}C NMR ($CDCl_3$): □ 66.8, 114.9, 116.2, 124.3, 126.3, 126.7, 127.58, 127.64, 129.2, 130.3. 130.7, 133.2, 136.0, 136.9, 143.1, 155.0, 170.3, 187.4.



D24

Ácido 4-Bromo-2-[1-(3-bromofenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-bromo-3-formilcromona, 3-bromofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 4.29 min, *m/z* 480.5 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 4.79 (s, 2H), 6.95 (d, *J* = 9.0 Hz, 1H), 7.28-7.40 (m, 1H), 7.53 (d, *J* = 9 Hz, 1H), 7.65 -7.73 (m, 3H), 7.96 (s, 1H), 8.18 (s, 1H); 8.51 (s, 1H).

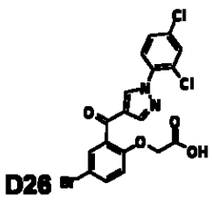


D25

Ácido 4-Bromo-2-[1-(3-trifluorometilfenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-bromo-3-formilcromona, 3-trifluorometilfenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 4.54 min, *m/z* 468.7 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 4.76 (s, 2H), 6.89 (d, *J* = 8.9 Hz, 1H), 7.57-7.66 (m, 3H),

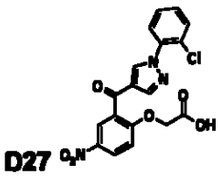
158

7.68 (d, *J* = 2.4 Hz, 1H), 7.89-7.96 (m, 1H), 8.04 (s, 1H), 8.20 (s, 1H), 8.59 (s, 1H), 9.15 (br s, 1H).



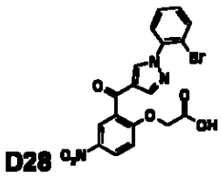
D26

Ácido 4-Bromo-2-[1-(2,4-diclorofenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-bromo-3-formilcromona, 2,4-diclorofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 4.35 min, *m/z* 468.6 $[M + H]^+$; ^1H NMR (DMSO-d_6): □ 4.76 (s, 2H), 7.03 (d, *J* = 9.0 Hz, 1H), 7.52 (m, 1H), 7.57-7.69 (m, 3H), 7.89 (m, 1H), 8.19 (s, 1H), 8.69 (s, 1H); ^{13}C NMR (DMSO-d_6): □ 55.8, 103.6, 106.2, 115.2, 119.5, 120.6, 120.7, 121.1, 122.4, 125.5, 125.6, 127.1, 128.3, 133.4, 145.1, 160.9, 177.4.



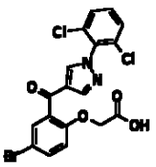
D27

ácido 4-Nitro-2-[1-(2-clorofenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-nitro-3-formilcromona 2-clorofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 2.42 min, *m/z* 401.8 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 4.83 (s, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 7.42-7.48 (m, 2H), 7.56-7.63 (m, 2H), 8.34-8.40 (m, 2H), 8.5 (s, 2H).



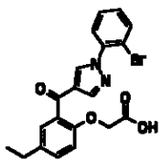
D28

Ácido 4-Nitro-2-[1-(2-bromofenil)-1H-pirazol-4-carbonil]fenoxiacético.
Preparado de 6-nitro-3-formilcromona, 2-bromofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 2.33 min, *m/z* 445.9 $[M - H]^+$; ^1H NMR ($CDCl_3$): □ 4.85 (s, 2H), 7.04 (d, *J* = 9 Hz, 1H), 7.37-7.81 (m, 4H), 8.32-8.44 (m, 3H), 8.50 (s, 1H).



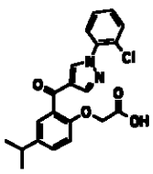
D29

Ácido 4-Bromo-2-[1-(2,6-diclorofenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-bromo-3-formilcromona, 2,6-diclorofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 2.56 min, *m/z* 468.6 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 4.72, 6.88 (d, *J* = 8.9 Hz, 1H), 7.37-7.44 (m, 1H), 7.45-7.52 (m, 2H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.70 (m, 1H), 8.14 (s, 1H), 8.26 (s, 1H).



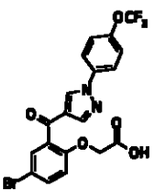
D30

Ácido 4-Ethyl-2-[1-(2-bromofenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-etil-3-formilcromona, 2-bromofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 2.88 min, *m/z* 428.8 $[M + H]^+$.



D31

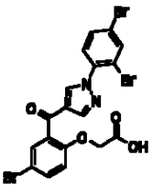
Ácido 2-[1-(2-Clorofenil)-1H-pirazol-4-carbonil]-4-isopropilfenoxiacético. Preparado de 6-isopropil-3-formilcromona, 2-clorofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 2.83 min, *m/z* 398.8 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 1.28 (d, *J* = 7.0 Hz, 6H), 2.93 (septet, *J* = 6.9 Hz, 1H), 4.82 (s, 2H), 7.04 (d, *J* = 8.5 Hz, 1H), 7.40-7.65 (m, 6H), 8.28 (s, 1H), 8.40 (s, 1H).



D32

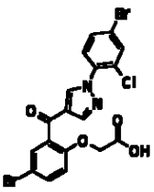
160

Ácido {4-Bromo-2-[1-(4-trifluorometoxifenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-bromo-3-formilcromona, 4-trifluorometoxifenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 3.24 min, *m/z* 484.6 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 4.75 (s, 2H), 6.89 (d, *J* = 8.9 Hz, 1H), 7.34 (d, *J* = 9.0 Hz, 2H), 7.61 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.67 (m, 1H), 7.72-7.80 (m, 2H), 8.17 (s, 1H), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 66.5, 115.0, 115.8, 121.4, 122.5, 125.0, 130.8, 132.0, 133.1, 136.0, 137.6, 143.4, 148.6, 148.7, 154.8, 170.8, 187.4.



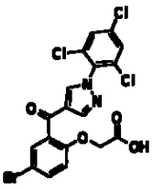
D33

Ácido4-Bromo-2-[1-(2,4-dibromofenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-bromo-3-formilcromona, 2,4-dibromofenilhidracina de acuerdo y etil bromoacetato a GP1, GP2 y GP3: LC/MS (un10p8): Rt 3.41 min, *m/z* 556.4 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 4.75 (s, 2H), 6.92 (d, *J* = 9.0 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.63 (m, 2H), 7.73 (d, *J* = 2.5 Hz, 1H), 7.92 (d, *J* = 2.1 Hz, 1H), 8.22 (s, 1H), 8.37 (s, 1H).



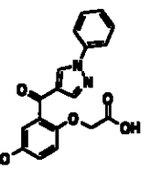
D34

Ácido 4-Bromo-2-[1-(4-bromo-2-clorofenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-bromo-3-formilcromona, 4-bromo-2-clorofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 3.34 min, *m/z* 512.5 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 4.78 (s, 2H), 6.95 (d, *J* = 8.6 Hz, 1H), 7.51-7.76 (m, 5H), 8.21 (s, 1H), 8.42 (s, 1H).



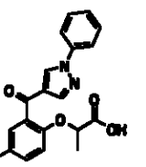
D35

Ácido 4-Bromo-2-[1-(2,4,6-triclorofenil)-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-bromo-3-formilcromona, 2,4,6-triclorofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 3.35 min, *m/z* 502.6 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 4.91 (s, 2H), 7.05 (d, *J* = 8.9 Hz, 1H), 7.68 (s, 2H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.88 (s, 1H), 8.31 (s, 1H), 8.43 (s, 1H), 9.03 (br s, 1H).



D36

Ácido 4-Metoxi-2-[1-fenil-1H-pirazol-4-carbonil]fenoxiacético. Preparado de 6-bromo-3-formilcromona, 2,4-diclorofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.46 min, *m/z* 350.9 $[M - H]^+$; ^1H NMR ($CDCl_3$): □ 3.81 (s, 3H), 4.77 (s, 2H), 7.02-7.16 (m, 3H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 8.17 (s, 1H), 8.52 (s, 1H).



D37

Ácido 2-[4-Bromo-2-(1-fenil-1H-pirazol-4-carbonil)fenoxi]propiónico. Preparado de (5-bromo-2-hidroxifenil)-(1-fenil-1H-pirazol-4-il)cetona y etil 2-bromopropionato de acuerdo a GP2 y GP3: LC/MS (un10p8) Rt 2.51 min, *m/z* 415 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 1.65 (d, *J* = 6.8 Hz, 3H), 4.93 (q, *J* = 6.8 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 1H), 7.35-7.43 (m, 1H), 7.46-7.53 (m, 2H), 7.62 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.70-7.76 (m, 3H), 8.17 (s, 1H), 8.52 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 18.8, 75.2, 114.8, 116.7, 120.1, 124.4, 128.3, 130.0, 133.3, 136.2, 139.2, 143.3, 155.0, 173.1, 187.8.

Ácido 2(*S*)-[4-Bromo-2-(1-fenil-1H-pirazol-4-carbonil)-fenoxi]-propiónico. (5-Bromo-2-hidroxifenil)-(1-fenil-1H-pirazol-4-il)cetona (100 mg, 0.29 mmol), ácido (R)-(+)-bromoacético (44 mg, 0.29 mmol) etil 2-bromopropionato y K2CO3 (80 mg, 0.58 mmol) en acetona se agitaron a temperatura ambiente durante 16 h. La mezcla de reacción se concentró y el residuo se particionó entre EtOAc y HCl diluido (pH ~1). La fase orgánica se secó (Na_2SO_4) y se concentró, y el residuo se purificó mediante cromatografía flash (EtOAc:heptano, 1:1) para producir 55 mg (46%) del compuesto

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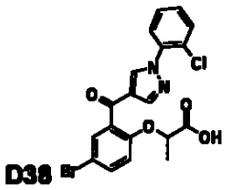
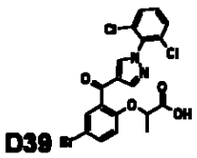
del título: HPLC quiral (Columna: Chiracel OD (0.46 cm x 24 cm); Eluyente: isocrático, 85% hexano + 15% 2-propanol + 0.1% TFA; Flujo 0.5 mL/min) Rt 15.7 min, >90% e.e. (eluyentes de material racémico con separación de línea base de enantiómeros: Rt 15.7 y 16.7 min.) Espectro MS y NMR corresponden a material racémico.



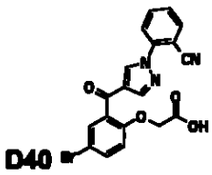
D38

Ácido 2-[4-Bromo-2-[1-(2-clorofenil)-1-H-pirazol-4-carbonil]fenoxi]propiónico. Preparado de 6-bromo-3-formilcromona, 2-clorofenilhidracina y etil 2-bromopropionato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.56 min, 448.9 *m/z* $[M - H]^+$; ^1H NMR ($CDCl_3$): □ 1.65 (d, *J* = 7.0 Hz, 3H), 4.93 (q, *J* = 7.0 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 1H), 7.41-7.47 (m, 2H), 7.55-7.64 (m, 3H), 7.74 (s, 1H), 8.23 (s, 1H), 8.42 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 18.9, 75.4, 115.0, 117.0, 124.1, 128.1, 128.4, 128.9, 130.7, 131.3, 133.6,136.4,136.8,137.3, 143.3, 155.2, 173.5, 188.0.



D39

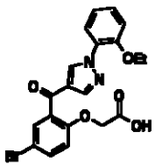
Ácido 2-[4-Bromo-2-[1-(2,6-diclorofenil)-1H-pirazolo-4-carbonil]fenoxi]-propiónico. Preparado de 6-bromo-3-formilcromona, 2,6-diclorofenilhidracina y etil 2-bromopropionato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.55 min, 482.9 *m/z* $[M - H]^+$; ^1H NMR ($CDCl_3$): □ 1.65 (d, *J* = 6.8 Hz, 3H), 4.91 (q, *J* = 6.8 Hz, 1H), 6.93 (d, *J* = 8.9 Hz, 1H), 7.41-7.53 (m, 3H), 7.62 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.74 (d, *J* = 2.4, 1H), 8.17 (s, 1H), 8.28 (s, 1H); ^{13}C NMR ($CDCl_3$): □ 18.9, 75.1, 114.9, 116.8, 124.2, 129.3, 130.7, 132.0,133.6, 134.5,135.6, 136.4, 137.6, 143.6, 155.1, 173.6, 187.8.



D40

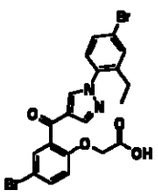
163

Ácido {4-Bromo-2-[1-(2-clano-fenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 2-hidracinobenzonitril (preparado de acuerdo a van der Mey, et al. *J. Med. Chem.* **2003**, 2008-2016) y etil bromoacetato de acuerdo a GP1, GP2 y GP3: ^{1}H NMR (DMSO-d_6): □ 4.72 (s, 2H), 7.17 (d, J = 8.9 Hz, 1H), 7.36 (t, *J* = 15.1, 7.3 Hz, 1 H), 7.8 (m, 4H), 8.29 (d, *J* = 8.3 Hz, 1 H), 9.03 (s, 1 H), 9.66 (s, 1H), 13.04 (br s, 1H).



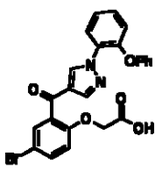
D41

Ácido {4-Bromo-2-[1-(2-etoxifenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 2-etoxifenilhidracina y etil 2-bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 2.33 min, *m/z* 446.7 $[M + H]^+$; ^{1}H NMR ($CDCl_3$): □ 1.47 (t, *J* = 7.0 Hz, 3H), 4.18 (q, *J* = 7.0 Hz, 2H), 4.78 (s, 2H), 6.97 (d, *J* = 8.9 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 2H), 7.36 (td, *J* = 7.9, 1.8 Hz, 1H), 7.64 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.79 (d, *J* = 2.5 Hz, 1H), 7.80 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.22 (s, 1H), 8.65 (s, 1H).



D42

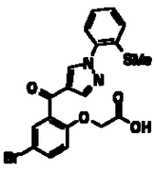
Ácido {4-Bromo-2-[1-(4-bromo-2-etilfenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 4-bromo-2-etilfenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.78 min, *m/z* 506.6 $[M - H]^-$; ^{1}H NMR ($CDCl_3$): □ 1.16 (td, *J* = 7.8, 2.4 Hz, 3H), 2.58 (qd, *J* = 7.8, 1.8 Hz, 2H), 4.77 (s, 2H), 6.94 (d, *J* = 9.0 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.56 (s, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.72 (s,1H), 8.15 (s, 1H), 8.19 (s, 1H).



D43

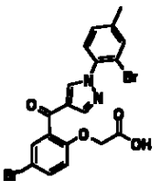
164

Ácido {4-Bromo-2-[1-(2-fenoxifenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 4-bromo-2-etilfenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.77 min, *m/z* 492.7 [M – H]⁻; ^{1}H NMR ($CDCl_3$): □ 4.75 (s, 2H), 6.95 (d, *J* = 8.6 Hz, 1H), 7.00-7.09 (m, 3H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.29-7.40 (m, 4H), 7.62-7.68 (m, 2H), 7.90 (d, *J* = 9.0 Hz, 1H), 8.17 (s, 1H), 8.60 (s, 1H).



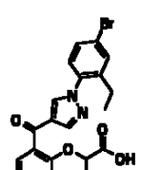
D44

Ácido {4-Bromo-2-[1-(2-metiltiofenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 2-metiltiofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.26 min, *m/z* 446.7 [M – H]⁻; ^{1}H NMR ($CDCl_3$): □ 2.46 (s, 3H), 4.77 (s, 2H), 6.93 (d, *J* = 8.9 Hz, 1H), 7.28-7.32 (m, 1H), 7.39-7.49 (m, 3H), 7.62 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.76 (s, 1H), 8.23 (s, 1H), 8.31 (s, 1H).



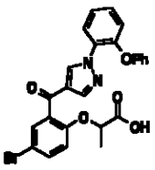
D45

Ácido {4-Bromo-2-[1-(2-bromo-4-metilfenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 2-bromo-4-metilfenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.47 min, *m/z* 492.6 [M – H]⁻; ^{1}H NMR ($CDCl_3$): □ 2.44 (s, 3H), 4.80 (s, 2H), 6.99 (d, *J* = 8.9 Hz, 1H), 7.27-7.30 (m, 1H), 7.46 (d, *J* = 8.1 Hz , 1H), 7.58 (s, 1H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.80 (s, 1H), 8.20 (s, 1H), 8.33 (s, 1H).



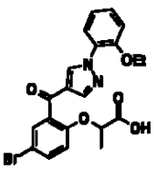
D46

Ácido 2-{4-Bromo-2-[1-(4-bromo-2-etilfenil)-1H-pirazol-4-carbonil]fenoxi} propiónico. Preparado de 6-bromo-3-formilcromona, 4-bromo-2-etilfenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 2.72 min, *m/z* 522.6 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 1.16 (t, *J* = 7.7 Hz, 3H), 1.67 (d, *J* = 6.8 Hz, 3H), 2.59 (q, *J* = 7.5 Hz, 2H), 4.95 (q, *J* = 7.0 Hz,1H), 6.96 (d, *J* = 9.0 Hz, 1H), 7.21 (d, *J* = 8.3 Hz, 1H), 7.47 (d, *J* = 8.7 Hz , 1H), 7.55 (s, 1H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.73 (s, 1H), 8.17 (s, 1H), 8.18 (s, 1H).



D47

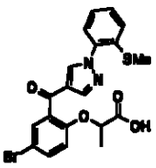
Ácido 2-{4-Bromo-2-[1-(2-fenoxifenil)-1H-pirazol-4-carbonil]fenoxi}propiónico. Preparado de 6-bromo-3-formilcromona, 2-fenoxifenilhidracina y etil 2-bromopropionato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 2.68 min, *m/z* 508.7 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 1.65 (d, *J* = 6.8 Hz, 3H), 4.92 (q, *J* = 7.3 Hz,1H), 6.96-7.18 (m, 5H), 7.26-7.39 (m, 4H), 7.62 (d, *J* = 8.6 Hz , 1H), 7.67 (s, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 8.17 (s, 1H), 8.61 (s, 1H).



D48

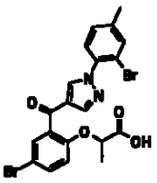
Ácido 2-{4-Bromo-2-[1-(2-etoxifenil)-1H-pirazol-4-carbonil]fenoxi}propiónico. Preparado de 6-bromo-3-formilcromona, 2-etoxifenilhidracina y etil 2-bromopropionato de acuerdo a GP1, GP2 y GP3:

LC/MS (un10p8): Rt 2.39 min, *m/z* 458.7 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 1.49 (t, *J* = 7.1 Hz, 3H), 1.86 (d, *J* = 7.1 Hz, 3H), 4.19 (m,2H), 4.98 (q, *J* = 6.9 Hz, 1H), 7.02-7.12 (m,3H), 7.37 (t, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 8.9 Hz , 1H), 7.78 (s, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 8.20 (s, 1H), 8.67 (s, 1H).



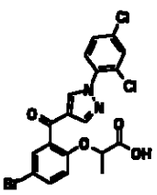
D49

Ácido 2-{4-Bromo-2-[1-(2-metiltio)-1H-pirazol-4-carbonil]fenoxi}propiónico. Preparado de 6-bromo-3-formilcromona, 2-etoxifenilhidracina y etil 2-bromopropionato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.56 min, 460.9 *m/z* $[M - H]^+$; ^1H NMR ($CDCl_3$): □ 1.71 (d, *J* = 6.8 Hz, 3H), 2.46 (s, 3H), 4.96 (q, *J* = 7.0 Hz , 1H), 7.00 (d, *J* = 8.9 Hz, 1H), 7.29-7.34 (m, 1H), 7.40-7.50 (m , 3H), 7.64 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.80 (s, 1H), 8.22 (s, 1H), 8.32 (s, 1H).



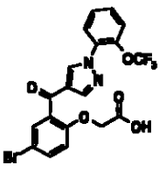
D50

Ácido 2-{4-Bromo-2-[1-(2-bromo-4-metilfenil)-1H-pirazol-4-carbonil]fenoxi}propiónico. Preparado de 6-bromo-3-formilcromona, 2-bromo-4-metilfenilhidracina y etil 2-bromopropionato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.74 min, 506.8 *m/z* $[M - H]^+$; ^1H NMR ($CDCl_3$): □ 1.72 (d, *J* = 7.0 Hz, 3H), 2.45 (s, 3H), 4.98 (q, *J* = 7.0 Hz , 1H), 7.03 (d, *J* = 8.9 Hz, 1H), 7.28-7.30 (m, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.59 (s, 1H), 7.67 (dd, *J* = 8.9,2.43 Hz, 1H), 7.81 (d, *J* = 2.6 Hz, 1H), 8.19 (s, 1H), 8.34 (s, 1H).



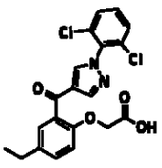
D51

Ácido 2-{4-Bromo-2-[1-(2,4-diclorofenil)-1H-pirazol-4-carbonil]fenoxi}propiónico. Preparado de 6-bromo-3-formilcromona, 2,4-diclorofenilhidracina y etil 2-bromopropionato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.83 min, 482.8 *m/z* $[M - H]^+$; ^1H NMR ($CDCl_3$): □ 1.50 (d, *J* = 6.0 Hz, 3H), 4.75 (q, *J* = 4.5 Hz , 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 7.40 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.54-7.57 (m, 2H), 7.61 (s, 1H), 8.16 (s, 1H), 8.32 (s, 1H).



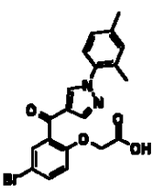
D52

Ácido {4-Bromo-2-[1-(2-trifluorometoxifenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 2-trifluorometoxifenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.43 min, *m/z* 482.7 [M - H]⁻; ^{1}H NMR ($CDCl_3$): □ 4.77 (s, 2H), 6.95 (d, *J* = 8.6 Hz, 1H), 7.45-7.50 (m, 3H), 7.65 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.82 (s, 1H), 8.23 (s, 1H), 8.40 (s, 1H).



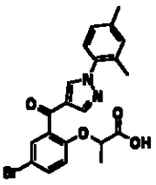
D53

Ácido {2-[1-(2,6-Diclorofenil)-1H-pirazol-4-carbonil]-4-etilfenoxi}acético. Preparado de 6-etil-3-formilcromona, 2,6-diclorofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.25 min, *m/z* 416.8 [M – H]⁻; ^{1}H NMR ($CDCl_3$): □ 1.26 (t, *J* = 7.5 Hz, 3H), 2.69 (q, *J* = 7.7 Hz, 2H), 4.82 (s, 2H), 7.04 (d, *J* = 8.7 Hz, 1H), 7.39-7.44 (m, 1H), 7.46-7.54 (m, 4H), 8.14 (s, 1H), 8.25 (s, 1H).



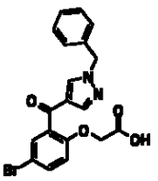
D54

Ácido {4-Bromo-2-[1-(2,4-dimetilfenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 2,4-dimetilfenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.41 min, *m/z* 428.7 [M – H]⁻; ^{1}H NMR ($CDCl_3$): □ 2.26 (s, 3H), 2.40 (s, 3H), 4.75 (s, 2H), 6.91 (d, *J* = 8.9 Hz, 1H), 7.11 (d, *J* = 8.1 Hz , 1H), 7.17 (s, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.60 (dd, *J* = 8.9, 2.46 Hz, 1H), 7.71 (s, 1H), 8.15 (s, 1H), 8.22 (s, 1H).



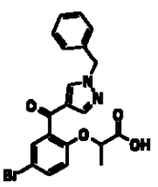
D55

Ácido 2-{4-Bromo-2-[1-(2,4-dimetilfenil)-1H-pirazol-4-carbonil]fenoxi}propiónico. Preparado de 6-bromo-3-formilcromona, 2,4-dimetilfenilhidracina y etil 2-bromopropionato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.40 min, *m/z* 442.7 [M – H]⁻; ^{1}H NMR ($CDCl_3$): □ 1.67 (d, *J* = 6.9 Hz, 3H), 2.25 (s, 3H), 2.40 (s, 3H), 4.93 (q, *J* = 6.8 Hz, 1H), 6.97 (d, *J* = 8.9 Hz, 1H), 7.12 (d, *J* = 8.1 Hz , 1H), 7.17 (s, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.62 (dd, *J* = 8.7, 1.52 Hz, 1H), 7.73 (s, 1H), 8.15-8.16 (m, 2H).



D56

Ácido [2-(1-Bencil-1H-pirazol-4-carbonil)-4-bromofenoxi]acético. Preparado de 6-bromo-3-formilcromona, bencilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.14 min, *m/z* 414.7 [M – H]⁻; ^{1}H NMR ($CDCl_3$): □ 4.70 (s, 2H), 5.36 (s, 2H), 6.88 (d, *J* = 8.7 Hz, 1H), 7.28-7.30 (m , 2H), 7.40-7.46 (m, 3H), 7.57 (d, *J* = 8.9 Hz, 1H), 7.63 (s, 1H), 8.01 (s, 1H), 8.04 (s, 1H).



D57

Ácido 2-[2-(1-Bencil-1H-pirazol-4-carbonil)-4-bromofenoxi]propiónico. Preparado de 6-bromo-3-formilcromona, bencilhidracina y etil 2-bromopropionato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.16 min, *m/z* 428.8 [M – H]⁻; ^{1}H NMR ($CDCl_3$): □ 1.59 (d, *J* = 6.8 Hz, 3H), 4.88 (q, *J* = 7.1 Hz, 1H), 5.35 (s, 2H), 6.91 (d, *J* = 8.9 Hz, 1H), 7.30-7.42 (m , 5H), 7.53-7.71 (m, 2H), 8.01 (s, 2H).

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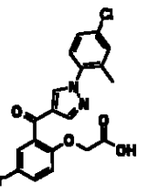
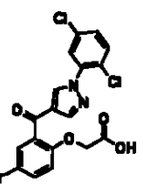


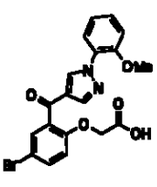
D58

Ácido {4-Bromo-2-[1-(4-cloro-2-metilfenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 4-cloro-2-metilfenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.49 min, *m/z* 448.7 [M – H]⁻; ^{1}H NMR ($CDCl_3$): □ 2.27 (s, 3H), 4.75 (s, 2H), 6.91 (d, *J* = 8.9 Hz, 1H), 7.31 (s , 2H), 7.36 (s, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.70 (s, 1H), 8.17 (s, 1H), 8.21 (s, 1H).



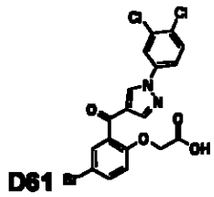
D59

Ácido {4-Bromo-2-[1-(2,5-diclorofenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 2,5-diclorofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.46 min, *m/z* 468.6 [M – H]⁻; ^{1}H NMR ($CDCl_3$): □ 4.78 (s, 2H), 6.92 (d, *J* = 8.9 Hz, 1H), 7.39 (dd, *J* = 8.7, 2.44 Hz , 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.61 (dd, *J* = 8.9, 2.53 Hz, 1H), 7.70 (dd, *J* = 8.1, 2.36 Hz, 2H), 8.22 (s, 1H), 8.45 (s, 1H).



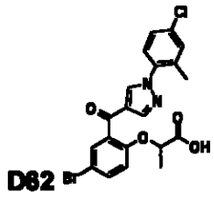
D60

Ácido {4-Bromo-2-[1-(2-metoxifenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 2-metilfenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.20 min, *m/z* 430.7 [M – H]⁻; ^{1}H NMR ($CDCl_3$): □ 3.96 (s,3H), 4.79 (s, 2H), 6.96 (d, *J* = 8.9 Hz, 1H), 7.11 (t, *J* = 8.2 Hz , 2H), 7.40 (t.d, *J* = 8.1, 1.5 Hz, 1H), 7.65 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.76 (d, *J* = 2.5 Hz, 2H), 8.18 (s, 1H), 8.60 (s, 1H).



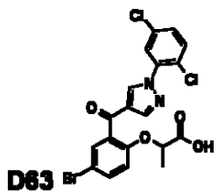
D61

Ácido {4-Bromo-2-[1-(3,4-diclorofenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 3,4-clorofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.77 min, *m/z* 468.6 [M – H]⁻; ^{1}H NMR ($CDCl_3$): □ 4.78 (s, 2H), 6.90 (d, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 8.1 Hz , 1H), 7.64 (d, *J* = 8.9 Hz, 1H), 7.69 (d, *J* = 2.43 Hz, 2H), 7.91 (d, *J* = 2.46 Hz, 1H), 8.18 (s, 1H), 8.53 (s, 1H).



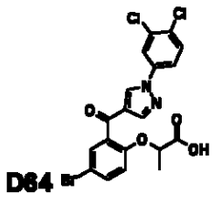
D62

Ácido 2-{4-Bromo-2-[1-(4-cloro-2-metilfenil)-1H-pirazol-4-carbonil]fenoxi}-propiónico. Preparado de 6-bromo-3-formilcromona, 4-cloro-2-metilfenilhidracina y etil 2-bromopropionato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.55 min, *m/z* 462.7 [M – H]⁻; ^{1}H NMR ($CDCl_3$): □ 1.65 (d, *J* = 6.9 Hz, 3H), 2.28 (s, 3H), 4.92 (d, *J* = 6.8 Hz, 1H), 6.95 (d, *J* = 8.9 Hz, 1H), 7.30 (s , 2H), 7.37 (s, 1H), 7.63 (d, *J* = 8.9 Hz, 1H), 7.72 (s, 1H), 8.19 (s, 2H).



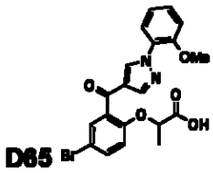
D63

Ácido 2-{4-Bromo-2-[1-(2,5-diclorofenil)-1H-pirazol-4-carbonil]fenoxi}propiónico. Preparado de 6-bromo-3-formilcromona, 2,5-diclorofenilhidracina y etil 2-bromopropionato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.51 min, *m/z* 482.6 [M – H]⁻; ^{1}H NMR ($CDCl_3$): □ 1.70 (d, *J* = 6.8 Hz, 3H), 4.90 (q, *J* = 6.9 Hz, 1H), 6.93 (d, *J* = 9.1 Hz, 1H), 7.40 (dd, *J* = 8.7, 2.5 Hz , 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.62 (dd, *J* = 8.9, 2.5 Hz , 1H), 7.68 (d, *J* = 2.3 Hz, 1H), 7.71 (d, *J* = 2.4 Hz, 1H), 8.22 (s, 1H) 8.45 (s, 1H).



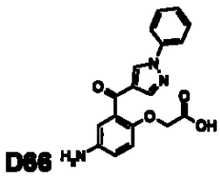
D64

Ácido 2-{4-Bromo-2-[1-(3,4-dicloro-fenil)-1H-pirazol-4-carbonil]fenoxi}propiónico. Preparado de 6-bromo-3-formilcromon, 3,4-diclorofenilhidracina y etil 2-bromopropionato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.83 min, *m/z* 482.6 [M – H]⁻; ^{1}H NMR ($CDCl_3$): □ 1.63 (d, *J* = 6.8 Hz, 3H), 4.93 (q, *J* = 6.9 Hz, 1H), 6.92 (d, *J* = 9.03 Hz, 1H), 7.55-7.65 (m, 3H), 7.70 (s,1H), 7.93 (d, *J* = 2.25 Hz, 1H), 8.20 (s, 1H), 8.57 (s, 1H).



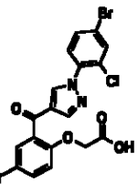
D65

Ácido 2-{4-Bromo-2-[1-(2-metoxifenil)-1H-pirazol-4-carbonil]fenoxi}propiónico. Preparado de 6-etil-3-formilcromona, 2,6-diclorofenilhidracina y etil 2-bromopropionato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.23 min, *m/z* 444.7 [M – H]⁻; ^{1}H NMR ($CDCl_3$): □ 1.68 (d, *J* = 7.0 Hz, 3H), 3.95 (s, 3H), 4.95 (d, *J* =7.0 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 7.10 (d, *J* = 8.5 Hz , 1H), 7.14 (s, 1H), 7.37-7.43 (m,1H), 7.63 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.77 (s, 1H), 7.79 (s,1H), 8.19 (s, 1H), 8.62 (s, 1H).



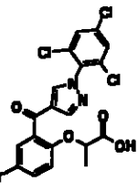
D66

Ácido [4-Amino-2-(1-fenil-1H-pirazol-4-carbonil)fenoxi]acético. Una mezcla de etil 4-nitro-2-(fenil-1H-pirazol-4-carbonil)fenoxiacetato (190 mg, 0.48 mmol) y 10% Pd/C (100 mg) en MeOH (50 mL) se agitó bajo una atmósfera de hidrógeno de 12 h, luego se filtró a través de una almohadilla de celita y se concentró, y el producto se hidrolizó de acuerdo a GP3 para dar el compuesto del título.



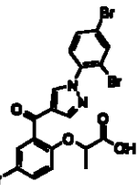
D67

Ácido {4-Bromo-2-[1-(4-bromo-2-clorofenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 4-bromo-2-clorofenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.57 min, *m/z* 526.6 [M – H]$^-$; ^{1}H NMR (DMSO): □ 1.31 (d, *J* = 6.8 Hz, 3H), 4.94 (q, *J* = 6.6 Hz, 1H), 6.92 (d, *J* = 8.9 Hz, 1H), 7.53 (d, *J* = 2.5 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.66 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.76 (dd, *J* = 8.5, 2.3 Hz, 1H), 8.04 (d, *J* = 2.1 Hz, 1H), 8.22 (s, 1H), 8.77 (s, 1H).



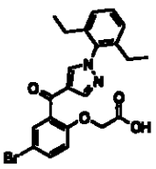
D68

Ácido 2-{4-Bromo-2-[1-(2,4,6-triclorofenil)-1H-pirazol-4-carbonil]fenoxi}-propiónico. Preparado de 6-bromo-3-formilcromona, 2,4,6-triclorofenilhidracina y etil 2-bromopropionato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.61 min, *m/z* 516.6 [M - H]$^+$; ^{1}H NMR (DMSO): □ 1.33 (d, *J* = 6.8 Hz, 3H), 4.94 (q, *J* = 7.0 Hz, 1H), 6.92 (d, *J* = 9.2 Hz, 1H), 7.54 (d, *J* = 2.4 Hz, 1H), 7.66 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.99 (s, 2H), 8.26 (s, 1H), 8.72 (s, 1H).



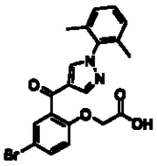
D69

Ácido 2-{4-Bromo-2-[1-(2,4-dibromofenil)-1H-pirazol-4-carbonil]fenoxi}-propiónico. Preparado de 6-bromo-3-formilcromona, 2,4-dibromofenilhidracina y etil 2-bromopropionato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 2.87 min, *m/z* 572.7 [M + H]$^+$; ^{1}H NMR (DMSO): □ 1.32 (d, *J* = 6.8 Hz, 3H), 4.93 (q, *J* = 6.8 Hz,1H), 6.91 (d, *J* = 8.9 Hz, 1H), 7.54 (dd, *J* = 8.3, 2.3 Hz, 2H), 7.66 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.78 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.15 (d, *J* = 2.1 Hz, 1H), 8.21 (s, 1H), 8.72 (s, 1H).



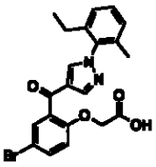
D70

Ácido {4-Bromo-2-[1-(2,6-dietil-fenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 2,6-dietilfenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.54 min, *m/z* 457.0 $[M - H]^+$; ^1H NMR ($CDCl_3$): □ 1.27 (t, *J* = 7.3 Hz, 6H), 2.35 (q, *J* = 7.3 Hz, 4H), 4.82 (s, 2H), 6.99 (d, *J* = 8.9 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.48 (m, 1H), 7.67 (m, 1H), 7.79 (s, 1H), 8.11 (s, 1H), 8.27 (s, 1H), 8.87 (br s, 1H).



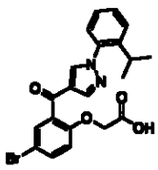
D71

Ácido {4-Bromo-2-[1-(2,6-dimetilfenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 2,6-dietilfenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.27 min, *m/z* 428.9 $[M - H]^+$; ^1H NMR ($CDCl_3$): □ 2.07 (s, 6H), 4.74 (s, 2H), 6.91 (d, *J* = 8.7 Hz, 1H), 7.19 (d, *J* = 7.3 Hz, 2H), 7.25-7.35 (m, 1H), 7.55-7.66 (m, 1H), 7.71 (s, 1H), 8.06 (s, 1H), 8.23 (s, 1H), 8.91 (br s, 1H).



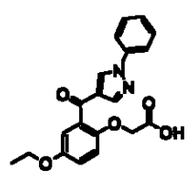
D72

Ácido {4-Bromo-2-[1-(2-etil-6-metilfenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 2-etil-6-metilfenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.43 min, *m/z* 443.0 $[M - H]^+$; ^1H NMR ($CDCl_3$): □ 1.12 (t, *J* = 7.8 Hz, 3H), 2.05 (s, 3H), 2.33 (q, *J* = 7.8 Hz, 2H), 4.76 (s, 2H), 6.94 (d, *J* = 8.7 Hz, 1H), 7.14-7.25 (m, 2H), 7.31-7.41 (m, 1H), 7.56-66 (m, 1H), 7.72 (s, 1H), 8.06 (s, 1H), 8.22 (s, 1H), 8.93 (br s, 1H).



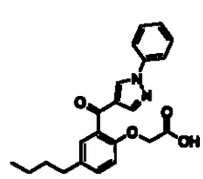
D73

Ácido {4-Bromo-2-[1-(2-isopropilfenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 2-etil-6-metilfenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 2.76 min, *m/z* 444.9 $[M + H]^+$; ^1H NMR (CDCl3-d): □ 1.22 (d, *J* = 6.5 Hz, 6H), 2.89 (septet, *J* = 6.1 Hz, 1H), 4.76 (s, 2H), 6.92 (d, *J* = 8.7 Hz, 1H), 7.30 (s, 2H), 7.49 (s, 2H), 7.62(d, 1H), 7.72 (s, 1H), 8.15 (s, 1H), 8.20 (s, 1H), 8.92 (br s, 1H).



D74

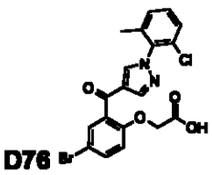
Ácido [4-Etoxi-2-(1-fenil-1H-pirazol-4-carbonil)fenoxi]acético. Preparado de 6-etoxi-3-formilcromona, fenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 1.97 min, *m/z* 367.1 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 1.43 (t, *J* = 6.8 Hz, 3H), 4.03 (q, *J* = 6.9 Hz, 2H), 4.78 (s, 2H), 7.01-7.13 (m, 2H), 7.15 (s, 1H), 7.36-7.43 (m, 1H), 7.46-7.57 (m, 2H), 7.71-7.75 (m, 2H), 8.16 (s, 1H), 8.50 (s, 1H).



D75

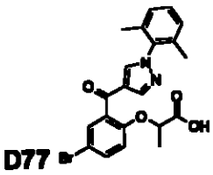
Ácido [4-Butil-2-(1-fenil-1H-pirazol-4-carbonil)fenoxi]acético. Una solución de etil [4-bromo-2-(1-fenil-1H-pirazol-4-carbonil)fenoxi]acetato (472 mg, 1.1 mmol), ácido 1-butilborónico (102 mg, 1.0 mmol) y Pd (dppf)Cl_2 (72 mg, 0.05 mmol) en THF (10 mL) y agua (1 mL) bajo argón se refluyeron durante 24 h. La mezcla de reacción se extrajo con CH_2Cl_2, la fase orgánica se filtró a través de celita y se concentró, y el residuo se purificó mediante cromatografía flash (SiO2, EtOAc:heptano, 1:10 to 1:1). La fracción más pura se concentró (~10 mg), y el residuo se hidrolizó de acuerdo a GP3: LC/MS (un10p8): Rt 2.59 min, *m/z* 379.1 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 0.88 (t, *J* = 7.5 Hz, 3H),

1.29 (m, 2 H), 1.49 (m, 2 H), 2.48 (m, 2 H), 4.51 (s, 2 H), 6.84 (m, 1 H), 7.14 (m, 1 H), 7.30 (m, 2H), 7.42 (m, 2H), 7.65 (m, 2H), 7.97 (s, 1H), 8.46 (s, 1H).



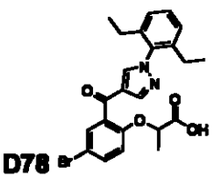
D76

Ácido {4-Bromo-2-[1-(2-cloro-6-metilfenil)-1H-pirazol-4-carbonil]fenoxi}acético. Preparado de 6-bromo-3-formilcromona, 2-cloro-6-metilfenilhidracina y etil bromoacetato de acuerdo a GP1, GP2 y GP3: LC/MS (un10p8): Rt 2.49 min, *m/z* 450.9 $[M + H]^+$; ^1H NMR ($CDCl_3$): □ 2.16 (s, 3H), 4.80 (s, 2H), 6.98 (d, *J* = 9.1 Hz, 1H), 7.30 (m, 1H), 7.34-7.40 (m, 2H), 7.66 (d, 1H), 7.77 (m, 1H), 8.13 (s, 1H); 8.24 (s, 1H).



D77

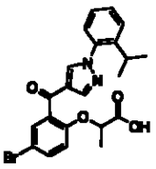
Ácido 2-{4-Bromo-2-[1-(2,6-dimetilfenil)-1H-pirazol-4-carbonil]fenoxi}propiónico. Preparado de 6-bromo-3-formilcromona, 2,6-dimetilfenilhidracina y etil 2-bromopropionato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.55 min, *m/z* 440.9 $[M - H]^+$; ^1H NMR ($CDCl_3$): □ 1.68(d, *J* = 6.8 Hz, 3H), 2.11 (s, 6H), 4.94 (q, *J* = 7.0 Hz 1H), 6.97 (d, *J* = 8.9 Hz, 1H), 7.19 (d, *J* = 7.5 Hz 2H), 7.28-7.32 (m, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.75 (m, 1H), 8.05 (s, 1H), 8.22 (s, 1H).



D78

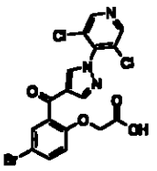
Ácido 2-{4-Bromo-2-[1-(2,6-dietilfenil)-1H-pirazol-4-carbonil]fenoxi}propiónico. Preparado de 6-bromo-3-formilcromona, 2,6-dietilfenilhidracina y etil 2-bromopropionato de acuerdo a GP1, GP2 y GP3: LC/MS (un10n8): Rt 2.85 min, *m/z* 469.0 $[M - H]^+$; ^1H NMR ($CDCl_3$): □ 1.08-1.21 (m, 6H), 1.69-1.76 (m, 3H), 2.18-2.48 (m, 4H), 2.67 (s,1H), 4.97 (q, *J* = 6.8 Hz 1H), 6.84 (d, *J* = 9.0 Hz, 1H), 7.00 (d, *J* = 9.0 Hz,

1H), 7.24 (d, *J* = 7.7 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.77 (s, 1H), 7.86 (s, 1H), 8.06 (s, 1H), 8.22 (s, 1H).



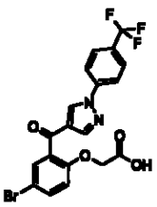
D79

Ácido 2-{4-Bromo-2-[1-(2-isopropilfenil)-1H-pirazol-4-carbonil]fenoxi}propiónico. Se prepara de 6-bromo-3-formilcromona, 2,6-dietil-fenilhidrazina y 2-bromopropionato de etilo de acuerdo con GP1, GP2 y GP3: LC/MS (an10p8): Ta 2.54 min, *m/z* 459.0 [M + H]$^+$; ^{1}H RMN ($CDCl_3$): □ 1.19-1.27 (m, 7H), 1.67 (d, *J* = 7.0 Hz, 2H), 4.92 (q, *J* = 6.8 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 1H), 7.27-7.53 (m, 4H), 7.58-7.67 (m, 1H), 7.73 (s, 1H), 8.17 (s, 1H), 8.20 (s,1H).



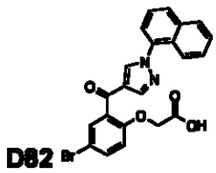
D80

Ácido {4-Bromo-2-[1-(3,5-dicloropiridin-4-il)-1H-pirazol-4-carbonil]fenoxi}-acético. Se prepara de 6-bromo-3-formilcromona, 2,6-dicloro-piridin-4-hidrazina y bromoacetato de etilo de acuerdo con GP1, GP2 y GP3: LC/MS (an10n8): Ta 2.08 min, *m/z* 469.8 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): □ 4.75 (s, 2H), 7.05 (d, *J* = 9.1 Hz, 1H), 7.56 (s, 1H), 7.64 (d, *J* = 9.1 Hz, 1H), 8.32 (s, 1H), 8.77 (s, 1H), 8.93 (s, 2H).



D81

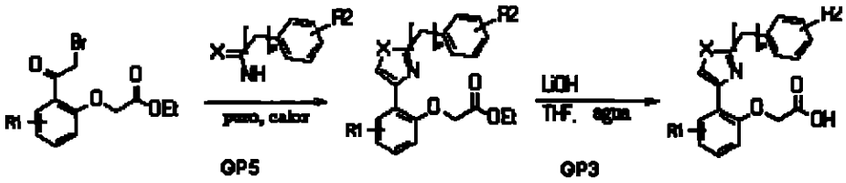
Ácido {4-Bromo-2-[1-(4-trifluorometilfenil)-1H-pirazol-4-carbonil]fenoxi}-acético. Se prepara de 6-bromo-3-formilcromona, 4-trifluorometilfenil-hidrazina y bromoacetato de etilo de acuerdo con GP1, GP2 y GP3: LC/MS (an10n8): Ta 2.88 min, *m/z* 468.9 [M - H]$^-$; ^{1}H RMN ($CDCl_3$): □ 4.78 (s, 2H), 6.92 (d, *J* = 8.9 Hz, 1H), 7.65 (d, *J* = 8.9 Hz, 1H), 7.71 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 2H), 7.91 (d, *J* = 8.9 Hz, 2H), 8.23 (s, 1H), 8.65 (s, 1H).



D82

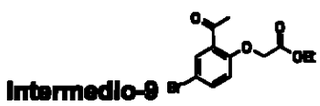
Ácido [4-Bromo-2-(1-naftalen-1-il-1H-pirazol-4-carbonil)fenoxi]acético. Se prepara de 6-bromo-3-formilcromona, 1-naftilhidrazina y bromoacetato de etilo de acuerdo con GP1, GP2 y GP3: LC/MS (an10p8): Ta 2.649 min, *m/z* 451.0 $[M + H]^+$; ^1H RMN ($CDCl_3$): □ 4.78 (s, 2H), 6.93 (d, *J* = 8.85 Hz, 1H), 7.52-7.68 (m, 6H), 7.73-7.82 (m , 2H), 7.93-8.05 (m, 2H), 8.33 (s, 1H), 8.38 (s, 1H).

Ruta sintética general IV



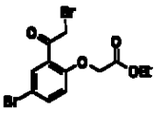
Procedimiento general 5 (GP5):

Una mezcla de 2-(2-bromoacetil)fenoxiacetato de etilo (0.1 mmol) y amida (X = O) o tioamida (X = S) (2.5 mmol) se calienta puro en el microondas durante 3 horas a 140° C. Después de enfriar, el residuo sólido se particiona entre EtOAc y $NaHCO_3$ ac. saturado. Las fases se separan y la fase orgánica se seca ($MgSO_4$) y se concentra *en vacuo*. Se purifica el sólido crudo mediante cromatografía flash para dar el derivado correspondiente de oxazol o tiazol.



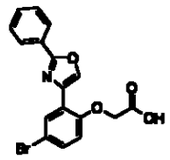
Intermedio-9

Éster de etilo de ácido (2-Acetil-4-bromofenoxi)acético Se prepara de 5'-bromo-2'-hidroxiacetofenona (2 g, 9.3 mmol) y bromoacetato de etilo (1.03 mL, 9.3 mmol) de acuerdo con GP2 para dar el compuesto del título como un sólido blanco (2.64 g, 8.7 mmol, 94%): LC/MS (an10p8) Ta 3.3 min, *m/z* 301 $[M + H]^+$; ^1H RMN ($CDCl_3$): □ 1.32 (t, 3H), 2.71 (s, 3H), 4.30 (q, 2H), 4.72 (s, 2H), 6.76 (d, 1H), 7.55 (dd, 1H), 7.88 (s, 1H).



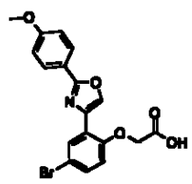
Intermedio-10

Éster de etilo de ácido [4-bromo-2-(2-bromoacetil)fenoxi]acético. A una solución fría (0° C) de éster de etilo de ácido (2-acetil-4-bromofenoxi)acético (2.5 g, 8.3 mmol) en $CHCl_3$ (25 mL) se agrega lentamente bromo (425 uL, 8.3 mmol). Después la mezcla de reacción terminada se le permite agitarse a temperatura ambiente durante 1 hora. La mezcla se particiona entre CH_2Cl_2 y solución salina. La fase orgánica se lava con solución salina, se seca ($MgSO_4$) y se concentra *in vacuo* para dar el compuesto del título como un sólido blanco (2.97 g, 7.8 mmol, 94%): ^{1}H RMN ($CDCl_3$): □ 1.35 (t, 3H), 4.32 (q, 2H), 4.75 (s, 2H), 4.76 (s, 2H), 6.77 (d, 1H), 7.60 (dd, 1H), 7.97 (s, 1H)



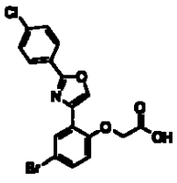
D83

Ácido [4-Bromo-2-(2-feniloxazol-4-il)fenoxi]acético. Se prepara el compuesto del título de éster de etilo de ácido [4-bromo-2-(2-bromoacetil)fenoxi]acético y benzamida de acuerdo con GP5 y GP3: LC/MS (an10p8) Ta 2.6 min, *m/z* 374/376 $[M + H]^+$.



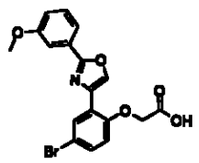
D84

Ácido {4-Bromo-2-[2-(4-metoxifenil)oxazol-4-il]fenoxi}acético. Se prepara el compuesto del título de éster de etilo de ácido [4-Bromo-2-(2-bromoacetil)fenoxi]acético y 4-metoxibenzamida de acuerdo con GP5 y GP3: LC/MS (an10p8) Ta 2.61 min, *m/z* 404 $[M + H]^+$.



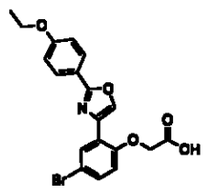
D85

Ácido {4-Bromo-2-[2-(4-clorofenil)oxazol-4-il]fenoxi}acético. Se prepara el compuesto del título de éster de etilo de ácido [4-bromo-2-(2-bromoacetil)fenoxi]acético y 4-clorobenzamida de acuerdo con GP5 y GP3: LC/MS (an10p8) Ta 2.90 min, *m/z* 407.7 $[M + H]^+$; ^{1}H RMN ($CDCl_3$): □ 4.89 (s, 2H), 7.09 (d, 1H), 7.48 (d, 1H), 7.64 (d, 2H), 8.08 (d, 2H), 8.20 (s, 1H), 8.89 (s, 1H), 13.2 (br s, 1H).



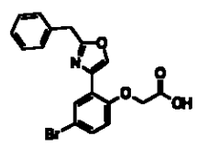
D86

Ácido {4-Bromo-2-[2-(3-metoxifenil)oxazol-4-il]fenoxi}acético. Se prepara el compuesto del título de éster de etilo de ácido [4-bromo-2-(2-bromoacetil)fenoxi]acético y 3-metoxibenzamida de acuerdo con GP5 y GP3: LC/MS (an10p8) Ta 2.68 min, *m/z* 404 $[M + H]^+$; ^{1}H RMN ($CDCl_3$): □ 3.87 (s, 1H), 4.89 (s, 2H), 7.09 (m, 2H), 7.4-7.7 (m, 4H), 8.22 (s, 1H), 8.89 (s, 1H), 13.3 (br s, 1H).



D87

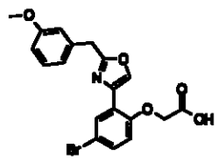
Ácido {4-Bromo-2-[2-(4-etoxifenil)oxazol-4-il]fenoxi}acético. Se prepara el compuesto del título de éster de etilo de ácido [4-bromo-2-(2-bromoacetil)fenoxi]acético y 4-etilbenzamida de acuerdo con GP5 y GP3: LC/MS (an10p8) Ta 2.80 min, *m/z* 418/420 $[M + H]^+$; ^{1}H RMN ($CDCl_3$): □ 1.36 (t, 3H), 4.10 (q, 2H), 4.88 (s, 2H), 7.07 (m, 3H), 7.47 (d, 1H), 8.00 (d, 2H), 8.20 (s, 1H), 8.82 (s, 1H), 13.4 (br s, 1H).



D88

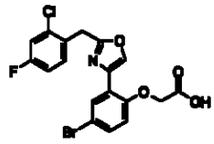
Ácido [2-(2-Benciloxazol-4-il)-4-bromofenoxi]acético. Se prepara el compuesto del título de éster de etilo de ácido [4-bromo-2-(2-bromoacetil)fenoxi]acético y 2-fenilacetamida de acuerdo con GP5 y GP3: LC/MS (an10p8) Ta 2.47 min, *m/z* 388 [M

+ H]$^+$; ^{1}H RMN ($CDCl_3$): □ 4.22 (s, 2H), 4.84 (s, 2H), 7.04 (d, 1H), 7.25 (m, 5H), 7.43 (d, 1H), 8.06 (s, 1H), 8.69 (s, 1H), 13 (br s, 1H).



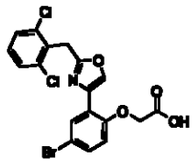
D89

Ácido {4-Bromo-2-[2-(3-metoxibencil)oxazol-4-il]fenoxi}acético. Se prepara el compuesto del título de éster de etilo de ácido [4-bromo-2-(2-bromoacetil)fenoxi]acético y 2-(3-metoxifenil)acetamida de acuerdo con GP5 y GP3: LC/MS (an10p8) Ta 2.45 min, *m/z* 418 [M + H]$^+$.



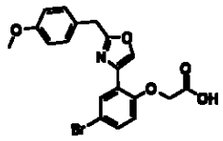
D90

Ácido {4-Bromo-2-[2-(2-cloro-4-fluorobencil)oxazol-4-il]fenoxi}acético. Se prepara el compuesto del título de éster de etilo de ácido [4-bromo-2-(2-bromoacetil)fenoxi]acético y 2-(2-cloro-4-fluorofenil)acetamida de acuerdo con GP5 y GP3: LC/MS (an10p8) Ta 2.75 min, *m/z* 440 [M + H]$^+$.



D91

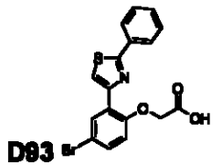
Ácido {4-Bromo-2-[2-(2,6-diclorobencil)oxazol-4-il]fenoxi}acético. Se prepara el compuesto del título de éster de etilo de ácido [4-bromo-2-(2-bromoacetil)fenoxi]acético y 2-(2,6-diclorofenil)acetamida de acuerdo con GP5 y GP3: LC/MS (an10p8) Ta 2.75 min, *m/z* 456/458/460 [M + H]$^+$.



D92

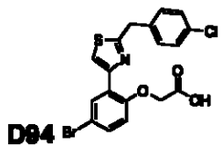
Ácido {4-Bromo-2-[2-(4-metoxibencil)oxazol-4-il]fenoxi}acético. Se prepara el compuesto del título de éster de etilo de ácido [4-bromo-2-(2-

bromoacetil)fenoxi]acético y 2-(4-metoxifenil)acetamida de acuerdo con GP5 y GP3: LC/MS (an10p8) Ta 2.40 min, *m/z* 418 [M + H]$^+$; ^{1}H RMN ($CDCl_3$): □3.72 (s, 3H), 4.14 (s, 1H), 4.85 (s, 1H), 6.92 (m, 2H), 7.02 (d, 1H), 7.2 (d, 1H), 7.23 (d, 1H), 7.44 (d, 1H), 8.05 (s, 1H), 8.67 (s, 1H), 13.2 (br s, 1H).



D93

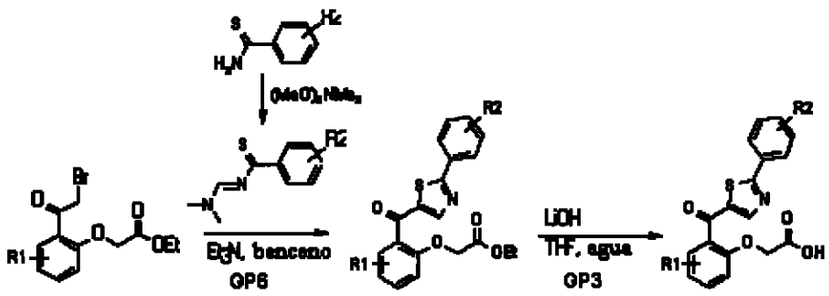
Ácido [4-Bromo-2-(2-feniltiazol-4-il)fenoxi]acético. Se prepara el compuesto del título de éster de etilo de ácido [4-bromo-2-(2-bromoacetil)fenoxi]acético y tiobenzamida de acuerdo con GP5 y GP3: LC/MS (an10p8) Ta 2.69 min, *m/z* 390 [M + H]$^+$.



D94

Ácido {4-Bromo-2-[2-(4-clorobencil)tiazol-4-il]fenoxi}acético Se prepara el compuesto del título de éster de etilo de ácido [4-bromo-2-(2-bromoacetil)fenoxi]acético y 2-(4-clorofenil)tioacetamida de acuerdo con GP5 y GP3: LC/MS (an10p8) Ta 2.69 min, *m/z* 390 [M + H]$^+$; ^{1}H RMN ($CDCl_3$): □4.42 (s, 2H), 4.86 (s, 2H), 7.06 (d, 1H), 7.45 (m, 5H), 8.33 (s, 1H), 8.41 (s, 1H), 13.2 (br s, 1H).

Ruta sintética general V



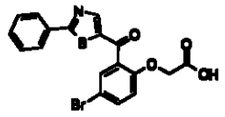
Procedimiento general 6 (GP6)

Síntesis de carboniltiazoles

182

Una mezcla de la tioamida (1.0 mmol) y N,N-dimetilformamida dimetilacetal (1.2 mmol) se agita durante 1 hora a temperatura ambiente bajo argón. Los materiales volátiles se remueven bajo presión reducida sin calor para dar la correspondiente N'-tioaroilformamidina la cual se usa sin purificación adicional en la siguiente etapa.

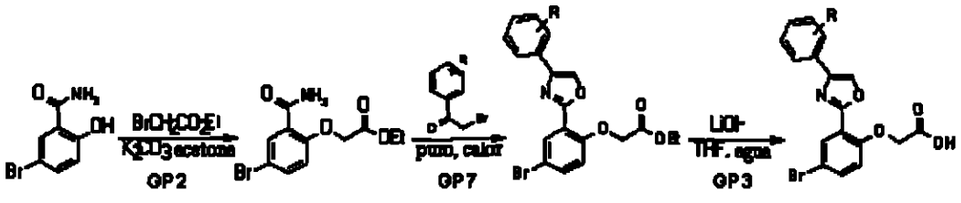
A una solución del 2-(2-bromoacetil)fenoxiacetato de etilo (1 mmol) y la N'-tioaroilformamidina (1 mmol) en benceno (2.6 mL) se agrega un exceso de trietilamina (5 mmol). Después de agitación durante la noche a temperatura ambiente, se remueve el solvente *en vacuo*. El residuo se particiona entre EtOAc y $NaHCO_3$ ac. saturado. La fase orgánica se seca ($MgSO_4$) y se concentra *en vacuo*. El material crudo se purifica mediante cromatografía flash para dar la tioamida.



D95

Ácido [4-Bromo-2-(2-fenitiazol-5-carbonil)fenoxi]acético. Se prepara el compuesto del título de éster de etilo de ácido [4-bromo-2-(2-bromoacetil)fenoxi]acético y tiobenzamida de acuerdo con GP6 y GP3: LC/MS (an10p8) Ta 2.44 min, *m/z* 418 [M + H]$^+$.

Ruta sintética general VI

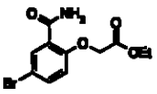


Procedimiento general 7 (GP7)

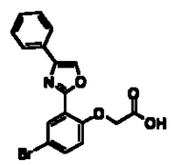
Síntesis de oxazol

Una mezcla de benzamida (1.0 mmol) y 2-bromoacetofenona (0.5 mmol) se calienta puro en horno microondas Emrys Optimizer durante 3 horas a 140° C. Después de enfriar se agregan EtOAc y CH_2Cl_2 y el precipitado formado se filtra. El filtrado se concentra *in vacuo* y se purifica mediante cromatografía flash para dar el correspondiente oxazol.

183

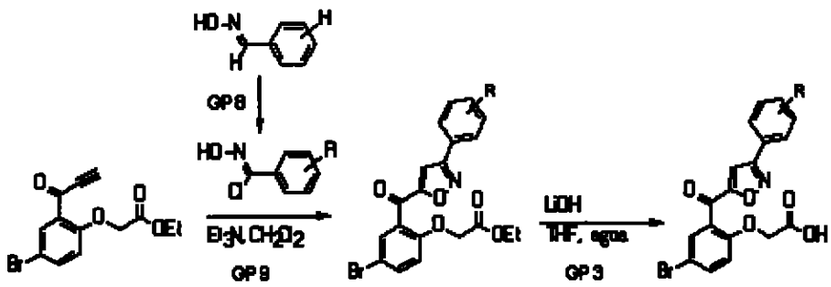
Intermedio-11 

Éster de etilo de ácido (4-Bromo-2-carbamoilfenoxi)acético . Se prepara de bromosalicilamida y bromoacetato de etilo de acuerdo con GP2: ^{1}H RMN ($CDCl_3$): □ 1.35 (t, 3H), 4.34 (q, 2H), 4.73 (s, 2H), 5.87 (br s, 1H), 6.76 (d, 1H), 7.56 (d, 1H), 8.33 (br s, 1H), 8.39 (s, 1H).

D96 

Ácido [4-Bromo-2-(4-fenil-oxazol-2-il)-fenoxi]acético. Se prepara el compuesto del título de éster de etilo de ácido (4-Bromo-2-carbamoilfenoxi)acético y 2-bromoacetofenona de acuerdo con GP7: LC/MS (an10p8) Ta 2.32 min, *m/z* 374/376 $[M + H]^+$.

Ruta sintética general VII



Procedimiento general 8 (GP8):

Síntesis de cloruro ácido hidroxímico

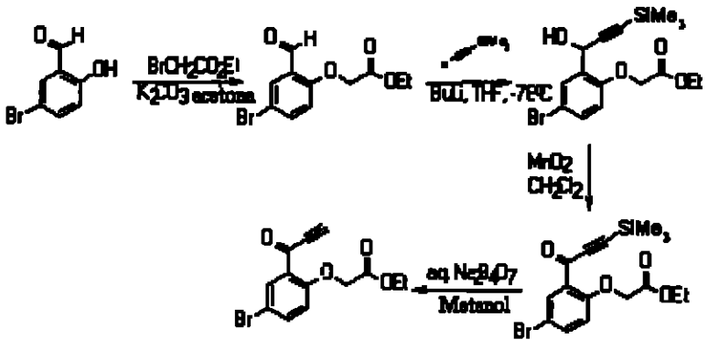
A una solución de la aldoxima (1.0 mmol) en CH_2Cl_2 (1.7 mL) se agrega N-clorosuccinimida (1.0 mmol) en una porción. La mezcla de reacción se agita durante 3 horas a temperatura ambiente bajo una atmósfera de argón. Se agrega agua. Las fases se separan. La fase orgánica se seca ($MgSO_4$) y se concentra *in vacuo* para dar el correspondiente derivado de cloruro ácido hidroxímico el cual se usa sin purificación adicional.

Procedimiento general 9 (GP9):

Síntesis de Isoxazol

A una solución del cloruro ácido hidroxímico (1.0 mmol) y éster de etilo de ácido (4-bromo-2-propinoil-fenoxi)acético (1.0 mmol) en CH_2Cl_2 seco (3.7 mL) se agrega lentamente una solución de Et_3N (1.0 mmol) en CH_2Cl_2 seco (0.6 mL) durante un periodo de 4 horas (uso de una jeringa-bomba). Después de la terminación de la adición, la mezcla de reacción se lava con agua, solución salina, se seca ($MgSO_4$) y se concentra *en vacuo*. El aceite crudo se purifica mediante cromatografía flash para dar el correspondiente derivado de isoxasol.

Síntesis de Intermedio-12



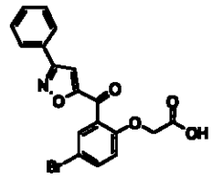
Éster de etilo de ácido (4-Bromo-2-formilfenoxi)acético. Se prepara de 5-bromo-2-hidroxibenzaldehído de acuerdo con GP2: LC/MS (an10p8) Ta 3.45 min, *m/z* 287 [M + H]$^+$; ^{1}H RMN ($CDCl_3$): □ 1.29 (t, 3H), 4.25 (q, 2H), 4.74 (s, 2H), 6.79 (d, 1H), 7.60 (d, 1H), 7.94 (s, 1H), 10.46 (s, 1H)

Éster de etilo de ácido [4-Bromo-2-(1-hidroxi-3-trimetilsilanilprop-2-inil)fenoxi]acético. A una solución fría (-78° C) de (trimetilsilil)acetileno (3.93 g, 40.0 mmol) en THF seco (40 mL) se agrega lentamente una solución 2.5 M de butillitio en hexanos (14.54 mL, 36.36 mmol). Después de agitar durante 30 minutos a -78° C, la mezcla se transfiere a una solución fría (-78° C) de éster de etilo de ácido (4-bromo-2-formil-fenoxi)acético (10.44 g, 36.36 mmol) en THF seco (120 mL). Luego de terminación, la mezcla de reacción se agita a -78° C durante 45 minutos. Se agrega lentamente NH_4Cl ac. saturado (40 mL) a la mezcla de reacción seguido por Et_2O (40 mL). La mezcla de reacción apagada se le permite calentar a temperatura ambiente. Las fases se separan y la fase acuosa se extrae con Et_2O (2x). Las fases orgánicas combinadas se lavan con solución salina, se secan ($MgSO_4$) y se concentran *en vacuo*. El aceite crudo se purifica mediante cromatografía de columna (SiO_2), entonces

se agita durante 90 min con trisamina apoyada por poliestireno (PS-Trisamina, 4.17 mmol/g, 8 g) en CH_2Cl_2 (160 mL). La resina se filtra y el filtrado se concentra *in vacuo* para dar el compuesto del título como un aceite amarillo pálido (7.6 g, 19.7 mmol, 54%). LC/MS (an10p8) Ta 4.30 min, *m/z* 408 $[M + Na]^+$; ^1H RMN ($CDCl_3$): □ 0.24 (s, 9H), 1.31 (t, 3H), 4.27 (q, 2H), 4.71 (s, 2H), 5.79 (s, 1H), 6.74 (d, 1H), 7.39 (dd, 1H), 7.79 (d, 1H).

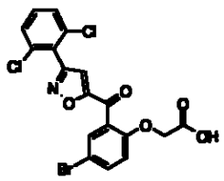
Éster de etilo de ácido [4-Bromo-2-(3-trimetilsilanilpropinoil)fenoxi]acético. A una solución de éster de etilo de ácido [4-Bromo-2-(1-hidroxi-3-trimetilsilanilprop-2-inil)fenoxi]acético (0.95 g, 2.46 mmol) en CH_2Cl_2 (10 mL) se agrega MnO_2 activado en 2 porciones (1.5 g + 1 g), y la reacción se agita durante 90 min. El sólido se filtra a través de una almohadilla de celita y el filtrado se concentra *in vacuo* para dar el compuesto del título como aceite amarillo (0.83 g, 2.16 mmol, 87%). LC/MS (an10p8) Ta 4.70min, *m/z* 383 $[M + H]^+$; ^1H RMN ($CDCl_3$): □ 0.30 (s, 9H), 1.30 (t, 3H), 4.27 (q, 2H), 4.72 (s, 2H), 6.81 (d, 1H), 7.58 (dd, 1H), 8.10 (s, 1H).

Éster de etilo de ácido (4-Bromo-2-propinoilfenoxi)acético. A una solución de éster de etilo de ácido [4-Bromo-2-(3-trimetilsilanilpropinoil)fenoxi]acético (0.83 g, 2.16 mmol) en metanol (20 mL) se agrega a solución acuosa 0.1 M de $Na_2B_4O_7$ (10 mL). Después de agitar durante 2 – 3 minutos a temperatura ambiente, Et_2O y 1N aq. HCl were added. Las fases se separan, y la fase orgánica se lava con solución salina, se seca ($MgSO_4$) y se concentra *in vacuo* para dar el compuesto del título como aceite amarillo la cual se recristaliza hasta reposo (0.65 g, 2.09 mmol, 96%). LC/MS (an10p8) Ta 3.58min, *m/z* 311 $[M + H]^+$; ^1H RMN ($CDCl_3$): □ 1.31 (t, 3H), 3.45 (s, 1H), 4.27 (q, 2H), 4.74 (s, 2H), 6.83 (d, 1H), 7.61 (dd, 1H), 8.14 (d, 1H).



D97

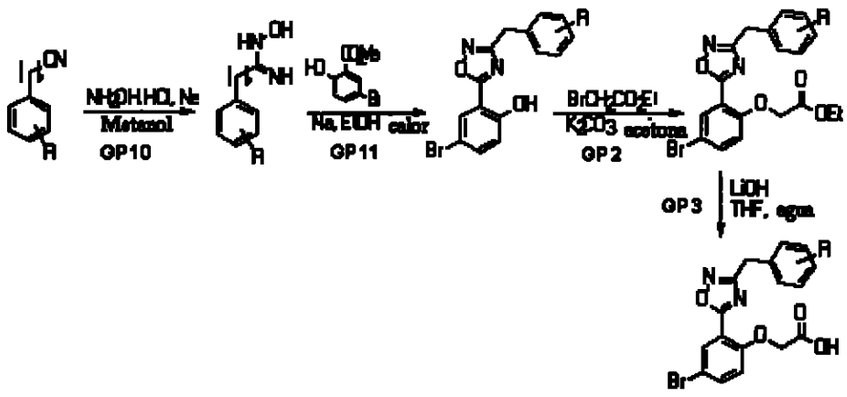
Ácido [4-Bromo-2-(3-fenilisoxazol-5-carbonil)fenoxi]acético Se prepara el compuesto del título de benzaldoxima y éster de etilo de ácido (4-bromo-2-propinoilfenoxi)-acético de acuerdo con GP8 y GP9: LC/MS (an10n8) Ta 3.07 min, *m/z* 400 $[M - H]^-$; ^1H RMN (DMSO): □4.77 (s, 2H), 7.13 (d, 1H), 7.53 (m, 3H), 7.73-7.92 (m, 5H).



D98

Ácido {4-Bromo-2-[3-(2,6-dicloro-fenil)isoxazol-5-carbonil]fenoxi}acético. Se prepara el compuesto del título de 2,6-diclorobenzaldoxima y éster de etilo de ácido (4-bromo-2-propinoilfenoxi)-acético de acuerdo con GP8 y GP9: LC/MS (an10n8) Ta 2.74 min, *m/z* 471.9 $[M + H]^+$.

Ruta sintética general VIII



Procedimiento general 10 (GP10)

Síntesis de amidoximas

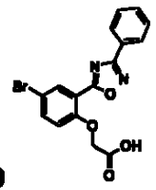
Se agrega sodio (1.25 mmol) a metanol seco (1 ml) para dar la solución A. Se disuelve clorhidrato de hidroxilamina (1.2 mmol) en metanol seco (1mL) para dar la solución B. Se mezclan la solución A y B, se enfrían en un baño de hielo y se filtran. Entonces se agrega al filtrado el nitrilo (1 mmol) y la mezcla de reacción se agita durante la noche a temperatura ambiente. Se remueve el solvente *in vacuo* para dar la correspondiente amidoxima. El compuesto se purifica sobre cromatografía de gel de sílice (EtOAc/Heptano: 1/2) o se utiliza sin purificación adicional.

Procedimiento general 11 (GP11)

Síntesis de oxadiazoles

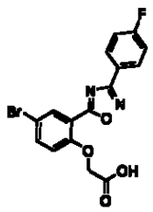
A una solución de sodio (3.3 mmol) en etanol seco (10 mL) se agregan sucesivamente la amidoxima (1.15 mmol), tamices moleculares (1g) y benzoato de metilo (1 mmol).

Después de agitar durante 12 h bajo reflujo, la mezcla de reacción se enfría y se filtra a través de una almohadilla de celita. La almohadilla de celita se lava con metanol y CH_2Cl_2. Se remueve el solvente *in vacuo* y el residuo se agita con agua. El precipitado se filtra y se seca para dar el correspondiente oxadiazol. El compuesto se purifica sobre cromatografía de gel de sílice (EtOAc:Heptano, 1:2) o se utiliza sin purificación adicional en.



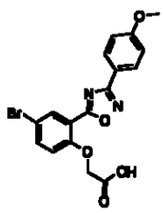
D99

Ácido [4-Bromo-2-(3-fenil-[1,2,4]oxadiazol-5-il)fenoxi]acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y benzonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8): Ta 2.41 min, *m/z* 373.4 [M - H]; ^{1}H RMN (DMSO-d_6): δ 4.97 (s, 2H), 7.2 (d, 1H), 7.62 (s, 3H), 7.82 (d, 2H), 8.10 (d, 1H), 8.2 (s, 1 H).



D100

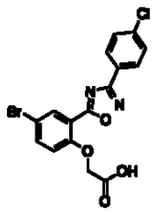
Ácido {4-Bromo-2-[3-(4-fluoro-fenil)-[1,2,4]oxadiazol-5-il]fenoxi}acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y 4-fluorobenzonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.49, *m/z* 391.4 [M - H].



D101

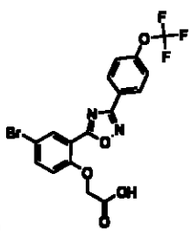
Ácido {4-Bromo-2-[3-(4-metoxi-fenil)-[1,2,4]oxadiazol-5-il]fenoxi}acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico

y 4-metoxibenzonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.44 min, *m/z* 403.4 [M - H]⁻.



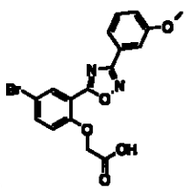
D102

Ácido {4-Bromo-2-[3-(4-clorofenil)-[1,2,4]oxadiazol-5-il]fenoxi}acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y 4-clorobenzonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.68 min, *m/z* 407.4 [M - H]⁻.



D103

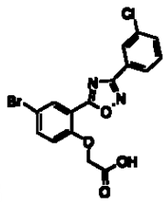
Ácido {4-Bromo-2-[3-(4-trifluorometoxifenil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y 4-trifluorometoxibenzonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.09 min, *m/z* 457.5 [M - H]⁻ ; ^{1}H RMN (DMSO-d_6): δ 4.96 (s, 2H), 7.21 (d, 1H), 7.59 (d, 2H), 7.82 (d, 1H), 8.22 (d, 3H).



D104

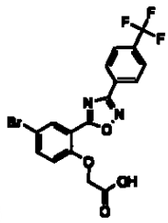
Ácido {4-Bromo-2-[3-(3-metoxifenil)-[1,2,4]oxadiazol-5-il]fenoxi}acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y 3-metoxibenzonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.47 min, *m/z* 403.4 [M - H]⁻ ; ^{1}H RMN (DMSO-d_6): δ 3.86 (s, 3H), 4.96 (s, 2H), 7.20 (d, 2H), 7.5 (t, 1H), 7.6 (s, 1H), 7.67 (d,1H), 7.8 (d, 1H), 8.2 (s, 1H).

189



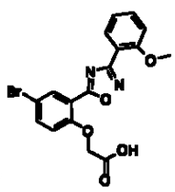
D105

Ácido {4-Bromo-2-[3-(3-clorofenil)-[1,2,4]oxadiazol-5-il]fenoxi}acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y 3-clorobenzonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.69 min, *m/z* 407.4 [M – H]⁻; ^{1}H RMN (DMSO): δ 4.97 (s, 2H), 7.2 (d, 1H), 7.6 (m, 2H), 7.7 (d, 1H), 7.8 (d 2 H), 8.2, (s, 1H).



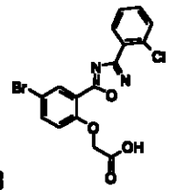
D106

Ácido {4-Bromo-2-[3-(4-trifluorometil-fenil)-[1,2,4]oxadiazol-5-il]fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y 4-trifluorometilbenzonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.83 min, *m/z* 441.4 [M - H]⁻; ^{1}H RMN (DMSO-d_6): δ 4.97 (s, 2H), 7.2 (d, 1H), 7.8 (dd, 1H), 7.9 (d, 2H), 8.2 (d, 1H), 8.3 (d, 2H).



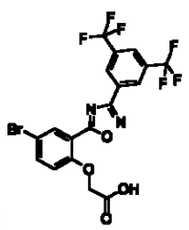
D107

Ácido {4-Bromo-2-[3-(2-metoxifenil)-[1,2,4]oxadiazol-5-il]fenoxi}acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y 2-metoxibenzonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.31 min, *m/z* 403.4 [M - H]⁻; ^{1}H RMN (DMSO-d_6): δ 2.5 (s, 3H), 4.94 (s, 2H), 7.2 (m, 3H), 7.5 (t, 1H), 7.7 (d, 1H), 7.9 (d, 1H), 8.1 (s, 1H).



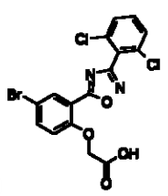
D108

Ácido {4-Bromo-2-[3-(2-clorofenil)-[1,2,4]oxadiazol-5-il]fenoxi}acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y 2-clorobenzonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.50 min, *m/z* 407.4 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 4.94 (s, 2H), 7.2 (d, 1H), 7.5-7.7 (m, 3H), 7.8 (dd, 1H), 8.0 (d, 1H), 8.1 (s,1H).



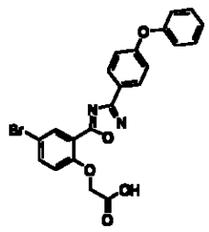
D109

Ácido {2-[3-(3,5-Bis-trifluorometil-fenil)-[1,2,4]oxadiazol-5-il]-4-bromo-fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y 3,5-bistrifluorometoxibenzonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 3,332 min, *m/z* 509.5 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 4.96 (s, 2H), 7.2 (d, 1H), 7.8 (d, 1H), 8.2 (s, 1H), 8.4 (s,1H), 8.5 (s, 1H), 8.6 (s, 1H).



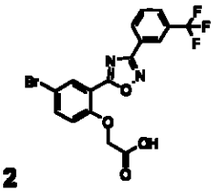
D110

Ácido {4-Bromo-2-[3-(2,6-diclorofenil)-[1,2,4]oxadiazol-5-il]fenoxi}acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y 2,6-Dicloro-benzonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.59 min, *m/z* 441.4 [M - H]$^-$.



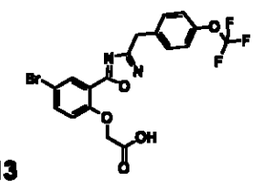
D111

Ácido {4-Bromo-2-[3-(4-fenoxi-fenil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y 4-fenoxibenzonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 3.29 min, *m/z* 465.5 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 4.95 (s,2H), 7.2 (m, 6H), 7.4 (t, 2H), 7.8 (d, 1H), 8.0 (d, 2H), 8.1 (s, 1H).



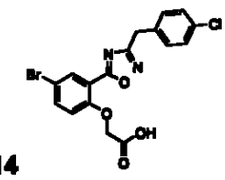
D112

Ácido {4-Bromo-2-[3-(3-trifluorometilfenil)-[1,2,4]oxadiazol-5-il]fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y 3-trifluorometilbenzonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.96 min, *m/z* 441.4 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 4.97 (s,2H), 7.2 (d, 1H), 7.8 (m, 2H), 8.0 (d, 1H), 8.2 (s, 1H), 8.3 (s, 1H), 8.4 (d, 1H).



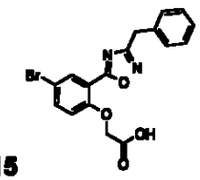
D113

Ácido {4-Bromo-2-[3-(4-trifluorometoxi-bencil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y (4-trifluorometoxifenil) acetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.76 min, *m/z* 4715 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 4.2 (s, 2H), 4.9 (s, 2H), 7.1 (d, 1H), 7.3 (d, 2H), 7.5 (d, 2H), 7.7 (d, 1H), 8.0 (s, 1H).



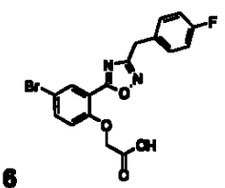
D114

Ácido {4-Bromo-2-[3-(4-cloro-bencil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y (4-clorofenil)acetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.54 min, *m/z* 421.4 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 4.2 (s, 2H), 4.9 (s, 2H), 7.1 (d, 1H), 7.4 (s, 4H), 7.8 (d, 1H), 8.0 (s, 1H).



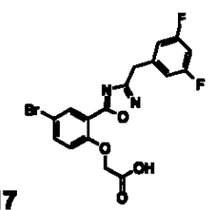
D115

Ácido [2-(3-bencil-[1,2,4]oxadiazol-5-il)-4-bromo-fenoxi]-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y fenilacetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.26 min, *m/z* 387.4 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 4.2 (s, 2H), 4.9 (s, 2H), 7.1 (d, 1H), 7.3 (m, 5H), 7.7 (d, 1H), 8.0 (s, 1H).



D116

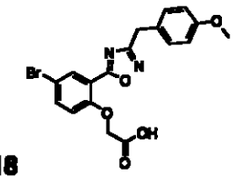
Ácido {4-Bromo-2-[3-(4-fluoro-bencil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y (4-fluorofenil)acetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.38 min, *m/z* 405.4 [M - H]$^-$.



D117

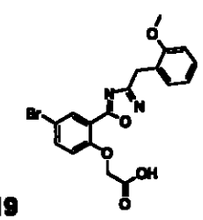
193

Ácido {4-Bromo-2-[3-(3,5-difluoro-bencil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y (3,5-difluorofenil)acetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.44 min, *m/z* 423.4 [M - H]⁻.



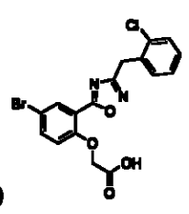
D118

Ácido {4-Bromo-2-[3-(4-metoxi-bencil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y (4-metoxifenil) acetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.25 min, *m/z* 417.4 [M –H]⁻; ^{1}H RMN (DMSO-d_6): δ 4.1 (s, 2H), 4.9 (s, 2H), 6.9 (d, 2H), 7.1 (d, 1H), 7.2 (d, 2H), 7.7 (d, 1H), 8.0 (s, 1H).



D119

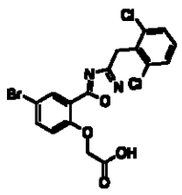
Ácido {4-Bromo-2-[3-(2-metoxi-bencil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y (2-Metoxi-fenil)-acetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.25 min, *m/z* 417.4 [M - H]⁻; ^{1}H RMN (DMSO-d_6): δ 3.7 (s, 3H), 4.1 (s, 2H), 4.9 (s, 2H), 6.9 (t, 1H), 7.0 (d, 1H), 7.1 (d, 1H), 7.2 (m, 2H), 7.7 (d, 1H), 8.0 (s, 1H).



D120

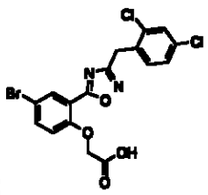
Ácido {4-Bromo-2-[3-(2-cloro-bencil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y (2-clorofenil)acetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8)

Ta 2.48 min, *m/z* 421.4 [M - H]⁻; ^{1}H RMN (DMSO-d_6): δ 4.2 (s, 2H), 4.9 (s, 2H), 7.1 (d, 1H), 7.3 (m, 2H), 7.4 (m, 2H), 7.7 (dd, 1H), 8.0 (d, 1H).



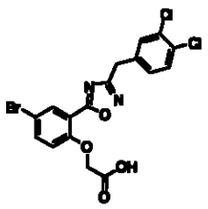
D121

Ácido {4-Bromo-2-[3-(2,6-dicloro-bencil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y (2,6-diclorofenil)acetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.58 min, *m/z* 455/457/459 [M - H]⁻; ^{1}H RMN (DMSO-d_6): δ 4.4 (s, 2H), 4.9 (s, 2H), 7.1 (d, 1H), 7.4 (t, 1H), 7.5 (d, 2H), 8.7-7.8 (dd, 1H), 8.0 (d, 1H).



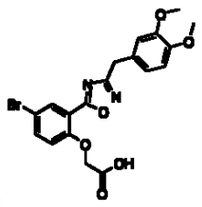
D122

Ácido {4-Bromo-2-[3-(2,4-dicloro-bencil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y (2,4-diclorofenil) acetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2,78 min, *m/z* 455/457/459 [M - H]⁻.



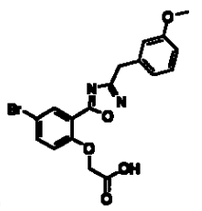
D123

Ácido {4-Bromo-2-[3-(3,4-diclorobencil)-[1,2,4]oxadiazol-5-il]-fenoxi}acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y (3,4-diclorofenil)acetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.81 min, *m/z* 455/457/459 [M - H]⁻; ^{1}H RMN (DMSO-d_6): δ 4.3 (s, 2H), 4.8 (s, 2H), 7.1 (d, 1H), 7.3 (dd, 1H), 7.6 (d, 1H), 7.6 (d, 1H), 7.7 (dd, 1H), 8.0 (d, 1H).



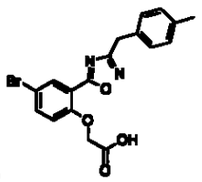
D124

Ácido {4-Bromo-2-[3-(3,4-dimetoxibencil)-[1,2,4]oxadiazol-5-il]fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y (3,4-bismetoxifenil)acetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.20 min, *m/z* 447,4 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 3.72 (s, 3H), 3.74 (s, 3H), 4.1 (s, 2H), 4.9 (s, 2H), 6.8 (m, 2H), 6.9 (s, 1H), 7.1 (d, 1H), 7.7 (dd, 1H), 8.0 (d, 1H).



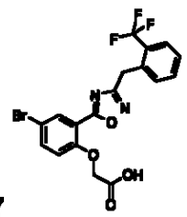
D125

Ácido {4-Bromo-2-[3-(3-metoxibencil)-[1,2,4]oxadiazol-5-il]fenoxi}acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y (3-metoxifenil)acetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.38 min, *m/z* 417.4 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 4.1 (s, 2H), 4.9 (s, 2H), 6.8 (d, 1H), 6.9 (m, 2H), 7.1 (d, 1H), 7.2 (t, 1H), 7:8 (m, 1H), 8.0 (d, 1H).



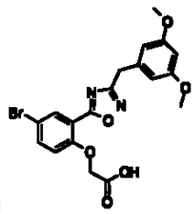
D126

Ácido {4-Bromo-2-[3-(4-metilbencil)-[1,2,4]oxadiazol-5-il]fenoxi}acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y (4-metilfenil)acetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.72 min, *m/z* 401.4 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 3.3 (s, 3H), 4.1 (s, 2H), 4.9 (s, 2H), 7.1 (m, 3H), 7.2 (d, 2H), 7.7 (dd, 1H), 8.0 (d, 1H).



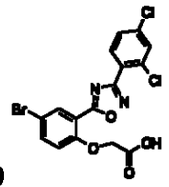
D127

Ácido {4-Bromo-2-[3-(2-trifluorometilbencil)-[1,2,4]oxadiazol-5-il]fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y (2-trifluorometilfenil)acetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.77 min, *m/z* 455.5 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 4.3 (s, 2H), 4.9 (s, 2H), 7.1 (d, 1H), 7.5-7.6 (m, 2H), 7.6-7.7 (t, 1H), 7.7-7.8 (m, 2H), 8.0 (d, 1H).



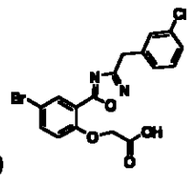
D128

Ácido {4-Bromo-2-[3-(3,5-dimetoxibencil)-[1,2,4]oxadiazol-5-il]fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y (3,5-bismetoxifenil)acetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.61 min, *m/z* 447.4 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 3.7 (s, 6H), 4.1 (s, 2H), 4.9 (s, 2H), 6.4 (d, 1H), 6.5 (d, 2H), 7.1 (d, 1H), 7.8 (dd, 1H), 8.0 (d, 1H).



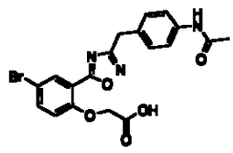
D129

Ácido {4-Bromo-2-[3-(2,4-diclorofenil)-[1,2,4]oxadiazol-5-il]fenoxi}acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxi-benzoico y 2,4-diclorobenzonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.93 *m/z* 441/443/445 [M – H]$^-$; ^{1}H RMN (DMSO): δ 4.7 (s, 1H), 6.95-6.98 (d, 1H), 7.42-7.44 (d, 1H), 7.58-7.60 (d, 1H), 7.67 (s, 1H), 7.82-7.85 (d, 1H), 7.94-7.95 (s, 1H).



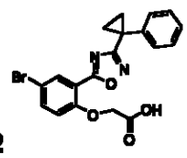
D130

Ácido {4-Bromo-2-[3-(3-clorobencil)-[1,2,4]oxadiazol-5-il]fenoxi}acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxi-benzoico y 3-clorofenilacetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.79 *m/z* 421.4 [M – H]$^-$; ^{1}H RMN (DMSO): δ 4.21 (s, 2H), 4.92 (s, 2H), 7.15-7.18(d, 1H), 7.32-7.39(m, 3H), 7.45 (s, 1H), 7.76-7.80 (dd, 1H), 8.03-8.04 (d, 1H).



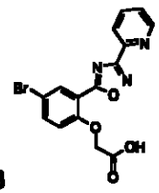
D131

Ácido {2-[3-(4-Acetilaminobencil)-[1,2,4]oxadiazol-5-il]-4-bromofenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y 4-acetamidofenilacetonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.15 *m/z* 444.4 [M – H]$^-$; ^{1}H RMN (DMSO): δ 2.02 (s, 3H), 4.10 (s, 2H), 4.92 (s, 2H), 7.14-7.17(d, 1H), 7.25-7.27(d, 2H), 7.52-7.54 (d, 2H), 7.76-7.78 (d, 1H), 8.03 (s, 1H).



D132

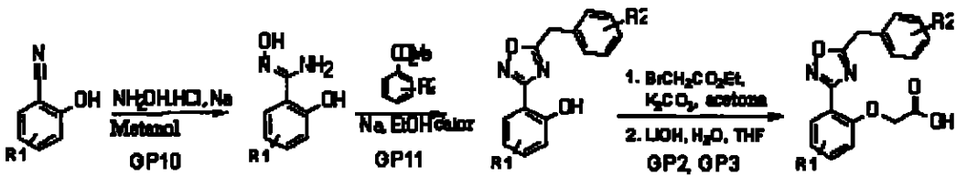
Ácido {4-Bromo-2-[3-(1-fenilciclopropil)-[1,2,4]oxadiazol-5-il]fenoxi}-acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxi-benzoico y 1-fenil-1-ciclopropanocarbonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta .2.756 *m/z* 413.4 [M –H]$^-$; ^{1}H RMN (DMSO-d_6): δ 0.92 (m, 2H), 1.11 (m, 2H), 4.38 (s, 2H), 6.63-6.66 (d, 1H), 6.79-6.88 (m, 3H), 6.93-6.95 (m, 2H), 7.25-7.29 (dd, 1H), 7.50-7.51 (d, 1H).

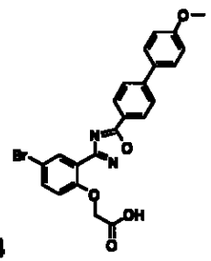


D133

Ácido [4-Bromo-2-(3-piridin-2-il-[1,2,4]oxadiazol-5-il)fenoxi]acético. Se prepara el compuesto del título de éster de metilo de ácido 5-bromo-2-hidroxibenzoico y Piridin-2-carbonitrilo de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 1.89 min, *m/z* 374.4 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 4.9 (s, 2H), 7.2 (d, 1H), 7.6 (m, 1H), 7.8 (d, 1H), 8.0 (t, 1H), 8.2 (m, 2H), 8.8 (d, 1H).

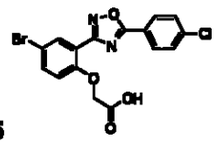
Ruta sintética general IX





D134

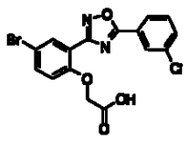
Ácido {4-Bromo-2-[5-(4'-metoxibifenil-4-il)-[1,2,4]oxadiazol-3-il]-fenoxi}acético. Se prepara el compuesto del título de 2-hidroxi-5-bromo-benzonitrilo y éster de metilo de ácido 4'-metoxi-bifenil-4-carboxílico de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.96 min, *m/z* 479.5 [M – H]$^-$.



D135

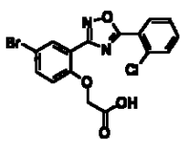
Ácido {4-Bromo-2-[5-(4-clorofenil)-[1,2,4]oxadiazol-3-il]fenoxi}acético. Se prepara el compuesto del título de 2-hidroxi-5-bromo-benzonitrilo y éster de metilo de ácido 4-clorobenzoico de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.61 min,

m/z 407.4 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 4.3 (s, 2H), 6.9 (d, 1H), 7.6 (dd, 1H), 7.7 (d, 2H), 8.0 (d, 1H), 8.2 (d, 2H).



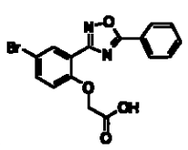
D136

Ácido {4-Bromo-2-[5-(3-clorofenil)-[1,2,4]oxadiazol-3-il]fenoxi}acético. Se prepara el compuesto del título de 2-hidroxi-5-bromobenzonitrilo y éster de metilo de ácido 3-clorobenzoico de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.61 min, *m/z* 407.4 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 4.4 (s, 2H), 6.9 (d, 1H), 7.6 (m, 2H), 7.8 (d, 1H), 8.0 (s, 1H), 8.2 (m, 2H).



D137

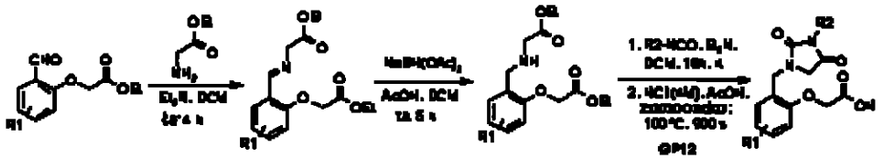
Ácido {4-Bromo-2-[5-(2-clorofenil)-[1,2,4]oxadiazol-3-il]fenoxi}acético. Se prepara el compuesto del título de 2-hidroxi-5-bromobenzonitrilo y éster de metilo de ácido 2-clorobenzoico de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.45 min, *m/z* 407.4 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 4.3 (s, 2H), 6.9 (d, 1H) 7.6-7.7 (m, 4H), 8.0 (s, 1H), 8.2 (d, 1H).

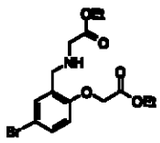


D138

Ácido [4-Bromo-2-(5-fenil-[1,2,4]oxadiazol-3-il)fenoxi]acético. Se prepara el compuesto del título de 2-hidroxi-5-bromobenzonitrilo y éster de metilo de ácido benzoico de acuerdo con GP10, GP11, GP2 y GP3: LC/MS (an10n8) Ta 2.33 min, *m/z* 373.4 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 4.8 (s, 2H), 7.1 (d, 1H), 7.6-7.7 (m, 4H), 8.0 (d, 1H), 8.2 (d, 2H).

Ruta sintética general X





Intermedio-13

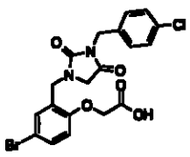
Ácido 4-Bromo-2-[(etoxicarbonilmetilamino)metil]fenoxiacético éster de etilo. Se disuelve éster de etilo de ácido 4-Bromo-2-formilfenoxiacético (1.44 g, 5 mmol) en diclorometano (50 mL) y se agrega clorhidrato de éster de etilo de glicina (1.39 g, 10 mmol) así como Et_3N (1.4 mL, 10 mmol). La mezcla se agita a temperatura ambiente durante 4 h. Se agrega agua y diclorometano y la fase orgánica se pasa a través de un filtro de separación de fase y entonces se evapora para dar éster de etilo de ácido {4-bromo-2-[(E)-etoxicarbonilmetilimino-metil]-fenoxi}-acético, el cual se redisuelve en diclorometano (50 mL) y se trata con $NaBH(OAc)_3$ (2.11 g, 10 mmol) y AcOH (1 mL), y entonces se agita a temperatura ambiente durante 5 h. Se agrega Na_2CO_3 saturado, agua y diclorometano, y la fase orgánica se pasa a través de un filtro de separación de fase y se evapora para dar el compuesto del título (1.56 g, 84% de rendimiento total).

Procedimiento general 12 (GP12)

<u>Reacción con isocianatos seguido por cierre de anillo/hidrólisis</u>

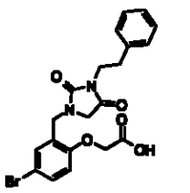
Se disuelve el aldehído (0.6 mmol) en diclorometano (6 mL), y se agrega el isocianato (1.2 mmol) y Et_3N (176 µL, 1.26 mmol). La mezcla se agita a temperatura ambiente durante la noche. Luego se agrega glicina (150 mg, 2 mmol) (como limpiador del exceso de isocianato) y la mezcla se agita adicionalmente durante 2 h. Finalmente se agrega agua y diclorometano y la fase orgánica se pasa a través de un filtro de separación de fase y entonces se evapora para dar la urea, la cual se disuelve en ácido acético (3.5 mL) y se coloca en un frasco de vidrio sellado. Entonces se agrega HCl 4 M(3.5 mL) y la mezcla se calienta en un microondas a 100° C durante 900 s. Después de enfriar a temperatura ambiente se forma un precipitado blanco, y se obtiene la hindatoina después de filtración y se lava con agua. En los casos en donde el producto no se precipita luego de la hidrólisis, se agrega diclorometano y agua a la mezcla, y la fase orgánica se pasa a través de un filtro de separación de fase. La evaporación de la fase orgánica da el producto, el cual en algunos casos se purifica

adicionalmente en una columna 1 g SAX Acetato SPE (equilibrada con 100% de MeOH y entonces se eluye con 10% AcOH en MeOH).



D139

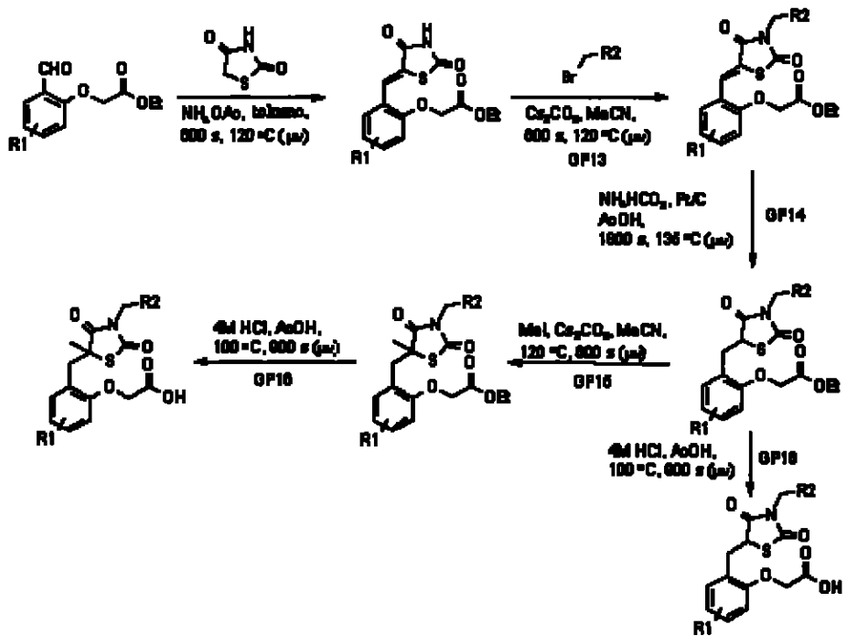
Ácido 4-Bromo-2-[3-(4-clorobencil)-2,4-dioxoimidazolidin-1-ilmetil]-fenoxiacético. Se prepara de éster de etilo de ácido 4-bromo-2-[(etoxicarbonil-metil-amino)-metil]fenoxiacético (235 mg, 0.63 mmol) y 4-clorobencil-isocianato (166 µL, 1.26 mmol) de acuerdo con GP12 (rendimiento: 183.4 mg, 62%): LC/MS (an10p8): Ta 2.3 min, *m/z* 465 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 4.05 (s, 2H), 4.48 (s, 2H), 4.55 (s, 2H), 4.73 (s, 2H), 6.92 (d, *J* = 8.3 Hz, 1H), 7.25-7.45 (m, 6H), 13.11 (br. s, 1H).



D140

Ácido 4-Bromo-2-(2,4-dioxo-3-fenetilimidazolidin-1-ilmetil)fenoxiacético. Se prepara de éster de etilo de ácido 4-bromo-2-[(etoxicarbonil-metil-amino)-metil]-fenoxi-acético y fenetilisocianato de acuerdo con GP12: LC/MS (an10p8): Ta 2.2 min, *m/z* 445 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): δ 2.84 (t, *J* = 7.2 Hz, 2H), 3.59 (t, *J* = 7.2 Hz, 2H), 3.94 (s, 2H), 4.45 (s, 2H), 4.76 (s, 2H), 6.93 (d, *J* = 8.6 Hz, 1H), 7.17-7.46 (m, 7H), 12.45 (br. s, 1H).

Ruta sintética general XI



Procedimiento general 13 (GP13)

Alquilación N

El éster de etilo de ácido 2-[2,4-dioxotiazolidin-(5Z)-ilidenemetil]fenoxiacético (0.85 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), y acetonitrilo (10 mL) se mezclan en un frasco de vidrio sellado. Se agrega entonces el agente de alquilación (1.0 mmol) y la mezcla se calienta en un microondas a 120° C durante 600 s. Se agrega agua y la mezcla se extrae con diclorometano. La fase orgánica se pasa a través de un filtro de separación de fase y entonces se evapora. El producto se utiliza directamente en la siguiente etapa o se purifica mediante cromatografía de columna (SiO_2).

Procedimiento general 14 (GP14)

Hidrogenación

La 5-bencilidenitiazolidin-2,4-diona (~0.8 mmol), ammonium formate (1.0 g, 16 mmol), Pt/C (5 wt%, 500 mg, 0.13 mmol), y ácido acético (12 mL) se mezclan en un frasco de vidrio sellado y se calienta en un microondas a 135 °C durante 1800 s. entonces metanol (15 mL) se agrega y la mezcla se filtran a través de un filtro 20 µm PE y luego a través de una columna 1 g SAX Acetate SPE, la cual se lava con metanol adicional (10 mL). Después de la evaporación del metanol, se agrega diclorometano y agua, y la fase orgánica se pasa a través de un filtro de separación de fase y se concentra para

dar el producto, el cual se utiliza directamente o se purifica mediante cromatografía de columna sobre SiO_2.

Procedimiento general 15 (GP15)

Alquilación de tiazolidin-2,4-dionas de posición 5

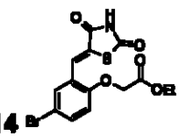
3-Alquil-5-arilmetiltiazolidin-2,4-diona (0.15 mmol), yoduro de metilo (28 □L, 0.45 mmol), Cs_2CO_3 (147 mg, 0.45 mmol), y acetonitrilo (10 mL) se mezclan en un frasco de vidrio sellado y se calientan en un microondas a 120 °C durante 3600 s. se agrega agua y diclorometano y la fase orgánica se pasa a través de un filtro de separación de fase y entonces se evapora para dar el producto, el cual se utiliza directamente para la hidrólisis.

Procedimiento general 16 (GP16)

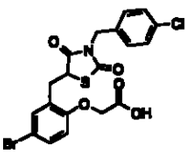
Hidrólisis de éster acídico

El fenoxiacetato de etilo (0.02-0.2 mmol) se disuelve en ácido acético (5 mL), HCl 4M (5 mL) se agrega y la mezcla se calienta en un microondas a 100 °C durante 900 s. Después de enfriar a temperatura ambiente se forma un precipitado blanco, el cual se filtra, se lava con agua y se seca para dar el producto. En los casos en donde el producto no se precipita luego de la hidrólisis, se agrega diclorometano, la fase orgánica se lava con agua y se concentra, y el residuo se purifica en una columna 1 g SAX Acetate SPE (equilibrada con 100% de MeOH y entonces se eluye con 10% AcOH en MeOH) para dar el producto.

Intermedio-14

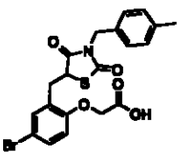


Ácido 4-Bromo-2-[2,4-dioxotiazolidinilidenemetil]fenoxiacético éster de etilo. éster de etilo de ácido 4-Bromo-2-formilfenoxiacético (2.47 g, 8.7 mmol), 2,4-tiazolidinediona (1.13 g (90%), 8.7 mmol), y acetato de amonio (671 mg, 8.7 mmol) se mezclan con tolueno (9 mL) en un frasco sellado y se calientan en un microondas a 120 °C durante 600 s. Después de enfriar a temperatura ambiente y raspar el interior del vidrio, el producto se precipita fuera. El precipitado se filtra y se lava con tolueno para dar el compuesto del título como un sólido amarillo (2.38 g, 71%).



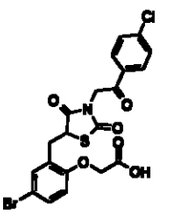
D141

Ácido 4-Bromo-2-[3-(4-clorobencil)-2,4-dioxotiazolidin-5-ilmetil]fenoxi-acético. Se prepara de 4-clorobencilbromuro y éster de etilo de ácido 4-bromo-2-[2,4-dioxotiazolidin-(5Z)-ilidenemetil]fenoxiacético de acuerdo con GP13, GP14 y GP16 para dar 50.4 mg (21% de rendimiento total) del compuesto del título: LC/MS (an10p8): Ta 2.6 min, *m/z* 482 [M - H]⁻. ^{1}H RMN (DMSO-d_6): δ 3.05 (dd, *J* = 13.8, 9.7 Hz, 1H), 3.57 (dd, *J* = 13.8, 4.9 Hz, 1H), 5.11 (dd, *J* = 9.7, 4.9 Hz, 1H), 4.67 (s, 2H), 4.75 (s, 2H), 6.91 (d, *J* = 8.7, 1H), 7.25-7.28 (m, 2H), 7.37-7.42 (m, 4H), 13.15 (br. s, 1H).



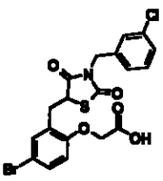
D142

Ácido 4-Bromo-2-[3-(4-metilbencil)-2,4-dioxotiazolidin-5-ilmetil]fenoxi-acético. Se prepara de 4-metilbencilbromuro y éster de etilo de ácido 4-bromo-2-[2,4-dioxotiazolidin-(5Z)-ilidenemetil]fenoxiacético de acuerdo con GP13, GP14 y GP16 (rendimiento: 14 mg, 21%): LC/MS (an10p8): Ta 2.5 min, *m/z* 462 [M - H]⁻. ^{1}H RMN (DMSO-d_6): δ 2.98-3.07 (m, 1H), 3.53-3.59 (m, 1H), 4.63 (s, 2H), 4.74 (s, 2H), 5.07-5.13 (m, 1H), 6.89-6.91 (m, 1H), 7.11-7.16 (m, 4H), 7.38-7.43 (m, 2H), 13.11 (br s, 1H).



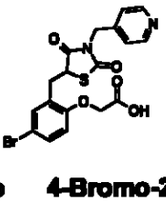
D143

Ácido 4-Bromo-2-[3-[2-(4-clorofenil)-2-oxoetil]-2,4-dioxotiazolidin-5-ilmetil]fenoxiacético. Se prepara de 2-bromo-1-(4-clorofenil)-etanona y éster de etilo de ácido 4-bromo-2-[2,4-dioxotiazolidin-(5Z)-ilidenemetil]fenoxiacético de acuerdo con GP13, GP14 y GP16 (rendimiento: 8.2 mg, 34%): LC/MS (an10p8): Ta 2.8 min, *m/z* 510 [M - H]⁻. ^{1}H RMN (DMSO-d6): δ 3.01-3.09 (m, 1H), 3.57-3.63 (m, 1H), 4.79 (s, 2H), 5.17 (s, 2H), 5.21-5.24 (m, 1H), 6.91-6.95 (m, 1H), 7.44 (m, 2H), 7.66-7.69 (m, 2H), 8.07-8.09 (m, 2H).



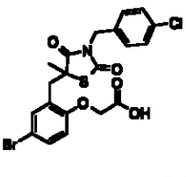
D144

Ácido 4-Bromo-2-[3-(3-clorobencil)-2,4-dioxotiazolidin-5-ilmetil]-fenoxi-acético (7d). Se prepara de 3-clorobencil bromuro y éster de etilo de ácido 4-bromo-2-[2,4-dioxotiazolidin-(5Z)-ilidenemetil]fenoxiacético de acuerdo con GP13, GP14 y GP16: LC/MS (an10p8): Ta 2.6 min, *m/z* 484 $[M + H]^+$. ^1H RMN (DMSO-*d6*): δ 3.02-3.10 (m, 1H), 3.54-3.60 (m, 1H), 4.69 (s, 2H), 4.75 (s, 2H), 5.09-5.14 (m, 1H), 6.89-6.92 (m, 1H), 7.18 (m, 1H), 7.33-7.43 (m, 5H), 13.01 (br s, 1H).



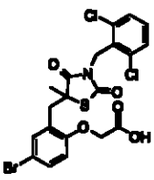
D145

Ácido 4-Bromo-2-(2,4-dioxo-3-piridin-4-ilmetiltiazolidin-5-ilmetil)fenoxi-acético. Se prepara de 4-bromometilpiridina y éster de etilo de ácido 4-bromo-2-[2,4-dioxotiazolidin-(5Z)-ilidenemetil]fenoxiacético de acuerdo con GP13, GP14 y GP16: LC/MS (an10p8): Ta 2.1 min, *m/z* 451 $[M + H]^+$.



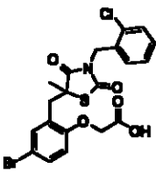
D146

Ácido 4-Bromo-2-[3-(4-clorobencil)-5-metil-2,4-dioxotiazolidin-5-ilmetil]-fenoxi-acético. Se prepara de 4-bromometilpiridina de acuerdo con GP13, GP14, GP15 y GP16 (rendimiento: 29 mg, 15%): LC/MS (an10p8): Ta 3.0 min, *m/z* 496 $[M - H]^-$; ^1H RMN (DMSO-*d6*): 1.71 (s, 3H), 3.24 (d, *J* = 13.8 Hz, 1H), 3.39 (d, *J* = 13.8 Hz, 1H), 4.63-4.68 (m, 4H), 6.86 (d, *J* = 8.6 Hz, 1H), 7.13-7.43 (m, 6H), 13.08 (br s, 1H).



D147

Ácido 4-Bromo-2-[3-(2,6-diclorobencil)-5-metil-2,4-dioxotiazolidin-5-ilmetil]fenoxiacético. Se prepara de 2,6-diclorobencilbromuro de acuerdo con GP13, GP14, GP15 y GP16 para dar 21.1 mg del compuesto del título: LC/MS (an10n8): Ta 2.9 min, *m/z* 532 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): □ 1.63 (s, 3H), 3.16 (d, *J* = 13.6 Hz, 1H), 3.40 (d, *J* = 13.6 Hz, 1H), 4.65 (s, 2H), 4.92 (s, 2H), 6.86 (d, *J* = 8.9 Hz, 1H), 7.21 (d, *J* = 2.5 Hz, 1H), 7.35-7.48 (m, 4H), 12.38 (br s, 1H).



D148

Ácido 4-Bromo-2-[3-(2-clorobencil)-5-metil-2,4-dioxotiazolidin-5-ilmetil]fenoxiacético. Se prepara de 2-clorobencilbromuro de acuerdo con GP13, GP14, GP15 y GP16 para dar 22.0 mg del compuesto del título: LC/MS (an10n8): Ta 2.8 min, *m/z* 498 [M - H]$^-$; ^{1}H RMN (DMSO-d_6): □ 1.76 (s, 3H), 3.28 (d, *J* = 13.7 Hz, 1H), 3.43 (d, *J* = 13.7 Hz, 1H), 4.67 (d, *J* = 3.2 Hz, 2H), 4.73 (s, 2H), 6.81 (d, *J* = 8.9 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 1H), 7.24-7.36 (m, 3H), 7.43-7.50 (m, 2H), 12.18 (br s, 1H).

Ensayos Biológicos

Materiales y Métodos

Generación/origen de las construcciones de cADN. La secuencia de codificación del receptor CRTH2 humano (no de acceso genbank NM_004778) se amplifica mediante PCR de una librería de cADN de hipocampo humano y se inserta en el casete de expresión pcADN3.1 (+) (Invitrogen) por vía del 5' HindIII y 3' EcoRI. Para generar una proteína de fusión (CRTH2-Rluc) luciferasa CRTH2-Renilla, la secuencia de codificación CRTH2 sin un codón de PARADA y Rluc se amplifica, se fusiona en cuadro por PCR y se subclona en el vector de expresión pcADN 3.1 (+) Zeo

(invitrogen). La β-arrestin2 (β-arr2) N-terminalmente etiquetada humana con GFP^2 (β arr2-GFP^2) y Renilla luciferasa se compran de BioSignal Packard Inc, (Montreal, Canadá). La identidad de secuencia de la construcción se verifica por restricción de digestos de endonucleasa y secuenciamiento en ambas direcciones en Prisma ABI (Applied Biosystems, Foster City, CA).

ID de Secuencia CRTH2 (secuencia de proteína)

MSANATLKPLCPILEQMSRLQSHSNTSIRYIDHAAVLLHGLASLLGLVEN
GVILFVVGCRMRQTVVTTWVLHLALSDLLASASLPFFTYFLAVGHSWELG
TTFCKLHSSIFFLNMFASGFLLSAISLDRCLQVVRPVWAQNHRTVAAAHK
VCLVLWALAVLNTVPYFVFRDTISRLDGRIMCYYNVLLLNPGPDRDATCN
SRQAALAVSKFLLAFLVPLAIIASSHAAVSLRLQHRGRRRPGRFVRLVAA
VVAAFALCWGPYHVFSLLEARAHANPGLRPLVWRGLPFVTSLAFFNSVAN
PVLYVLTCPDMLRKLRRSLRTVLESVLVDDSELGGAGSSRRRRTSSTARS
ASPLALCSRPEEPRGPARLLGWLLGSCAASPQTGPLNRALSSTSS

ID de Secuencia CRTH2 (secuencia de nucleótido):

atgtcggc
caacgccaca ctgaagccac tctgccccat cctggagcag atgagccgtc tccagagcca
cagcaacacc agcatccgct acatcgacca cgcggccgtg ctgctgcacg ggctggcctc
gctgctgggc ctggtggaga atggagtcat cctcttcgtg gtgggctgcc gcatgcgcca
gaccgtggtc accacctggg tgctgcacct ggcgctgtcc gacctgttgg cctctgctic
cctgcccttc ttcacctact tcttggccgt gggccactcg tgggagctgg gcaccacctt
ctgcaaactg cactcctcca tctcttict caacatgttc gccagcggct tcctgctcag
cgccatcagc ctggaccgct gcctgcaggt ggtgcggccg gtgtgggcgc agaaccaccg
caccgtggcc gcggcgcaca aagtctgcct ggtgctttgg gcactagcgg tgctcaacac
ggtgccctat ttcgtgttcc gggacaccat ctcgcggctg gacgggcgca ttatgtgcta
ctacaatgtg ctgctcctga acccggggcc tgaccgcgat gccacgtgca actcgcgcca
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ctcgagccac gcggccgtga gcctgcggtt gcagcaccgc ggccgccggc ggccaggccg
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gcgcgggctg cccttcgtca ccagcctggc cttcttcaac agcgtggcca acccggtgct
ctacgtgctc acctgccccg acatgctgcg caagctgcgg cgctcgctgc gcacggtgct
ggagagcgtg ctggtggacg acagcgagct gggtggcgcg ggaagcagcc gccgccgccg

cacctcctcc accgcccgct cggcctcccc ttagctctc tgcagccgcc cggaggaacc
gcggggcccc gcgcgtctcc tcggctggct gctgggcagc tgcgcagcgt ccccgcagac
gggccccctg aaccgggcgc tgagcagcac ctcgagttag

Transfección y Cultivo Celular. Se hace crecer células COS-7 en medio Eagle modificado de Dulbecco (DMEM) 1885 complementado con 10% de suero bovino fetal, 100 unidades/ml penicilina, 1000µg/ml estreptomicina, y se mantiene a 37° C en 10% de una atmósfera de CO_2. Se mantiene células HEK293 en Medio Esencial Mínimo (MEM) complementado con 10% (v/v) de suero de ternero fetal inactivo caliente (HIFCS), 2mM de Glutamax™-I, 1% de aminoácidos no esenciales (NEAA), 1% de piruvato de sodio y 10 μg/ml de gentamicina. Para experimentos de unión, se transfectan transitoriamente células COS7 con el receptor CRTH2 utilizando un método de coprecipitación de ADN fosfato de calcio con la adición de cloroquina (como se describe por Holst et al., 2001◆). Para desarrollar los ensayos de Transferencia de Energía por Resonancia de Bioluminicencia (BRET) funcional, se genera un clon de célula HEK293 estable que expresa βarr2-GFP[2] y CRTH2-Rluc (células CRTH2-HEK293).

Ensayo de Unión. 24h después de transfección de las células COS-7 se siembran en placas de 96 pozos en una densidad de 30.000 células/pozo. Los experimentos de unión de competición en cuyas células se desarrollan alrededor de 18-24 h después de utilizar 0.1 nM [^{3}H]PGD2 (NEN, 172 Ci/mmol) en un amortiguador de unión que consiste de HBSS (GIBCO) y 10 mM HEPES. Se diluyen ligandos de competición en DMSO que se mantienen constantes en 1% (v/v) del volumen de incubación final. Se determina la unión no específica y total en la ausencia y presencia de 10 μM PGD2. Se conducen rutinariamente reacciones de unión durante 3h a 4° C y se terminan mediante 2 lavadas (100 μl cada una) con hielo junto con amortiguador. La radioactividad de determina mediante conteo de centelleo líquido en un TOPCOUNTER (Packard) seguido por incubación en la noche en Microscint 20. Se siembran células HEK293 estables en una densidad de 30000 células/pozo 18-24h antes del ensayo de unión que se desarrolla esencialmente como se describe para las células CSO7 anteriores. Se hace las determinaciones en duplicados.

Ensayo BRET. Se desarrollan ensayos BRET funcionales en las células HEK293 establemente que expresan el CRTH2-RUC y GFP[2]-β-arr2 humano. Antes de su uso

en células de ensayo BRET se separa y resuspenden en D-PBS con 1000 mg/L L-Glucosa en una densidad de $2x10^6$ células/mL. Se diluye DeepBlueC™ a 50 µM en D-PBS con 1000 mg/L L-Glucosa (sensible a la luz). 100 µL de suspensión celular se transfiere a pozos en una microplaca de 96 pozos (blanco OptiPlate) y colocado en el instrumento Mithras LB 940 (BERTHOLD TECHNOLOGIES, Bad Wildbad, Alemania). Agonista de 12 µL/pozo se inyecta luego mediante el inyector 1 y 10 µL/pozo DeepBlueC™ se inyecta simultáneamente mediante el inyector 2. Cinco segundos después de las inyecciones se mide la salida de la luz del pozo secuencialmente a 400 nm y 515 nm, y la señal BRET (índice mBRET) se calcula por el índice de fluorescencia emitida por el GFP^2-β-arr2 (515 nm) sobre la luz emitida por el receptor-Rluc (400 nm). Se agregan antagonistas antes de colocar las microplacas en el Mithras LB 940 y se le permite incubar durante 15 minutos antes de la adición de agonista y DeepBlueC™. Se disuelven los compuestos en DMSO y la concentración de DMSO final se mantiene constante en 1% en el ensayo.

Ensayo de cambio de forma eosinófilo humana. La sangre se muestrea de voluntarios saludables de acuerdo con un protocolo aprobado por el Ethics Committee de la Universidad de Graz y procesados según se describió previamente (Bohm et al., 2004). Preparaciones de Leucocitos polimorfonucleares (que contienen eosinófilos y neutrófilos) se preparan mediante sedimentación de dextrano de sangre completa citrada y gradientes de Histopaque. Las células resultantes se lavan y resuspenden en amortiguador de ensayo (que comprenden PBS con Ca^{2+}/Mg^{2+} complementado con 0.1% BSA, 10 mM HEPES y 10 mM glucosa, pH 7.4) en 5 x 10^6 células/mL. Las células se incuban con los antagonistas o vehículo (PBS o DMSO) durante 10 min a 37° C y luego estimulado con varias concentraciones de los agonistas (PGD2 o eotaxin) durante 4 min a 37° C. Para retener la reacción, se transfieren las muestras a hielo y se fijan con 250 µL de solución fija. Las muestras se analizan inmediatamente en un citómetro de flujo FACSCalibur (Becton Dickinson) y se identifican los eosinófilos de acuerdo con su autofluorescencia en los canales FL-1 y FL-2. Las respuestas a los cambios de formas se cuantifican como porcentaje de la respuesta máxima para el PGD2 o eotaxin en la ausencia de un antagonista.

Materiales

Los medios de cultivo de tejido y reactivos se compran de Gibco Invitrogen corporation (Breda, Holanda). PGD2 se obtiene de Cayman y [3H]PGD2 de NEN.

Análisis de Datos

Se desarrolla análisis de curva con el software GraphPadPrism 3.0 (Graphpad Prism Inc., San Diego, USA) y se calculan los valores IC_{50} como una medición de las potencias antagonísticas.

Referencias

Holst B, Hastrup H, Raffetseder U, Martini L, Schwartz TW. Two active molecular phenotypes of the tachykinin NK1 receptor revealed by G-protein fusions and mutagenesis. J Biol Chem. 2001 Jun 8;276(23):19793-9. Epub 2001 Feb 22.

Datos Biológicos

Se ensayan los compuestos en el ensayo de unión de receptor y el ensayo de antagonista funcional se describe adelante. Y se evalúan sus valores IC_{50}. Los compuestos se agrupan en tres clases

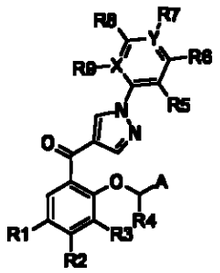
A: valor IC_{50} menor de 0.5 μM

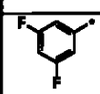
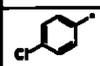
B: valor IC_{50} entre 0.5 μM y 5 μM

C: valor IC_{50} mayor de 5 μM

Las Tablas 1 a 7 den los resultados del ensayo biológico para los compuestos sintetizados anteriormente y para algunos compuestos adicionales adquiridos de fuente comerciales. La capacidad de los compuestos anteriores para inhibir la prostaglandina D2 inducida por el cambio de forma de eosinófilo se demuestra mediante los ejemplos en la Figura 1.

Tabla 1



	A	R1	R 2	R 3	R 4	R5	R6	R7	R 8	R 9	X	Y	Unión IC_{50}	Antag. IC_{50}
D1	COOH	Br	H	H	H	H	H	H	H	H	C	C	A	A
D2	COOH	H	H	H	H	H	H	H	H	H	C	C	A	B
D3	COOH	F	H	H	H	H	H	H	H	H	C	C	A	B
D4	Tetrazol	Br	H	H	H	H	H	H	H	H	C	C	A	C
D5	COOH	Ph	H	H	H	H	H	H	H	H	C	C	A	A
D6	COOH	Br	H	H	H	H	H	H	H	-	N	C	A	A
D7	COOH	Br	H	H	H	H	H	OMe	H	H	C	C	A	A
D8	COOH		H	H	H	H	H	H	H	H	C	C	A	B
D9	COOH		H	H	H	H	H	H	H	H	C	C	A	A
D10	COOH	Cl	H	H	H	H	H	H	H	H	C	C	A	B
D11	COOH	Me	H	H	H	H	H	H	H	H	C	C	A	B
D12	COOH	Cl	Me	H	H	H	H	H	H	H	C	C	B	C
D13	COOH	Cl	H	Cl	H	H	H	H	H	H	C	C	C	C
D14	COOH	Br	H	H	H	Cl	H	H	H	H	C	C	C	A
D15	COOH	Br	H	H	H	H	Cl	H	H	H	C	C	A	A
D16	COOH	Br	H	H	H	H	H	Br	H	H	C	C	A	A
D1	COOH	Br	H	H	H	H	H	Cl	H	H	C	C	A	A

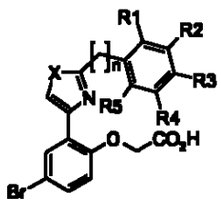
7														
D18	COOH	Br	H	H	H	Et	H	H	H	H	C	C	A	A
D19	COOH	NO_2	H	H	H	H	H	Cl	H	H	C	C	A	A
D20	COOH	NO_2	H	H	H	H	H	H	H	H	C	C	A	A
D21	COOH	Br	H	H	H	Br	H	H	H	H	C	C	A	A
D22	COOH	Br	H	H	H	F	H	H	H	H	C	C	A	A
D23	COOH	Br	H	H	H	CF_3	H	H	H	H	C	C	A	A
D24	COOH	Br	H	H	H	H	Br	H	H	H	C	C	A	A
D25	COOH	Br	H	H	H	H	CF_3	H	H	H	C	C	A	A
D26	COOH	Br	H	H	H	Cl	H	Cl	H	H	C	C	A	A
D27	COOH	NO_2	H	H	H	Cl	H	H	H	H	C	C	A	A
D28	COOH	NO_2	H	H	H	Br	H	H	H	H	C	C	A	A
D29	COOH	Br	H	H	H	Cl	H	H	H	Cl	C	C	A	A
D30	COOH	Et	H	H	H	Br	H	H	H	H	C	C	A	A
D31	COOH	i-Pr	H	H	H	Cl	H	H	H	H	C	C	A	A
D32	COOH	Br	H	H	H	H	H	OCF_3	H	H	C	C	A	A
D33	COOH	Br	H	H	H	Br	H	Br	H	H	C	C	A	A
D3	COOH	Br	H	H	H	Cl	H	Br	H	H	C	C	A	A

4														
D35	COOH	Br	H	H	H	Cl	H	Cl	H	Cl	C	C	A	A
D36	COOH	OMe	H	H	H	H	H	H	H	H	C	C	A	B
D37	COOH	Br	H	H	Me	H	H	H	H	H	C	C	A	A
(S)-D37	COOH	Br	H	H	Me	H	H	H	H	H	C	C	A	A
D38	COOH	Br	H	H	Me	Cl	H	H	H	H	C	C	A	A
D39	COOH	Br	H	H	Me	Cl	H	H	H	Cl	C	C	A	A
D40	COOH	Br	H	H	H	CN	H	H	H	H	C	C	A	A
D41	COOH	Br	H	H	H	OEt	H	H	H	H	C	C	A	A
D42	COOH	Br	H	H	H	Et	H	Br	H	H	C	C	A	A
D43	COOH	Br	H	H	H	OPh	H	H	H	H	C	C	A	A
D44	COOH	Br	H	H	H	SMe	H	H	H	H	C	C	A	A
D45	COOH	Br	H	H	H	Br	H	Me	H	H	C	C	A	A
D46	COOH	Br	H	H	Me	Et	H	Br	H	H	C	C	A	A
D47	COOH	Br	H	H	Me	OPh	H	H	H	H	C	C	A	A
D48	COOH	Br	H	H	Me	OEt	H	H	H	H	C	C	A	A
D4	COOH	Br	H	H	M	SMe	H	H	H	H	C	C	A	A

9					e									
D50	COOH	Br	H	H	Me	Br	H	Me	H	H	C	C	A	A
D51	COOH	Br	H	H	Me	OPh	H	H	H	H	C	C	A	A
D52	COOH	Br	H	H	H	OCF_3	H	H	H	H	C	C	A	A
D53	COOH	Et	H	H	H	Me	H	H	H	Me	C	C	A	A
D54	COOH	Br	H	H	H	Me	H	Me	H	H	C	C	A	A
D55	COOH	Br	H	H	Me	Me	H	Me	H	H	C	C	A	A
D58	COOH	Br	H	H	H	Me	H	Cl	H	H	C	C	A	A
D59	COOH	Br	H	H	H	Cl	H	H	Cl	H	C	C	A	A
D60	COOH	Br	H	H	H	OMe	H	H	H	H	C	C	A	A
D61	COOH	Br	H	H	H	H	Cl	Cl	H	H	C	C	A	A
D62	COOH	Br	H	H	Me	Me	H	Cl	H	H	C	C	A	A
D63	COOH	Br	H	H	Me	Cl	H	Cl	H	H	C	C	A	A
D64	COOH	Br	H	H	Me	H	Cl	Cl	H	H	C	C	A	A
D65	COOH	Br	H	H	Me	OMe	H	H	H	H	C	C	A	A
D66	COOH	NH_2	H	H	H	H	H	H	H	H	C	C	B	A
D67	COOH	Br	H	H	Me	Cl	H	Br	H	H	C	C	A	A
D6	COOH	Br	H	H	M	Cl	H	Cl	H	Cl	C	C	A	A

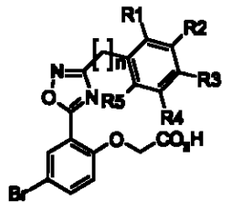
8					e									
D69	COOH	Br	H	H	Me	Br	H	Br	H	H	C	C	A	A
D70	COOH	Br	H	H	H	Et	H	H	H	Et	C	C	A	A
D71	COOH	Br	H	H	H	Me	H	H	H	Me	C	C	A	A
D72	COOH	Br	H	H	H	Et	H	H	H	Me	C	C	A	A
D73	COOH	Br	H	H	H	i-Pr	H	H	H	H	C	C	A	A
D74	COOH	EtO	H	H	H	H	H	H	H	H	C	C	B	C
D75	COOH	n-Bu	H	H	H	H	H	H	H	H	C	C	A	C
D76	COOH	Br	H	H	H	Cl	H	H	H	Me	C	C	A	A
D77	COOH	Br	H	H	Me	Me	H	H	H	Me	C	C	A	A
D78	COOH	Br	H	H	Me	Et	H	H	H	Et	C	C	A	A
D79	COOH	Br	H	H	Me	i-Pr	H	H	H	H	C	C	A	A
D80	COOH	Br	H	H	H	Cl	H	H	H	Cl	C	N	A	A
D81	COOH	Br	H	H	H	H	H	CF_3	H	H	C	C	A	A

Tabla 2



	n	X	R1	R2	R3	R4	R5	Unión IC_{50}	Antag. IC_{50}
D83	0	O	H	H	H	H	H	A	C
D84	0	O	H	H	OMe	H	H	A	B
D85	0	O	H	H	Cl	H	H	A	C
D86	0	O	H	OMe	H	H	H	A	A
D87	0	O	H	H	OEt	H	H	A	C
D88	1	O	H	H	H	H	H	A	A
D89	1	O	H	OMe	H	H	H	A	A
D90	1	O	Cl	H	F	H	H	A	A
D91	1	O	Cl	H	H	H	Cl	A	A
D92	1	O	H	H	OMe	H	H	A	A
D93	0	S	H	H	H	H	H	A	A
D94	1	S	H	H	Cl	H	H	A	A

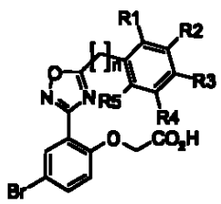
Tabla 3



	n	R1	R2	R3	R4	R5	Unión IC_{50}	Antag. IC_{50}
D99	0	H	H	H	H	H	A	A
D100	0	H	H	F	H	H	A	A
D101	0	H	H	OMe	H	H	A	A
D102	0	H	H	Cl	H	H	A	A
D103	0	H	H	OCF_3	H	H	A	A
D104	0	H	OMe	H	H	H	A	A
D105	0	H	Cl	H	H	H	A	A
D106	0	H	H	CF_3	H	H	A	A
D107	0	OMe	H	H	H	H	A	A
D108	0	Cl	H	H	H	H	A	A

D109	0	H	CF_3	H	CF_3	H	A	C
D110	0	Cl	H	H	H	Cl	A	A
D111	0	H	H	OPh	H	H	A	A
D112	0	H	CF_3	H	H	H	A	A
D113	1	H	H	OCF_3	H	H	A	A
D114	1	H	H	Cl	H	H	A	A
D115	1	H	H	H	H	H	A	A
D116	1	H	H	F	H	H	A	A
D117	1	H	F	H	F	H	A	A
D118	1	H	H	OMe	H	H	A	A
D119	1	H	OMe	H	H	H	A	A
D120	1	Cl	H	H	H	H	A	A
D121	1	Cl	H	H	H	Cl	A	A
D122	1	Cl	H	Cl	H	H	A	A
D123	1	H	Cl	Cl	H	H	A	A
D124	1	H	OMe	OMe	H	H	A	A
D125	1	H	OMe	H	H	H	A	C
D126	1	H	H	Me	H	H	A	A
D127	1	CF_3	H	H	H	H	A	A
D128	1	H	OMe	H	OMe	H	A	B
D129	0	Cl	H	Cl	H	H	A	A
D130	1	H	Cl	H	H	H	A	A
D131	1	H	H	NHAc	H	H	A	A

Tabla 4



	n	R1	R2	R3	R4	R5	Actividad	Unión IC_{50}	Antag. IC_{50}
D134	0	H	H	4-PhOMe	H	H	A	A	A
D135	0	H	H	Cl	H	H	A	A	A
D136	0	H	Cl	H	H	H	A	A	A

D137	0	Cl	H	H	H	H	A	A	A
D138	0	H	H	H	H	H	A	A	C

Tabla 5

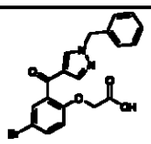
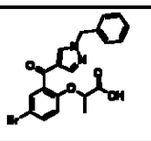
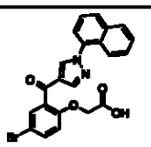
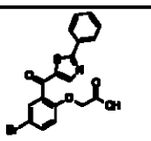
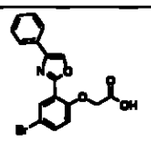
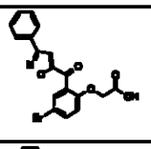
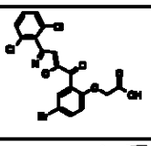
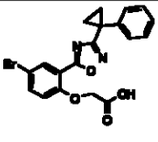
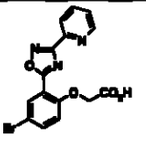
	Estructura	Unión IC_{50}	Antag. IC_{50}
D56		A	A
D57		A	A
D82		A	A
D95		A	A
D96		A	B
D97		A	A
D98		A	
D132		A	A
D133		A	C

Tabla 6

	Estructura	Unión	Antag.

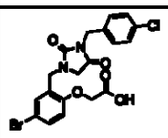
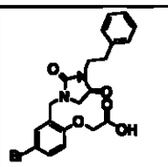
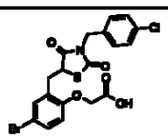
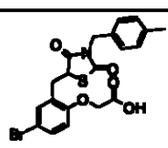
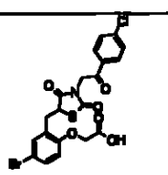
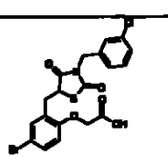
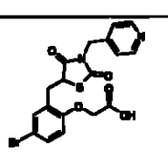
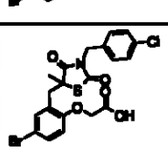
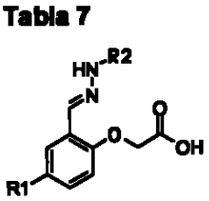
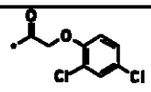
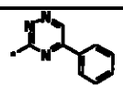
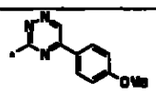
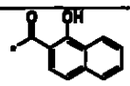
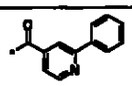
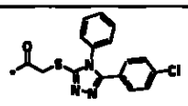
		IC_{50}	IC_{90}
D139		A	A
D140		A	B
D141		A	A
D142		A	A
D143		A	A
D144		A	A
D145		A	A
D146		A	A

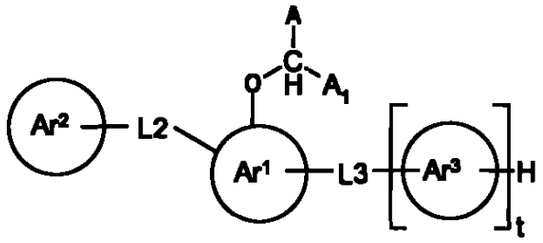
Tabla 7



Cmp	R1	R2	Unión IC_{50}	Antag. IC_{50}
D149	H		A	A
D150	Br		A	C
D151	Br		A	C
D152	Br		A	B
D153	H		B	C
D154	H		A	A
D155	H		A	B
D156	H		A	B

Reivindicaciones:

1. El uso de un compuesto de fórmula (I) o una sal, hidrato o solvato de este en la fabricación de una composición para el tratamiento de enfermedad sensible a la modulación de actividad de receptor CRTH2:



(I)

en donde

A representa un grupo carboxilo –COOH, o a bioisóstero carboxilo;

A_1 es hidrógeno o metilo;

el anillo Ar^1 es un anillo fenilo opcionalmente sustituido o un anillo heteroarilo monocíclico de 5 a 6 miembros, en el cual AA_1CHO- y L2 se unen a los átomos del anillo adyacente;

los anillos Ar^2, Ar^3 cada uno representa independientemente un fenilo o anillo heteroarilo monocíclico de 5 a 6 miembros, o un sistema de anillo bicíclico que consiste de un anillo carbocíclico de 5 o 6 miembros o anillo heterocíclico que está benzo-fusionado o fusionado a un anillo heteroarilo monocíclico de 5 o 6 miembros, dicho anillo o sistema de anillo es opcionalmente sustituido

t es 0 o 1;

L2 y L3 cada uno independientemente representa un radical divalente de fórmula $–(Alq^1)_m–(Z)_n–(Alq^2)_p$ en donde

m, n y p son independientemente 0 o 1,

Alq^1 y Alq^2 son independientemente radicales alquileno C_1-C_3 o alquenileno C_2-C_3 de cadena recta o ramificada opcionalmente sustituidos que pueden

contener un enlace –O-, -S- o –NR- compatible en donde R es hidrógeno o alquilo C_1-C_3, y

Z es –O-; -S-; -C(=O)-; -SO_2-; -SO-; -NR-, -$NRSO_2$-, SO_2NR-, -C(=O)NR-, -NRC(=O)-, -NRCONH-, -NHCONR-, -NRC(=NR)NH-, -NHC(=NR)NR-, -C(R)=N-NR-, o -NR-N=C(R)- en donde R es hidrógeno o alquilo C_1-C_3; o un radical divalente heterocíclico, carbocíclico o monocíclico de 5 a 6 miembros,

CON LA CONDICIÓN DE QUE

(A) la longitud total de L2 y L3 no excede la de una cadena saturada no ramificada de 10 átomos de carbono; y

(B) L2 no es –C(=O)-, -C(=O)NR-, o -NRC(=O)- cuando Ar^2 es fenilo opcionalmente sustituido; y

(C) (a) L2 no es un enlace y (b) p en L2 no es 0 cuando n es 1 y Z es arilo o heteroarilo, y

(D) (a) L2 no es –O-, -SO_2-, -NR-, -CHR^XR^Y- o –$CH(R^X)(OR^Y)$-, en donde R^X y R^Y son independientemente hidrógeno, halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, o cicloalquilo C_3-C_7, o se unen para formar un anillo, y (b) cuando p es 1 y n es 1 y Z es arilo o heteroarilo entonces Alq^2 no es -CHR^XR^Y- o –$CH(R^X)(OR^Y)$-, en donde R^X y R^Y son independientemente hidrógeno, halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, o cicloalquilo C_3-C_7, o se unen para formar un anillo.

2. Un método para el tratamiento de una enfermedad sensible a la modulación de actividad de receptor CRTH2 comprende administrar a un sujeto que sufre de dicha enfermedad y una cantidad efectiva de un compuesto como se define en la reivindicación 1.

3. Uso como se reivindica en la reivindicación 1 o un método como se reivindica en la reivindicación 2, en donde , en el compuesto (I), (I) la longitud de cada uno de L2 y L3 no excede la de una cadena saturada no ramificada de 5 átomos de carbono y (II) la longitud total de L2 y L3 no excede la de una cadena saturada no ramificada de 7

átomos de carbono, y (iii) ninguna de L2 y L3 incluye más de dos sustituyentes R diferentes de hidrógeno,

4. Uso o un método como se reivindica en una cualquiera de las reivindicaciones precedentes en donde, en el compuesto (I), A_1 es hidrógeno y Z es –O-; -S-; -C(=O)-; -SO_2-; -SO-; -NR-, -$NRSO_2$- -C(=O)NR-, -NRCONH-, -NRC(=NR)NH-, o –C(R)=N-NR-, en donde R es hidrógeno o alquilo C_1-C_3; o un radical divalente heterocíclico, carbocíclico o monocíclico de 5 a 6 miembros.

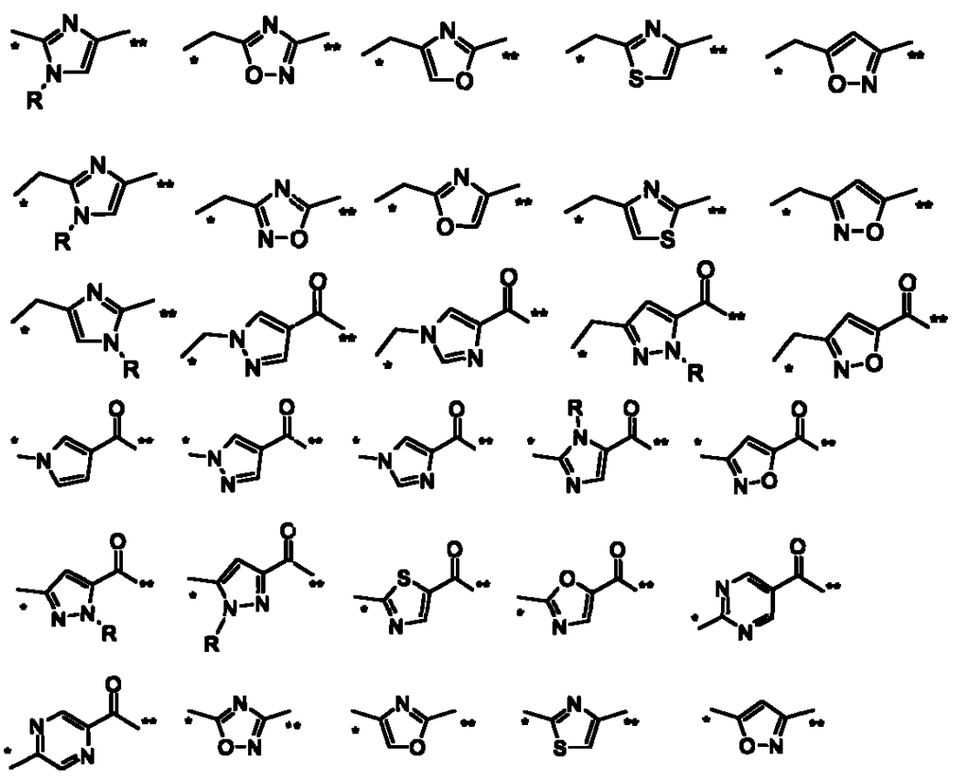
5. El uso o un método como se reivindica en una cualquiera de las reivindicaciones 1 a 4 en donde, en el compuesto (I), L2 es -N=CR-, -OCR_2C(=O)NR-N=CR-, -C(=O)NR-, -N=CR-, -C(=O)-, -CH=CHC(=O)-, -$(CH_2)_{0-3}$NRC(=O)-, -NRC(=O)$(CH_2)_{0-3}$-, –O-N=CH-, -CH_2NRCH_2-, -$NR(CH_2)_{1-3}$-, -$(CH_2)_{1-3}$NR-, -S-, -CH_2OCH_2-, -$O(CH_2)_{1-3}$-, -$(CH_2)_{1-3}$O-, -CH_2SCH_2-, -$S(CH_2)_{0-3}$-, -$(CH_2)_{0-3}$S-, un radical alquileno (C_2-C_8) divalente, un radical alquenileno (C_2-C_8) divalente, o un radical (C_2-C_8) alquinileno divalente, en donde R es hidrógeno o alquilo C_1-C_3.

6. El uso o un método como se reivindica en una cualquiera de las reivindicaciones 1 a 4 en donde, en el compuesto (I), L2 es –NRN=CH-, -ON=CH-, o -N=CH-.

7. El uso o un método como se reivindica en una cualquiera de las reivindicaciones 1 a 4 en donde, en el compuesto (I), L2 es –C(=O)-.

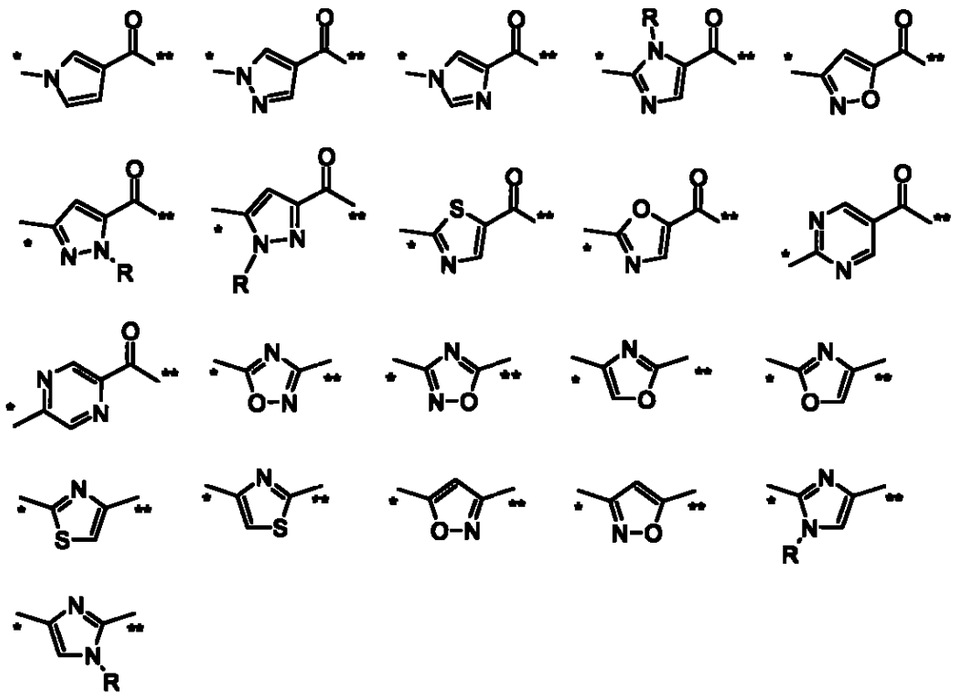
8. El uso o un método como se reivindica en una cualquiera de las reivindicaciones 1 a 4 en donde, en el compuesto (I), L2 es –NHC(=O)- o –C(=O)NH-.

9. El uso o un método como se reivindica en una cualquiera de las reivindicaciones 1 a 4 en donde, en el compuesto (I), L2 es un radical divalente seleccionado de una de las siguientes fórmulas, en donde cada uno de (I) el enlace marcado * está unido a Ar^2 mientras que el enlace marcado ** está unido a Ar^1, o (II) el enlace marcado * está unido a Ar^1 mientras que el enlace marcado ** está unido a Ar^2:



en donde R es hidrógeno o alquilo C_1-C_3.

10. El uso o método como se reivindica en la reivindicación 9 en donde, en el compuesto (I), A1 es hidrógeno y L2 has una de las siguientes fórmulas en donde el enlace marcado * está unido a Ar^2 mientras que el enlace marcado ** está unido a Ar^1:



en donde R es hidrógeno o alquilo C_1-C_3.

11. El uso o método como se reivindica en una cualquiera de las reivindicaciones precedentes en donde la enfermedad está asociada con un elevado nivel de prostaglandina D2 (PGD2) o uno o más metabolitos activos de estos.

12. El uso o método como se reivindica en una cualquiera de las reivindicaciones 1 a 10 en donde la enfermedad es una enfermedad inflamatoria, autoinmune, respiratoria o alérgica.

13. El uso o método como se reivindica en una cualquiera de las reivindicaciones 1 a 10 en donde la enfermedad se selecciona de asma, rinitis, síndrome alérgico de vías aéreas, ridobronquitis alérgica, bronquitis, enfermedad pulmonar obstructiva crónica (COPD), poliposis nasal, sarcoidosis, pulmón de campesino, pulmón fibroide, fibrosis cística, tos crónica, conjuntivitis, dermatitis atópica, enfermedad de Alzheimer,

esclerosis lateral amiotrófica, complejo de demencia de SIDA, enfermedad de Huntington, demencia frontotemporal, demencia del cuerpo Lewy, demencia vascular, síndrome de Guillain-Barre, poliradiculoneuropatía desmielinizante crónica, neuropatía motora multifocal, plexopatía, esclerosis múltiple, encefalomielitis, panencefalitis, degeneración cerebelar y en encefalomielitis, trauma del CNS, migraña, ataques, artritis reumatoide, espondilitis anquilosante, enfermedad de Behçet's, bursitis, síndrome del túnel carpiano, enfermedad del intestino inflamatorio, enfermedad de Crohn, colitis ulcerativa, dermatomiositis, Síndrome de Ehlers-Danlos (EDS), fibromialgia, dolor miofacial, osteoartritis (OA), osteonecrosis, artritis soriática, síndrome de Reiter (artritis reactiva), sarcoidosis, esclerodermo, Síndrome de Sjogren, enfermedad de tejido blando, Enfermedad de Still, tendinitis, poliarteritis Nodossa, Granulomatisis de Wegener, miositis (polimiositis dermatomiositis), gota, arteroscleroses, lupus eritematoso, lupus sistémico eritematoso (SLE), diabetes tipo I, síndrome nefrítico, glomerulonefritis, falla renal aguda y crónica, fascitis eosinofilia, síndrome hiper IgE, sepsis, choque séptico, daño por reperfusión isquémica en el corazón, rechazo de aloinjerto después de transplantes, y síndrome del injerto contra el hospedador.

14. El uso o método como se reivindica en una cualquiera de las reivindicaciones 1 a 10 en donde la enfermedad incluye asma, rinitis, síndrome alérgico de vías aéreas, y ridobronquitis alérgica.

15. El uso o un método como se reivindica en una cualquiera de las reivindicaciones precedentes en donde, en el compuesto (I), el anillo Ar^2 es (I) an fenilo opcionalmente sustituido o anillo naftilo; (ii) un anillo fenilo fusionado a un anillo heterocíclico que contiene nitrógeno de 5 a 6 miembros, cualquiera o ambos de dichos anillos son opcionalmente sustituidos; (iii) un anillo heteroarilo que contiene nitrógeno de 5 a 6 miembros opcionalmente sustituido; o (iv) un anillo heterocíclico de 5 a 6 miembros que contienen nitrógeno fusionado a un anillo fenilo cualquiea de los tales anillos son opcionalmente sustituidos.

16. El uso o método como se reivindica en la reivindicación 15 en donde, en el compuesto (I), el anillo Ar^2 es fenilo opcionalmente sustituido, piridilo, pirimidilo, diazolilo, tiazolilo, oxazolilo, triazinilo, quinolinilo, pyrrolilo, furanilo, tiazolil.

17. V como se reivindica en la reivindicación 15 o reivindicación 16 en donde, en el compuesto (I), sustituyentes opcionales en Ar^2 se seleccionan de flúor, cloro, bromo, alquilo (C_1-C_3), trifluorometilo, alkoxi (C_1-C_3), trifluorometoxi, trifluorometiltio, dimetilamino, ciano, (alquil C_1-C_3)SO_2-, NH_2SO_2-, (alquil C_1-C_3)$NHSO_2$-, (alquil C_1-C_3)$_2NSO_2$-, y nitro.

18. El uso o un método como se reivindica en una cualquiera de las reivindicaciones precedentes en donde, en el compuesto (I), Ar^1 es un anillo heteroarilo que contiene nitrógeno de 5 o 6 miembros, opcionalmente sustituido.

19. El uso o método como se reivindica en cualquiera de las reivindicaciones 1 a 17 en donde en el compuesto (I), Ar^1 es un anillo fenilo y L3 está unido a la posición 4 de este relativo al radical $ACHA_1O$-.

20. El uso o un método como se reivindica en una cualquiera de las reivindicaciones precedentes en donde en el compuesto (I), t es 1 y Ar^3 es un anillo heteroarilo de 5 o 6 miembros, opcionalmente sustituido.

21. El uso o un método como se reivindica en una cualquiera de las reivindicaciones precedentes en donde en el compuesto (I), t es 1 y Ar^3 es un anillo fenilo, opcionalmente sustituido.

22. El uso o un método como se reivindica en una cualquiera de las reivindicaciones precedentes en donde en el compuesto (I), cualquier sustituyente opcional en el anillo Ar^1 o Ar^3 se seleccionan de flúor, cloro, bromo, yodo, ciano, nitro, trifluorometilo, trifluorometoxi, trifluorometiltio, (alquil C_1-C_3)SO_2-, NH_2SO_2-, (alquil C_1-C_3)$NHSO_2$-, (alquil C_1-C_3)$_2NSO_2$-, alquilo C_1-C_6, alkoxi C_1-C_6, cicloalquilo, arilo, ariloxi, aril(C_1-C_6)- o aril(alkoxi C_1-C_6)-.

23. El uso o método como se reivindica en cualquiera de las reivindicaciones 1 a 19 en donde en el compuesto (I), t es 0 y L3 es un enlace.

24. El uso o un método como se reivindica en una cualquiera de las reivindicaciones precedentes en donde, en el compuesto (I), A es –COOH.

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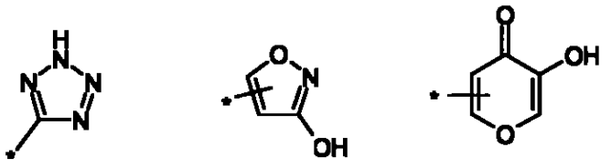
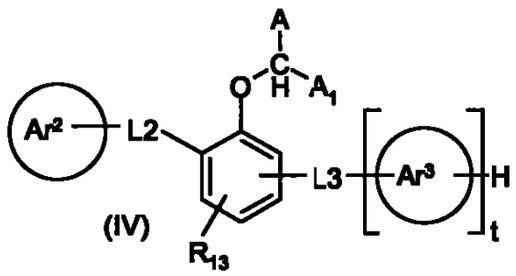
25. El uso o método como se reivindica en cualquiera de las reivindicaciones 1 a 23 en donde, en el compuesto (I), A es a bioisóstero carboxilo seleccionado de -SO_2NHR y -P(=O)(OH)(OR) en donde R es hidrógeno metilo o etilo, -SO_2OH, -$P(=O)(OH)(NH_2)$, –C(=O)NHCN y grupos de fórmulas:



26. El uso o un método como se reivindica en una cualquiera de las reivindicaciones precedentes en donde, en el compuesto (I), A_1 es hidrógeno.

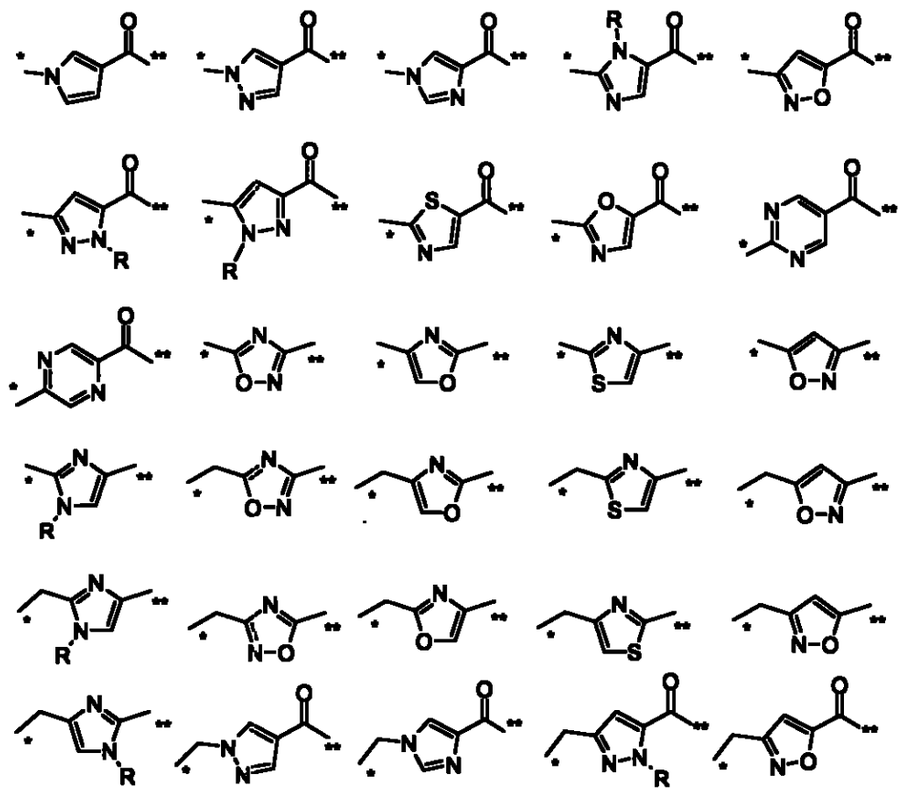
27. Un compuesto de fórmula (IV) o una sal, hidrato o solvato de este



en donde A, A_1, L3, Ar^3, Ar^2, y t son como se define en la reivindicación 1 o reivindicación 2,

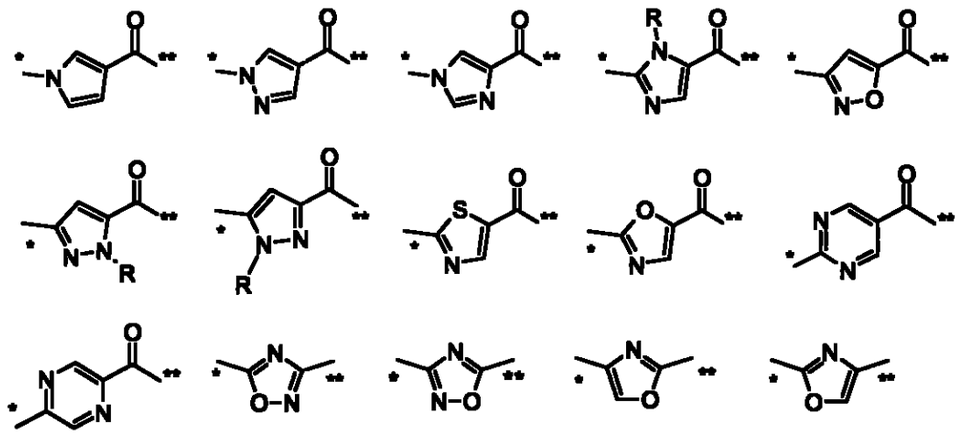
R_{13} representa hidrógeno o uno o más sustituyentes opcionales,

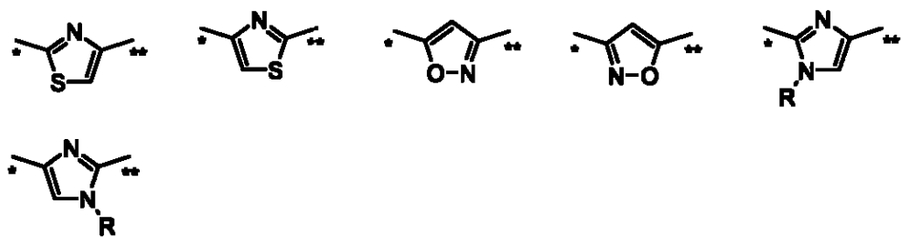
L2 es un radical divalente seleccionado del siguiente en donde cada uno de (I) el enlace marcado * está unido a Ar^2 mientras que el enlace marcado ** está unido a Ar^1, o (II) el enlace marcado * está unido a Ar^1 mientras que el enlace marcado ** está unido a Ar^2:



en donde R es hidrógeno o alquilo C_1-C_3.

28. Un compuesto como se reivindica en la reivindicación 26 en donde A_1 es hidrógeno y L2 se selecciona del siguiente en donde el enlace marcado * está unido a Ar^2 mientras que el enlace marcado ** está unido a Ar^1:

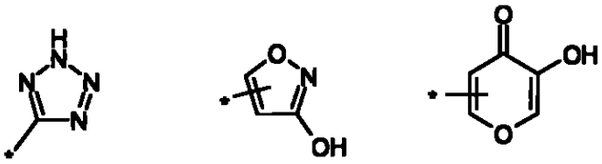




en donde R es hidrógeno o alquilo C_1-C_3.

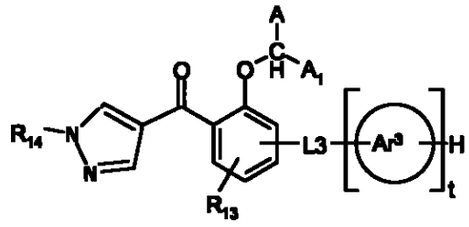
29. Un compuesto como se reivindica en la reivindicación 27 o reivindicación 28 en donde A es –COOH.

30. Un compuesto como se reivindica en la reivindicación 27 o reivindicación 28 en donde A es un bioisóstero carboxilo seleccionado de $-SO_2NHR$ y $-P(=O)(OH)(OR)$ en donde R es hidrógeno metilo o etilo, $-SO_2OH$, $-P(=O)(OH)(NH_2)$, $–C(=O)NHCN$ y grupos de fórmulas:



31. Un compuesto como se reivindica en cualquiera de las reivindicaciones 27 a 30 en donde R_{13} representa uno o más sustituyentes seleccionados de flúor, cloro, bromo, yodo, ciano, nitro, trifluorometilo, trifluorometoxi, trifluorometiltio, (alquil C_1-C_3)SO_2-, NH_2SO_2-, (alquil C_1-C_3)$NHSO_2$-, (alquil C_1-C_3)$_2NSO_2$-, alquilo C_1-C_6, alkoxi C_1-C_6, cicloalquilo, arilo, ariloxi, aril(C_1-C_6)- o aril(alkoxi C_1-C_6)-.

32. Un compuesto de fórmula (IVA) o una sal, hidrato o solvato de este



(IVA)

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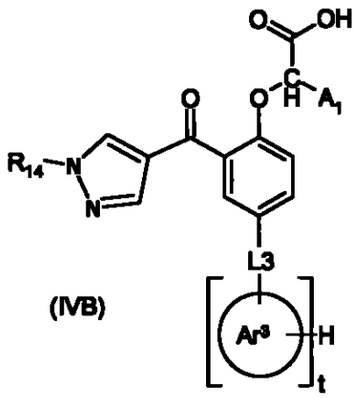
en donde A, L3, t, Ar^3, R_{13} son como se define en cualquiera de las reivindicaciones 26 a 30 y R_{14} es fenilo opcionalmente sustituido o heteroarilo de 5 o 6 miembros.

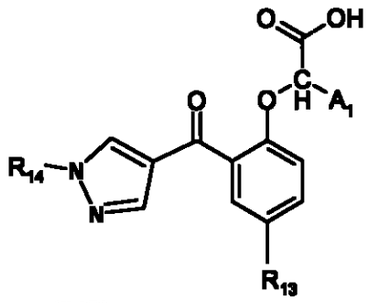
33. Un compuesto de fórmula (IVB) o una sal hidrato o solvato de este



(IVB)

en donde L3, t, y Ar^3 son como se define en cualquiera de las reivindicaciones 26 a 30 y R_{14} es fenilo opcionalmente sustituido o heteroarilo de 5 o 6 miembros.

34. Un compuesto de fórmula (IVC) o un sal hidrato o solvato de este



(IVC)

en donde R_{13} representa un sustituyente seleccionado de flúor, cloro, bromo, yodo, alquilo (C_1-C_6), trifluorometilo, alkoxi (C_1-C_6), alquilmercapto (C_1-C_6), trifluorometoxi, trifluorometilitio, dimetilamino, ciano, (alquil C_1-C_3)SO_2-, NH_2SO_2-, (alquil C_1-C_3)$NHSO_2$-, (alquil C_1-C_3)$_2NSO_2$-, y nitro, y R_{14} es fenilo opcionalmente sustituido o heteroarilo de 5 o 6 miembros.

35. Un compuesto como se reivindica en la reivindicación 34 en donde R_{14} es un anillo fenilo 2-sustituido, 2,4-disustituido, 2,6-disustituido o 2,4,6-trisustituido en donde

los sustituyentes se seleccionan de flúor, cloro, bromo, yodo, alquilo (C_1-C_6), trifluorometilo, alkoxi (C_1-C_6), alquilmercapto (C_1-C_6), trifluorometoxi, trifluorometiltio, dimetilamino, (alquil C_1-C_3)SO_2-, NH_2SO_2-, (alquil C_1-C_3)$NHSO_2$-, (alquil C_1-C_3)$_2NSO_2$-, y ciano

36. Un compuesto como se reivindica en la reivindicación 34 en donde R_{14} es un anillo fenilo 2-sustituido, 2,4-disustituido, o 2,6-disustituido en donde los sustituyentes se seleccionan de flúor, cloro, alquilo (C_1-C_6), trifluorometilo, alkoxi (C_1-C_6), alquilmercapto (C_1-C_6), trifluorometoxi, trifluorometiltio, y ciano.

37. Un compuesto como se reivindica en la reivindicación 34 en donde R_{14} es un anillo piridilo 2-sustituido o 2,6-disustituido en donde los sustituyentes se seleccionan de flúor, cloro, alquilo (C_1-C_6), trifluorometilo, alkoxi (C_1-C_6), alquilmercapto (C_1-C_6),, trifluorometoxi, trifluorometiltio, y ciano.

38. Un compuesto como se reivindica en la reivindicación 34 en donde R_{13} es seleccionado de flúor, cloro, bromo, yodo, alquilo (C_1-C_6), alkoxi (C_1-C_6), trifluorometoxi y trifluorometiltio, y R_{14} es fenilo opcionalmente sustituido o opcionalmente sustituido heteroarilo de 5 o 6 miembros.

39. Un compuesto como se reivindica en cualquiera de las reivindicaciones 27 a 38 en donde A_1 es hidrógeno.

40. Un enantiómero de un compuesto como se reivindica en cualquiera de las reivindicaciones 27 a 38 en donde A_1 es metilo, y el átomo de carbono al cual este está unido tiene la configuración estereoquímica S.

41. Un compuesto como se reivindica en la reivindicación 27 se selecciona del grupo que consiste de:

Ácido 4-cloro-2-(1-fenil-1H-pirazol-4-carbonil)fenoxiacético,
Ácido 4-bromo-2-(1-fenil-1H-pirazol-4-carbonil)fenoxiacético,
Ácido [4-bromo-2-(1-piridin-2-il-1H-pirazol-4-carbonil)fenoxi]acético,
Ácido {4-bromo-2-[1-(2-clorofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {4-bromo-2-[1-(3-clorofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {4-bromo-2-[1-(4-bromofenil)-1H-pirazol-4-carbonil]fenoxi}acético,

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Ácido {4-bromo-2-[1-(4-clorofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {4-bromo-2-[1-(2-etilfenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {4-bromo-2-[1-(2-bromofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {4-bromo-2-[1-(2-fluorofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {4-bromo-2-[1-(2-trifluorometilfenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {4-bromo-2-[1-(3-bromofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {4-bromo-2-[1-(2,4-diclorofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {2-[1-(2-clorofenil)-1H-pirazol-4-carbonil]-4-nitrofenoxi}acético,
Ácido {4-bromo-2-[1-(2,6-diclorofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {2-[1-(2-bromofenil)-1H-pirazol-4-carbonil]-4-etilfenoxi}acético,
Ácido {4-bromo-2-[1-(2,4-dibromofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {4-bromo-2-[1-(4-bromo-2-clorofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {4-bromo-2-[1-(2,4,6-triclorofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido 2-[4-bromo-2-(1-fenil-1H-pirazol-4-carbonil)fenoxi]propiónico,
Ácido (S)-2-[4-bromo-2-(1-fenil-1H-pirazol-4-carbonil)fenoxi]propiónico,
Ácido 2-{4-Bromo-2-[1-(2-clorofenil)-1-H-pirazol-4-carbonil]fenoxi}propiónico,
Ácido (S)-2-{4-Bromo-2-[1-(2-clorofenil)-1-H-pirazol-4-carbonil]fenoxi}-propiónico,
Ácido 2-{4-Bromo-2-[1-(2,6-diclorofenil)-1H-pirazol-4-carbonil]fenoxi}propiónico,
Ácido (S)-2-{4-Bromo-2-[1-(2,6-diclorofenil)-1H-pirazol-4-carbonil]fenoxi}propiónico,
Ácido {4-Bromo-2-[1-(2-etoxifenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {4-Bromo-2-[1-(4-bromo-2-etilfenil)-1H-pirazol-4-carbonil]-fenoxi}-acético,
Ácido {4-Bromo-2-[1-(2-fenoxifenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {4-Bromo-2-[1-(2-metiltiofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {4-Bromo-2-[1-(2-bromo-4-metilfenil)-1H-pirazol-4-carbonil]fenoxi}-acético,
Ácido 2-{4-Bromo-2-[1-(4-bromo-2-etilfenil)-1H-pirazol-4-carbonil]-fenoxi}-propiónico,
Ácido 2-{4-Bromo-2-[1-(2-fenoxifenil)-1H-pirazol-4-carbonil]fenoxi}propiónico,
Ácido (S)-2-{4-Bromo-2-[1-(2-fenoxifenil)-1H-pirazol-4-carbonil]fenoxi}propiónico,
Ácido 2-{4-Bromo-2-[1-(2-metiltio)-1H-pirazol-4-carbonil]fenoxi}propiónico,
Ácido (S)-2-{4-Bromo-2-[1-(2-metiltio)-1H-pirazol-4-carbonil]fenoxi}propiónico,
Ácido {4-Bromo-2-[1-(2,4-dimetilfenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {4-Bromo-2-[1-(4-cloro-2-metilfenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {4-Bromo-2-[1-(2,5-diclorofenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido 2-{4-Bromo-2-[1-(4-cloro-2-metilfenil)-1H-pirazol-4-carbonil]fenoxi}propiónico,
Ácido 2-{4-Bromo-2-[1-(2,4,6-triclorofenil)-1H-pirazol-4-carbonil]fenoxi}-propiónico,
Ácido {4-Bromo-2-[1-(2,6-dietil-fenil)-1H-pirazol-4-carbonil]fenoxi}acético,

Ácido {4-Bromo-2-[1-(2,6-dimetilfenil)-1H-pirazol-4-carbonil]fenoxi}acético
Ácido {4-Bromo-2-[1-(2-etil-6-metilfenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {4-Bromo-2-[1-(2-cloro-6-metilfenil)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido {4-Bromo-2-[1-(3,5-dicloropiridin-4-il)-1H-pirazol-4-carbonil]fenoxi}acético,
Ácido [4-Bromo-2-(1-naftalen-1-il-1H-pirazol-4-carbonil)fenoxi]acético,
Ácido {4-Bromo-2-[2-(4-clorobencil)tiazol-4-il]fenoxi}acético,
Ácido {4-Bromo-2-[3-(4-fluoro-fenil)-[1,2,4]oxadiazol-5-il]fenoxi}acético,
Ácido {4-Bromo-2-[3-(4-metoxi-fenil)-[1,2,4]oxadiazol-5-il]fenoxi}acético,
Ácido {4-Bromo-2-[3-(4-clorofenil)-[1,2,4]oxadiazol-5-il]fenoxi}acético,
Ácido {4-Bromo-2-[3-(4-fluoro-bencil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético,
Ácido {4-Bromo-2-[3-(2,6-dicloro-bencil)-[1,2,4]oxadiazol-5-il]-fenoxi}-acético,
Ácido {4-Bromo-2-[3-(2-trifluorometilbencil)-[1,2,4]oxadiazol-5-il]fenoxi}-acético,
Ácido 4-Bromo-2-[3-(2,6-dicloro-fenil)isoxazol-5-carbonil]fenoxi}acético,
Ácido {4-Bromo-2-[3-(1-fenilciclopropil)-[1,2,4]oxadiazol-5-il]fenoxi}acético,
Ácido {4-Bromo-2-[3-(2,4-diclorofenil)-[1,2,4]oxadiazol-5-il]fenoxi}acético,

y sales, hidratos y solvatos de estos.

42. Una composición farmacéutica que comprende un compuesto como se reivindica en cualquiera de las reivindicaciones 27 a 41, junto con un portador farmacéuticamente aceptable.

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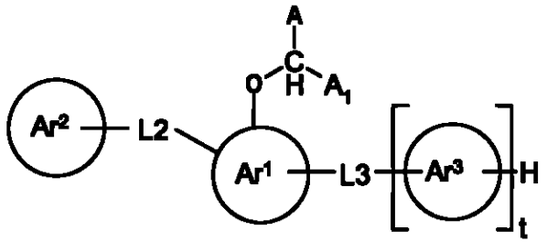
RESUMEN

Los compuestos de fórmula (I) son útiles para el tratamiento de enfermedad sensible a la modulación de actividad de receptor CRTH2, tales como asma, rinitis, síndrome alérgico de vías aéreas, y ridobronquitis alérgica:



(I)

en donde A representa un grupo carboxilo –COOH, o un bioisóstero carboxilo ; A_1 es hidrógeno o metilo; el anillo Ar^1 es un anillo fenilo opcionalmente sustituido o anillo heteroarilo monocíclico de 5 a 6 miembros, en el cual AA_1CHO- y L2 se unen a los átomos del anillo adyacente; los anillos Ar^2, Ar^3 cada uno representa independientemente un fenilo o anillo heteroarilo monocíclico de 5 a 6 miembros, o un sistema de anillo bicíclico que consiste de un anillo carbocíclico de 5 o 6 miembros o anillo heterocíclico que está benzo-fusionado o fusionado a un anillo heteroarilo monocíclico de 5 o 6 miembros, dicho anillo o sistema de anillo es opcionalmente sustituido; t es 0 o 1; L2 y L3 son radicales ligadores como se define en la descripción.

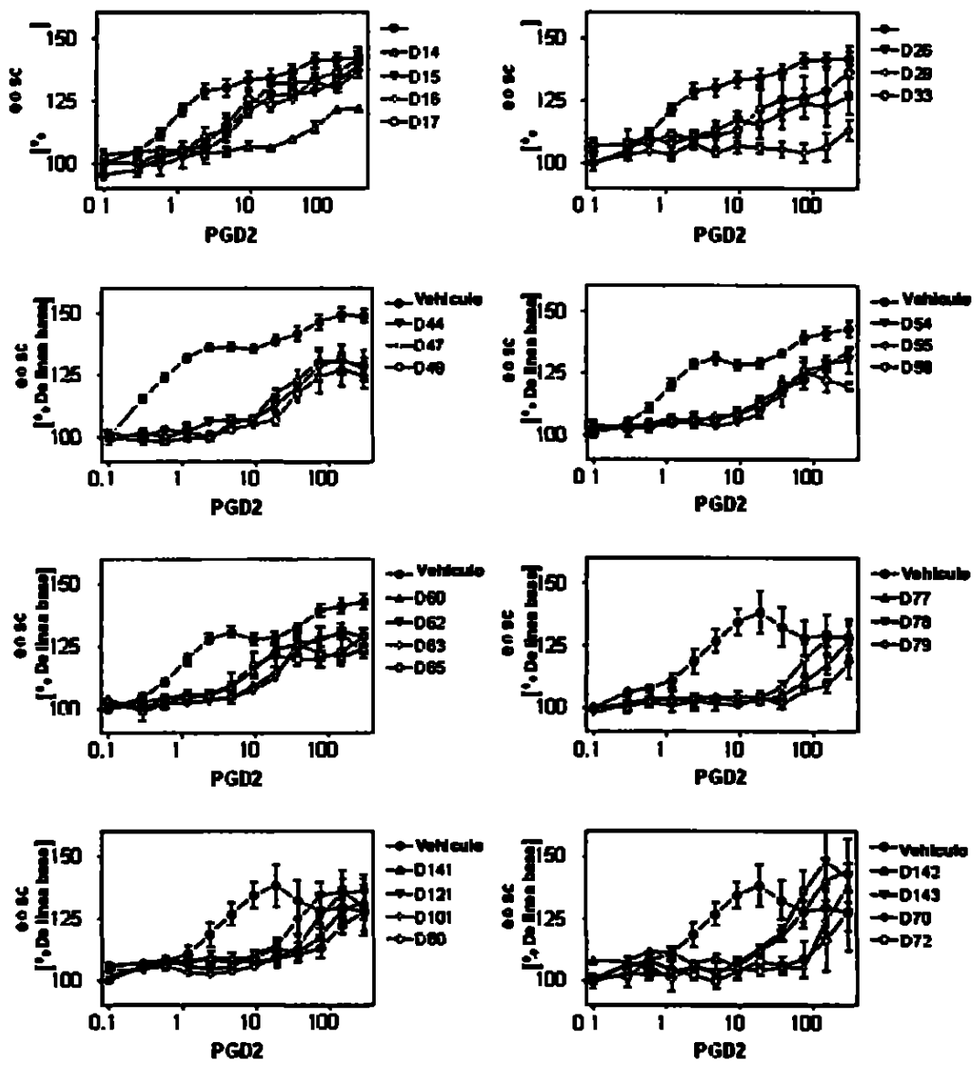

150
125
100
0.1
1
10
100
PGD2
D14
D15
D16
D17
D26
D28
D33
Vehicule
D44
D47
D49
D54
D55
D58
D60
D62
D63
D65
D77
D78
D79
D141
D121
D101
D80
D142
D143
D70
D72

Figura 1

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FORMATO DE DIGITALIZACIÓN
RELACION DE ANEXOS

Royal Technologies S.A.

Item		Expediente No 06-129545	No de Folio
		No de unidades	√
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA	1	✓
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones:
CONTIENE ANEXO FINAL

240
239

Rad: 08-129545- -00000-0000
Fec: 2006-12-27 16:27:40 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEIVE
Fol: 375 FASENACIONALI
Act: 411 PRESENTACION
Folios: 239

SUPERINTENDENCIA de Industria y Comercio

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 [ ]

Edgar Navarro

Firma Responsable

Fecha 27-12-06

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240

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
RODRIGUEZ DILIA MARIA

802

REFERENCIA	Radicación No.	06 129545
	Solicitud internacional	PCT/EP2005/005884
	Fecha inicio fase nacional	29/12/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	0 0 0 1933

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. debe aclarar el lugar de constitución de la sociedad solicitante (Art.27-c) Decisión 486.

3. 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 09 FEB. 2007
adpa10