G. H LLMANN RESTREPO
ABOGADOS LTDA.

55495

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE SIGNOS DISTINTIVOS

E. S. D.

Re: **Expediente No. 04 016637**

Solicitud de patente PCT fase nacional

Solicitud Internacional No. PCT/EP02/09221

Titular: AVENTIS PHARMA DEUTSCHLAND GMBH

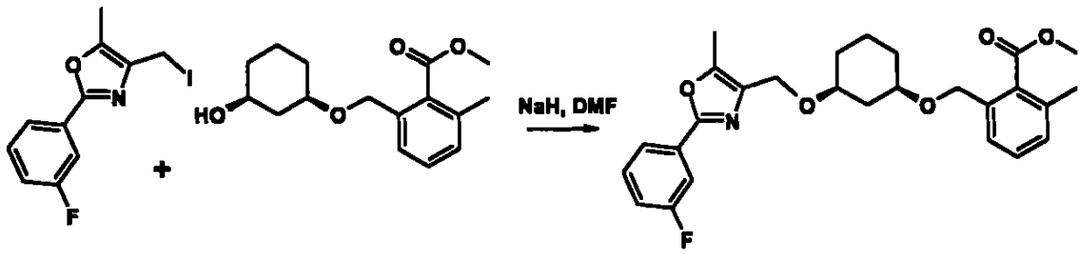
Yo, GUSTAVO HOLLMANN RESTREPO, vecino de Bogotá D.C., portador de la tarjeta profesional No. 5903, obrando como apoderado en este negocio, manifiesto a usted que acompaño al presente memorial los Ejemplos Adicionales presentados en la solicitud internacional No. PCT/EP02/09221 con su correspondiente traducción al español, para que sean agregados al expediente de la referencia.

Señor Superintendente,

GUSTAVO HOLLMANN RESTREPO
C.C. No. 2.878.023 de Bogotá
T.P. No. 5903

Additional Examples:

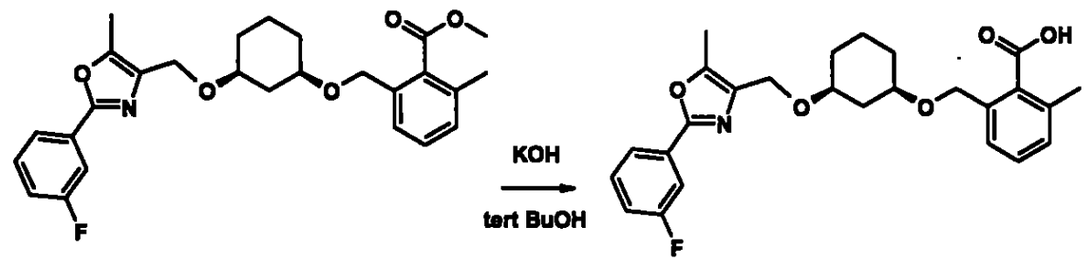
EXAMPLE XLVIII



72

[001] Methyl-2-{*1R,3S*-3-[2-(3-Fluoro-phenyl)-5-methyl-oxazol-4-ylmethoxy]-cyclohexyloxymethyl}-6-methylbenzoate (**72**)

[002] At room temperature, 50 mg of a 60% sodium hydride suspension and then 1.08 mmol of 2-(3-fluorophenyl)-4-iodomethyl-5-methyloxazole were added to a solution of 200 mg of methyl-2-(*1R,3S*-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate (**47a**) in 5 ml of dimethylformamide. After the reaction was monitored by TLC to be complete (approximately one hour), methyl tert-butyl ether (~ 30 ml) was added, and the mixture was extracted with water. The organic phase was dried over magnesium sulfate, the solvents were removed under reduced pressure and the residue was purified by RP-HPLC. This gave **72** as a light-yellow oil. $C_{27}H_{30}FNO_5$ (467.54), MS(ESI): 468 ($M + H^+$).

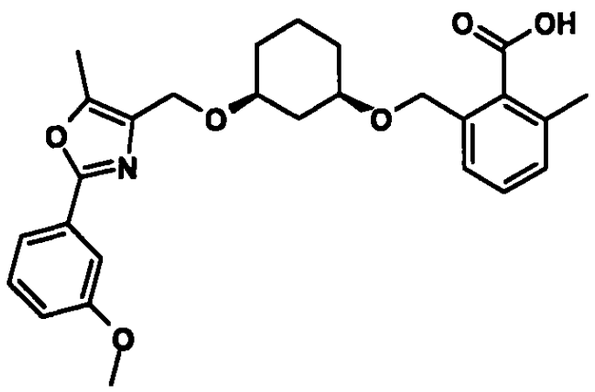


72 **73**

2-{*1R,3S*-3-[2-(3-Fluoro-phenyl)-5-methyl-oxazol-4-ylmethoxy]-cyclohexyloxymethyl}-6-methylbenzoic acid (**73**)

[003] 100 mg of **72** were stirred in a mixture of 10 ml of tert-butanol and 1 ml of 10 N aqueous potassium hydroxide solution at 90°C. After he reaction was complete according to TLC (up to two days), the mixture was acidified with hydrochloric acid and extracted with ethyl acetate. The combined organic phases were dried over magnesium sulfate, the solvents were removed under reduced pressure and the residue was purified by RP-HPLC. This gave as an amorphous solid the product **73** of molecular weight 453.52 ($C_{28}H_{28}FNO_5$), MS(ESI): 454.35 ($M + H^+$).

EXAMPLE XLIX

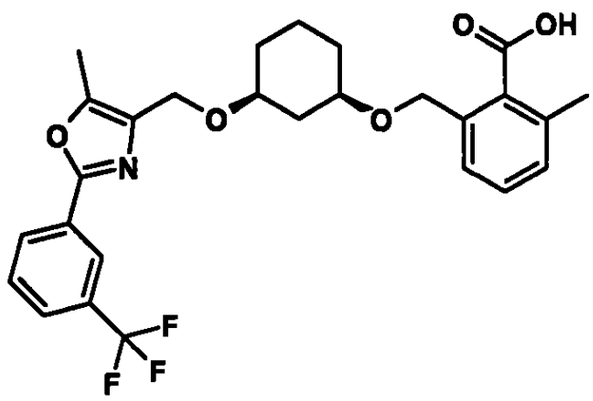


74

2-{*1R,3S*-3-[2-(3-Methoxy-phenyl)-5-methyl-oxazol-4-ylmethoxy]-cyclohexyloxymethyl}-6-methylbenzoic acid **(74)**

[004] Methyl 2-(*1R,3S*-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(3-methoxyphenyl)-4-iodomethyl-5-methyloxazole gave under the same conditions as described for **72** and **73** the product **74** of molecular weight 465.55 ($C_{27}H_{31}NO_6$), MS(ESI): 466.37 ($M + H^+$).

EXAMPLE L



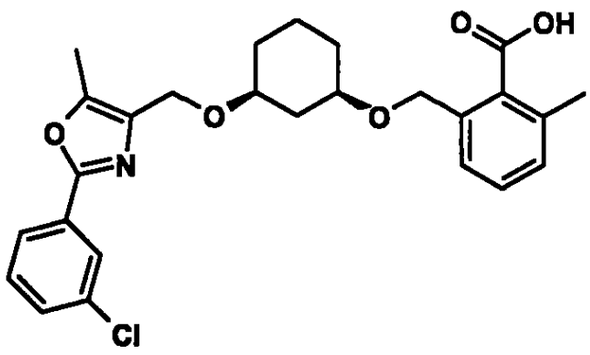
75

152

2-{1*R*,3*S*-3-[2-(3-Trifluoromethylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid (**75**)

[005] Methyl 2-(1*R*,3*S* -3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(3-trifluoromethylphenyl)-4-iodomethyl-5-methyloxazole gave under the same conditions as described for **72** and **73** the product **75** of molecular weight 503.52 ($C_{27}H_{28}F_3NO_5$), MS(ESI): 504.37 ($M + H^+$).

EXAMPLE LI

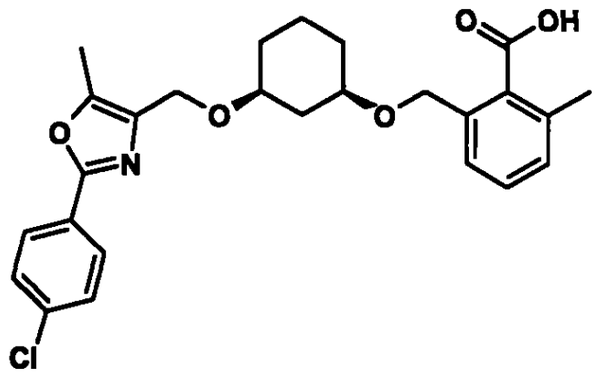


76

2-{1*R*,3*S*-3-[2-(3-Chlorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid (**76**)

[006] Methyl 2-(1*R*,3*S*-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(3-chlorophenyl)-4-iodomethyl-5-methyloxazole gave under the same conditions as described for **72** and **73** the product **76** of molecular weight 469.97 ($C_{26}H_{28}ClNO_5$), MS(ESI): 470.43 ($M + H^+$).

EXAMPLE LII

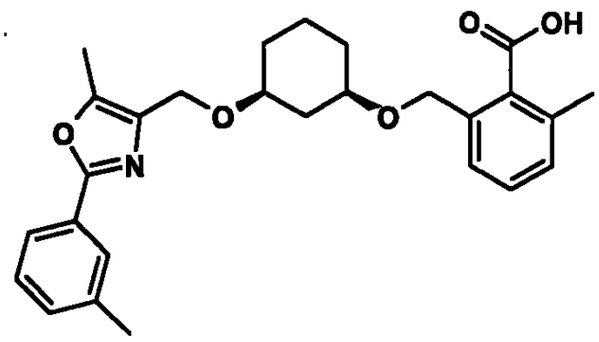


77

2-{1*R*,3*S*-3-[2-(4-Chlorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid (**77**)

[007] Methyl 2-(1*R*,3*S*-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(4-chlorophenyl)-4-iodomethyl-5-methyloxazole gave, under the same conditions as described for 72 and 73 , the product 77 of molecular weight 469.97 ($C_{28}H_{28}ClNO_5$), MS(ESI): 470.40 ($M + H^+$).

EXAMPLE LIII



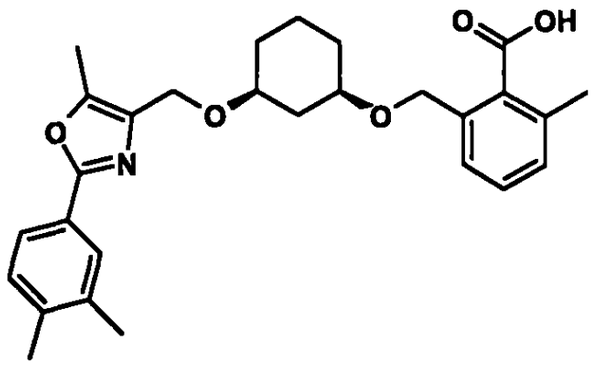
154 7

78

2-{1*R*,3*S*-3-[2-(3-Methylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid (**78**)

[008] Methyl 2-(1*R*,3*S*-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(3-methylphenyl)-4-iodomethyl-5-methyloxazole gave, under the same conditions as described for **72** and **73** the product **78** of molecular weight 449.55 ($C_{27}H_{31}NO_5$), MS(ESI): 450.53 ($M + H^+$).

EXAMPLE LIV



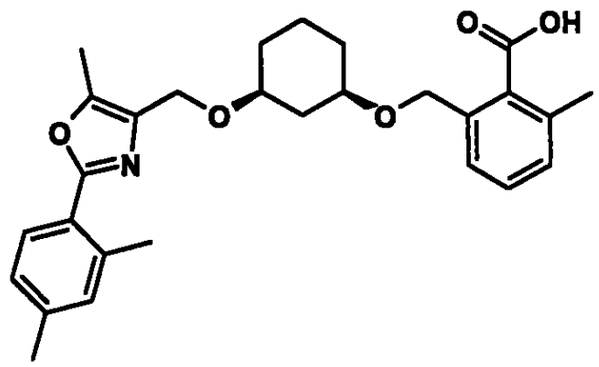
79

2-{1*R*,3*S*-3-[2-(3,4-Dimethylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **79**

[009] Methyl 2-(1*R*,3*S*-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(3,4-dimethylphenyl)-4-iodomethyl-5-methyloxazole gave under the same

conditions as described for 72 and 73 the product 79 of molecular weight 463.58 ($C_{28}H_{33}NO_5$), MS(ESI): 464.22 ($M + H^+$).

EXAMPLE LV

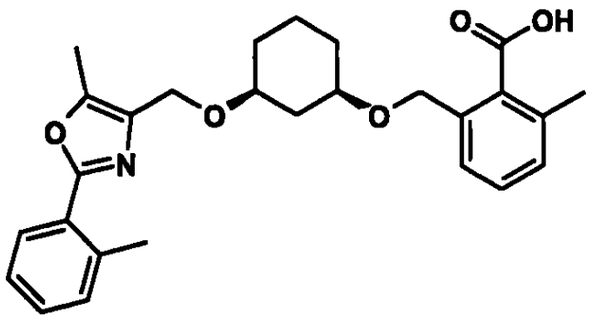


80

2-{1*R*,3*S*-3-[2-(2,4-Dimethylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid (**80**)

[010] Methyl 2-(1*R*,3*S*-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(2,4-dimethylphenyl)-4-iodomethyl-5-methyloxazole gave, under the same conditions as described for 72 and 73, the product 80 of molecular weight 463.58 ($C_{28}H_{33}NO_5$), MS(ESI): 464.22 ($M + H^+$).

EXAMPLE LVI

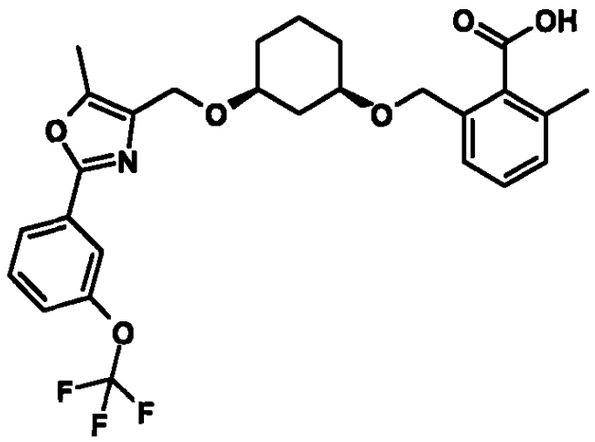


81

2-{1*R*,3*S*-3-[2-(2-Methylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid (**81**)

[011] Methyl 2-(1*R*,3*S*-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(2-methylphenyl)-4-iodomethyl-5-methyloxazole gave under the same conditions as described for 72 and 73 the product 81 of molecular weight 449.55 ($C_{27}H_{31}NO_5$), MS(ESI): 450.20 ($M + H^+$).

EXAMPLE LVII



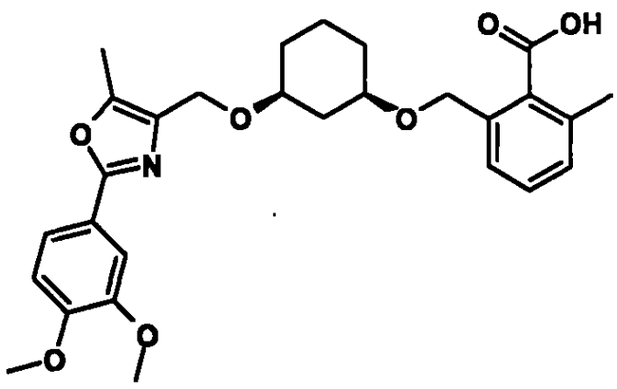
82

158-10

2-{1*R*,3*S*-3-[2-(3-Trifluoromethoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid (**82**)

[012] Methyl 2-(1*R*,3*S*-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(3-trifluoromethoxyphenyl)-4-iodomethyl-5-methyloxazole gave, under the same conditions as described for **72** and **73** the product **82** of molecular weight 519.52 ($C_{27}H_{28}F_3NO_6$), MS(ESI): 520.20 ($M + H^+$).

EXAMPLE LVIII



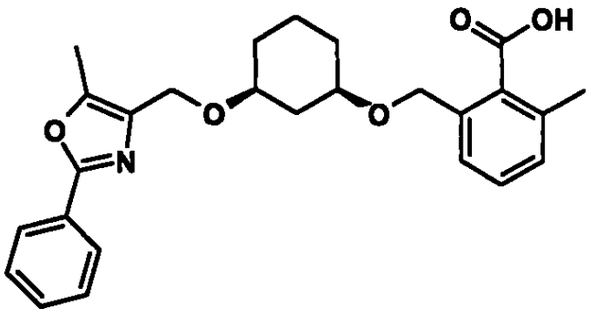
83

2-{1*R*,3*S*-3-[2-(3,4-Dimethoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid (**83**)

[013] Methyl 2-(1*R*,3*S*-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(3,4-dimethoxyphenyl)-4-iodomethyl-5-methyloxazol gave under the same

conditions as described for 72 and 73 the product 83 of molecular weight 495.58 ($C_{28}H_{33}NO_7$), MS(ESI): 496.20 ($M + H^+$).

EXAMPLE LIX



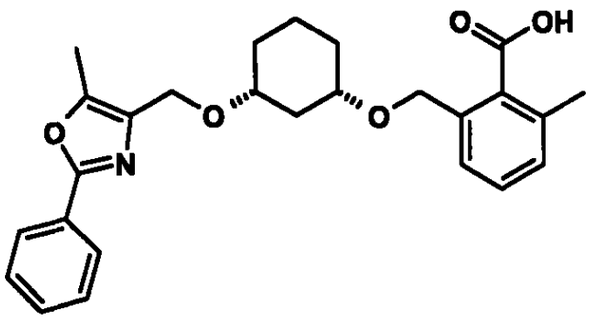
84

2-Methyl-6-[1*R*,3*S*-3-(5-methyl-2-phenyloxazol-4-ylmethoxy)cyclohexyloxymethyl]benzoic acid (84)

[014] Methyl 2-(1*R*,3*S*-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-phenyl-4-iodomethyl-5-methyloxazole gave under the same conditions as described for 72 and 73 the product 84 of molecular weight 435.52 ($C_{26}H_{29}NO_5$), MS(ESI): 436.32 ($M + H^+$).

159

EXAMPLE LX

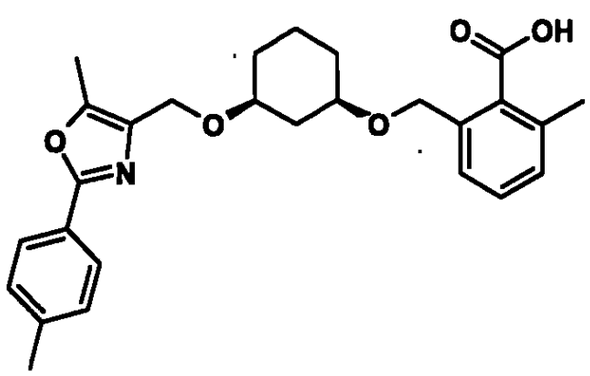


85

2-Methyl-6-[1*S*,3*R*-3-(5-methyl-2-phenyloxazol-4-ylmethoxy)cyclohexyloxymethyl]benzoic acid (85)

[015] Methyl 2-(1*S*,3*R*-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate (**47b**) and 2-phenyl-4-iodomethyl-5-methyloxazole gave under the same conditions as described for **72** and **73** the product **85** of molecular weight 435.52 ($C_{28}H_{29}NO_5$), MS(ESI): 436.32 ($M + H^+$).

EXAMPLE LXI



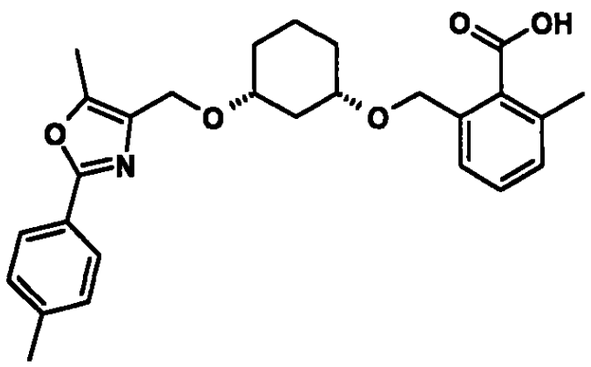
86

160[13]

2-Methyl-6-[1*R*,3*S*-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]benzoic acid **(86)**

[016] Methyl 2-(1*R*,3*S*-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(4-methylphenyl)-4-iodomethyl-5-methyloxazole gave under the same conditions as described for **72** and **73** the product **86** of molecular weight 449.55 ($C_{27}H_{31}NO_5$), MS(ESI): 450.36 ($M + H^+$).

EXAMPLE LXII



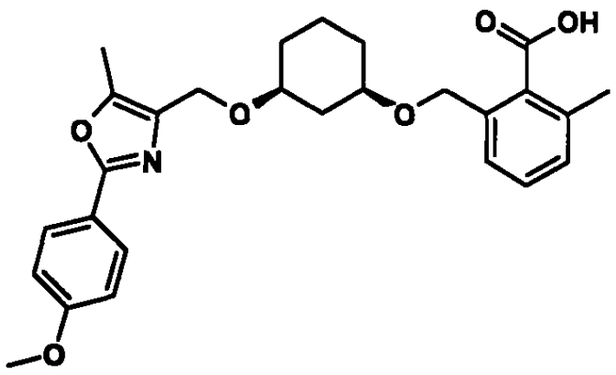
87

2-Methyl-6-[1*S*,3*R*-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]benzoic acid **(87)**

[017] Methyl 2-(1S,3*R*-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(4-methylphenyl)-4-iodomethyl-5-methyloxazole gave under the same conditions

as described for 72 and 73 the product 87 of molecular weight 449.55 ($C_{27}H_{31}NO_5$), MS(ESI): 450.36 ($M + H^+$).

EXAMPLE LXIII

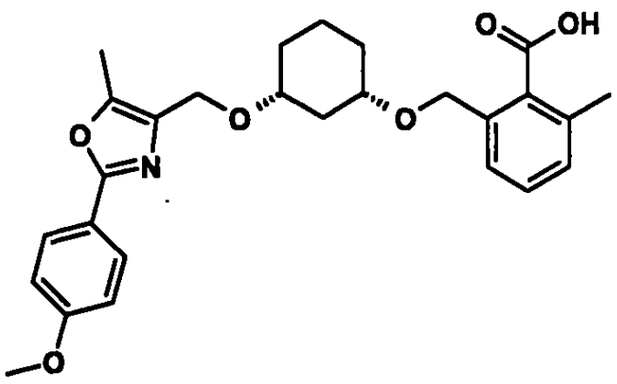


88

2-{1*R*,3*S*-3-[2-(4-Methoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **(88)**

[018] Methyl 2-(1*R*,3*S*-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(4-methoxyphenyl)-4-iodomethyl-5-methyloxazole gave under the same conditions as described for 72 and 73 the product 88 of molecular weight 465.55 ($C_{27}H_{31}NO_6$), MS(ESI): 466.37($M + H^+$).

EXAMPLE LXIV

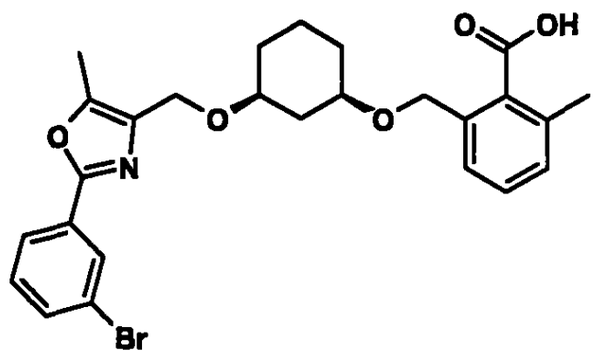


89

2-{1*S*,3*R*-3-[2-(4-Methoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **(89)**

[019] Methyl 2-(1*S*,3*R*-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(4-methoxyphenyl)-4-iodomethyl-5-methyloxazole gave under the same conditions as described for **72** and **73** the product **89** of molecular weight 465.55 ($C_{27}H_{31}NO_6$), MS(ESI): 466.37($M + H^+$).

EXAMPLE LXVI

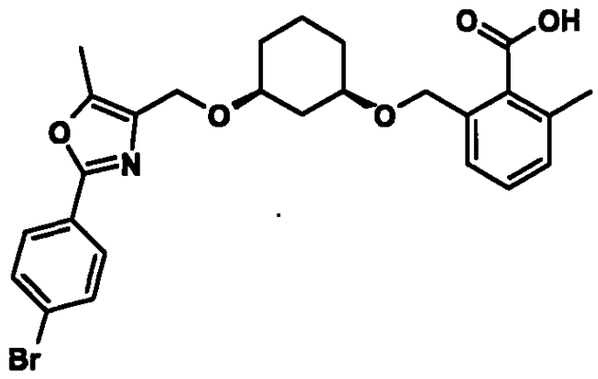


90

2-{*1R,3S*-3-[2-(3-Bromophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **(90)**

[020] Methyl 2-(*1R,3S*-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(3-bromophenyl)-4-iodomethyl-5-methyloxazole gave under the same conditions as described for **72** and **73** the product **90** of molecular weight 514.42, ($C_{28}H_{28}BrNO_5$), MS(ESI): 514.30, 516.30 ($M + H^+$).

EXAMPLE LXVI



91

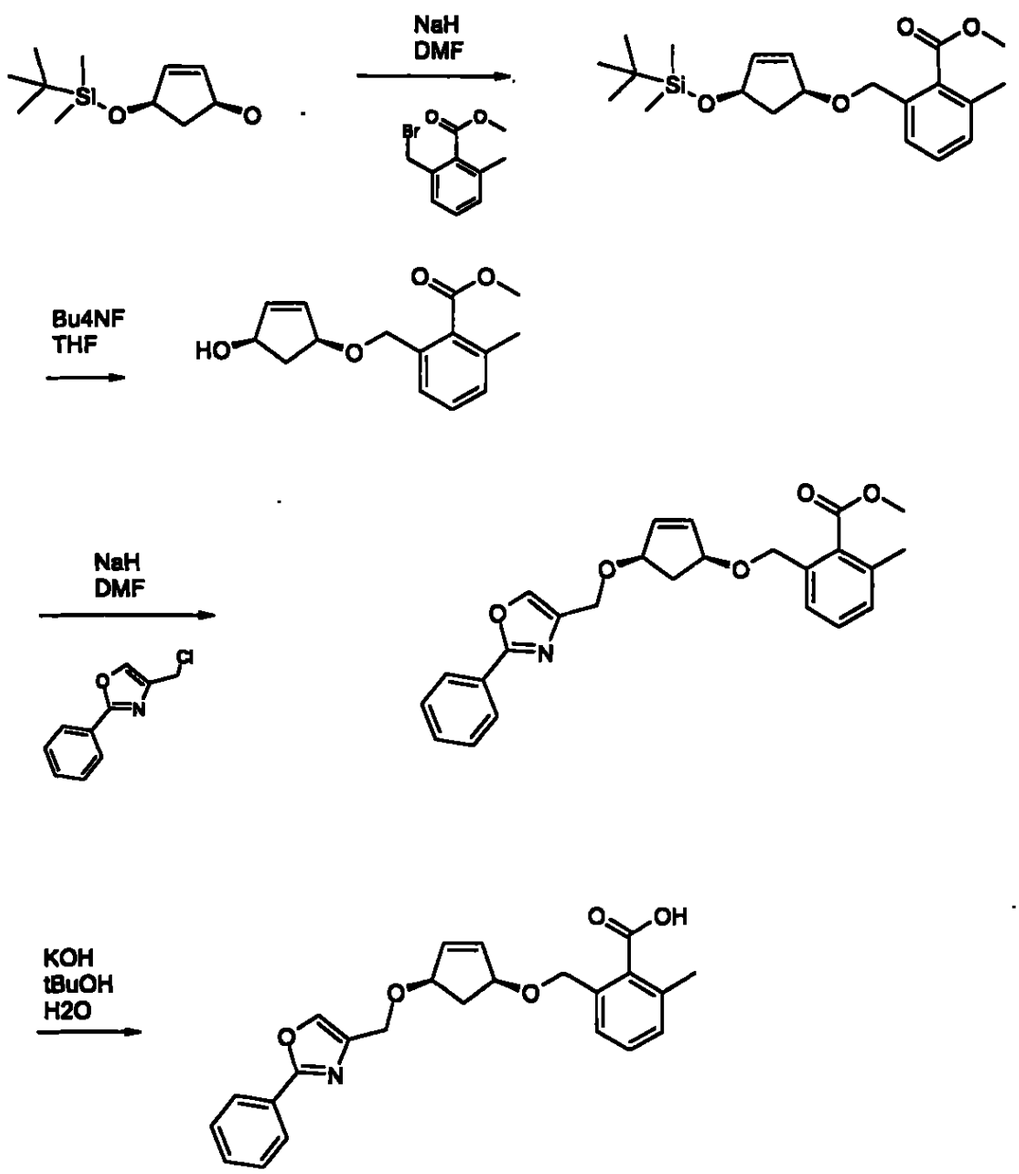
2-{*1R,3S*-3-[2-(4-Bromophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **(91)**

[021] Methyl 2-(*1R*,3S-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(4-bromophenyl)-4-iodomethyl-5-methyloxazole gave under the same conditions

as described for 72 and 73 the product 91 of molecular weight 514.42, ($C_{26}H_{28}BrNO_5$), MS(ESI): 514.29; 516.29 ($M + H^+$).

Example LXVII

Process:



Methyl-[2-(*1S,4R*-4-tert-butyldimethylsilanyloxycyclopent-2-enyloxymethyl)-6-methyl] benzoate

8,2 g *1S,4R*-4-tert-Butyldimethylsilanyloxycyclopent-2-enol in 20 ml dry dimethyl formamide (DMF) are added dropwise under Argon atmosphere at 0°C to a suspension of 1,6 g 60% NaH in 12 ml dry DMF. Then 20 ml 60% (2-Bromomethyl-6-methy)-methyl-benzoate are added at 0°C. After the addition is completed the ice-bath is removed and the mixture is stirred at room temperature for 6 h. 200 ml Methyl-t-butyl-ether (MTBE) are then added and the organic phase is washed with 200 ml water and 200ml of saturated NaCl-solution . The organic layer is dried over MgSO4 and the solvents are removed. The remaining residue is purified by chromatography (SiO_2, n-heptane /MTBE 8:1 => 3:1), yielding the product Methyl-[2-(*1S,4R*-4-tert-butyldimethylsilanyloxycyclopent-2-enyloxymethyl)-6-methyl]benzoate as a yellow oil. C21H32O4Si (376,57), LCMS (ESI): 377 (MH^+).

Methyl-[2-(*1S,4R*-4-hydroxycyclopent-2-enyloxymethyl)-6-methyl]benzoate

To a solution of 2,3 g Methyl-[2-(*1S,4R*-4-tert-butyldimethylsilanyloxycyclopent-2-enyloxymethyl)-6-methyl]benzoate in 20 ml THF 10 ml 1M solution of tetrabutylammoniumfluoride in THF are added and stirred for 20 min at room temperature. The mixture is diluted with 100 ml MTBE and washed 3 times with 100 ml water, then with 50 ml of saturated NaCl-solution. The organic layer is dried over $MgSO_4$ and the solvent is removed. The remaining residue is purified by chromatography (SiO_2, n-heptane /MTBE 1:1), yielding the product Methyl-[2-(*1S,4R*-

4-hydroxycyclopent-2-enyloxymethyl)-6-methyl]benzoate as a yellowish oil. C15H18O4 (262,31). LCMS (ESI): 263 (MH^+).

Methyl-{2-methyl-6-[*1S,4R*-4-(5-methyl-2-phenyloxazole-4-ylmethoxy)-cyclopent-2-enyloxymethyl]}benzoate

300 mg Methyl-[2-(*1S,4R*-4-Hydroxycyclopent-2-enyloxymethyl)-6-methyl]benzoate, in 2 ml dry DMF are given dropwise under Argon atmosphere to a suspension of 55 mg 60% NaH in 3 ml dry DM. After 20 min of stirring at room temperature a solution of 320 mg 5-Methyl-2-phenyloxazole-4-ylmethylchlorid in 1 ml DMF is added. The mixture is stirred for 90 min at room temperature, then 0,5 ml isopropanol are added followed by 20 ml MTBE. The solution is washed 3 times with 20 ml water, then with 20 ml of saturated NaCl-solution, the organic layer is dried over MgSO4 and the solvents are removed. The remaining residue is purified by chromatography (SiO_2, n-heptane /MTBE 5:1). Fractions containing the product are collected and once more submitted to chromatography after removal of the solvents (SiO_2, n-heptane/ethylacetate 10:1), yielding the product Methyl-{2-methyl-6-[*1S,4R*-4-(5-methyl-2-phenyloxazole-4-ylmethoxy)-cyclopent-2-enyloxymethyl]}benzoate as a yellowish oil. C25H25NO5 (419,48). LCMS (ESI): 420 (MH^+).

2-Methyl-6-[*1S,4R*-4-(5-methyl-2-phenyloxazole-4-ylmethoxy)-cyclopent-2-enyloxymethyl]-benzoic acid

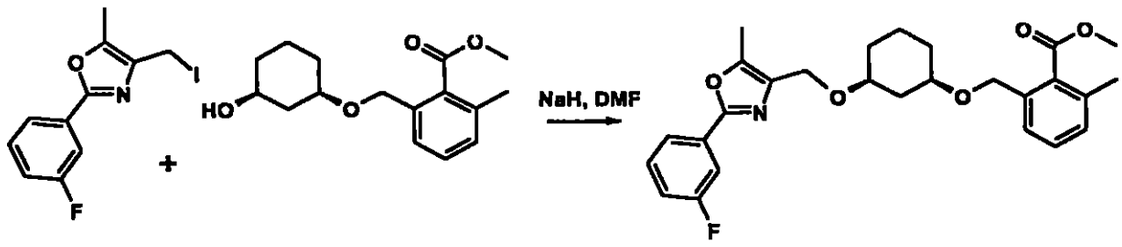
60 mg Methyl-{2-methyl-6-[*1S,4R*-4-(5-methyl-2-phenyloxazole-4-ylmethoxy)-cyclopent-2-enyloxymethyl]}benzoate in 1 ml 10 M aqueous KOH und 1 ml tert-butanol are stirred for 4 days at 100 °C. The mixture is diluted with 10 ml water and extracted 3 times with 10 ml ethylacetate. The combined organic layers are dried over MgSO4 and the solvents are removed. Purification of the remaining residue by HPLC yields 2-Methyl-6-[*1S,4R*-4-(5-methyl-2-phenyloxazole-4-ylmethoxy)-cyclopent-2-enyloxymethyl]-benzoic acid as a colorless oil. C24H23NO5 (405,45). LCMS (ESI): 406 (MH^+).

TABLE Ia

Example No.	EC50 PPARα [nM]
XLVIII	0.25
XLIX	0.52
L	0.19
LI	0.31
LII	0.10
LIII	0.40
LIV	0.08
LV	0.09
LVI	0.54
LVII	0.13
LVIII	0.46
LIX	0.20
LX	10
LXI	0.08
LXII	0.56
LXIII	0.13
LXIV	1.1
LXV	0.48

Ejemplos Adicionales:

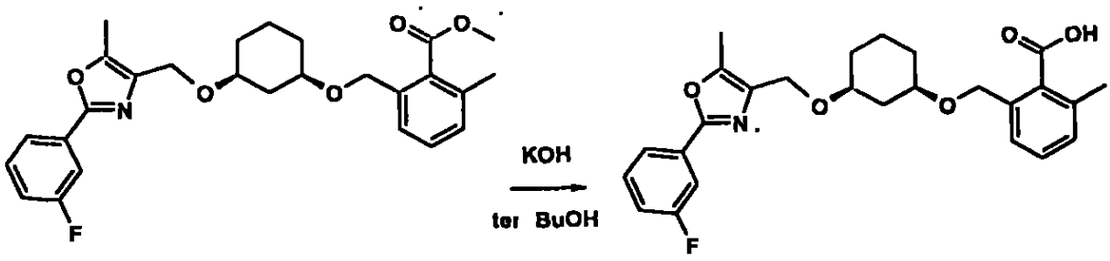
EJEMPLO XLVIII



72

[001] Metil-2-{1R,3S-3-[2-(3-fluoro-fenil)-5-metil-oxazol-4-ilmetoxi]-ciclohexiloximetil}-6-metilbenzoato (**72**)

[002] A temperatura ambiente se añadieron 50 mg de una suspensión de hidruro de sodio al 60% y luego 1,08 mmol de 2-(3-fluorofenil)-4-yodometil-5-metiloxazol a una solución de 200 mg de metil-2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato (**47a**) en 5 ml de dimetilformamida. Después se monitoreo mediante TLC la reacción hasta que estuvo completa (aproximadamente una hora), se añadió ter-éter butílico (~ 30 ml) y la mezcla fue extraída con agua. La fase orgánica fue secada sobre sulfato de magnesio, se eliminaron los solventes bajo presión reducida y el residuo se purificó mediante RP-HPLC. Esto produjo **72** como un aceite amarillo claro. $C_{27}H_{30}FNO_5$ (467,74), MS(ESI): 468 ($M+H^+$).

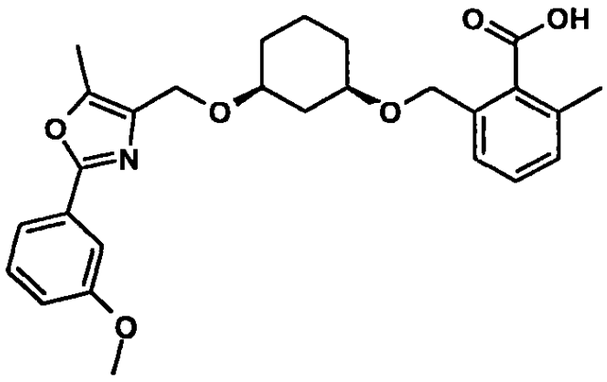


72 73

Acido 2-{1R,3S-3-[2-(3-fluoro-fenil)-5-metil-oxazol-4-ilmetoxi]-ciclohexilmetiloximetil}-6-metilbenzoico (**73**)

[003] Se agitaron 100 mg de **72** en una mezcla de 10 ml de ter-butanol y 1 ml de solución 10 N de hidróxido de potasio acuosa a 90°C. Después de que la reacción estuvo completa según TLC (hasta dos días), la mezcla se acidificó con ácido clorhídrico y fue extraída con acetato de etilo. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se eliminaron los solventes bajo presión reducida y el residuo fue purificado mediante RP-HPLC. Esto dio el producto **73** como un sólido amorfo de peso molecular 453,52 ($C_{26}H_{28}FNO_5$), MS(ESI): 454,35 ($M+H^+$).

EJEMPLO XLIX

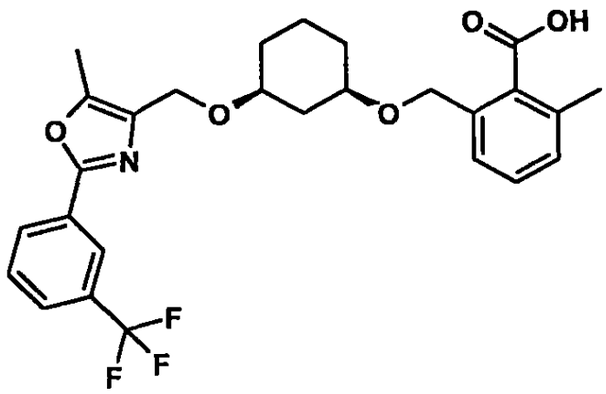


74

Acido 2-{1R,3S-3-[2-(3-metoxi-fenil)-5-metil-oxazol-4-ilmetoxi]-ciclohexiloximetoxi)-6-metilbenzoico (**74**)

[004] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol dieron bajo las mismas condiciones descritas para **72** y **73** el producto **74** de peso molecular 465,55 ($C_{27}H_{31}NO_6$), MS(ESI): 466,37 ($M+H^+$).

EJEMPLO L

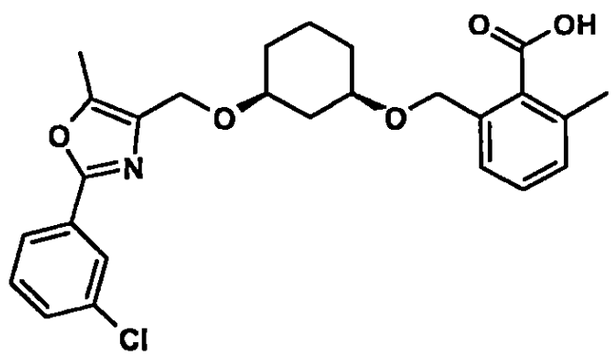


75

Acido 2-[1R,3S-3-[2-(3-trifluorometilfenil)-5-metiloxazol-4-ilmetoxi]ciclohexiloximetil}-6-metilbenzoico (**75**)

[005] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol dieron bajo las mismas condiciones descritas para **72** y **73** el producto **75** de peso molecular 503,52 ($C_{27}H_{28}F_3NO_5$), MS(ESI): 504,37 ($M+H^+$).

EJEMPLO LI

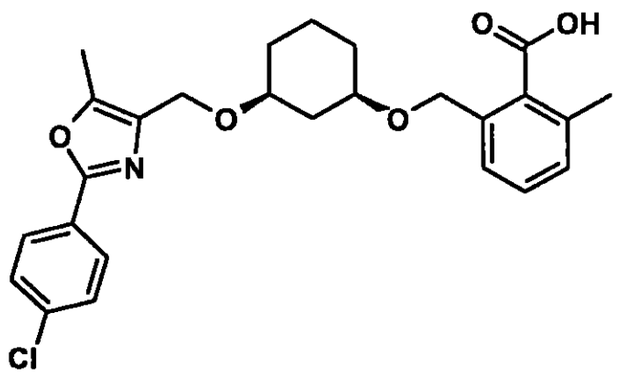


76

Acido 2-{1R,3S-3-[2-(3-clorofenil)-5-metiloxazol-4-ilmetoxi]ciclohexiloximetil}-6-metilbenzoico (**76**)

[006] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol dieron bajo las mismas condiciones descritas para **72** y **73** el producto **76** de peso molecular 469,97 ($C_{26}H_{28}ClNO_5$), MS(ESI): 470,43 ($M+H^+$).

EJEMPLO LII

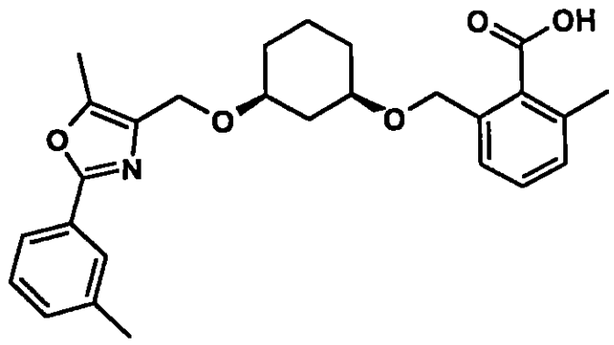


77

Acido 2-{1R,3S-3-{2-(4-clorofenil)-5-metiloxazol-4-ilmetoxi]ciclohexiloximetil}-6-metilbenzoico (77)

[007] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol dieron bajo las mismas condiciones descritas para 72 y 73 el producto 77 de peso molecular 469,97 ($C_{26}H_{28}ClNO_5$), MS(ESI): 470,40 ($M+H^+$).

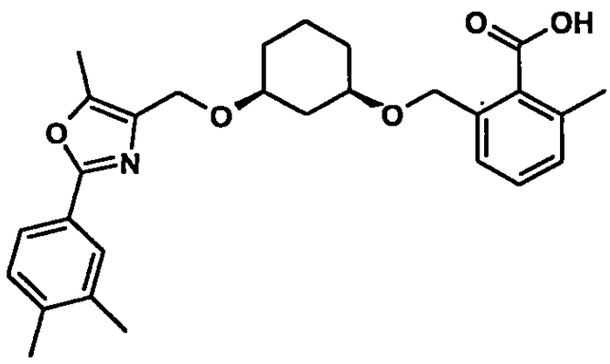
EJEMPLO LIII



Acido 2-1R,3S-3-[2-(3-metilfenil)-5-metiloxazol-4-ilmetoxi]ciclohexiloximetil)-6-metilbenzoico (**78**)

[008] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol dieron bajo las mismas condiciones descritas para **72** y **73** el producto **77** de peso molecular 449,55 ($C_{27}H_{31}NO_5$), MS(ESI): 450,53 ($M+H^+$).

EJEMPLO LIV



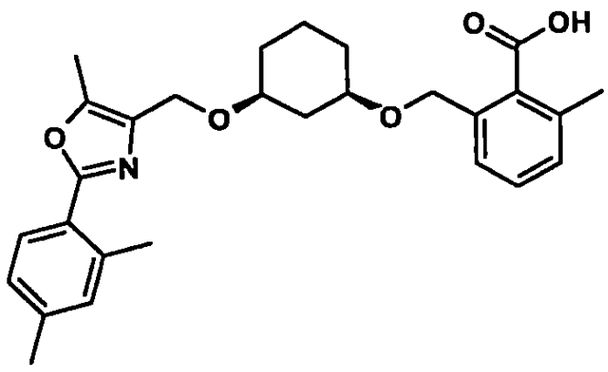
79

Acido 2-[1R,3S,3-[2-(3,4-dimetilfenil)-metiloxazol-4-ilmetoxi]ciclohexiloximetil)-6-metilbenzoico **79**

[009] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol

dieron bajo las mismas condiciones descritas para **72** y **73** el producto **79** de peso molecular 463,58 ($C_{28}H_{33}NO_5$), MS(ESI): 464,22 ($M+H^+$).

EJEMPLO LV

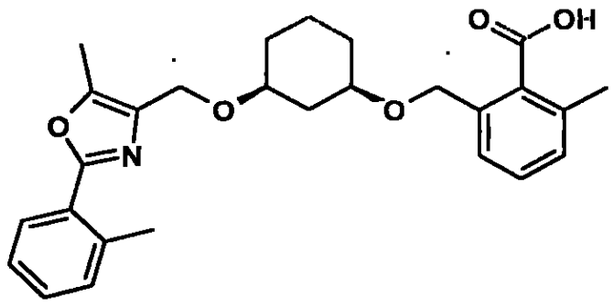


80

Acido 2-[1R,3S-3-[2-(2,4-dimetilfenil)-5-metiloxazol-4-ilmetoxi]ciclohexiloximetil-6-metilbenzoico (**80**)

[010] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol dieron bajo las mismas condiciones descritas para **72** y **73** el producto **80** de peso molecular 463,58 ($C_{28}H_{33}NO_5$), MS(ESI): 464,22 ($M+H^+$).

EJEMPLO LVI

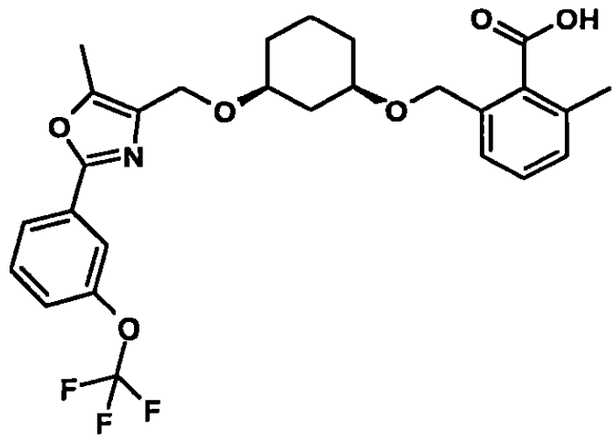


81

Acido 2-{1R,3S-3-[2-(2-metilfenil)-metiloxazol-4-ilmetiloxi]ciclohexiloximetil}-6-metilbenzoico (**81**)

[011] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol dieron bajo las mismas condiciones descritas para **72** y **73** el producto **81** de peso molecular 449,55 ($C_{27}H_{31}NO_5$), MS(ESI): 450,20 ($M+H^+$).

EJEMPLO LVII

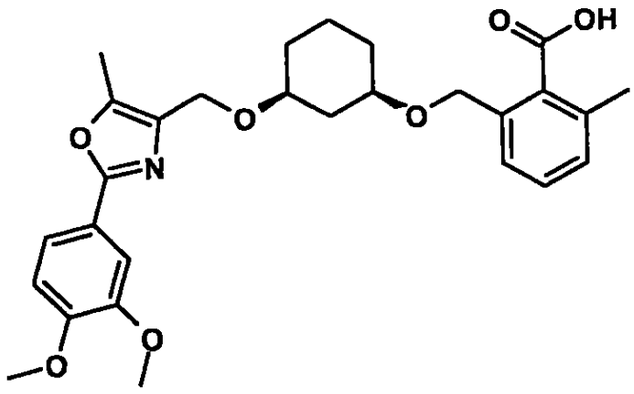


82

Acido 2-{1R,3S-3-[2-(trifluorometoxifenil)-5-metiloxazol-4-ilmetoxi]ciclohexiloximetil}-6-metilbenzoico (**82**)

[012] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol dieron bajo las mismas condiciones descritas para **72** y **73** el producto **82** de peso molecular 519,52 ($C_{27}H_{28}F_3NO_6$), MS(ESI): 520,20 ($M+H^+$).

EJEMPLO LVIII



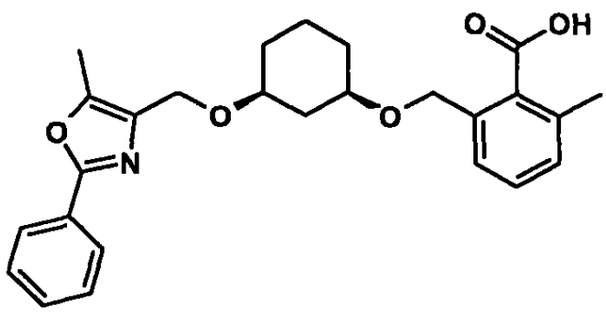
83

Acido 2-{1R,3S-3-(2-(3,4-dimetoxifenil)-5-metiloxazol-4-ilmetoxi}ciclohexiloximetil}-6-metilbenzoico (**83**)

[013] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol

dieron bajo las mismas condiciones descritas para **72** y **73** el producto **83** de peso molecular 495,58 ($C_{28}H_{33}NO_7$), MS(ESI): 496,20 ($M+H^+$).

EJEMPLO LIX

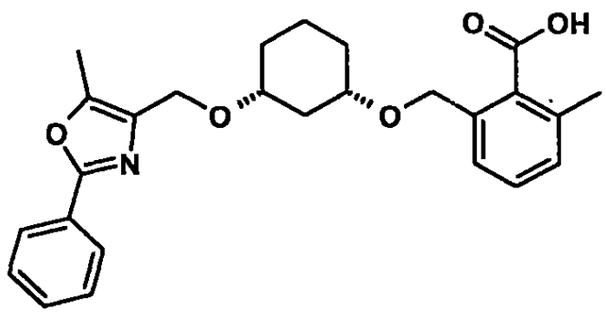


84

Acido 2-metil-6-[1R,3S-3-(5-metil-2-fenioxazol-4-ilmetoxi)ciclohexiloximetil]benzoico (**84**)

[014] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol dieron bajo las mismas condiciones descritas para **72** y **73** el producto **84** de peso molecular 435,52 ($C_{26}H_{29}NO_5$), MS(ESI): 436,32 ($M+H^+$).

EJEMPLO LX

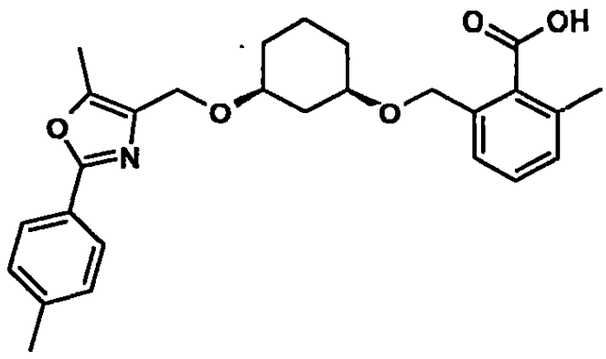


85

Acido 2-metil-6-[1S,3R-3-(5-metil-2-feniloxazol-4-ilmetoxi)ciclohexiloximetil]benzoico (**85**)

[015] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol dieron bajo las mismas condiciones descritas para **72** y **73** el producto **85** de peso molecular 435,52 ($C_{26}H_{29}NO_5$), MS(ESI): 436,32 ($M+H^+$).

EJEMPLO LXI

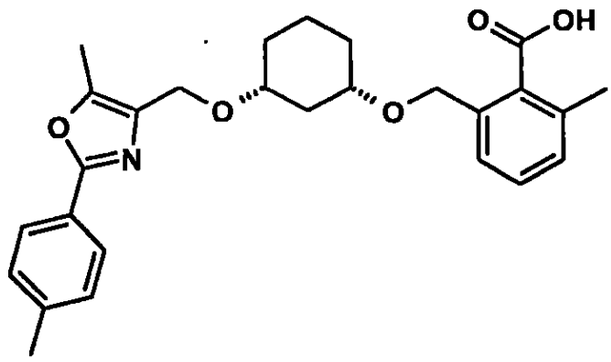


86

Acido 2-metil-6-[1R,3S-3-(5-metil-2-p-toliloxazol-4-ilmetoxi]ciclohexiloximetil]benzoico (**86**)

[016] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol dieron bajo las mismas condiciones descritas para **72** y **73** el producto **86** de peso molecular 449,55 ($C_{27}H_{31}NO_5$), MS(ESI): 450,36 ($M+H^+$).

EJEMPLO LXII



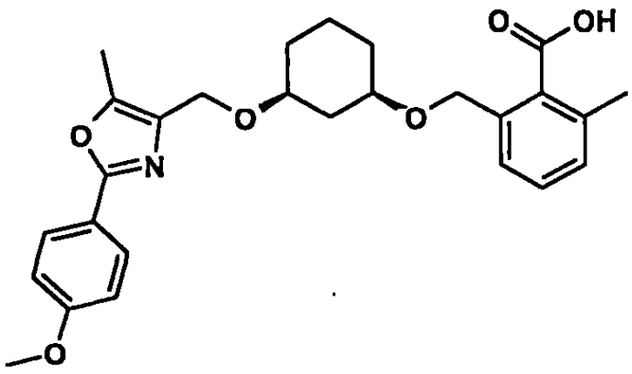
87

Acido 2-metil-6-[1S,3R-3-(5-metil-2-p-toliloxazol-4-ilmetoxi)ciclohexiloximetil]benzoico (**87**)

[017] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol dieron bajo las mismas condiciones descritas para **72** y **73**

el producto **87** de peso molecular 449,55 ($C_{27}H_{31}NO_5$), MS(ESI): 450,36 ($M+H^+$).

EJEMPLO LXIII

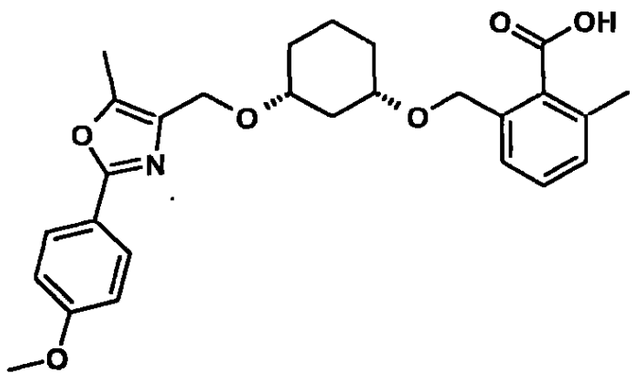


88

Acido 2-{1R,3S-3-[2-(4-metoxifenil)-5-metiloxazol-4-ilmetoxi]ciclohexiloximetil}-6-metilbenzoico (**88**)

[018] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol dieron bajo las mismas condiciones descritas para **72** y **73** el producto **88** de peso molecular 465,55 ($C_{27}H_{31}NO_6$), MS(ESI): 466,37 ($M+H^+$).

EJEMPLO LXIV

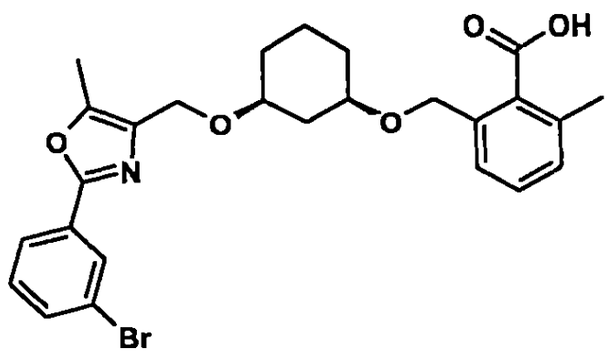


89

Acido 2-{1S,3R-3-[2-(4-metoxifenil)-5-metiloxazol-4-ilmetoxi]ciclohexiloximetil}-6-metilbenzoico (**89**)

[019] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol dieron bajo las mismas condiciones descritas para **72** y **73** el producto **89** de peso molecular 465,55 ($C_{27}H_{31}NO_6$), MS(ESI): 466,37 ($M+H^+$).

EJEMPLO LXVI

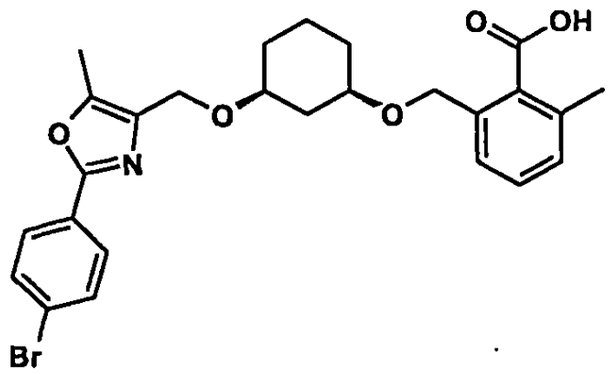


90

Acido 2-{1R,3S-3-[2-(3-bromofenil)-5-metiloxazol-4-ilmetoxi]ciclohexiloximetil}-6-metilbenzoico (**90**)

[020] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol dieron bajo las mismas condiciones descritas para **72** y **73** el producto **90** de peso molecular 514,42 ($C_{26}H_{28}BrNO_5$), MS(ESI): 514,30; 516,30 ($M+H^+$).

EJEMPLO LXVI



91

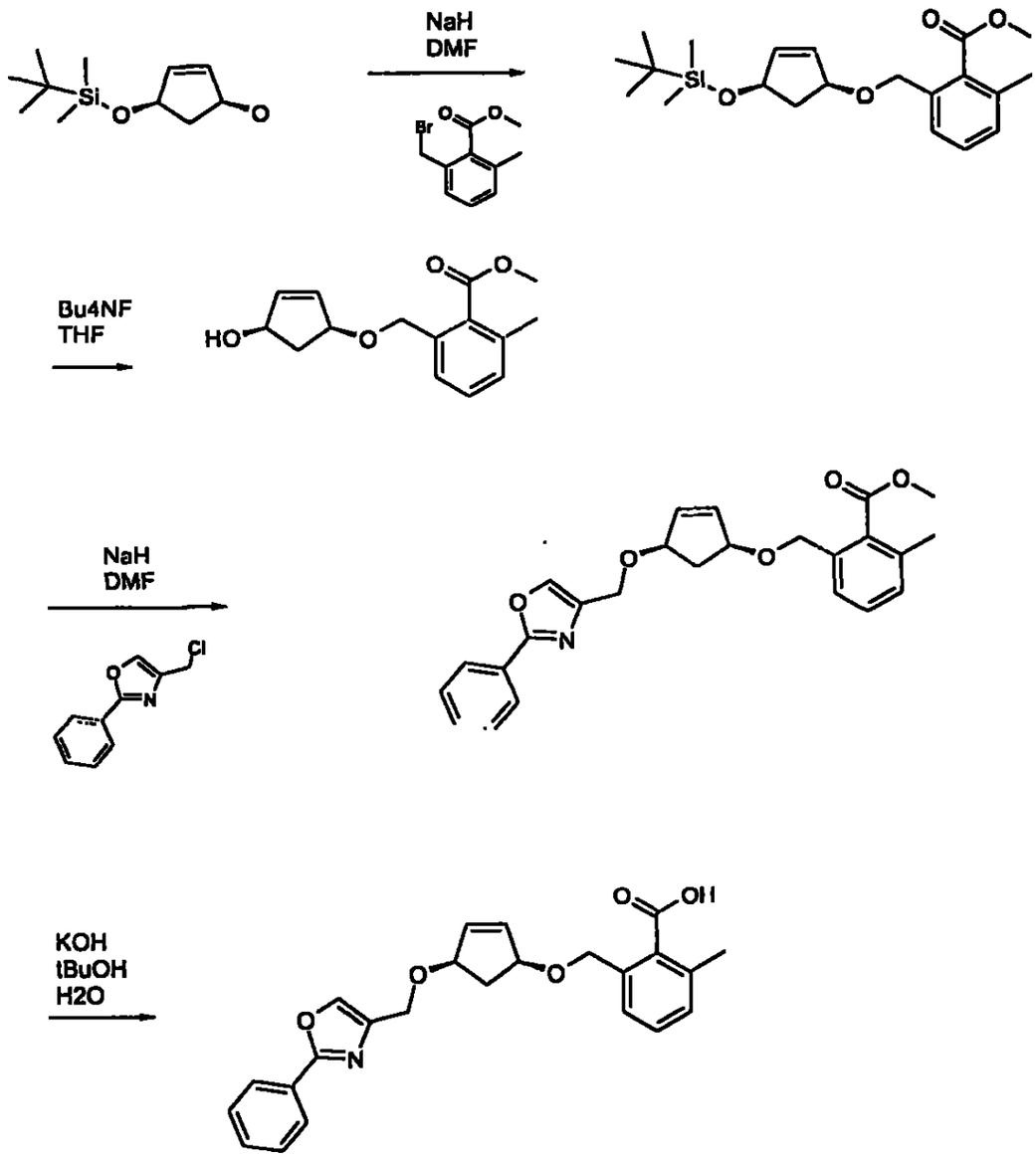
Acido 2-{1R,3S-3-[2-(4-bromofenil)-5-metiloxazol-4-ilmetoxi]ciclohexiloximetil}-6-metilbenzoico (**91**)

[021] Metil 2-(1R,3S-3-hidroxiciclohexiloximetil)-6-metilbenzoato y 2-(3-metoxifenil)-4-yodometil-5-metiloxazol

dieron bajo las mismas condiciones descritas para **72** y **73** el producto **91** de peso molecular 514,42 ($C_{26}H_{28}BrNO_5$), MS(ESI): 514,29; 516,29 ($M+H^+$).

EJEMPLO LXVII

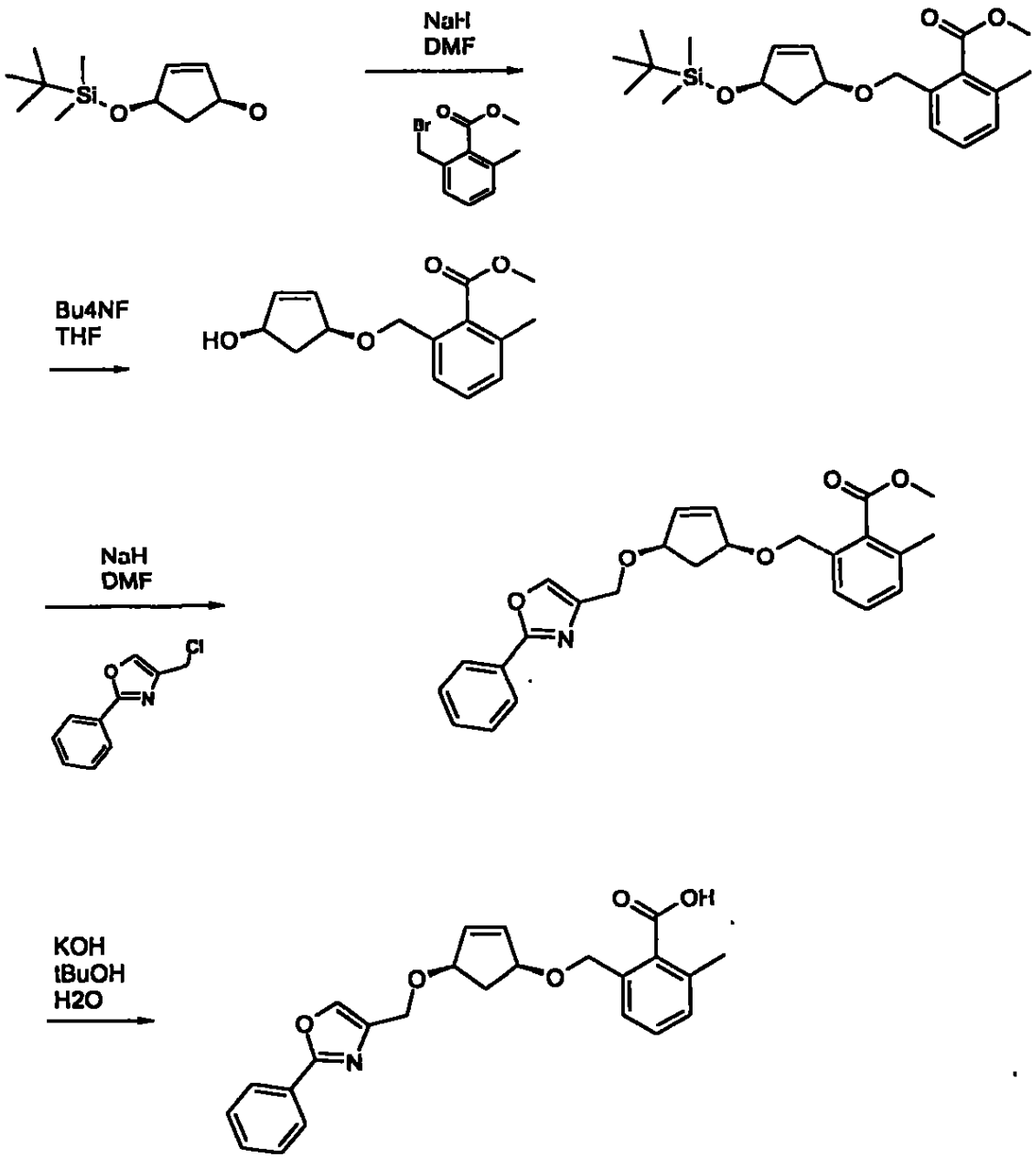
Proceso:



dieron bajo las mismas condiciones descritas para **72** y **73** el producto **91** de peso molecular 514,42 ($C_{26}H_{28}BrNO_5$), MS(ESI): 514,29; 516,29 (M+H').

EJEMPLO LXVII

Proceso:



Metil-[2-(1S-4R-4-ter-butildimetilsilaniloxiciclopent-2-eniloximetil)-6-metil]benzoato

8,2 gr de 1S,4R-4-ter-butildimetilsilaniloxiciclopent-2-enol en 20 ml de dimetilformamida (DMF) seca se añaden gota a gota bajo atmósfera de argón a 0°C a una suspensión de 1,6 gr de NaH al 60% en 12 ml de DMF seca. Luego se añaden a 0°C 20 ml de (2-bromometil-6-metil)-metil-benzoato al 60%. Después de que se ha completado esta adición se elimina el baño de hielo y la mezcla se agita a temperatura ambiente durante 6 horas. Luego se agregan 200 ml de éter metilbutílico (MTBE) y la fase orgánica se lava con 200 ml de agua y 200 ml de solución de NaCl saturada. La capa orgánica se seca sobre $MgSO_4$ y se eliminan lo solventes. El residuo sobrante se purifica mediante cromatografía (SiO_2, n-heptano/MTBE 8:1 => 3:1), resultando el producto metil-[2-1S,4R-4-ter-butildimetilsilaniloxiciclopent-2-eniloximetil)-6-metil]benzoato como un aceite amarillo. C21H3204Si (376,57), LCMS (ESI): 377 (MH^+).

Metil -[2-(1S-4R-4-hidroxiciclopent-2-eniloximetil)-6-metil]benzoato

A una solución de 2,3 gr de metil-[2-(1S,4R-4-ter-butildimetilsilaniloxiciclopent-2-eniloximetil)-6-metil]benzoato en 20 ml de THF se le añaden 10 ml de una solución 1M de tetrabutilamoniofluoruro en THF y se agitan durante 20 minutos a temperatura ambiente. La mezcla se diluye con 100 ml de MTBE y se lava 3 veces con 100 ml de agua, luego con 50 ml de solución de NaCl saturada. La capa orgánica se seca sobre $MgSO_4$ y se elimina el solvente. El residuo sobrante se purifica mediante cromatografía (SiO_2, n-heptano/MTBE 1:1), resultando el producto metil-[2-1S,4R-4-hidroxiciclopent-2-eniloximetil)-6-metil]benzoato como un aceite amarillento. C15H1804Si (262,31), LCMS (ESI): 263 (MH^+).

Metil-{2-metil-6-[1S,4R-4-(5-metil-2-feniloxazol-4-ilmetoxi)-ciclopent-2-eniloximetil}benzoato

300 mg de metil-[2-(1S,4R-4-hidroxiciclopent-2-eniloximetil)-6-metil]benzoato en 2 ml de DMF seca se agregan gota a gota bajo atmósfera de argón a una suspensión de 55 mg de NaH al 60% en 3 ml de DM seco. Después de 20 minutos de agitación a temperatura ambiente se agrega una solución de 320 mg de 5-metil-2-feniloxazol-4-ilmetilcloruro en 1 ml de DMF. La mezcla se agita durante 90 minutos a temperatura ambiente, luego de agregan 0,5 ml de isopropanol seguidos por 20 ml de MTBE. La solución se lava 3 veces con 20 ml de agua, luego con 20 ml de solución de NaCl saturada, la capa orgánica se seca sobre $MgSO_4$ y se eliminan los solventes. El residuo sobrante se purifica mediante cromatografía SiO_2, n-heptano/MTBE 5:1). Las fracciones que contienen el producto se recogen y se someten una vez más a cromatografía luego de eliminar los solventes (SiO_2, n-heptano/etilacetato 10:1), resultando el producto metil-{2-metil-6-[1S,4R-4-(5-metil-2-feniloxazol-4-ilmetoxi)-ciclopent-2-eniloximetil}benzoato como un aceite amarillento. $C_{25}H_{25}NO_5$ (419,48). LCM (ESI): 420 (MH^+).

Acido 2-metil-6-[1S,4R-4-(5-metil-2-feniloxazol-4-ilmetoxi)-ciclopent-2-eniloximetil]-benzoico

60 mg de metil-{2-metil-6-[1S,4R-4-(5-metil-2-feniloxazol-4-ilmetoxi)-ciclopent-2-eniloximetil}benzoato en 1 ml de 10 M KOH acuoso y 1 ml de ter-butanol se agitan durante 4 días a 100°C. La mezcla se diluye con 10 ml de agua y se extrae 3 veces con 10 ml de etilacetato. La capas orgánicas combinadas se secan sobre $MgSO_4$ y se eliminan los solventes. La purificación del residuo sobrante mediante HPLC produce ácido 2-metil-6-[1S,4R-4-(5-metil-2-feniloxazol-4-ilmetoxi)-ciclopent-2-eniloximetil]-benzoico como un aceite incoloro. $C_{24}H_{23}NO_5$ (405,45). LCMS (ESI): 406 (MH^+).

TABLA Ia

Ejemplo No.	EC50 PPARα [nM]
XLVIII	0,25
XLIX	0,52
L	0,19
LI	0,31
LII	0,10
LIII	0,40
LIV	0,08
LV	0,09
LVI	0,54
LVII	0,13
LVIII	0,46
LIX	0,20
LX	10
LXI	0,08
LXII	0,56
LXIII	0,13
LXIV	1,1
LXV	0,48