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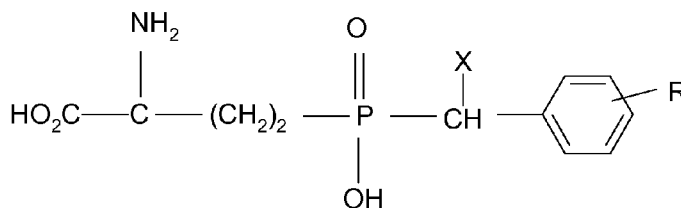
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(54) Title: HYPOPHOSPHOROUS ACID DERIVATIVES HAVING ANTIHYPERALGIC ACTIVITY AND BIOLOGICAL APPLICATIONS THEREOF



(57) Abstract: The invention relates to hypophosphorous acid derivatives of formula (I) wherein - X is H or OH, - R represents one or several radicals R¹-R⁵, identical or different, two of R¹-R⁵ optionally occupying the same position on the phenyl group, one to four of R¹-R⁵ being H and the others being selected in the group comprising - O-(CH₂)_n-COOH; - S-(CH₂)_n-COOH; -NH-(CH₂)_n-COOH; - O-(CH₂)_n-COOH; -O-(CH₂)_n-OH; OR', -R' being a C₁-C₃ alkyl radical; -OH; -COOH; halogen, particularly -F, -Cl, -Br, -I, -CF₃; -N₃; -NO₂; -CH=CH-COOH; - (CH₂)_n-COOH; O - (CH₂)_n- P(=O)(OH)₂; O - (CF₂)_n- P(=O)(OH)₂; O - (CH₂)_n- SO₃H; O - (CH₂)_n- CONHOH; O - (CH₂)_n-tetrazol; O - (CH₂)_n-hydroxyisoxazol - n = 1 to 5, preferably 1-3; said hypophosphorous acid derivatives being diastereoisomers or enantiomers.

**Hypophosphorous acid derivatives having antihyperalgetic activity
and biological applications thereof**

The invention relates to hypophosphorous acid derivatives having antihyperalgetic activity and biological applications thereof.

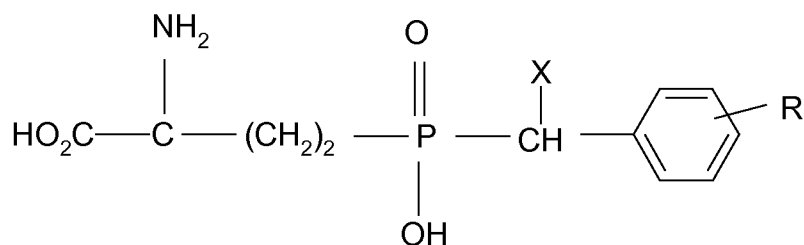
In WO 2007/052169, in the name of CNRS, inventors of the present application have disclosed hypophosphorous acid derivatives having agonist or antagonist properties for metabotropic glutamate receptors (mGluRs), particularly for group III, subtype 4 (mGlu4Rs), useful for treating neurodegenerative disease and brain disorders.

By pursuing their works in this domain, the inventors have now found that a specific group of the hypophosphorous acid derivatives disclosed in said WO application surprisingly have an agonist activity among the most powerful known on subtype 4 of the mGlu receptors and also are subtype 7 agonist of high value.

Accordingly, this is an object of the invention to provide a new group of hypophosphorous acid derivatives.

It is also an object of the invention to provide such derivatives for use as drugs, particularly for the treatment of neuropathic and inflammatory pain.

The hypophosphorous acid derivatives of the invention have formula (I).



wherein

- X is H or OH,
- R represents one or several radicals $\text{R}^1\text{-R}^5$, identical or different, two of $\text{R}^1\text{-R}^5$ optionally occupying the same position on the phenyl group, one to four of $\text{R}^1\text{-R}^5$ being H and the others being selected in the group comprising
- $\text{O-(CH}_2\text{)}_n\text{-COOH}$; - $\text{S-(CH}_2\text{)}_n\text{-COOH}$; - $\text{NH-(CH}_2\text{)}_n\text{-COOH}$; - $\text{O-(CH}_2\text{R')-COOH}$; - $\text{O-(CH}_2\text{)}_n\text{-OH}$; OR' , - R' being a $\text{C}_1\text{-C}_3$ alkyl radical; -OH; --COOH; halogen, particularly -F, -Cl, -Br, -I, -CF₃; -OCF₃; -NO₂; -CH=CH-COOH;

$-(\text{CH}_2)_n\text{-COOH}$; $\text{O} - (\text{CH}_2)_n\text{-PO}_3\text{H}_2$; $\text{O} - (\text{CF}_2)_n\text{-PO}_3\text{H}_2$; $\text{O} - (\text{CH}_2)_n\text{-SO}_3\text{H}$; $\text{O} - (\text{CH}_2)_n\text{-CONHOH}$; $\text{O} - (\text{CH}_2)_n\text{-tetrazol}$; $\text{O} - (\text{CH}_2)_n\text{-hydroxyisoxazol}$
- $n = 1$ to 5 , preferably $1-3$; said hypophosphorous acid derivatives being diastereoisomers or enantiomers.

As illustrated hereinafter in the Examples, the pharmacological peculiarity of the above compounds lies in their strong agonist activity on mGlu4R.

Depending on the substitutions, they may also be selective with respect to other metabotropic receptors, particularly mGlu7 or mGlu8, resulting in specific properties.

They may thus have a higher agonist effect on mGlu7R compared to all known agonists, both subtypes mGlu4 and mGlu7 acting then in synergy for the treatment of pain. It will be measured that such a simultaneous activation has a high therapeutic interest.

In another embodiment, they may have mGlu8/4 EC_{50} ratio of interest, particularly above 100.

Derivatives of a first preferred group have a EC_{50} with respect to mGlu4 ≤ 0.2 μM .

Particularly preferred derivatives of said group also have a EC_{50} with respect to mGlu7 ≤ 15 μM .

They include derivatives of formula (I) wherein $\text{X} = \text{-OH}$ and R represents one substituent in para, or two substituents in meta and para, or three substituents, particularly two in meta and one in para, respectively.

In particularly preferred derivatives of said first group, the phenyl group is substituted by one substituent. A particularly preferred substituent is- $\text{O} - (\text{CH}_2)_n\text{-COOH}$ with $n=1$ or - $\text{S} - (\text{CH}_2)_n\text{-COOH}$ with $n=1$;

In other preferred derivatives of said first group, two substituents are present on the phenyl group, one being - $\text{O} - (\text{CH}_2)_n\text{-COOH}$ with preferably $n=1$, and the other is - OR' , with R' preferably being - CH_3 or - CF_3 ;

In still other preferred derivatives, three substituents are present, one being - $\text{O} - (\text{CH}_2)_n\text{-COOH}$ with preferably $n=1$, the second one is - OR' , with R' preferably being - CH_3 and the third one is -F, -Cl, -I or - NO_2 .

Derivatives of a second preferred group have a EC_{50} with respect to mGlu4 $<$ about 1 μM . They include derivatives of formula (I) wherein $\text{X} = \text{-OH}$ or H and R represents one substituent in para, or two substituents in meta and para, or three substituents, particularly two in meta and one in para, respectively.

In particularly preferred derivatives of said second group, the phenyl group is substituted by one substituent. A particularly preferred substituent is $-O-(CH_2)_n-COOH$ with $n=1$ and $X=H$; or $-O-(CH_2)_n-PO_3H_2$ with $n=1$ and $X=-OH$; or $-(CH_2)_n-COOH$ with $n=2$ and $X=-OH$; or $-CH=CH-COOH$ and $X=-OH$.

5 In other preferred derivatives of said second group, two substituents are present on the phenyl group, one being $-O-(CH_2)_n-COOH$ with preferably $n=1$, and the other is $-OR'$, with R' preferably being $-CH_3$, or is $-OH$, or is NO_2 ; or one is $-S-(CH_2)_{n1}-COOH$ with preferably $n1=1$ and the other is $-NO_2$.

10 In other preferred derivatives, three substituents are present, one being $-O-(CH_2)_n-COOH$ with preferably $n=1$ and the two others, identical or different, being selected from R as above defined or $-OR'$, with R' preferably being $-CH_3$, or $-NO_2$, $-F$, $-Cl$, or $-I$.

15 More particularly, the invention thus relates to the simultaneous activation of mGluR subtypes 4 and 7 for the treatment of neuropathic and inflammatory pain comprising using an effective therapeutic amount of said derivatives.

Other derivatives of interest have a EC_{50} with respect to mGluR7 receptors above $15 \mu M$, even above $100 \mu M$. They correspond to derivatives having a high selectivity for mGluR4.

20 Other derivatives of high value have a high selectivity with respect to mGlu8 with $EC_{50} \text{ mGlu8} > 10 / EC_{50} \text{ mGlu4} < 0.5$.

The invention thus also relates to pharmaceutical compositions comprising an effective amount of at least one of the hypophosphorous acid derivatives such as above defined in combination with a pharmaceutically acceptable carrier.

25 Advantageously, the pharmaceutical compositions of the invention are under a form suitable for an administration by the oral route, such as tablets, pills or capsules.

They preferably comprise 1 to 100 mg of active ingredient per dose unit.

Alternatively, the pharmaceutical compositions of the invention are under a form suitable for an administration by injection, such as injectable solutions for the intravenous, subcutaneous or intramuscular route. Such compositions advantageously comprise 1 to 30 mg
30 of active ingredient per dose unit.

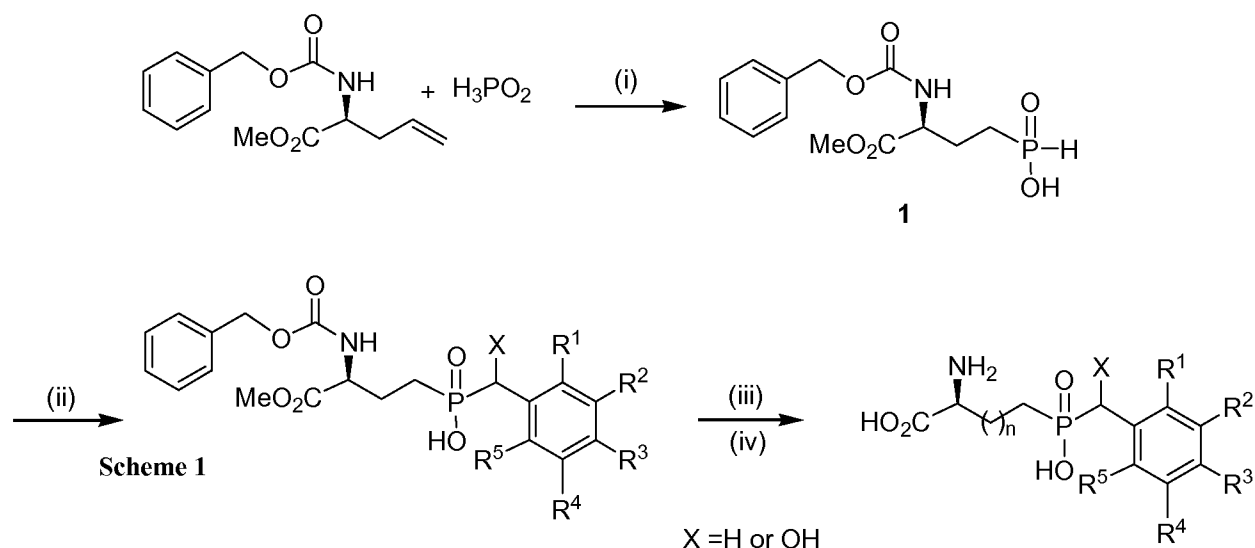
The invention also relates to a method for treating neuropathic and inflammatory pain comprising simultaneously activating glutamate metabotropic receptors sub-groups 4 and 7 by administering to a patient in need thereof an efficient amount of at least one hypophosphorous acid derivative of formula (I) as above defined.

The derivatives of the invention are advantageously obtained by using the methods disclosed in above mentioned WO 2007/052169.

Other characteristics and advantages of the invention are given in the following Examples with reference to Figures 1-5, which represent, respectively,

- 5 - Figure 1: the lack of effect of intrathecal administration of derivative 1 in healthy rats when pain is evoked by a mechanical stimulus,
- Figure 2: the antihyperalgesic effect of intrathecal administration of derivative 1 on the vocalization threshold to paw pressure in the carrageenan inflammatory pain model,
- 10 - Figure 3: the antihyperalgesic effect of intrathecal administration of derivative 1 on the vocalization threshold to paw pressure in the CCI neuropathic pain model,
- Figure 4: the antihyperalgesic effect of intrathecal administration of derivative A on the vocalization threshold to paw pressure in the CCI neuropathic model (decrease when ODN against mGlu4R are injected),
- 15 - Figure 5: the antihyperalgesic effect of derivative 1 (i.p.) in a rat model of inflammatory pain ("carrageenan") treated.
- Figure 6: the mechanical antihyperalgesic effect of derivative 2 is profoundly impaired in inflamed genetically modified mice lacking the gene encoding for the mglu4 receptor
- 20 - Figure 7: the knockdown of spinal mGlu₄ expression by antisense oligonucleotides reduces mechanical antihyperalgesia induced by derivative 2 or ACPT-I

Example 1: experimental part



(i) ref (Selvam et al 2010) (ii) procedure A or B; (iii) and (iv) procedure C or D. For R¹⁻⁵ and X see Table1.

General. All chemicals and solvents were purchased from commercial suppliers (Acros, Aldrich) and used as received. Z-L-vinyl glycine methyl ester was purchased from Ascent Scientific Ltd (North Somerset, UK). Solvents for reactions were dried on 4Å molecular sieves (Carlo Erba – SDS). ¹H (250.13 or 500.16 MHz), ¹³C (62.9 or 125.78 MHz) and ³¹P (101.25 or 202.47 MHz) NMR spectra were recorded on an ARX 250 or an Avance II 500 Bruker spectrometer. Chemical shifts (δ, ppm) are given with reference to residual ¹H or ¹³C of deuterated solvents (CDCl₃ 7.24, 77.00; CD₃OD 3.31, 49.0; D₂O 4.80) or external reference (H₃PO₄ 95%). Product visualization was achieved with 2% (w/v) ninhydrin in ethanol. Thin layer chromatography (TLC) system for routine monitoring the course of certain reactions and confirming the purity of analytical samples employed aluminium-backed silica gel plates (Merck DC Kieselgel 60 F₂₅₄): CH₂Cl₂/MeOH or cyclohexane/ethyl acetate were used as developing solvents and detection of spots was made by UV light and/or by iodine vapours. Merck silica gel (230-400 mesh) was used for flash chromatography. Optical rotations were measured at the sodium D line (589 nm) at room temperature with a Perkin-Elmer 341 polarimeter using a 1 dm path length cell. Mass spectra (MS) were recorded with a LCQ-advantage (ThermoFinnigan) mass spectrometer with positive (ESI+) or negative (ESI-) electrospray ionization (ionization tension 4.5 kV, injection temperature 240 °C). HPLC analyses were carried out on a Gilson analytical instrument with a 321 pump, column

temperature of Crownpak columns was controlled with an Igloo-CIL Peltier effect thermostat, eluted peaks were detected by a UV-vis 156 detector and retention times are reported in minutes. Two columns were used on analytic scale: a Daicel Crownpak CR(+) column (150 mm × 4 mm), further designed as "Crownpak", eluted with pH 2.0 perchloric acid at a 0.4 mL.min⁻¹ flow rate, and a Phenomenex RP Polar column (250 mm × 4.6 mm, 4 μm), further designed as "RP Polar", eluted at a 0.5 mL.min⁻¹ flow rate with the following method: solvent A: water / formic acid 1000 : 1, solvent B: water / acetonitrile / formic acid 900 : 100 : 1, 100% A for 10 min, linear gradient to 100% B from 10 to 30 min, 100% B from 30 to 40 min. Preparative scale HPLC was performed with a Daicel Crownpak CR(+) 150 × 10 mm column, further designed as "Preparative Crownpak", eluted with a pH 2.0 hydrochloric acid aqueous solution. HPLC-MS analyses were performed on a Thermo Finnigan LCQ Advantage Instrument as described above, equipped for HPLC with a Phenomenex RP Polar column (250 mm × 4.6 mm, 4 μm). Products were eluted with the following gradient using solvent A (water / acetonitrile / formic acid 950 : 50 : 1) and solvent B (water / acetonitrile / formic acid 900 : 100 : 1), 100% A for 10 min, linear increase from 0 to 100% B between 10 and 20 min, 100% B from 20 to 30 min. Purity of the tested compounds was established by analytical HPLC-MS or by HPLC and was at least 95%.

[[((3S)-3-(N-Benzyloxycarbonyl)amino-3-methoxycarbonyl)propyl]phosphinic Acid (1). 1

was synthesized according to previously published procedure. (WO2007/052169, Selvam et al JMedChem 2010).

General procedure A: To a solution of H-phosphinic acid **1** (1.0 mmol, 1 eq) and aldehyde (X = OH) or halide (X = H) (2.2 eq) in 2.0 mL of dichloromethane at 0 °C under an argon atmosphere was added dropwise *N,O*-bis(trimethylsilyl)acetamide (BSA) (4.4 eq). The mixture was allowed to warm to room temperature and stirred overnight, then cooled to 0 °C and 25 mL of 1N HCl were added, then extracted with ethyl acetate. The organic layer was concentrated in vacuo. This residue was dissolved in 10 mL of water, the pH was adjusted to 7 using saturated sodium hydrogenocarbonate solution, then extracted with ethylacetate (2 × 50 mL). The organic layer was separated, and the aqueous phase was treated with aqueous HCl to adjust the pH to 1. The aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined acidic organic extracts were dried over magnesium sulfate, filtered and concentrated in vacuo.

General procedure B: To a solution of 1.0 mmol of H-phosphinic acid **1** and 2.2 mmol of aldehyde (X = OH) or bromide (X = H) in 2.0 mL of dry dichloromethane at 0 °C under argon was added dropwise *N,O*-bis(trimethylsilyl)-acetamide (BSA, 1.08 mL, 4.4 mmol). The mixture was allowed to warm to room temperature and stirred overnight under argon, then
5 cooled to 0 °C. 1N hydrochloric acid (20 mL) was added, then extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude product, still containing aldehyde or bromide in excess, was directly deprotected.

General procedure C: The crude product synthesised by general procedure A or B was dissolved in 6N hydrochloric acid (10.0 mL). The mixture was stirred at 100 °C for 5 h, then cooled to room temperature. The solution was diluted with ethyl acetate (50 mL) and water (10 mL). The separated organic layer was extracted with 1N hydrochloric acid (3 × 10 mL). The combined aqueous phases were concentrated under vacuum, then the residue was purified
15 using a Dowex AG 50W-X4 cation exchange resin column (H⁺, 50-100 mesh, water or 1N NH₄OH elution). If necessary, another purification was made on an anion exchange chromatography (Dowex AG 1-X4, AcO⁻, 200-400 mesh). The loading solution was prepared in 500 mL of freshly boiled and cooled pure water (the pH was adjusted to 5). The resin was first eluted with freshly boiled and cooled water, then with formic acid.

General procedure D: The crude product synthesised by general procedure A or B was dissolved in 6N hydrochloric acid (5.0 mL). The mixture was stirred at 100 °C for 5 h, then cooled to room temperature. The solution was diluted with ethyl acetate (50 mL) and water (10 mL). The separated organic layer was extracted with 1N hydrochloric acid (3 × 10
25 mL). The combined aqueous phases were concentrated under vacuum. The residue was purified using an anion exchange chromatography (Dowex AG 1-X4, AcO⁻, 200-400 mesh). The loading solution was prepared in 500 mL of freshly boiled and cooled pure water (The pH was adjusted to 5). The resin was first eluted with freshly boiled and cooled water, then with dilute HCl.

General procedure E (preparation of aryloxyacetic acid ethyl ester): To a solution of phenol (1eq) in dry acetone, anhydrous potassium carbonate (1.3 eq) was added at room temperature. After 10 minutes, ethylbromoacetate (1.5eq) was added and the mixture was

refluxed and monitored by TLC until completion. After cooling, the solvent was removed under reduced pressure. The residue was added with water, then extracted with dichloromethane and washed with brine. The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under vacuum. Ethanol or isopropanol was added and evaporated by azeotropic distillation in order to eliminate the ethylbromoacetate in excess. The solvent was evaporated to dryness, affording a residue which was chromatographed on a silica gel column (dichloromethane/ ethyl acetate as eluent) to afford aryloxyacetic acid ethyl ester.

General procedure F (preparation of alcohol): NaBH₄ (1,1eq) was added to a stirred and ice-bath cooled solution of aldehyde (1eq) in THF and water (50/50). The reaction mixture was stirred for 45 minutes at 0°C and, after distilling off the organic solvent, the aqueous residue was added with water (50ml) and then extracted with dichloromethane (50ml). The organic layer was washed with 10% Na₂CO₃ (20ml) and brine (20ml), then dried over Na₂SO₄, filtered, and evaporated in vacuo to dryness, affording a residue which was chromatographed on a silica gel column (dichloromethane/ ethyl acetate as eluent).

General procedure G (preparation of bromide): PBr₃ (1eq) was carefully added to a solution of alcohol (1eq) in distilled dichloromethane at 0°C under argon. The reaction mixture was stirred at 0°C for 3h and extracted with dichloromethane. The organic layer was washed with brine, dried over Na₂SO₄, filtered, and evaporated in vacuo to dryness without further purification.

Derivative 2

[[((3S)-3-(N-Benzyloxycarbonyl)amino-3-methoxycarbonyl)propyl][(4-(carboxymethoxy)phenyl)hydroxymethyl]phosphinic Acid. The compound was prepared according to general procedure B with H-phosphinic acid 1 (252 mg, 0.8 mmol) and 4-formylphenoxyacetic acid (317 mg, 1.8 mmol). 629 mg of crude product were obtained. ³¹P NMR (101 MHz, CD₃OD): δ 49.3.

[[((3S)-3-Amino-3-carboxy)propyl][(4-(carboxymethoxy)phenyl)hydroxymethyl]phosphinic Acid (Derivative 2). The previous compound was deprotected according to general procedure C. 150 mg of pure derivative 2 were obtained (54% yield, 2 steps). ¹H NMR (250 MHz, D₂O): δ 1.71-1.94 (m, 2H), 1.98-2.00 (m, 2H), 3.95 (bs, 1H), 4.58 (s, 2H), 4.81 (bs, 1H), 6.85 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 7.8

Hz, 2H). ^{31}P NMR (101 MHz, D_2O): δ 55.4. ^{13}C NMR (126 MHz, D_2O): δ 22.8 and 22.9 (2d, $J = 89$ Hz), 24.1, 54.5 (d, $J = 15$ Hz), 66.2, 73.0 (d, $J = 111$ Hz), 110.0, 130.0, 131.3, 158.5, 172.8, 174.7. HPLC – MS: $t_{\text{R}} = 6.05$ min. HPLC (Crownpak, $T = 5.0^\circ\text{C}$, detection $\lambda = 210 / 254$ nm): $t_{\text{R}} = 18.4$ min.

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Derivative 3

(((3*S*)-3-(*N*-Benzyloxycarbonyl)amino-3-methoxycarbonyl)propyl)[(3-methoxy-4-(methoxy carbonyl)methoxyphenyl)hydroxymethyl]phosphinic Acid). The compound was prepared according to general procedure B with H-phosphinic acid **1** (292 mg, 0.9 mmol) and methyl 4-formyl-2-methoxyphenoxyacetate (457 mg, 2.0 mmol). 863 mg of crude product were obtained. ^{31}P NMR (101 MHz, CD_3OD): δ 47.4.

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(((3*S*)-3-Amino-3-carboxy)propyl)[(3-methoxy-4-(carboxymethoxy)phenyl)hydroxymethyl] phosphinic Acid (Derivative 3). The previous compound was deprotected according to general procedure D. The pure compound was obtained with a purification on anion exchange resin on 95 mg of crude product on a 14×1 cm column. The desired product was eluted with a 1.0×10^{-2} N hydrochloric acid aqueous solution. 61 mg of pure derivative **3** were obtained (18% yield, 2 steps). ^1H NMR (500 MHz, D_2O): δ 1.73-1.90 (m, 2H), 2.04-2.11 (m, 2H), 3.86 (s, 3H), 4.03 (q, $J = 6.0$ Hz, 1H), 4.76 (s, 2H), 4.87 (d, $J = 8.5$ Hz, 1H), 6.93 (d, $J = 8.5$ Hz, 1H), 6.97 (d, $J = 8.5$ Hz, 1H), 7.11 (s, 1H). ^{31}P NMR (101 MHz, D_2O): δ 56.2. ^{13}C NMR (126 MHz, D_2O): δ 22.7 (2d, $J = 89$ Hz), 24.0, 54.4 (d, $J = 15$ Hz), 57.2, 66.8, 73.0 (d, $J = 111$ Hz), 112.6, 114.6, 121.2, 131.9, 147.7, 149.8, 172.6, 174.3. MS (ESI): m/z 376.0 (M-1). HPLC (Crownpak, $T = 10.0^\circ\text{C}$, detection $\lambda = 210 / 254$ nm): $t_{\text{R}} = 15.4$ min. HPLC (RP Polar, detection $\lambda = 230 / 270$ nm): $t_{\text{R}} = 10.0$ min.

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Derivative 4

(((3*S*)-3-(*N*-Benzyloxycarbonyl)amino-3-methoxycarbonyl)propyl)[(3,5-dimethoxy-4-(carboxy methoxy)phenyl)hydroxymethyl]phosphinic Acid). The compound was prepared according to general procedure B with H-phosphinic acid (292 mg, 0.9 mmol) and 4-formyl-2,6-dimethoxyphenoxyacetic acid (250 mg, 1.0 mmol). ^{31}P NMR (101 MHz, CD_3OD): δ 47.8.

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(((3*S*)-3-Amino-3-carboxy)propyl)[3,5-dimethoxy-4-(carboxymethoxy)phenyl]hydroxymethyl] phosphinic Acid (Derivative 4). The previous compound was deprotected according to general procedure D. The pure compound was obtained with a purification on anion exchange resin on 300 mg of crude product on a 13×2

cm column. The desired product was eluted with a 1.5×10^{-2} N hydrochloric acid aqueous solution. 155 mg of pure derivative **4** were obtained (42% yield, 2 steps). ^1H NMR (500 MHz, D_2O): δ 1.85-1.96 (m, 2H), 2.06-2.11 (m, 2H), 3.81 (2s, 6H), 4.03 (m, 1H), 4.59 (m, 2H), 4.95 (d, $J = 8.5$ Hz, 1H), 6.77 (s, 2H). ^{31}P NMR (101 MHz, D_2O): δ 57.6. ^{13}C NMR (126 MHz, D_2O): δ 22.8 (d, $J = 89$ Hz), 24.0, 54.4 (d, $J = 15$ Hz), 57.6, 70.8, 73.2 (d, $J = 110$ Hz), 105.9, 134.5, 136.4, 153.2, 172.5, 174.8. MS (ESI): m/z 405.9 (M-1). HPLC (Crownpak, $T = 10.0^\circ\text{C}$, detection $\lambda = 210 / 254$ nm): $t_R = 22.7$ and 25.0 min. HPLC (RP Polar, detection $\lambda = 230 / 270$ nm): $t_R = 14.7$ min.

Derivative 5

Ethyl 4-formyl-2-methoxy-6-nitrophenoxyacetate: To a solution of 5-nitrovanilline (591 mg, 3.0 mmol) in DMF (9.0 mL) was added cesium carbonate (2.00 g, 6.16 mmol), followed by ethyl bromoacetate (3.33 mL, 30 mmol). The red mixture was left under stirring at 110°C until it became yellow, and then for further 3 minutes. After evaporation of DMF under reduced pressure, 22 mL of water were added and the mixture was extracted with dichloromethane (60 mL). The organic phase was washed with brine (15 mL), dried over magnesium sulfate and concentrated under vacuum. The residue was purified by column chromatography over silica gel (eluent: dichloromethane) to give 625 mg of a solid (74% yield). ^1H NMR (250 MHz, CDCl_3): δ 1.30 (t, $J = 7.2$ Hz, 3H), 4.01 (s, 3H), 4.27 (q, $J = 7.2$ Hz, 2H), 4.91 (s, 2H), 7.65 (s, 1H), 7.90 (s, 1H), 9.95 (s, 1H). ^{13}C NMR (63 MHz, CDCl_3): δ 14.6, 57.2, 62.0, 70.0, 113.9, 120.4, 132.0, 145.2, 145.9, 154.2, 168.5, 189.3.

[((3S)-3-(N-Benzyloxycarbonyl)amino-3-methoxycarbonyl)propyl][(3-methoxy-5-nitro-4-(ethoxycarbonyl)methoxyphenyl)hydroxymethyl]phosphinic Acid: The compound was prepared according to general procedure A with H-phosphinic acid **1** (243 mg, 0.77 mmol) and ethyl 4-formyl-2-methoxy-6-nitrophenoxyacetate (481 mg, 1.7 mmol). 169 mg of crude product were obtained. ^{31}P NMR (101 MHz, CD_3COCD_3): δ 44.8.

[((3S)-3-Amino-3-carboxy)propyl][(3-methoxy-5-nitro-4-(carboxymethoxy)phenyl)hydroxymethyl] phosphinic Acid (Derivative 5). The previous compound was deprotected according to general procedure C. 42.4 mg of pure product derivative **5** were obtained (13% yield, 2 steps). ^1H NMR (250 MHz, D_2O): δ 1.63-1.90 (m, 2H), 1.97-2.17 (m, 2H), 3.84 (s, 3H), 4.03 (m, 1H), 4.72 (s, 2H), 4.90 (d, $J = 9.5$ Hz, 1H), 7.31 (s, 1H), 7.43 (s, 1H). ^{31}P NMR (101 MHz, D_2O): δ 52.1. ^{13}C NMR (126 MHz, D_2O): δ 23.1 and 23.2 (2d, $J = 89$ Hz), 24.2, 54.6 (d, $J = 14$ Hz), 71.2, 72.9 (d, $J = 108$ Hz), 115.8,

117.5, 136.3, 140.9, 144.9, 154.3, 172.8, 174.3. MS (ESI): m/z 423.1 (M+1), 421.0 (M-1). HPLC – MS (Method A): t_R = 9.51 min.

Derivative 6

5 **Ethyl 2-(2-fluoro-4-formyl-6-methoxyphenoxy)acetate:** To a solution of 3-fluoro-4-hydroxy-5-methoxybenzaldehyde (302 mg, 1.78 mmol) in acetone (20 mL) was added cesium carbonate (765mg, 2.35 mmol), followed by ethyl bromoacetate (0.30 mL, 2.7 mmol). The mixture was refluxed in acetone under stirring for 1 hour. After evaporation of acetone under reduced pressure, 100 mL of water were added and the mixture was extracted with
10 dichloromethane (200 mL). The organic phase was washed with brine (100 mL), dried over magnesium sulfate and concentrated under vacuum. The residue was purified by column chromatography over silica gel (eluent: dichloromethane) to give 361 mg of an oil (79% yield). ^1H NMR (500MHz, CD_3COCD_3): δ 1.25 (t, J = 7.2 Hz, 3H), 3.98 (s, 3H), 4.20 (q, J = 7.2 Hz, 2H), 4.89 (t, J = 1.6Hz 2H), 7.34 (dd, J = 10.3Hz, 1.6Hz, 1H), 7.41 (s, 1H), 9.88 (d, J = 1.5Hz, 1H). ^{13}C NMR (126 MHz, CD_3COCD_3): δ 15.0, 57.6, 62.1, 70.3(d, J = 1.9Hz), 110.0, 111.8(d, J = 20.6Hz), 133.1(d, J = 7.2Hz), 141.8,(d, J = 12.7Hz), 154.8(d, J = 4.5Hz), 155.0 d, J = 46.1Hz),, 169.7, 191.3.

[[[(3S)-3-(N-Benzyloxycarbonyl)amino-3-methoxycarbonyl)propyl][(3-fluoro-5-methoxy-4-(ethoxycarbonyl)methoxyphenyl)hydroxymethyl]phosphinic Acid: The compound was
20 prepared according to general procedure A with H-phosphinic acid (465 mg, 1.48 mmol) and ethyl 2-(2-fluoro-4-formyl-6-methoxyphenoxy)acetate (361 mg, 1.41 mmol). 1.3 g of crude product were obtained. ^{31}P NMR (101 MHz, CD_3OD): δ 47.6. MS (ESI): m/z 570.1 (M-1)

[[[(3S)-3-Amino-3-carboxy)propyl][(3- fluoro -5-methoxy-4-(carboxymethoxy) phenyl hydroxymethyl] phosphinic Acid (Derivative 6). The previous compound was deprotected
25 according to general procedure C. 115.0 mg of pure derivative 6 were obtained (21% yield, 2 steps). ^1H NMR (500 MHz, D_2O): δ 1.80-1.80 (m, 2H), 1.99-2.08 (m, 2H), 3.77 (s, 3H), 3.95 (m, 1H), 4.60 (s, 2H), 4.74 (d, J = 9.7 Hz, 1H), 6.77 (d, J = 11.3Hz, 1H), 6.83 (s, 1H). ^{31}P NMR (202 MHz, D_2O): δ 40.3. ^{13}C NMR (126 MHz, D_2O): δ 23.0 and 23.8 (dd, J = 89.4; 7.7 Hz), 24.4, 54.8 (d, J = 14.1 Hz), 57.7, 71.0, 73.5 (d, J = 107.7 Hz), 108.5, 108.8(d, J = 20.9 Hz),
30 135.0(d, J = 12.8 Hz), 135.7(d, J = 8.5 Hz), 153.7, 156.0(d, J = 244Hz), 173.1, 174.6. MS (ESI): m/z 396.0 (M+1). HPLC – MS (Method A): t_R = 7.91 min.

Derivative 7

Ethyl 2-(2-chloro-4-formyl-6-methoxyphenoxy)acetate: To a solution of 5-chlorovanilline (505 mg, 2.7 mmol) in acetone (25 mL) was added cesium carbonate (1.16 g, 3.56 mmol), followed by ethyl bromoacetate (0.45 mL, 4.05 mmol). The mixture was refluxed in acetone under stirring for 1 hour. After evaporation of acetone under reduced pressure, 100 mL of water were added and the mixture was extracted with dichloromethane (200 mL). The organic phase was washed with brine (100 mL), dried over magnesium sulfate and concentrated under vacuum. The residue was purified by column chromatography over silica gel (eluent: dichloromethane) to give 330 mg of an oil (45% yield). ¹H NMR (250 MHz, CD₃COCD₃): δ 1.27 (t, *J* = 7.2 Hz, 3H), 3.98 (s, 3H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.87 (s, 2H), 7.50 (s, 1H), 7.58 (s, 1H), 9.90 (s, 1H). ¹³C NMR (126 MHz, CD₃COCD₃): δ 15.1, 57.5, 62.1, 70.5, 112.3, 125.8, 128.9, 134.0, 149.7, 154.5, 169.5, 191.2.

[[(3*S*)-3-(*N*-Benzyloxycarbonyl)amino-3-methoxycarbonyl]propyl][(3-chloro-5-methoxy-4-(ethoxycarbonyl)methoxyphenyl)hydroxymethyl]phosphinic Acid: The compound was prepared according to general procedure A with H-phosphinic acid (398 mg, 1.3 mmol) and Ethyl 2-(2chloro-4-formyl-6-methoxyphenoxy)acetate (330 mg, 1.2 mmol). 819 mg of crude product were obtained. ³¹P NMR (101 MHz, CD₃COCD₃): δ 48.2. MS (ESI): *m/z* 587.8 (M+1), 585.9 (M-1)

[[(3*S*)-3-Amino-3-carboxy]propyl][(3-chloro-5-methoxy-4-(carboxymethoxy) phenyl hydroxymethyl] phosphinic Acid (Derivative 7). The previous compound was deprotected according to general procedure C. 120.0 mg of pure derivative 7 were obtained (26% yield, 2 steps). ¹H NMR (500 MHz, D₂O): δ 1.78-1.87 (m, 2H), 2.05-2.11 (m, 2H), 3.78 (s, 3H), 4.03 (m, 1H), 4.57 (s, 2H), 4.85 (d, *J* = 9.2 Hz, 1H), 6.98 (s, 1H), 7.02 (s, 1H). ³¹P NMR (202 MHz, D₂O): δ 43.6. ¹³C NMR (126 MHz, D₂O): δ 22.5 and 23.3 (dd, *J* = 88.3; 6.6 Hz), 24.1, 54.5 (d, *J* = 14.6 Hz), 57.6, 70.6, 72.9 (d, *J* = 108.9 Hz), 111.8, 121.5, 128.4, 136.0, 143.5, 154.0, 172.7, 174.4. MS (ESI): *m/z* 410.0 (M-1). HPLC – MS (Method A): *t_R* = 9.00 min.

Derivative 8

Ethyl 2-(2-iodo-4-formyl-6-methoxyphenoxy)acetate: To a solution of 5-iodovanilline (502 mg, 1.8 mmol) in acetone (25 mL) was added cesium carbonate (766 mg, 2.35 mmol), followed by ethyl bromoacetate (0.30 mL, 2.7 mmol). The mixture was refluxed in acetone under stirring for 1 hour. After evaporation of acetone under reduced pressure, 100 mL of water were added and the mixture was extracted with dichloromethane (200 mL). The organic

phase was washed with brine (100 mL), dried over magnesium sulfate and concentrated under vacuum. The residue was purified by column chromatography over silica gel (eluent: dichloromethane) to give 320 mg of a yellow solid (49% yield). ¹H NMR (250 MHz, CD₃COCD₃): δ 1.28 (t, *J* = 7.2 Hz, 3H), 3.97 (s, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.85 (s, 2H), 7.55 (s, 1H), 7.95 (s, 1H), 9.89 (s, 1H). ¹³C NMR (126 MHz, CD₃COCD₃): δ 15.2, 57.4, 62.1, 70.5, 92.4, 113.9, 135.1, 135.5, 153.1 (2C), 169.4, 169.5, 191.0.

[[((3*S*)-3-(*N*-Benzyloxycarbonyl)amino-3-methoxycarbonyl)propyl][(3-iodo-5-methoxy-4-(ethoxycarbonyl)methoxyphenyl)hydroxymethyl]phosphinic Acid: The compound was prepared according to general procedure A with H-phosphinic acid (289 mg, 0.92 mmol) and Ethyl 2-(2-iodo-4-formyl-6-methoxyphenoxy)acetate (320 mg, 0.88 mmol). 516 mg of crude product were obtained. ³¹P NMR (101 MHz, CD₃COCD₃): δ 48.1. MS (ESI): *m/z* 677.9 (M-1)

[[((3*S*)-3-Amino-3-carboxy)propyl][(3-iodo-5-methoxy-4-(carboxymethoxy)phenyl)hydroxymethyl]phosphinic Acid (Derivative 8). The previous compound was deprotected according to general procedure C. 90.0 mg of pure derivative **8** were obtained (20% yield, 2 steps). ¹H NMR (500 MHz, D₂O): δ 1.73-1.77 (m, 2H), 2.05-2.08 (m, 2H), 3.81 (s, 3H), 4.00 (m, 1H), 4.56 (s, 2H), 4.78 (d, *J* = 9.4 Hz, 1H), 7.07 (s, 1H), 7.40 (s, 1H). ³¹P NMR (202 MHz, D₂O): δ 40.4. ¹³C NMR (126 MHz, D₂O): δ 23.1 and 23.9 (dd, *J* = 89.2; 10.4 Hz), 24.5, 54.9 (d, *J* = 13.9 Hz), 57.5, 70.6, 73.1 (d, *J* = 108.0 Hz), 92.2, 113.6, 130.1, 138.2, 147.1, 152.9, 173.2, 174.5. MS (ESI): *m/z* 501.9 (M-1). HPLC – MS (Method A): *t_R* = 12.15 min.

Derivative 9

ethyl 2-(2,6-dichloro-4-formylphenoxy)acetate: To a solution of 3,5-dichloro-4-hydroxybenzaldehyde (302 mg, 1.6 mmol) in acetone (15 mL) was added cesium carbonate (700 mg, 2.15 mmol), followed by ethyl bromoacetate (0.27 mL, 2.43 mmol). The mixture was refluxed in acetone under stirring for 1 hour. After evaporation of acetone under reduced pressure, 100 mL of water were added and the mixture was extracted with dichloromethane (200 mL). The organic phase was washed with brine (100 mL), dried over magnesium sulfate and concentrated under vacuum. The residue was purified by column chromatography over silica gel (eluent: dichloromethane) to give 264 mg of an oil (59% yield). ¹H NMR (500 MHz, CDCl₃): δ 1.29 (t, *J* = 7.2 Hz, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 4.85 (s, 2H), 7.96 (s, 2H), 9.98 (s, 1H). ¹³C NMR (126 MHz, CD₃COCD₃): δ 15.0, 62.3, 70.8, 131.2, 131.4, 135.4, 156.4, 168.4, 190.5.

[[((3S)-3-(N-Benzyloxycarbonyl)amino-3-methoxycarbonyl)propyl][(3,5-dichloro-4-(ethoxycarbonyl)methoxyphenyl)hydroxymethyl]phosphinic Acid: The compound was

prepared according to general procedure A with H-phosphinic acid (315 mg, 1.0 mmol) and ethyl 2-(2,6-dichloro-4-formylphenoxy)acetate (264 mg, 0.956 mmol). 553mg of crude product were obtained. ³¹P NMR (101 MHz, CD₃COCD₃): δ 47.3 MS (ESI): *m/z* 591.0(M-1)

[[((3S)-3-Amino-3-carboxy)propyl][(3,5-dichloro-4-(carboxymethoxy) phenyl hydroxy methyl] phosphinic Acid (Derivative 9). The previous compound was deprotected according

to general procedure C. 102.0 mg of pure dervative **9** were obtained (26% yield, 2 steps). ¹H NMR (250 MHz, D₂O): δ 1.69-1.81 (m, 2H), 2.02-2.12 (m, 2H), 4.03 (m, 1H), 4.69 (s, 2H), 4.78 (d, *J* = 9.6 Hz, 1H), 7.41 (s, 1H). ³¹P NMR (101 MHz, D₂O): δ 39.3. ¹³C NMR (126 MHz, D₂O): δ 23.6 and 24.4 (dd, *J* = 78.7; 13.8Hz), 24.8, 55.5, 70.8, 73.2 (d, *J* = 117.4 Hz), 128.7, 129.8, 138.6, 150.1, 174.3, 174.4 MS (ESI): *m/z* 413.9 (M-1). HPLC – MS (Method A): *t_R* = 11.34 min.

Derivative 10

ethyl 2-(4-formyl-2,6-dimethylphenoxy)acetate: To a solution of 4-hydroxy-3,5-dimethylbenzaldehyde (500 mg, 3.33 mmol) in acetone (20 mL) was added cesium carbonate (1.41g, 4.33 mmol), followed by ethyl bromoacetate (0.555mL, 5 mmol). The mixture was refluxed in acetone under stirring for 1 hour. After evaporation of acetone under reduced pressure, 100 mL of water were added and the mixture was extracted with dichloromethane (200 mL). The organic phase was washed with brine (100 mL), dried over magnesium sulfate and concentrated under vacuum. The residue was purified by column chromatography over silica gel (eluent: dichloromethane) to give 580 mg of an oil (74% yield). ¹H NMR (250 MHz, CDCl₃): δ 1.25(t, *J* = 6.9 Hz, 3H), 4.27 (s, 6H), 4.21 (q, *J* = 6.9 Hz, 2H), 4.38 (s, 2H), 7.44 (s, 2H), 9.77 (s, 1H). ¹³C NMR (126 MHz, CDCl₃): δ 15.2, 17.4, 62.2, 70.1, 131.6, 132.8, 133.8, 161.7, 169.5, 192.1.

[[((3S)-3-(N-Benzyloxycarbonyl)amino-3-methoxycarbonyl)propyl][(3,5-dimethyl-4-(ethoxycarbonyl)methoxyphenyl)hydroxymethyl]phosphinic Acid: The compound was

prepared according to general procedure A with H-phosphinic acid (809 mg, 2.57 mmol) and ethyl 2-(4-formyl-2,6-dimethylphenoxy)acetate (580 mg, 2.46 mmol). 1.4g of crude product were obtained. ³¹P NMR (101 MHz, CDCl₃): δ 50.1 MS (ESI): *m/z* 550.1(M-1)

[[((3S)-3-Amino-3-carboxy)propyl][(3,5-dimethyl-4-(carboxymethoxy) phenyl hydroxy methyl] phosphinic Acid (Derivative 10). The previous compound was deprotected

according to general procedure C. 238.0 mg of pure derivative **10** were obtained (26% yield, 2 steps). ^1H NMR (500 MHz, D_2O): δ 1.70-1.86 (m, 2H), 1.98-2.06 (m, 2H) 2.16 (s, 6H), 3.97 (m, 1H), 4.41 (s, 2H), 4.77 (d, $J = 8.7$ Hz, 1H), 7.03 (s, 2H). ^{31}P NMR (202 MHz, D_2O): δ 43.3. ^{13}C NMR (126 MHz, D_2O): δ 16.8, 22.6 and 23.3 (dd, $J = 88.5$; 8.7Hz), 24.2, 54.6(d, $J=14.5\text{Hz}$), 69.9, 73.2 (d, $J = 109.3$ Hz), 128.9, 132.6, 134.5, 155.4, 172.9, 174.6 MS (ESI): m/z 374.1 (M-1), 376.0(M+1). HPLC – MS (Method A): $t_R = 8.33$ min.

Derivative 11

[[((3S)-3-(N-Benzyloxycarbonyl)amino-3-methoxycarbonyl)propyl][(4-((E)-2-

carboxyethenyl) phenyl)hydroxymethyl]phosphinic Acid). The compound was prepared according to general procedure B with H-phosphinic acid (315 mg, 1.0 mmol) and (E)-4-formyl-phenylacrylic acid (388 mg, 2.2 mmol). The reaction was stirred for 48h to achieve complete conversion. ^{31}P NMR (101 MHz, CD_3OD): δ 48.7.

[[((3S)-3-Amino-3-carboxy)propyl][(4-((E)-2-carboxyethenyl)phenyl)hydroxymethyl]

phosphinic Acid (Derivative 11). The previous compound was deprotected according to general procedure C. After the cation exchange resin, 355 mg of compound were obtained. A second purification on an anion exchange resin (AG 1-X4, 200-400 Mesh, 18 x 2.5 cm, AcO^-) was necessary to obtain a pure compound. The crude compound was diluted in 500 mL of pure and freshly boiled and cooled water, and the pH was brought to 9 (with a freshly prepared 1N sodium hydroxide aqueous solution). The resin was eluted with formic acid (1N to 5N) and the desired compound was eluted with 3N formic acid. 158 mg of pure derivative **11** were obtained (46% yield, 2 steps). ^1H NMR (500 MHz, D_2O): δ 1.76-1.87 (m, 2H), 2.05-2.16 (m, 2H), 4.05 (t, $J = 6.0$ Hz, 1H), 4.94 (d, $J = 10.0$ Hz, 1H), 6.47 and 6.48 (2d, $J = 16.0$ Hz, 1H), 7.45 (d, $J = 7.5$ Hz, 2H), 7.61 (d, $J = 5.5$ Hz, 2H), 7.67 and 7.68 (2d, $J = 16.0$ Hz, 1H). ^{31}P NMR (101 MHz, D_2O): δ 53.0. ^{13}C NMR (126 MHz, D_2O): δ 23.2 (d, $J = 86$ Hz), 24.4, 54.8, 74.0 (d, $J = 106$ Hz), 118.9, 128.9, 129.9, 135.1, 141.3, 147.5, 172.4, 173.0. HPLC – MS: $t_R = 7.49$ min.

Derivative 12

Ethyl 3-(4-formyl)-phenylpropanoate. the compound was prepared according to a previously described procedure (a) Battistuzzi, G.; Cacchi, S.; Fabrizi, G.; Bernini, R. 3-Arylpropanoate esters through the palladium-catalyzed reaction of aryl halides with acrolein diethyl acetal. *Synlett* **2003**, 8, 1133-1136. b) Giannini, G.; Marzi, M.; Pezzi, R.; Brunetti, T.;

Battistuzzi, G.; Di Marzo, M.; Cabri, W.; Vesci, L.; Pisano, C. *N*-hydroxy-(4-oxime)-cinnamide: a versatile scaffold for the synthesis of novel histone deacetylase (HDAC) inhibitors. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2346-2349). To a solution of 4-bromobenzaldehyde (740 mg, 4.0 mmol), acrolein diethylacetal (1.83 mL, 12 mmol), tetra-*n*-butylammonium chloride (1.11 g, 4.0 mmol), tributylamine (1.91 mL, 8.0 mmol) in 16 mL of DMF, palladium(II) acetate (27 mg, 0.12 mmol) was added. The mixture was warmed at 90 °C and stirred overnight. After cooling, the reaction mixture was diluted with 2N HCl (60 mL) and extracted with diethyl ether (60 mL x 3). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (eluent: 5 – 15% EtOAc/cyclohexane) to give 538 mg of a yellow oil (65% yield). ¹H NMR (250 MHz, CDCl₃): δ 1.25 (t, *J* = 7.0 Hz, 3H), 2.68 (d, *J* = 7.5 Hz, 2H), 3.06 (d, *J* = 7.5 Hz, 2H), 4.14 (q, *J* = 7.0 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.83 (d, *J* = 8.2 Hz, 2H), 10.00 (s, 1H). ¹³C NMR (63 MHz, CDCl₃): δ 14.6, 31.5, 35.7, 61.1, 129.4, 130.4, 135.2, 148.3, 172.8, 192.4.

[(*(3S)*-3-(*N*-Benzyloxycarbonyl)amino-3-methoxycarbonyl)propyl][(4-(ethoxycarbonyl ethyl)phenyl)hydroxymethyl]phosphinic Acid. The compound was prepared according to general procedure A with H-phosphinic acid **1** (375 mg, 1.19 mmol) and ethyl 3-(4-formyl)-phenylpropanoate (540 mg, 2.62 mmol). 336 mg of crude product were obtained. ³¹P NMR (101 MHz, CD₃COCD₃): δ 45.6.

[(*(3S)*-3-Amino-3-carboxy)propyl][(4-(carboxyethyl)phenyl)hydroxymethyl] phosphinic Acid (Derivative **12).** The previous compound was deprotected according to general procedure C. 152.6 mg of pure product derivative **12** were obtained (37% yield, 2 steps). ¹H NMR (500 MHz, D₂O): δ 1.74-1.99 (m, 2H), 2.01-2.15 (m, 2H), 2.68 (t, *J* = 7.3 Hz, 2H), 2.91 (t, *J* = 7.3 Hz, 2H), 4.05 (m, 1H), 4.94 (d, *J* = 9.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H). ³¹P NMR (101 MHz, D₂O): δ 55.7. ¹³C NMR (126 MHz, D₂O): δ 22.7 and 22.8 (2d, *J* = 89 Hz), 24.1, 31.4, 36.7, 54.5 (d, *J* = 14 Hz), 73.5 (d, *J* = 109 Hz), 128.7, 129.9, 135.8, 142.3, 172.7, 179.3. MS (ESI): *m/z* 346.0 (M+1), 344.0 (M-1). HPLC – MS (Method A): *t_R* = 9.27 min.

Derivative 13

[(*(3S)*-3-(*N*-Benzyloxycarbonyl)amino-3-methoxycarbonyl)propyl][(4-(2-hydroxyethoxy) phenyl)hydroxymethyl]phosphinic Acid: The compound was prepared according to general procedure B with H-phosphinic acid **1** (304 mg, 1.0 mmol) and 4-(2-

hydroxyethoxy)benzaldehyde (353 mg, 2.2 mmol). 773 mg of crude product were obtained.
³¹P NMR (101 MHz, CD₃OD): δ 49.2.

(((3*S*)-3-Amino-3-carboxy)propyl)[(4-(2-

hydroxyethoxy)phenyl)hydroxymethyl]phosphinic Acid (Derivative 13). The previous
 5 compound was deprotected according to general procedure D. The purification on anion
 exchange column was performed with 73 mg of crude product on a 21 × 1 cm column. The
 desired product was eluted with a 2.5 × 10⁻² N hydrochloric acid aqueous solution. 49.0 mg of
 pure derivative **13** were obtained (15% yield, 2 steps). ¹H NMR (500 MHz, D₂O): δ 1.78-1.87
 (m, 2H), 2.06-2.09 (m, 2H), 3.87 (m, 2H), 4.03 (q, *J* = 5.0 Hz, 1H), 4.11 (m, 2H), 4.88 (d, *J* =
 10 7.5 Hz, 1H), 7.00 (dd, *J* = 2.5 / 8.0 Hz, 2H), 7.35 (dd, *J* = 3.0 / 8.0 Hz, 2H). ³¹P NMR (101
 MHz, D₂O): δ 55.1. ¹³C NMR (126 MHz, D₂O): δ 22.9 and 23.0 (2d, *J* = 89 Hz), 24.2, 54.6
 (d, *J* = 15 Hz), 61.6, 70.8, 73.2 (d, *J* = 111 Hz), 116.3, 130.0, 130.7, 159.6, 172.9. MS (ESI):
m/z 332.0 (M-1). HPLC (Crownpak, T = 10.0°C, detection λ = 210 / 254 nm): *t_R* = 9.9 min.
 HPLC (RP Polar, detection λ = 230 / 270 nm): *t_R* = 8.7 min.

Derivative 14

diisopropyl (4-formylphenoxy)methylphosphonate: To a solution of 4-
 hydroxybenzaldehyde (152 mg, 1.25 mmol) in DMF (20 mL) was added potassium carbonate
 (223 mg, 1.62 mmol), followed by diisopropyl bromomethylphosphonate (484mg, 1.87
 20 mmol). The mixture was heating in DMF at 90°C under stirring for 17 hours. After
 evaporation of DMF under reduced pressure, 100 mL of water were added and the mixture
 was extracted with ethyl acetate (3*200 mL). The organic phase was washed with brine (100
 mL), dried over magnesium sulfate and concentrated under vacuum. The residue was purified
 by column chromatography over silica gel (eluent: cyclohexane/ ethyl acetate (5:5)) to give
 25 98.2 mg of an oil (26% yield). ¹H NMR (250 MHz, CDCl₃): δ 1.33(t, *J* = 6.0 Hz, 12H), 4.25
 (d, *J*=10.2Hz, 2H), 4.82 (q, *J* = 6.0 Hz, 2H), 7.05 (d, *J*=8.7Hz, 2H), 7.81 (d, *J*=8.7Hz, 2H),
 9.87 (s, 1H). ¹³C NMR (126 MHz, CDCl₃): δ 25.4(dd,*J*=12.7; 3.4Hz), 64.0(d, *J*=171.0Hz)
 73.3(d, *J*=6.2Hz), 116.3, 132.2, 133.3, 164.8(d, *J*=13.4Hz), 192.0. ³¹P NMR (202 MHz,
 CDCl₃): δ 16.0

(((3*S*)-3-(*N*-Benzyloxycarbonyl)amino-3-methoxycarbonyl)propyl)[(4-

((diisopropoxyphosphoryl)methoxy)phenyl)hydroxymethyl]phosphinic Acid: The
 compound was prepared according to general procedure A with H-phosphinic acid (68.8 mg,
 0.22 mmol) and diisopropyl (4-formylphenoxy)methylphosphonate (98.2 mg, 0.327 mmol).

115mg of crude product were obtained. ^{31}P NMR (101 MHz, CD_3OD): δ 47.7; 18.2 MS (ESI): m/z 616.0(M+1)

[[((3S)-3-Amino-3-carboxy)propyl][(4-

phosphonomethoxyphenyl)hydroxymethyl]phosphinic Acid (Derivative 14). The previous

5 compound was deprotected according to general procedure C. After the cation exchange resin, 52.1 mg of compound were obtained. A second purification on an anion exchange resin (AG 1-X4, 200-400 Mesh, 10.5 x 1.5 cm, AcO^-) was necessary to obtain a pure compound. The crude compound was diluted in 150 mL of pure and freshly boiled and cooled water, and the pH was brought to 9 (with a freshly prepared 1N sodium hydroxide aqueous solution). The
10 resin was eluted with formic acid (1.8N to 3.5N) and the desired compound was eluted with 3N formic acid. 14.6 mg of pure derivative **14** were obtained (17% yield, 2 steps). ^1H NMR (500 MHz, D_2O): δ 1.62-1.77 (m, 2H), 2.01-2.09(m, 2H), 3.9 (m, 1H), 4.12 (d, J = 9.2 Hz, 2H), 4.76 (d, J = 7.6 Hz, 1H), 7.02 (d, J = 7.0 Hz, 2H), 7.34 (d, J = 7.0 Hz, 2H). ^{31}P NMR (202 MHz, D_2O): δ 39.4; 14.7. ^{13}C NMR (126 MHz, D_2O): δ 23.4 (dd, J = 89.6; 16.4 Hz),
15 24.9, 55.6, 65.6 (d, J = 158.3 Hz), 73.9 (d, J =109.3Hz), 116.1, 129.8, 132.0, 160.0 (d, J =12.2Hz), 174.1. HPLC – MS (Method A): t_R = 5.14, (ESI): m/z 383.9(M+1) m/z 382.0 (M-1)

Derivative 15

20 **[[((3S)-3-(*N*-Benzyloxycarbonyl)amino-3-methoxycarbonyl)propyl][(3-(ethoxycarbonyl) methoxyphenyl)hydroxymethyl]phosphinic Acid:** The compound was prepared according to general procedure B with H-phosphinic acid **1** (315 mg, 1.0 mmol) and ethyl 3-formylphenoxyacetate (458 mg, 2.2 mmol). The reaction had to be stirred for 48 h to achieve complete conversion. ^{31}P NMR (101 MHz, CD_3OD): δ 57.8.

25 **[[((3S)-3-Amino-3-carboxy)propyl][(3-**

(carboxymethoxy)phenyl)hydroxymethyl]phosphinic Acid (Derivative 15). The previous

compound was deprotected according to general procedure C. 229 mg of pure product derivative **15** were obtained (66% yield, 2 steps). ^1H NMR (500 MHz, D_2O): δ 1.79-1.93 (m, 2H), 2.05-2.12 (m, 2H), 4.05 (q, J = 6.0 Hz, 1H), 4.94 (d, J = 9.5 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.99 (d, J = 1.5 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H). ^{31}P NMR (101 MHz, D_2O): δ 56.6. ^{13}C NMR (126 MHz, D_2O): δ 22.6 (2d, J = 89 Hz), 23.9, 54.4 (d, J = 15 Hz), 66.2, 73.2 (d, J = 109 Hz), 114.5, 115.8, 122.0, 131.4, 139.6, 158.6, 172.5, 174.6.

MS (ESI): m/z 346.1 (M-1). HPLC (Crownpak, T = 10.0 °C, detection λ = 210 / 254 nm): t_R = 20.6 and 22.9 min.

[[((3S)-3-Ammonium-3-carboxy)propyl][(3-(carboxymethoxy)phenyl)hydroxymethyl]

5 **phosphinic Acid Hydrochloride (Derivative 16-diaI and Derivative 17-diaII).** The diastereoisomers of derivative **15** were separated by HPLC using the preparative Crownpak column at 4.0 °C with a 1.0 mL.min⁻¹ flow, a 2 mL injection loop, and a dual UV detection at 210 and 254 nm. 21 injections were performed in order to obtain enough product for pharmacological tests. Each injection was prepared with 2.5 mg of derivative **15** in 1.5 mL of
10 pH 2.0 hydrochloric acid. The diastereoisomer with the shortest retention time was named -I and the other one -II. 18 mg of pure dia-I derivative **16** and 22 mg of pure dia-II derivative **17** were obtained. **Derivative 16-diaI:** ¹H NMR (500 MHz, D₂O): δ 1.78 (m, 2H), 2.08 (m, 2H), 4.03 (bs, 1H), 4.76 (s, 2H), 4.88 (d, J = 9.5 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 7.02 (bs, 1H), 7.08 (d, J = 7.0 Hz, 1H), 7.35 (dd, J = 7.5 / 8.0 Hz, 1H). ¹³C NMR (126 MHz, D₂O): δ 22.9
15 (d, J = 88 Hz), 24.1, 54.6 (d, J = 14 Hz), 66.4, 73.6 (d, J = 108 Hz), 114.5, 115.7, 122.1, 131.4, 140.2, 158.6, 172.8, 174.8. MS (ESI): m/z 346.1 (M-1). HPLC (Crownpak, T = 4.0 °C, detection λ = 210 / 254 nm): t_R = 21.3 min. $[\alpha]_D^{20}$: + 3.3 (H₂O, c 0.9). **Derivative 17-diaII:** ¹H NMR (500 MHz, D₂O): δ 1.73-1.88 (m, 2H), 2.08-2.13 (m, 2H), 4.03 (bs, 1H), 4.76 (s, 2H), 4.91 (d, J = 7.5 Hz, 1H), 6.93 (d, J = 6.0 Hz, 1H), 7.01 (bs, 1H), 7.07 (d, J = 4.0 Hz, 1H),
20 7.35 (bs, 1H). ¹³C NMR (126 MHz, D₂O): δ 22.8 (d, J = 89 Hz), 24.0, 54.6, 66.3, 73.9, 114.5, 115.8, 122.1, 131.4, 139.9, 158.6, 172.7, 174.7. MS (ESI): m/z 346.1 (M-1). HPLC (Crownpak, T = 4.0 °C, detection λ = 210 / 254 nm): t_R = 23.9 min. $[\alpha]_D^{20}$: + 17.5 (H₂O, c 1.1).

25 **Derivative 18**

3,4-Bis(ethoxycarbonylmethoxy)benzaldehyde.

To a suspension of 3,4-dihydroxybenzaldehyde (691 mg, 5.0 mmol) in dimethylformamide (10.0 mL) was added potassium carbonate (2.76 g, 4 eq). This mixture was stirred for 30 min at room temperature then cooled at 0 °C. Ethylbromoacetate (1.66 mL, 15.0 mmol) was
30 added, and the mixture was allowed to warm at room temperature and stirred for 19 h. The mixture was then diluted in water (50 mL) and extracted with ethyl acetate (2 x 150 mL). The combined organic phases were washed with brine (20 mL), dried with magnesium sulfate, filtered and concentrated under vacuum. A brown oil was obtained and filtered on a silica gel

layer, using cyclohexane / ethyl acetate (1 : 1, 250 mL). The filtrates containing the desired product were concentrated under vacuum. This orange oil, still containing traces of dimethylformamide, was directly engaged in the following step.

A sample of crude 3,4-bis(ethoxycarbonylmethoxy)benzaldehyde was purified by silica gel chromatography (eluant cyclohexane / ethyl acetate in gradient from 3 : 1 to 6 : 4) to afford pure compound that was used for the NMR characterization. ¹H NMR (500 MHz, CDCl₃): δ 1.23 (2t, *J* = 7.5 Hz, 6H), 4.20 (q, *J* = 7.5 Hz, 4H), 4.72 and 4.75 (2s, 4H), 6.89 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 1.5 Hz, 1H), 7.41 (dd, *J* = 1.5 / 8.0 Hz, 1H), 9.77 (s, 1H). ¹³C NMR (126 MHz, CDCl₃): δ 15.5, 62.8 and 62.9, 67.5 and 67.6, 114.5 and 115.0, 128.1, 132.4, 149.6, 154.4, 169.4 and 169.7, 191.8. TLC: *R_f* = 0.5 (cyclohexane / ethyl acetate 1 : 1).

[[((3*S*)-3-(*N*-Benzyloxycarbonyl)amino-3-methoxycarbonyl)propyl][(3,4-di(ethoxycarbonyl methoxy)phenyl)hydroxymethyl]phosphinic Acid.

This compound was synthesized according to general procedure B with **1** (282 mg, 0.9 mmol) and the previously synthesized 3,4-bis(ethoxycarbonylmethoxy)benzaldehyde. ³¹P NMR (101 MHz, CD₃OD): δ 48.9.

[[((3*S*)-3-Amino-3-carboxy)propyl][(3,4-di(carboxymethoxy)phenyl)hydroxymethyl]phosphinic Acid (Derivative 18).

The deprotection was achieved according to general procedure C. Two cation exchange columns were necessary to obtain the pure compound. 51 mg of a pure fraction of derivative **18** were obtained (13% yield, 2 steps). ¹H NMR (500 MHz, D₂O): δ 1.73-1.86 (m, 2H), 2.03-2.09 (m, 2H), 4.03 (q, *J* = 6.0 Hz, 1H), 4.79 and 4.80 (2s, 4H), 4.85 (d, *J* = 9.0 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 7.0-7.04 (m, 2H). ³¹P NMR (101 MHz, D₂O): δ 53.0. ¹³C NMR (126 MHz, D₃O): δ 23.0 and 23.1 (2d, *J* = 89 Hz), 24.3, 54.7 (d, *J* = 15 Hz), 67.1, 73.4 (d, *J* = 109 Hz), 114.2, 115.5, 122.6, 132.7, 148.0 and 148.1, 173.0, 174.6. HPLC – MS (Method A): *t_R* = 6.25 (ESI): *m/z* 422.0 (M+1) *m/z* 420.0 (M-1).

Ethyl 2-(2chloro-4-formyl-6-methoxyphenoxy)acetate:

The compound was prepared according to general procedure E with 5-chlorovanillin (2.7 mmol) in dry acetone (25ml), anhydrous K₂CO₃ (3.5 mmol), and ethylbromoacetate (4.05 mmol) at reflux for 1h30. Ethanol was added and evaporated by azeotropic distillation with ethylbromoacetate. 957 mg of crude product were obtained and purified by silica gel chromatography (eluent dichloromethane). 330 mg of purified compound were obtained (45% yield). ¹H NMR (250 MHz, CD₃COCD₃): δ 1.27 (t, *J* = 7.2 Hz, 3H), 3.98 (s, 3H), 4.22 (q, *J* =

7.2Hz, 2H), 4.87 (s, 2H), 7.50 (s, 1H), 7.58 (s, 1H), 9.90 (s, 1H) ^{13}C NMR (126 MHz, CD_3COCD_3): δ 15.1, 57.5, 62.1, 70.5, 112.3, 125.8, 128.9, 134.0, 149.7, 154.5, 169.5, 191.2. MS (ESI): m/z 272.9 and 274.9 $[\text{M}+\text{H}]^+$.

5 **Ethyl 2-(2-iodo-4-formyl-6-methoxyphenoxy)acetate:**

The compound was prepared according to general procedure E with 5-iodovanillin (1.8 mmol) in dry acetone (25ml), anhydrous K_2CO_3 (2.4 mmol), and ethylbromoacetate (2.7 mmol) at reflux for 1h15. Ethanol was added and evaporated by azeotropic distillation with ethylbromoacetate. 673 mg of crude product were obtained and purified by silica gel chromatography (eluent dichloromethane). 320 mg of purified compound were obtained (49% yield). ^1H NMR (250 MHz, CD_3COCD_3): δ 1.28 (t, $J=7.2\text{Hz}$, 3H), 3.97 (s, 3H), 4.23 (q, $J=7.2\text{Hz}$, 2H), 4.85 (s, 2H), 7.55 (s, 1H), 7.95 (s, 1H), 9.90 (s, 1H) ^{13}C NMR (126 MHz, CD_3COCD_3): δ 15.2, 57.4, 62.1, 70.5, 92.4, 113.9, 135.1, 135.5, 153.1, 169.4, 191.1. MS (ESI): m/z 364.9 $[\text{M}+\text{H}]^+$.

15

Ethyl 2-(2-fluoro-4-formyl-6-methoxyphenoxy)acetate:

The compound was prepared according to general procedure E with 3-fluoro-4-hydroxy-5-methoxybenzaldehyde (1.8 mmol) in dry acetone (20ml), anhydrous K_2CO_3 (2.4 mmol), and ethylbromoacetate (2.7 mmol) at reflux for 1h. Ethanol was added and evaporated by azeotropic distillation with ethylbromoacetate. 395 mg of crude product were obtained and purified by silica gel chromatography (eluent dichloromethane). 361 mg of purified compound were obtained (79% yield). ^1H NMR (500 MHz, CD_3COCD_3): δ 1.25 (t, $J=$, 3H), 3.98 (s, 3H), 4.21 (q, $J=$, 2H), 4.89 (s, 2H), 7.34 (dd, $J=10.3$ and 1.6 Hz , 1H), 7.40 (t, $J=1.6\text{Hz}$, 1H), 9.88 (d, $J=1.6\text{Hz}$, 1H) ^{13}C NMR (126 MHz, CD_3COCD_3): δ 15.0, 57.6, 62.1, 70.3, 110.0, 111.8 (d, $J=20.6\text{Hz}$), 133.1 (d, $J=7.2\text{Hz}$), 141.8 (d, $J=12.7\text{Hz}$), 154.5 (d, $J=4.5\text{Hz}$), 156.0 (d, $J=246\text{Hz}$), 169.7, 191.3. MS (ESI): m/z 256.9 $[\text{M}+\text{H}]^+$.

25

Ethyl 2-(2,6-dichloro-4-formyl-6-methoxyphenoxy)acetate:

The compound was prepared according to general procedure E with 3,5-dichloro-4-hydroxybenzaldehyde (1.6 mmol) in dry acetone (15ml), anhydrous K_2CO_3 (2.1 mmol), and ethylbromoacetate (2.4 mmol) at reflux for 1h. Ethanol was added and evaporated by azeotropic distillation with ethylbromoacetate. 354 mg of crude product were obtained and purified by silica gel chromatography (eluent dichloromethane). 264 mg of purified compound were obtained (60% yield). ^1H NMR (500 MHz, CD_3COCD_3): δ 1.32 (t, $J=7.2\text{Hz}$

30

,3H), 4.30 (q, J= 7.2Hz ,2H), 4.74 (s, 2H), 7.82 (s, 2H), 9.67(s, 1H) ¹³C NMR (126 MHz, CD₃COCD₃): δ 15.0, 62.3, 70.8, 131.2, 131.4, 135.4, 156.4, 168.4, 190.5

Ethyl 2-(2,6 dimethyl-4-formyl-6-methoxyphenoxy)acetate:

5 The compound was prepared according to general procedure E with 3,5-dimethyl-4-hydroxybenzaldehyde (3.3 mmol) in dry acetone (20ml) , anhydrous K₂CO₃ (4.3 mmol),and ethylbromoacetate (5 mmol) at reflux for 1h. Ethanol was added and evaporated by azeotropic distillation with ethylbromoacetate. 774 mg of crude product were obtained and purified by silica gel chromatography (eluent dichloromethane). 580 mg of purified
10 compound were obtained (74% yield). ¹H NMR (250 MHz, CDCl₃): δ 1.26 (t, J= 7.2Hz ,3H), 2.33 (s, 6H), 4.23 (q, J= 7.2Hz ,2H), 4.42 (s, 2H), 7.50 (s, 2H), 9.82 (s, 1H) ¹³C NMR (126 MHz, CDCl₃): δ 15.2, 17.4, 62.2, 70.1, 131.6, 132.8, 133.8, 161.7, 169.5, 192.1

Diisopropyl (4-formylphenoxy) methylphosphonate:

15 The compound was prepared according to general procedure E with 4-hydroxybenzaldehyde (1.2 mmol) in dry DMF (20ml) , anhydrous K₂CO₃ (1.6 mmol),and diisopropyl bromomethyl phosphonate (1.9 mmol) heating at 110° C overnight. Isopropanol was added and evaporated by azeotropic distillation with diisopropyl bromomethyl phosphonate. 418 mg of crude product were obtained and purified by silica gel chromatography (eluent: cyclohexane / ethyl
20 acetate 5/5). 98 mg of purified compound were obtained (26% yield). ¹H NMR (250 MHz, CDCl₃): δ 1.32 (d, J= 6.0Hz ,6H), 1.34 (d, J=6.0Hz, 6H), 4.27 (d, J=10.2Hz, 4.78 (q, J=6.0Hz, 1H), 4.83 (q, 6.0Hz, 1H), 7.05 (d, J=8.7Hz, 2H), 7.82 (d, J= 8.7Hz, 2H), 9.87 (s, 1H) ¹³C NMR (126 MHz, CDCl₃): δ 25.3, 25.3, 25.4, 25.5 (4 CH₃ isopropyl), 63.7 (d, J=171Hz), 73.2, 73.3 (2 CH isopropyl), 116.3, 132.2, 133.3, 164.8, 192.0. ³¹P NMR (202
25 MHz, CDCl₃): δ 16.0. MS (ESI): *m/z* 300.9 [M+H]⁺.

Ethyl 2-(2-ethoxy-4-formylphenoxy)acetate:

The compound was prepared according to general procedure E with 3-ethoxy-4-hydroxybenzaldehyde (2.4 mmol) in dry acetone (15ml) , anhydrous K₂CO₃ (3.1 mmol),and
30 ethylbromoacetate (3.6 mmol) at reflux for 1h30. Ethanol was added and evaporated by azeotropic distillation with ethylbromoacetate. 565 mg of crude product were obtained and purified by silica gel chromatography (eluent dichloromethane). 385 mg of purified compound were obtained (63% yield). ¹H NMR (250 MHz, CDCl₃): δ 1.31 (t, J= 7.0Hz ,3H), 1.49 (t, J=7.0Hz, 3H), 4.18 (q, J= 7.0Hz ,2H), 4.31 (q, J=7.0Hz, 2H), 4.79 (s, 2H), 6.91 (d,

J=8.0Hz, 1H), 7.42 (d, J=8.0Hz, 1H), 7.45 (s, 1H) 9.86 (s, 1H) ^{13}C NMR (63 MHz, CDCl_3): δ 14.0, 14.5, 61.2, 64.4, 65.9, 111.2, 113.0, 125.5, 131.0, 149.1, 152.7, 168.1, 191.5. MS (ESI): m/z 253.0 $[\text{M}+\text{H}]^+$.

5 **Ethyl 2-(4-formyl-2-(trifluoromethoxyphenoxy))acetate**

The compound was prepared according to general procedure E with 4-hydroxy-3-(trifluoromethoxy)benzaldehyde (1.5 mmol) in dry acetone (15ml) , anhydrous K_2CO_3 (1.9 mmol),and ethylbromoacetate (2.2 mmol) at reflux for 1h. Ethanol was added and evaporated by azeotropic distillation with ethylbromoacetate. 311 mg of pure compound were obtained (73% yield). ^1H NMR (250 MHz, CDCl_3): δ 1.22 (t, J= 7.0Hz ,3H), 4.19 (q, J= 7.0Hz ,2H), 4.76 (s, 2H), 6.99 (d, J=9.0Hz, 1H), 7.72 (d, J=9.0Hz, 1H), 7.74 (s, 1H) 9.82 (s, 1H) ^{13}C NMR (63 MHz, CDCl_3): δ 13.8, 61.6, 65.6, 113.6, 120.5 (d, J=259Hz), 123.3, 130.4, 130.5, 138.5, 155.1, 167.3, 189.4

15 **Ethyl 2-(4-formyl-2-(trifluoromethyl)phenoxy)acetate**

The compound was prepared according to general procedure E with 4-hydroxy-3-(trifluoromethyl)benzaldehyde (1.3 mmol) in dry acetone (20ml) , anhydrous K_2CO_3 (1.7 mmol),and ethylbromoacetate (2.2 mmol) at reflux for 1h. Ethanol was added and evaporated by azeotropic distillation with ethylbromoacetate. The crude product was purified by silica gel chromatography (eluent dichloromethane). 215 mg of purified compound were obtained (59% yield). ^1H NMR (250 MHz, CDCl_3): δ 1.30 (t, J= 7.0Hz ,3H), 4.28 (q, J= 7.2Hz ,2H), 4.85 (s, 2H), 7.02 (d, J=8.7Hz, 1H), 8.04 (dd, J=8.9 and 2.0Hz, 1H), 8.16 (d, J=2.0Hz, 1H) 9.95 (s, 1H) ^{13}C NMR (63 MHz, CDCl_3): δ 13.8, 61.6, 65.5, 112.9, 120.5 (d, J=32.0 Hz), 122.8 (d, J=273Hz), 128.9, 129.6, 135.0, 160.1, 167.2, 189.6 MS (ESI): m/z 573.1 $[2\text{M}+\text{Na}]^+$.

25

Ethyl 2-(4-formyl-2-methoxyphenoxy)acetate

The compound was prepared according to general procedure E with vanillin (5.3 mmol) in dry acetone (20ml) , anhydrous K_2CO_3 (6.8 mmol),and ethylbromoacetate (6.3 mmol) at reflux for 1h. Ethanol was added and evaporated by azeotropic distillation with ethylbromoacetate. 980mg of pure compound were obtained (78% yield). ^1H NMR (250 MHz, CDCl_3): δ 1.23 (m , 3H), 3.88 (s, 3H), 4.21 (m, 2H), 4.78 (s, 2H), 6.90 (m, 1H), 7.38 (m,, 2H), 9.80 (s, 1H) ^{13}C NMR (63 MHz, CDCl_3): δ 13.9, 55.7, 61.2, 65.6, 109.8, 112.3, 125.7, 130.8, 149.7, 152.4, 167.9, 190.6 MS (ESI): m/z 253.0 $[\text{M}+\text{H}]^+$.

Ethyl 2-(4-formylphenoxy)propanoate

The compound was prepared according to general procedure E with 4-hydroxybenzaldehyde (3.3 mmol) in dry acetone (15ml) , anhydrous K₂CO₃ (4.3 mmol), and ethyl-2-bromopropionate (3.6 mmol) at reflux for 2h45. Isopropanol was added and evaporated by azeotropic distillation with ethyl-2-bromopropionate. 609mg of pure compound were obtained (83% yield). ¹H NMR (250 MHz, CDCl₃): δ 1.10 (t, J=7.1Hz, 3H), 1.52(d,J=6.8Hz, 3H), 4.10 (q, J=7.1Hz, 2H), 4.76 (q, J=6.8Hz, 1H) 6.85 (d, J=8.7Hz 2H), 7.70 (d, J=8.9Hz, 2H), 9.74 (s, 1H) ¹³C NMR (63 MHz, CDCl₃): δ 14.0, 18.2, 61.4, 72.4, 115.1, 130.4, 131.8, 162.4, 171.1, 190.5

Ethyl 2-(4-formyl-2-hydroxyphenoxy)acetate

The compound was prepared according to general procedure E with 3,4-dihydroxybenzaldehyde (3.7 mmol) in dry acetone (20ml) , anhydrous K₂CO₃ (2.3 mmol), and ethylbromoacetate (3.4 mmol) at 0°. The mixture was stirred at room temperature for 20h. Ethanol was added and evaporated by azeotropic distillation with ethylbromoacetate. The crude product was purified by silica gel chromatography (eluent dichloromethane). 112 mg of purified compound were obtained (15% yield). ¹H NMR (250 MHz, CDCl₃): δ 1.31 (t, J=7.1Hz, 3H), 4.28 (q, J=7.1Hz, 2H), 4.78 (q, J=6.8Hz, 1H) 6.95 (d, J=8.8Hz, 1H), 7.46 (d, J=8.9Hz, 1H), 7.55 (s, 1H), 9.86 (s, 1H) ¹³C NMR (63 MHz, CDCl₃): δ 15.2, 63.5, 67.1, 113.9, 117.1, 125.3, 132.8, 148.6, 152.4, 170.8, 193.3

2-ethoxy-2-oxoethyl 2-(2-ethoxy-2-oxoethoxy)-5-formylbenzoate

The compound was prepared according to general procedure E with syringaldehyde (2.1 mmol) in dry acetone (10ml) , anhydrous K₂CO₃ (2.7 mmol), and ethylbromoacetate (2.5mmol) at reflux for 4h. Ethanol was added and evaporated by azeotropic distillation with Ethylbromoacetate. The crude product was purified by silica gel chromatography (eluent dichloromethane). 221 mg of purified compound were obtained (31% yield). ¹H NMR (250 MHz, CDCl₃): δ 1.30 (t, J=7.2Hz, 3H), 4.24 (q, J=7.4Hz, 2H), 4.81 (s, 2H), 4.84 (s, 2H), 6.98 (d, J=8.7Hz, 1H), 8.0 (dd, J=8.9 and 1.9Hz, 1H), 8.44 (d, J=1.9Hz, 1H) , 9.91 (s, 1H) ¹³C NMR (126 MHz, CDCl₃): δ 15.3, 62.7, 67.2, 115.0, 121.3, 131.2, 135.9, 135.9 (2C), 163.3, 165.0, 168.9, 191.2

Ethyl 2-(4-formyl-2-nitrophenylthio)acetate

To a solution of ethyl-2-mercaptoacetate (0.7mmol) in dry DMF(2.5ml), sodium hydride(0.85mmol) was added 0°C. After 15 minutes, 4-fluoro-3nitrobenzaldehyde (0.7mmol) was added and the mixture was heated at 60°C overnight and monitored by TLC until completion. After cooling, the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column (cyclogexane/ ethyl acetate 4/1 as eluent) to give 46 mg of ethyl 2-(4-formyl-2-nitrophenylthio)acetate as yellow compound (yield 24%). ¹H NMR, (250 MHz, CDCl₃) : δ 1.25 (t, J= 7.5 Hz, 3H,), 3.80 (s, 2H,), 4.21 (q, J=7.75, 2H), 7.64 (d, J=9.75, 1H), 8.03 (d, J=9.75, 1H), 8.68 (s, 1H,), 10.00 (s, 1H) ¹³C NMR (126 MHz, CDCl₃) : δ 15.4, 36.5, 63.8, 128.5, 129.3, 133.9, 145.6, 147.1, 169.5, 190.1.

2-(4-formyl-2-nitrophenoxy)acetate

The compound was prepared according to general procedure E with 4-hydroxy-3-nitrobenzaldehyde (1.8 mmol) in dry DMF (15ml) , anhydrous K₂CO₃ (2.2 mmol),and ethylbromoacetate (2.2mmol) at 80°C overnight. Ethanol was added and evaporated by azeotropic distillation with ethylbromoacetate. The crude product was purified by silica gel chromatography (eluent cyclohexane/ethylacetate 9/1). 166 mg of purified compound were obtained (37% yield). ¹H NMR (250 MHz, CDCl₃) : δ 1.28 (t, J=7.25, 3H), 4.26 (q, 2H), 4.87 (s, 2H), 7.07 (d, J=9.75, 1H), 8.04 (d, J=9.75, 1H), 8.06 (s, 1H), 9.93 (s, 1H,)

Ethyl 2-(4-formylphenylthio)acetate

The compound was prepared according to general procedure E. To a solution of ethyl-2-mercaptoacetate (1.7mmol) in dry DMF (5ml), sodium hydride (2.0 mmol) was added at 0°C. After 10 minutes, 4-bromobenzaldehyde (1.4mmol) was added and the mixture was heated for 3hours. After cooling, the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column (cyclohexane/ ethyl acetate 9/1 as eluent) to give 188 mg of ethyl 2-(4-formylphenylthio)acetate (yield 59%). ¹H NMR (250 MHz, CDCl₃) : δ 1.23 (t, J=7.5 Hz, 3H), 3.73 (s, 2H), 4.18 (q, 2H), 7.42 (d, J=8.75 Hz, 2H), 7.76 (d, J=8.75 Hz, 2H), 9.93 (s, 1H).

Ethyl 2-(p-tolylamino)acetate

The compound was prepared according to general procedure E. To a solution of p-toluidine(4.7mmol) in dry acetone (20ml), ethylbromoacetate(4.7mmol) was added. The mixture was refluxed for 3 hours. After cooling, the solvent was removed under reduced

pressure. The residue was chromatographed on a silica gel column (dichloromethane/ ethyl acetate 9/1 as eluent) to give 326 mg of ethyl 2-(*p*-tolylamino)acetate (yield 36%). ¹H NMR (500 MHz, CDCl₃): δ 1.29 (t, J=7.4Hz, 3H), 2.28 (s, 3H), 3.90 (s, 2H), 4.26 (q, J= 7.4Hz, 2H), 6.58 (d, J=8.2Hz, 2H), 7.05 (d, J=8.2, 2H) ¹³C NMR (126 MHz, CDCl₃): δ 15.6, 21.8, 47.7, 62.5, 114.8, 131.2, 146.3, 172.8. MS (ESI): *m/z* 193.9 [M+H]⁺

Ethyl 2-(4-formylphenylamino)acetate

To a solution of ethyl 2-(*p*-tolylamino)acetate (1.69mmol) in methanol/water (20ml/20ml) was added the 2,3 dichloro-5,6-dicyanobenzoquinone(2.87mmol) and the mixture was stirred for 4 hours at room temperature. The residue was chromatographed on a silica gel column (dichloromethane/ ethyl acetate 8/2 as eluent) to give 88 mg of ethyl 2-(4-formylphenylamino)acetate. (yield 25%). MS (ESI): *m/z* 208.0 [M+H]⁺

3,5-difluoro-4-hydroxybenzaldehyde

A stirring solution of 2,6-difluorophenol (2 g, 15.4 mmol) and hexamethylenetetramine (2.16 g, 15.4 mmol) in TFA (16 mL) was heated at reflux under argon overnight. On cooling to room temperature the solvent was evaporated in vacuum and the crude residue was taken up in DCM (35 mL). The mixture was washed with an aqueous solution of NaHCO₃ (sat.) and the separated aqueous layer acidified to pH 1 with concentrated HCl. The aqueous layer was extracted with DCM (2 x 25 mL), the combined organic fractions dried (MgSO₄) and evaporated in vacuum to afford desired product as a cream solid (1.76 g, 73%). R_f=0.39 (SiO₂; cyclohexane/EtOAc (6/4); UV) ¹H NMR (300 MHz ; CDCl₃) δ : 6.38 (br, 1H) ; 7.50 (d, 2H, J=6.6 Hz) ; 9.82 (s, 1H). ¹³C NMR (75 MHz ; CDCl₃) δ : 113.2 (dd, J_{CF}=13.8 Hz and 7.8 Hz) ; 128.2 (t, J_{CF}=6.0 Hz) ; 139.0 (t, J_{CF}=16.1 Hz) ; 151.9 (dd, J_{CF}=246.9 Hz and 5.3Hz) ; 189.1. ¹⁹F NMR (282 MHz ; CDCl₃) δ : -52.2

Synthesis of ethyl 2-(2,6-difluoro-4-formylphenoxy)acetate

656 mg (4.74 mmol) of K₂CO₃ and 0.44 mL (3.95 mmol) of ethyl 2-bromoacetate were added to a solution of 3,5-difluoro-4-hydroxybenzaldehyde (0.5 g, 3.16 mmol) in 40 mL of acetone. The reaction mixture was refluxed under argon during 1 hour. After cooling, acetone was evaporated under vacuum. The mixture was diluted in 40 mL of DCM and washed with brine (3x). The combined organic phase was dried under MgSO₄. Evaporation of the solvent and chromatography of the oily residue [SiO₂, cyclohexane/DCM (8/2)] afforded a yellowish oil (580 mg, 75%). R_f=0.23 (SiO₂; cyclohexane/DCM : 1/1; UV). ¹H NMR (250 MHz ; CDCl₃) δ

(ppm) : 1.31 (t, 3H, J=7.5 Hz) ; 4.28 (q, 2H, J=7.5 Hz) ; 4.92 (s, 2H) ; 7.48 (d, 2H, J=8.75 Hz) ; 9.86 (s, 1H). ¹³C NMR (125 MHz ; CDCl₃) δ (ppm) : 15.5 ; 63.1 ; 70.6 ; 114.9 (dd, J_{CF}=17.6 Hz and 6.0 Hz) ; 132.1 (t, J_{CF}=7.0 Hz) ; 141.3 (t, J_{CF}=13.6 Hz) ; 156.3 (dd, J_{CF}=251.1 Hz and 5.6 Hz) ; 169.4 ; 190.1. ¹⁹F NMR (282 MHz ; CDCl₃) δ (ppm) : -50.9.

5

Ethyl 2-(2chloro-4-(hydroxymethyl)-6-methoxyphenoxy)acetate:

The compound was prepared according to general procedure **F** with Ethyl 2-(2chloro-4-formyl-6-methoxyphenoxy)acetate (1.5 mmol) in THF (20ml) and water (20ml) and NaBH₄ (1.5mmol). 355mg of compound were obtained. This compound was used without further purification. ¹H NMR (250 MHz, CDCl₃): δ 1.31 (t, J=7.1Hz, 3H), 3.86 (s, 3H), 4.25 (q, J=7.1Hz, 2H), 4.55 (s, 2H), 4.60 (s, 2H) 6.95 (s, 1H), 6.98 (s, 1H). MS (ESI): *m/z* 274.9 and 276.9 [M+H]⁺, 570.7 and 572.7 [2M+Na]⁺

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Ethyl 2-(2 fluoro-4-(hydroxymethyl)-6-methoxyphenoxy)acetate:

The compound was prepared according to general procedure **F** with Ethyl 2-(2-fluoro-4-formyl-6-methoxyphenoxy)acetate (1.4 mmol) in THF (20ml) and water (20ml) and NaBH₄ (1.4mmol). 220mg of compound were obtained. This compound was used without further purification. ¹H NMR (250 MHz, CDCl₃): δ 1.33 (t, J=7.1Hz, 3H), 3.90 (s, 3H), 4.28 (q, J=7.1Hz, 2H), 4.65 (s, 2H), 4.71(s, 2H) 6.95 (s, 1H), 6.76(m, 2H). MS (ESI): *m/z* 538.8 [2M+Na]⁺

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Ethyl 2-(4-hydroxymethyl-2-(trifluoromethoxyphenoxy))acetate

The compound was prepared according to general procedure **F** with ethyl 2-(4-formyl-2-(trifluoromethoxyphenoxy))acetate (2.5 mmol) in THF (40ml) and water (40ml) and NaBH₄ (2.7 mmol). 526 mg of crude product were obtained and purified by silica gel chromatography (eluent dichloromethane). 140 mg of purified compound were obtained (19% yield). ¹H NMR (250 MHz, CDCl₃): δ 1.26 (t, J=7.1Hz, 3H), 2.97 (s, 1H, OH), 4.22 (q, J=7.2Hz, 2H), 4.54 (s, 2H), 4.67 (s, 2H) 6.85 (d, J=8.6Hz, 1H), 7.15 (d, J=8.3Hz, 1H), 7.24 (s, 1H). ¹³C NMR (63 MHz, CDCl₃): δ 13.9, 61.5, 63.6, 66.2, 114.4, 120.6 (d, J=257Hz), 121.7, 126.1, 135.4, 138.2, 149.4, 168.6. MS (ESI): *m/z* 610.7 [2M+Na]⁺

25

30

Ethyl 2-(4-hydroxymethyl-2-(trifluoromethylphenoxy))acetate

The compound was prepared according to general procedure **F** with ethyl 2-(4-formyl-2-(trifluoromethylphenoxy))acetate (2.7 mmol) in THF (40ml) and water (40ml) and NaBH₄

(2.9 mmol). 611 mg of crude product were obtained and purified by silica gel chromatography (eluent dichloromethane/ ethyl acetate 9:1). 408 mg of purified compound were obtained (55% yield). ^1H NMR (250 MHz, CDCl_3): δ 1.27 (t, $J=7.0\text{Hz}$, 3H), 3.29 (s, 1H, OH), 4.24 (q, $J=7.1\text{Hz}$, 2H), 4.53 (s, 2H), 4.67 (s, 2H) 6.81 (d, $J=8.4\text{Hz}$, 1H), 7.37 (d, $J=8.2\text{Hz}$, 1H), 7.53 (s, 1H).) ^{13}C NMR (63 MHz, CDCl_3): δ 13.9, 61.6, 63.7, 65.8, 113.0, 119.6 (q, $J=30.4\text{Hz}$) 123.4 (d, $J=273\text{Hz}$), 126.1 (q, $J=5.1\text{Hz}$), 131.7, 134.1, 155.0, 168.4. MS (ESI): m/z 300.9 $[\text{M}+\text{Na}]^+$

Ethyl 2-(4-(hydroxymethyl)-2-methoxyphenoxy)acetate

The compound was prepared according to general procedure **F** with ethyl 2-(4-formyl-2-methoxyphenoxy)acetate (5.9 mmol) in THF (40ml) and water (40ml) and NaBH_4 (6.5 mmol). 437 mg of crude product were obtained and purified by silica gel chromatography (eluent dichloromethane). 249 mg of purified compound were obtained (18% yield). ^1H NMR (250 MHz, CDCl_3): δ 1.19 (t, $J=7.0\text{Hz}$, 3H), 3.15 (s, 1H, OH), 3.74 (s, 3H) 4.15 (q, $J=7.1\text{Hz}$, 2H), 4.46 (s, 2H), 4.55 (s, 2H) 6.70 (s, 1H), 6.71 (s, 1H), 6.83 (s, 1H).) ^{13}C NMR (63 MHz, CDCl_3): δ 14.1, 55.7, 61.2, 64.5, 66.5, 111.0, 114.3, 118.9, 135.7, 146.4, 149.6, 169.1. MS (ESI): m/z 502.7 $[2\text{M}+\text{Na}]^+$

Ethyl 2-(4-(bromomethyl)-2-chloro-6-methoxyphenoxy)acetate:

The compound was prepared according to general procedure **G** with ethyl 2-(2chloro-4-(hydroxymethyl)-6-methoxyphenoxy)acetate (1.3 mmol) in dichloromethane (12ml) and PBr_3 (1.3 mmol). 338mg of compound were obtained (78% yield). This compound was used without further purification. ^1H NMR (250 MHz, CD_3OD): δ 1.29 (m, 3H), 3.83 (s, 3H), 4.15 (m, 2H), 4.55 (s, 2H), 4.94 (s, 2H) 6.80 (d, $J=2.0\text{Hz}$, 1H), 6.85 (d, $J=2.0\text{Hz}$, 1H). MS (ESI): m/z 336.9 $[\text{M}-\text{H}]^-$, 360.8 $[\text{M}+\text{Na}]^+$

Ethyl 2-(4-(bromomethyl)-2-fluoro-6-methoxyphenoxy)acetate:

The compound was prepared according to general procedure **G** with ethyl 2-(2-fluoro-4-(hydroxymethyl)-6-methoxyphenoxy)acetate (0.4 mmol) in dichloromethane (5ml) and PBr_3 (0.4 mmol). 67mg of compound were obtained (54% yield). . This compound was used without further purification. ^1H NMR (250 MHz, CDCl_3): δ 1.29 (t, $J=7.0\text{Hz}$, 3H), 3.89 (s, 3H), 4.25 (q, $J=7.0\text{Hz}$, 2H), 4.41 (s, 2H), 4.71 (s, 2H) 6.74 (m, 1H), 6.81 (m, 1H). MS (ESI): m/z 319.9 $[\text{M}+\text{H}]^+$

Ethyl 2-(4-(bromomethyl)-2-(trifluoromethoxy)phenoxy)acetate:

The compound was prepared according to general procedure **G** with ethyl 2-(4-hydroxymethyl-2-(trifluoromethoxyphenoxy))acetate (0.5 mmol) in dichloromethane (5ml) and PBr₃ (0.5 mmol). 139mg of compound were obtained (82% yield). . This compound was used without further purification. ¹H NMR (250 MHz, CDCl₃): δ 1.28 (t, J=7.2Hz, 3H), 4.26 (q, J=7.0Hz, 2H), 4.44 (s, 2H), 4.69 (s, 2H), 7.25 (d, J=8.6Hz, 1H), 7.27 (d,J=8.7Hz, 1H), 7.32 (s, 1H). ¹³C NMR (126 MHz, CDCl₃): δ 13.6, 31.7, 61.2, 65.8, 114.1, 122.0 (d, J=258Hz), 123.6, 128.1, 131.5, 137.9, 150.0, 167.7. MS (ESI): *m/z* 378.9 (100%), 379.8 (13%), 380.9 (100%), 381.9 (13%) [M+Na]⁺

Ethyl 2-(4-(bromomethyl)-2-(trifluoromethylphenoxy))acetate:

The compound was prepared according to general procedure **G** with ethyl 2-(4-hydroxymethyl-2-(trifluoromethylphenoxy))acetate (1.5 mmol) in dichloromethane (10ml) and PBr₃ (1.5 mmol). 421mg of compound were obtained (82% yield). . This compound was used without further purification. ¹H NMR (500 MHz, CDCl₃): δ 1.26 (t, J=7.1Hz, 3H), 4.10 (q, J=7.1Hz, 2H), 4.46 (s, 2H), 4.70 (s, 2H), 6.86 (d, J=8.6Hz, 1H), 7.49 (dd,J=8.7 and 2.1Hz, 1H), 7.62 (d, J=2.1Hz, 1H). ¹³C NMR (126 MHz, CDCl₃): δ 15.4, 33.5, 63.0, 67.2, 114.6, 121.0 (q, J= 32.0Hz), 124.0 (d, J= 272.0Hz), 128.6, 132.3, 135.3, 157.1, 169.3.

Ethyl 2-(4-(bromomethyl)-2-methoxyphenoxy)acetate:

The compound was prepared according to general procedure **G** with ethyl 2-(4-hydroxymethyl-2-methoxyphenoxy))acetate (1.0 mmol) in dichloromethane (5ml) and PBr₃ (1.0 mmol). 261mg of compound were obtained (83% yield). . This compound was used without further purification. ¹H NMR (500 MHz, CDCl₃): δ 1.23 (t, J=7.2Hz, 3H), 3.81(s, 3H) 4.22(q, J=7.2Hz, 2H), 4.42 (s, 2H), 4.62 (s, 2H), 6.71 (d, J=8.3Hz, 1H), 6.84 (dd,J=8.3 and 1.9Hz, 1H), 6.89 (d, J=1.9Hz, 1H). ¹³C NMR (126 MHz, CDCl₃): δ 14.2, 34.0, 55.9, 61.3, 66.4, 112.9, 114.0, 121.4 131.9, 147.4, 149.6, 168.7 MS (ESI): *m/z* 324.9 (100%), 325.9 (13%), 326.8 (100%), 327.9 (13%) [M+Na]⁺

3-(benzyloxycarbonylamino)-4-methoxy-4-oxobutyl((3-ethoxy-4-(2-ethoxy-2-oxoethoxy)phenyl)(hydroxy)methyl)phosphinic acid

The compound was prepared according to general procedure **B** with H-phosphinic acid **1** (1.5mmol), ethyl 2-(2-ethoxy-4-formylphenoxy)acetate (1.5mmol) and BSA (6.1mmol).

1.5g of crude product were obtained and used without further purification. ^{31}P NMR (101 MHz, CD_3OH): δ 47.9. MS (ESI): m/z 566.1 $[\text{M}-\text{H}]^-$

3-(benzyloxycarbonylamino)-4-methoxy-4-oxobutyl((4-(2-ethoxy-2-oxoethoxy)-3-(trifluoromethoxy)phenyl)(hydroxy)methyl)phosphinic acid

The compound was prepared according to general procedure **B** with H-phosphinic acid **1** (1.0mmol), ethyl 2-(4-formyl-2-(trifluoromethoxyphenoxy))acetate (1.0mmol) and BSA (4.2mmol). 684mg of crude product were obtained and used without further purification. ^{31}P NMR (101 MHz, CD_3OH): δ 47.9. MS (ESI): m/z 607.9 $[\text{M}+\text{H}]^+$ and 1214.9 $[2\text{M}+\text{H}]^+$

3-(benzyloxycarbonylamino)-4-methoxy-4-oxobutyl((4-(2-ethoxy-2-oxoethoxy)-3-(trifluoromethyl)phenyl)(hydroxy)methyl)phosphinic acid

The compound was prepared according to general procedure **B** with H-phosphinic acid **1** (0.8mmol), ethyl 2-(4-formyl-2-(trifluoromethylphenoxy)) acetate (0.8mmol) and BSA (3.12mmol). 219mg of crude product were obtained and used without further purification. ^{31}P NMR (101 MHz, CDCl_3): δ 50.8

3-(benzyloxycarbonylamino)-4-methoxy-4-oxobutyl((4-(2-ethoxy-2-oxoethoxy)-3-hydroxyphenyl)(hydroxy)methyl)phosphinic acid

The compound was prepared according to general procedure **B** with H-phosphinic acid **1** (0.6mmol), ethyl 2-(4-formyl-2-hydroxyphenoxy)acetate (0.6mmol) and BSA (2.4mmol). 308mg of crude product were obtained and used without further purification. ^{31}P NMR (101 MHz, CDCl_3): δ 47.7

3-(benzyloxycarbonylamino)-4-methoxy-4-oxobutyl((4-(2-ethoxy-2-oxoethoxy)-3-((2-ethoxy-2-oxoethoxy)carbonyl)phenyl)(hydroxy)methyl)phosphinic acid

The compound was prepared according to general procedure **B** with H-phosphinic acid **1** (0.7mmol), ethyl 3-(2-(2-ethoxy-2-oxoethoxy)-5-formylphenyl)-3-oxopropanoate (0.7mmol) and BSA (2.8mmol). 467mg of crude product were obtained and used without further purification. ^{31}P NMR (101 MHz, CDCl_3): δ 50.3. MS (ESI): m/z 652.1 $[\text{M}-\text{H}]^-$

3-(benzyloxycarbonylamino)-4-methoxy-4-oxobutyl(4-(2-ethoxy-2-oxoethoxy)-3-nitrobenzyl)phosphinic acid

The compound was prepared according to general procedure **B** with H-phosphinic acid **1** (0.66mmol), 2-(4-formyl-2-nitrophenoxy)acetate (0.66mmol) and BSA (2.64mmol). 492mg of crude product were obtained and used without further purification. ³¹P NMR (101 MHz, CDCl₃): δ = 39.7

3-(benzyloxycarbonylamino)-4-methoxy-4-oxobutyl(4-(2-ethoxy-2-oxoethylthio)-3-nitrobenzyl)phosphinic acid

The compound was prepared according to general procedure **B** with H-phosphinic acid **1** (0.17mmol), ethyl 2-(4-formyl-2-nitrophenylthio)acetate (0.17mmol) and BSA (0.68mmol). 140mg of crude product were obtained and used without further purification.

3-(benzyloxycarbonylamino)-4-methoxy-4-oxobutyl(4-(2-ethoxy-2-oxoethylthio)benzyl)phosphinic acid

The compound was prepared according to general procedure **B** with H-phosphinic acid **1** (0.84mmol), ethyl 2-(4-formylphenylthio)acetate (0.84mmol) and BSA (3.36mmol). 294mg of crude product were obtained and used without further purification.

³¹P NMR (101 MHz, CDCl₃): δ = 41.9

3-(benzyloxycarbonylamino)-4-methoxy-4-oxobutyl(4-(2-ethoxy-2-oxoethylamino)benzyl)phosphinic acid

The compound was prepared according to general procedure **B** with H-phosphinic acid **1** (0.43mmol), ethyl 2-(4-formylphenylamino)acetate (0.43mmol) and BSA (1.7mmol). 367mg of crude product were obtained and used without further purification. ³¹P NMR (101 MHz, CDCl₃): δ = 48.0

3-(((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutyl((4-(2-ethoxy-2-oxoethoxy)-3,5-difluorophenyl)(hydroxy)methyl)phosphinic acid

The compound was prepared according to general procedure **B** with H-phosphinic acid **1** (0.99 mmol), ethyl 2-(4-formylphenylamino)acetate (0.99 mmol) and BSA (3.96 mmol). 552 mg of crude product were obtained and used without further purification. ³¹P NMR (101 MHz, CDCl₃): δ = 50.0

3-(benzyloxycarbonylamino)-4-methoxy-4-oxobutyl((4-(1-ethoxy-1-oxopropan-2-yloxy)phenyl)(hydroxy)methyl)phosphinic acid

The compound was prepared according to general procedure **B** with H-phosphinic acid **1** (2.7mmol), ethyl 2-(4-formylphenoxy)propanoate (2.7mmol) and BSA (11.0mmol). 750mg of crude product were obtained and used without further purification. ³¹P NMR (101 MHz, CDCl₃): δ 47.7. MS (ESI): *m/z* 536.1 [M-H]⁻

[((3*S*)-3-(*N*-Benzyloxycarbonyl)amino-3-methoxycarbonyl)propyl][(4-(carboxymethoxy)phenyl)methyl]phosphinic Acid

The compound was prepared according to general procedure **B** with H-phosphinic acid **1** (315 mg, 1.0 mmol) and 4-bromomethyl-phenoxyacetic acid (539 mg, 2.2 mmol). 967 mg of crude product were obtained. ³¹P NMR (101 MHz, CD₃OD): δ 50.7.

3-(benzyloxycarbonylamino)-4-methoxy-4-oxobutyl(4-(2-ethoxy-2-oxoethoxy)-3-methoxybenzyl)phosphinic acid

The compound was prepared according to general procedure **B** with H-phosphinic acid **1** (0.9mmol), ethyl 2-(4-(bromomethyl)-2-methoxyphenoxy)acetate (0.9mmol) and BSA (3.5mmol). 555mg of crude product were obtained and used without further purification. ³¹P NMR (101 MHz, MeOD): δ 53.0. MS (ESI): *m/z* 536.0 [M-H]⁻ and 1072.9 [2M-H]⁻

3-(benzyloxycarbonylamino)-4-methoxy-4-oxobutyl(4-(2-ethoxy-2-oxoethoxy)-3-(trifluoromethoxy)benzyl)phosphinic acid

The compound was prepared according to general procedure **B** with H-phosphinic acid **1** (0.4mmol), ethyl 2-(4-(bromomethyl)-2-(trifluoromethoxy)phenoxy)acetate (0.4mmol) and BSA (1.6mmol). 293mg of crude product were obtained and used without further purification. ³¹P NMR (101 MHz, MeOD): δ 51.2. MS (ESI): *m/z* 590.0 [M-H]⁻ and 1180.9 [2M-H]⁻

3-(benzyloxycarbonylamino)-4-methoxy-4-oxobutyl(4-(2-ethoxy-2-oxoethoxy)-3-(trifluoromethyl)benzyl)phosphinic acid

The compound was prepared according to general procedure **B** with H-phosphinic acid **1** (0.8mmol), ethyl 2-(4-(bromomethyl)-2-(trifluoromethyl)phenoxy)acetate (0.8mmol) and BSA (3.2mmol). 555mg of crude product were obtained and used without further purification. ³¹P NMR (101 MHz, MeOD): δ 48.6. MS (ESI): *m/z* 574.0 [M-H]⁻ and 1148.8 [2M-H]⁻

3-(benzyloxycarbonylamino)-4-methoxy-4-oxobutyl(4-(2-ethoxy-2-oxoethoxy)-3-fluoro-5-methoxybenzyl)phosphinic acid

The compound was prepared according to general procedure **B** with H-phosphinic acid **1** (0.6mmol), ethyl 2-(4-(bromomethyl)-2-fluoro-6-methoxyphenoxy)acetate (0.6mmol) and BSA (2.5mmol). 510mg of crude product were obtained and used without further purification. ³¹P NMR (101 MHz, MeOD): δ 48.5

3-(benzyloxycarbonylamino)-4-methoxy-4-oxobutyl(3-chloro-4-(2-ethoxy-2-oxoethoxy)-5-methoxybenzyl)phosphinic acid

The compound was prepared according to general procedure **B** with H-phosphinic acid **1** (1mmol), ethyl 2-(4-(bromomethyl)-2-chloro-6-methoxyphenoxy)acetate (1mmol) and BSA (4mmol). 307mg of crude product were obtained and used without further purification. ³¹P NMR (101 MHz, MeOD): δ 41.9. MS (ESI): *m/z* 569.9 [M-H]⁻

derivative 19

2-amino-4-(((4-(carboxymethoxy)-3-ethoxyphenyl)(hydroxy)methyl)(hydroxy)phosphoryl)butanoic acid

The compound was prepared according to general procedure **C** applied to the protected derivative. The purification was performed using a Dowex AG 50W-X4 cation exchange resin column (H⁺, 50-100 mesh, water elution). Another purification was made on an anion exchange chromatography (Dowex AG 1-X4, AcO⁻, 200-400 mesh). The resin was first eluted with freshly boiled and cooled water, then with formic acid 2.5M. 37mg of pure derivative 19 were obtained (6% yield in 2 steps). ¹H NMR (250 MHz, D₂O): δ 1.34 (t, J=7Hz, 3H), 1.77 (m, 2H), 2.08(m, 2H), 4.03 (m, 1H), 4.08 (q, J=7Hz, 2H), 4.70(s, 2H), 4.88 (d, J=8Hz), 6.92 (m, 2H), 7.07 (s, 1H). ³¹P NMR (101 MHz, D₂O): δ 44.4. ¹³C NMR (63 MHz, D₂O): δ 13.8, 21.7(d, J=123 Hz), 22.6, 52.9, 65.1, 65.6, 71.8 (d, J=110Hz), 112.5, 113.6, 119.8, 130.8, 146.5, 147.5, 171.3, 173.1. MS (ESI): *m/z* 383.9 [M+H]⁺, 391.9[M-H]⁻. HPLC – MS *t_R* = 8.27 min.

derivative 20

2-amino-4-(((4-(carboxymethoxy)-3-(trifluoromethoxy)phenyl)(hydroxy)methyl)(hydroxy)phosphoryl)butanoic acid

The compound was prepared according to general procedure **C** applied to the protected derivative. The purification was performed using a Dowex AG 50W-X4 cation exchange

resin column (H^+ , 50-100 mesh, water elution. 127mg of pure derivative 20 were obtained (28% yield in 2 steps). 1H NMR (250 MHz, D_2O): δ 1.67 (m, 2H), 2.06(m, 2H), 3.90 (m, 1H), 4.80(m, 3H), 7.06 (d, $J=8Hz$, 1H), 7.33 (d, $J=8Hz$, 1H), 7.40 (s, 1H). ^{31}P NMR (101 MHz, D_2O): δ 38.4. ^{13}C NMR (63 MHz, D_2O): δ 22.2(d, $J=85 Hz$), 23.2, 54.1, 65.8, 71.8 (d, $J=109Hz$), 114.5, 120.4 (d, $J=258Hz$), 121.5, 126.6, 132.1, 137.5, 149.0, 172.1 173.8. MS (ESI): m/z 431.9 $[M+H]^+$, 430.0 $[M-H]^-$. HPLC – MS t_R = 12.52 min.

derivative 21

2-amino-4-(((4-(carboxymethoxy)-3-

(trifluoromethyl)phenyl)(hydroxy)methyl)(hydroxy)phosphoryl)butanoic acid

The compound was prepared according to general procedure C applied to the protected derivative. The purification was performed using a Dowex AG 50W-X4 cation exchange resin column (H^+ , 50-100 mesh, water elution.). Another purification was made on an anion exchange chromatography (Dowex AG 1-X4, AcO^- , 200-400 mesh). The resin was first eluted with freshly boiled and cooled water, then with formic acid. 16mg of pure derivative 21 were obtained (4% yield in 2 steps). 1H NMR (500 MHz, D_2O): δ 1.73 (m, 2H), 2.08(m, 2H), 3.99 (q, $J=6Hz$, 1H), 4.82(s, 2H), 4.84 (d, $J=8Hz$, 1H), 7.07 (d, $J=9Hz$, 1H), 7.57 (d, $J=8Hz$, 1H), 7.68 (s, 1H). ^{31}P NMR (101 MHz, D_2O): δ 39.1 ^{13}C NMR (126 MHz, D_2O): δ 23.1(d, $J=87 Hz$), 24.6, 55.3, 67.3, 73.3 (d, $J=107Hz$), 115.1, 119.5 (d, $J=31Hz$), 125.0 (d, $J=273Hz$), 127.3, 132.4, 133.7, 156.3, 173.5, 174.5. MS (ESI): m/z 415.9 $[M+H]^+$. HPLC – MS t_R = 12.74 min.

derivative 22

2-amino-4-(((4-(carboxymethoxy)-3-

hydroxyphenyl)(hydroxy)methyl)(hydroxy)phosphoryl)butanoic acid (derivative 22)

The compound was prepared according to general procedure C applied to the protected derivative. The purification was performed using a Dowex AG 50W-X4 cation exchange resin column (H^+ , 50-100 mesh, water elution.). Another purification was made on an anion exchange chromatography (Dowex AG 1-X4, AcO^- , 200-400 mesh). The resin was first eluted with freshly boiled and cooled water, then with formic acid 2.3M. 17.9mg of pure derivative 22 were obtained (9% yield in 2 steps). 1H NMR (500 MHz, D_2O): δ 1.72 (m, 2H), 2.04(m, 2H), 3.95 (t, $J=6.8Hz$, 1H), 4.72 (s, 2H), 4.73(d, $J=9Hz$, 1H), 6.89 (m, 2H), 6.96 (s, 1H), . ^{31}P NMR (101 MHz, D_2O): δ 40.3 ^{13}C NMR (126 MHz, D_2O): δ 23.5(d, $J=89Hz$),

24.6(d, $J=2$ Hz), 55.2 (d, $J=15$ Hz), 67.4, 73.8 (d, $J=110$ Hz) 115.1, 116.2, 120.8, 127.5, 133.4, 146.4, 146.7, 173.6, 175.2. . MS (ESI): m/z 363.9 $[M+H]^+$. HPLC – MS t_R = 6.49 min.

derivative 23

5 5-(((3-amino-3-carboxypropyl)(hydroxy)phosphoryl)(hydroxy)methyl)-2-(carboxymethoxy)benzoic acid

The compound was prepared according to general procedure C applied to the protected derivative. The purification was performed using a Dowex AG 50W-X4 cation exchange resin column (H^+ , 50-100 mesh, water elution.). Another purification was made on an anion exchange chromatography (Dowex AG 1-X4, AcO^- , 200-400 mesh). The resin was first eluted with freshly boiled and cooled water, then with formic acid 4M. 40mg of pure derivative 23 were obtained (16% yield in 2 steps). 1H NMR (500 MHz, D_2O): δ 1.71 (m, 2H), 2.06 (m, 2H), 3.96 (q, $J=5.7$ Hz, 1H), 4.80 (s, 2H), 4.82 (d, $J=8.8$ Hz, 1H), 7.04 (d, $J=8.8$ Hz, 1H), 7.56 (d, $J=8.8$ Hz, 1H), 7.82 (s, 1H). ^{31}P NMR (101 MHz, D_2O): δ 39.4 ^{13}C NMR (126 MHz, D_2O): δ 23.6(d, $J=90$ Hz), 24.6, 55.1, 67.6, 73.3 (d, $J=108$ Hz), 115.5, 120.8, 131.6, 132.9, 134.6, 157.7, 171.1, 173.5, 174.7 MS (ESI): m/z 392.0 $[M+H]^+$. HPLC – MS t_R = 6.93 min.

derivative 24

20 2-amino-4-(((4-(carboxymethoxy)-3-nitrophenyl)(hydroxy)methyl)(hydroxy)phosphoryl)butanoic acid

The compound was prepared according to general procedure C applied to the protected derivative. The purification was performed using a Dowex AG 50W-X4 cation exchange resin column (H^+ , 50-100 mesh, water elution.). 75mg of pure derivative 24 were obtained (29% yield in 2 steps). 1H NMR (250 MHz, D_2O): δ 1.74 (m, 2H), 2.09 (m, 2H), 4.00 (m, 1H), 4.86 (s, 2H), 4.85 (d, $J=8.5$ Hz, 1H), 7.16 (d, $J=9.25$, 1H), 7.63 (d, $J=9.25$, 1H), 7.97 (s, 1H). ^{13}C NMR (63 MHz, D_2O): δ 22.2 (d, $J=87$ Hz), 23.3, 53.5, 66.3, 71.5 (d, $J=107$ Hz), 115.5, 124.4, 132.0, 133.7, 138.9, 150.5, 171.8, 172.6. ^{31}P NMR (101 MHz, D_2O) δ 39.7. MS (ESI): m/z 393.0 $[M+H]^+$. HPLC – MS: t_R = 8.02 min

derivative 25

2-amino-4-(((4-(carboxymethylthio)-3-nitrophenyl)(hydroxy)methyl)(hydroxy)phosphoryl)butanoic acid

The compound was prepared according to general procedure C applied to the protected derivative. The purification was performed using a Dowex AG 50W-X4 cation exchange resin column (H^+ , 50-100 mesh, water elution.). 17mg of pure derivative 25 were obtained (24% yield in 2 steps). 1H NMR (250 MHz, D_2O): δ 1.92 (m, 2H), 2.11 (m, 2H), 3.97 (m, 3H), 4.87 (d, $J=9.75$, 1H), 7.45 (d, $J=7.5$, 1H), 7.65 (d, $J=7.75$, 1H), 8.24 (s, 1H) ^{13}C NMR (500 MHz, D_2O): δ 23.8 (d, $J=87Hz$), 250, 36.3, 55.4, 73.2 (d, $J=107Hz$), 125.7, 128.7, 134.3, 135.8, 138.7, 147.5, 173.7, 174.9. ^{31}P NMR (101 MHz, D_2O) δ 38.5. MS (ESI): m/z 408.9.0 $[M+H]^+$.

derivative 26

2-amino-4-(((4-

(carboxymethylthio)phenyl)(hydroxy)methyl)(hydroxy)phosphoryl)butanoic acid

The compound was prepared according to general procedure C applied to the protected derivative. The purification was performed using a Dowex AG 50W-X4 cation exchange resin column (H^+ , 50-100 mesh, water elution.). 88mg of pure derivative 26 were obtained (28% yield in 2 steps). 1H NMR (250 MHz, D_2O): δ 1.70 (m, 2H), 2.06 (m, 2H), 3.78 (s, 2H), 3.93 (m, 1H), 4.81 (d, $J=9.5$ Hz, 1H), 7.40 (m, 4H) ^{13}C NMR (250 MHz, D_2O): δ 21.5 (d, $J=87Hz$), 21.6, 34.6, 52.0, 71.2 (d, $J=111$ Hz), 125.1, 126.2, 128.2, 132.6, 135.6, 139.9, 170.8, 172.8. ^{31}P NMR (101 MHz, D_2O): δ 41.92. MS (ESI): m/z 363.9 $[M+H]^+$. HPLC –

MS: t_R = 9.38 min

derivative 28

2-amino-4-(((4-(carboxymethoxy)-3,5-

difluorophenyl)(hydroxy)methyl)(hydroxy)phosphoryl)butanoic acid

A solution of ((S)-3-(((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutyl)((4-(2-ethoxy-2-oxoethoxy)-3,5-difluorophenyl)(hydroxy)methyl)phosphinic acid (552 mg, 0.99 mmol) in 6 N HCl (6M) was refluxed during 3 h. Then, the mixture was cooled to room temperature and the solvent was evaporated under vacuum. The residue was diluted in EtOAc (50 mL) and extracted with 1 N HCl (2 x 80 mL). The combined aqueous layers were washed twice with EtOAc and the solvent was evaporated to afford 238 mg (0.62 mmol) of crude product which was purified by cation (and anion) exchange resin chromatography. Cation exchange resin chromatography: 238 mg of crude compound were deposited on a Dowex AG 50W-X4, H^+ , 50-100 mesh. The compound was eluted with water and 85 mg of desired product were

collected. Anion exchange resin chromatography: 85 mg of compound were deposited on a Dowex AG 50W-X4, AcO⁻, 200-400 mesh. The compound was eluted with boiled water and formic acid. 27 mg (yield 7% on 2 steps) of pure product derivative 28 were collected (2 M HCOOH). ¹H NMR (250 MHz ; D₂O) δ (ppm) : 1.87 (m, 2H) ; 2.17 (m, 2H) ; 4.13 (m, 1H) ; 4.87 (s, 2H) ; 4.94 (d, J_{HP}=9.4 Hz, 1H) ; 7.13 (d, J=9.1 Hz, 2H). ¹³C NMR (63 MHz ; D₂O) δ (ppm) : 21.7 (d, J_{CP}= 91.0 Hz) ; 22,8 ; 53.1 (d, J_{CP}= 14.8 Hz); 69.8 ; 71.3 (d, J_{CP}= 109.5 Hz) ; 110.8 (dd, J_{CF}=23.3 Hz and 4.0 Hz) ; 133.2 (t, J_{CF}=14,0 Hz); 134.0 (t, J_{CF}=8.1 Hz) ; 154.7 (dd, J_{CF}=246.6 Hz and 5.4 Hz); 171.4 ; 172,9. ³¹P NMR (200 MHz ; D₂O) δ (ppm) : 41,5 (s). ¹⁹F NMR (376 MHz: D₂O) δ (ppm) : -129.0 (s) MS (ESI) m/z : 384 [M+H⁺]. HPLC: t_R =10.1 min

derivative 29

2-amino-4-(((4-(1-carboxyethoxy)phenyl)(hydroxymethyl)(hydroxy)phosphoryl)butanoic acid

The compound was prepared according to general procedure C applied to the protected derivative. The purification was performed using a Dowex AG 50W-X4 cation exchange resin column (H⁺, 50-100 mesh, water elution.). 259mg of pure derivative 29 were obtained (26% yield in 2 steps). ¹H NMR (250 MHz, D₂O): δ 1.52 (d, J=7Hz, 3H), 1.69 (m, 2H), 2.04(m, 2H), 3.93 (m, 1H), 4.80(d, J=8Hz,1H), 4.85 (q, J=7Hz, 1H), 6.89 (d, J=9Hz, 2H), 7.30 (d, J=9Hz, 2H) . ³¹P NMR (101 MHz, D₂O): δ 40.8 ¹³C NMR (126 MHz, D₂O): δ 19.0, 23.3(d, J =85 Hz), 24.3, 54.9 (d, J=13Hz), 73.2 (d, J=108Hz), 73.9, 116.3, 129.9, 131.9, 157.8, 173.3, 178.0. MS (ESI): m/z 361.9 [M+H]⁺. HPLC – MS t_R = 8.43 min.

Derivative 30

[[((3S)-3-Amino-3-carboxy)propyl][(4-(carboxymethoxy)phenyl)methyl]phosphinic Acid (Derivative 30). The protected derivative was deprotected according to general procedure C. 54.0 mg of pure product derivative 30 were obtained (16% yield, 2 steps). ¹H NMR (500 MHz, D₂O): δ 1.70-1.90 (m, 2H), 2.03-2.10 (m, 2H), 3.13 (d, J = 16.5 Hz, 2H), 4.04 (t, J = 6.0 Hz, 1H), 4.67 (s, 2H), 6.91 (d, J = 8.5 Hz, 2H), 7.19 (2d, J = 8.5 Hz, 2H). ³¹P NMR (101 MHz, D₂O): δ 60.8. ¹³C NMR (126 MHz, D₂O): δ 24.0, 24.6 (d, J = 92 Hz), 36.7 (d, J = 88 Hz), 54.4 (d, J = 15 Hz), 66.3, 116.4, 126.4, 132.4, 132.5, 157.7, 172.6, 174.7. MS (ESI): m/z 330.2 (M-1). HPLC – MS: t_R = 8.02 min. HPLC (RP Polar, elution water / acetonitrile /

formic acid 900 : 100 : 1, detection $\lambda = 240 / 270$ nm): $t_R = 8.3$ min. $[\alpha]_D^{20}$: + 7.8 (H₂O, c 0.2).

derivative 31

5 2-amino-4-((4-(carboxymethoxy)-3-methoxybenzyl)(hydroxy)phosphoryl)butanoic acid

The compound was prepared according to general procedure C applied to the protected derivative. The purification was performed using a Dowex AG 50W-X4 cation exchange resin column (H⁺, 50-100 mesh, water elution.). 55mg of pure derivative 31 were obtained (18% yield in 2 steps). ¹H NMR (500 MHz, D₂O): δ 1.64 (m, 2H), 2.01(m, 2H), 2.96 (d, J=17Hz, 2H), 3.78 (s, 3H), 3.88(t, J=6Hz, 1H), 4.59 (s, 2H), 6.72 (d, J=8Hz, 1H), 6.77 (d, J=8Hz, 1H), 6.88 (s, 1H) . ³¹P NMR (101 MHz, D₂O): δ 44.1 ¹³C NMR (126 MHz, D₂O): δ 24.6, 25.4(d, $J = 92$ Hz), 37.9 (d, $J = 87$ Hz), 55.0 (d, $J = 14$ Hz), 57.2, 67.0, 114.9, 115.3, 123.5, 128.7, 146.6, 149.7, 173.5, 174.8. MS (ESI): m/z 362.0 [M+H]⁺ 360.1 [M-H]⁻. HPLC – MS $t_R = 10.27$ min. $[\alpha]_D^{20} + 10.8$ (H₂O, c 1.0).

15 derivative 32

2-amino-4-((4-(carboxymethoxy)-3-(trifluoromethoxy)benzyl)(hydroxy)phosphoryl)butanoic acid

The compound was prepared according to general procedure C applied to the protected derivative. The purification was performed using a Dowex AG 50W-X4 cation exchange resin column (H⁺, 50-100 mesh, water elution.). Another purification was made on an anion exchange chromatography (Dowex AG 1-X4, AcO⁻, 200-400 mesh). The resin was first eluted with freshly boiled and cooled water, then with formic acid 3M. 27mg of pure derivative 32 were obtained (17% yield in 2 steps). ¹H NMR (500 MHz, D₂O): δ 1.78 (m, 2H), 2.03(m, 2H), 3.12 (d, J=17Hz, 2H), 4.01(t, J=6Hz, 1H), 4.80 (s, 2H), 6.98 (d, J=9Hz, 1H), 7.1 (d, J=8Hz, 1H), 7.2 (s, 1H) . ³¹P NMR (101 MHz, D₂O): δ 48.2 ¹³C NMR (126 MHz, D₂O): δ 23.9, 24.8(d, $J = 93$ Hz), 36.6 (d, $J = 88$ Hz), 54.3 (d, $J = 15$ Hz), 67.1, 116.4, 121.8 (d, $J = 256$ Hz), 125.5 (d, $J = 4$ Hz), 127.5 (d, $J = 8$ Hz), 130.8 (d, $J = 9$ Hz), 139.0, 149.9, 172.5, 174.0 MS (ESI): m/z 416.0 [M+H]⁺. HPLC – MS $t_R = 23.35$ min. $[\alpha]_D^{20} + 9.2$ (H₂O, c 1.0).

derivative 33**2-amino-4-((4-(carboxymethoxy)-3-(trifluoromethyl)benzyl)(hydroxy)phosphoryl)butanoic acid**

The compound was prepared according to general procedure C applied to the protected derivative. The purification was performed using a Dowex AG 50W-X4 cation exchange resin column (H^+ , 50-100 mesh, water elution.). Another purification was made on an anion exchange chromatography (Dowex AG 1-X4, AcO^- , 200-400 mesh). The resin was first eluted with freshly boiled and cooled water, then with formic acid 2.5M. 38mg of pure derivative 33 were obtained (12% yield in 2 steps). 1H NMR (250 MHz, D_2O): δ 1.64 (m, 2H), 2.01(m, 2H), 3.00 (d, $J=16Hz$, 2H), 3.93(t, $J=6Hz$, 1H), 4.74 (s, 2H), 6.97 (d, $J=9Hz$, 1H), 7.37 (d, $J=8Hz$, 1H), 7.49 (s, 1H) . ^{31}P NMR (101 MHz, D_2O): δ 43.2 ^{13}C NMR (126 MHz, D_2O): δ 24.5, 25.5(d, $J=92$ Hz), 37.3 (d, $J=86Hz$), 55.0 (d, $J=15Hz$), 67.2, 115.4, 119.7 (d, $J=29Hz$), 124.9 (d, $J=272Hz$), 127.8, 129.6, 136.2, 167.2, 173.3, 174.4 MS (ESI): m/z 399.9 $[M+H]^+$. HPLC – MS t_R = 21.72 min. $[\alpha]_D^{20} + 8.0$ (H_2O , c 1.0).

derivative 34**2-amino-4-((4-(carboxymethoxy)-3-fluoro-5-methoxybenzyl)(hydroxy)phosphoryl)butanoic acid**

The compound was prepared according to general procedure C applied to the protected derivative. The purification was performed using a Dowex AG 50W-X4 cation exchange resin column (H^+ , 50-100 mesh, water elution.). 70mg of pure derivative 34 were obtained (31% yield in 2 steps). 1H NMR (250 MHz, D_2O): δ 1.64 (m, 2H), 2.03(m, 2H), 2.98 (d, $J=17Hz$, 2H), 3.85 (s, 3H), 3.90(t, $J=6Hz$, 1H), 4.68 (s, 2H), 6.73 (d, $J=11Hz$, 1H), 6.78 (s, 1H) . ^{31}P NMR (101 MHz, D_2O): δ 41.0 ^{13}C NMR (126 MHz, D_2O): δ 24.6, 25.6(d, $J=92$ Hz), 38.3 (d, $J=86Hz$), 55.0 (d, $J=15Hz$), 57.7, 71.1, 111.3, 111.5, 131.6, 134.3, 153.8, 156.1 (d, $J=245$), 173.4, 174.8.. MS (ESI): m/z 380.0 $[M+H]^+$. HPLC – MS: t_R = 11.91 min. $[\alpha]_D^{20} + 8.4$ (H_2O , c 1.0).

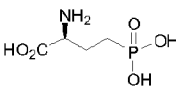
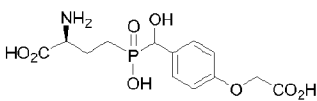
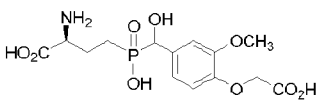
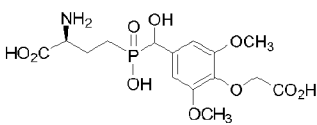
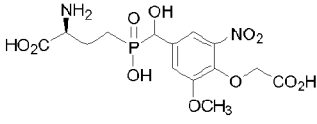
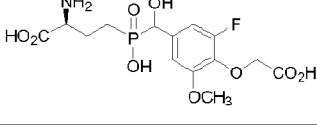
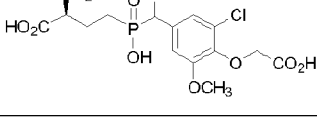
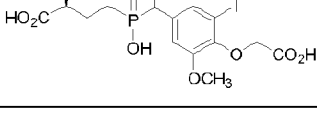
derivative 35**2-amino-4-((4-(carboxymethoxy)-3-chloro-5-methoxybenzyl)(hydroxy)phosphoryl)butanoic acid**

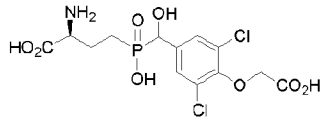
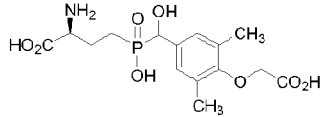
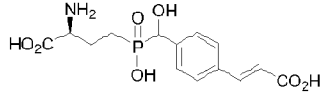
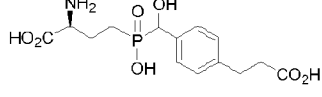
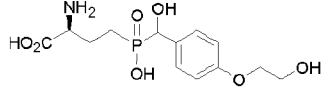
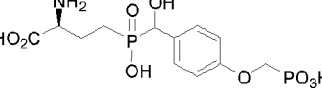
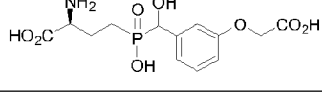
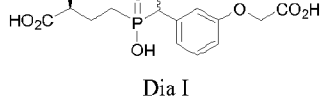
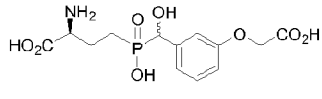
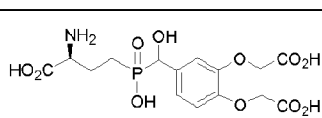
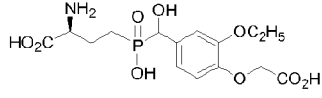
The compound was prepared according to general procedure C applied to the protected derivative. The purification was performed using a Dowex AG 50W-X4 cation exchange resin column (H^+ , 50-100 mesh, water elution.). 6mg of pure derivative 35 were obtained (1%

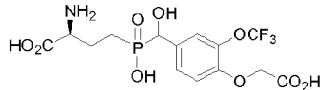
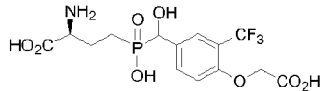
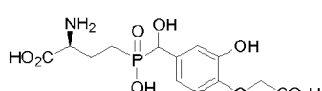
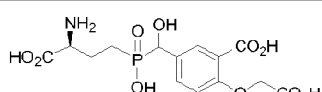
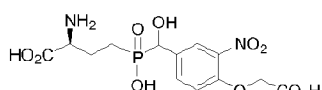
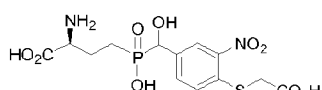
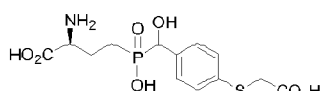
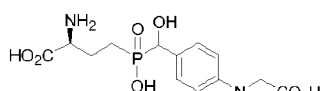
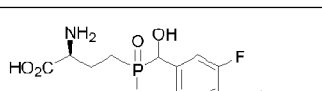
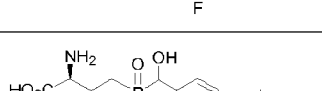
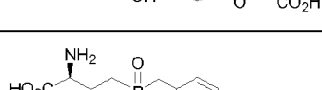
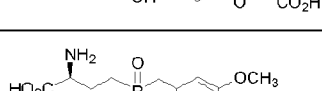
yield in 2 steps). ^1H NMR (500 MHz, D_2O): δ 1.63 (m, 2H), 2.03(m, 2H), 2.98 (d, $J=17\text{Hz}$, 2H), 3.83 (s, 3H), 3.90(t, $J=6\text{Hz}$, 1H), 4.61 (s, 2H), 6.90 (s, 1H), 6.93 (s, 1H) . ^{31}P NMR (101 MHz, D_2O): δ 40.4 ^{13}C NMR (126 MHz, D_2O): δ 24.8, 25.8(d, $J=91\text{ Hz}$), 38.5 (d, $J=88\text{Hz}$), 55.3 (d, $J=15\text{Hz}$), 57.6, 70.9, 114.6, 124.0, 128.3, 133.1, 142.6, 154.0, 173.8, 174.8 . MS
5 (ESI): m/z 395.9 (100%), 397.9 (32%), 398.9 (6%) $[\text{M}+\text{H}]^+$. HPLC – MS $t_{\text{R}} = 17.49\text{ min}$.
 $[\alpha]_{\text{D}}^{20} + 1.1$ (H_2O , c 0.2).

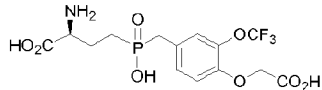
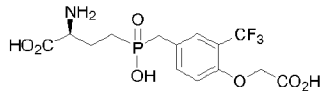
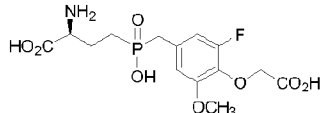
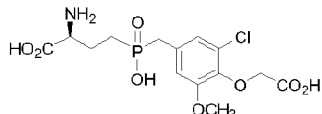
Agonist activities (EC₅₀) of derivatives 1 to 35 have been determined for group III metabotropic glutamate receptors (mGlu4, mGlu6, mGlu7 and mGlu8) expressed in transfected cells by measuring the ligand-induced intracellular calcium release via the fluorescent probe Fluo4-AM. The EC₅₀'s are compared to those of L-AP4 (L-2-amino-4-phosphonobutyric acid) used as a reference.

Table 1

reference	structure	mGlu4 EC ₅₀ μM (n)	mGlu8 EC ₅₀ μM (n)	mGlu8/ 4 EC ₅₀ ratio	mGlu6 EC ₅₀ μM (n)	mGlu7 EC ₅₀ μM (n)	mGlu 7/4 EC ₅₀ ratio
L-AP4		0.13±0.02 (34)	0.29±0.07 (44)	2	1.03±0.27 (7)	>100 (5)	>1000
Derivative 2		0.11±0.02 (30)	29.2±4.2 (27)	256	4.2±0.6 (14)	11.6±1.9 (19)	100
Derivative 3		0.10±0.02 (3)	18.4±2.4 (3)	182	4.7±3.4 (2)	11.5±4.2 (3)	115
Derivative 4		0.5±0.12 (5)	27.2±4.0 (5)	56	9±0.8 (3)	127±24 (6)	254
Derivative 5		0.28±0.05 (3)	3.72±0.31 (3)	13	5.95±0.79 (3)	>100 (2)	>350
Derivative 6		0.08±0.02 (3)	10.3±1.3 (3)	129	-	3.5±1.3 (3)	44
Derivative 7		0.13±0.02 (6)	44±7 (6)	341	-	11.4±0.1 (3)	88
Derivative 8		0.15±0.03 (6)	28±4 (6)	193	-	6.6±1.5 (3)	44

Derivative 9		0.38±0.09 (3)	109±15 (3)	484	-	22.9±7.8 (3)	60
Derivative 10		0.53±0.12 (3)	21.9±6.3 (3)	41	18.4± (1)	51.6±16.1 (3)	97
Derivative 11		0.48±0.15 (3)	49±22 (4)	103	3.8±0.27 (2)	N.E.	>100
Derivative 12		0.98±0.18 (6)	48.7±9.6 (6)	50	-	37±5 (3)	38
Derivative 13		12.2±0.1 (3)	28± 6 (2)	2.3	54±0.0 (2)	N.E. (2)	>100
Derivative 14		0.37±0.12 (4)	112±46 (4)	303	-	34±10 (4)	92
Derivative 15		7.6±2.0 (3)	71±25 (3)	9.4	-	-	-
Derivative 16	 Dia I	4.9±1.0 (4)	36±18 (4)	7.4	-	-	-
Derivative 17	 Dia II	13.0±2.9 (3)	29.3±7.2 (3)	2.3	-	-	-
Derivative 18		2.5±1.1 (3)	14.1±7.3 (3)	6	-	-	-
Derivative 19		1.67±0.33 (3)	25.0±6.0 (3)	15	-	60.2±10.6 (3)	36

Derivative 20		0.06±0.02 (3)	55.6±12.0 (3)	927	-	1.97±0.34 (3)	33
Derivative 21		0.90±0.06 (3)	6.86±1.83 (3)	8	-	35.5±4.0 (3)	39
Derivative 22		1.1±0.4 (3)	34±19 (3)	31	-	15±3.6 (3)	14
Derivative 23		4.0±0.6 (3)	7.4±1.2 (3)	1.9	-	65±13 (3)	16
Derivative 24		0.26±0.07 (3)	1.59±0.82 (3)	6.1	-	11.2±3.9 (3)	43
Derivative 25		1.10±0.36 (3)	11.5±5. (4)	10.4	-	15.2±3.9 (4)	1.4
Derivative 26		0.21±0.04 (3)	1.23±0.48 (3)	5.9	-	13.0±1.1 (3)	62
Derivative 27							
Derivative 28		0.33±0.14 (3)	27.5±6.7 (3)	83	2.5±0.6 (3)	3.87±0.45 (3)	11.7
Derivative 29		0.95±0.16 (2)	14.3±5.6 (3)	15		103±7 (3)	109
Derivative 30		1.0±0.2 (5)	>100 (4)	>100	13.0±4.0 (3)	>100 (4)	>100
Derivative 31		7.41±1.55 (3)	>300 (3)	>40	-	N.E. (3)	

Derivative 32		1.22±0.15 (3)	>100 (4)	>82	-	16.2±3.5 (3)	13
Derivative 33		62.5±20.5 (3)	>100 (3)	1.6	-	301±73 (3)	5
Derivative 34		3.09±0.62 (3)	9.17±2.37 (3)	3	-	232±85 (3)	75
Derivative 35		6.20±0.58 (3)	38.2±7.1 (3)	6	-	>300 (3)	>48

It results from the examination of the above data that derivatives **2** to **4**, **6** to **8** and **20** have a high activity with respect to mGlu4R. At low concentrations, these compounds are mGlu4R selective. Advantageously, derivatives **2**, **3**, **6** to **8** and **20** display a higher affinity on mGlu7 than ever known, then producing an advantageous synergistic effect at higher concentrations through the activation of both mGlu4 and mGlu7 for pain treatment compared to reference derivative L-AP4. Derivates **4**, **5** and **30** are particularly selective for mGlu4, with a decreased activity on mGlu7R compared to the reference derivative.

10

Example 2: Tests *in vivo*

Antihyperalgesic properties

Antihyperalgesic properties of derivative **2** have been tested *in vivo* on healthy animals and animal models for inflammatory (inflammation caused by injection of carrageenan) or neuropathic (chronic constriction of the sciatic nerve) pain.

After the induction period of the neuropathy or inflammation, various amounts of derivative **2** dissolved in serum have been injected in rats, (from 0.5 to 15 µg/rat, i.t., from 1 to 30 mg/kg, i.p.) on time-course of vocalization threshold to paw pressure. The results obtained on healthy animals are given on Figure 1. They are expressed by the time course curves of means ± SEM of vocalization threshold in grams (n=6-8 rats per group) (A) or by the area under the curve (B). Morphine (10 µg/rat, i.t.) is used as a positive control. Significantly different from the vehicle group, *** P< 0.001.

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As previously shown for other agonists of mGluRs of group III, derivative **2** does not modify the perception of the mechanical acute pain in healthy animal (Fig.1).

On the contrary, derivative **2** abolishes the excess of mechanical pain observed on animals with neuropathic or inflammatory pains in a dose and time-dependent manner (Fig. 2 and 3).

Figure 2 illustrates the effect of intrathecal administration of derivative **2** on the vocalization threshold to paw pressure in the carrageenan inflammatory pain model (effect of derivative **2** (0.5, 1, 5, 10 µg/rat, i.t.) on time-course of vocalization threshold to paw pressure). Morphine (10 µg/rat, i.t.) is used as a positive control. Results are expressed by the time course curves of means $\pm$ SEM of vocalization threshold in grams (n=6-8 rats per group) (A) or by the area under the curve (B), significantly different from the vehicle group, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. Moreover, while derivative **2** also dose-dependently reduced the mechanical hypersensitivity measured using Von Frey filaments eliciting innocuous to noxious mechanical stimuli in a model of inflammation induced by carrageenan in C57BL6 mice, intrathecal administration of derivative **2** (10 µg/mice, i.t.) is significantly decreased in mice lacking mGluR4 receptor as compared to their wild-type littermates in this inflammatory pain model (carrageenan) Fig 3.

Figure 4 illustrates the effect of intrathecal administration of derivative **2** on the vocalization threshold to paw pressure in the CCI neuropathic pain model (effect of derivative **2** (1, 5, 10 µg/rat, i.t.) on time-course of vocalization threshold to paw pressure). Gabapentin (100 mg/kg, p.o.) is used as a positive control. Results are expressed by the time course curves of means $\pm$ SEM of vocalization threshold in grams (n=7-8 rats per group) (A) or by the area under the curve (B), significantly different from the vehicle group, ** $P < 0.01$, *** $P < 0.001$.

The antihyperalgesic effect of derivative **2** is significantly higher than the one of gabapentine (100 mg/kg, per os) used as control in the neuropathy model and close to the one of morphine used as control on the inflammatory pain.

The effect of intrathecal administration of derivative **2** (10 µg/rat, i.t.) on the vocalization threshold to paw pressure in the CCI neuropathic pain model after mGluR4 or mismatch ODN treatment is illustrated by Figure 4. Results are expressed by the time course curves of means $\pm$ SEM of vocalization threshold in grams (n=5-8 rats per group) (A) or by the area under the curve (B), significantly different from the considered group, * $P < 0.05$, *** $P < 0.001$.

On neuropathic rats treated with antisens oligonucleotides against mGlu4, the antihyperalgesic effect of derivative **2** is significantly reduced with respect to the control conditions (saline or “mismatch” antisens targeting no target), illustrating that a great part of derivative **2** effect is induced *via* mGlu4 R.

Figure 5 illustrates the effect of systemic injection of derivative **2** on the vocalization threshold to paw pressure in a rat model of inflammatory pain (carageenan) (effect of derivative **2** (1, 10, 30 mg/kg, i.p.)) on time-course of vocalization threshold to paw pressure). Results are expressed by the time course curves of means $\pm$ SEM of vocalization threshold in grams (n=7-8 rats per group) (A) or by the area under the curve (B), significantly different from the vehicle group, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

The above results demonstrate the strong antihyperalgesic potential of derivative **2** in chronic pains of inflammatory or neuropathic origin.

Material & Methods

Animals

Adult male Sprague–Dawley rats weighting 175–200 g were purchased from Charles River. C57/BL6 mice were from Elevage Janvier, and homozygous mGlu4 (-/-) and wild-type (+/+) littermates were generated from crosses between heterozygous animals. Animals were housed under controlled environmental conditions (22°C; 55% humidity) and kept under a 12/12 h light/dark cycle, with food and water *ad libitum* for a week prior to start the experiments in order to acclimatize. Animal care and experiments were carried out in accordance with the Committee for Research and Ethical Issues of the IASP (Zimmermann M., 1983; Goudet C., 2008).

Mechanical testing in rats using the paw pressure test

The animals were submitted to the paw pressure test previously described by Randall and Selitto (1957). Nociceptive thresholds, expressed in grams (g), were measured with a Ugo Basile analgesimeter (Apelex, tip diameter of the probe: 1 mm, weight: 30 g) by applying an increasing pressure to the right hind paw of rats until a squeak (vocalization threshold) was obtained (cut-off was 750 g except carrageenan treated animals for which the cut-off was 500 g). The treatments were done after the measurement of two consecutive stable vocalization threshold values and their effects were assessed 15, 30, 45, 60, 90, and 120 min after.

Mechanical testing in mice using the von Frey test

Mechanical allodynia and hyperalgesia were assessed using the von Frey hair filaments of 3 different bending forces (0.07g, 0.6 g, 1.4 g). For each filament, 5 stimuli were applied with an interval of 3–5 s.

5

Persistent pain models: inflammatory and neuropathic pain models

Carrageenan-induced mechanical hyperalgesia

Thresholds to mechanically induced vocalization were assessed with rats presenting an hyperalgesia elicited by a subcutaneous injection of λ -carrageenan (200 μ g) into the right hind paw (200 μ L). Four hours later, vocalization thresholds were significantly decreased from 336 ± 6 g to 137 ± 2 g.

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Chronic Constriction Injury (CCI) model

Unilateral peripheral mononeuropathy was induced according to the method described by Bennett and Xie (1988). Briefly, after determining vocalization thresholds, rats were anesthetized with sodium pentobarbital (50 mg/kg i.p.) and four chromic gut (5–0) ligatures were tied loosely (with about 1-mm spacing) around the right common sciatic nerve. The nerve was constricted to a barely discernible degree, so that circulation through the epineurial vasculature was not interrupted. Only animals presenting a decrease $\geq 15\%$ of the presurgery value of vocalization threshold were selected, i.e., 90% of ligated animals (presurgery value: 379 ± 7 g, pre-drug value: 188 ± 7 g).

20

Experimental procedure and drugs

Treatment protocol

For all experiments, treatments were randomized and administered according to the method of blocks in order to assess the effect of the different treatments at the same time interval to avoid uncontrolled influences (one block includes a number of animals corresponding to the number of the different treatments administered; all animals in a same block are tested in the same short laps of time; the number of blocks corresponds to the number of animals per treatment). Different animals were used for each experiment (n=6–10 per treatment, according to the experiments) performed in a blinded manner in a quiet room and animal behaviors were observed by a single experimenter.

30

Intrathecal injections

Intrathecal injections were performed, under isoflurane anesthesia (4% induction, 2% maintenance), as previously described (Mestre *et al.*, 1994). Briefly, the anesthetized rat was held in one hand by the pelvic girdle and a 25-gauge X1-inch needle connected to a 25 μ L Hamilton syringe was inserted into the subarachnoidal space between lumbar vertebrae L5 and L6, until a tail flick was elicited. The syringe was held in position for few seconds after the injection of a volume of 10 μ L/rat.

Drugs

Gabapentin, derivative **2** and morphine were dissolved in saline (0.9% NaCl, B. Braun, Melsungen, Germany). All solutions were prepared immediately prior to injection.

Oligodeoxynucleotides targeting mGluR4 subunit

AS ODN was designed based on rat mGluR4 sequence in regions lacking known splice variants. They were synthesized by Eurogentec and sequences were as follows: AS-mGluR4, 5'-CGGATAGAGTTCATGTGG-3'. One ODN with scramble arrangement in the base composition compared to the 18-mer specific ASs was used as control for sequence-independent effects of ODN treatments. A blast search revealed that this mismatch ODNs were not complementary to any registered nucleotide sequences.

Intrathecal ODN administration

I.t. administrations of ODNs (12.5 μ g/rat) or saline were performed in a volume of 10 μ l via direct transcutaneous injection (with a 25-gauge needle connected to a 25 μ l Hamilton syringe) between the L5 and L6 dorsal spinous processes (Mestre *et al.*, 1994) under animal anaesthesia with isofluran (3.5%). This treatment was repeated twice daily for 4 days (days 1-4). Pain scores were determined using standard methods in strict conformity with ethical standards (Zimmermann M., 1983) before ODN treatments and then on day 4 in the afternoon. Treatments were randomized and all experiments were performed blind by the same experimenter using the method of equal blocks to avoid any uncontrollable environmental influence that might induce a modification in behavioural response.

Expression of results and statistical analysis

For the mechanical pain test, the results are expressed as vocalization thresholds, in grams (g). To investigate global effects, areas under the time-course curves (AUCs, g.min)

of the antihyperalgesic effects were calculated from individual scores at each time, using the trapezoidal method. Data were analyzed by a two-way ANOVA followed, when the F value was significant, by a Dunnett's test, when the time-course of the effects was studied. One-way ANOVA followed by a Student-Newman-Keuls' test was used to analyze the effect of the different treatments determined by the AUCs. The level of statistical significance was set at $p < 0.05$.

Pharmacological assays on recombinant mGluRs

Metabotropic glutamate receptors were transiently transfected in HEK293 cells by electroporation as described elsewhere (Brabet I. *et al.*, 1998) and plated in 96-well microplates. The high affinity glutamate transporter EAAC1 was co-transfected with the receptor in order to avoid any influence of glutamate released by the cells in the assay medium. In the experiments carried out by the inventors, Group-III mGluRs were co-transfected with a chimeric G-protein which couples the activation of the receptor to the phospholipase-C (PLC) pathway. Thus receptor activation induces production of inositol phosphate (IP) which in turn induces intracellular Ca^{2+} release. Receptor activity was then determined by measurement of the IP production or Ca release as already described (Goudet C. *et al.*, PNAS 2004). For intracellular calcium measurements, cells expressing mGluRs were loaded with Ca^{2+} -sensitive fluorescent dye Fluo-4 AM (Invitrogen, Cergy-Pontoise, France) dissolved in Hanks' balanced salt solution (HBSS, Invitrogen, Cergy-Pontoise, France) containing 2.5 mM Probenicid (Sigma-Aldrich Chemie, Saint-Quentin Fallavier, France) for 1 h at 37°C, then washed and incubated with HBSS containing probenecid. A drug plate was prepared with the various concentrations of agonist to be tested and drug solution was added in each well after 20 s of recording. Fluorescence signals (excitation 485 nm, emission 525 nm) were measured by using the fluorescence microplate reader Flexstation III (Molecular Devices, Saint-Grégoire, France) at sampling intervals of 1.5 s for 60 s. All points are realized in triplicate.

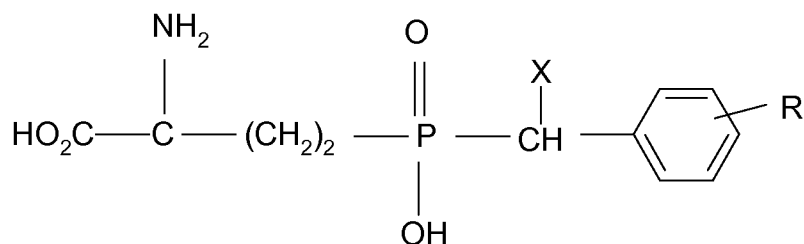
The dose-response curves were fitted using the GraphPad Prism program and the following equation: $y = [(y_{\text{max}} - y_{\text{min}}) / (1 + (x / \text{EC}_{50})^n)] + y_{\text{min}}$ where EC_{50} is the concentration of the compound necessary to obtain the half maximal effect and n is the Hill coefficient.

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Claims

1. Hypophosphorous acid derivatives of formula (I)



10 wherein

- X is H or OH,
- R represents one or several radicals $\text{R}^1\text{-R}^5$, identical or different, two of $\text{R}^1\text{-R}^5$ optionally occupying the same position on the phenyl group, one to four of $\text{R}^1\text{-R}^5$ being H and the others being selected in the group comprising
- 15 - $\text{O}-(\text{CH}_2)_n\text{-COOH}$; - $\text{S}-(\text{CH}_2)_n\text{-COOH}$; - $\text{NH}-(\text{CH}_2)_n\text{-COOH}$; - $\text{O}-(\text{CH}_2)_n\text{-COOH}$; - $\text{O}-(\text{CH}_2)_n\text{-OH}$; OR' , - R' being a $\text{C}_1\text{-C}_3$ alkyl radical; -OH; -COOH; halogen, particularly -F, -Cl, -Br, -I, -CF₃; -OCF₃; -NO₂; -CH=CH-COOH;
- $-(\text{CH}_2)_n\text{-COOH}$; $\text{O}-(\text{CH}_2)_n\text{-PO}_3\text{H}_2$; $\text{O}-(\text{CF}_2)_n\text{-PO}_3\text{H}_2$; $\text{O}-(\text{CH}_2)_n\text{-SO}_3\text{H}$; $\text{O}-(\text{CH}_2)_n\text{-CONHOH}$; $\text{O}-(\text{CH}_2)_n\text{-tetrazol}$; $\text{O}-(\text{CH}_2)_n\text{-hydroxyisoxazol}$
- 20 - $n = 1$ to 5 , preferably $1\text{-}3$;

said hypophosphorous acid derivatives being diastereoisomers or enantiomers.

2. The hypophosphorous acid derivatives of claim 1, having a EC_{50} with respect to mGlu4 $< 0.2 \mu\text{M}$.

3. The hypophosphorous acid derivatives of claim 2, having a EC_{50} with respect to mGlu 7 $< 15 \mu\text{M}$.

4. The hypophosphorous acid derivatives of claim 3, wherein $\text{X}=\text{OH}$ and R represents one substituent in para, or two substituents in meta and para, or three substituents two in meta and one in para, respectively.

5. The hypophosphorous acid derivatives of claim 4, wherein the phenyl group is substituted by - $\text{O}-(\text{CH}_2)_n\text{-COOH}$, with $n=1$ or - $\text{S}-(\text{CH}_2)_n\text{-COOH}$ with $n=1$.

6. The hypophosphorous acid derivatives of claim 4, wherein the phenyl group is substituted by two substituents, one being - $\text{O}-(\text{CH}_2)_n\text{-COOH}$ with preferably $n=1$, and the other is - OR' , with R' preferably being - CH_3 or CF_3 .

7. The hypophosphorous acid derivatives of claim 4, wherein the phenyl group is substituted by three substituents, one being -O-(CH₂)_n-COOH with preferably n=1, the second one is -OR', with R' preferably being -CH₃ and the third one is -F, -Cl, -I or -NO₂.

8 - The hypophosphorous acid derivatives of claim 1, having a EC₅₀ with respect to mGlu4 < about 1 μM.

9 - The hypophosphorous acid derivatives of claim 8, wherein X=-OH or H and R represents one substituent in para, or two substituents in meta and para, or three substituents with two in meta and one in para, respectively.

10 - The hypophosphorous acid derivatives of claim 9, wherein the phenyl group is substituted by one substituent, said substituent being -O-(CH₂)_n-COOH with n=1 and X=H or -O-(CH₂)_n-PO₃H₂ with n=1 and X=-OH or -(CH₂)_n-COOH with n=2 and X=-OH, or -CH=CH-COOH and X=-OH.

11 - The hypophosphorous acid derivatives of claim 9, wherein two substituents are present on the phenyl group, one being -O-(CH₂)_n-COOH with preferably n=1, and the other is -OR', with R' preferably being -CH₃, or is -OH, or is NO₂; or one is -S-(CH₂)_{n1}-COOH with preferably n1=1 and the other is -NO₂.

12 - The hypophosphorous acid derivatives of claim 9, comprising three substituents are present, one being -O-(CH₂)_n-COOH with preferably n=1 and the two others, identical or different, being selected from R as above defined or -OR', with R' preferably being -CH₃, or -NO₂, -F, -Cl, or -I.

13 - Pharmaceutical compositions comprising an effective amount of at least one of the hypophosphorous acid derivatives such as above defined in anyone of claims 1 to 12, in combination with a pharmaceutically acceptable carrier.

14- The pharmaceutical compositions of claim 13, comprising derivatives which simultaneously activate mGluR subtypes 4 and 7 for the treatment of neuropathic and inflammatory pain.

15- The pharmaceutical compositions of claim 13, comprising derivatives having a EC₅₀ with respect to mGluR7 receptors above 15 μM, even above 100 μM with a high selectivity for mGluR4.

16- The pharmaceutical compositions of claim 13, comprising derivatives having a high selectivity with respect to mGlu8 with EC₅₀ mGlu8 > 10/EC₅₀ mGlu4 < 0.5,

17 - The pharmaceutical compositions of anyone of claims 13 to 16, under a form suitable for an administration by the oral route, such as tablets, pills or capsules.

18 - The pharmaceutical compositions of claim 17, comprising 1 to 100 mg of active ingredient per dose unit.

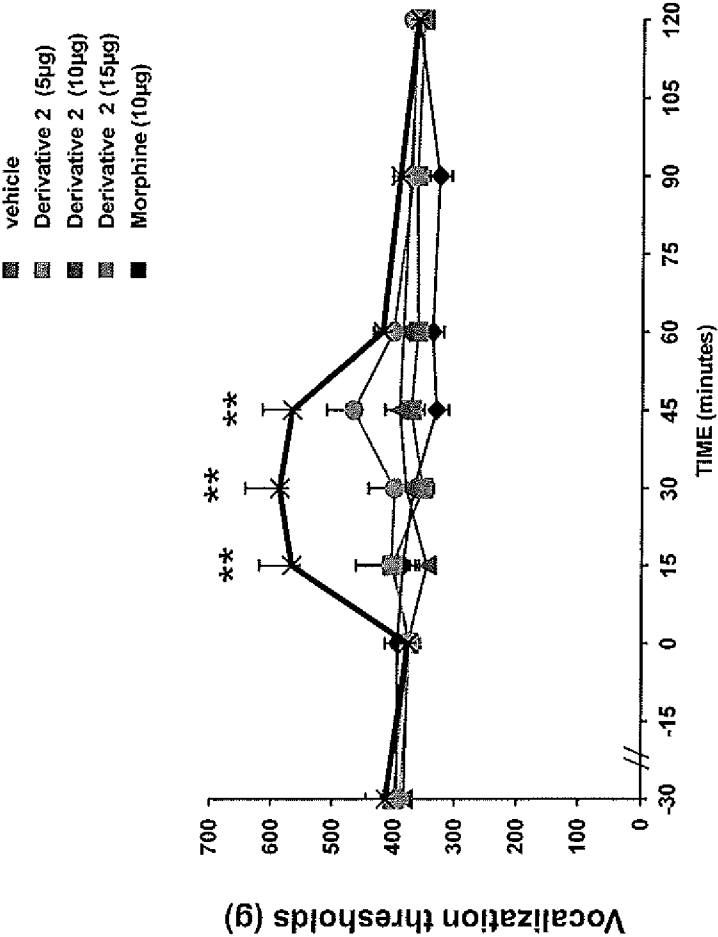
19 - The pharmaceutical compositions of claim 17 or 18, under a form suitable for an administration by injection, such as injectable solutions for the intravenous, subcutaneous or
5 intramuscular route.

20 - The pharmaceutical compositions of claim 19, comprising 1 to 30 mg of active ingredient per dose unit.

21 - A method for treating neuropathic and inflammatory pain comprising simultaneously activating glutamate metabotropic receptors sub-groups 4 and 7 by
10 administering to a patient in need thereof an efficient amount of at least one derivative of formula (I) according to claim 1 to 12.

Figure 1

A



B

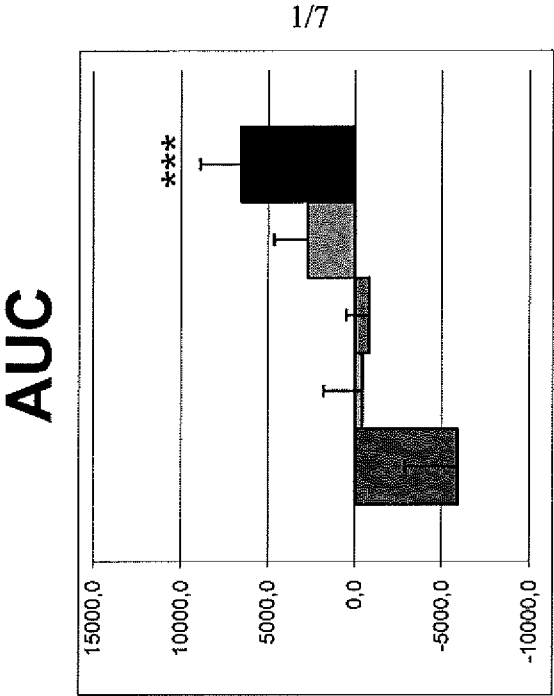


Figure 2

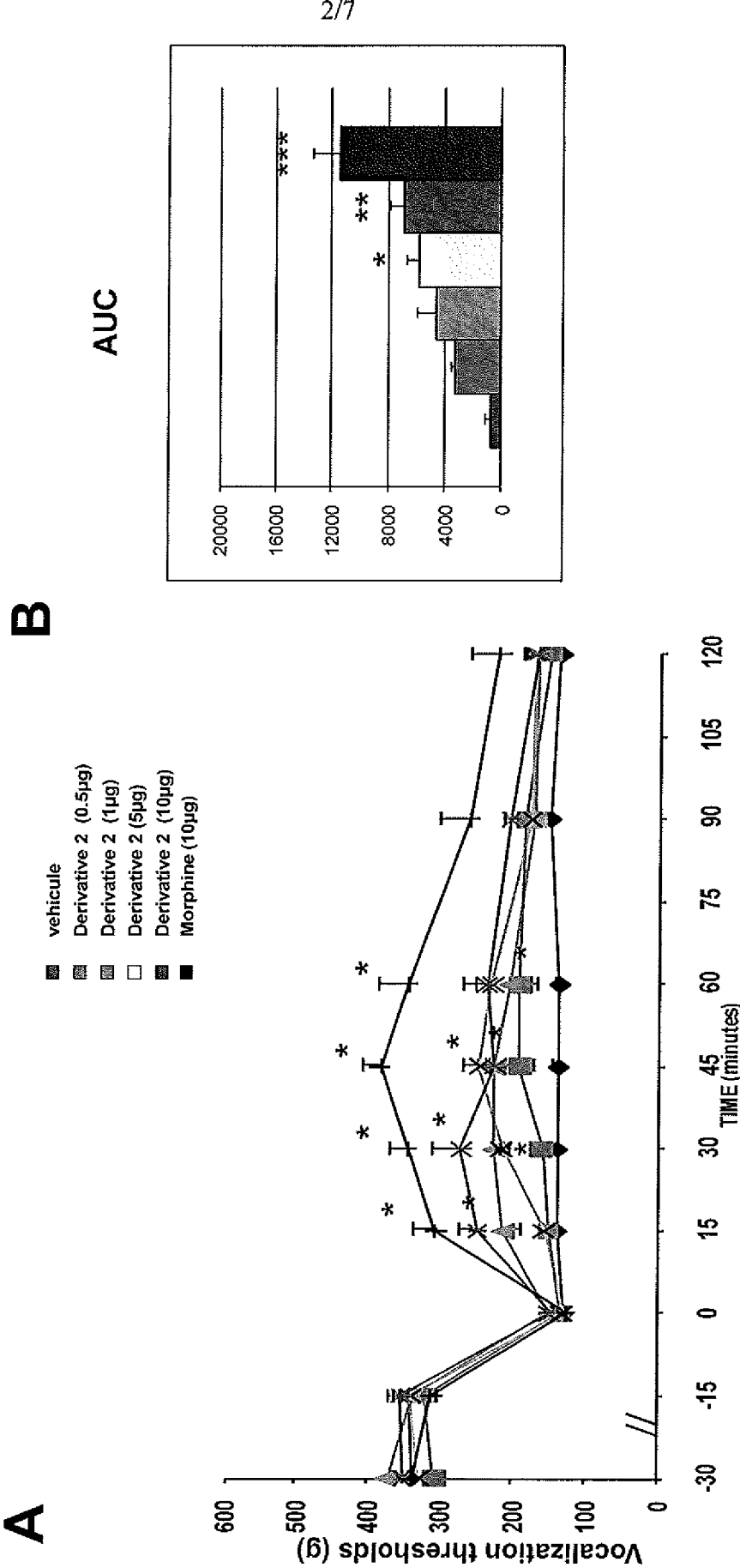
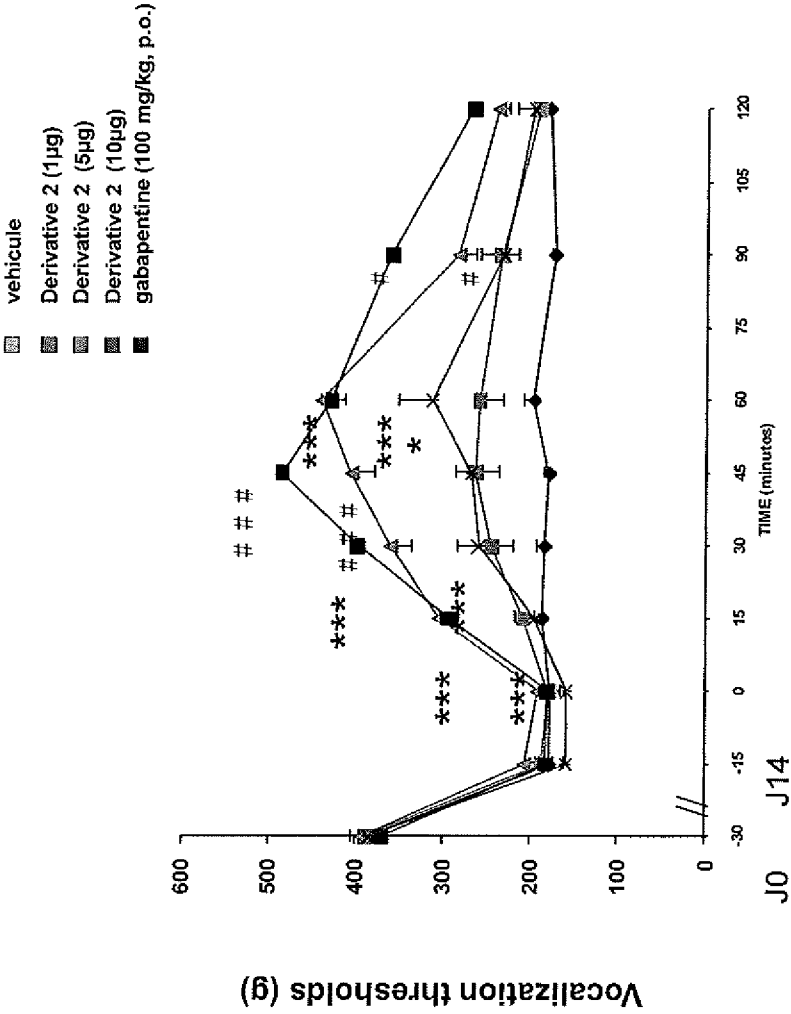


Figure 3

A



B

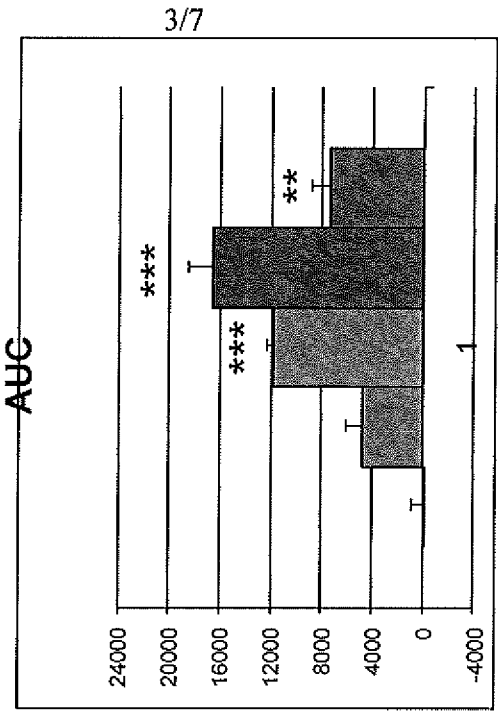
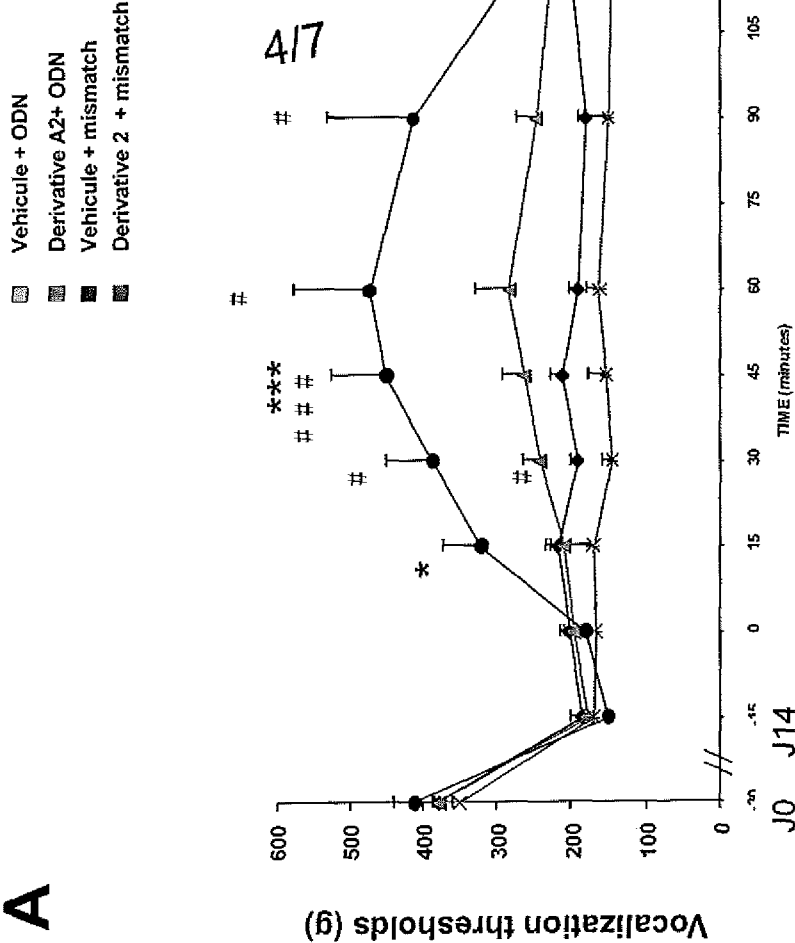


Figure 4



B

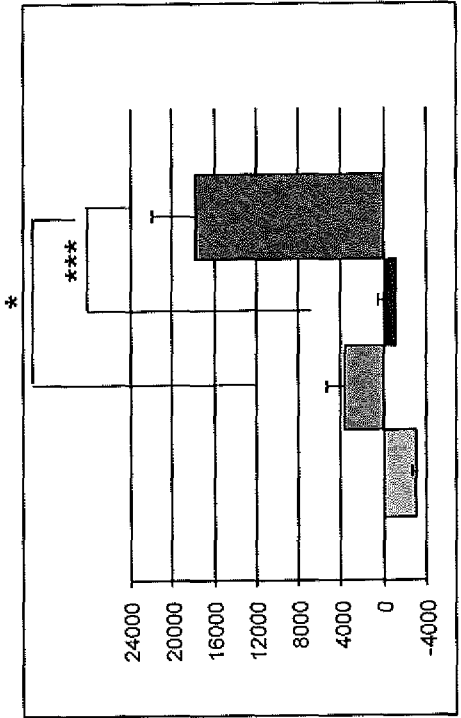


Figure 5

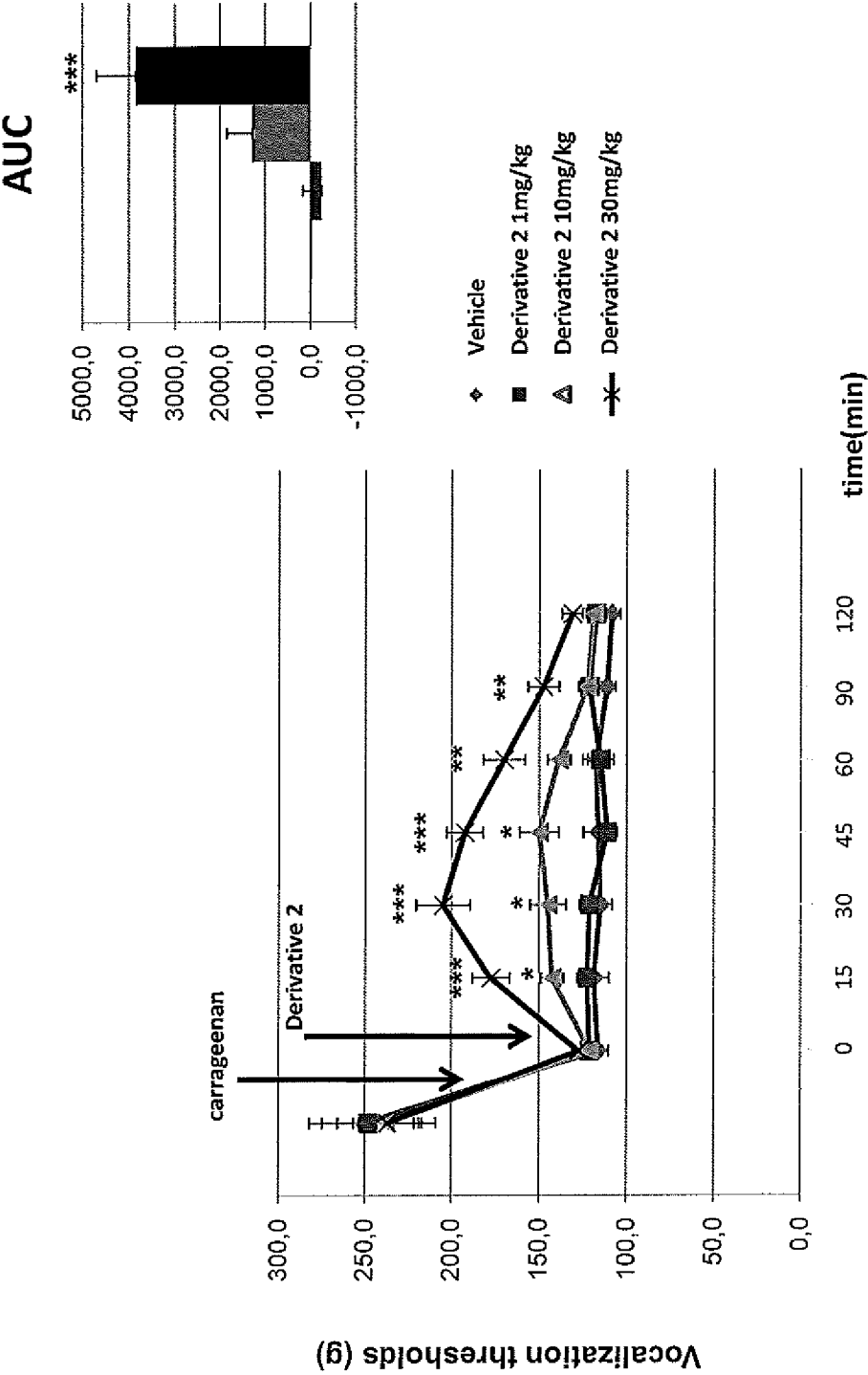


Figure 6

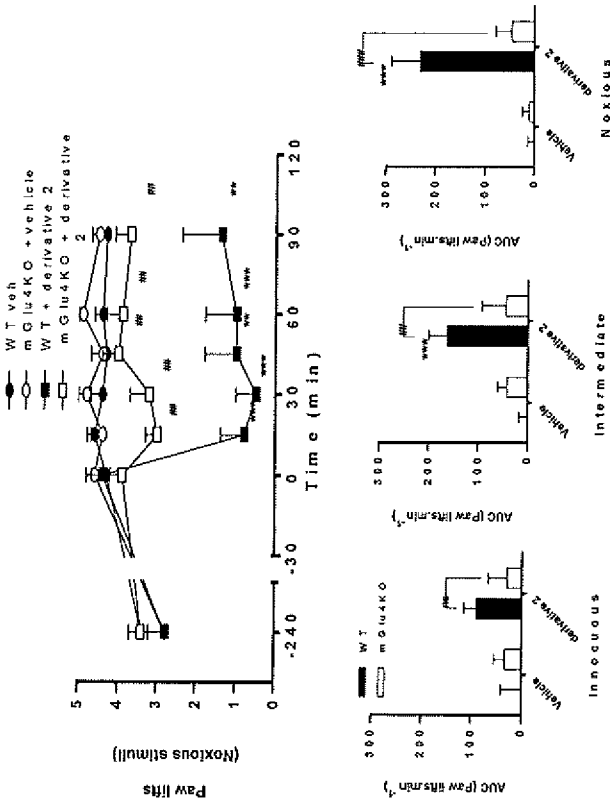
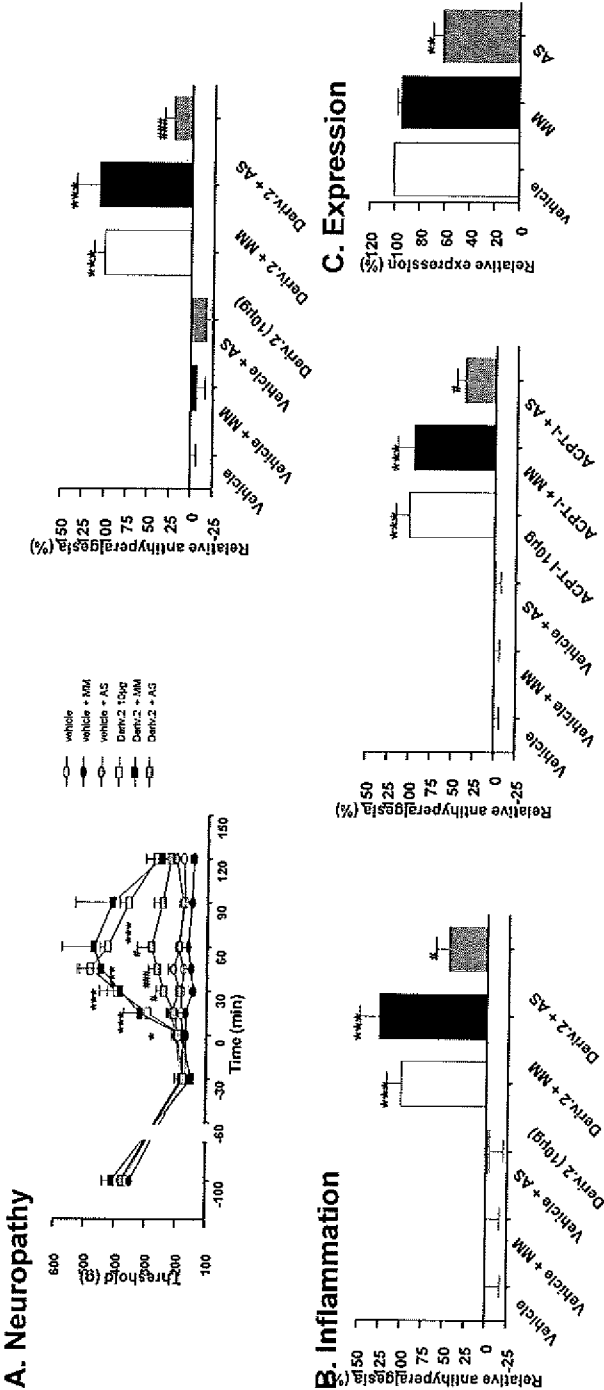


Figure 7



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/052467

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07F9/30 A61K31/662 A61P25/00
ADD.

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)

C07F A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MAIER L ET AL: "ORGANIC PHOSPHORUS COMPOUNDS 761 SYNTHESIS AND PROPERTIES OF PHOSPHINOTHRICIN DERIVATIVES", PHOSPHORUS AND SULFUR AND THE RELATED ELEMENTS, GORDON AND BREACH - HARWOOD ACADEMIC, CH, vol. 17, 1 January 1983 (1983-01-01), pages 1-20, XP009046741, ISSN: 0308-664X	1-3
A	page 9; table IV; compounds 33, 35	4-21
X	WO 2010/106526 A1 (CENTRE NAT RECH SCIENT [FR]; ACHER FRANCINE [FR]; SELVAM CHELLIAH [IN]) 23 September 2010 (2010-09-23) page 1 claim 1 page 24 - page 28; compounds LSP1-2093, LSP1-2101, LSP1-2109, LSP-2111	1-21
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Further documents are listed in the continuation of Box C.



See patent family annex.

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"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

12 July 2012

Date of mailing of the international search report

23/07/2012

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Jeanjean, Fabien

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/052467

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/052169 A2 (CENTRE NAT RECH SCIENT [FR]; ACHER FRANCINE [FR]; SELVAM CHELLIAH [FR]) 10 May 2007 (2007-05-10) cited in the application page 1 page 78 - page 83; table 2; compounds 22, 24, 38, 40, 46, 50, 54, 56, 58, 62, 64, 66, 70 page 86; claim 1 page 105; claim 37 -----	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2012/052467

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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