Supporting Information

Design, synthesis and docking-based 3D-QSAR study of novel 2-substituted 2-aminopropane-1, 3-diols as potent and selective agonists of sphingosine-1-phosphate 1 (S1P₁) receptor

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**IP₁ functional assay**

The CHO-S1P₁ and CHO-S1P₃ cells (purchased from Multispan) were plated into 384-well plates at 7×10⁴ cells/well in Stimulation Buffer (containing LiCl). Then different concentrations of test agonists were added into each well and incubated at 37°C in 5% CO₂ for 2 hours. Then D2-labeled IP₁ and Ab-Cryp were subsequently added into each well in lysis buffer and incubated for 1 h at room temperature according to the manufacturer’s instructions. The plates were read in EnVision reader (PE company), with data expressed as the ratio of 665 nm/615 nm fluorescence.¹

**Determination of in vivo lymphopenia activity**

For the assessment of lymphopenia activities of agonists in conscious rats, male Sprague-Dawley rats (200-220g) were purchased from Beijing Vital River Laboratory Animal Technology Co, Ltd. The rats (three per group) were dosed through intragastric administration with 1 mg/kg of test compound dissolved in DMSO. 10 μL of blood was withdrawn via tail vein and the peripheral blood lymphocyte counts at the time 0h, 1h, 4h, 8h, 12h and 24h after administration were assessed using MEK-7222K hematology analyzer. The maximum lymphocyte-decreasing rate of test compound (the maximum decreasing lymphocyte counts/ lymphocyte counts at 0h) within 24h was calculated.²

**Determination of heart rate**

Male Sprague-Dawley rats (200-220g) were purchased from Beijing Vital River Laboratory Animal Technology Co, Ltd. The conscious rats (three per group) were dosed through intragastric administration with 10 mg/kg of test compound dissolved in DMSO and vehicle. The heart rate at the time 0h, 1h, 4h, 8h, 12h and 24h after administration were assessed using intelligent non-invasive blood pressure measurement meter (Softron, Japan).

(All the in vivo experiments were performed in compliance with the relevant laws and institutional guidelines. The institutional committee has approved the experiments.)

**Molecular docking**

29 S1P₁ agonists were used for the docking research. For all 29 compounds, partial atomic charges were calculated by the Gasteiger–Huckel method and energy minimizations were carried out using the Tripos force field with a distance-dependent dielectric and the Powell conjugate gradient algorithm with an energy convergence gradient value of 0.05kcal/(mol*Å). The N-protonated and carboxylate forms of the molecules, which are the prevalent species at physiological pH, were used in the calculations.³ The crystal structure of S1P₁ receptor complexing with inhibitor ML056 was obtained from the RCSB protein data bank (PDB entry code: 3V2Y).³⁻⁴ The hetero atoms (cofactors, water molecules, and ligands) were removed and polar
hydrogen atoms were added. The protein was optimized using molecular mechanics method with the following parameters: a distance-dependent dielectric constant of 1.0; nonbonded cutoff 8 Å, AMBER7 FF99 force field and AMBER7 FF99 charges; and conjugate gradient minimization until the energy gradient RMS < 0.05 kcal/(mol*Å). Other parameters are established by default in software. All the calculations were performed using SYBYL-X-2.0.

Surflex-Dock in SYBYL-X-2.0 was applied to study molecular docking, which uses an empirical scoring function and a patented search engine to dock ligands into a protein’s binding site. Protomol, a computational representation of the intended binding site to which putative ligands are aligned, is used to guide molecular docking. The production of protomol supplies three manners: (1) Automatic: Surflex-Dock finds the largest cavity in the receptor protein; (2) Ligand: A ligand in the same coordinate space as the receptor; (3) Residues: Specified residues in the receptor.

**Figure S1** Binding mode of compound ML056 within the binding site of S1P1 receptor. The crystallized ligand is represented in green.

**3D-QSAR study**

To explore the specific contributions of steric, electrostatic, hydrophobic, hydrogen bond acceptor and donor in binding modes for the 29 agonists with active site of S1P1 receptor, both COMFA and COMSIA studies were performed based on the binding conformational alignment from the molecular docking. The COMFA/COMSIA results were graphically interpreted by field contribution maps (contour maps) using the STDEV*COEFF field type. The STDEV*COEFF is a standard deviation coefficient with default values of 80% favored contribution and 20% disfavored contribution.

**COMFA** The COMFA steric and electrostatic interactions were calculated using the Tripos force field with a distance-dependent dielectric constant at all intersections in a regularly spaced (2Å) grid taking a sp³ carbon atom as steric probe and a +1 charge as electrostatic probe. The cutoff value of 30 kcal/mol was adopted for both steric and electrostatic field. The regression analysis was carried out using the full cross-validated partial least squares (PLS) method (leave one out) with COMFA standard options for scaling of variables. The column filter was set to 2.0 kcal/mol to improve the signal-to-noise ratio by omitting the lattice points whose energy variation was below the threshold. The final model (no-validation conventional analysis) was
developed with the optimum number of components obtained in the cross-validated step.

**COMSIA**

COMSIA fields were derived with the same lattice as the COMFA used. Five descriptor, i.e. steric (S), electrostatic (E), hydrophobic (H), hydrogen bond donor (D) and hydrogen bond acceptor (A) were evaluated at grid lattice point using a common probe atom of 1 Å radius, as well as the charge, hydrophobicity, and hydrogen bond properties of +1. COMSIA similarity indices ($A_{F,k}$) for a molecule $j$ with atoms $i$ at a grid point $q$ were computed as Eq. 1,

$$A_{F,k}^q(j) = -\sum_{i=1}^{n} W_{probe,k} W_{i,k} e^{-\alpha r_{iq}}$$  

where $W_{ik}$ is the actual value of the physicochemical property $k$ of atom $i$, and $W_{probe,k}$ is the value of the probe atom. A Gaussian type distance dependence was used between the grid point $q$ and each atom $i$ of the molecule, where $r$ represents the distance. The attenuation factor ($\alpha$) was set to 0.3 as default. The statistical evaluation for the COMSIA analyses was performed in the same way for COMFA.

**Model validation**

The COMFA and COMSIA descriptors were used as independent variables and pEC$_{50}$ as the dependent variable. PLS method was used to linearly correlate these COMFA and COMSIA descriptors to the biological activity values. PLS algorithm is a variation of principal component regression in which the original variables are replaced by a small set of linear combination thereof.

The cross-validated correlation coefficient ($q^2$) that resulted in optimum number of components (N) and lowest standard error of estimation (SEE) was used as the diagnostic tool to evaluate the predictive power of the QSAR model. Generally, the model was considered predictable when $q^2$ is larger than 0.5 and linear regression analysis was considered significant when Non-cross validated value ($r^2$) is greater than 0.7. The $r^2$, $q^2$ and SEE were calculated using the following equations (Eqs. 2, 3, and 4):

$$r^2 = 1 - \frac{\sum_{i=1}^{n} (Y_i - \bar{Y})^2}{\sum_{i=1}^{n} (Y_i - \bar{Y}_{fit})^2}$$  

$$q^2 = 1 - \frac{\sum_{i=1}^{n} (Y_i - \bar{Y})^2}{\sum_{i=1}^{n} (Y_i - \bar{Y}_{cv})^2}$$  

$$SEE = \sqrt{\frac{\sum_{i=1}^{n} (Y_i - \bar{Y}_{cv})^2}{N}}$$

where $Y_i$=experimental value; $Y_{fit}$=recalculated value; $\bar{Y}$=mean value; $Y_{cv}$=predicted value; $N$= number of objects.

The external predictive power of the generated model was evaluated by predicting the activities of the test set compounds. The predictive correlation coefficient $r^2_{pred}$ based on test set molecules is computed by using Eq.5,
\[ r_{\text{pred}}^2 = \frac{(SD - PRESS)}{SD} \]  

(5)

where \( SD \) is the sum of squared deviation between the biological activities of the test set molecule and the mean activity of the training set molecules, and \( PRESS \) presents the sum of squared deviations between the experimental and predicted activities of the test molecules.

Table S1 Experimental and predicted S1P1 agonistic activities of target compounds for COMFA and COMSIA models

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<th>Compound</th>
<th>pEC_{50}</th>
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<td>Residuals</td>
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\(^a\) test set

Chemistry

General experimental information
Equipment  Melting points were determined on Yanaco MP-J3 microscope melting point apparatus; NMR spectra were recorded on a Varian-600, Bruker-500, Mercury-400 和 Mercury-300 spectrometer; Chemical shifts are referenced to the residual solvent peak and reported in ppm (δ scale) and all coupling constant (J) values are given in Hz. The following multiplicity abbreviations are used: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, and (br) broad; ESI-MS and HR-ESI-MS data were measured on Micromass AutoSpec Ultima-TOF spectrometer; Flash column chromatography was performed on Biotage Isolera one.

Solvents and chemicals CH$_2$Cl$_2$ was distilled under Ar$_2$ from P$_2$O$_5$ and stored over 4Å molecular sieves. THF was distilled under Ar$_2$ from sodium/benzophenone and stored over 4Å molecular sieves. All other solvents and chemicals were obtained from commercial sources and used without further purification.

Synthetic procedures and spectroscopic data of compounds

Synthesis of 2-chloro-1-(4-4-ethylphenethyl)phenyl)ethanone (7a)

Chloroacetyl chloride (3.9 g, 34.9 mmol) in CH$_2$Cl$_2$(10mL) was added dropwise to a cooled solution (0°C) of 6a (7.0 g, 33.3 mmol) in CH$_2$Cl$_2$(80mL), then AlCl$_3$ (4.9 g, 36.6 mmol) was added in portions in 30min. The solution was then allowed to return to room temperature and stirred for further 2 h. The mixture was poured slowly into 2NHCl-ice mixture (50mL) and stirred for 1 h. The aqueous phase was extracted with CH$_2$Cl$_2$ (10mL×3). The combined organic layers were washed with saturated aq. NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc/PE) to afford compound 7a (4.4g, 33% yield) as yellow solid.

mp: 16-18 °C; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.87 (d, $J = 8.1$ Hz, 2 H) 7.28 (d, $J = 7.8$ Hz, 2 H) 7.09 (dd, $J = 14.1$ Hz, 7.8 Hz, 4 H) 4.68 (s, 2 H) 2.96 (d, $J = 6.3$ Hz, 2 H) 2.91 (d, $J = 6.9$ Hz, 2 H) 2.62 (q, $J = 7.8$ Hz, 2 H) 1.22 (t, $J = 7.8$ Hz, 3 H); ESI (m/z) 287(M+H$^+$) 309(M+Na$^+$)

Synthesis of diethyl 2-acetamido-2-(2-(4-(4-ethylphenethyl) phenyl)-2-oxoethyl) malonate (8a):

To a solution of NaH (0.7g, 19.3mmol) in THF (20mL), diethyl acetamidomalonate (4.4 g, 20.1mmol) was added in portions at room temperature. The mixture was stirred for a further 2h and a solution of 7a (4.6 g, 16.1 mmol) in THF was added. The
mixture was heated at 70°C for further 12h and concentrated. The residue was diluted with EtOAc(30mL), washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc/PE) to afford compound 8a (3.0g, 79.3% yield) as yellow syrup.

**1H NMR (300 MHz CDCl₃):** δ 7.88 (d, J = 8.1 Hz, 2 H) 7.26-7.23 (m, 2 H) 7.16-7.06 (m, 4 H) 4.31-4.24 (m, 6 H) 2.96-2.92 (m, 4 H) 2.63 (q, J = 8.1 Hz, 2 H) 1.97 (s, 3 H) 1.33-1.20 (m, 9 H); ESI (m/z) 468 (M+H⁺) 490 (M+Na⁺)

**Synthesis of diethyl 2-acetamido-2-(4-(4-ethylphenethyl)phenethyl)malonate (9a):**

![Chemical Structure]

A solution of 8a (1.6 g, 3.4 mmol) in CH₂Cl₂ (20mL) was added dropwise to a solution of Et₃SiH (1.5 g, 12.8 mmol) in CH₂Cl₂ at room temperature under Ar₂ protection. TiCl₄ (2.4 g, 12.8 mmol) was added with a syringe and the reaction mixture was stirred for 12 h at room temperature. The solution was poured slowly into ice water (20mL). The aqueous phase was extracted with CH₂Cl₂ (5mL×3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated, yielding crude product 9a (1.5g, 97.4% yield) as yellow oil.

ESI (m/z) 454 (M+H⁺) 476 (M+Na⁺)

**Synthesis of N-(4-(4-(4-ethylphenethyl)phenyl)-1-hydroxy-2-(hydroxymethyl)butan-2-yl)acetamide (10a):**

![Chemical Structure]

To a solution of 9a (1.5 g, 3.4 mmol) in EtOH (20mL) was added K₂HPO₄ (6.1 g, 26.8 mmol) buffer and NaBH₄ (0.66 g, 17.4 mmol), then stirred for 12 h at room temperature. The solution was poured slowly into a mixture of saturated aq. NH₄Cl and EtOAc (20mL). The aqueous phase was extracted with EtOAc (5mL×3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash column chromatography (CH₂Cl₂/MeOH) to afford compound 10a (1.2g, 98.4% yield) as white solid.

mp: 32-34 °C; **1H NMR (300 MHz, CDCl₃):** δ 7.30-7.11 (m, 8 H) 5.89 (s, 1 H) 3.86 (d, J = 11.7 Hz, 2 H) 3.62 (d, J = 11.7 Hz, 2 H) 2.87 (d, J = 7.5 Hz, 4 H) 2.66-2.58 (m, 4 H) 1.98-1.93 (m, 5 H) 1.22 (t, J = 7.5 Hz, 3 H); ESI (m/z) 370 (M+H⁺) 392 (M+Na⁺)

**Synthesis of 2-amino-2-(4-(4-ethylphenethyl)phenethyl)propane-1,3-diol (11a):**
To a solution of 10a (0.11 g, 0.3 mmol) in MeOH (5 mL) was added NaOH (0.01 g, 0.3 mmol) and heated for 8 h at 80 °C. The mixture was added HCl-EtOH solution until pH = 2-3 and concentrated. The residue was purified by silica gel flash column chromatography (CH$_2$Cl$_2$/MeOH) to afford compound 11a (0.1 g, 95% yield) as white solid.

mp: 56-58 °C; 1H NMR (300 MHz, CD$_3$OD): δ 7.09-7.01 (m, 8 H) 3.64 (brs, 4 H) 2.79 (brs, 4 H) 2.61-2.52 (m, 4 H) 1.92-1.86 (m, 2 H) 1.52 (t, J = 7.5 Hz, 3 H); 13C NMR (100 MHz, CD$_3$OD): δ 142.90, 141.12, 140.21, 139.77, 129.75, 129.46, 129.16, 128.68, 62.52, 62.05, 38.73, 34.70, 29.68, 29.44, 16.26; HRMS calcd. for C$_{21}$H$_{30}$NO$_2$ (M+H$^+$) 328.2276, found 328.2278

Synthesis of benzyl (4-(4-(4-ethylphenethyl)phenyl)-1-hydroxy-2-(hydroxymethyl)butan-2-yl)carbamate (12a):

To a solution of 11a (100 mg, 0.27 mmol) in saturated aq. NaHCO$_3$ and EtOAc mixture (5 mL) was added CbzCl (56 mg, 0.33 mmol). The mixture was stirred for 4 h at room temperature. The aqueous phase was extracted with EtOAc (2 mL × 3). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by silica gel flash column chromatography (CH$_2$Cl$_2$/MeOH) to afford compound 12a (100 mg, 54.2% yield) as colorless oil.

1H NMR (300 MHz, CDCl$_3$): δ 7.34-7.07 (m, 13 H) 5.35 (s, 1 H) 5.07 (s, 2 H) 3.88 (d, J = 11.7 Hz, 2 H) 3.65 (d, J = 11.4 Hz, 2 H) 2.86 (d, J = 6.9 Hz, 4 H) 2.63-2.53 (m, 4 H) 1.88 (t, J = 8.4 Hz, 2 H) 1.22 (t, J = 7.8 Hz, 3 H); ESI (m/z) 462 (M+H$^+$)

Synthesis of benzyl (1-((bis(benzyloxy)phosphoryl)oxy)-4-(4-(4-ethylphenethyl)phenyl)-2-(hydroxymethyl)butan-2-yl)carbamate (13a):

To a solution of 12a (100 mg, 0.22 mmol) in CH$_2$Cl$_2$ (5 mL) was added tetrabenzylpyrophosphate (142 mg, 0.26 mmol), silver(I) oxide (102 mg, 0.44 mmol) and tetrahexylammonium iodide (212 mg, 0.44 mmol). After stirring at room temperature under Ar$_2$ protection for 20 h, the reaction mixture was filtered through celite to
remove insoluble materials, and then the filtrate was concentrated. The residue was purified by silica gel flash column chromatography (CH$_2$Cl$_2$/MeOH) to afford compound 13a (60mg, 37.8% yield) as colorless oil.

$^1$H NMR (300 MHz, CD$_3$COCD$_3$): δ 7.38-7.05 (m, 23 H) 6.16 (s, 1 H) 5.09-5.05 (m, 6 H) 4.37-4.23 (m, 2 H) 3.83-3.68 (m, 2 H) 2.87-2.78 (m, 4 H) 2.58 (q, $J = 9.9$ Hz, 4 H) 2.14-1.89 (m, 2 H) 1.17 (t, $J = 7.8$ Hz, 3 H); ESI (m/z) 721 (M+H$^+$)

**Synthesis of 2-amino-4-(4-(4-ethylphenethyl)phenyl)-2-(hydroxymethyl)butyl dihydrogen phosphate (14a):**

![Chemical structure of 14a]

To a solution of 13a (60mg, 0.08mmol) in MeOH was added 10%Pd/C (600mg) and stirred under H$_2$ atm for 8h. The reaction mixture was filtered through celite to remove Pd/C and concentrated to afford 14a (30mg, 92.1% yield) as white solid.

mp: 158-161 °C; $^1$H NMR (300 MHz, CD$_3$OD): δ 7.16-7.00 (m, 8 H) 3.86-3.75 (m, 2 H) 3.56 (dd, $J = 11.1$ Hz, 4.8 Hz, 2 H) 2.79 (d, $J = 9.0$ Hz, 4 H) 2.56-2.49 (m, 4 H) 1.82-1.72 (m, 2 H) 1.14 (t, $J = 7.8$ Hz, 3 H); $^{13}$C NMR (100 MHz, CD$_3$OD): δ 142.90, 141.12, 140.21, 139.77, 129.75, 129.46, 129.16, 128.68, 62.52, 62.05, 38.73, 34.70, 29.68, 29.44, 16.26; HRMS calcd. for C$_{21}$H$_{31}$NO$_5$P (M+H$^+$) 408.1934, found 408.1915

**Synthesis of 2-chloro-1-(4-(4-propylphenethyl)phenyl)ethanone (7b)**

![Chemical structure of 7b]

7b was prepared using the same procedure as that described for compound 7a. Yellow solid(5.4g, 17.5% yield).

mp: 17-19 °C; $^1$H NMR (300 MHz, CD$_3$COCD$_3$): δ 7.27-7.91 (m, 2 H) 7.41-7.38 (m, 2 H) 7.15-7.07 (m, 4 H) 4.98 (s, 2 H) 3.03-2.91 (m, 4 H) 2.53 (t, $J = 7.2$ Hz, 2 H) 1.63-1.55 (m, 2 H) 0.89 (t, $J = 7.5$ Hz, 3 H); ESI (m/z) 301 (M+H$^+$) 323 (M+Na$^+$)

**Synthesis of diethyl 2-acetamido-2-(2-oxo-2-(4-(4-propylphenethyl)phenyl)ethyl) malonate (8b)**

![Chemical structure of 8b]

8b was prepared using the same procedure as that described for compound 8a.
Yellow solid (2.8g, 33.3% yield).
mp: 33-35 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.88-7.85 (m, 2 H) 7.26-7.23 (m, 2 H) 7.11-7.04 (m, 4 H) 2.98-2.86 (m, 6 H) 2.55 (t, J = 7.5 Hz, 2 H) 2.04 (s, 3 H) 1.66-1.58 (m, 2 H) 1.26-1.22 (m, 6 H) 0.93 (t, J = 7.2 Hz, 3 H); ESI (m/z) 482 (M+H⁺) 504 (M+Na⁺)

**Synthesis of diethyl 2-acetamido-2-(4-(4-propylphenethyl)phenethyl)malonate (9b)**

9b was prepared using the same procedure as that described for compound 9a. Yellow oil (0.8g, 85.6% yield).
¹H NMR (300 MHz, CDCl₃): δ 7.30-7.04 (m, 8 H) 6.75 (s, 1 H) 4.32-4.11 (m, 4 H) 2.89-2.77 (m, 4 H) 2.73-2.38 (m, 6 H) 2.05 (s, 3 H) 1.66-1.59 (m, 2 H) 1.38-1.21 (m, 6 H) 0.93 (t, J = 7.5 Hz, 3 H); ESI (m/z) 468 (M+H⁺) 490 (M+Na⁺)

**Synthesis of N-(1-hydroxy-2-(hydroxymethyl)-4-(4-(4-propylphenethyl)phenyl)butan-2-yl)acetamide (10b)**

10b was prepared using the same procedure as that described for compound 10a. White solid (0.36g, 31.3% yield).
mp: 48-50 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.12 (s, 4 H) 7.09 (s, 4 H) 5.82 (s, 1 H) 3.86 (d, J = 11.7 Hz, 2 H) 3.62 (d, J = 11.4 Hz, 2 H) 2.86 (s, 4 H) 2.63 (t, J = 7.8 Hz, 2 H) 1.55 (t, J = 7.2 Hz, 2 H) 1.97 (s, 3 H) 1.98-1.94 (m, 2 H) 1.66-1.59 (m, 2 H) 0.93 (t, J = 7.2 Hz, 3 H); ESI (m/z) 384 (M+H⁺) 406 (M+Na⁺)

**Synthesis of 2-amino-2-(4-(4-propylphenethyl)phenethyl)propane-1,3-diol (11b)**

11b was prepared using the same procedure as that described for compound 11a. White solid (0.27g, 79.6% yield).
mp: 155-158 °C; ¹H NMR (300 MHz, CD₃OD): δ 7.08-7.01 (q, 4 H) 6.98 (s, 4 H) 3.62 (s, 4 H) 2.77 (s, 4 H) 2.59-2.53 (m, 2 H) 2.47 (t, J = 7.8 Hz, 2 H) 1.90-1.84 (m, 2 H) 1.58-1.48 (m, 2 H) 0.86 (t, J = 7.5 Hz, 3 H); ¹³C NMR (100 MHz, CD₃OD): δ
Synthesis of benzyl (1-hydroxy-2-(hydroxymethyl)-4-(4-(4-propylphenethyl)phenyl)butan-2-yl)carbamate (12b)

12b was prepared using the same procedure as that described for compound 12a. Colorless oil (117 mg, 65.8% yield).

1H NMR (300 MHz, CDCl3): δ 7.36 (s, 4 H) 7.09 (brs, 9 H) 5.28 (s, 1 H) 5.09 (s, 2 H) 3.91 (d, J = 12.0 Hz, 2 H) 3.67 (d, J = 11.1 Hz, 2 H) 2.85 (s, 4 H) 2.57 (q, J = 9.3 Hz, 4 H) 1.89 (t, J = 7.8 Hz, 2 H) 1.66-1.59 (m, 2 H) 0.93 (t, J = 7.2 Hz, 3 H); ESI (m/z) 476(M+H^+) 

Synthesis of benzyl (1-((bis(benzyloxy)phosphoryl)oxy)-2-(hydroxymethyl)-4-(4-(4-propylphenethyl)phenyl)butan-2-yl)carbamate(13b)

13b was prepared using the same procedure as that described for compound 13a. Colorless oil (61 mg, 33.2% yield).

1H NMR (300 MHz, CDCl3): δ 7.35-7.28 (m, 15 H) 7.10-7.00 (m, 8 H) 5.11-4.97 (m, 6 H) 4.17-4.03 (m, 2 H) 3.69 (d, J = 11.1 Hz, 2 H) 2.85 (s, 4 H) 2.58-2.41 (m, 4 H) 2.15-2.05 (m, 1 H) 1.81-1.56 (m, 3 H) 0.93 (t, J = 6.9 Hz, 3 H); ESI (m/z) 736(M+H^+) 

Synthesis of 2-amino-2-(hydroxymethyl)-4-(4-(4-propylphenethyl)phenyl)butyl dihydrogen phosphate (14b)

14b was prepared using the same procedure as that described for compound 14a. White solid (30 mg, 88.2% yield).

mp: 180-183 °C; 1H NMR (300 MHz, CD3OD): δ 8.13-7.82 (m, 2 H) 7.49-7.03 (m, 6 H) 4.00 (brs, 2 H) 3.69 (brs, 2 H) 3.07-2.49 (m, 8 H) 1.98-1.93 (m, 2 H) 1.70-1.56 (m, 2 H) 0.91 (t, J = 6.9 Hz, 3 H); 13C NMR (100 MHz, CD3OD) δ 141.20, 141.12, 140.28, 139.68, 129.74, 129.39, 129.34, 129.22, 65.83, 62.50, 61.41, 38.77, 38.67,
34.88, 29.62, 25.82, 14.06 HRMS calcd. for C_{22}H_{32}NO_{5}P(M+H\textsuperscript{+}) 422.2091, found 422.2050

**Synthesis of 1-(4-(4-butylphenethyl)phenyl)-2-chloroethanone (7c)**

![Chemical structure of 7c]

7c was prepared using the same procedure as that described for compound 7a. Yellow solid (8.1g, 26.1% yield).

mp: 22-25 °C; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 7.86 (d, J = 8.4 Hz, 2 H) 7.28 (d, J = 7.8 Hz, 2 H) 7.08 (dd, J = 12.0 Hz, 8.7 Hz, 4 H) 4.69 (s, 2 H) 2.57 (t, J = 7.8 Hz, 2 H) 1.60-1.53 (m, 2 H) 1.38-1.31 (m, 2 H) 0.92 (t, J = 7.2 Hz, 3 H); ESI (m/z) 315 (M+H\textsuperscript{+}), 337 (M+Na\textsuperscript{+})

**Synthesis of diethyl 2-acetamido-2-(2-(4-(4-butylphenethyl)phenyl)-2-oxoethyl)malonate (8c)**

![Chemical structure of 8c]

8c was prepared using the same procedure as that described for compound 8a. Yellow syrup (2.4g, 53.2% yield).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 7.87 (d, J = 7.8 Hz, 2 H) 7.25 (d, J = 7.2 Hz, 2 H) 7.11-7.05 (m, 4 H) 4.31-4.20 (m, 6 H) 3.00-2.86 (m, 4 H) 2.58 (t, J = 7.8 Hz, 2 H) 1.97 (s, 3 H) 1.64-1.56 (m, 2 H) 1.42-1.29 (m, 2 H) 1.25 (t, J = 7.2 Hz, 6 H) 0.93 (t, J = 7.2 Hz, 3 H); ESI (m/z) 496 (M+H\textsuperscript{+}), 518 (M+Na\textsuperscript{+})

**Synthesis of diethyl 2-acetamido-2-(4-(4-butylphenethyl)phenethyl)malonate (9c)**

![Chemical structure of 9c]

9c was prepared using the same procedure as that described for compound 9a. Crude product as yellow oil (1.3g, 98.2% yield).

ESI (m/z) 482 (M+H\textsuperscript{+}), 504 (M+Na\textsuperscript{+})

**Synthesis of N-(4-(4-(4-butylphenethyl)phenyl)-1-hydroxy-2-(hydroxymethyl)butan-2-yl)acetamide (10c)**
10c was prepared using the same procedure as that described for compound 10a. White solid (1.0 g, 94.3% yield).

mp: 53-54 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.12-7.09 (m, 8 H) 5.89 (s, 1 H) 3.86 (d, $J = 11.7$ Hz, 2 H) 3.62 (d, $J = 11.7$ Hz, 2 H) 2.86 (brs, 4 H) 2.66-2.58 (m, 4 H) 1.98-1.93 (m, 5 H) 1.63-1.53 (m, 2 H) 1.38-1.29 (m, 2 H) 0.92 (t, $J = 7.5$ Hz, 3 H); ESI (m/z) 398 (M+H$^+$) 420 (M+Na$^+$)

Synthesis of 2-amino-2-(4-(4-butylenethyl)phenethyl)propane-1,3-diol (11c)

11c was prepared using the same procedure as that described for compound 11a. White solid (0.3 g, 76.7% yield).

mp: 134-137 °C; $^1$H NMR (300 MHz, CD$_3$OD): $\delta$ 7.07 (d, $J = 7.8$ Hz, 2 H) 7.03 (d, $J = 8.1$ Hz, 2 H) 6.98 (brs, 4 H) 3.63 (brs, 4 H) 2.78 (brs, 4 H) 2.60-2.47 (m, 4 H) 1.91-1.85 (m, 2 H) 1.56-1.46 (m, 2 H) 1.34-1.25 (m, 2 H) 0.87 (t, $J = 7.5$ Hz, 3 H); $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 141.42, 141.13, 140.20, 139.77, 129.75, 129.39, 129.27, 129.15, 62.53, 62.05, 38.75, 36.22, 35.03, 34.70, 29.68, 23.32, 14.28; HRMS calcd. for C$_{23}$H$_{34}$NO$_2$ (M+H$^+$) 356.2589, found 356.2595

Synthesis of benzyl (4-(4-(4-butylenethyl)phenyl)-1-hydroxy-2-(hydroxymethyl)butan-2-yl)carbamate (12c)

12c was prepared using the same procedure as that described for compound 12a. Colorless oil (80 mg, 64.0% yield).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.36 (brs, 5 H) 7.19-7.10 (m, 8 H) 5.32 (brs, 1 H) 5.09 (s, 2 H) 3.91 (d, $J = 12.0$ Hz, 2 H) 3.67 (d, $J = 11.7$ Hz, 2 H) 2.86 (brs, 4 H) 2.58 (t, $J = 8.1$ Hz, 4 H) 1.90 (t, $J = 9.0$ Hz, 2 H) 1.62-1.54 (m, 2 H) 1.39-1.32 (m, 2 H) 0.93 (t, $J = 7.5$ Hz, 3 H); ESI (m/z) 490(M+H$^+$)

Synthesis of benzyl (1-((bis(benzyloxy)phosphoryl)oxy)-4-(4-(4-butylenethyl)phenyl)-2-(hydroxymethyl)butan-2-yl)carbamate (13c)
13c was prepared using the same procedure as that described for compound 13a. Colorless oil (40 mg, 33.4% yield).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.31-7.07 (m, 23 H) 5.27-4.98 (m, 6 H) 4.11-4.08 (m, 2 H) 3.70-3.68 (m, 2 H) 2.83 (brs, 4 H) 2.55 (t, $J = 8.1$ Hz, 4 H) 1.62-1.54 (m, 2 H) 1.26-1.19 (m, 4 H) 0.90 (t, $J = 6.0$ Hz, 3 H); ESI (m/z) 750 (M+H$^+$)

Synthesis of 2-amino-4-(4-(butylphenethyl)phenyl)-2-(hydroxymethyl)butyl dihydrogen phosphate (14c)

14c was prepared using the same procedure as that described for compound 14a. White solid (18 mg, 82.8% yield).

mp: 182-185 °C; $^1$H NMR (300 MHz, CD$_3$OD): $\delta$ 7.16-6.98 (m, 8 H) 3.93 (t, $J = 6.3$ Hz, 2 H) 3.66 (dd, $J = 12.9$ Hz, 6.9 Hz, 3 H) 2.77 (brs, 4 H) 2.63-2.47 (m, 4 H) 1.95-1.81 (m, 2 H) 1.53-1.45 (m, 2 H) 1.34-1.25 (m, 2 H) 0.86 (t, $J = 7.2$ Hz, 3 H); $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 141.42, 141.13, 140.20, 139.77, 129.75, 129.39, 129.27, 129.15, 62.53, 62.05, 38.75, 36.22, 35.03, 34.70, 29.68, 23.32, 14.28; HRMS calcd. for C$_{23}$H$_{35}$NO$_5$P (M+H$^+$) 436.2247, found 436.2233

Synthesis of 2-chloro-1-(4-(3-(4-ethylphenyl)propyl)phenyl)ethanone (7d)

7d was prepared using the same procedure as that described for compound 7a. White solid (7.1 g, 23.8% yield).

mp: 18-20 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.88 (d, $J = 8.4$ Hz, 2 H) 7.30 (d, $J = 8.4$ Hz, 2 H) 7.11 (dd, $J = 12.3$ Hz, 8.4 Hz, 4 H) 4.69 (s, 2 H) 2.71 (t, $J = 7.5$ Hz, 2 H) 2.66-2.58 (m, 4 H) 2.01-1.91 (m, 2 H) 1.22 (t, $J = 7.5$ Hz, 3 H); ESI (m/z) 301 (M+H$^+$) 323 (M+Na$^+$)

Synthesis of diethyl 2-acetamido-2-(2-(4-(3-(4-ethylphenyl)propyl)phenyl)-2-oxoethyl)malonate (8d)
8d was prepared using the same procedure as that described for compound 8a. Yellow solid (4.0g, 37.6% yield).
mp: 31-34 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.88 (d, \(J = 8.4\) Hz, 2 H) 7.27 (d, \(J = 8.4\) Hz, 2 H) 7.14-7.07 (m, 4 H) 4.30-4.23 (m, 6 H) 2.69 (t, \(J = 7.2\) Hz, 2 H) 2.66-2.58 (m, 4 H) 1.96 (s, 3 H) 2.00-1.89 (m, 2 H) 1.29-1.18 (m, 9 H); ESI (m/z) 482 (M+H\(^+\)) 504 (M+Na\(^+\))

**Synthesis of diethyl 2-acetamido-2-(4-(4-ethylphenyl)propyl)phenethyl) malonate (9d)**

\[
\text{EtOOC} \quad \begin{array}{c}
\text{NHAc} \\
\text{EtOOC}
\end{array}
\]

9d was prepared using the same procedure as that described for compound 9a. Yellow oil (2.1g, 89.9% yield).
\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.27-7.03 (m, 8 H) 6.76 (s, 1 H) 4.29-4.11 (m, 4 H) 2.87-2.57 (m, 8 H) 2.44 (d, \(J = 6.9\) Hz, 2 H) 1.99 (s, 3 H) 2.10-1.91 (m, 2 H) 1.31-1.17 (m, 9 H); ESI (m/z) 468 (M+H\(^+\)) 490 (M+Na\(^+\))

**Synthesis of N-(4-(4-(3-(4-ethylphenyl)propyl)phenyl)-1-hydroxy-2-(hydroxymethyl)butan-2-yl)acetamide (10d)**

\[
\begin{array}{c}
\text{HO} \\
\text{NHAc}
\end{array}
\]

10d was prepared using the same procedure as that described for compound 10a. White solid (1.2g, 44.8% yield).
mp: 42-44 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.25 (s, 4 H) 7.11 (s, 4 H) 5.82 (s, 1 H) 3.86 (d, \(J = 11.1\) Hz, 2 H) 3.74 (s, 2 H) 3.62 (d, \(J = 11.1\) Hz, 2 H) 2.65-2.58 (q, 8 H) 1.94 (s, 3 H) 2.06-1.86 (m, 2 H) 1.67-1.60 (m, 2 H) 1.31-1.19 (m, 3 H); ESI (m/z) 384 (M+H\(^+\)) 406 (M+Na\(^+\))

**Synthesis of 2-amino-2-(4-(3-(4-ethylphenyl)propyl)phenethyl)propane-1,3-diol (11d)**

\[
\begin{array}{c}
\text{HO} \\
\text{NH}_2
\end{array}
\]

11d was prepared using the same procedure as that described for compound 11a. White solid (0.75g, 73.3% yield).
mp: 55-57 °C; \(^1\)H NMR (300 MHz, CD\(_3\)OD): \(\delta\) 7.10-7.01 (m, 8 H) 3.62 (s, 4 H) 2.60-2.48 (m, 8 H) 1.91-1.81 (m, 4 H) 1.14 (t, \(J = 7.5\) Hz, 3 H); \(^{13}\)C NMR (100 MHz, CD\(_3\)OD): \(\delta\) 142.80, 141.58, 140.71, 139.68, 129.67, 129.38, 129.23, 128.74, 62.53, 62.05, 35.98, 35.97, 34.74, 34.67, 29.69, 29.45, 16.28; HRMS calcd. for C\(_{22}\)H\(_{32}\)NO\(_2\)
Synthesis of benzyl (4-(4-(3-(4-ethylphenyl)propyl)phenyl)-1-hydroxy-2-(hydroxymethyl)butan-2-yl)carbamate (12d)

12d was prepared using the same procedure as that described for compound 12a. Colorless oil (70mg, 66.9% yield).

$^1$H NMR (300 MHz, CD$_3$COCD$_3$): $\delta$ 7.38-7.25 (m, 8 H) 7.09-7.07 (m, 7 H) 5.04 (s, 2 H) 3.79 (d, $J = 11.1$ Hz, 2 H) 3.68 (d, $J = 11.1$ Hz, 2 H) 2.62-2.53 (m, 8 H) 2.03-1.86 (m, 4 H) 1.16 (t, $J = 7.5$ Hz, 3 H); ESI (m/z) 476 (M+H$^+$)

Synthesis of benzyl (1-((bis(benzyloxy)phosphoryl)oxy)-4-(4-(3-(4-ethylphenyl)propyl)phenyl)-2-(hydroxymethyl)butan-2-yl)carbamate (13d)

13d was prepared using the same procedure as that described for compound 13a. Colorless oil (40mg, 36.3% yield).

$^1$H NMR (300 MHz, CD$_3$COCD$_3$): $\delta$ 7.37-7.24 (m, 15 H) 7.10-7.08 (m, 8 H) 5.08-5.04 (m, 6 H) 4.37-4.22 (m, 2 H) 3.74 (q, $J = 11.1$ Hz, 2 H) 2.61-2.54 (m, 8 H) 2.05-1.86 (m, 4 H) 1.17 (t, $J = 7.5$ Hz, 3 H); ESI (m/z) 736 (M+H$^+$)

Synthesis of 2-amino-4-(4-(3-(4-ethylphenyl)propyl)phenyl)-2-(hydroxymethyl)butyl dihydrogen phosphate (14d)

14d was prepared using the same procedure as that described for compound 14a. White solid (18mg, 79.2% yield).

mp: 155-158 °C; $^1$H NMR (300 Hz, CD$_3$OD): $\delta$ 7.09-7.02 (m, 8 H) 3.93 (brs, 2 H) 3.64 (brs, 2 H) 2.62-2.53 (m, 8 H) 1.85-1.83 (m, 4 H) 1.15 (t, $J = 7.8$ Hz, 3 H); $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 142.79, 141.50, 140.74, 139.76, 129.63, 129.40, 129.31, 128.74, 65.92, 62.76, 61.13, 61.09, 35.98, 35.12, 34.67, 30.75, 29.64, 29.46, 16.29; HRMS calcd. for C$_{22}$H$_{33}$NO$_5$P (M+H$^+$) 422.2091, found 422.2084

Synthesis of 2-chloro-1-(4-(4-(4-isopropylphenyl)butyl)phenyl)ethanone (7e)
7e was prepared using the same procedure as that described for compound 7a. Crude product as yellow oil (14g, 93.3% yield).
ESI (m/z) 329 (M+H⁺); 351 (M+Na⁺)

**Synthesis of diethyl 2-acetamido-2-(2-(4-(4-isopropylphenyl)butyl)phenyl)-2-oxoethyl)malonate (8e)**

8e was prepared using the same procedure as that described for compound 8a. Yellow solid (4g, 19.9% yield).
mp: 26-28 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.87 (d, J = 6.0 Hz, 2 H) 7.24 (d, J = 6.0 Hz, 2 H) 7.13 (d, J = 6.0 Hz, 1 H) 7.08 (t, J = 8.4 Hz, 2 H) 4.29-4.23 (q, 6 H) 2.88-2.85 (m, 1 H) 2.68 (t, J = 4.8 Hz, 2 H) 2.59 (t, J = 5.4 Hz, 2 H) 1.96 (s, 3 H) 1.67-1.63 (m, 4 H) 1.23 (t, J = 5.1 Hz, 12 H); ESI (m/z) 510 (M+H⁺) 532 (M+Na⁺)

**Synthesis of diethyl 2-acetamido-2-(4-(4-isopropylphenyl)butyl)phenethyl)malonate (9e)**

9e was prepared using the same procedure as that described for compound 9a. Crude product as yellow oil (2.0g, 98.0% yield).
ESI (m/z) 496 (M+H⁺); 518 (M+Na⁺)

**Synthesis of N-(1-hydroxy-2-(hydroxymethyl)-4-(4-(4-isopropylphenyl)butyl)phenyl)butan-2-yl)acetamide (10e)**
**10e** was prepared using the same procedure as that described for compound **10a**. White solid (0.3 g, 14.3% yield).

mp: 28-30 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.25 (s, 4 H) 7.14-7.06 (q, 4 H) 5.77 (s, 1 H) 3.87 (d, \(J = 11.4\) Hz, 2 H) 3.62 (d, \(J = 11.7\) Hz, 2 H) 2.91-2.82 (m, 1 H) 2.65-2.59 (m, 6 H) 1.93 (s, 3 H) 1.98-1.95 (m, 2 H) 1.63 (brs, 4 H) 1.23 (d, \(J = 7.2\) Hz, 6 H); ESI (m/z) 412 (M+H\(^+\)) 434 (M+Na\(^+\))

**Synthesis of 2-amino-2-(4-(4-(4-isopropylphenyl)butyl)phenethyl)propane-1,3-diol (11e)**

**11e** was prepared using the same procedure as that described for compound **11a**. White solid (0.11 g, 42.2% yield).

mp: 160-162 °C; \(^1\)H NMR (300 MHz, CD\(_3\)OD): \(\delta\) 7.08-6.97 (m, 8 H) 3.62 (s, 4 H) 2.80-2.76 (m, 1 H) 2.59-2.51 (m, 6 H) 1.90-1.84 (m, 2 H) 1.54 (brs, 4 H) 1.16 (d, \(J = 6.9\) Hz, 6 H); \(^{13}\)C NMR (100 MHz, CD\(_3\)OD): \(\delta\) 147.34, 141.78, 141.10, 139.58, 129.63, 129.32, 129.17, 127.20, 62.53, 62.04, 36.28, 34.99, 34.75, 32.29, 29.67, 24.53; HRMS calcd. for C\(_{24}\)H\(_{36}\)NO\(_2\) (M+H\(^+\)) 370.2746, found 370.2743

**Synthesis of benzyl (1-hydroxy-2-(hydroxymethyl)-4-(4-(4-(4-isopropylphenyl)butyl)phenyl)butan-2-yl)carbamate (12e)**

**12e** was prepared using the same procedure as that described for compound **12a**. Colorless oil (70 mg, 69.6% yield).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.35-7.01 (m, 13 H) 5.07 (s, 2 H) 3.88 (d, \(J = 11.4\) Hz, 2 H) 3.66 (d, \(J = 11.4\) Hz, 2 H) 2.88-2.84 (m, 1 H) 2.58-2.47 (m, 6 H) 1.89 (t, \(J = 8.7\) Hz, 2 H) 1.63 (brs, 4 H) 1.23 (d, \(J = 7.2\) Hz, 6 H); ESI (m/z) 504 (M+H\(^+\))

**Synthesis of benzyl (1-((bis(benzyloxy)phosphoryl)oxy)-2-(hydroxymethyl)-4-
(4-(4-(4-isopropylphenyl)butyl)phenyl)butan-2-yl)carbamate (13e)

13e was prepared using the same procedure as that described for compound 13a. Crude product as colorless oil (30 mg, 28.0% yield).
ESI (m/z) 764 (M+H⁺);

Synthesis of 2-amino-2-(hydroxymethyl)-4-(4-(4-isopropylphenyl)butyl)phenyl)butyl dihydrogen phosphate (14e)

14e was prepared using the same procedure as that described for compound 14a. White solid (12 mg, 68.5% yield).

mp: 145-148 °C; ¹H NMR (300 MHz, CD₃OD) δ 7.09-6.97 (m, 8 H) 3.93-3.84 (m, 2 H) 3.63 (dd, J = 15.3 Hz, 8.4 Hz, 2 H) 2.80-2.73 (m, 1 H) 2.61-2.51 (m, 6 H) 1.90-1.86 (m, 2 H) 1.54 (brs, 4 H) 1.15 (d, J = 6.9 Hz, 6 H); ¹³C NMR (100 MHz, CD₃OD): δ 147.32, 141.71, 141.12, 139.61, 129.59, 129.32, 129.24, 127.20, 65.87, 62.64, 61.20, 36.39, 35.01, 32.31, 29.62, 24.53; HRMS calcd. for C₂₄H₃₇NO₅P (M+H⁺) 450.2404, found 450.2403

Synthesis of 2-chloro-1-(6-hexynaphthalen-2-yl)ethanone (7f)

7f was prepared using the same procedure as that described for compound 7a. Yellow oil (6.0 g, 23.9% yield).

1H NMR (300 MHz, CDCl₃): δ 8.43 (s, 1 H) 8.02-7.73 (m, 3 H) 7.65 (s, 1 H) 7.50-7.41 (q, 1 H) 4.79 (s, 2 H) 3.09 (t, J = 7.8 Hz, 2 H) 1.73-1.68 (m, 2 H) 1.32 (brs, 6 H) 0.88 (t, J = 6.3 Hz, 3 H); ESI (m/z) 289 (M+H⁺) 311 (M+Na⁺)

Synthesis of diethyl 2-acetamido-2-(2-(6-hexynaphthalen-2-yl)-2-oxoethyl)malonate (8f)
8f was prepared using the same procedure as that described for compound 8a. Yellow oil (3.4g, 17.9% yield).

1H NMR (300 MHz, CDCl₃): δ 8.48 (s, 1 H) 7.99-7.73 (m, 3 H) 7.63 (s, 1 H) 7.42 (d, J = 8.1 Hz, 1 H) 7.15 (s, 1 H) 4.39-4.25 (m, 6 H) 2.79 (t, J = 7.2 Hz, 2 H) 1.97 (s, 3 H) 1.73-1.67 (m, 2 H) 1.32-1.23 (m, 12 H) 0.96 (t, J = 4.5 Hz, 3 H); ESI (m/z) 470 (M+H⁺) 492 (M+Na⁺)

Synthesis of diethyl 2-acetamido-2-(2-(6-hexynaphthalen-2-yl)ethyl)malonate (9f)

9f was prepared using the same procedure as that described for compound 9a. Yellow oil (0.8g, 33.2% yield).

1H NMR (300 MHz, CDCl₃): δ 7.67 (d, J = 7.8 Hz, 2 H) 7.54 (s, 2 H) 7.31-7.22 (m, 2 H) 6.79 (s, 1 H) 4.25-4.14 (m, 4 H) 2.80-2.71 (m, 4 H) 2.65-2.60 (m, 2 H) 1.97 (s, 3 H) 1.70-1.65 (m, 2 H) 1.31-1.20 (m, 12 H) 0.87 (t, J = 7.2 Hz, 3 H); ESI (m/z) 456 (M+H⁺) 478 (M+Na⁺)

Synthesis of N-(4-(6-hexynaphthalen-2-yl)-1-hydroxy-2-(hydroxymethyl)butan-2-yl)acetamide (10f)

10f was prepared using the same procedure as that described for compound 10a. White solid (1.1g, 71.9% yield).

mp: 50-51 °C; 1H NMR (300 MHz, CDCl₃): δ 7.69 (t, J = 8.4 Hz, 2 H) 7.57 (d, J = 9.3 Hz, 2 H) 7.31 (d, J = 8.7 Hz, 2 H) 5.87 (s, 1 H) 3.91 (d, J = 10.2 Hz, 2 H) 3.72 (s, 2 H) 3.65 (d, J = 12.3 Hz, 2 H) 2.83-2.72 (m, 4 H) 2.08-1.94 (m, 2 H) 1.93 (s, 3 H) 1.66 (t, J = 6.6 Hz, 2 H) 1.31 (s, 6 H) 0.87 (s, 3 H); ESI (m/z) 372 (M+H⁺) 394 (M+Na⁺)

Synthesis of 2-amino-2-(2-(6-hexynaphthalen-2-yl)ethyl)propane-1,3-diol (11f)

11f was prepared using the same procedure as that described for compound 11a. White solid (0.58g, 60.9% yield).

mp: 175-178 °C; 1H NMR (300 MHz, CD₃OD): δ 7.65 (t, J = 7.8 Hz, 2 H) 7.58 (s, 1 H) 7.51 (s, 1 H) 7.31-7.24 (m, 2 H) 3.67 (s, 4 H) 2.79-2.66 (m, 4 H) 2.02-1.96 (m, 2 H) 1.89-1.83 (m, 2 H) 1.28 (s, 6 H) 0.85-0.81 (s, 3 H); 13C NMR (100 MHz, CD₃OD): δ 141.14, 139.00, 133.86, 133.65, 128.73, 128.58, 128.36, 127.93, 127.10, 127.08,
Synthesis of benzyl (4-(6-hexynaphthalen-2-yl)-1-hydroxy-2-(hydroxymethyl)butan-2-yl)carbamate (12f)

12f was prepared using the same procedure as that described for compound 12a. Colorless oil (110 mg, 79.2% yield).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.66 (dd, $J = 7.5$ Hz, 5.4 Hz, 2 H) 7.54 (s, 2 H) 7.34-7.25 (m, 7 H) 5.07 (s, 2 H) 3.94 (d, $J = 11.1$ Hz, 2 H) 3.70 (d, $J = 11.4$ Hz, 2 H) 2.76-2.73 (m, 4 H) 1.98 (t, $J = 8.4$ Hz, 2 H) 1.68-1.65 (m, 2 H) 1.31 (brs, 6 H) 0.87 (brs, 3 H); ESI (m/z) 464 (M+H$^+$)

Synthesis of benzyl (1-((bis(benzyloxy)phosphoryl)oxy)-4-(6-hexynaphthalen-2-yl)-2-(hydroxymethyl)butan-2-yl)carbamate (13f)

13f was prepared using the same procedure as that described for compound 13a. Colorless oil (70 mg, 40.3% yield).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.67-7.19 (m, 21 H) 5.11-5.00 (m, 6 H) 4.16-3.69 (m, 4 H) 2.74 (t, $J = 7.2$ Hz, 4 H) 2.02-1.66 (m, 4 H) 1.31 (brs, 6 H) 0.88 (brs, 3 H); ESI (m/z) 724 (M+H$^+$)

Synthesis of 2-amino-4-(6-hexynaphthalen-2-yl)-2-(hydroxymethyl)butyl dihydrogen phosphate (14f)

14f was prepared using the same procedure as that described for compound 14a. White solid (38 mg, 95.8% yield).

mp: 118-120 ºC; $^1$H NMR (300 MHz, CD$_3$OD) δ 7.66-7.21 (m, 6 H) 4.08-3.64 (m, 4 H) 2.68 (t, $J = 7.5$ Hz, 4 H) 2.08-2.05 (m, 2 H) 1.64-1.61 (m, 2 H) 1.28 (brs, 6 H) 0.84 (brs, 3 H); $^{13}$C NMR (100 MHz, CD$_3$OD): δ141.14, 139.00, 133.86, 133.65, 128.73, 128.58, 128.36, 127.93, 127.10, 127.08, 67.10, 63.21, 60.44, 37.04, 33.66, 32.91, 32.60, 30.54, 30.11, 23.69, 14.41; HRMS calcd. for C$_{21}$H$_{33}$NO$_5$P (M+H$^+$) 410.2091, found 410.2085

Synthesis of 2-chloro-1-(6-hexynaphthalen-1-yl)ethanone (7g)

62.56, 62.12, 37.00, 34.56, 32.89, 32.56, 30.20, 30.07, 23.67, 14.40; HRMS calcd. for C$_{21}$H$_{32}$NO$_2$ (M+H$^+$) 330.2427, found 330.2424
7g was prepared using the same procedure as that described for compound 7a. Yellow oil (15.9 g, 63.5%).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.55 (d, $J = 7.8$ Hz, 1 H) 7.83-7.81 (m, 2 H) 7.70 (s, 1 H) 7.58-7.50 (m, 2 H) 4.78 (s, 2 H) 2.80 (t, $J = 7.5$ Hz, 2 H) 1.74-1.66 (m, 2 H) 1.33 (brs, 6 H) 0.89 (t, $J = 6.3$ Hz, 3 H); ESI (m/z) 289 (M+H$^+$) 311 (M+Na$^+$)

Synthesis of diethyl 2-acetamido-2-(2-(6-hexynaphthalen-1-yl)-2-oxoethyl) malonate (8g)

8g was prepared using the same procedure as that described for compound 8a. Yellow oil (2.4 g, 12.6%).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.63 (d, $J = 9.0$ Hz, 1 H) 7.84-7.78 (m, 2 H) 7.50 (t, $J = 4.5$ Hz, 1 H) 7.30-7.08 (m, 2 H) 7.02 (s, 1 H) 4.37-4.30 (m, 6 H) 2.82-2.59 (m, 2 H) 2.00 (s, 3 H) 1.67 (brs, 2 H) 1.33-1.25 (m, 12 H) 0.89 (brs, 3 H); ESI (m/z) 470 (M+H$^+$) 492 (M+Na$^+$)

Synthesis of diethyl 2-acetamido-2-(2-(6-hexynaphthalen-1-yl)ethyl)malonate (9g)

9g was prepared using the same procedure as that described for compound 9a. Yellow oil (0.9 g, 37.3% yield).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.75 (d, $J = 8.4$ Hz, 1 H) 7.66 (m, 2 H) 7.33-7.23 (m, 3 H) 6.91 (s, 1 H) 4.31-4.10 (m, 4 H) 2.95-2.91 (m, 2 H) 2.85-2.74 (m, 4 H) 2.07 (s, 3 H) 1.72-1.65 (m, 2 H) 1.33-1.25 (m, 6 H) 1.22 (t, $J = 7.2$ Hz, 6 H) 0.88 (t, $J = 6.9$ Hz, 3 H); ESI (m/z) 456 (M+H$^+$) 478 (M+Na$^+$)

Synthesis of N-(4-(6-hexynaphthalen-1-yl)-1-hydroxy-2-(hydroxymethyl)butan-2-yl)acetamide (10g)
**10g** was prepared using the same procedure as that described for compound **10a**. Yellow oil (0.4g, 19.3%).

$^1$H NMR (300 MHz, CDCl$_3$): δ 7.81-7.66 (m, 3 H) 7.35-7.30 (m, 3 H) 5.93 (s, 1 H) 3.96 (d, $J$ = 11.4 Hz, 2 H) 3.65 (d, $J$ = 11.7 Hz, 2 H) 3.10 (t, $J$ = 8.1 Hz, 2 H) 2.80 (t, $J$ = 7.5 Hz, 2 H) 2.08 (t, $J$ = 8.4 Hz, 2 H) 1.98 (s, 3 H) 1.76-1.68 (m, 2 H) 1.33-1.25 (m, 6 H) 0.89 (brs, 3 H); ESI (m/z) 372 (M+H$^+$) 394 (M+Na$^+$)

**Synthesis of 2-amino-2-(2-(6-hexynaphthalen-1-yl)ethyl)propane-1,3-diol (11g)**

**11g** was prepared using the same procedure as that described for compound **11a**. White solid (0.25g, 69.4%).

mp: 140-142 °C; $^1$H NMR (300 MHz, CD$_3$OD): δ 7.86 (s, 1 H) 7.71 (d, $J$ = 8.7 Hz, 1 H) 7.63-7.60 (m, 1 H) 7.28-7.23 (m, 3 H) 3.75 (s, 4 H) 3.11-3.05 (m, 2 H) 2.75 (t, $J$ = 7.5 Hz, 2 H) 2.05-1.99 (m, 2 H) 1.69-1.62 (m, 2 H) 1.29 (brs, 6 H) 0.84 (t, $J$ = 6.6 Hz, 3 H); $^{13}$C NMR (100 MHz, CD$_3$OD): δ 141.91, 137.85, 133.94, 133.10, 129.76, 128.04, 127.82, 127.05, 125.78, 123.18, 62.61, 62.19, 37.50, 33.84, 32.94, 32.78, 30.25, 27.46, 23.71, 14.43; HRMS calcd. for C$_{21}$H$_{32}$NO$_2$ (M+H$^+$) 330.2427, found 330.2428

**Synthesis of benzyl (4-(6-hexynaphthalen-1-yl)-1-hydroxy-2-(hydroxymethyl)butan-2-yl)carbamate (12g)**

**12g** was prepared using the same procedure as that described for compound **12a**. Colorless oil (90mg, 94.1%).

$^1$H NMR (300 MHz, CD$_3$COCD$_3$): δ 8.06 (s, 1 H) 7.77 (d, $J$ = 8.7 Hz, 1 H) 7.68-7.62 (m, 1 H) 7.42-7.28 (m, 8 H) 5.11 (s, 2 H) 3.90 (d, $J$ = 10.8 Hz, 2 H) 3.77 (d, $J$ = 10.8 Hz, 2 H) 3.15-3.09 (m, 2 H) 2.16-2.02 (m, 4 H) 1.72-1.69 (m, 2 H) 1.33 (brs, 6 H) 0.85 (t, $J$ = 6.6 Hz, 3 H); ESI (m/z) 464(M+H$^+$)

**Synthesis of benzyl (1-((bis(benzyloxy)phosphoryl)oxy)-4-(6-hexynaphthalen-1-yl)-2-(hydroxymethyl)butan-2-yl)carbamate (13g)**
13g was prepared using the same procedure as that described for compound 13a. Colorless oil (50mg, 43.2% yield).

$^1$H NMR (300 MHz, CD$_3$COCD$_3$): $\delta$ 8.02 (s, 1 H) 7.79 (d, $J = 8.4$ Hz, 1 H) 7.68 (dd, $J = 7.2$ Hz, 2.7 Hz, 1 H) 7.39-7.28 (m, 18 H) 5.17-5.03 (m, 6 H) 4.42 (dd, $J = 10.2$ Hz, 6.6 Hz, 1 H) 4.30 (dd, $J = 10.2$ Hz, 6.6 Hz, 1 H) 3.86 (q, $J = 11.4$ Hz, 2 H) 3.11-3.05 (m, 2 H) 2.62-2.05 (m, 2 H) 1.73-1.65 (m, 2 H) 1.31-1.26 (m, 6 H) 0.83 (t, $J = 7.2$ Hz, 3 H) $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 142.05, 137.68, 133.91, 133.12, 129.75, 128.01, 127.82, 127.11, 125.80, 123.15, 66.13, 62.43, 61.00, 37.51, 33.86, 32.98, 32.89, 30.28, 27.20, 23.72, 14.43; HRMS calcd. for C$_{21}$H$_{33}$NO$_5$P (M+H$^+$) 410.2091, found 410.2093

Synthesis of 2-amino-4-(6-hexynaphthalen-1-yl)-2-(hydroxymethyl)butyl dihydrogen phosphate (14g)

14g was prepared using the same procedure as that described for compound 14a. White syrup (20mg, 69.8%).

$^1$H NMR (300 MHz, CD$_3$OD): $\delta$ 7.80 (s, 1 H) 7.67 (d, $J = 8.4$ Hz, 1 H) 7.57 (d, $J = 7.5$ Hz, 1 H) 7.26-7.23 (m, 3 H) 4.05 (bbrs, 2 H) 3.76 (bbrs, 2 H) 3.06 (bbrs, 2 H) 2.73 (t, $J = 7.2$ Hz, 2 H) 2.05-1.99 (m, 2 H) 1.69-1.62 (m, 2 H) 1.26 (bbrs, 6 H) 0.81 (t, $J = 6.6$ Hz, 3 H); $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 142.05, 137.68, 133.91, 133.12, 129.75, 128.01, 127.82, 127.11, 125.80, 123.15, 66.13, 62.43, 61.05, 37.51, 33.86, 32.98, 32.89, 30.28, 27.20, 23.72, 14.43; HRMS calcd. for C$_{21}$H$_{33}$NO$_5$P (M+H$^+$) 410.2091, found 410.2093

Synthesis of 2-chloro-1-(2-hexylchroman-6-yl)ethanone (7h)

7h was prepared using the same procedure as that described for compound 7a. Yellow solid (7.6g, 90.1%).

mp: 25-27 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.72-7.69 (m, 2 H) 6.85 (d, $J = 8.7$ Hz, 1 H) 4.64 (s, 2 H) 4.11-4.06 (m, 1 H) 2.93-2.77 (m, 2 H) 2.07-1.19 (m, 12 H) 0.90 (t, $J = 6.9$ Hz, 3 H); ESI (m/z) 295 (M+H$^+$) 317 (M+Na$^+$)

Synthesis of diethyl 2-acetamido-2-(2-(2-hexylchroman-6-yl)-2-oxoethyl)
**Synthesis of diethyl 2-acetamido-2-(2-(2-hexylchroman-6-yl)ethyl)malonate (9h)**

9h was prepared using the same procedure as that described for compound 9a. Crude product as yellow oil (2.5 g, 96.2% yield). 

ESI (m/z) 462 (M+H+) 484 (M+Na+)

**Synthesis of N-(4-(2-hexylchroman-6-yl)-1-hydroxy-2-(hydroxymethyl)butan-2-yl)acetamide (10h)**

10h was prepared using the same procedure as that described for compound 10a. White solid (1.2 g, 36.6% yield).

mp: 46-49 °C; 1H NMR (300 MHz, CDCl3): δ 6.91 (s, 1 H) 6.84 (d, J = 8.1 Hz, 1 H) 6.68-6.55 (m, 1 H) 6.03-5.99 (m, 1 H) 3.92-3.60 (m, 4 H) 3.48 (s, 1 H) 2.79-2.43 (m, 5 H) 1.97 (s, 3 H) 2.04-1.27 (m, 13 H) 0.90 (t, J = 4.5 Hz, 3 H); ESI (m/z) 378 (M+H+) 400 (M+Na+)

**Synthesis of 2-amino-2-(2-(2-hexylchroman-6-yl)ethyl)propane-1,3-diol (11h)**

11h was prepared using the same procedure as that described for compound 11a. White solid (0.4 g, 54.1% yield).

mp: 56-59 °C; 1H NMR (300 MHz, CD3OD): δ 6.83 (s, 1 H) 6.76 (t, J = 7.2 Hz, 1 H) 6.57 (d, J = 7.8 Hz, 1 H) 6.45 (d, J = 8.1 Hz, 1 H) 3.62 (s, 1 H) 3.58 (s, 4 H) 2.78-2.19 (m, 5 H) 1.90-1.25 (m, 13 H) 0.86 (t, J = 6.6 Hz, 3 H); 13C NMR (100MHz, CD3OD):
δ ; HRMS calcd. for C_{20}H_{34}NO_{3} (M+H\(^+\)) 336.2538, found 336.2536

**Synthesis of benzyl (4-(2-hexylchroman-6-yl)-1-hydroxy-2-(hydroxymethyl)butan-2-yl)carbamate (12h)**

![Chemical Structure of 12h](image)

**12h** was prepared using the same procedure as that described for compound **12a**. Colorless oil (150mg, 88.8% yield).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 7.36 (brs, 5 H) 6.89-6.83 (m, 2 H) 6.66-6.54 (m, 1 H) 5.09 (s, 2 H) 4.18-4.08 (m, 1 H) 3.90 (d, \(J = 11.7\) Hz, 2 H) 3.67 (d, \(J = 11.4\) Hz, 2 H) 2.54-1.23 (m, 18 H) 0.88 (t, \(J = 4.5\) Hz, 3 H); ESI (m/z) 470 (M+H\(^+\))

**Synthesis of benzyl ((2R)-1-((bis(benzyloxy)phosphoryl)oxy)-4-(2-hexylchroman-6-yl)-2-(hydroxymethyl)butan-2-yl)carbamate (13h)**

![Chemical Structure of 13h](image)

**13h** was prepared using the same procedure as that described for compound **13a**. Colorless oil (70mg, 30.0% yield).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 7.36-7.31 (m, 18 H) 5.17-5.00 (m, 6 H) 3.82-3.55 (m, 5 H) 2.60-1.28 (m, 18 H) 0.85 (t, \(J = 4.5\) Hz, 3 H); ESI (m/z) 730 (M+H\(^+\))

**Synthesis of 2-amino-4-(2-hexylchroman-6-yl)-2-(hydroxymethyl)butyl dihydrogen phosphate (14h)**

![Chemical Structure of 14h](image)

**14h** was prepared using the same procedure as that described for compound **14a**. White solid (30mg, 75.3% yield).

mp: 115-118 °C; \(^1\)H NMR (300 MHz, CD\(_2\)OD): δ 7.29-6.79 (m, 3 H) 3.96-3.61 (m, 5 H) 3.06-2.52 (m, 5 H) 1.89-1.24 (m, 13 H) 0.87 (t, \(J = 6.6\) Hz, 3 H); \(^{13}\)C NMR (100 MHz, CD\(_2\)OD): δ 151.22, 142.25, 136.35, 129.49, 127.11, 121.14, 62.66, 62.02, 59.78, 53.97, 34.84, 32.40, 30.84, 29.46, 28.72, 27.36, 25.83, 24.72, 23.52, 14.46; HRMS calcd. for C\(_{20}\)H\(_{35}\)NO\(_6\)P (M+H\(^+\)) 416.2197, found 416.2173

**Synthesis of 1-(4-(4-butylphenoxy)phenyl)-2-chloroethanone (7i)**

![Chemical Structure of 7i](image)
7i was prepared using the same procedure as that described for compound 7a. Yellow oil (14.2 g, 95.9% yield).

$^1$H NMR (300 MHz, CDCl$_3$): δ 7.93 (d, $J = 8.7$ Hz, 2 H) 7.21 (d, $J = 8.1$ Hz, 2 H) 6.99 (dd, $J = 8.7$ Hz, 2.7 Hz, 4 H) 4.65 (s, 2 H) 2.63 (t, $J = 7.8$ Hz, 2 H) 1.67-1.57 (m, 2 H) 1.42-1.34 (m, 2 H) 0.95 (t, $J = 7.2$ Hz, 3 H); ESI (m/z) 303 (M+H$^+$) 325 (M+Na$^+$)

**Synthesis of diethyl 2-acetamido-2-(2-(4-(4-butylyphenoxy)phenyl)-2-oxoethyl) malonate (8i)**

8i was prepared using the same procedure as that described for compound 8a. Yellow solid (6.9 g, 30.4% yield).

mp: 160-163 °C; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.92 (d, $J = 8.4$ Hz, 2 H) 7.20 (d, $J = 8.1$ Hz, 2 H) 7.11 (brs, 1 H) 6.97 (d, $J = 8.7$ Hz, 4 H) 4.27 (dd, $J = 14.1$ Hz, 7.2 Hz, 4 H) 4.21 (s, 2 H) 2.65 (t, $J = 7.8$ Hz, 2 H) 1.97 (s, 3 H) 1.64-1.57 (m, 2 H) 1.41-1.29 (m, 2 H) 1.24 (t, $J = 7.2$ Hz, 6 H) 0.95 (t, $J = 7.2$ Hz, 3 H); ESI (m/z) 484 (M+H$^+$) 506 (M+Na$^+$)

**Synthesis of diethyl 2-acetamido-2-(4-(4-butylyphenoxy)phenethyl)malonate (9i)**

9i was prepared using the same procedure as that described for compound 9a. White solid (1.78 g, 90.4% yield).

mp: 145-148 °C; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.12 (t, $J = 8.7$ Hz, 4 H) 6.90 (dd, $J = 8.1$ Hz, 2.7 Hz, 4 H) 6.79 (brs, 1 H) 4.26-4.20 (m, 4 H) 2.69 (dd, $J = 9.9$ Hz, 7.2 Hz, 2 H) 2.59 (t, $J = 7.5$ Hz, 2 H) 2.46 (dd, $J = 9.0$ Hz, 6.6 Hz, 2 H) 2.02 (s, 3 H) 1.65-1.55 (m, 2 H) 1.41-1.33 (m, 2 H) 1.27 (t, $J = 6.9$ Hz, 6 H) 0.95 (t, $J = 7.2$ Hz, 3 H); ESI (m/z) 470 (M+H$^+$) 492 (M+Na$^+$)

**Synthesis of N-(4-(4-(4-butylyphenoxy)phenyl)-1-hydroxy-2-(hydroxymethyl) butan-2-yl)acetamide (10i)**

10i was prepared using the same procedure as that described for compound 10a. White solid (0.65 g, 46.9% yield).

mp: 140-143 °C; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.13 (dd, $J = 8.1$ Hz, 5.7 Hz, 4 H) 6.90 (t, $J = 7.8$ Hz, 4 H) 5.92 (brs, 1 H) 3.86 (d, $J = 11.7$ Hz, 2 H) 3.79 (brs, 2 H) 3.63 (d, $J = 11.1$ Hz, 2 H) 2.65-2.55 (m, 4 H) 2.04-1.93 (m, 5 H) 1.63-1.53 (m, 2 H)
1.42-1.29 (m, 2 H) 0.93 (t, J = 7.5 Hz, 3 H); ESI (m/z) 386 (M+H⁺)

**Synthesis of 2-amino-2-(4-(4-butylphenoxy)phenethyl)propane-1,3-diol (11i)**

![Chemical Structure](image)

11i was prepared using the same procedure as that described for compound 11a. White solid (0.51 g, 89.0% yield). mp: 146-150 °C; ¹H NMR (300 MHz, CD₃OD): δ 7.17 (d, J = 8.4 Hz, 2 H) 7.11 (d, J = 8.7 Hz, 2 H) 6.83 (dd, J = 8.4 Hz, 2.1 Hz, 4 H) 3.47 (q, J = 10.8 Hz, 4 H) 2.64-2.53 (m, 4 H) 1.66-1.51 (m, 4 H) 1.40-1.30 (m, 2 H) 0.92 (t, J = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, CD₃OD): δ 180.38, 157.04, 138.90, 130.58, 119.62, 119.54, 66.54, 56.75, 37.82, 35.86, 35.10, 29.68, 23.30, 14.26; HRMS calcd. for C₂₁H₃₀NO₃ (M+H⁺) 344.2220, found 360.2223

**Synthesis of benzyl (4-(4-(4-(4-butyloxy)phenyl)-1-hydroxy-2-(hydroxymethyl)butan-2-yl)carbamate (12i)**

![Chemical Structure](image)

12i was prepared using the same procedure as that described for compound 12a. Colorless oil (120 mg, 96.7% yield). ¹H NMR (300 MHz, CDCl₃): δ 7.37 (brs, 5 H) 7.10 (t, J = 7.5 Hz, 4 H) 6.89 (d, J = 8.4 Hz, 4 H) 5.09 (s, 2 H) 3.92 (d, J = 12.0 Hz, 2 H) 3.68 (d, J = 11.1 Hz, 2 H) 2.58 (t, J = 8.4 Hz, 4 H) 1.90 (t, J = 8.7 Hz, 2 H) 1.61-1.53 (m, 2 H) 1.39-1.32 (m, 2 H) 0.93 (t, J = 7.2 Hz, 3 H); ESI (m/z) 478 (M+H⁺)

**Synthesis of benzyl (1-((bis(benzyloxy)phosphoryl)oxy)-4-(4-(4-butylphenoxy)phenyl)-2-(hydroxymethyl)butan-2-yl)carbamate (13i)**

![Chemical Structure](image)

13i was prepared using the same procedure as that described for compound 13a. Colorless oil (70 mg, 38.0% yield). ¹H NMR (300 MHz, CDCl₃): δ 7.32-7.24 (m, 15 H) 7.11 (d, J = 8.4 Hz, 2 H) 7.03 (d, J = 8.1 Hz, 2 H) 6.88 (dd, J = 8.4 Hz, 4.8 Hz, 4 H) 5.09-4.96 (m, 6 H) 4.18-4.04 (m, 2 H) 3.60 (s, 2 H) 2.58 (t, J = 7.5 Hz, 2 H) 2.52-2.47 (m, 2 H) 2.11-2.07 (m, 1 H) 1.82-1.76 (m, 1 H) 1.63-1.53 (m, 2 H) 1.39-1.29 (m, 2 H) 0.93 (t, J = 7.2 Hz, 3 H); ESI (m/z) 738 (M+H⁺)

**Synthesis of 2-amino-4-(4-(4-butylphenoxy)phenyl)-2-(hydroxymethyl)butyl**
**dihydrogen phosphate (14i)**

![Dihydrogen Phosphate Structure](image)

14i was prepared using the same procedure as that described for compound 14a. White solid (25mg, 61.6% yield). 

mp: 190-193 °C; $^1$H NMR (300 MHz, CD$_3$OD): δ 7.16 (d, $J =$ 8.1 Hz, 2 H) 7.08 (d, $J =$ 8.1 Hz, 2 H) 6.80 (t, $J =$ 6.9 Hz, 4 H) 3.96 (s, 2 H) 3.66 (s, 2 H) 2.63-2.50 (m, 4 H) 1.95-1.90 (m, 2 H) 1.58-1.48 (m, 2 H) 1.36-1.23 (m, 2 H) 0.88 (t, $J =$ 7.2 Hz, 3 H) $^{13}$C NMR (100 MHz, CD$_3$OD): δ 157.53, 156.69, 139.03, 137.01, 130.64, 119.70, 119.65, 65.82, 62.46, 61.36, 61.28, 35.86, 35.09, 34.91, 29.27, 23.30, 14.26; HRMS calcd. for C$_{21}$H$_{31}$NO$_6$P (M+H$^+$) 424.1884, found 424.1869

**Synthesis of 2-bromo-1-(4-phenoxyphenyl)ethanone (16, X=H):**

![2-Bromo-1-(4-Phenoxyphenyl)ethanone Structure](image)

Bromoacetyl bromide (23.7g, 115.0mmol) in CH$_2$Cl$_2$ (50mL) was added dropwise to a cooled solution (0°C) of 15 (19.6g, 115.0mmol) in CH$_2$Cl$_2$ (150mL), then AlCl$_3$ (16.1g, 121.0mmol) was added in portions in 30min. The solution was then allowed to return to room temperature and stirred for further 2 h. The mixture was poured slowly into 2NHCl-ice mixture (100mL) and stirred for 2 h. The aqueous phase was extracted with CH$_2$Cl$_2$ (20mL×3). The combined organic layers were washed with saturated aq. NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, filtered and concentrated, yielding crude product 16(X=H) (1.5g, 97.4% yield) as yellow oil.

ESI (m/z) 291 (M+H$^+$); 313 (M+Na$^+$)

**Synthesis of 2-bromo-1-(4-(4-bromophenoxy)phenyl)ethanone (16, X=Br):**

![2-Bromo-1-(4-(4-Bromophenoxy)phenyl)ethanone Structure](image)

16(X=Br) was prepared using the same procedure as that described for compound 16( X=H). Yellow oil (24.6g, 83.4% yield).

$^1$H NMR (300 MHz, CDCl$_3$): δ: 7.97 (d, $J =$ 8.7 Hz, 2H), 7.51 (d, J=8.7 Hz, 2H), 6.98 (m, 4H), 4.40 (s, 2H); ESI (m/z) 371 (M+H$^+$); 393 (M+Na$^+$)

**Synthesis of diethyl 2-acetamido-2-(2-oxo-2-(4-phenoxyphenyl)ethyl)malonate (17, X=H):**
**17(X=H)** was prepared using the same procedure as that described for compound **8a**. Yellow oil (3.6 g, 49.0% yield)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.94 (d, \(J = 8.7\) Hz, 2H), 7.40 (t, \(J = 8.0\) Hz, 2H), 7.21 (t, \(J = 7.4\) Hz, 1H), 7.12 (br, 1H), 7.06 (d, \(J = 8.4\) Hz, 2H), 6.99 (d, \(J = 9.0\) Hz, 2H), 4.27 (q, \(J = 7.2\) Hz, 4H), 4.22 (s, 2H), 1.98 (s, 3H), 1.25 (t, \(J = 7.2\) Hz, 6H). ESI (m/z) 428 (M+H)\(^+\); 450 (M+Na\(^+\))

**Synthesis of diethyl 2-acetamido-2-(2-(4-(bromophenoxy)phenyl)-2-oxoethyl) malonate (17, X=Br)**

**17(X=Br)** was prepared using the same procedure as that described for compound **8a**. Yellow oil (29.2 g, 89.0% yield)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.95 (d, \(J = 9.0\) Hz, 2H), 7.50 (d, \(J = 9.0\) Hz, 2H), 7.13 (br, 1H), 6.97 (m, 4H), 4.27 (m, 6H), 1.98 (s, 3H), 1.27 (m, 6H).

ESI (m/z) 506 (M+H)\(^+\)

**Synthesis of diethyl 2-acetamido-2-(2-(4-(benzoylphenoxy)phenyl)-2-oxoethyl) malonate (18a)**

Benzoyl chloride (0.36 g, 2.58 mmol) in CH\(_2\)Cl\(_2\) (3mL) was added dropwise to a cooled solution (0°C) of **17(X=H)** (1.0 g, 2.34 mmol) in CH\(_2\)Cl\(_2\) (10mL), then AlCl\(_3\) (1.56 g, 11.7 mmol) was added in portions in 30min. The solution was then allowed to return to room temperature and stirred for further 4 h. The mixture was poured slowly into 2NHCl-ice mixture (10mL) and stirred for 2 h. The aqueous phase was extracted with CH\(_2\)Cl\(_2\) (3mL× 3). The combined organic layers were washed with saturated aq. NaHCO\(_3\) and brine, dried over Na\(_2\)SO\(_4\), filtered and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc/PE) to afford compound **18a** (0.65 g, 52.0% yield) as brown oil.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 8.00 (d, \(J = 8.4\) Hz, 2H), 7.87 (d, \(J = 8.1\) Hz, 2H), 7.80 (d, \(J = 8.4\) Hz, 2H), 7.59 (m, 1H), 7.52 (t, \(J = 7.2\) Hz, 2H), 7.09 (m, 4H), 4.26 (m, 6H), 1.98 (s, 3H), 1.28 (m, 6H). ESI (m/z) 532 (M+H)\(^+\)

**Synthesis of diethyl 2-acetamido-2-(2-(4-(4-methylbenzoyl)phenoxy)phenyl)-2-oxoethyl malonate (18a)**
phenyl)-2-oxoethyl)malonate (18b)

18b was prepared using the same procedure as that described for compound 18a. Yellow oil (0.55 g, 55.0% yield)

$^1$H NMR (300 MHz, CDCl$_3$) δ: 8.00 (d, $J = 8.7$ Hz, 2H), 7.85 (d, $J = 8.4$ Hz, 2H), 7.72 (d, $J = 8.1$ Hz, 2H), 7.30 (d, $J = 7.5$ Hz, 2H), 7.10 (m, 4H), 4.28 (m, 6H), 2.45 (s, 3H), 1.99 (s, 3H), 1.25 (t, $J = 7.1$ Hz, 6H). ESI (m/z) 546 (M+H)$^+$

**Synthesis of diethyl 2-acetamido-2-(2-(4-(4-ethylbenzoyl)phenoxy)phenyl)-2-oxoethyl)malonate (18c)**

18c was prepared using the same procedure as that described for compound 18a. Yellow solid (0.51 g, 39.0% yield)

mp: 72-74 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ: 8.01 (d, $J = 8.7$ Hz, 2H), 7.86 (d, $J = 8.4$ Hz, 2H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.32 (d, $J = 8.1$ Hz, 2H), 7.11 (m, 4H), 4.28 (m, 6H), 2.74 (q, $J = 7.7$ Hz, 2H), 1.99 (s, 3H), 1.28 (m, 9H). ESI (m/z) 560 (M+H)$^+$

**Synthesis of diethyl 2-acetamido-2-(2-(4-(4-fluorobenzoyl)phenoxy)phenyl)-2-oxoethyl)malonate (18d)**

18d was prepared using the same procedure as that described for compound 18a. Yellow oil (0.68 g, 53.0% yield)

$^1$H NMR (300 MHz, CDCl$_3$) δ: 8.01 (d, $J = 9.0$ Hz, 2H), 7.84 (m, 4H), 7.12 (m, 6H), 4.27 (m, 6H), 1.99 (s, 3H), 1.25 (t, $J = 7.2$ Hz, 6H). ESI (m/z) 550 (M+H)$^+$

**Synthesis of diethyl 2-acetamido-2-(2-(4-(4-chlorobenzoyl)phenoxy)phenyl)-2-oxoethyl)malonate (18e)**

18e was prepared using the same procedure as that described for compound 18a. Yellow oil (0.7 g, 53.0% yield)

$^1$H NMR (300 MHz, CDCl$_3$) δ: 8.00 (d, $J = 8.4$ Hz, 2H), 7.83 (d, $J = 8.7$ Hz, 2H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.47 (d, $J = 8.1$ Hz, 2H), 7.10 (m, 4H), 4.27 (m, 6H), 1.98 (s, 3H), 1.25 (t, $J = 7.1$ Hz, 6H). ESI (m/z) 566 (M+H)$^+$
Synthesis of diethyl 2-acetamido-2-(4-(4-benzylphenoxy)phenethyl)malonate (19a)

A solution of 18a (1.6 g, 3.0 mmol) in CH$_2$Cl$_2$ (20 mL) was added dropwise to a solution of Et$_3$SiH (2.5 g, 21.1 mmol) in CH$_2$Cl$_2$ at room temperature under Ar$_2$ protection. TiCl$_4$ (4.0 g, 21.1 mmol) was added with a syringe and the reaction mixture was stirred for 12 h at room temperature. The solution was poured slowly into ice water (20 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (5 mL x 3). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc/PE) to afford compound 19a (1.0 g, 67.0% yield) as white solid. mp: 62-64 ºC; $^1$H NMR (300 MHz, CDCl$_3$) δ: 7.28 (m, 2H), 7.20 (m, 3H), 7.11 (m, 4H), 6.89 (m, 4H), 6.79 (br, 1H), 4.24 (m, 4H), 3.95 (s, 2H), 2.68 (m, 2H), 2.46 (m, 2H), 2.01 (s, 3H), 1.25 (t, $J$ = 7.1 Hz, 3H). ESI (m/z) 504 (M+H)$^+$

Synthesis of diethyl 2-acetamido-2-(4-(4-(4-methylbenzyl)phenoxy)phenethyl)malonate (19b)

19b was prepared using the same procedure as that described for compound 19a. White solid (0.43 g, 83.0% yield) mp: 20-22 ºC; $^1$H NMR (300 MHz, CDCl$_3$) δ: 7.09 (m, 8H), 6.88 (m, 4H), 6.77 (br, 1H), 4.22 (q, $J$ = 7.2 Hz, 4H), 3.91 (s, 2H), 2.67 (m, 2H), 2.45 (m, 2H), 2.32 (s, 3H), 2.01 (s, 3H), 1.25 (t, $J$ = 7.2 Hz, 6H). ESI (m/z) 518 (M+H)$^+$

Synthesis of diethyl 2-acetamido-2-(4-(4-(4-ethylbenzyl)phenoxy)phenethyl)malonate (19c)

19c was prepared using the same procedure as that described for compound 19a. Colorless oil (0.4 g, 84.0% yield) $^1$H NMR (300 MHz, CDCl$_3$) δ: 7.11 (m, 8H), 6.89 (m, 4H), 6.79 (br, 1H), 4.23 (m, 4H), 3.92 (s, 2H), 2.64 (m, 4H), 2.46 (m, 2H), 2.02 (s, 3H), 1.24 (m, 9H). ESI (m/z) 532 (M+H)$^+$

Synthesis of diethyl 2-acetamido-2-(4-(4-(4-fluorobenzyl)phenoxy)phenethyl)
malonate (19d)

19d was prepared using the same procedure as that described for compound 19a. White solid (0.47 g, 72.0% yield) mp: 32-34 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ: 7.11 (m, 6H), 6.97 (t, $J = 8.7$ Hz, 2H), 6.89 (m, 4H), 6.78 (br, 1H), 4.23 (m, 4H), 3.92 (s, 2H), 2.68 (m, 2H), 2.46 (m, 2H), 2.01 (s, 3H), 1.25 (t, $J = 7.1$ Hz, 6H). ESI (m/z) 522 (M+H)$^+$

Synthesis of diethyl 2-acetamido-2-(4-(4-chlorobenzyl)phenoxy)phenethyl) malonate (19e)

19e was prepared using the same procedure as that described for compound 19a. Yellow oil (0.6 g, 91.0% yield) $^1$H NMR (300 MHz, CDCl$_3$) δ: 7.25 (m, 2H), 7.11 (m, 6H), 6.89 (m, 4H), 6.80 (br, 1H), 4.21 (q, $J = 7.1$ Hz, 4H), 3.91 (s, 2H), 2.68 (m, 2H), 2.46 (m, 2H), 2.02 (s, 3H), 1.26 (t, $J = 7.1$ Hz, 6H). ESI (m/z) 538 (M+H)$^+$

Synthesis of 2-amino-2-(4-(4-benzylphenoxy)phenethyl)propane-1,3-diol (20a)

20a was prepared using the same procedure as that described for compound 11a. White solid (0.6 g, two steps 70.6% yield) m.p.: 205-208 °C. $^1$H NMR (300 MHz, CD$_3$OD) δ: 7.17 (m, 9H), 6.83 (m, 4H), 3.88 (s, 2H), 3.65 (s, 4H), 2.61 (m, 2H), 1.90 (m, 2H); $^{13}$C NMR (400MHz, CD$_3$OD) δ: 157.3, 157.1, 142.8, 137.7, 137.3, 131.2, 130.6, 129.8, 129.5, 127.1, 119.8, 119.7, 62.5, 62.0, 42.0, 34.8, 29.3. HRMS calcd for C$_{24}$H$_{28}$NO$_3$ (M+H)$^+$ 378.2064; found: 378.2057.

Synthesis of 2-amino-2-(4-(4-methylbenzyl)phenoxy)phenethyl)propane-1,3-diol (20b)

20b was prepared using the same procedure as that described for compound 11a.
White solid (0.3g, two steps 84.6% yield)
m.p.: 218-220 °C. $^1$H NMR (300 MHz, CD$_3$OD) $\delta$: 7.14 (d, $J = 8.7$ Hz, 2H), 7.08 (d, $J = 8.4$ Hz, 2H), 7.01 (m, 4H), 6.81 (m, 4H), 3.83 (s, 2H), 3.63 (s, 4H), 2.57 (m, 2H), 2.23 (s, 3H), 1.88 (m, 2H); $^{13}$C NMR (400 MHz, CD$_3$OD) $\delta$: 157.4, 157.0, 139.7, 138.1, 137.2, 136.6, 131.1, 130.6, 130.1, 129.7, 119.8, 119.7, 62.5, 62.0, 41.6, 34.8, 29.3, 21.0. HRMS calcd for C$_{25}$H$_{30}$NO$_3$ (M+H$^+$) 392.2220; found: 392.2229.

**Synthesis of 2-amino-2-(4-(4-ethylbenzyl)phenoxy)phenethyl)propane-1,3-diol (20c)**

20c was prepared using the same procedure as that described for compound 11a. White solid (0.18g, two steps 59.3% yield)
m.p.: 176-178 °C. $^1$H NMR (300 MHz, CD$_3$OD) $\delta$: 7.14 (d, $J = 8.4$ Hz, 2H), 7.08 (d, $J = 8.1$ Hz, 2H), 7.03 (m, 4H), 6.81 (m, 4H), 3.83 (s, 2H), 3.63 (s, 4H), 2.56 (m, 4H), 1.88 (m, 2H), 1.14 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (400 MHz, CD$_3$OD) $\delta$: 157.4, 157.0, 143.2, 139.9, 138.1, 137.2, 131.1, 130.6, 129.8, 128.9, 119.8, 119.7, 62.5, 62.0, 41.6, 34.8, 29.4, 29.3, 16.3. HRMS calcd for C$_{26}$H$_{32}$NO$_3$ (M+H$^+$) 406.2377; found: 406.2383.

**Synthesis of 2-amino-2-(4-(4-fluorobenzyl)phenoxy)phenethyl)propane-1,3-diol (20d)**

20d was prepared using the same procedure as that described for compound 11a. White solid (0.3g, two steps 86.5% yield)
m.p.: 178-180 °C. $^1$H NMR (300 MHz, CD$_3$OD) $\delta$: 7.12 (m, 6H), 6.93 (m, 2H), 6.82 (m, 4H), 3.87 (s, 2H), 3.63 (s, 4H), 2.59 (m, 2H), 1.89 (m, 2H); $^{13}$C NMR (500 MHz, CD$_3$OD) $\delta$: 162.8 ($J = 241$ Hz), 157.3, 157.2, 138.8 ($J = 3$ Hz), 137.6, 137.3, 131.4 ($J = 8$ Hz), 131.1, 130.6, 119.9, 119.8, 116.0 ($J = 21$ Hz), 62.5, 62.0, 41.1, 34.8, 29.4. HRMS calcd for C$_{24}$H$_{27}$FNO$_3$ (M+H$^+$) 396.1969; found: 396.1987.

**Synthesis of 2-amino-2-(4-(4-chlorobenzyl)phenoxy)phenethyl)propane-1,3-diol (20e)**

20e was prepared using the same procedure as that described for compound 11a. White solid (0.37g, two steps 83.3% yield)
m.p.: 172-175 °C. $^1$H NMR (300 MHz, CD$_3$OD) δ: 7.19 (m, 3H), 7.11 (m, 5H), 6.83 (m, 4H), 3.86 (s, 2H), 3.63 (s, 4H), 2.59 (m, 2H), 1.89 (m, 2H). $^{13}$C NMR (500 MHz, CD$_3$OD) δ: 157.3, 157.2, 141.7, 137.3, 137.2, 132.9, 131.4, 131.2, 130.6, 129.5, 119.9, 119.8, 62.5, 62.0, 41.2, 34.8, 29.4. HRMS calcd for C$_{24}$H$_{27}$ClNO$_3$ (M+H$^+$) 412.1674; found: 412.1688.

**Synthesis of 2-amino-4-(4-(benzylphenoxy)phenyl)-2-(hydroxymethyl)butyl dihydrogen phosphate (21a)**

21a was prepared using the same procedure as that described for compound 14a. White solid (15mg, three steps 13.9% yield) m.p.: 195-198 °C. $^1$H NMR (300 MHz, CD$_3$OD) δ: 7.15 (m, 9H), 6.81 (m, 4H), 3.94 (m, 2H), 3.88 (s, 2H), 3.64 (m, 2H), 2.61 (m, 2H), 1.89 (m, 2H). $^{13}$C NMR (600 MHz, CD$_3$OD) δ: 157.3, 157.1, 142.8, 137.8, 137.2, 131.2, 130.7, 129.8, 129.5, 127.1, 119.8, 119.7, 65.8, 62.5, 61.4, 42.0, 34.9, 29.3. HRMS calcd for C$_{24}$H$_{29}$NO$_6$P (M+H$^+$) 458.1727; found: 458.1727.

**Synthesis of 2-amino-2-(hydroxymethyl)-4-(4-(4-(methylphenyl)phenoxy)phenyl)butyl dihydrogen phosphate (21b)**

21b was prepared using the same procedure as that described for compound 14a. White solid (15mg, three steps 13.4% yield) m.p.: 190-192 °C. $^1$H NMR (300 MHz, CD$_3$OD) δ: 7.13 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 6.99 (m, 4H), 6.79 (m, 4H), 3.91 (m, 2H), 3.80 (s, 2H), 3.62 (m, 2H), 2.57 (m, 2H), 2.20 (s, 3H), 1.89 (m, 2H). $^{13}$C NMR (500 MHz, DMSO) δ: 155.3, 155.2, 138.5, 136.8, 136.7, 135.1, 130.3, 129.9, 129.3, 128.8, 118.8, 118.5, 64.3, 61.2, 59.5, 33.8, 27.8, 20.8. HRMS calcd for C$_{25}$H$_{31}$NO$_6$P(M+H$^+$) 472.1884; found: 472.1860.

**Synthesis of 2-amino-4-(4-(4-(4-ethylbenzyl)phenoxy)phenyl)-2-(hydroxymethyl)butyl dihydrogen phosphate (21c)**

21c was prepared using the same procedure as that described for compound 14a. White solid (10mg, three steps 9.1% yield) m.p.: 198-200 °C. $^1$H NMR (300 MHz, CD$_3$OD) δ: 7.16 (d, J = 8.1 Hz, 2H), 7.09 (d, J
= 8.1 Hz, 2H), 7.04 (m, 4H), 6.81 (m, 4H), 3.94 (m, 2H), 3.84 (s, 2H), 3.65 (m, 2H),
2.56 (m, 4H), 1.92 (m, 2H), 1.14 (t, J = 7.7 Hz, 3H). 13C NMR (500 MHz, CD3OD) δ:
157.7, 157.3, 143.5, 140.3, 138.3, 137.4, 131.4, 131.0, 130.1, 129.2, 120.1, 120.0,
66.0, 62.8, 61.6, 41.9, 35.2, 29.8, 29.6, 16.6. HRMS calcd for C28H33NO6P (M+H+)
486.2040; found: 486.2019.

Synthesis of 2-amino-4-(4-(4-(4-fluorobenzyl)phenoxy)phenyl)-2-(hydroxymethyl)
butyl dihydrogen phosphate (21d)

21d was prepared using the same procedure as that described for compound 14a.
White solid (20mg, three steps 16.5% yield)
m.p.: 203-205 °C. 1H NMR (300 MHz, CD3OD) δ: 7.13 (m, 6H), 6.93 (t, J = 8.8 Hz,
2H), 6.82 (m, 4H), 3.94 (m, 2H), 3.86 (m, 2H), 3.65 (m, 2H), 2.61 (m, 2H), 1.91 (m,
2H). 13C NMR (500 MHz, DMSO) δ: 160.8 (J = 240 Hz), 155.3, 154.9, 137.6, 136.8,
136.1, 130.5 (J = 8 Hz), 130.2, 129.8, 118.7, 118.5, 115.2 (J = 21 Hz), 64.3, 61.0, 59.3,
33.7, 27.7. HRMS calcd for C24H28FNO6P (M+H+) 476.1633; found: 476.1610.

Synthesis of 2-amino-4-(4-(4-(4-chlorobenzyl)phenoxy)phenyl)-2-(hydroxymethyl)
butyl dihydrogen phosphate (21e)

21e was prepared using the same procedure as that described for compound 14a.
White solid (15mg, three steps 12.7% yield)
m.p.: 215-217 °C. 1H NMR (400 MHz, CD3OD) δ: 7.17 (m, 4H), 7.09 (m, 4H), 6.80
(m, 4H), 3.92 (m, 2H), 3.85 (m, 2H), 3.64 (m, 2H), 2.60 (m, 2H), 1.90 (m, 2H). 13C
NMR (500 MHz, CD3OD) δ: 157.4, 157.1, 141.7, 137.7, 137.1, 132.9, 131.4, 131.2,
130.7, 129.5, 119.9, 119.7, 66.1, 63.1, 60.7, 41.2, 35.4, 29.4. HRMS calcd for C24H28ClNO6P (M+H+) 492.1337; found: 492.1324.

Synthesis of diethyl 2-acetamido-2-(4-phenoxyphenethyl)malonate (22, X=H)

22(X=H) was prepared using the same procedure as that described for compound
9a. Crude product as yellow oil (10.0g, 98.9% yield)
ESI (m/z) 414 (M+H)+; 436(M+Na)+

Synthesis of diethyl 2-acetamido-2-(4-(4-bromophenoxy)phenethyl)malonate (22,
X=Br)

22(X=Br) was prepared using the same procedure as that described for compound 9a. White solid (1.1 g, 98.0% yield)
mp: 53-54 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.40 (d, \(J = 8.7\) Hz, 2H), 7.12 (d, \(J = 8.4\) Hz, 2H), 6.90 (d, \(J = 8.4\) Hz, 2H), 6.85 (m, 3H), 4.22 (q, \(J = 7.2\) Hz, 4H), 2.68 (m, 2H), 2.47 (m, 2H), 2.03 (s, 3H), 1.26 (t, \(J = 7.2\) Hz, 6H). ESI (m/z) 492 (M+H)\(^+\)

Synthesis of diethyl 2-(4-((1,1'-biphenyl)-4-yloxy)phenethyl)-2-acetamido malonate (23a)

To a solution of 22(X=Br)(0.4 g, 0.8 mmol) in a mixture of toluene and EtOH(6 mL/2 mL) was added phenylboronic acid (0.1 g, 0.8 mmol), Pd(PPh\(_3\))\(_4\) (0.04, 0.03 mmol) and 2M aq.Na\(_2\)CO\(_3\) (3 mL). The mixture was heated to reflux for 3 h under Ar protection, then cooled to room temperature. The aqueous phase was extracted with EtOAc(3 mL x 3). The combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\), filtered and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc/PE) to afford compound 23a (0.25 g, 63.0% yield) as white solid.
mp: 62-64 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.55 (m, 4H), 7.43 (t, \(J = 7.5\) Hz, 2H), 7.32 (t, \(J = 7.2\) Hz, 1H), 7.13 (d, \(J = 8.1\) Hz, 2H), 7.04 (d, \(J = 8.1\) Hz, 2H), 6.97 (d, \(J = 8.4\) Hz, 2H), 6.79 (br, 1H), 4.22 (q, \(J = 6.9\) Hz, 4H), 2.70 (m, 2H), 2.47 (m, 2H), 2.02 (s, 3H), 1.26 (t, \(J = 6.9\) Hz, 6H). ESI (m/z) 490 (M+H)\(^+\)

Synthesis of diethyl 2-acetamido-2-(4-((4'-ethyl-[1,1'-biphenyl]-4-yl)oxy)phenethyl)malonate (23b)

23b was prepared using the same procedure as that described for compound 23a.
Yellow solid (0.3 g, 71.0% yield)
mp: 116-118 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.50 (m, 4H), 7.27 (m, 2H), 7.13 (d, \(J = 8.1\) Hz, 2H), 7.02 (d, \(J = 8.7\) Hz, 2H), 6.96 (d, \(J = 8.1\) Hz, 2H), 6.80 (br, 1H), 4.22 (q, \(J = 6.6\) Hz, 4H), 2.69 (m, 4H), 2.47 (m, 2H), 2.03 (s, 3H), 1.27 (m, 9H). ESI (m/z) 518 (M+H)\(^+\)

Synthesis of diethyl 2-acetamido-2-(4-((3'-methoxy-[1,1'-biphenyl]-4-yl)oxy)
phenethyl)malonate (23c)

23c was prepared using the same procedure as that described for compound 23a. Yellow oil (0.62g, 98.0% yield)

$^1$H NMR (600 MHz, CDCl$_3$) δ: 7.52 (d, $J = 8.4$ Hz, 2H), 7.34 (t, $J = 7.5$ Hz, 1H), 7.14 (m, 3H), 7.09 (t, $J = 2.1$ Hz, 1H), 7.03 (d, $J = 8.4$ Hz, 2H), 6.97 (d, $J = 8.4$ Hz, 2H), 6.88 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 1H), 6.80 (br, 1H), 4.26 (m, 4H), 3.90 (s, 3H), 2.74 (m, 2H), 2.53 (m, 2H), 2.08 (s, 3H), 1.33 (t, $J = 6.9$ Hz, 6H).

ESI (m/z) 520 (M+H)$^+$

Synthesis of 2-(4-((1,1'-biphenyl)-4-yl)oxy)phenethyl)-2-aminopropane-1,3-diol (24a)

24a was prepared using the same procedure as that described for compound 11a. White solid (0.44g, two steps 85.5% yield)
m.p.: 180-182 °C. $^1$H NMR (300 MHz, CD$_3$OD) δ: 7.53 (m, 4H), 7.36 (t, $J = 7.5$ Hz, 2H), 7.26 (d, $J = 7.5$ Hz, 1H), 7.20 (d, $J = 8.4$ Hz, 2H), 6.93 (d, $J = 8.7$ Hz, 2H), 6.92 (d, $J = 8.4$ Hz, 2H), 3.65 (s, 4H), 2.62 (m, 2H), 1.92 (m, 2H), 1.20 (t, $J = 7.5$ Hz, 3H). $^{13}$C NMR (400 MHz, CD$_3$OD) δ: 158.5, 157.0, 141.8, 137.7, 137.6, 130.7, 129.9, 129.4, 128.1, 127.7, 120.2, 119.8, 62.5, 62.0, 34.8, 24.9. HRMS calcd for C$_{23}$H$_{26}$NO$_3$(M+H)$^+$ 364.1907; found: 364.1918.

Synthesis of 2-amino-2-(4-((4'-ethyl-[1,1'-biphenyl]-4-yl)oxy)phenethyl)propane-1,3-diol (24b)

24b was prepared using the same procedure as that described for compound 11a. White solid (0.13g, two steps 58.8% yield)
m.p.: 238-240 °C. $^1$H NMR (300 MHz, CD$_3$OD) δ: 7.52(d, $J = 8.1$ Hz, 2H), 7.44 (d, $J = 8.1$ Hz, 2H), 7.20 (d, $J = 8.4$ Hz, 4H), 6.93 (m, 4H), 3.65 (s, 4H), 2.62 (m, 4H), 1.92 (m, 2H), 1.20 (t, $J = 7.5$ Hz, 3H). $^{13}$C NMR (400 MHz, CD$_3$OD) δ: 158.3, 157.1, 144.5, 139.1, 137.6, 137.5, 130.7, 129.3, 129.2, 127.7, 120.2, 119.8, 62.5, 62.0, 34.8, 29.5, 29.4, 16.2. HRMS calcd for C$_{23}$H$_{30}$NO$_3$(M+H)$^+$ 392.2220; found: 392.2203.

Synthesis of 2-amino-2-(4-((3'-methoxy-[1,1'-biphenyl]-4-yl)oxy)phenethyl)propane-1,3-diol (24c)
24c was prepared using the same procedure as that described for compound 11a. White solid (0.3 g, two steps 68.0% yield) m.p.: 210–212 °C. 1H NMR (600 MHz, CD3OD) δ: 7.47 (d, J = 7.8 Hz, 2H), 7.22 (t, J = 7.8 Hz, 1H), 7.16 (d, J = 7.8 Hz, 2H), 7.05 (d, J = 7.2 Hz, 1H), 7.01 (m, 1H), 6.92 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 6.79 (dd, J = 7.8 Hz, J2 = 1.8 Hz, 1H), 3.77 (s, 3H), 3.64 (s, 4H), 2.63 (m, 2H), 1.93 (m, 2H). 13C NMR (600 MHz, CD3OD) δ: 161.6, 158.6, 156.9, 143.2, 137.7, 137.4, 130.9, 130.7, 129.4, 120.3, 120.2, 119.7, 113.5, 113.4, 62.5, 62.1, 55.7, 34.8, 29.4. HRMS calcd for C24H28NO4 (M+H+) 394.2013; found: 394.1996.

Synthesis of 4-(4-((1,1'-biphenyl)-4-yl)oxy)phenyl)-2-amino-2-(hydroxymethyl) butyldihydrogen phosphate (25a)

25a was prepared using the same procedure as that described for compound 14a. White solid (10 mg, three steps 8.3% yield) m.p.: 115–118 °C. 1H NMR (300 MHz, CD3OD) δ: 7.53 (m, 4H), 7.33 (m, 3H), 7.25 (m, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.11 (m, 2H), 3.67 (m, 2H), 2.54 (m, 2H), 1.95 (m, 2H). 13C NMR (400 MHz, CD3OD) δ: 158.8, 156.4, 141.9, 139.1, 137.3, 130.9, 129.8, 129.3, 129.0, 127.7, 120.2, 119.6, 67.0, 62.8, 60.2, 34.0, 29.6. HRMS calcd for C23H27NO6P (M+H+) 444.1571; found: 444.1555.

Synthesis of 2-amino-4-(4-((4'-ethyl-[1,1'-biphenyl]-4-yl)oxy)phenyl)-2-(hydroxymethyl)butyl dihydrogen phosphate (25b)

25b was prepared using the same procedure as that described for compound 14a. White solid (15 mg, three steps 14.2% yield) m.p.: 190–192 °C. 1H NMR (300 MHz, CD3OD) δ: 7.51 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.19 (m, 4H), 6.92 (m, 4H), 3.94 (m, 2H), 3.66 (m, 2H), 2.61 (m, 4H), 1.95 (m, 2H), 1.20 (t, J = 7.6 Hz, 3H). 13C NMR (500 MHz, CD3OD) δ: 158.6, 157.4, 144.7, 139.5, 137.8, 131.1, 129.6, 129.4, 128.0, 120.5, 120.1, 62.8, 61.6, 58.6, 35.2, 29.8, 18.7, 16.5. HRMS calcd for C25H31NO6P(M+H+) 472.1884; found: 472.1872.

Synthesis of 2-amino-2-(hydroxymethyl)-4-(4-((3'-methoxy-[1,1'-biphenyl]-4-yl) oxy)phenyl)butyl dihydrogen phosphate (25c)
25c was prepared using the same procedure as that described for compound 14a. White solid (35mg, three steps 24.4% yield) m.p.: 216–218 °C. 1H NMR (400 MHz, CD3OD) δ: 7.52 (d, J = 8.4 Hz, 2H), 7.26 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.0 Hz, 1H), 7.05 (s, 1H), 6.95 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.0 Hz, 1H), 3.95 (m, 2H), 3.78 (s, 3H), 3.66 (m, 2H), 2.64 (m, 2H), 1.95 (m, 2H). 13C NMR (600 MHz, CD3OD) δ: 162.4, 159.5, 157.7, 144.1, 138.4, 138.2, 131.6, 130.2, 121.1, 121.0, 120.5, 114.3, 114.2, 66.6, 63.3, 62.2, 56.5, 30.1. HRMS calcd for C23H29NO7P (M+H+) 474.1676; found: 474.1662.

Synthesis of diethyl 2-acetamido-2-(4-(4-(2-chloroacetyl)phenoxy)phenethyl) malonate (26)

Chloroacetyl chloride (4.7 g, 41.2 mmol) in CH2Cl2 (20mL) was added dropwise to a cooled solution (0°C) of 22 (X=H) (15.5 g, 37.5 mmol) in CH2Cl2 (150mL), then AlCl3 (25 g, 188 mmol) was added in portions in 30min. The solution was then allowed to return to room temperature and stirred for further 5 h. The mixture was poured slowly into 2NHCl-ice mixture (50mL) and stirred for 2h. The aqueous phase was extracted with CH2Cl2 (10mL×3). The combined organic layers were washed with saturated aq. NaHCO3 and brine, dried over Na2SO4, filtered and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc/PE) to afford compound 26 (4.1g, 22.4% yield) as yellow solid.

mp: 78-80 °C; 1H NMR (300 MHz, CDCl3): δ 7.93 (d, J = 8.7 Hz, 2 H) 7.19 (d, J = 8.7 Hz, 2 H) 6.98 (d, J = 8.7 Hz, 4 H) 6.81 (brs, 1 H) 4.65 (s, 2 H) 4.28-4.20 (m, 4 H) 2.70 (dd, J = 11.4 Hz, 7.2 Hz, 2 H) 2.50 (dd, J = 9.3 Hz, 5.1 Hz, 2 H) 2.04 (s, 3 H) 1.25 (t, J = 7.2 Hz, 6 H); ESI (m/z) 490 (M+H+) 512 (M+Na+)

Synthesis of diethyl 2-acetamido-2-(4-(4-(2-acetoxyacetyl)phenoxy)phenethyl) malonate (27a)

To a solution of 26 (1.7 g, 3.4 mmol) in CH3CN (20mL) was added acetic acid(0.47 g, 7.8 mmol) and Et3N(0.72 g, 7.2 mmol). The mixture was heated to reflux for 2h, then concentrated. The residue was diluted with CH2Cl2 (30mL), washed with brine, dried over Na2SO4, filtered and concentrated. The residue was purified by silica gel
flash column chromatography (EtOAc/PE) to afford compound 27a (1.6g, 92.8% yield) as yellow syrup.

\[ ^1H \text{NMR (300 MHz, CDCl}_3\text{): } \delta 7.88 (d, J = 8.7 Hz, 2 H) 7.18 (d, J = 8.7 Hz, 2 H) 6.98 (d, J = 8.7 Hz, 4 H) 6.80 (brs, 1 H) 5.30 (d, J = 1.5 Hz, 2 H) 4.28-4.20 (m, 4 H) 2.70 (dd, J = 11.4 Hz, 7.5 Hz, 2 H) 2.50 (dd, J = 9.6 Hz, 5.7 Hz, 2 H) 2.23 (s, 3 H) 2.03 (s, 3 H) 1.27 (t, J = 7.2 Hz, 6 H); ESI (m/z) 514 (M+H\(^+\)) 536 (M+Na\(^+\)) \]

**Synthesis of diethyl 2-acetamido-2-(4-(2-(propionyloxy)acetyl)phenoxy)phenethyl)malonate (27b)**

27b was prepared using the same procedure as that described for compound 27a. Yellow solid (1.1g, 86.9% yield)

mp: 84-86 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta 7.88 \text{ (d, } J = 8.7 \text{ Hz, } 2 \text{ H) } 7.18 \text{ (d, } J = 8.7 \text{ Hz, } 2 \text{ H) } 6.98 \text{ (d, } J = 8.7 \text{ Hz, } 4 \text{ H) } 6.80 \text{ (brs, } 1 \text{ H) } 5.30 \text{ (s, } 2 \text{ H) } 4.27-4.20 \text{ (m, } 4 \text{ H) } 2.70 \text{ (dd, } J = 10.8 \text{ Hz, } 6.9 \text{ Hz, } 2 \text{ H) } 2.56-2.46 \text{ (m, } 4 \text{ H) } 2.03 \text{ (s, } 3 \text{ H) } 1.29-1.19 \text{ (m, } 9 \text{ H) \}; ESI (m/z) 528 (M+H\(^+\)) 550 (M+Na\(^+\)) \]

**Synthesis of diethyl 2-acetamido-2-(4-(4-(2-((cyclopropanecarbonyl)oxy)acetyl)phenoxy)phenethyl)malonate (27c)**

27c was prepared using the same procedure as that described for compound 27a. Yellow syrup (1.2g, 82.5% yield)

\[ ^1H \text{NMR (300 MHz, CDCl}_3\text{): } \delta 7.88 \text{ (d, } J = 6.9 \text{ Hz, } 2 \text{ H) } 7.17 \text{ (d, } J = 7.2 \text{ Hz, } 2 \text{ H) } 6.97 \text{ (d, } J = 7.2 \text{ Hz, } 4 \text{ H) } 6.79 \text{ (brs, } 1 \text{ H) } 5.29 \text{ (s, } 2 \text{ H) } 4.23 \text{ (q, } J = 7.2 \text{ Hz, } 4 \text{ H) } 2.70 \text{ (dd, } J = 8.7 \text{ Hz, } 7.2 \text{ Hz, } 2 \text{ H) } 2.50 \text{ (dd, } J = 8.1 \text{ Hz, } 6.9 \text{ Hz, } 2 \text{ H) } 2.02 \text{ (s, } 3 \text{ H) } 1.79-1.78 \text{ (m, } 1 \text{ H) } 1.26 \text{ (t, } J = 7.2 \text{ Hz, } 6 \text{ H) } 1.03 \text{ (m, } 2 \text{ H) } 0.96 \text{ (m, } 2 \text{ H) \}; ESI (m/z) 540(M+H\(^+\)) \]

**Synthesis of diethyl 2-acetamido-2-(4-(4-(2-methyloxazol-4-yl)phenoxy)phenethyl)malonate (28a)**

To a solution of 27a (1.62 g, 3.2 mmol) in xylene(30mL) was added acetamide (0.93 g, 15.8 mmol) and 47%BF\(_3\)-Et\(_2\)O(0.3 mL). The mixture was heated to reflux for 40h, then concentrated. The residue was diluted with EtOAc(40mL), washed with brine, dried over Na\(_2\)SO\(_4\), filtered and concentrated. The residue was purified by silica
gel flash column chromatography (EtOAc/PE) to afford compound 28a (1.2g, 75.2% yield) as yellow solid.

mp: 112-114 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.75 (s, 1 H) 7.65 (d, $J = 9.0$ Hz, 2 H) 7.12 (d, $J = 8.4$ Hz, 2 H) 6.99 (d, $J = 8.4$ Hz, 2 H) 6.94 (d, $J = 8.4$ Hz, 2 H) 6.78 (brs, 1 H) 4.27-4.17 (m, 4 H) 2.69 (dd, $J = 11.1$ Hz, 6.9 Hz, 2 H) 2.51-2.44 (m, 5 H) 2.02 (s, 3 H) 1.26 (t, $J = 7.2$ Hz, 6 H); ESI (m/z) 495 (M+H$^+$) 517 (M+Na$^+$)

Synthesis of diethyl 2-acetamido-2-(4-(2-ethyloxazol-4-yl)phenoxy)phenethyl) malonate (28b)

\[ \text{EtOOC} \quad \text{NHAc} \quad \text{EtOOC} \]

28b was prepared using the same procedure as that described for compound 28a. Yellow oil (0.85g, 79.7% yield)

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.76 (s, 1 H) 7.66 (d, $J = 8.4$ Hz, 2 H) 7.12 (d, $J = 8.4$ Hz, 2 H) 6.99 (d, $J = 8.7$ Hz, 2 H) 6.93 (d, $J = 8.7$ Hz, 2 H) 6.79 (brs, 1 H) 4.25-4.18 (m, 4 H) 2.84 (q, $J = 7.8$ Hz, 2 H) 2.69 (dd, $J = 11.1$ Hz, 7.2 Hz, 2 H) 2.48 (dd, $J = 14.1$ Hz, 5.4 Hz, 2 H) 2.02 (s, 3 H) 1.37 (t, $J = 7.5$ Hz, 3 H) 1.26 (t, $J = 7.2$ Hz, 6 H); ESI (m/z) 509 (M+H$^+$) 531 (M+Na$^+$)

Synthesis of diethyl 2-acetamido-2-(4-(2-cyclopropyloxazol-4-yl)phenoxy) phenethyl)malonate (28c)

\[ \text{EtOOC} \quad \text{NHAc} \quad \text{EtOOC} \]

28c was prepared using the same procedure as that described for compound 28a. Yellow oil (0.4g, 34.9% yield)

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.68 (s, 1 H) 7.66 (d, $J = 8.4$ Hz, 2 H) 7.11 (d, $J = 8.1$ Hz, 2 H) 6.99 (d, $J = 8.7$ Hz, 2 H) 6.93 (d, $J = 8.7$ Hz, 2 H) 6.79 (brs, 1 H) 4.29-4.19 (m, 4 H) 2.69 (dd, $J = 10.5$ Hz, 6.3 Hz, 2 H) 2.45 (dd, $J = 8.7$ Hz, 5.1 Hz, 2 H) 2.23-2.17 (m, 1 H) 2.02 (s, 3 H) 1.27 (t, $J = 7.2$ Hz, 6 H) 1.23-0.99 (m, 4 H); ESI (m/z) 521 (M+H$^+$)

Synthesis of 2-amino-2-(4-(3-methyloxazol-4-yl)phenoxy)phenethyl)propane-1,3-diol (29a)

Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications
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29a was prepared using the same procedure as that described for compound 11a. White solid (0.27g, two steps 58.2% yield)
mp: 179-181 ºC; \(^1\)H NMR (300 MHz, CD\(_2\)OD): \(\delta\) 8.03 (s, 1 H) 7.63 (d, \(J = 8.7\) Hz, 2 H) 7.22 (d, \(J = 8.1\) Hz, 2 H) 6.92 (d, \(J = 8.1\) Hz, 2 H) 6.91 (d, \(J = 8.1\) Hz, 2 H) 3.65 (s, 4 H) 2.66-2.60 (m, 2 H) 2.44 (s, 3 H) 1.95-1.89 (m, 2 H); \(^{13}\)C NMR (100 MHz, CD\(_2\)OD): \(\delta\) 163.95, 158.99, 156.64, 141.20, 137.93, 134.96, 130.79, 128.00, 127.18, 120.39, 119.58, 62.51, 62.06, 34.76, 29.39, 13.55; HRMS calcd. for C\(_{21}\)H\(_{25}\)N\(_2\)O\(_4\) (M+H\(^+\)) 369.1808, found 369.1814

Synthesis of 2-amino-2-(4-(4-(2-ethyloxazol-4-yl)phenoxy)phenethyl)propane-1,3-diol (29b)

29b was prepared using the same procedure as that described for compound 11a. White solid (0.4g, two steps 62.1% yield)
mp: 166-169 ºC; \(^1\)H NMR (300 MHz, CD\(_2\)OD): \(\delta\) 8.37 (s, 1 H) 7.68 (d, \(J = 8.4\) Hz, 2 H) 7.27 (d, \(J = 8.1\) Hz, 2 H) 7.02 (d, \(J = 8.4\) Hz, 2 H) 6.96 (d, \(J = 7.8\) Hz, 2 H) 3.68 (s, 4 H) 3.04 (q, 2 H) 2.69-2.64 (m, 2 H) 1.98-1.92 (m, 2 H) 1.41 (t, \(J = 7.8\) Hz, 3 H); \(^{13}\)C NMR (100 MHz, CD\(_2\)OD): \(\delta\) 169.75, 160.19, 156.05, 138.41, 137.97, 136.47, 130.93, 128.69, 123.33, 120.76, 119.54, 62.50, 62.03, 34.71, 29.41, 22.26, 10.65; HRMS calcd. for C\(_{22}\)H\(_{27}\)N\(_2\)O\(_4\) (M+H\(^+\)) 383.1965, found 383.1971

Synthesis of 2-amino-2-(4-(4-(2-cyclopropyloxazol-4-yl)phenoxy)phenethyl)propane-1,3-diol (29c)

29c was prepared using the same procedure as that described for compound 11a. White solid (74mg, two steps 34.2% yield)
mp: 65-68 ºC; \(^1\)H NMR (300 MHz, CD\(_2\)OD): \(\delta\) 8.19 (s, 1 H) 7.58 (d, \(J = 8.4\) Hz, 2 H) 7.19 (d, \(J = 8.4\) Hz, 2 H) 6.92 (d, \(J = 8.7\) Hz, 2 H) 6.87 (d, \(J = 8.7\) Hz, 2 H) 3.60 (s, 4 H) 2.62-2.56 (m, 2 H) 2.29-2.25 (m, 1 H) 1.90-1.84 (m, 2 H) 1.27-1.24 (m, 4 H); \(^{13}\)C NMR (100 MHz, CD\(_2\)OD): \(\delta\) 170.16, 160.19, 156.05, 138.41, 137.97, 136.47, 130.93, 128.69, 123.33, 120.76, 119.54, 62.51, 62.07, 34.73, 29.43, 10.58, 9.46; HRMS calcd. for C\(_{23}\)H\(_{27}\)N\(_2\)O\(_4\) (M+H\(^+\)) 395.1965, found 395.1946

Synthesis of 2-amino-2-(hydroxymethyl)-4-(4-(2-methyloxazol-4-yl)phenoxy)phenyl)butyl dihydrogen phosphate (30a)
30a was prepared using the same procedure as that described for compound 14a. White solid (23mg, three steps 22.5% yield)
mp: 218-220 °C; 
\(^1\)H NMR (300 MHz, CD\(_3\)OD): \(\delta\) 8.01 (s, 1 H) 7.61 (d, \(J = 8.4\) Hz, 2 H) 7.21 (d, \(J = 8.4\) Hz, 2 H) 6.91 (t, \(J = 6.9\) Hz, 4 H) 3.95 (brs, 2 H) 3.66 (s, 2 H) 2.64 (q, \(J = 7.8\) Hz, 2 H) 2.43 (s, 3 H) 1.94 (q, \(J = 5.7\) Hz, 2 H); 
\(^{13}\)C NMR (100 MHz, CD\(_3\)OD): \(\delta\) 163.94, 159.00, 156.65, 141.23, 137.84, 134.94, 130.86, 127.99, 127.17, 120.39, 119.58, 65.79, 65.74, 62.48, 61.39, 61.32, 34.91, 29.33, 13.54; HRMS calcd. for C\(_{21}\)H\(_{26}\)N\(_2\)O\(_7\)P (M+H\(^+\)) 449.1472, found 449.1465

Synthesis of 2-amino-4-(4-(2-ethyloxazol-4-yl)phenoxy)phenyl)-2-(hydroxymethyl)butyl dihydrogen phosphate (30b)

30b was prepared using the same procedure as that described for compound 14a. White solid (17mg, three steps 15.5% yield)
mp: 220-223 °C; 
\(^1\)H NMR (300 MHz, CD\(_3\)OD): \(\delta\) 7.94-7.72 (m, 1 H) 7.39-7.18 (m, 4 H) 6.96-6.84 (m, 4 H) 3.96 (s, 2 H) 3.67 (s, 2 H) 2.69-2.64 (m, 2 H) 1.98-1.92 (m, 2 H) 1.41 (t, \(J = 7.8\) Hz, 3 H); 
\(^{13}\)C NMR (100 MHz, CD\(_3\)OD): \(\delta\) 169.75, 160.19, 156.05, 138.41, 137.97, 136.47, 130.93, 128.69, 123.33, 120.76, 119.54, 62.50, 62.03, 34.71, 29.41, 22.26, 10.65; HRMS calcd. for C\(_{22}\)H\(_{28}\)N\(_2\)O\(_7\)P (M+H\(^+\)) 463.1629, found 463.1646

Synthesis of 2-amino-4-(4-(2-cyclopropyloxazol-4-yl)phenoxy)phenyl)-2-(hydroxymethyl)butyl dihydrogen phosphate (30c)

30c was prepared using the same procedure as that described for compound 14a. White solid (18mg, three steps 14.7% yield)
mp: 140-143 °C; 
\(^1\)H NMR(300 MHz, CD\(_3\)OD): \(\delta\) 7.92 (s, 1 H) 7.59 (d, \(J = 8.4\) Hz, 2 H) 7.20 (d, \(J = 8.4\) Hz, 2 H) 6.92 (d, \(J = 8.4\) Hz, 2 H) 6.87 (d, \(J = 8.7\) Hz, 2 H) 3.95 (s, 2 H) 3.68 (s, 2 H) 2.65-2.62 (m, 2 H) 2.09-2.05 (m, 1 H) 1.96-1.91 (m, 2 H) 1.03-1.01 (m, 4 H); 
\(^{13}\)C NMR (100 MHz, CD\(_3\)OD): \(\delta\) 168.19, 158.96, 156.63, 141.20, 137.84,
134.06, 130.87, 128.03, 127.25, 119.54, 65.77, 62.49, 61.35, 61.28, 34.91, 30.74, 29.33, 9.57, 8.40; HRMS calcd. for C_{23}H_{27}N_{2}O_{7}P (M+H)^+ 475.1629, found 475.1586

Synthesis of diethyl 2-acetamido-2-(4-(4-(2-ethyl-1H-imidazol-4-yl)phenoxy)phenethyl)malonate (31)

To a solution of 27b (1.0 g, 1.9 mmol) in xylene (20mL) was added acetamide (0.29 g, 3.8 mmol). The mixture was heated to reflux for 40h, then concentrated. The residue was diluted with EtOAc (30mL), washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc/PE) to afford compound 31 (0.2g, 20.8% yield) as yellow oil.

$^1$H NMR (300 MHz, CDCl$_3$): δ 7.63 (d, $J = 8.4$ Hz, 2 H) 7.13 (s, 1 H) 7.09 (d, $J = 8.1$ Hz, 2 H) 6.96 (d, $J = 8.4$ Hz, 2 H) 6.91 (d, $J = 8.1$ Hz, 2 H) 6.80 (brs, 1 H) 4.23 - 4.18 (m, 4 H) 2.81 (q, $J = 7.8$ Hz, 2 H) 2.69 (dd, $J = 9.0$ Hz, 6.6 Hz, 2 H) 2.46 (dd, $J = 8.4$ Hz, 7.8 Hz, 2 H) 2.01 (s, 3 H) 1.32 (t, $J = 7.5$ Hz, 3 H) 1.25 (t, $J = 7.2$ Hz, 6 H); ESI (m/z) 508 (M+H$^+$)

Synthesis of 2-amino-2-(4-(2-ethyl-1H-imidazol-4-yl)phenoxy)phenethyl)propane-1,3-diol (32)

32 was prepared using the same procedure as that described for compound 11a. Yellow solid (0.1g, two steps 60.5% yield) mp: 130-133 ºC; $^1$H NMR (300 MHz, CD$_3$OD): δ 7.63 (d, $J = 8.4$ Hz, 2 H) 7.62 (s, 1 H) 7.23 (d, $J = 8.4$ Hz, 2 H) 6.99 (d, $J = 8.4$ Hz, 2 H) 6.93 (d, $J = 8.7$ Hz, 2 H) 3.64 (s, 4 H) 2.99 (q, $J = 7.8$ Hz, 2 H) 2.66-2.60 (m, 2 H) 1.94-1.88 (m, 2 H) 1.37 (t, $J = 7.5$ Hz, 3 H); $^{13}$C NMR (100 MHz, CD$_3$OD): δ 160.39, 155.90, 150.90, 138.61, 134.17, 130.98, 128.36, 122.72, 120.88, 119.61, 114.77, 62.49, 62.05, 34.71, 29.42, 20.40, 11.89; HRMS calcd. for C$_{23}$H$_{28}$N$_3$O$_3$ (M+H$^+$) 382.2125, found 382.2120

Synthesis of 2-amino-4-(4-(2-ethyl-1H-imidazol-4-yl)phenoxy)phenyl)-2-(hydroxymethyl)butyl dihydrogen phosphate (33)
33 was prepared using the same procedure as that described for compound 14a. White solid (3mg, three steps 5.1% yield)
mp: 125-128 °C; \( ^1 \)H NMR (300 MHz, CD\(_3\)OD): \( \delta \) 8.47 (s, 1 H) 7.58 (d, \( J = 8.4 \) Hz, 2 H) 7.37 (d, \( J = 8.1 \) Hz, 2 H) 7.12 (d, \( J = 8.4 \) Hz, 2 H) 6.90 (d, \( J = 7.8 \) Hz, 2 H) 3.60 (s, 4 H) 3.14 (q, 2 H) 2.69-2.64 (m, 2 H) 1.98-1.92 (m, 2 H) 1.51 (t, \( J = 7.8 \) Hz, 3 H); \( ^{13} \)C NMR (125 MHz, CD\(_3\)OD): \( \delta \) 170.75, 162.19, 153.05, 135.41, 138.97, 134.47, 132.93, 128.54, 123.77, 119.56, 119.23, 60.57, 60.03, 36.71, 31.50, 24.26, 13.66; HRMS calcd. for C\(_{22}\)H\(_{29}\)N\(_3\)O\(_6\)P (M+H\(^+\)) 462.1788, found 462.1775

**Synthesis of 1-(4-bromophenyl)butan-1-one (35)**

A mixture of butyric acid (25 mL, 277 mmol) and PCl\(_3\) (10 mL, 111 mmol) was stirred for 3h at 50-60°C, then cooled to room temperature and filtered. The filtrate was added to a solution of bromobenzene (17g, 111mmol) in CH\(_2\)Cl\(_2\) (200mL). Then AlCl\(_3\) (29 g, 222 mmol) was added in portions in 30min. The solution was then allowed to return to room temperature and stirred for further 2 h. The mixture was poured slowly into 2NHCl-ice mixture (100mL) and stirred for 1 h. The aqueous phase was extracted with CH\(_2\)Cl\(_2\) (20mL× 3). The combined organic layers were washed with saturated aq. NaHCO\(_3\) and brine, dried over Na\(_2\)SO\(_4\), filtered and concentrated, yielding crude product 35 (23.6g, 94% yield) as brown solid.
mp: 36-38 °C; \( ^1 \)H NMR (300 MHz, CDCl\(_3\)) \( \delta \): 7.82 (d, \( J = 8.7 \) Hz, 2H), 7.59 (d, \( J = 8.7 \) Hz, 2H), 2.91 (t, \( J = 7.2 \) Hz, 2H), 1.78 (m, 2H), 1.00 (t, \( J = 7.5 \) Hz, 3H). ESI (m/z) 227 (M+H\(^+\))

**Synthesis of 1-(4-(2-fluorophenoxy)phenyl)butan-1-one (36a)**

To a solution of 35 (8.4 g, 37.2 mmol) in DMF (80mL) was added 2-fluorophenol (5 g, 44.6 mmol), Cs\(_2\)CO\(_3\) (14.5g, 44.6mmol) and CuBr (0.27g, 1.86mmol). The mixture was heated for 20h at 150 °C under Ar\(_2\) protection, then cooled to room temperature, filtered through celite to remove insoluble materials, and the filtrate was concentrated. The residue was purified by silica gel flash column chromatography (EtOAc/PE) to afford compound 36a (7.8g, 71.0% yield) as yellow oil.
\( ^1 \)H NMR (300 MHz, CDCl\(_3\)) \( \delta \): 7.95 (d, \( J = 8.7 \) Hz, 2H), 7.18 (m, 4H), 6.97 (d, \( J = 8.7 \)
Hz, 2H), 2.90 (t, \( J = 7.4 \) Hz, 2H), 1.76 (m, 2H), 1.00 (t, \( J = 7.5 \) Hz, 3H). ESI (m/z) 259 (M+H)

**Synthesis of 1-(4-(3-fluorophenoxy)phenyl)butan-1-one (36b)**

![Compound 36b](image)

36b was prepared using the same procedure as that described for compound 36a. Yellow oil (5.9g, 62.0% yield)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) δ: 7.97 (d, \( J = 8.4 \) Hz, 2H), 7.30 (m, 1H), 7.03 (d, \( J = 8.4 \) Hz, 2H), 6.85 (m, 3H), 2.91 (t, \( J = 7.4 \) Hz, 2H), 1.77 (m, 2H), 1.01 (t, \( J = 7.4 \) Hz, 3H). ESI (m/z) 259 (M+H)

**Synthesis of 1-(4-(3-chlorophenoxy)phenyl)butan-1-one (36c)**

![Compound 36c](image)

36c was prepared using the same procedure as that described for compound 36a. Yellow oil (1.2g, 50.0% yield)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) δ: 7.97 (d, \( J = 8.7 \) Hz, 2H), 7.31 (t, \( J = 8.0 \) Hz, 1H), 7.16 (d, \( J = 7.8 \) Hz, 1H), 7.06 (s, 1H), 7.02 (d, \( J = 8.4 \) Hz, 2H), 6.95 (dd, \( J_1 = 8.1 \) Hz, \( J_2 = 2.4 \), 1H), 2.92 (t, \( J = 7.2 \) Hz, 2H), 1.77 (m, 2H), 1.01 (t, \( J = 7.5 \) Hz, 3H). ESI (m/z) 275 (M+H)

**Synthesis of diethyl 2-acetamido-2-(2-(4-(4-butyrylphenoxy)-3-fluorophenyl)-2-oxoethyl)malonate (37a)**

![Compound 37a](image)

37a was prepared using the same procedure as that described for compound 8a. Yellow oil (1.9g, two steps 19.8% yield)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) δ: 7.99 (d, \( J = 8.4 \) Hz, 2H), 7.79 (t, \( J = 10.5 \) Hz, 1H), 7.13 (m, 2H), 7.04 (d, \( J = 8.4 \) Hz, 2H), 4.27 (m, 6H), 4.27 (t, \( J = 7.2 \) Hz, 2H), 2.08 (s, 3H), 1.76 (m, 2H), 1.28 (m, 6H), 1.00 (t, \( J = 7.4 \) Hz, 3H). ESI (m/z) 516 (M+H)

**Synthesis of diethyl 2-acetamido-2-(2-(4-(4-butyrylphenoxy)-2-fluorophenyl)-2-oxoethyl)malonate (37b)**

![Compound 37b](image)
37b was prepared using the same procedure as that described for compound 8a. Yellow solid (2.2g, two steps 28.1% yield)
mp: 18-21 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 8.03 (d, \(J = 8.7\) Hz, 2H), 7.88 (t, \(J = 8.4\) Hz, 1H), 7.13 (m, 2H), 6.85 (dd, \(J_1 = 8.7\) Hz, \(J_2 = 2.1\) Hz, 1H), 6.75 (dd, \(J_1 = 12.0\) Hz, \(J_2 = 2.1\) Hz, 1H), 4.24 (m, 6H), 2.94 (m, 2H), 2.03 (s, 3H), 1.78 (m, 2H), 1.25 (m, 6H), 1.02 (t, \(J = 7.4\) Hz, 3H). ESI (m/z) 516 (M+H)

**Synthesis of diethyl 2-acetamido-2-(2-(4-(4-butylylphenoxy)-2-chlorophenyl)-2-oxoethyl)malonate (37c)**

37c was prepared using the same procedure as that described for compound 8a. Yellow solid (0.61g, two steps 29.1% yield)
mp: 44-46 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 8.02 (d, \(J = 8.4\) Hz, 2H), 7.64 (d, \(J = 8.4\) Hz, 1H), 7.10 (m, 3H), 6.96 (d, \(J = 8.4\) Hz, 1H), 4.28 (m, 6H), 2.94 (t, \(J = 7.2\) Hz, 2H), 2.08 (s, 3H), 1.78 (m, 2H), 1.28 (m, 6H), 1.02 (t, \(J = 7.2\) Hz, 3H). ESI (m/z) 532 (M+H)

**Synthesis of diethyl 2-acetamido-2-(4-(4-butylphenoxy)-3-fluorophenethyl) malonate (38a)**

38a was prepared using the same procedure as that described for compound 19a. White solid (0.62g, 37.0% yield)
mp: 63-66 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.10 (d, \(J = 8.7\) Hz, 2H), 6.94 (m, 2H), 6.83 (m, 3H), 4.24 (m, 4H), 2.68 (m, 2H), 2.57 (m, 2H), 2.45 (m, 2H), 2.03 (s, 3H), 1.57 (m, 2H), 1.34 (m, 2H), 1.26 (t, \(J = 7.1\) Hz, 6H), 0.92 (t, \(J = 7.4\) Hz, 3H). ESI (m/z) 488 (M+H)

**Synthesis of diethyl 2-acetamido-2-(4-(4-butylphenoxy)-2-fluorophenethyl) malonate (38b)**

38b was prepared using the same procedure as that described for compound 19a. Yellow oil (0.62g, 32.0% yield)
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.15 (d, \(J = 7.5\) Hz, 2H), 7.07 (t, \(J = 8.7\) Hz, 1H), 6.91 (d, \(J = 6.6\) Hz, 2H), 6.66 (m, 2H), 4.22 (m, 4H), 2.61 (m, 4H), 2.45 (m, 2H), 2.05 (s, 3H), 1.60 (m, 2H), 1.38 (m, 2H), 1.26 (m, 6H), 0.93 (t, \(J = 7.1\) Hz, 3H). ESI (m/z) 488
(M+H)$^+$

**Synthesis of diethyl 2-acetamido-2-(4-(4-butylphenoxy)-2-chlorophenethyl) malonate (38c)**

![Structure of 38c]

38c was prepared using the same procedure as that described for compound 19a. Crude product as yellow oil (1.0g, 70.0% yield)

ESI (m/z) 504 (M+H)$^+$

**Synthesis of 2-amino-2-(4-(4-butylphenoxy)-3-fluorophenethyl)propane-1,3-diol (39a)**

![Structure of 39a]

39a was prepared using the same procedure as that described for compound 11a. White solid (386mg, two steps 71.5% yield)

m.p.: 176-179 °C. $^1$H NMR (300 MHz, CD$_3$OD) $\delta$: 7.05 (m, 3H), 6.94 (m, 1H), 6.88 (m, 1H), 6.73 (d, $J = 8.4$ Hz, 2H), 3.61 (s, 4H), 2.60 (m, 2H), 2.49 (t, $J = 7.7$ Hz, 2H), 1.88 (m, 2H), 1.47 (m, 2H), 1.26 (m, 2H), 0.84 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (400 MHz, CD$_3$OD) $\delta$: 157.0, 155.5 ($J = 246$ Hz), 143.5 ($J = 12$ Hz), 139.9 ($J = 6$ Hz), 138.9, 130.6, 125.6 ($J = 3$ Hz), 122.9, 117.9, 117.7 ($J = 19$ Hz), 62.5, 62.0, 35.8, 35.1, 34.4, 29.4, 23.3, 14.3. HRMS calcd for C$_{21}$H$_{29}$FNO$_3$ (M+H)$^+$ 362.2126; found: 362.2128.

**Synthesis of 2-amino-2-(4-(4-butylphenoxy)-2-fluorophenethyl)propane-1,3-diol (39b)**

![Structure of 39b]

39b was prepared using the same procedure as that described for compound 11a. White solid (350mg, two steps 52.9% yield)

m.p.: 165-167 °C. $^1$H NMR (300 MHz, CD$_3$OD) $\delta$: 7.13 (t, $J = 8.7$ Hz, 1H), 7.07 (d, $J = 8.1$ Hz, 2H), 6.79 (d, $J = 8.4$ Hz, 2H), 6.58 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.1$ Hz, 1H), 6.52 (dd, $J_1 = 11.4$ Hz, $J_2 = 2.4$ Hz, 1H), 3.59 (s, 4H), 2.57 (m, 2H), 2.48 (t, $J = 7.7$ Hz, 2H), 1.83 (m, 2H), 1.48 (m, 2H), 1.23 (m, 2H), 0.82 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (400 MHz, CD$_3$OD) $\delta$: 162.6 ($J = 243$ Hz), 159.2 ($J = 11$ Hz), 155.6, 140.0, 132.2 ($J = 7$ Hz), 130.9, 123.2 ($J = 16$ Hz), 120.4, 114.8, 106.4 ($J = 26$ Hz), 62.5, 62.0, 35.9, 35.0, 33.2, 23.3, 22.9, 14.3. HRMS calcd for C$_{21}$H$_{29}$FNO$_3$ (M+H)$^+$ 362.2126; found: 362.2135.
Synthesis of 2-amino-2-(4-(4-butylphenoxy)-2-chlorophenethyl)propane-1,3-diol (39c)

39c was prepared using the same procedure as that described for compound 11a. White solid (61mg, two steps 78.0% yield) m.p.: 208-210 °C. ¹H NMR (300 MHz, CD₃OD) δ: 7.25 (d, J = 8.7 Hz, 1H), 7.15 (d, J = 8.4 Hz, 2H), 6.87 (m, 2H), 6.84 (s, 1H), 6.79 (dd, J₁ = 8.4 Hz, J₂ = 2.4 Hz, 1H), 3.68 (s, 4H), 2.72 (m, 2H), 2.56 (t, J = 7.7 Hz, 2H), 1.88 (m, 2H), 1.55 (m, 2H), 1.32 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H). ¹³C NMR (400 MHz, CD₃OD) δ: 158.7, 155.6, 140.1, 135.2, 134.1, 132.4, 130.9, 120.4, 119.9, 118.0, 62.5, 62.0, 35.9, 35.0, 33.1, 27.4, 23.3, 14.3. HRMS calcd for C₂₁H₂₉ClNO₃ (M+H)⁺ 378.1830; found: 378.1838.

Synthesis of 2-amino-4-(4-(4-butylphenoxy)-3-fluorophenyl)-2-(hydroxymethyl)butyl dihydrogen phosphate (40a)

40a was prepared using the same procedure as that described for compound 14a. White solid (36mg, three steps 33.7% yield) m.p.: 185-187 °C. ¹H NMR (300 MHz, CD₃OD) δ: 7.08 (m, 3H), 6.98 (m, 1H), 6.91 (m, 1H), 6.76 (d, J = 8.4 Hz, 2H), 3.94 (m, 2H), 3.65 (m, 2H), 2.65 (m, 2H), 2.52 (t, J = 7.7 Hz, 1H), 1.94 (m, 2H), 1.52 (m, 2H), 1.29 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H). ¹³C NMR (600 MHz, CD₃OD) δ: 157.0, 155.5 (J = 245 Hz), 143.6 (J = 12 Hz), 139.8 (J = 6 Hz), 138.9, 130.6, 125.7 (J = 3 Hz), 122.9, 118.0, 117.8 (J = 19 Hz), 65.7, 62.5, 61.3, 35.8, 35.1, 34.6, 29.3, 23.3, 14.3. HRMS calcd for C₂₁H₂₉FNO₆P (M+H)⁺ 442.1789; found: 442.1810.

Synthesis of 2-amino-4-(4-(4-butylphenoxy)-2-fluorophenyl)-2-(hydroxymethyl)butyl dihydrogen phosphate (40b)

40b was prepared using the same procedure as that described for compound 14a. White solid (32mg, three steps 25.5% yield) m.p.: 195-197 °C. ¹H NMR (300 MHz, CD₃OD) δ: 7.20 (t, J = 8.6 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 6.85(d, J = 8.7 Hz, 2H), 6.64 (dd, J₁ = 8.1 Hz, J₂ = 1.8 Hz, 1H), 6.58 (dd, J₁ = 11.4 Hz, J₂ = 2.4 Hz, 1H), 3.96 (m, 2H), 3.66 (m, 2H), 2.64 (m, 2H), 2.55 (t, J = 7.7 Hz, 2H), 1.91 (m, 2H), 1.54 (m, 2H), 1.28 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H).
\^13C NMR (600 MHz, CD\textsubscript{3}OD) $\delta$: 162.6 ($J = 243$ Hz), 159.3 ($J = 10$ Hz), 155.7, 140.0, 132.3 ($J = 6$ Hz), 130.9, 123.1 ($J = 16$ Hz), 120.4, 114.9, 106.4 ($J = 26$ Hz), 65.8, 62.5, 61.2, 35.9, 35.0, 33.4, 23.3, 22.9, 14.3. HRMS calcd for C\textsubscript{21}H\textsubscript{30}FNO\textsubscript{6}P (M+H)$^+$ 442.1789; found: 442.1808.

**Synthesis of 2-amino-4-(4-butylphenoxy)-2-chlorophenyl-2-(hydroxymethyl) butyl dihydrogen phosphate (40c)**

![Image of molecule]

40c was prepared using the same procedure as that described for compound 14a. White solid (5mg, three steps 8.6% yield) m.p.: 205-207 °C. \(^1H\) NMR (400 MHz, CD\textsubscript{3}OD) $\delta$: 7.27 (d, $J = 8.0$ Hz, 1H), 7.16 (d, $J = 8.0$ Hz, 2H), 6.88 (m, 3H), 6.81 (d, $J = 8.0$ Hz, 1H), 3.99 (m, 2H), 3.71 (m, 2H), 2.76 (m, 2H), 2.58 (m, 2H), 1.92 (m, 2H), 1.57 (m, 2H), 1.33 (m, 2H), 0.92 (t, $J = 8.0$ Hz, 3H). \(^{13}C\) NMR (500 MHz, DMSO) $\delta$: 156.4, 153.9, 138.2, 133.4, 131.5, 129.9, 119.1, 118.7, 117.3, 64.6, 63.4, 61.0, 34.1, 33.3, 31.7, 25.7, 21.8, 13.9. HRMS calcd for C\textsubscript{21}H\textsubscript{30}ClNO\textsubscript{6}P (M+H)$^+$ 458.1494; found: 458.1498.

**Synthesis of 1-(4-bromophenyl)-2-chloroethanone (41)**

![Image of molecule]

41 was prepared using the same procedure as that described for compound 7a. Yellow solid (1.4g, 95.0% yield) mp: 116-118 °C; \(^1H\) NMR (300 MHz, CDCl\textsubscript{3}) $\delta$: 7.83 (d, $J = 8.7$ Hz, 2H), 7.65 (d, $J = 8.7$ Hz, 2H), 4.65 (s, 2H). ESI (m/z) 232 (M+H)$^+$

**Synthesis of 4-(4-bromophenyl)-2-ethyloxazole (42)**

![Image of molecule]

42 was prepared using the same procedure as that described for compound 28a. Yellow solid (0.54g, two steps 35.7% yield) mp: 98-100 °C; \(^1H\) NMR (300 MHz, CDCl\textsubscript{3}) $\delta$: 7.81 (s, 1H), 7.59 (d, $J = 8.4$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 2H), 2.84 (q, $J = 7.6$ Hz, 2H), 1.37 (t, $J = 7.6$ Hz, 3H). ESI (m/z) 252 (M+H)$^+$

**Synthesis of 4-(4-(3-chlorophenoxy)phenyl)-2-ethyloxazole (43)**

![Image of molecule]
43 was prepared using the same procedure as that described for compound 36a. Yellow oil (3.1g, 66.0% yield)

$^1$H NMR (300 MHz, CDCl$_3$) δ: 7.78 (s, 1H), 7.70 (d, $J = 8.7$ Hz, 2H), 7.25 (m, 1H), 7.03 (m, 3H), 6.89 (d, $J = 8.1$ Hz, 1H), 2.85 (q, $J = 7.6$ Hz, 2H), 1.38 (t, $J = 7.6$ Hz, 3H). ESI (m/z) 300 (M+H)$^+$

**Synthesis of Diethyl 2-acetamido-2-(2-chloro-4-(4-(2-ethyloxazol-4-yl)phenoxy)phenyl)-2-oxoethyl)malonate (44)**

44 was prepared using the same procedure as that described for compound 8a. Yellow solid (2.2g, two steps 38.3% yield)

mp: 78-80 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ: 7.82 (s, 1H), 7.77 (d, $J = 8.7$ Hz, 2H), 7.63 (d, $J = 9.0$ Hz, 1H), 7.10 (m, 3H), 7.00 (d, $J = 2.4$ Hz, 1H), 6.91 (dd, $J_1 = 8.7$ Hz, $J_2 = 2.4$ Hz, 1H), 4.27 (m, 6H), 2.88 (q, $J = 7.6$ Hz, 2H), 2.01 (s, 3H), 1.40 (t, $J = 7.5$ Hz, 3H), 1.26 (t, $J = 7.1$ Hz, 6H). ESI (m/z) 557 (M+H)$^+$

**Synthesis of Diethyl 2-acetamido-2-(2-chloro-4-(4-(2-ethyloxazol-4-yl)phenoxy)phenethyl)malonate (45)**

45 was prepared using the same procedure as that described for compound 9a. Yellow solid (0.91g, 72.0% yield)

mp: 68-69 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.78 (s, 1H), 7.69 (d, $J = 8.4$ Hz, 2H), 7.14 (d, $J = 8.4$ Hz, 1H), 7.01 (m, 3H), 6.85 (m, 2H), 4.25 (m, 4H), 2.85 (q, $J = 7.6$ Hz, 2H), 2.65 (m, 2H), 2.55 (m, 2H), 2.07 (s, 3H), 1.38 (t, $J = 7.6$ Hz, 3H), 1.28 (m, 6H). ESI (m/z) 543(M+H)$^+$

**Synthesis of 2-amino-2-(2-chloro-4-(4-(2-ethyloxazol-4-yl)phenoxy)phenethyl)propane-1,3-diol (46)**
46 was prepared using the same procedure as that described for compound 11a. White solid (88mg, two steps 62.0% yield)
m.p.: 198-200 °C. $^1$H NMR (300 MHz, CD$_3$OD) δ: 8.10 (s, 1H), 7.64 (d, $J = 8.4$ Hz, 2H), 7.25 (d, $J = 8.4$ Hz, 1H), 6.95 (m, 3H), 6.84 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 1H), 3.65 (s, 4H), 2.81 (q, $J = 7.7$ Hz, 2H), 2.72 (m, 2H), 1.86 (m, 2H), 1.29 (t, $J = 7.7$ Hz, 3H).

$^{13}$C NMR (400 MHz, CD$_3$OD) δ: 168.6, 158.2, 157.7, 140.1, 135.5, 135.4, 135.0, 132.5, 128.4, 127.2, 120.8, 120.3, 118.8, 62.5, 61.9, 33.0, 27.4, 22.4, 11.3. HRMS calcd for C$_{22}$H$_{26}$ClN$_2$O$_4$ (M+H)$^+$ 417.1581; found: 417.1582.

Synthesis of 2-amino-4-(2-chloro-4-(4-(2-ethyloxazol-4-yl)phenoxy)phenyl)-2-(hydroxymethyl)butyl dihydrogen phosphate (47)

47 was prepared using the same procedure as that described for compound 14a. White solid (1.6mg, three steps 12.0% yield)
m.p.: 125-128 °C. $^1$H NMR (500 MHz, CD$_3$OD) δ: 8.05 (s, 1H), 7.68 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 1H), 6.98 (m, 3H), 6.88 (m, 1H), 3.96 (m, 2H), 3.68 (m, 2H), 2.77 (m, 4H), 1.90 (m, 2H), 1.31 (t, $J = 8.0$ Hz, 3H).

$^{13}$C NMR (500 MHz, CD$_3$OD) δ: 168.5, 158.3, 158.1, 141.3, 135.7, 135.4, 135.3, 132.9, 128.5, 120.9, 120.6, 119.0, 66.4, 63.4, 61.0, 33.9, 27.7, 22.7, 11.9. HRMS calcd for C$_{22}$H$_{27}$ClN$_2$O$_7$P (M+H)$^+$ 497.1244; found: 497.1242.

Synthesis of diethyl 2-(2-([1,1'-(biphenyl)-4-yl]-2-oxoethyl)-2-acetamidomalonate (49)

49 was prepared using the same procedure as that described for compound 17. Crude product as yellow oil (6.0g, two steps 62.0% yield)
ESI (m/z) 412 (M+H)$^+$, 434 (M+Na$^+$)

Synthesis of diethyl 2-(2-([1,1'-(biphenyl)-4-yl]ethyl)-2-acetamidomalonate (50)
**50** was prepared using the same procedure as that described for compound **9a**. Yellow oil (5.0g, 86.9% yield)

$^1$H NMR (300 MHz, CDCl$_3$): δ 7.56 (d, $J = 7.8$ Hz, 2 H) 7.50 (d, $J = 7.8$ Hz, 2 H) 7.42 (t, $J = 7.5$ Hz, 2 H) 7.33 (d, $J = 7.2$ Hz, 1 H) 7.22 (d, $J = 8.4$ Hz, 2 H) 6.78 (brs, 1 H) 4.26-4.16 (m, 4 H) 2.73 (dd, $J = 10.5$ Hz, 7.2 Hz, 2 H) 2.53 (dd, $J = 9.3$ Hz, 5.7 Hz, 2 H) 1.98 (s, 3 H) 1.25 (t, $J = 7.2$ Hz, 6 H); ESI (m/z) 398 (M+H$^+$) 420 (M+Na$^+$)

**Synthesis of diethyl 2-acetamido-2-(4''-(2-chloroacetyl)-[1,1''-biphenyl]-4-yl)ethyl)malonate (51)**

**51** was prepared using the same procedure as that described for compound **26**. Yellow solid (5.2g, 87.3% yield)

mp: 80-83 °C; $^1$H NMR (300 MHz, CDCl$_3$): δ 8.02 (d, $J = 8.4$ Hz, 2 H) 7.69 (d, $J = 8.1$ Hz, 2 H) 7.54 (d, $J = 8.1$ Hz, 2 H) 7.27 (d, $J = 8.4$ Hz, 2 H) 6.79 (brs, 1 H) 4.73 (s, 2 H) 4.27-4.19 (m, 4 H) 2.73 (dd, $J = 10.8$ Hz, 6.3 Hz, 2 H) 2.53 (dd, $J = 9.3$ Hz, 5.4 Hz, 2 H) 2.04 (s, 3 H) 1.26 (t, $J = 7.2$ Hz, 6 H); ESI (m/z) 474 (M+H$^+$) 496 (M+Na$^+$)

**Synthesis of diethyl 2-acetamido-2-(2-(4''-(2-methyloxazol-4-yl)-[1,1''-biphenyl]-4-yl)ethyl)malonate (52a)**

**52a** was prepared using the same procedure as that described for compound **28a**. Yellow solid (0.9g, two steps 62.8% yield)

mp: 123-125 °C; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.84 (s, 1 H) 7.77 (d, $J = 8.4$ Hz, 2 H) 7.60 (d, $J = 8.7$ Hz, 2 H) 7.53 (d, $J = 8.1$ Hz, 2 H) 7.23 (d, $J = 8.4$ Hz, 2 H) 6.78 (brs, 1 H) 4.27-4.18 (m, 4 H) 2.73 (dd, $J = 10.5$ Hz, 6.6 Hz, 2 H) 2.55-2.50 (m, 5 H) 1.99 (s, 3 H) 1.25 (t, $J = 7.2$ Hz, 6 H); ESI (m/z) 479 (M+H$^+$) 501 (M+Na$^+$)

**Synthesis of diethyl 2-acetamido-2-(2-(4''-(2-propyloxazol-4-yl)-[1,1''-biphenyl]-4-yl)ethyl)malonate (52b)**
52b was prepared using the same procedure as that described for compound 28a. Yellow solid (0.95g, two steps 72.2% yield)
mp: 131-134 °C; 1H NMR (300 MHz, CDCl3): δ 7.85 (s, 1 H) 7.77 (d, J = 8.4 Hz, 2 H) 7.59 (d, J = 8.1 Hz, 2 H) 7.52 (d, J = 8.4 Hz, 2 H) 7.22 (d, J = 8.4 Hz, 2 H) 6.78 (brs, 1 H) 4.27-4.16 (m, 4 H) 2.82 (t, J = 7.2 Hz, 2 H) 2.73 (dd, J = 10.5 Hz, 6.6 Hz, 2 H) 2.52 (dd, J = 15.9 Hz, 9.3 Hz, 2 H) 1.99 (s, 3 H) 1.89-1.79 (m, 2 H) 1.25 (t, J = 7.2 Hz, 6 H) 1.03 (t, J = 7.2 Hz, 3 H); ESI (m/z) 507 (M+H+) 529 (M+Na+)

Synthesis of 2-amino-2-(2-(4'-(2-methylazol-4-yl)-[1,1'-biphenyl]-4-yl)ethyl)propane-1,3-diol (53a)

53a was prepared using the same procedure as that described for compound 11a. White solid (0.15g, two steps 64.5% yield)
mp: 78-80 °C; 1H NMR (300 MHz, CD3OD): δ 8.21 (s, 1 H) 7.72 (d, J = 7.8 Hz, 2 H) 7.62 (d, J = 8.7 Hz, 2 H) 7.54 (d, J = 8.4 Hz, 2 H) 7.28 (d, J = 8.4 Hz, 2 H) 3.66 (s, 4 H) 2.69-2.64 (m, 2 H) 2.52 (s, 3 H) 1.97-1.91 (m, 2 H); 13C NMR (100 MHz, CD3OD): δ 164.62, 142.11, 141.93, 140.61, 139.70, 135.97, 130.15, 129.91, 128.66, 128.42, 126.99, 62.53, 62.07, 34.58, 29.76, 13.53; HRMS calcd. for C21H25N2O3 (M+H+) 353.1865, found 353.1872

Synthesis of 2-amino-2-(2-(4'-(2-propyloxazol-4-yl)-[1,1'-biphenyl]-4-yl)ethyl)propane-1,3-diol (53b)

53b was prepared using the same procedure as that described for compound 11a. White solid (0.42g, two steps 71.6% yield)
mp: 170-172 °C; 1H NMR (300 MHz, DMSO): δ 8.52 (s, 1 H) 7.83 (d, J = 8.4 Hz, 2 H) 7.70 (d, J = 8.7 Hz, 2 H) 7.61 (d, J = 8.1 Hz, 2 H) 7.29 (d, J = 7.8 Hz, 2 H) 4.49 (brs, 2 H) 3.34 (brs, 1 H) 3.31-3.22 (m, 4 H) 2.78 (t, J = 7.2 Hz, 2 H) 2.66-2.61 (m, 2 H)
H) 1.82-1.70 (m, 2 H) 1.56-1.51 (m, 2 H) 0.96 (t, J = 7.5 Hz, 3 H); \(^{13}\)C NMR (100 MHz, DMSO): \(\delta\) 164.60, 142.90, 139.29, 139.17, 136.72, 134.60, 129.83, 128.79, 126.64, 126.30, 125.53, 65.38, 55.42, 36.73, 29.24, 28.60, 19.95, 13.46; HRMS calcd. for \(\text{C}_{23}\text{H}_{29}\text{N}_{2}\text{O}_{3}\) (M+H\(^{+}\)) 381.2178, found 381.2183

**Synthesis of 2-amino-2-(hydroxymethyl)-4-(4'-(2-methyloxazol-4-yl)-[1,1’-biphenyl]-4-yl)butyl dihydrogen phosphate (54a)**

![54a](image)

54a was prepared using the same procedure as that described for compound 14a. White solid (30 mg, three steps 34.0% yield)

mp: 220-223 °C; \(^1\)H NMR (300 MHz, CD\(_3\)OD): \(\delta\) 8.12 (s, 1 H) 7.73 (d, \(J = 8.4\) Hz, 2 H) 7.60 (d, \(J = 8.4\) Hz, 2 H) 7.54 (d, \(J = 7.8\) Hz, 2 H) 7.28 (d, \(J = 8.1\) Hz, 2 H) 3.66 (s, 4 H) 2.70-2.64 (m, 2 H) 2.46 (s, 3 H) 1.97-1.91 (m, 2 H); \(^{13}\)C NMR (125 MHz, CD\(_3\)OD): \(\delta\) 164.08, 141.85, 141.78, 141.43, 139.84, 135.57, 131.09, 129.88, 128.13, 127.99, 126.90, 62.59, 62.00, 58.33, 52.66, 52.61, 34.62, 29.76, 13.56; HRMS calcd. for \(\text{C}_{23}\text{H}_{29}\text{N}_{2}\text{O}_{3}\) (M+H\(^{+}\)) 433.1478, found 433.1485

**Synthesis of 2-amino-2-(hydroxymethyl)-4-(4'-(2-propyloxazol-4-yl)-[1,1’-biphenyl]-4-yl)butyl dihydrogen phosphate (54b)**

![54b](image)

54b was prepared using the same procedure as that described for compound 14a. White solid (50 mg, three steps 45.2% yield)

mp: 110-113 °C; \(^1\)H NMR (300 MHz, CD\(_3\)OD): \(\delta\) 8.09 (s, 1 H) 7.68-7.16 (m, 8 H) 4.97-4.92 (m, 6 H) 3.97-3.56 (m, 4 H) 2.73-2.55 (m, 4 H) 1.95-1.74 (m, 4 H) 0.78 (t, \(J = 7.8\) Hz, 3 H); \(^{13}\)C NMR (100 MHz, CD\(_3\)OD) \(\delta\) 164.60, 143.26, 141.78, 138.45, 135.37, 130.98, 130.08, 129.47, 128.95, 127.97, 126.90, 67.14, 66.57, 63.04, 36.77, 30.79, 30.05, 21.62, 13.92; HRMS calcd. for \(\text{C}_{23}\text{H}_{30}\text{N}_{2}\text{O}_{6}\text{P}\) (M+H\(^{+}\)) 461.1836, found 461.1826

**References**