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 ($S1P_1$) receptor

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IP_1 functional assay

The CHO-$S1P_1$ and CHO-$S1P_3$ cells (purchased from Multispan) were plated into 384-well plates at 7×10^4 cells/well in Stimulation Buffer (containing LiCl). Then different concentrations of test agonists were added into each well and incubated at 37℃ in 5% CO_2 for 2 hours. Then D2-labeled IP_1 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 activitiy

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were dosed through intragastric administration with 1 mg/kg of test compound dissolved in DMSO. 10 μL of blood was withdrawn via tail vein and the peripheral blood lymphocyte counts at the time 0h, 1h, 4h, 8h, 12h and 24h after administration were assessed using MEK-7222K hematology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 $S1P_1$ 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 $S1P_1$ 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 < 0.05kcal/(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.[5] Protomol, a computational representation of the intended binding site to which putative ligands are aligned, is used to guide molecular docking[5]. 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.[6]

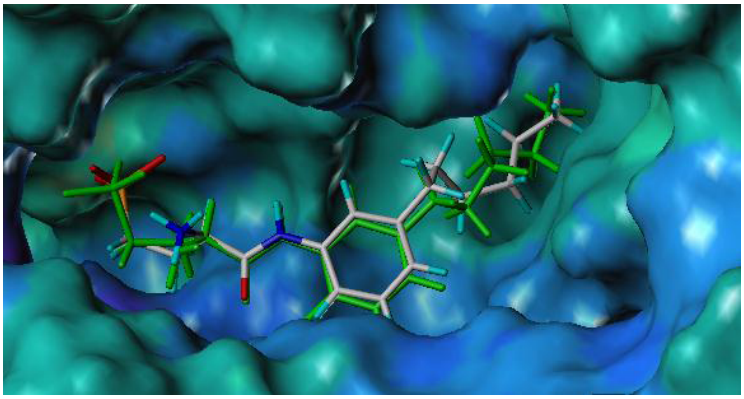


Figure S1 Binding mode of compound ML056 within the binding site of $S1P_1$ receptor. The crystallized ligand is represented in green.

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 $S1P_1$ 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 sp^3 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.[7] 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,

$$A_{F,k}^{q}(j) = -\sum_{i=1}^{n} W_{probe,k} W_{ik} e^{-\alpha r_{iq}^2} \quad (1)$$

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 (α) 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):

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

$$q^2 = 1 - \frac{\sum_{i=1}^{n}(Y_i - \bar{Y})^2}{\sum_{i=1}^{n}(Y_i - Y_{cv})^2} \quad (3)$$

$$SEE = \sqrt{\frac{\sum_{i=1}^{n}(Y_i - Y_{cv})^2}{N}} \quad (4)$$

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,

$$r^2_{pred} = \frac{(SD - PRESS)}{SD} \qquad (5)$$

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 $S1P_1$ agonistic activities of target compounds for COMFA and COMSIA models

Compound	pEC_{50}	COMFA		COMSIA	
		Predicted	Residuals	Predicted	Residuals
3	1.854	1.681	0.173	1.473	0.381
5[a]	0.932	0.698	0.234	0.866	0.066
14a[a]	1.039	0.848	0.191	0.613	0.426
14b	1.432	1.605	-0.173	1.699	-0.267
14c	1.143	1.166	-0.023	0.954	0.189
14d	0.693	0.648	0.045	0.638	0.055
14e[a]	0.467	0.416	0.051	0.425	0.042
14f	0.053	0.035	0.018	0.282	-0.229
14g	0.031	-0.023	0.054	-0.045	0.076
14h	0.097	0.037	0.06	0.156	-0.059
14i[a]	1.178	1.07	0.108	1.316	-0.138
21a[a]	1.067	0.986	0.081	0.931	0.136
21b	0.764	0.838	-0.074	0.688	0.076
21c	0.804	0.801	0.003	0.746	0.058
21d[a]	1.456	1.42	0.036	1.427	0.029
21e[a]	0.595	0.613	-0.018	0.631	-0.036
25a	1.292	1.331	-0.039	1.393	-0.101
25b[a]	0.277	0.405	-0.128	0.19	0.087
25c	0.483	0.427	0.056	0.373	0.11
30a	1.388	1.417	-0.029	1.384	0.004
30b	1.051	1.088	-0.037	1.256	-0.205
30c	1.703	1.693	0.01	1.577	0.126
33	1.318	1.284	0.034	1.447	-0.129
40a	1.178	1.222	-0.044	1.145	0.033
40b	1.277	1.255	0.022	1.327	-0.05
40c	1.854	1.801	0.053	1.857	-0.003
47	1.569	1.538	0.031	1.534	0.035
54a	0.057	0.175	-0.118	0.09	-0.033
54b	0.199	0.22	-0.021	0.264	-0.065

[a] test set

Chemistry

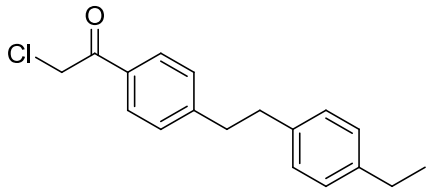
General experimental information

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_2Cl_2 was distilled under Ar_2 from P_2O_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

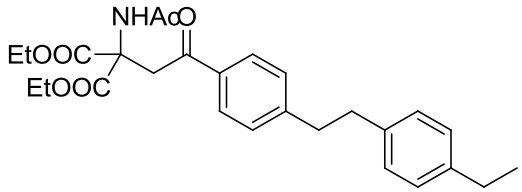
Synthesis of 2-chloro-1-(4-4-ethylphenethyl)phenyl)ethanone (7a)



Chloroacetyl chloride (3.9 g, 34.9 mmol) in CH_2Cl_2(10mL) was added dropwise to a cooled solution (0 ℃) of **6a** (7.0 g, 33.3 mmol) in CH_2Cl_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_2Cl_2 (10mL×3). The combined organic layers were washed with saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_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 ^oC; ^1H 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($M+Na^+$)

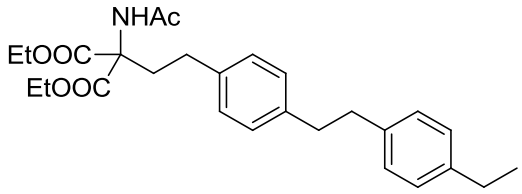
Synthesis of diethyl 2-acetamido-2-(2-(4-(4-ethylphenethyl) phenyl)-2-oxoethyl) malonate (8a):



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

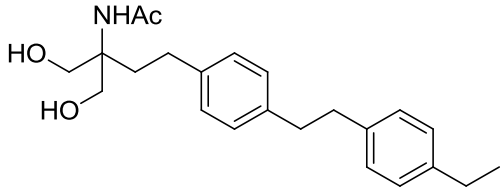
mixture was heated at 70 ℃ for further 12h and concentrated. The residue was diluted with EtOAc(30mL), washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc/PE) to afford compound **8a** (3.0g, 79.3% yield) as yellow syrup.
^{1}H NMR (300 MHz $CDCl_3$): 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):



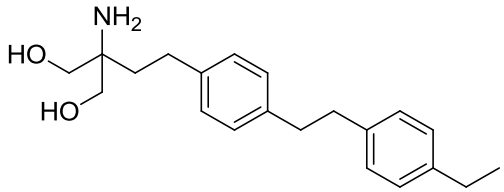
A solution of **8a** (1.6 g, 3.4 mmol) in CH_2Cl_2 (20mL) was added dropwise to a solution of Et_3SiH (1.5 g, 12.8 mmol) in CH_2Cl_2 at room temperature under Ar_2 protection. $TiCl_4$ (2.4 g, 12.8 mmol) was added with a syringe and the reaction mixture was stirred for 12 h at room temperature. The solution was poured slowly into ice water (20mL). The aqueous phase was extracted with CH_2Cl_2(5mL×3). The combined organic layers were washed with brine, dried over Na_2SO_4, 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):



To a solution of **9a** (1.5 g, 3.4 mmol) in EtOH(20mL) was added K_2HPO_4 (6.1 g, 26.8 mmol) buffer and $NaBH_4$ (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. NH_4Cl and EtOAc(20mL). The aqueous phase was extracted with EtOAc(5mL×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH) to afford compound **10a** (1.2g, 98.4% yield) as white solid.
mp: 32-34 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): 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-.93 (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+)

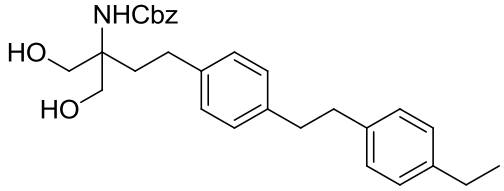
Synthesis of 2-amino-2-(4-(4-ethylphenethyl)phenethyl)propane-1,3-diol (11a):



To a solution of **10a** (0.11 g, 0.3 mmol) in MeOH(5mL) was added NaOH(0.01 g, 0.3 mmol) and heated for 8h 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_2Cl_2/MeOH) to afford compound **11a** (0.1g, 95% yield) as white solid.

mp: 56-58 °C; 1H NMR (300 MHz, CD_3OD): 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_3OD): 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 C21H30NO2 (M+H+) 328.2276, found 328.2278

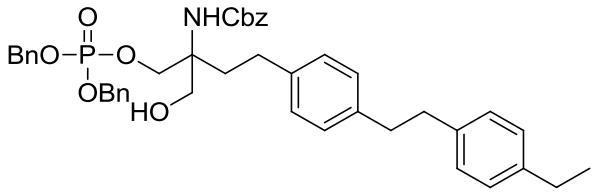
Synthesis of benzyl (4-(4-(4-ethylphenethyl)phenyl)-1-hydroxy-2-(hydroxymethyl) butan-2-yl)carbamate (12a):



To a solution of **11a** (100mg, 0.27mmol)in saturated aq. $NaHCO_3$ and EtOAc mixture(5mL) was added CbzCl(56mg, 0.33mmol). The mixture was stirred for 4h at room temperature. The aqueous phase was extracted with EtOAc(2mL×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH) to afford compound **12a** (100mg, 54.2% yield) as colorless oil.

^{1}H 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+)

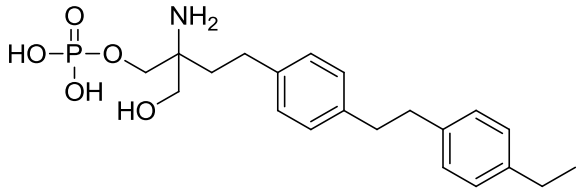
Synthesis of benzyl (1-((bis(benzyloxy)phosphoryl)oxy)-4-(4-(4-ethylphenethyl) phenyl)-2-(hydroxymethyl)butan-2-yl)carbamate (13a):



To a solution of **12a**(100mg, 0.22mmol) in CH_2Cl_2(5mL) was added tetrabenzylpyrophosphate(142mg, 0.26mmol), silver(I) oxide(102mg, 0.44mmol) and tetrahexylammonium iodide(212mg, 0.44mmol). After stirring at room temperature under Ar_2 protection for 20 h, the reaction mixture was filtered through celite to

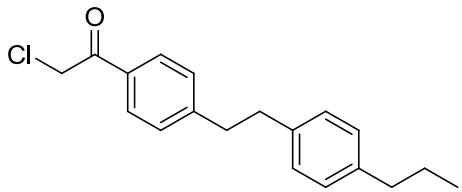
remove insoluble materials, and then the filtrate was concentrated. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH) to afford compound **13a** (60mg, 37.8% yield) as colorless oil.
^{1}H NMR (300 MHz, CD_3COCD_3): δ 7.38-7.05 (m, 23 H) 6.16 (s, 1 H) 5.09-5.05 (m, 6 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):



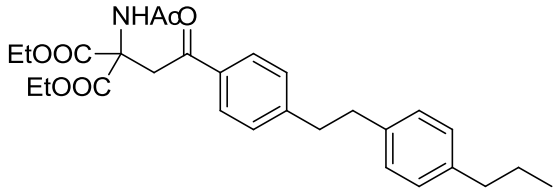
To a solution of **13a** (60mg, 0.08mmol) in MeOH was added 10%Pd/C (600mg) and stirred under H_2 atm for 8h. The reaction mixture was filtered through celite to remove Pd/C and concentrated to afford **14a** (30mg, 92.1% yield) as white solid.
mp: 158-161 ^{o}C ; ^{1}H NMR (300 MHz, CD_3OD): δ 7.16-7.00 (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_3OD): 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 $C_{21}H_{31}NO_5P$ ($M+H^+$) 408.1934, found 408.1915

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



7b was prepared using the same procedure as that described for compound **7a**. Yellow solid(5.4g, 17.5% yield).
mp: 17-19 ^{o}C; ^{1}H NMR (300 MHz, CD_3COCD_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 ($M+Na^+$)

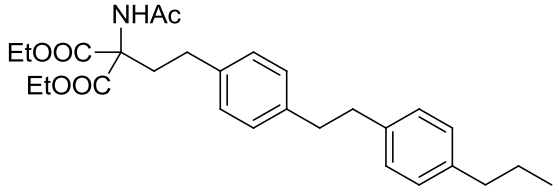
Synthesis of diethyl 2-acetamido-2-(2-oxo-2-(4-(4-propylphenethyl)phenyl)ethyl) malonate (8b)



8b was prepared using the same procedure as that described for compound **8a**.

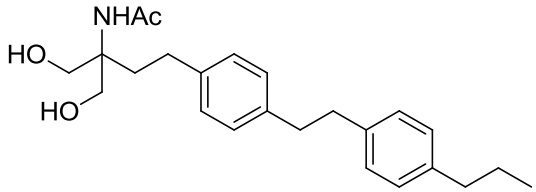
Yellow solid(2.8g, 33.3% yield).
mp: 33-35 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88-7.85 (m, 2 H) 7.26-7.23 (m, 2 H) 7.11-7.04 (m, 4 H) 4.30-4.23 (m, 6 H) 2.98-2.86 (m, 4 H) 2.55 (t, *J* = 7.5 Hz, 2 H) 2.04 (s, 3 H) 1.66-1.58 (m, 2 H) 1.26-1.22 (m, 6 H) 0.93 (t, *J* = 7.2 Hz, 3 H); ESI (m/z) 482 ($M+H^+$) 504 ($M+Na^+$)

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



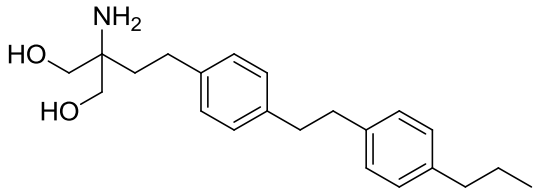
9b was prepared using the same procedure as that described for compound **9a**. Yellow oil(0.8g, 85.6% yield).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.04 (m, 8 H) 6.75 (s, 1 H) 4.32-4.11 (m, 4 H) 2.89-2.77 (m, 4 H) 2.73-2.38 (m, 6 H) 2.05 (s, 3 H) 1.66-1.59 (m, 2 H) 1.38-1.21 (m, 6 H) 0.93 (t, *J* = 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 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): 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 ($M+Na^+$)

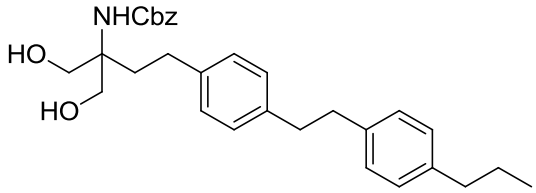
Synthesis of 2-amino-2-(4-(4-propylphenethyl)phenethyl)propane-1,3-diol (11b)



11b was prepared using the same procedure as that described for compound **11a**. White solid(0.27g, 79.6% yield).
mp: 155-158 ^{o}C; ^{1}H NMR (300 MHz, CD_3OD): 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); ^{13}C NMR (100 MHz, CD_3OD): δ

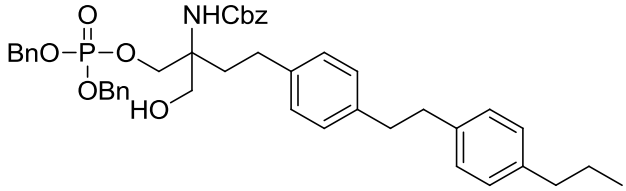
141.16, 140.25, 139.75, 129.77, 129.38, 129.35, 129.15, 62.54, 62.06, 38.76, 38.67, 34.72, 29.69, 25.81, 14.06; HRMS calcd. for $C_{22}H_{32}NO_2$ ($M+H^+$) 342.2433, found 342.2430

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



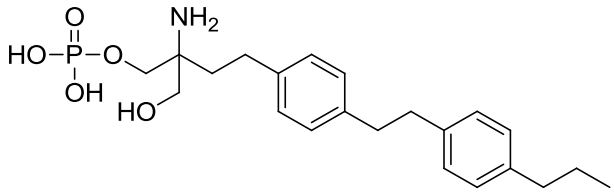
12b was prepared using the same procedure as that described for compound **12a**. Colorless oil(117mg, 65.8% yield).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (s, 4 H) 7.09 (brs, 9 H) 5.28 (s, 1 H) 5.09 (s, 2 H) 3.91 (d, *J* = 12.0 Hz, 2 H) 3.67 (d, *J* = 11.1 Hz, 2 H) 2.85 (s, 4 H) 2.57 (q, *J* = 9.3 Hz, 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(61mg, 33.2% yield).
^{1}H NMR (300 MHz, $CDCl_3$): 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($M+H^+$)

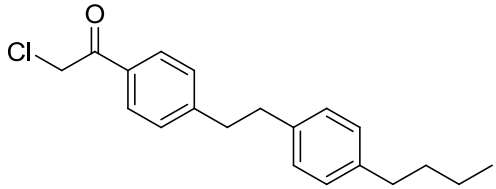
Synthesis of 2-amino-2-(hydroxymethyl)-4-(4-(4-propylphenethyl)phenyl)butyl dihydrogen phosphate (14b)



14b was prepared using the same procedure as that described for compound **14a**. White solid(30mg, 88.2% yield).
mp: 180-183 ^{o}C ; ^{1}H NMR (300 MHz, CD_3OD): 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); ^{13}C NMR (100 MHz, CD_3OD) 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,

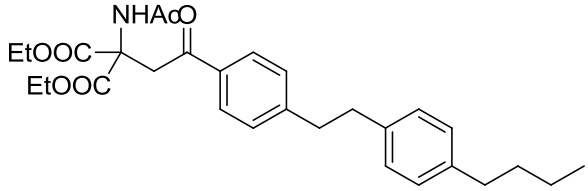
34.88, 29.62, 25.82, 14.06 HRMS calcd. for $C_{22}H_{32}NO_5P(M+H^+)$ 422.2091, found 422.2050

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



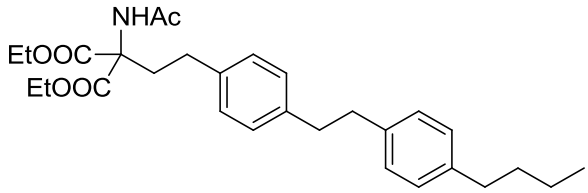
7c was prepared using the same procedure as that described for compound **7a**. Yellow solid(8.1g, 26.1% yield).
mp: 22-25 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.4 Hz, 2 H) 7.28 (d, *J* = 7.8 Hz, 2 H) 7.08 (dd, *J* = 12.0 Hz, 8.7 Hz, 4 H) 4.69 (s, 2 H) 3.00-2.86 (m, 4 H) 2.57 (t, *J* = 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 $(M+H^+)$ 337 $(M+Na^+)$

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



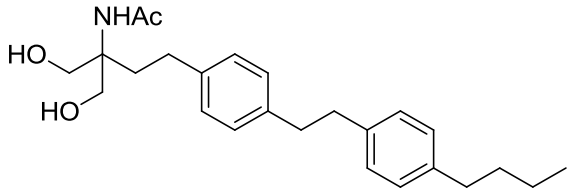
8c was prepared using the same procedure as that described for compound **8a**. Yellow syrup(2.4g, 53.2% yield).
^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, *J* = 7.8 Hz, 2 H) 7.25 (d, *J* = 7.2 Hz, 2 H) 7.11-7.05 (m, 4 H) 4.31-4.20 (m, 6 H) 3.00-2.86 (m, 4 H) 2.58 (t, *J* = 7.8 Hz, 2 H) 1.97 (s, 3 H) 1.64-1.56 (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 $(M+H^+)$ 518 $(M+Na^+)$

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



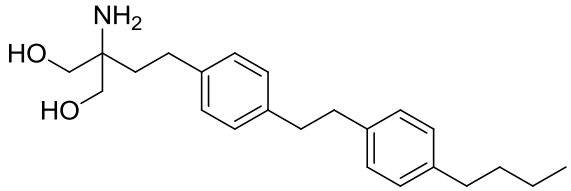
9c was prepared using the same procedure as that described for compound **9a**. Crude prodct as yellow oil(1.3g, 98.2% yield).
ESI (m/z) 482$(M+H^+)$ 504 $(M+Na^+)$

Synthesis of N-(4-(4-(4-butylphenethyl)phenyl)-1-hydroxy-2-(hydroxymethyl) butan-2-yl)acetamide (10c)



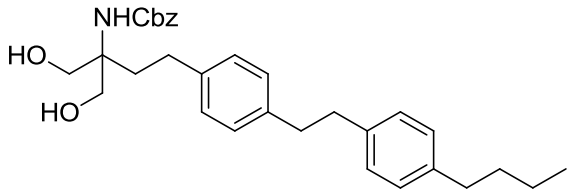
10c was prepared using the same procedure as that described for compound **10a**. White solid(1.0g, 94.3% yield).
mp: 53-54 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12-7.09 (m, 8 H) 5.89 (s, 1 H) 3.86 (d, *J* = 11.7 Hz, 2 H) 3.62 (d, *J* = 11.7 Hz, 2 H) 2.86 (brs, 4 H) 2.66-2.58 (m, 4 H) 1.98-1.93 (m, 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-butylphenethyl)phenethyl)propane-1,3-diol (11c)



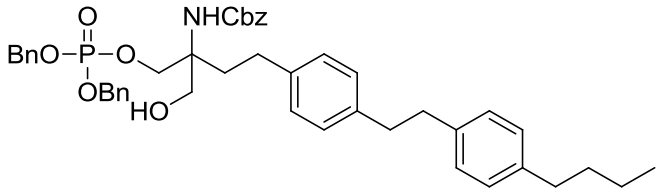
11c was prepared using the same procedure as that described for compound **11a**. White solid(0.3g, 76.7% yield).
mp: 134-137 ^{o}C; ^{1}H NMR (300 MHz, CD_3OD): δ 7.07 (d, *J* = 7.8 Hz, 2 H) 7.03 (d, *J* = 8.1 Hz, 2 H) 6.98 (brs, 4 H) 3.63 (brs, 4 H) 2.78 (brs, 4 H) 2.60-2.47 (m, 4 H) 1.91-1.85 (m, 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_3OD): δ 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-butylphenethyl)phenyl)-1-hydroxy-2-(hydroxymethyl) butan-2-yl)carbamate (12c)



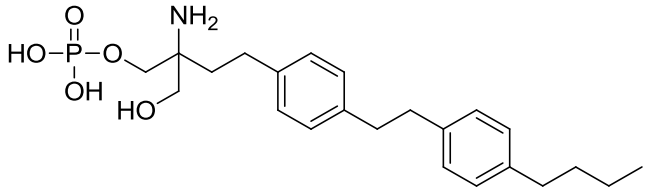
12c was prepared using the same procedure as that described for compound **12a**. Colorless oil(80mg, 64.0% yield).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (brs, 5 H) 7.19-7.10 (m, 8 H) 5.32 (brs, 1 H) 5.09 (s, 2 H) 3.91 (d, *J* = 12.0 Hz, 2 H) 3.67 (d, *J* = 11.7 Hz, 2 H) 2.86 (brs, 4 H) 2.58 (t, *J* = 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-butylphenethyl) phenyl)-2-(hydroxymethyl)butan-2-yl)carbamate (13c)



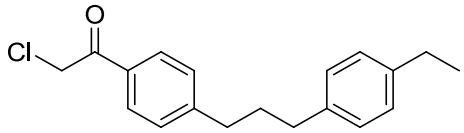
13c was prepared using the same procedure as that described for compound **13a**. Colorless oil(40mg, 33.4% yield).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.07 (m, 23 H) 5.27-4.98 (m, 6 H) 4.11-4.08 (m, 2 H) 3.70-3.68 (m, 2 H) 2.83 (brs, 4 H) 2.55 (t, *J* = 8.1 Hz, 4 H) 1.62-1.54 (m, 2 H) 1.26-1.19 (m, 4 H) 0.90 (t, *J* = 6.0 Hz, 3 H); ESI (m/z) 750($M+H^+$)

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



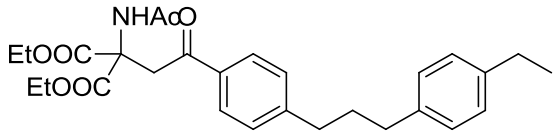
14c was prepared using the same procedure as that described for compound **14a**. White solid(18mg, 82.8% yield).
mp: 182-185 ^{o}C ; ^{1}H NMR (300 MHz, CD_3OD): δ 7.16-6.98 (m, 8 H) 3.93 (t, *J* = 6.3 Hz, 2 H) 3.66 (dd, *J* = 12.9 Hz, 6.9 Hz, 3 H) 2.77 (brs, 4 H) 2.63-2.47 (m, 4 H) 1.95-1.81 (m, 2 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_3OD): δ 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 $C_{23}H_{35}NO_5P$ ($M+H^+$) 436.2247, found 436.2233

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



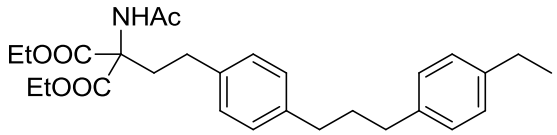
7d was prepared using the same procedure as that described for compound **7a**. White solid(7.1g, 23.8% yield).
mp: 18-20 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.4 Hz, 2 H) 7.30 (d, *J* = 8.4 Hz, 2 H) 7.11 (dd, *J* = 12.3 Hz, 8.4 Hz, 4 H) 4.69 (s, 2 H) 2.71 (t, *J* = 7.5 Hz, 2 H) 2.66-2.58 (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)



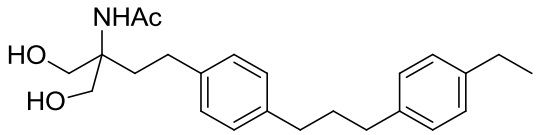
8d was prepared using the same procedure as that described for compound **8a**. Yellow solid(4.0g, 37.6% yield).
mp: 31-34 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.4 Hz, 2 H) 7.27 (d, *J* = 8.4 Hz, 2 H) 7.14-7.07 (m, 4 H) 4.30-4.23 (m, 6 H) 2.69 (t, *J* = 7.2 Hz, 2 H) 2.66-2.58 (m, 4 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-(3-(4-ethylphenyl)propyl)phenethyl) malonate (9d)



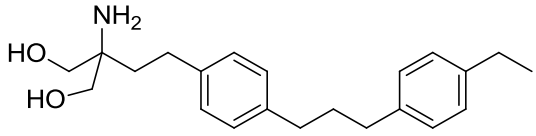
9d was prepared using the same procedure as that described for compound **9a**. Yellow oil(2.1g, 89.9% yield).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.03 (m, 8 H) 6.76 (s, 1 H) 4.29-4.11 (m, 4 H) 2.87-2.57 (m, 8 H) 2.44 (d, *J* = 6.9 Hz, 2 H) 1.99 (s, 3 H) 2.10-1.91 (m, 2 H) 1.31-1.17 (m, 9 H); ESI (m/z) 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)



10d was prepared using the same procedure as that described for compound **10a**. White solid(1.2g, 44.8% yield).
mp: 42-44^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 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 ($M+Na^+$)

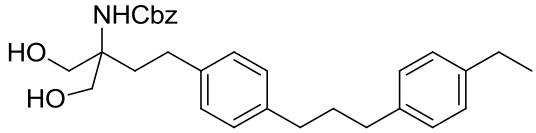
Synthesis of 2-amino-2-(4-(3-(4-ethylphenyl)propyl)phenethyl)propane-1,3-diol (11d)



11d was prepared using the same procedure as that described for compound **11a**. White solid(0.75g, 73.3% yield).
mp: 55-57 ^{o}C; ^{1}H NMR (300 MHz, CD_3OD): δ 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_3OD): δ 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 $C_{22}H_{32}NO_2$

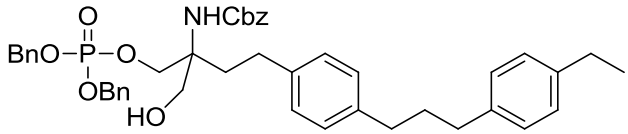
$(M+H^+)$ 342.2433, found 342.2433

Synthesis of benzyl (4-(4-(3-(4-ethylphenyl)propyl)phenyl)-1-hydroxy-2-(hydroxymethyl)butan-2-yl)carbamate (12d)



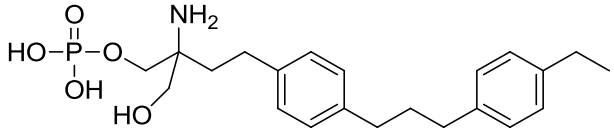
12d was prepared using the same procedure as that described for compound **12a**. Colorless oil(70mg, 66.9% yield).
^{1}H NMR (300 MHz, CD_3COCD_3): δ 7.38-7.25 (m, 8 H) 7.09-7.07 (m, 7 H) 5.04 (s, 2 H) 3.79 (d, *J* = 11.1 Hz, 2 H) 3.68 (d, *J* = 11.1 Hz, 2 H) 2.62-2.53 (m, 8 H) 2.03-1.86 (m, 4 H) 1.16 (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)



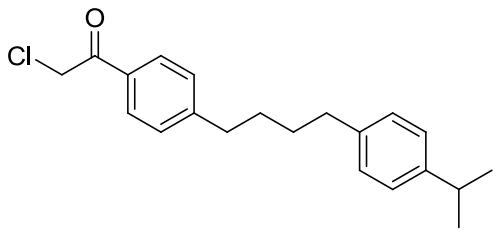
13d was prepared using the same procedure as that described for compound **13a**. Colorless oil(40mg, 36.3% yield).
^{1}H NMR (300 MHz, CD_3COCD_3): δ 7.37-7.24 (m, 15 H) 7.10-7.08 (m, 8 H) 5.08-5.04 (m, 6 H) 4.37-4.22 (m, 2 H) 3.74 (q, *J* = 11.1 Hz, 2 H) 2.61-2.54 (m, 8 H) 2.05-1.86 (m, 4 H) 1.17 (t, *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)



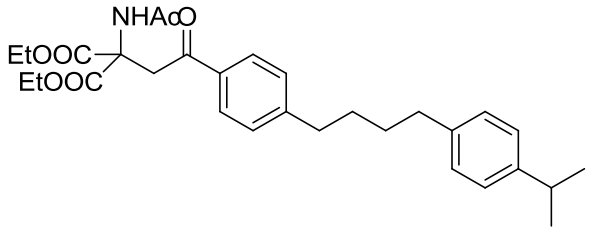
14d was prepared using the same procedure as that described for compound **14a**. White solid(18mg, 79.2% yield).
mp: 155-158 ^{o}C ; ^{1}H NMR (300 Hz, CD_3OD): δ 7.09-7.02 (m, 8 H) 3.93 (brs, 2 H) 3.64 (brs, 2 H) 2.62-2.53 (m, 8 H) 1.85-1.83 (m, 4 H) 1.15 (t, *J* = 7.8 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD): δ 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 $C_{22}H_{33}NO_5P$ $(M+H^+)$ 422.2091, found 422.2084

Synthesis of 2-chloro-1-(4-(4-(4-isopropylphenyl)butyl)phenyl)ethanone (7e)



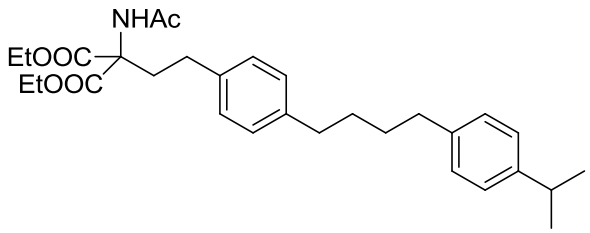
7e was prepared using the same procedure as that described for compound **7a**. Crude product as yellow oil(14g, 93.3% yield).
ESI (m/z) 329 ($M+H^+$); 351($M+Na^+$)

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



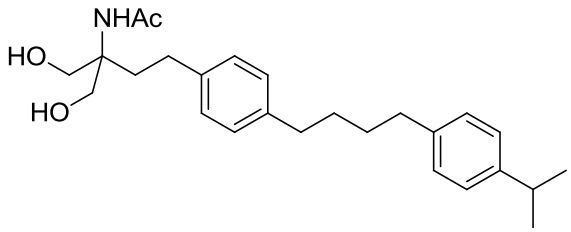
8e was prepared using the same procedure as that described for compound **8a**. Yellow solid(4g, 19.9% yield).
mp: 26-28 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, *J* = 6.0 Hz, 2 H) 7.24 (d, *J* = 6.0 Hz, 2 H) 7.13 (d, *J* = 6.0 Hz, 1 H) 7.08 (t, *J* = 8.4 Hz, 2 H) 4.29-4.23 (q, 6 H) 2.88-2.85 (m, 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-(4-isopropylphenyl)butyl)phenethyl) malonate (9e)



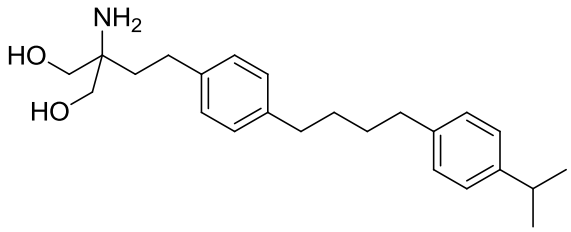
9e was prepared using the same procedure as that described for compound **9a**. Crude product as yellow oil(2.0g, 98.0% yield).
ESI (m/z) 496 ($M+H^+$); 518($M+Na^+$)

Synthesis of N-(1-hydroxy-2-(hydroxymethyl)-4-(4-(4-(4-isopropylphenyl)butyl) phenyl)butan-2-yl)acetamide (10e)



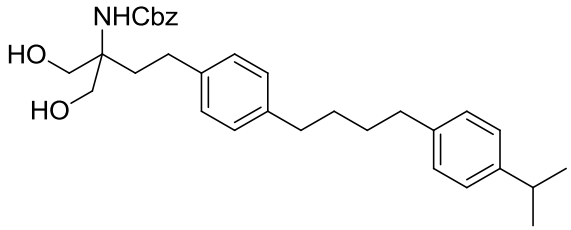
10e was prepared using the same procedure as that described for compound **10a**. White solid(0.3g, 14.3% yield).
mp: 28-30 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (s, 4 H) 7.14-7.06 (q, 4 H) 5.77 (s, 1 H) 3.87 (d, *J* = 11.4 Hz, 2 H) 3.68 (s, 2 H) 3.62 (d, *J* = 11.7 Hz, 2 H) 2.91-2.82 (m, 1 H) 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(0.11g, 42.2% yield).
mp: 160-162 ^{o}C; ^{1}H NMR (300 MHz, CD_3OD): δ 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_3OD): δ 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

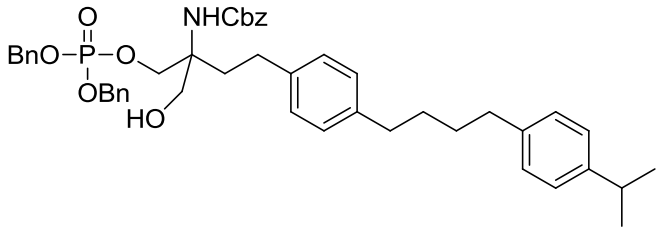
Synthesis of benzyl (1-hydroxy-2-(hydroxymethyl)-4-(4-(4-(4-isopropylphenyl) butyl)phenyl)butan-2-yl)carbamate (12e)



12e was prepared using the same procedure as that described for compound **12a**. Colorless oil(70mg, 69.6% yield).
^{1}H NMR (300 MHz, $CDCl_3$): δ 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 ($M+H^+$);

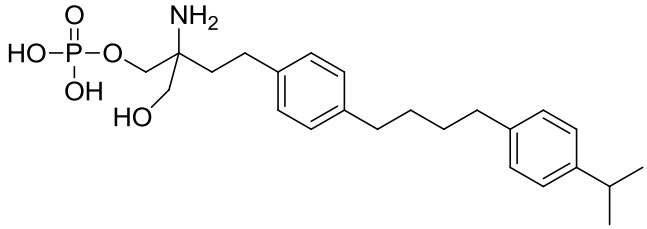
Synthesis of benzyl (1-((bis(benzyloxy)phosphoryl)oxy)-2-(hydroxymethyl)-4-

(4-(4-(4-isopropylphenyl)butyl)phenyl)butan-2-yl)carbamate (13e)



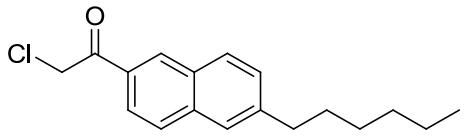
13e was prepared using the same procedure as that described for compound **13a**. Crude product as colorless oil(30mg, 28.0% yield).
ESI (m/z) 764 ($M+H^+$);

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



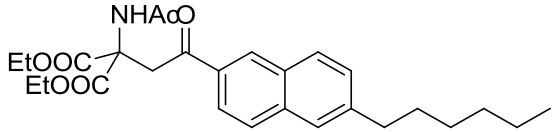
14e was prepared using the same procedure as that described for compound **14a**. White solid(12mg, 68.5% yield).
mp: 145-148 ^oC; ^1H NMR (300 MHz, CD_3OD) δ 7.09-6.97 (m, 8 H) 3.93-3.84 (m, 2 H) 3.63 (dd, *J* = 15.3 Hz, 8.4 Hz, 2 H) 2.80-2.73 (m, 1 H) 2.61-2.51 (m, 6 H) 1.90-1.86 (m, 2 H) 1.54 (brs, 4 H) 1.15 (d, *J* = 6.9 Hz, 6 H); ^{13}C NMR (100 MHz, CD_3OD): 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 $C_{24}H_{37}NO_5P$ ($M+H^+$) 450.2404, found 450.2403

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



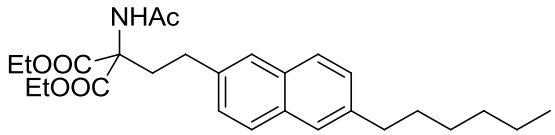
7f was prepared using the same procedure as that described for compound **7a**. Yellow oil(6.0g, 23.9% yield).
1H NMR (300 MHz, $CDCl_3$): δ 8.43 (s, 1 H) 8.02-7.73 (m, 3 H) 7.65 (s, 1 H) 7.50-7.41 (q, 1 H) 4.79 (s, 2 H) 3.09 (t, *J* = 7.8 Hz, 2 H) 1.73-1.68 (m, 2 H) 1.32 (brs, 6 H) 0.88 (t, *J* = 6.3 Hz, 3 H); ESI (m/z) 289 ($M+H^+$) 311 ($M+Na^+$)

Synthesis of diethyl 2-acetamido-2-(2-(6-hexylnaphthalen-2-yl)-2-oxoethyl) malonate (8f)



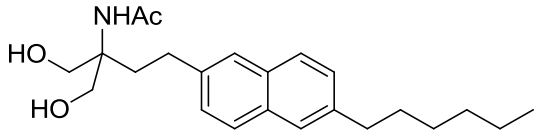
8f was prepared using the same procedure as that described for compound **8a**. Yellow oil(3.4g, 17.9% yield).
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.48 (s, 1 H) 7.99-7.73 (m, 3 H) 7.63 (s, 1 H) 7.42 (d, *J* = 8.1 Hz, 1 H) 7.15 (s, 1 H) 4.39-4.25 (m, 6 H) 2.79 (t, *J* = 7.2 Hz, 2 H) 1.97 (s, 3 H) 1.73-1.67 (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-hexylnaphthalen-2-yl)ethyl)malonate (9f)



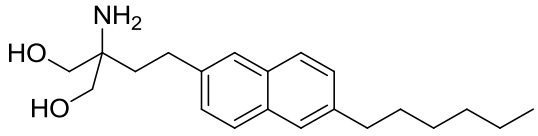
9f was prepared using the same procedure as that described for compound **9a**. Yellow oil(0.8g, 33.2% yield).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.8 Hz, 2 H) 7.54 (s, 2 H) 7.31-7.22 (m, 2 H) 6.79 (s, 1 H) 4.25-4.14 (m, 4 H) 2.80-2.71 (m, 4 H) 2.65-2.60 (m, 2 H) 1.97 (s, 3 H) 1.70-1.65 (m, 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-hexylnaphthalen-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 sollid(1.1g, 71.9% yield).
mp: 50-51 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): 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 (brs, 6 H) 0.87 (brs, 3 H); ESI (m/z) 372 ($M+H^+$) 394 ($M+Na^+$)

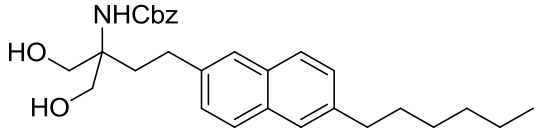
Synthesis of 2-amino-2-(2-(6-hexylnaphthalen-2-yl)ethyl)propane-1,3-diol (11f)



11f was prepared using the same procedure as that described for compound **11a**. White sollid(0.58g, 60.9% yield).
mp: 175-178 ^{o}C; ^{1}H NMR (300 MHz, CD_3OD): 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 (brs, 6 H) 0.85-0.81 (m, 3 H); ^{13}C NMR (100 MHz, CD_3OD): δ 141.14, 139.00, 133.86, 133.65, 128.73, 128.58, 128.36, 127.93, 127.10, 127.08,

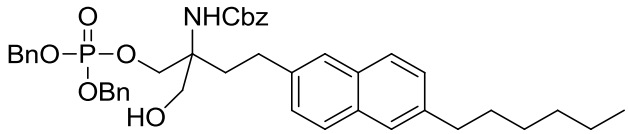
62.56, 62.12, 37.00, 34.56, 32.89, 32.56, 30.20, 30.07, 23.67, 14.40; HRMS calcd. for $C_{21}H_{32}NO_2$ ($M+H^+$) 330.2427, found 330.2424

Synthesis of benzyl (4-(6-hexylnaphthalen-2-yl)-1-hydroxy-2-(hydroxymethyl) butan-2-yl)carbamate (12f)



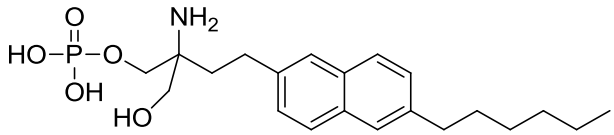
12f was prepared using the same procedure as that described for compound **12a**. Colorless oil(110mg, 79.2% yield).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 7.5 Hz, 5.4 Hz, 2 H) 7.54 (s, 2 H) 7.34-7.25 (m, 7 H) 5.07 (s, 2 H) 3.94 (d, *J* = 11.1 Hz, 2 H) 3.70 (d, *J* = 11.4 Hz, 2 H) 2.76-2.73 (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-hexylnaphthalen-2 -yl)-2-(hydroxymethyl)butan-2-yl)carbamate (13f)



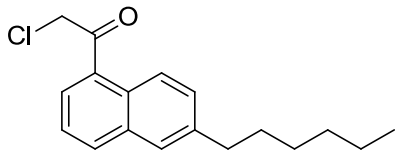
13f was prepared using the same procedure as that described for compound **13a**. Colorless oil(70mg, 40.3% yield).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.19 (m, 21 H) 5.11-5.00 (m, 6 H) 4.16-3.69 (m, 4 H) 2.74 (t, *J* = 7.2 Hz, 4 H) 2.02-1.66 (m, 4 H) 1.31 (brs, 6 H) 0.88 (brs, 3 H); ESI (m/z) 724($M+H^+$)

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



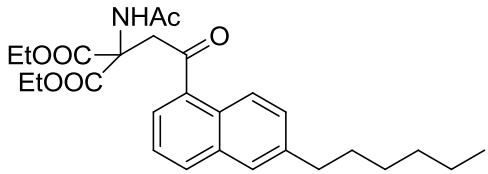
14f was prepared using the same procedure as that described for compound **14a**. White solid(38mg, 95.8% yield).
mp: 118-120 ^{o}C ; ^{1}H NMR (300 MHz, CD_3OD) δ 7.66-7.21 (m, 6 H) 4.08-3.64 (m, 4 H) 2.68 (t, *J* = 7.5 Hz, 4 H) 2.08-2.05 (m, 2 H) 1.64-1.61 (m, 2 H) 1.28 (brs, 6 H) 0.84 (brs, 3 H); ^{13}C NMR (100 MHz, CD_3OD): 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 $C_{21}H_{33}NO_5P$ ($M+H^+$) 410.2091, found 410.2085

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



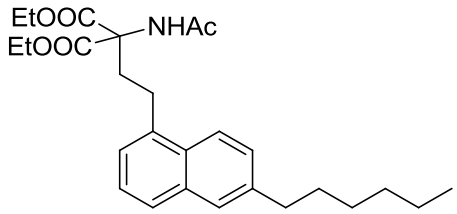
7g was prepared using the same procedure as that described for compound **7a**. Yellow oil(15.9g, 63.5%).
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (d, *J* = 7.8 Hz, 1 H) 7.83-7.81 (m, 2 H) 7.70 (s, 1 H) 7.58-7.50 (m, 2 H) 4.78 (s, 2 H) 2.80 (t, *J* = 7.5 Hz, 2 H) 1.74-1.66 (m, 2 H) 1.33 (brs, 6 H) 0.89 (t, *J* = 6.3 Hz, 3 H); ESI (m/z) 289 ($M+H^+$) 311 ($M+Na^+$)

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



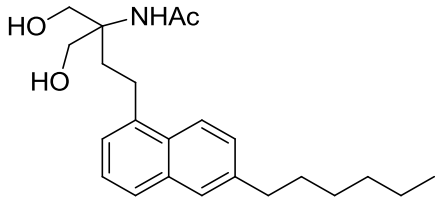
8g was prepared using the same procedure as that described for compound **8a**. Yellow oil(2.4g, 12.6%).
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (d, *J* = 9.0 Hz, 1 H) 7.84-7.78 (m, 2 H) 7.50 (t, *J* = 4.5 Hz, 1 H) 7.30-7.08 (m, 2 H) 7.02 (s, 1 H) 4.37-4.30 (m, 6 H) 2.82-2.59 (m, 2 H) 2.00 (s, 3 H) 1.67 (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-hexylnaphthalen-1-yl)ethyl)malonate (9g)



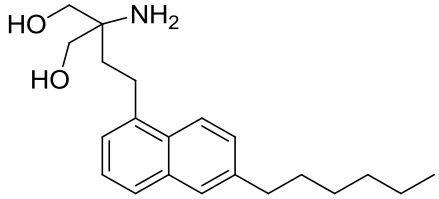
9g was prepared using the same procedure as that described for compound **9a**. Yellow oil(0.9g, 37.3% yield).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.4 Hz, 1 H) 7.66 (m, 2 H) 7.33-7.23 (m, 3 H) 6.91 (s, 1 H) 4.31-4.10 (m, 4 H) 2.95-2.91 (m, 2 H) 2.85-2.74 (m, 4 H) 2.07 (s, 3 H) 1.72-1.65 (m, 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-hexylnaphthalen-1-yl)-1-hydroxy-2-(hydroxymethyl)butan -2-yl)acetamide (10g)



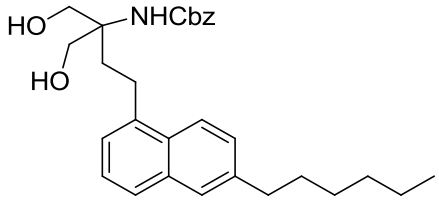
10g was prepared using the same procedure as that described for compound **10a**. Yellow oil(0.4g, 19.3%).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81-7.66 (m, 3 H) 7.35-7.30 (m, 3 H) 5.93 (s, 1 H) 3.96 (d, *J* = 11.4 Hz, 2 H) 3.65 (d, *J* = 11.7 Hz, 2 H) 3.10 (t, *J* = 8.1 Hz, 2 H) 2.80 (t, *J* = 7.5 Hz, 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-hexylnaphthalen-1-yl)ethyl)propane-1,3-diol (11g)



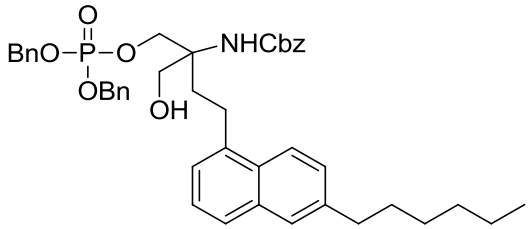
11g was prepared using the same procedure as that described for compound **11a**. White solid(0.25g, 69.4%).
mp: 140-142 ^{o}C; ^{1}H NMR (300 MHz, CD_3OD): δ 7.86 (s, 1 H) 7.71 (d, *J* = 8.7 Hz, 1 H) 7.63-7.60 (m, 1 H) 7.28-7.23 (m, 3 H) 3.75 (s, 4 H) 3.11-3.05 (m, 2 H) 2.75 (t, *J* = 7.5 Hz, 2 H) 2.05-1.99 (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_3OD): 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-hexylnaphthalen-1-yl)-1-hydroxy-2-(hydroxymethyl) butan-2-yl)carbamate (12g)



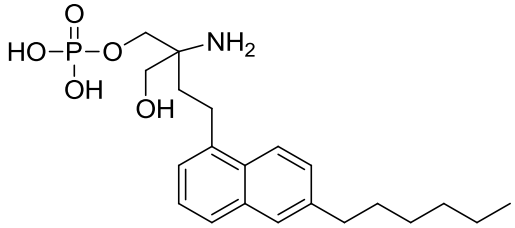
12g was prepared using the same procedure as that described for compound **12a**. Colorless oil(90mg, 94.1%).
^{1}H NMR (300 MHz, CD_3COCD_3): δ 8.06 (s, 1 H) 7.77 (d, *J* = 8.7 Hz, 1 H) 7.68-7.62 (m, 1 H) 7.42-7.28 (m, 8 H) 5.11 (s, 2 H) 3.90 (d, *J* = 10.8 Hz, 2 H) 3.77 (d, *J* = 10.8 Hz, 2 H) 3.15-3.09 (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-hexylnaphthalen -1-yl)-2-(hydroxymethyl)butan-2-yl)carbamate (13g)



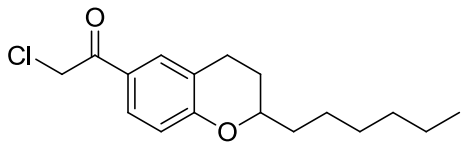
13g was prepared using the same procedure as that described for compound **13a**. Colorless oil(50mg, 43.2% yield).
^{1}H NMR (300 MHz, CD_3COCD_3): δ 8.02 (s, 1 H) 7.79 (d, *J* = 8.4 Hz, 1 H) 7.68 (dd, J = 7.2 Hz, 2.7 Hz, 1 H) 7.39-7.28 (m, 18 H) 5.17-5.03 (m, 6 H) 4.42 (dd, *J* = 10.2 Hz, 6.6 Hz, 1 H) 4.30 (dd, *J* = 10.2 Hz, 6.6 Hz, 1 H) 3.86 (q, *J* = 11.4 Hz, 2 H) 3.11 (dd, *J* = 9.9 Hz, 8.1 Hz, 2 H) 2.78 (t, *J* = 7.8 Hz, 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); ESI (m/z) 724($M+H^+$)

Synthesis of 2-amino-4-(6-hexylnaphthalen-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_3OD): δ 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 (brs, 2 H) 3.76 (brs, 2 H) 3.06 (brs, 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 (brs, 6 H) 0.81 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD): δ 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 $C_{21}H_{33}NO_5P$ ($M+H^+$) 410.2091, found 410.2093

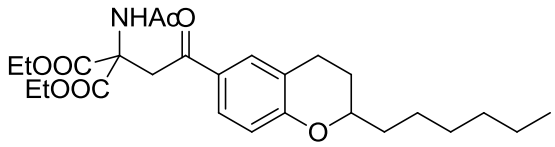
Synthesis of 2-chloro-1-(2-hexylchroman-6-yl)ethanone (7h)



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, $CDCl_3$): δ 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 ($M+Na^+$)

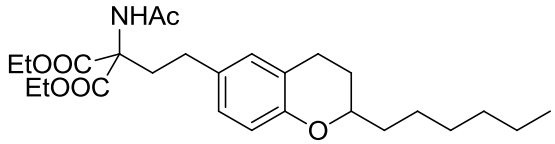
Synthesis of diethyl 2-acetamido-2-(2-(2-hexylchroman-6-yl)-2-oxoethyl)

malonate (8h)



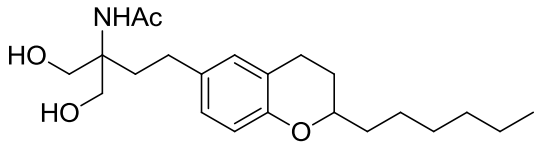
8h was prepared using the same procedure as that described for compound **8a**. Yellow syrup(5.0g, 40.8%).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72-7.70 (m, 2 H) 7.09 (s, 1 H) 6.81 (d, *J* = 9.0 Hz, 1 H) 4.29-4.22 (q, 4 H) 4.18 (s, 2 H) 4.13-4.04 (m, 1 H) 2.84-2.79 (m, 2 H) 2.00 (brs, 1 H) 1.96 (s, 3 H) 1.74-1.28 (m, 11 H) 1.24 (t, *J* = 6.9 Hz, 6 H) 0.89 (t, *J* = 6.9 Hz, 3 H); ESI (m/z) 476 ($M+H^+$) 498 ($M+Na^+$)

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



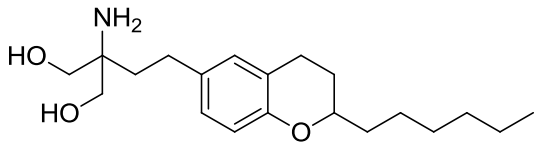
9h was prepared using the same procedure as that described for compound **9a**. Crude product as yellow oil(2.5g, 96.2% yield).
ESI (m/z) 462 ($M+H^+$) 484 ($M+Na^+$)

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(1.2g, 36.6% yield).
mp: 46-49 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): 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 ($M+Na^+$)

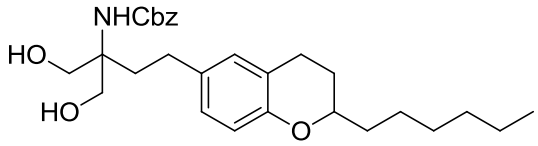
Synthesis of 2-amino-2-(2-(2-hexylchroman-6-yl)ethyl)propane-1,3-diol (11h)



11h was prepared using the same procedure as that described for compound **11a**. White solid(0.4g, 54.1% yield).
mp: 56-59 ^{o}C; ^{1}H NMR (300 MHz, CD_3OD): 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); ^{13}C NMR (100MHz, CD_3OD):

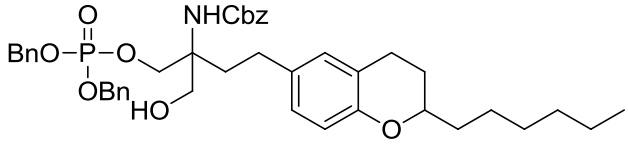
δ ; HRMS calcd. for $C_{20}H_{34}NO_3$ ($M+H^+$) 336.2538, found 336.2536

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



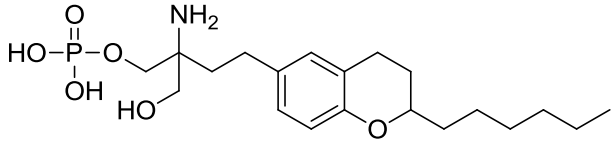
12h was prepared using the same procedure as that described for compound **12a**. Colorless oil(150mg, 88.8% yield).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (brs, 5 H) 6.89-6.83 (m, 2 H) 6.66-6.54 (m, 1 H) 5.09 (s, 2 H) 4.18-4.08 (m, 1 H) 3.90 (d, *J* = 11.7 Hz, 2 H) 3.67 (d, *J* = 11.4 Hz, 2 H) 2.54-1.23 (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)



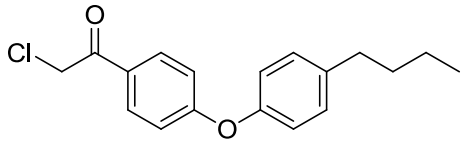
13h was prepared using the same procedure as that described for compound **13a**. Colorless oil(70mg, 30.0% yield).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.31 (m, 18 H) 5.17-5.00 (m, 6 H) 3.82-3.55 (m, 5 H) 2.60-1.28 (m, 18 H) 0.85 (t, *J* = 4.5 Hz, 3 H); ESI (m/z) 730 ($M+H^+$)

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



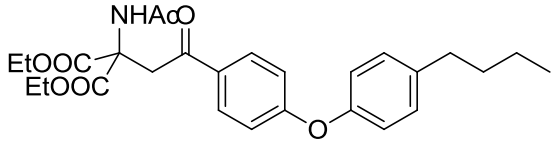
14h was prepared using the same procedure as that described for compound **14a**. White solid(30mg, 75.3% yield).
mp: 115-118 ^{o}C ; ^{1}H NMR (300 MHz, CD_3OD): δ 7.29-6.79 (m, 3 H) 3.96-3.61 (m, 5 H) 3.06-2.52 (m, 5 H) 1.89-1.24 (m, 13 H) 0.87 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD): 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 $C_{20}H_{35}NO_6P$ ($M+H^+$) 416.2197, found 416.2173

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



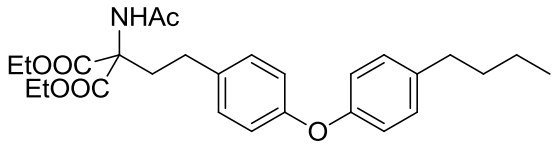
7i was prepared using the same procedure as that described for compound **7a**. Yellow oil(14.2g, 95.9% yield).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.7 Hz, 2 H) 7.21 (d, *J* = 8.1 Hz, 2 H) 6.99 (dd, *J* = 8.7 Hz, 2.7 Hz, 4 H) 4.65 (s, 2 H) 2.63 (t, *J* = 7.8 Hz, 2 H) 1.67-1.57 (m, 2 H) 1.42-1.34 (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-butylphenoxy)phenyl)-2-oxoethyl) malonate (8i)



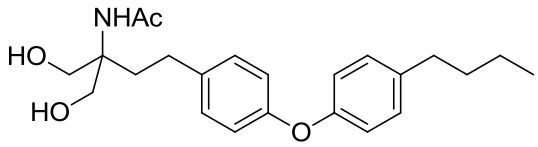
8i was prepared using the same procedure as that described for compound **8a**. Yellow solid(6.9g, 30.4% yield).
mp: 160-163 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.4 Hz, 2 H) 7.20 (d, *J* = 8.1 Hz, 2 H) 7.11 (brs, 1 H) 6.97 (d, *J* = 8.7 Hz, 4 H) 4.27 (dd, *J* = 14.1 Hz, 7.2 Hz, 4 H) 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-butylphenoxy)phenethyl)malonate (9i)



9i was prepared using the same procedure as that described for compound **9a**. White solid(1.78g, 90.4% yield).
mp: 145-148 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$): 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 ($M+Na^+$)

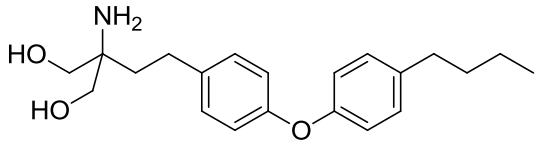
Synthesis of N-(4-(4-(4-butylphenoxy)phenyl)-1-hydroxy-2-(hydroxymethyl) butan-2-yl)acetamide (10i)



10i was prepared using the same procedure as that described for compound **10a**. White solid(0.65g, 46.9% yield).
mp: 140-143 ^{o}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)

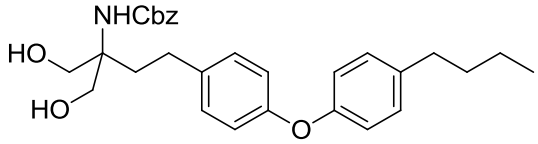
1.42-1.29 (m, 2 H) 0.93 (t, *J* = 7.5 Hz, 3 H); ESI (m/z) 386 ($M+H^+$)

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



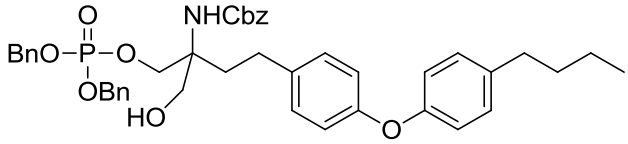
11i was prepared using the same procedure as that described for compound **11a**. White solid(0.51g, 89.0% yield).
mp: 146-150 ^oC; ^1H NMR (300 MHz, CD_3OD): δ 7.17 (d, *J* = 8.4 Hz, 2 H) 7.11 (d, *J* = 8.7 Hz, 2 H) 6.83 (dd, *J* = 8.4 Hz, 2.1 Hz, 4 H) 3.47 (q, *J* = 10.8 Hz, 4 H) 2.64-2.53 (m, 4 H) 1.66-1.51 (m, 4 H) 1.40-1.30 (m, 2 H) 0.92 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD): 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 $C_{21}H_{30}NO_3$ ($M+H^+$) 344.2220, found 360.2223

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



12i was prepared using the same procedure as that described for compound **12a**. Colorless oil(120mg, 96.7% yield).
^1H NMR (300 MHz, $CDCl_3$): 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 ($M+H^+$)

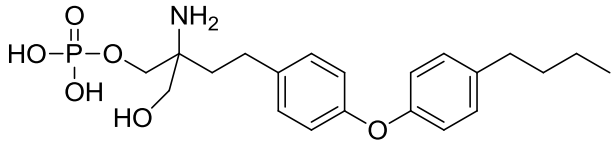
Synthesis of benzyl (1-((bis(benzyloxy)phosphoryl)oxy)-4-(4-(4-butylphenoxy) phenyl)-2-(hydroxymethyl)butan-2-yl)carbamate (13i)



13i was prepared using the same procedure as that described for compound **13a**. Colorless oil(70mg, 38.0% yield).
^1H NMR (300 MHz, $CDCl_3$): 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 ($M+H^+$)

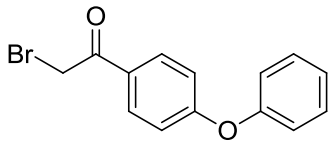
Synthesis of 2-amino-4-(4-(4-butylphenoxy)phenyl)-2-(hydroxymethyl)butyl

dihydrogen phosphate (14i)



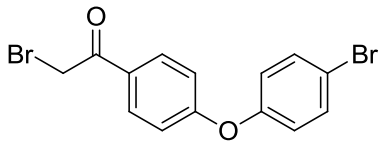
14i was prepared using the same procedure as that described for compound **14a**. White solid(25mg, 61.6% yield).
mp: 190-193 ^{o}C ; ^{1}H NMR (300 MHz, CD_3OD): δ 7.16 (d, *J* = 8.1 Hz, 2 H) 7.08 (d, *J* = 8.1 Hz, 2 H) 6.80 (t, *J* = 6.9 Hz, 4 H) 3.96 (s, 2 H) 3.66 (s, 2 H) 2.63-2.50 (m, 4 H) 1.95-1.90 (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_3OD): 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 $C_{21}H_{31}NO_6P$ ($M+H^+$) 424.1884, found 424.1869

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



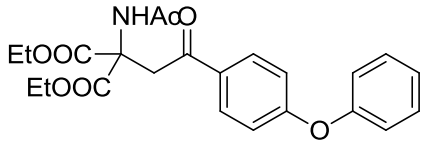
Bromoacetyl bromide (23.7g, 115.0mmol) in CH_2Cl_2 (50mL) was added dropwise to a cooled solution (0 ℃) of **15** (19.6g, 115.0mmol) in CH_2Cl_2 (150mL), then $AlCl_3$ (16.1g, 121.0mmol) was added in portions in 30min. The solution was then allowed to return to room temperature and stirred for further 2 h. The mixture was poured slowly into 2NHCl-ice mixture (100mL) and stirred for 2 h. The aqueous phase was extracted with CH_2Cl_2(20mL×3). The combined organic layers were washed with saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_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):



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 ($M+Na^+$)

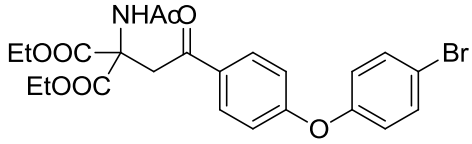
Synthesis of diethyl 2-acetamido-2-(2-oxo-2-(4-phenoxyphenyl)ethyl)malonate (17, X=H)



17(X=H) was prepared using the same procedure as that described for compound **8a**. Yellow oil(3.6g, 49.0% yield)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 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 $(M+Na^+)$

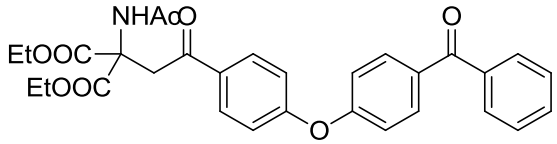
Synthesis of diethyl 2-acetamido-2-(2-(4-(4-bromophenoxy)phenyl)-2-oxoethyl) malonate (17, X=Br)



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

^{1}H NMR (300 MHz, $CDCl_3$) δ: 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-(4-benzoylphenoxy)phenyl)-2-oxoethyl) malonate (18a)

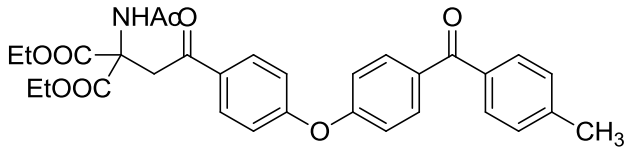


Benzoyl chloride (0.36 g, 2.58 mmol) in CH_2Cl_2(3mL) was added dropwise to a cooled solution (0 ℃) of **17**(X=H) (1.0 g, 2.34 mmol) in CH_2Cl_2(10mL), then $AlCl_3$ (1.56 g, 11.7 mmol) was added in portions in 30min. The solution was then allowed to return to room temperature and stirred for further 4 h. The mixture was poured slowly into 2NHCl-ice mixture(10mL) and stirred for 2 h. The aqueous phase was extracted with CH_2Cl_2(3mL×3). The combined organic layers were washed with saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc/PE) to afford compound **18a**(0.65g, 52.0% yield) as brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 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-(4-methylbenzoyl)phenoxy)

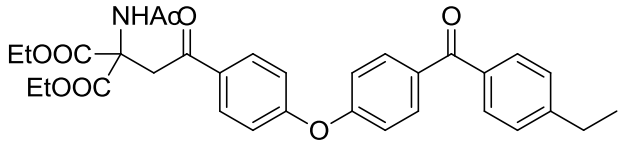
phenyl)-2-oxoethyl)malonate (18b)



18b was prepared using the same procedure as that described for compound **18a**. Yellow oil(0.55g, 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 $(M+H)^+$

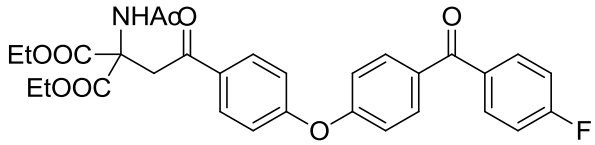
Synthesis of diethyl 2-acetamido-2-(2-(4-(4-(4-ethylbenzoyl)phenoxy)phenyl) -2-oxoethyl)malonate (18c)



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

mp:72-74 ^{o}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 $(M+H)^+$

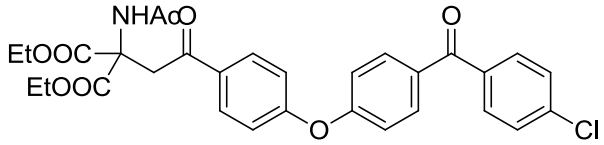
Synthesis of diethyl 2-acetamido-2-(2-(4-(4-(4-fluorobenzoyl)phenoxy)phenyl) -2-oxoethyl)malonate (18d)



18d was prepared using the same procedure as that described for compound **18a**. Yellow oil(0.68g, 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 $(M+H)^+$

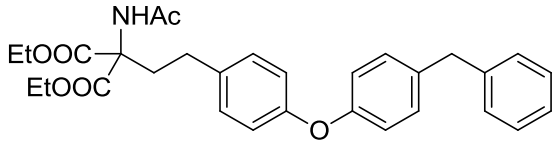
Synthesis of diethyl 2-acetamido-2-(2-(4-(4-(4-chlorobenzoyl)phenoxy)phenyl)-2-oxoethyl)malonate (18e)



18e was prepared using the same procedure as that described for compound **18a**. Yellow oil(0.7g, 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 $(M+H)^+$

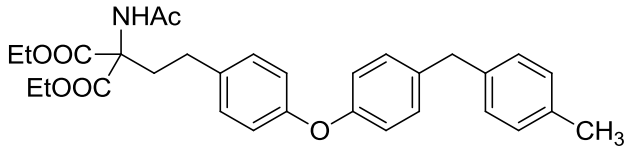
Synthesis of diethyl 2-acetamido-2-(4-(4-benzylphenoxy)phenethyl)malonate (19a)



A solution of **18a** (1.6 g, 3.0 mmol) in CH_2Cl_2 (20mL) was added dropwise to a solution of Et_3SiH (2.5g, 21.1 mmol) in CH_2Cl_2 at room temperature under Ar_2 protection. $TiCl_4$ (4.0g, 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 (20mL). The aqueous phase was extracted with CH_2Cl_2(5mL×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc/PE) to afford compound **19a** (1.0g, 67.0% yield) as white solid.

mp: 62-64 ^oC; ^1H 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 $(M+H)^+$

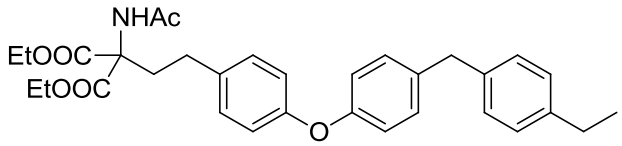
Synthesis of diethyl 2-acetamido-2-(4-(4-(4-methylbenzyl)phenoxy)phenethyl) malonate (19b)



19b was prepared using the same procedure as that described for compound **19a**. White solid(0.43g, 83.0% yield)

mp: 20-22 ^oC; ^1H 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)

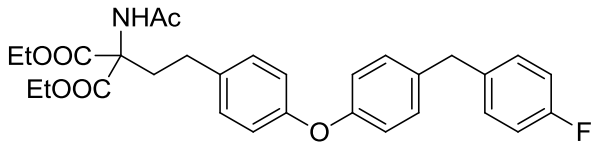


19c was prepared using the same procedure as that described for compound **19a**. Colorless oil(0.4g, 84.0% yield)

^1H 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 $(M+H)^+$

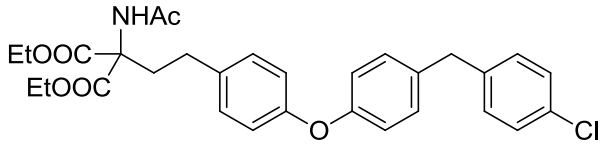
Synthesis of diethyl 2-acetamido-2-(4-(4-(4-fluorobenzyl)phenoxy)phenethyl)

malonate (19d)



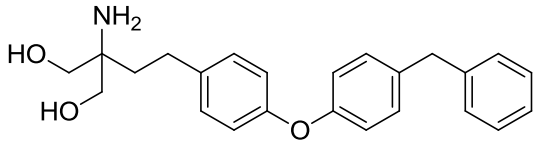
19d was prepared using the same procedure as that described for compound **19a**. White solid(0.47g, 72.0% yield)
mp: 32-34 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.11 (m, 6H), 6.97 (t, *J* = 8.7 Hz, 2H), 6.89 (m, 4H), 6.78 (br, 1H), 4.23 (m, 4H), 3.92 (s, 2H), 2.68 (m, 2H), 2.46 (m, 2H), 2.01 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 6H). ESI (m/z) 522 $(M+H)^+$

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



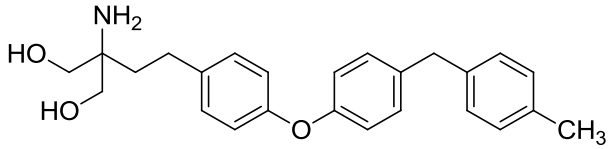
19e was prepared using the same procedure as that described for compound **19a**. Yellow oil(0.6g, 91.0% yield)
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.25 (m, 2H), 7.11 (m, 6H), 6.89 (m, 4H), 6.80 (br, 1H), 4.21 (q, *J* = 7.1 Hz, 4H), 3.91 (s, 2H), 2.68 (m, 2H), 2.46 (m, 2H), 2.02 (s, 3H), 1.26 (t, *J* = 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 (0.6g, two steps 70.6% yield)
m.p.: 205-208 ℃. ^{1}H NMR (300 MHz, CD_3OD) 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_3OD) 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.

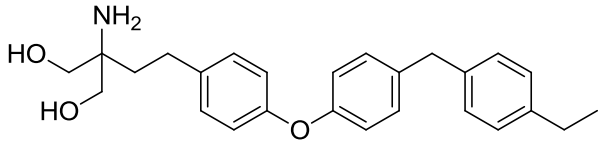
Synthesis of 2-amino-2-(4-(4-(4-methylbenzyl)phenoxy)phenethyl)propane-1,3-diol (20b)



20b was prepared using the same procedure as that described for compound **11a**.

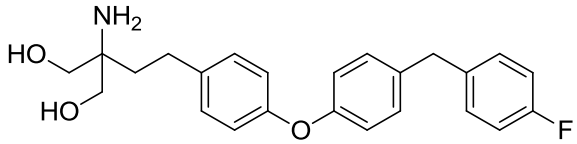
White solid (0.3g, two steps 84.6% yield)
m.p.: 218-220 ℃. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.14 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.01 (m, 4H), 6.81 (m, 4H), 3.83 (s, 2H), 3.63 (s, 4H), 2.57 (m, 2H), 2.23 (s, 3H), 1.88 (m, 2H); ^{13}C NMR (400 MHz, CD_3OD) δ: 157.4, 157.0, 139.7, 138.1, 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-(4-ethylbenzyl)phenoxy)phenethyl)propane-1,3-diol (20c)



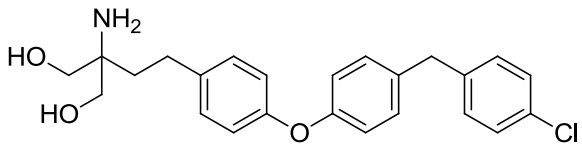
20c was prepared using the same procedure as that described for compound **11a**. White solid (0.18g, two steps 59.3% yield)
m.p.: 176-178 ℃. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.14 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 7.03 (m, 4H), 6.81 (m, 4H), 3.83 (s, 2H), 3.63 (s, 4H), 2.56 (m, 4H), 1.88 (m, 2H), 1.14 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (400 MHz, CD_3OD) δ: 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-(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 ℃. ^{1}H NMR (300 MHz, CD_3OD) δ: 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_3OD) δ: 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.

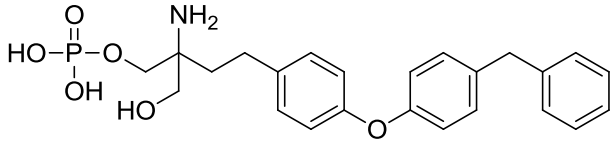
Synthesis of 2-amino-2-(4-(4-(4-chlorobenzyl)phenoxy)phenethyl)propane-1,3-diol (20e)



20e was prepared using the same procedure as that described for compound **11a**. White solid (0.37g, two steps 83.3% yield)

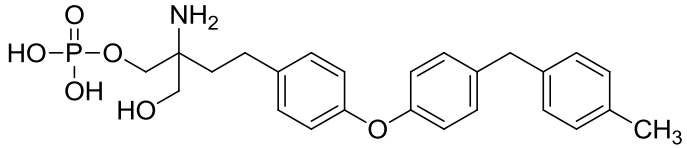
m.p.: 172-175 ℃. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.19 (m, 3H), 7.11 (m, 5H), 6.83 (m, 4H), 3.86 (s, 2H), 3.63 (s, 4H), 2.59 (m, 2H), 1.89 (m, 2H). ^{13}C NMR (500 MHz, CD_3OD) δ: 157.3, 157.2, 141.7, 137.3, 137.2, 132.9, 131.4, 131.2, 130.6, 129.5, 119.9, 119.8, 62.5, 62.0, 41.2, 34.8, 29.4. HRMS calcd for $C_{24}H_{27}ClNO_3(M+H^+)$ 412.1674; found: 412.1688.

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



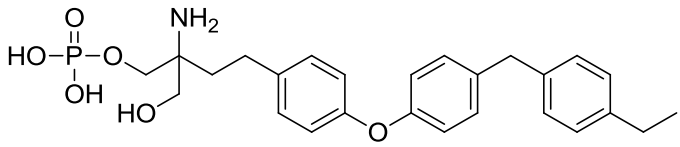
21a was prepared using the same procedure as that described for compound **14a**. White solid (15mg, three steps 13.9% yield)
m.p.: 195-198 ℃. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.15 (m, 9H), 6.81 (m, 4H), 3.94 (m, 2H), 3.88 (s, 2H), 3.64 (m, 2H), 2.61 (m, 2H), 1.89 (m, 2h). ^{13}C NMR (600 MHz, CD_3OD) 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 $C_{24}H_{29}NO_6P(M+H^+)$ 458.1727; found: 458.1727.

Synthesis of 2-amino-2-(hydroxymethyl)-4-(4-(4-(4-methylbenzyl)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 ℃. ^{1}H NMR (300 MHz, CD_3OD) 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 $C_{25}H_{31}NO_6P(M+H^+)$ 472.1884; found: 472.1860.

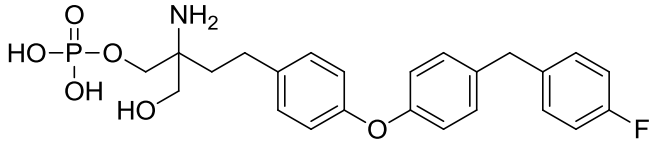
Synthesis of 2-amino-4-(4-(4-(4-ethylbenzyl)phenoxy)phenyl)-2-(hydroxymethyl) butyl dihydrogen phosphate (21c)



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 ℃. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.16 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J*

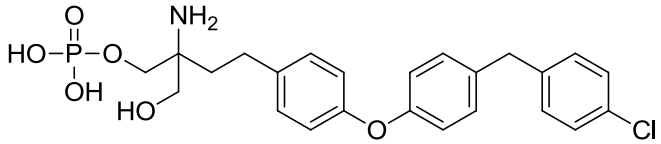
= 8.1 Hz, 2H), 7.04 (m, 4H), 6.81 (m, 4H), 3.94 (m, 2H), 3.84 (s, 2H), 3.65 (m, 2H), 2.56 (m, 4H), 1.92 (m, 2H), 1.14 (t, *J* = 7.7 Hz, 3H). ^{13}C NMR (500 MHz, CD_3OD) δ: 157.7, 157.3, 143.5, 140.3, 138.3, 137.4, 131.4, 131.0, 130.1, 129.2, 120.1, 120.0, 66.0, 62.8, 61.6, 41.9, 35.2, 29.8, 29.6, 16.6. HRMS calcd for $C_{26}H_{33}NO_6P$ ($M+H^+$) 486.2040; found: 486.2019.

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



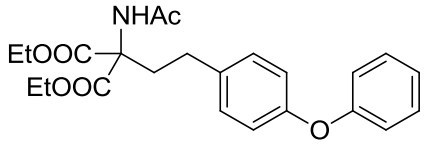
21d was prepared using the same procedure as that described for compound **14a**. White solid (20mg, three steps 16.5% yield)
m.p.: 203-205 ℃. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.13 (m, 6H), 6.93 (t, *J* = 8.8 Hz, 2H), 6.82 (m, 4H), 3.94 (m, 2H), 3.86 (m, 2H), 3.65 (m, 2H), 2.61 (m, 2H), 1.91 (m, 2H). ^{13}C 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 $C_{24}H_{28}FNO_6P$ ($M+H^+$) 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 ℃. ^{1}H NMR (400 MHz, CD_3OD) 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). ^{13}C NMR (500 MHz, CD_3OD) 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 $C_{24}H_{28}ClNO_6P$ ($M+H^+$) 492.1337; found: 492.1324.

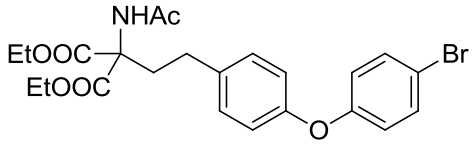
Synthesis of diethyl 2-acetamido-2-(4-phenoxyphenethyl)malonate (22, X=H)



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,

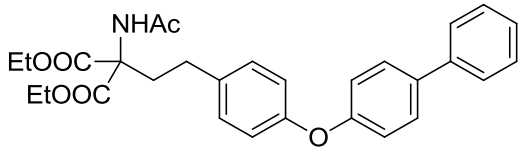
X=Br)



22(X=Br) was prepared using the same procedure as that described for compound **9a**. White solid (1.1g, 98.0% yield)

mp: 53-54 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 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 $(M+H)^+$

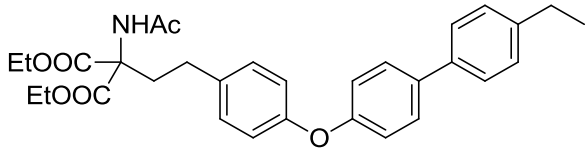
Synthesis of diethyl 2-(4-([1,1'-biphenyl]-4-yloxy)phenethyl)-2-acetamido malonate (23a)



To a solution of **22**(X=Br)(0.4g,0.8mmol) in a mixture of toluene and EtOH(6mL/2mL) was added phenylboronic acid(0.1g, 0.8 mmol), $Pd(PPh)_4$(0.04, 0.03mmol) and 2M aq.Na_2CO_3(3mL). The mixture was heated to reflux for 3h under Ar_2 proteciton, then cooled to room tempeture. The aqueous phase was extracted with EtOAc(3mL×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc/PE) to afford compound **23a** (0.25g, 63.0% yield) as white solid.

mp: 62-64 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 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)

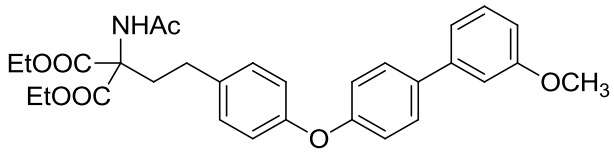


23b was prepared using the same procedure as that described for compound **23a**. Yellow solid (0.3g, 71.0% yield)

mp: 116-118 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 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)

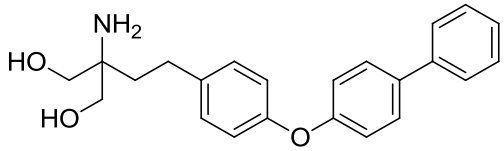
phenethyl)malonate (23c)



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 $(M+H)^+$

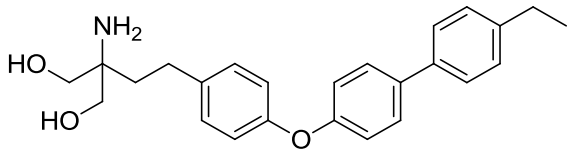
Synthesis of 2-(4-([1,1'-biphenyl]-4-yloxy)phenethyl)-2-aminopropane-1,3-diol (24a)



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 ℃. ^{1}H NMR (300 MHz, CD_3OD) 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), 6.97 (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). ^{13}C NMR (400 MHz, CD_3OD) 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, 29.4. HRMS calcd for $C_{23}H_{26}NO_3(M+H^+)$ 364.1907; found: 364.1918.

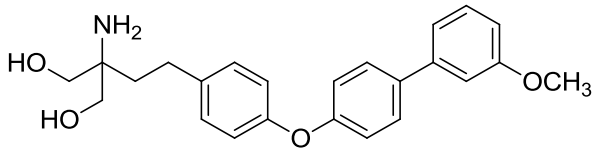
Synthesis of 2-amino-2-(4-((4'-ethyl-[1,1'-biphenyl]-4-yl)oxy)phenethyl)propane-1,3-diol (24b)



24b was prepared using the same procedure as that described for compound **11a**. White solid (0.13g, two steps 58.8% yield)

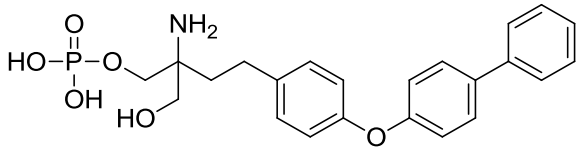
m.p.: 238-240 ℃. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.52(d, *J* =8.7 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 4H), 6.93 (m, 4H), 3.65 (s, 4H), 2.62 (m, 4H), 1.92 (m, 2H), 1.20 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (400 MHz, CD_3OD) δ: 158.3, 157.1, 144.5, 139.1, 137.6, 137.5, 130.7, 129.3, 129.2, 127.7, 120.2, 119.8, 62.5, 62.0, 34.8, 29.5, 29.4, 16.2. HRMS calcd for $C_{25}H_{30}NO_3$ $(M+H^+)$ 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)



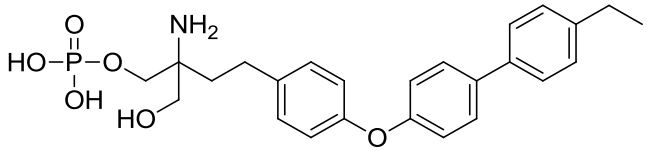
24c was prepared using the same procedure as that described for compound **11a**. White solid (0.3g, two steps 68.0% yield)
m.p.: 210-212 ℃. ^{1}H NMR (600 MHz, CD_3OD) δ: 7.47 (d, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.05 (d, *J* = 7.2 Hz, 1H), 7.01 (m, 1H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.79 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 3.77 (s, 3H), 3.64 (s, 4H), 2.63 (m, 2H), 1.93 (m, 2H). ^{13}C NMR (600 MHz, CD_3OD) 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 $C_{24}H_{28}NO_4$ ($M+H^+$) 394.2013; found: 394.1996.

Synthesis of 4-(4-([1,1'-biphenyl]-4-yloxy)phenyl)-2-amino-2-(hydroxymethyl) butyldihydrogen phosphate (25a)



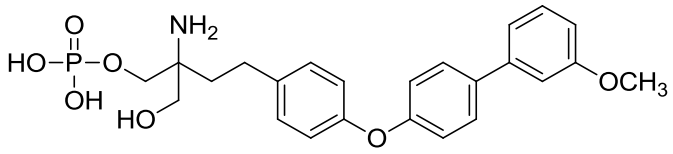
25a was prepared using the same procedure as that described for compound **14a**. White solid (10mg, three steps 8.3% yield)
m.p.: 115-118 ℃. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.53 (m, 4H), 7.33 (m, 3H), 7.25 (m, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.11 (m, 2H), 3.67 (m, 2H), 2.54 (m, 2H), 1.95 (m, 2H). ^{13}C NMR (400 MHz, CD_3OD) 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 $C_{23}H_{27}NO_6P$($M+H^+$) 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)



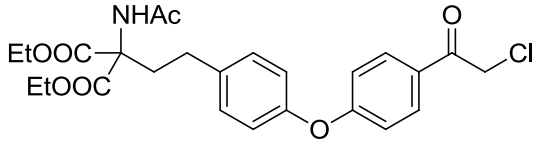
25b was prepared using the same procedure as that described for compound **14a**. White solid (15mg, three steps 14.2% yield)
m.p.: 190-192 ℃. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.51 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.1Hz, 2H), 7.19 (m, 4H), 6.92 (m, 4H), 3.94 (m, 2H), 3.66 (m, 2H), 2.61 (m, 4H), 1.95 (m, 2H), 1.20 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (500 MHz, CD_3OD) 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 $C_{25}H_{31}NO_6P$($M+H^+$) 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)



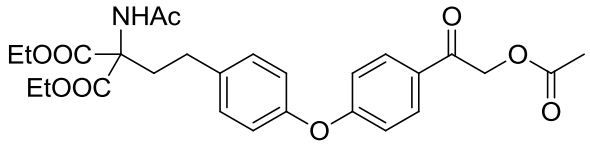
25c was prepared using the same procedure as that described for compound **14a**. White solid (35mg, three steps 24.4% yield)
m.p.: 216-218 ℃. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.52 (d, *J* = 8.4 Hz, 2H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.05 (s, 1H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.0 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). ^{13}C NMR (600 MHz, CD_3OD) 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, 35.7, 30.1. HRMS calcd for $C_{24}H_{29}NO_7P(M+H^+)$ 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 l) in CH_2Cl_2(20mL) was added dropwise to a cooled solution (0 ℃) of **22**(X=H) (15.5 g, 37.5 mmol) in CH_2Cl_2(150mL), then $AlCl_3$ (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 CH_2Cl_2 (10mL×3). The combined organic layers were washed with saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_4, 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 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): 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 ($M+Na^+$)

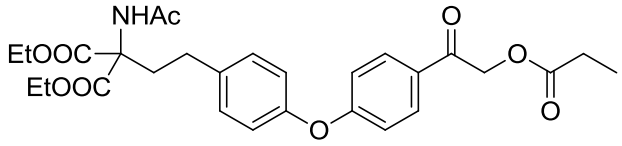
Synthesis of diethyl 2-acetamido-2-(4-(4-(2-acetoxyacetyl)phenoxy)phenethyl) malonate (27a)



To a solution of **26** (1.7 g, 3.4 mmol) in CH_3CN (20mL) was added acetic acid(0.47 g, 7.8 mmol) and Et_3N(0.72 g, 7.2 mmol). The mixture was heated to reflux for 2h, then concentrated. The residue was diluted with CH_2Cl_2 (30mL), washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel

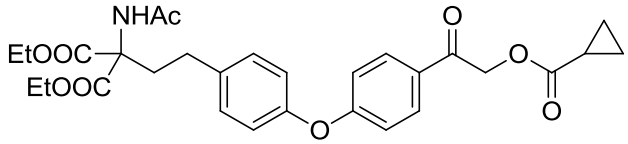
flash column chromatography (EtOAc/PE) to afford compound **27a** (1.6g, 92.8% yield) as yellow syrup.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.7 Hz, 2 H) 7.18 (d, *J* = 8.7 Hz, 2 H) 6.98 (d, *J* = 8.7 Hz, 4 H) 6.80 (brs, 1 H) 5.30 (d, *J* = 1.5 Hz, 2 H) 4.28-4.20 (m, 4 H) 2.70 (dd, *J* = 11.4 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-(4-(2-(propionyloxy)acetyl)phenoxy) phenethyl)malonate (27b)



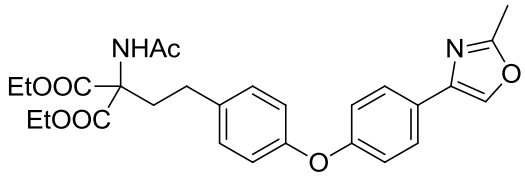
27b was prepared using the same procedure as that described for compound **27a**. Yellow solid (1.1g, 86.9% yield)
mp: 84-86 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.7 Hz, 2 H) 7.18 (d, *J* = 8.7 Hz, 2 H) 6.98 (d, *J* = 8.7 Hz, 4 H) 6.80 (brs, 1 H) 5.30 (s, 2 H) 4.27-4.20 (m, 4 H) 2.70 (dd, *J* = 10.8 Hz, 6.9 Hz, 2 H) 2.56-2.46 (m, 4 H) 2.03 (s, 3 H) 1.29-1.19 (m, 9 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)
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, *J* = 6.9 Hz, 2 H) 7.17 (d, *J* = 7.2 Hz, 2 H) 6.97 (d, *J* = 7.2 Hz, 4 H) 6.79 (brs, 1 H) 5.29 (s, 2 H) 4.23 (q, *J* = 7.2 Hz, 4 H) 2.70 (dd, *J* = 8.7 Hz, 7.2 Hz, 2 H) 2.50 (dd, *J* = 8.1 Hz, 6.9 Hz, 2 H) 2.02 (s, 3 H) 1.79-1.78 (m, 1 H) 1.26 (t, *J* = 7.2 Hz, 6 H) 1.03 (m, 2 H) 0.96 (m, 2 H); ESI (m/z) 540($M+H^+$)

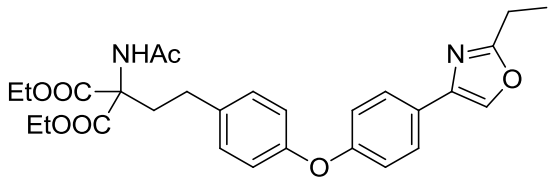
Synthesis of diethyl 2-acetamido-2-(4-(4-(2-methyloxazol-4-yl)phenoxy)phenethyl) malonate (28a)



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 Łt_2O(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_2SO_4, filtered and concentrated. The residue was purified by silica

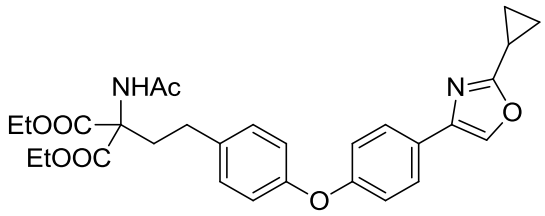
gel flash column chromatography (EtOAc/PE) to afford compound **28a** (1.2g, 75.2% yield) as yellow solid.
mp: 112-114 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (s, 1 H) 7.65 (d, *J* = 9.0 Hz, 2 H) 7.12 (d, *J* = 8.4 Hz, 2 H) 6.99 (d, *J* = 8.4 Hz, 2 H) 6.94 (d, *J* = 8.4 Hz, 2 H) 6.78 (brs, 1 H) 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-(4-(2-ethyloxazol-4-yl)phenoxy)phenethyl) malonate (28b)



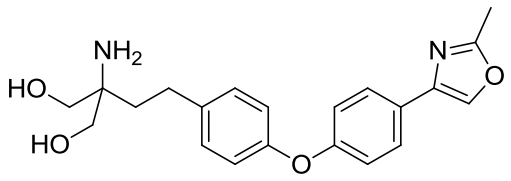
28b was prepared using the same procedure as that described for compound **28a**. Yellow oil (0.85g, 79.7% yield)
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (s, 1 H) 7.66 (d, *J* = 8.4 Hz, 2 H) 7.12 (d, *J* = 8.4 Hz, 2 H) 6.99 (d, *J* = 8.7 Hz, 2 H) 6.93 (d, *J* = 8.7 Hz, 2 H) 6.79 (brs, 1 H) 4.25-4.18 (m, 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-(4-(2-cyclopropyloxazol-4-yl)phenoxy) phenethyl)malonate (28c)



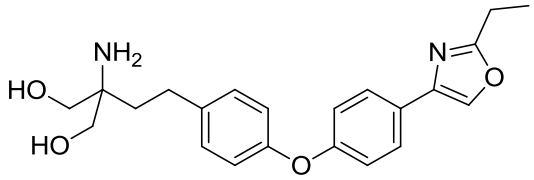
28c was prepared using the same procedure as that described for compound **28a**. Yellow oil (0.4g, 34.9% yield)
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (s, 1 H) 7.66 (d, *J* = 8.4 Hz, 2 H) 7.11 (d, *J* = 8.1 Hz, 2 H) 6.99 (d, *J* = 8.7 Hz, 2 H) 6.93 (d, *J* = 8.7 Hz, 2 H) 6.79 (brs, 1 H) 4.29-4.19 (m, 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-(4-(2-methyloxazol-4-yl)phenoxy)phenethyl)propane-1,3-diol (29a)



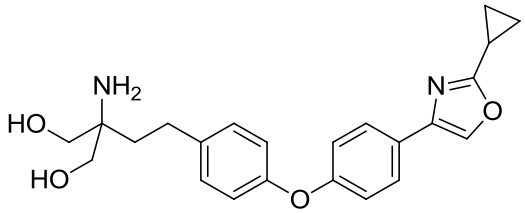
29a was prepared using the same procedure as that described for compound **11a**. White solid (0.27g, two steps 58.2% yield)
mp: 179-181 ^{o}C; ^{1}H NMR (300 MHz, CD_3OD): δ 8.03 (s, 1 H) 7.63 (d, *J* = 8.7 Hz, 2 H) 7.22 (d, *J* = 8.1 Hz, 2 H) 6.92 (d, *J* = 8.1 Hz, 2 H) 6.91 (d, *J* = 8.1 Hz, 2 H) 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_3OD): δ 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 $C_{21}H_{25}N_2O_4$ ($M+H^+$) 369.1808, found 369.1814

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



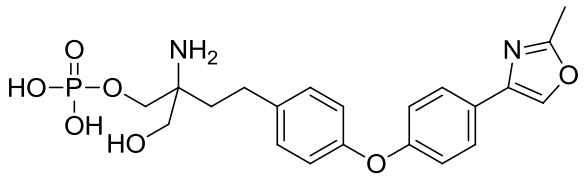
29b was prepared using the same procedure as that described for compound **11a**. White solid (0.4g, two steps 62.1% yield)
mp: 166-169 ^{o}C; ^{1}H NMR (300 MHz, CD_3OD): δ 8.37 (s, 1 H) 7.68 (d, *J* = 8.4 Hz, 2 H) 7.27 (d, *J* = 8.1 Hz, 2 H) 7.02 (d, *J* = 8.4 Hz, 2 H) 6.96 (d, *J* = 7.8 Hz, 2 H) 3.68 (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_3OD): δ 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 $C_{22}H_{27}N_2O_4$ ($M+H^+$) 383.1965, found 383.1971

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



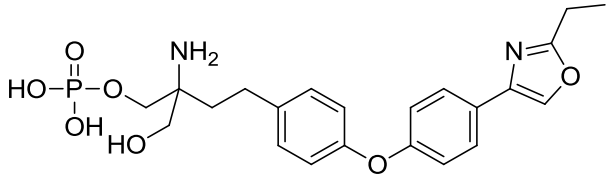
29c was prepared using the same procedure as that described for compound **11a**. White solid (74mg, two steps 34.2% yield)
mp: 65-68 ^{o}C; ^{1}H NMR(300 MHz, CD_3OD): δ 8.19 (s, 1 H) 7.58 (d, *J* = 8.4 Hz, 2 H) 7.19 (d, *J* = 8.4 Hz, 2 H) 6.92 (d, *J* = 8.7 Hz, 2 H) 6.87 (d, J = 8.7 Hz, 2 H) 3.60 (s, 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_3OD): δ 170.16, 160.34, 156.01, 138.52, 135.73, 130.97, 128.70, 122.81, 120.81, 119.54, 62.51, 62.07, 34.73, 29.43, 10.58, 9.46; HRMS calcd. for $C_{23}H_{27}N_2O_4$ ($M+H^+$) 395.1965, found 395.1946

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



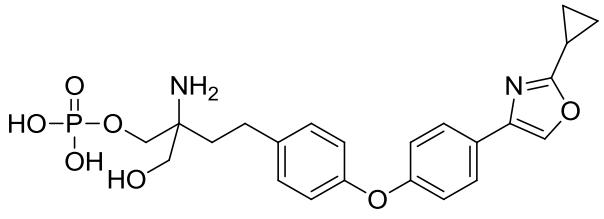
30a was prepared using the same procedure as that described for compound **14a**. White solid (23mg, three steps 22.5% yield)
mp: 218-220 ^{o}C ; ^{1}H NMR (300 MHz, CD_3OD): δ 8.01 (s, 1 H) 7.61 (d, *J* = 8.4 Hz, 2 H) 7.21 (d, *J* = 8.4 Hz, 2 H) 6.91 (t, *J* = 6.9 Hz, 4 H) 3.95 (brs, 2 H) 3.66 (s, 2 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_3OD): δ 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 $C_{21}H_{26}N_2O_7P$ ($M+H^+$) 449.1472, found 449.1465

Synthesis of 2-amino-4-(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 ^{o}C ; ^{1}H NMR (300 MHz, CD_3OD): δ 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_3OD): δ 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 $C_{22}H_{28}N_2O_7P$ ($M+H^+$) 463.1629, found 463.1646

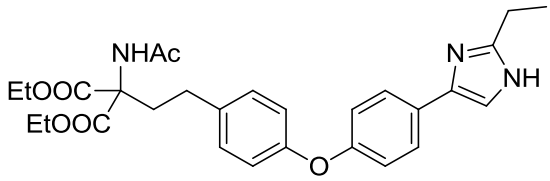
Synthesis of 2-amino-4-(4-(4-(2-cyclopropyloxazol-4-yl)phenoxy)phenyl)-2-(hydroxymethyl)butyl dihydrogen phosphate (30c)



30c was prepared using the same procedure as that described for compound **14a**. White solid (18mg, three steps 14.7% yield)
mp: 140-143 ^{o}C ; ^{1}H NMR(300 MHz, CD_3OD): δ 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_3OD): δ 168.19, 158.96, 156.63, 141.20, 137.84,

134.06, 130.87, 128.03, 127.25, 120.37, 119.54, 65.77, 62.49, 61.35, 61.28, 34.91, 30.74, 29.33, 9.57, 8.40; HRMS calcd. for $C_{23}H_{27}N_2O_7P$ ($M+H^+$) 475.1629, found 475.1586

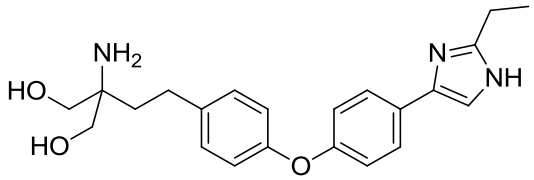
Synthesis of diethyl 2-acetamido-2-(4-(4-(2-ethyl-1H-imidazol-4-yl)phenoxy) phenethyl)malonate (31)



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_2SO_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 ($M+H^+$)

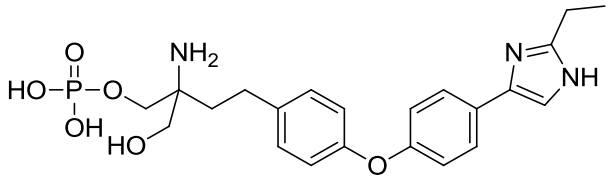
Synthesis of 2-amino-2-(4-(4-(2-ethyl-1H-imidazol-4-yl)phenoxy)phenethyl) propane-1,3-diol (32)



32 was prepared using the same procedure as that described for compound **11a**. Yellow solid (0.1g, two steps 60.5% yield)

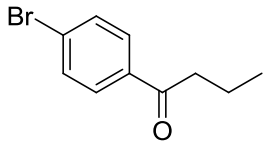
mp: 130-133 ^{o}C; ^{1}H NMR (300 MHz, CD_3OD): δ 7.63 (d, *J* = 8.4 Hz, 2 H) 7.62 (s, 1 H) 7.23 (d, *J* = 8.4 Hz, 2 H) 6.99 (d, *J* = 8.4 Hz, 2 H) 6.93 (d, *J* = 8.7 Hz, 2 H) 3.64 (s, 4 H) 2.99 (q, *J* = 7.8 Hz, 2 H) 2.66-2.60 (m, 2 H) 1.94-1.88 (m, 2 H) 1.37 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD): 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 $C_{23}H_{28}N_3O_3$ ($M+H^+$) 382.2125, found 382.2120

Synthesis of 2-amino-4-(4-(4-(2-ethyl-1H-imidazol-4-yl)phenoxy)phenyl)-2-(hydroxymethyl)butyl dihydrogen phosphate (33)



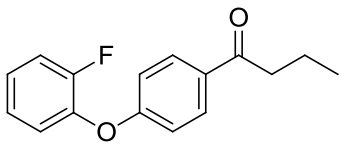
33 was prepared using the same procedure as that described for compound **14a**. White solid (3mg, three steps 5.1% yield)
mp: 125-128 ^{o}C ; ^{1}H NMR (300 MHz, CD_3OD): δ 8.47 (s, 1 H) 7.58 (d, *J* = 8.4 Hz, 2 H) 7.37 (d, *J* = 8.1 Hz, 2 H) 7.12 (d, *J* = 8.4 Hz, 2 H) 6.90 (d, *J* = 7.8 Hz, 2 H) 3.60 (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_3OD): δ 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 $C_{22}H_{29}N_3O_6P$ ($M+H^+$) 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 ℃, then cooled to room temperature and filtered. The filtrate was added to a solution of bromobenzene(17g, 111mmol) in CH_2Cl_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_2Cl_2 (20mL×3). The combined organic layers were washed with saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated, yielding crude product **35** (23.6g, 94% yield) as brown solid.
mp: 36-38 ^{o}C ;^{1}H NMR (300 MHz, $CDCl_3$) δ: 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 $(M+H)^+$

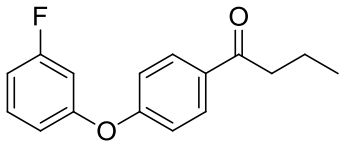
Synthesis of 1-(4-(2-fluorophenoxy)phenyl)butan-1-one (36a)



To a solution of **35 (**8.4 g, 37.2 mmol) in DMF(80mL) was added 2-fluorophenol (5 g, 44.6 mmol), Cs_2CO_3 (14.5g, 44.6mmol) and CuBr (0.27g, 1.86mmol). The mixture was heated for 20h at 150 ℃ 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, $CDCl_3$) δ: 7.95 (d, *J* = 8.7 Hz, 2H), 7.18 (m, 4H), 6.97 (d, *J* = 8.7

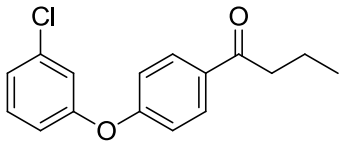
Hz, 2H), 2.90 (t, *J* = 7.4 Hz, 2H), 1.76 (m, 2H), 1.00 (t, *J* = 7.5 Hz, 3H). ESI (m/z) 259 $(M+H)^+$

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



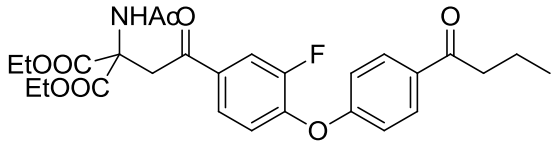
36b was prepared using the same procedure as that described for compound **36a**. Yellow oil (5.9g, 62.0% yield)
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 8.4 Hz, 2H), 7.30 (m, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.85 (m, 3H), 2.91 (t, *J* = 7.4 Hz, 2H), 1.77 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). ESI (m/z) 259 $(M+H)^+$

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



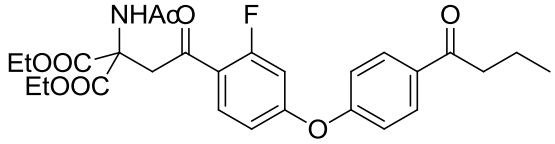
36c was prepared using the same procedure as that described for compound **36a**. Yellow oil (1.2g, 50.0% yield)
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 8.7 Hz, 2H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.06 (s, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.95 (dd, J_1 = 8.1 Hz, J_2 = 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)



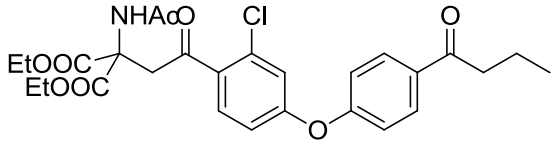
37a was prepared using the same procedure as that described for compound **8a**. Yellow oil (1.9g, two steps 19.8% yield)
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (d, *J* = 8.4 Hz, 2H), 7.79 (t, *J* = 10.5 Hz, 1H), 7.13 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 4.27 (m, 6H), 2.92 (t, *J* = 7.2 Hz, 2H), 2.08 (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)



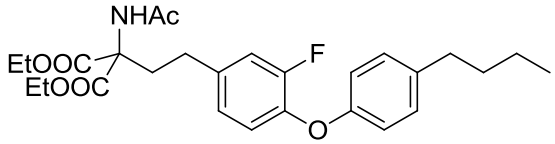
37b was prepared using the same procedure as that described for compound **8a**. Yellow solid (2.2g, two steps 28.1% yield)
mp: 18-21 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.03 (d, J = 8.7 Hz, 2H), 7.88 (t, J = 8.4 Hz, 1H), 7.13 (m, 2H), 6.85 (dd, J_1 = 8.7 Hz, J_2 = 2.1 Hz, 1H), 6.75 (dd, J_1 = 12.0 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-butyrylphenoxy)-2-chlorophenyl) -2-oxoethyl)malonate (37c)



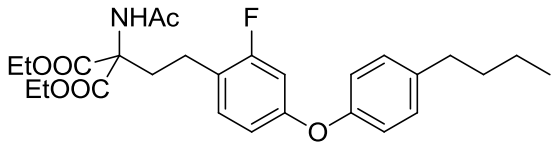
37c was prepared using the same procedure as that described for compound **8a**. Yellow solid (0.61g, two steps 29.1% yield)
mp: 44-46 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.10 (m, 3H), 6.96 (d, J = 8.4 Hz, 1H), 4.28 (m, 6H), 2.94 (t, J = 7.2 Hz, 2H), 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, $CDCl_3$) δ: 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 $(M+H)^+$

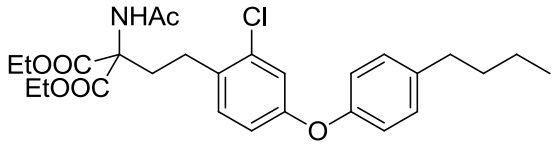
Synthesis of diethyl 2-acetamido-2-(4-(4-butylphenoxy)-2-fluorophenethyl) malonate (38b)



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, $CDCl_3$) δ: 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

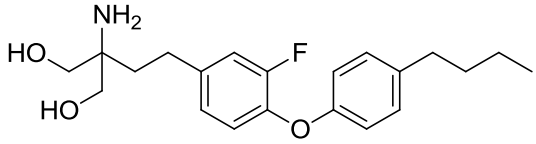
$(M+H)^+$

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



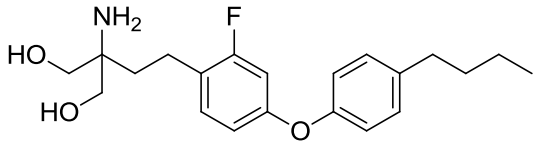
38c was prepared using the same procedure as that described for compound **19a**. Crude product as yellow oil (1.0g, 70.0% yield)
ESI (m/z) 504 $(M+H)^+$

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



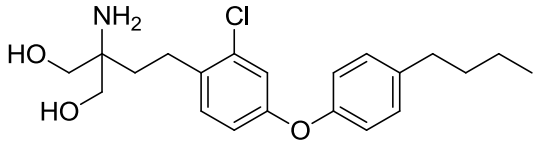
39a was prepared using the same procedure as that described for compound **11a**. White solid (386mg, two steps 71.5% yield)
m.p.: 176-179 ℃. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.05 (m, 3H), 6.94 (m, 1H), 6.88 (m, 1H), 6.73 (d, J = 8.4 Hz, 2H), 3.61 (s, 4H), 2.60 (m, 2H), 2.49 (t, J = 7.7 Hz, 2H), 1.88 (m, 2H), 1.47 (m, 2H), 1.26 (m, 2H), 0.84 (t, J = 7.4 Hz, 3H). ^{13}C NMR (400 MHz, CD_3OD) δ: 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)



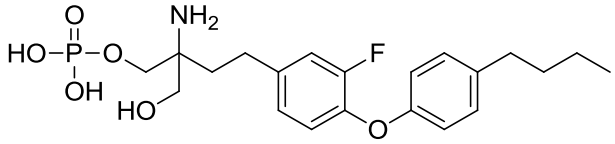
39b was prepared using the same procedure as that described for compound **11a**. White solid (350mg, two steps 52.9% yield)
m.p.: 165-167 ℃. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.13 (t, J = 8.7 Hz, 1H), 7.07 (d, J = 8.1 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 6.58 (dd, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 1H), 6.52 (dd, 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_3OD) δ: 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)



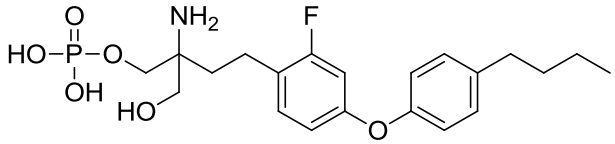
39c was prepared using the same procedure as that described for compound **11a**. White solid (61mg, two steps 78.0% yield)
m.p.: 208-210 ℃. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.25 (d, J = 8.7 Hz, 1H), 7.15 (d, J = 8.4 Hz, 2H), 6.87 (m, 2H), 6.84 (s, 1H), 6.79 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 3.68 (s, 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). ^{13}C NMR (400 MHz, CD_3OD) 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 $C_{21}H_{29}ClNO_3$ $(M+H)^+$ 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 ℃. ^{1}H NMR (300 MHz, CD_3OD) 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, 2H), 1.94 (m, 2H), 1.52 (m, 2H), 1.29 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (600 MHz, CD_3OD) 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 $C_{21}H_{30}FNO_6P$ $(M+H)^+$ 442.1789; found: 442.1810.

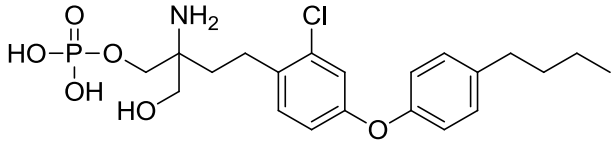
Synthesis of 2-amino-4-(4-(4-butylphenoxy)-2-fluorophenyl)-2-(hydroxymethyl) butyl dihydrogen phosphate (40b)



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 ℃. ^{1}H NMR (300 MHz, CD_3OD) 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, J_1 = 8.1 Hz, J_2= 1.8 Hz, 1H), 6.58 (dd, J_1 = 11.4 Hz, J_2 = 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).

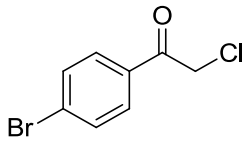
^{13}C NMR (600 MHz, CD_3OD) δ: 162.6 (*J* = 243 Hz), 159.3 (*J* = 10 Hz), 155.7, 140.0, 132.3 (*J* = 6 Hz), 130.9, 123.1 (*J* = 16 Hz), 120.4, 114.9, 106.4 (*J* = 26 Hz), 65.8, 62.5, 61.2, 35.9, 35.0, 33.4, 23.3, 22.9, 14.3. HRMS calcd for $C_{21}H_{30}FNO_6P$ $(M+H)^+$ 442.1789; found: 442.1808.

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



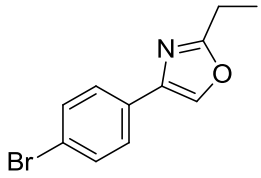
40c was prepared using the same procedure as that described for compound **14a**. White solid (5mg, three steps 8.6% yield)
m.p.: 205-207 ℃. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.27 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.88 (m, 3H), 6.81 (d, *J* = 8.0 Hz, 1H), 3.99 (m, 2H), 3.71 (m, 2H), 2.76 (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) δ: 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 $C_{21}H_{30}ClNO_6P$ $(M+H)^+$ 458.1494; found: 458.1498.

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



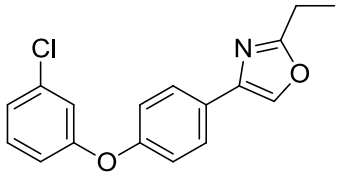
41 was prepared using the same procedure as that described for compound **7a**. Yellow solid (1.4g, 95.0% yield)
mp: 116-118 ^{o}C ;^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 8.7 Hz, 2H), 7.65 (d, *J* = 8.7 Hz, 2H), 4.65 (s, 2H). ESI (m/z) 232 $(M+H)^+$

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



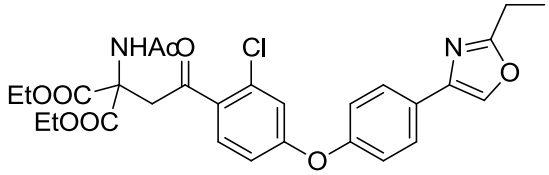
42 was prepared using the same procedure as that described for compound **28a**. Yellow solid (0.54g, two steps 35.7% yield)
mp: 98-100 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.81 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 2.84 (q, *J* = 7.6 Hz, 2H), 1.37 (t, *J* = 7.6 Hz, 3H). ESI (m/z) 252 $(M+H)^+$

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



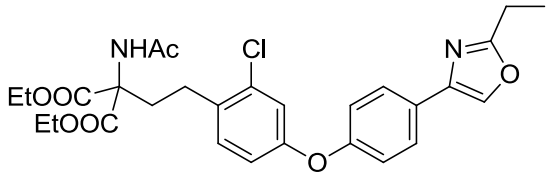
43 was prepared using the same procedure as that described for compound **36a**.Yellow oil (3.1g, 66.0% yield)
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78 (s, 1H), 7.70 (d, *J* = 8.7 Hz, 2H), 7.25 (m, 1H), 7.03 (m, 3H), 6.89 (d, *J* = 8.1 Hz, 1H), 2.85 (q, *J* = 7.6 Hz, 2H), 1.38 (t, *J* = 7.6 Hz, 3H). ESI (m/z) 300 $(M+H)^+$

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



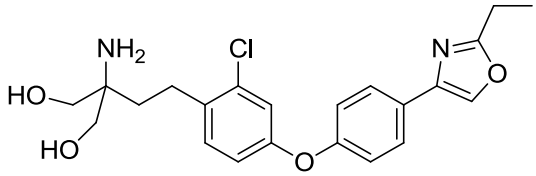
44 was prepared using the same procedure as that described for compound **8a**. Yellow solid (2.2g, two steps 38.3% yield)
mp: 78-80 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.82 (s, 1H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.10 (m, 3H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.91 (dd, J_1 = 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)



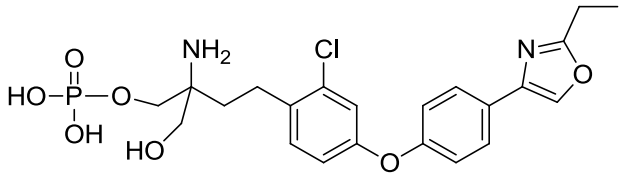
45 was prepared using the same procedure as that described for compound **9a**. Yellow solid (0.91g, 72.0% yield)
mp: 68-69 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.01 (m, 3H), 6.85 (m, 2H), 4.25 (m, 4H), 2.85 (q, *J* = 7.6 Hz, 2H), 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)



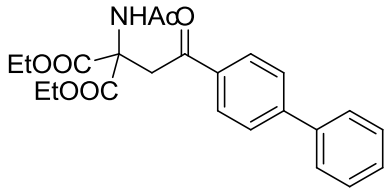
46 was prepared using the same procedure as that described for compound **11a**. White solid (88mg, two steps 62.0% yield)
m.p.: 198-200 ℃. ^{1}H NMR (300 MHz, CD_3OD) δ: 8.10 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 1H), 6.95 (m, 3H), 6.84 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 3.65 (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_3OD) 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 $C_{22}H_{26}ClN_2O_4$ $(M+H)^+$ 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)



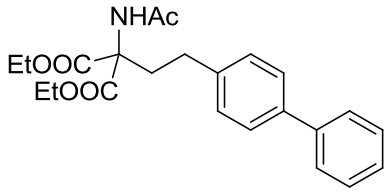
47 was prepared using the same procedure as that described for compound **14a**. White solid (1.6mg, three steps 12.0% yield)
m.p.: 125-128 ℃. ^{1}H NMR (500 MHz, CD_3OD) δ: 8.05 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 1H), 6.98 (m, 3H), 6.88 (m, 1H), 3.96 (m, 2H), 3.68 (m, 2H), 2.77 (m, 4H), 1.90 (m, 2H), 1.31 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (500 MHz, CD_3OD) 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 $C_{22}H_{27}ClN_2O_7P$ $(M+H)^+$ 497.1244; found: 497.1242.

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



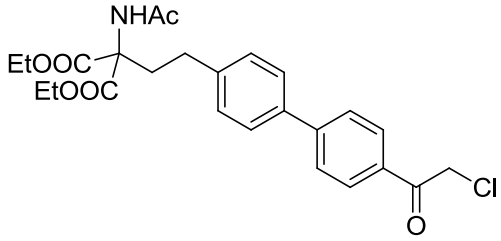
49 was prepared using the same procedure as that described for compound **17**. Crude product as yellow oil (6.0g, two steps 62.0% yield)
ESI (m/z) 412 $(M+H)^+$434 $(M+Na^+)$

Synthesis of diethyl 2-(2-([1,1'-biphenyl]-4-yl)ethyl)-2-acetamidomalonate (50)



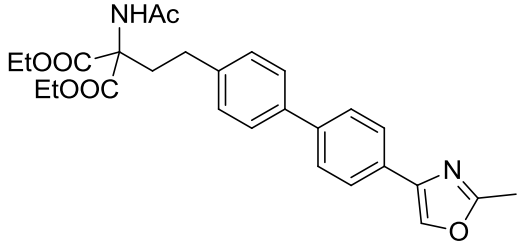
50 was prepared using the same procedure as that described for compound **9a**. Yellow oil (5.0g, 86.9% yield)
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.8 Hz, 2 H) 7.50 (d, *J* = 7.8 Hz, 2 H) 7.42 (t, *J* = 7.5 Hz, 2 H) 7.33 (d, J = 7.2 Hz, 1 H) 7.22 (d, *J* = 8.4 Hz, 2 H) 6.78 (brs, 1 H) 4.26-4.16 (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-(2-(4'-(2-chloroacetyl)-[1,1'-biphenyl]-4-yl) ethyl)malonate (51)



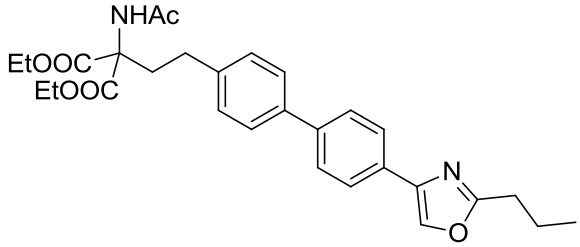
51 was prepared using the same procedure as that described for compound **26**. Yellow solid (5.2g, 87.3% yield)
mp: 80-83 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.4 Hz, 2 H) 7.69 (d, *J* = 8.1 Hz, 2 H) 7.54 (d, *J* = 8.1 Hz, 2 H) 7.27 (d, *J* = 8.4 Hz, 2 H) 6.79 (brs, 1 H) 4.73 (s, 2 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)



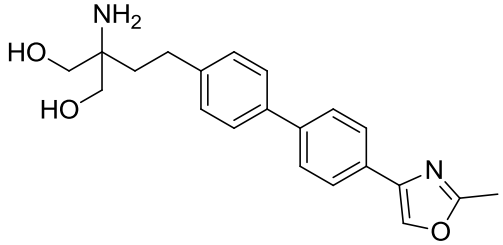
52a was prepared using the same procedure as that described for compound **28a**. Yellow solid (0.9g, two steps 62.8% yield)
mp: 123-125 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (s, 1 H) 7.77 (d, *J* = 8.4 Hz, 2 H) 7.60 (d, *J* = 8.7 Hz, 2 H) 7.53 (d, *J* = 8.1 Hz, 2 H) 7.23 (d, *J* = 8.4 Hz, 2 H) 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)



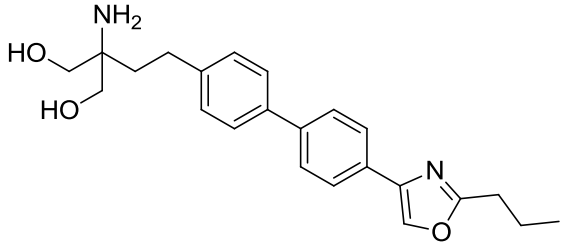
52b was prepared using the same procedure as that described for compound **28a**. Yellow solid (0.95g, two steps 72.2% yield)
mp: 131-134 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (s, 1 H) 7.77 (d, *J* = 8.4 Hz, 2 H) 7.59 (d, *J* = 8.1 Hz, 2 H) 7.52 (d, *J* = 8.1 Hz, 2 H) 7.22 (d, *J* = 8.4 Hz, 2 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-methyloxazol-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 ^{o}C; ^{1}H NMR (300 MHz, CD_3OD): 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); ^{13}C NMR (100 MHz, CD_3OD): 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 $C_{21}H_{25}N_2O_3$ ($M+H^+$) 353.1865, found 353.1872

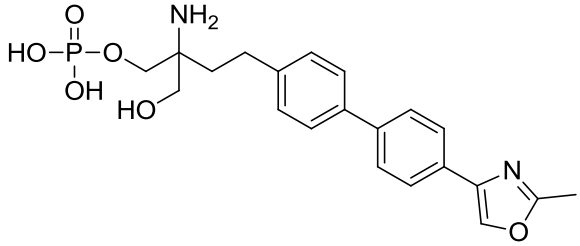
Synthesis of 2-amino-2-(2-(4'-(2-propyloxazol-4-yl)-[1,1'-biphenyl]-4-yl)ethyl) propane-1,3-diol (53b)



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 ^{o}C; ^{1}H 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

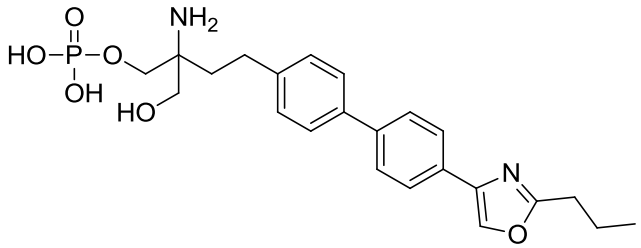
H) 1.82-1.70 (m, 2 H) 1.56-1.51 (m, 2 H) 0.96 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO): δ 164.60, 142.90, 139.29, 139.17, 136.72, 134.60, 129.83, 128.79, 126.64, 126.30, 125.53, 65.38, 55.42, 36.73, 29.24, 28.60, 19.95, 13.46; HRMS calcd. for $C_{23}H_{29}N_2O_3$ ($M+H^+$) 381.2178, found 381.2183

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



54a was prepared using the same procedure as that described for compound **14a**. White solid (30mg, three steps 34.0% yield)
mp: 220-223 °C ; ^{1}H NMR (300 MHz, CD_3OD): δ 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_3OD): δ 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 $C_{23}H_{29}N_2O_3$ ($M+H^+$) 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 was prepared using the same procedure as that described for compound **14a**. White solid (50mg, three steps 45.2% yield)
mp: 110-113 °C ; ^{1}H NMR (300 MHz, CD_3OD): δ 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_3OD) δ 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 $C_{23}H_{30}N_2O_6P$ ($M+H^+$) 461.1836, found 461.1826

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