**Supplementary Information**

# Sol-moiety: Discovery of a water-soluble prodrug technology for enhanced oral bioavailability of insoluble therapeutics

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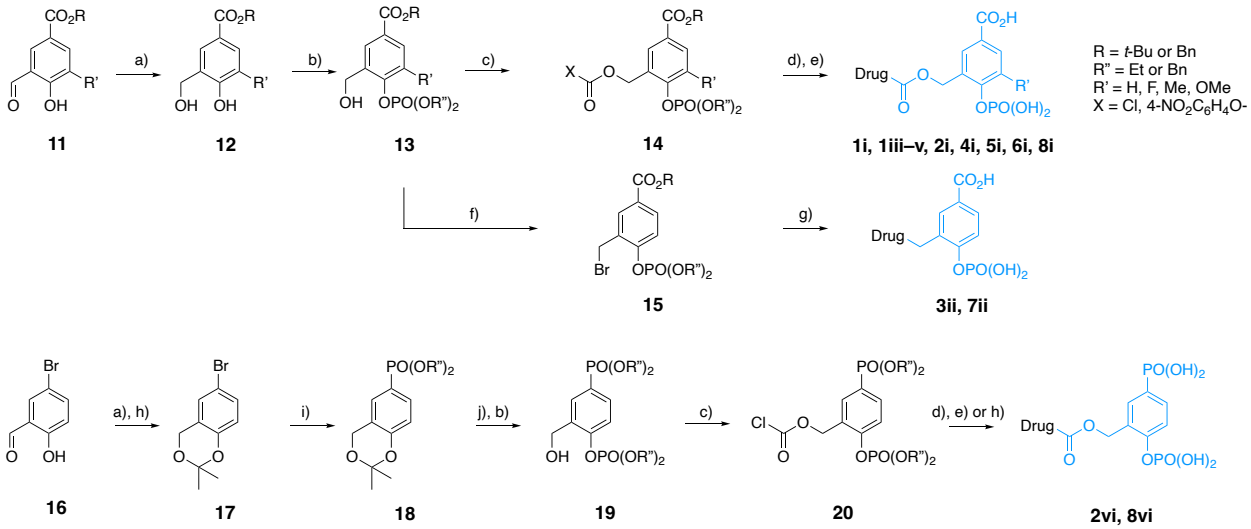
**Supplementary Discussion**

The Sol-moiety prototypes used in this study were synthesized in a relatively straightforward manner as highlighted in Scheme 1. In general, the carbonyl linkage was used for the Sol-moiety-drug conjugates (**1i, 1iii–v**, **2i**, **2vi**, **4i**, **5i**, **6i, 8i** and **8vi)**. However, for chemical ease and stability, the sulfonamide on dabrafenib (**3ii**) and piperidine on desloratadine (**7ii**) were linked directly.

Reduction of 3-hydroxy-4-formyl benzoic acid *tert*-butyl or benzyl esters of type **11** with sodium borohydride followed by selective phosphorylation under Atherton–Todd conditions[1] yielded the desired phosphate esters **13** (Supplementary Fig. 1). These were then converted to the corresponding chloroformates or 4-nitrophenyl carbonates (of type **14**), from a reaction with either triphosgene, bis(4-nitrophenyl)carbonate, or 4-nitrophenyl chloroformate. Coupling to the drugs enzalutamide, vemurafenib, apixaban, carvedilol, lenalidomide, and paclitaxel was performed under basic conditions followed by deprotection using either trimethylsilyl bromide or, in the case of benzyl-protected Sol-moiety building block, hydrogenation conditions using palladium on carbon. The phosphonate derivative was chosen as this was found to be stable under deprotection conditions, whereas its carboxylic ester was quite unstable. We chose to connect desloratadine directly to Sol-moiety as we also found the carbonyl linkage to the piperidine on desloratadine to be unstable under standard deprotection conditions. Therefore, bromination of **15** under Appel[2] followed by benzylation of desloratadine and deprotection using bromotrimethylsilane gave **7ii**. The phosphonate-based Sol-vemurafenib **2vi** and Sol-paclitaxel **8vi** were synthesized from 5-bromosalicylaldehyde **16** via a reduction with sodium borohydride, acetal protection, and a palladium-catalyzed cross-coupling reaction to insert the phosphonate group. Deprotection followed by phosphorylation using Atherton–Todd conditions provided the key benzyl alcohol precursor **19**. Treatment with triphosgene followed by coupling to either vemurafenib or paclitaxel followed by deprotection to give the desired products **2vi** and **8vi**. As a standard, the phosphonooxymethyl prodrug of paclitaxel **8vii** was synthesized according to literature conditions.[3] The Sol-moiety by-products, **10** and **11** were prepared by deprotection of intermediates **13** and **19** under acidic or hydrogenation conditions respectively.




a) $NaBH_4$, EtOH; b) $HPO(OBn)_2$, $CCl_4$, $Et_3N$, MeCN or $(EtO)_2POCl$, DIPEA, $CH_2Cl_2$; c) $(Cl_3C)_2CO$, $CH_2Cl_2$, or 4-$NO_2PhCOCl$, DMAP, $CH_2Cl_2$; d) Drug, $Cs_2CO_3$, MeCN or LiHMDS, MeCN or DMAP, Pyridine, $CH_2Cl_2$; e) TMSBr in $CH_2Cl_2$ or Pd/C, $H_2$, EtOH, f) $PPh_3$, $CBr_4$,$CH_2Cl_2$; g) $Cs_2CO_3$, DMSO or DIPEA, $CH_2Cl_2$; h) DMP, PTSA, Acetone; i) $PdP(Ph_3)_4$, $HPO(OR")_2$, THF; j) HCl, THF.; h) Pd/C, $H_2$, EtOH.

**Supplementary Fig. 1 Synthetic routes to the Sol-moiety drug prototypes 1i–v, 2i, 2vi, 3ii, 4i, 5i, 6i, 7ii, 8i and 8vi**.

**Supplementary Methods**

Reactions were performed under ambient atmosphere unless otherwise noted. Qualitative TLC analysis was performed on 250 mm thick, 60 G, glass backed, F254 silica (EMD Millipore). All solvents used were ACS grade Sure-Seal, and all other reagents were used as received unless otherwise noted. Chromatography was performed on a Biotage Selekt using silica (Biotage Sfar for normal phase columns) or C18 (reverse phase) (Biotage SNAP Ultra C-18 HP Sphere 25 $\mu$m) pre-packed cartridges. Structure determination was performed using $^1$H spectra that were recorded on a Bruker Neo-500 spectrometer, and low-resolution mass spectra (ESI-MS) that were collected on an Agilent LCMS instrument. HPLC was principally used with an Agilent 1260 Infinity II system made of a Binary Pump (G7112B) and a DAD (G7115A) photodiode array detector. HPLC data was collected on Agilent OpenLab version 2.7 CDS software. Samples were eluted using an analytical 4.6 × 100 mm Poroshell 120 EC-C18 2.7 µm column from Agilent using a combination of mobile solvent A ($H_2O$ with 0.1% TFA) and B (acetonitrile with 0.1% TFA).

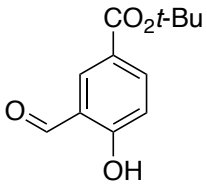
**Abbreviations:**

Bn: benzyl, *t*-Bu: *tert*-Butyl, $CCl_4$: carbon tetrachloride, $CDCl_3$: chloroform-d, $Cs_2CO_3$: cesium carbonate, DIPEA: *N,N*-diisopropylethylamine, DMAP: *N,N*-dimethylaminopyridine, DMF: *N*,*N*-dimethylformamide, DMSO-$d_6$: dimethylsulfoxide-$d_6$, EtOH: ethanol, MeOH: methanol,, MeTHF: 2-methyltetrahydrofuran, $Na_2SO_4$: sodium sulfate, $Na_2CO_3$: sodium carbonate, $NaHCO_3$: sodium bicarbonate, $Na_2S_2O_3$: sodium thiosulfate, $NH_4Cl$: ammonium chloride, NIS: *N*-idodosuccinimide, THF: tetrahydrofuran.

**Commercial Reagents**

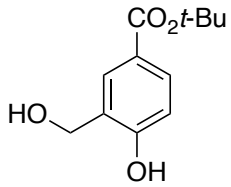
The following reagents were purchased from commercial sources: Dibenzyl phosphite (CAS: 17176-77-1); di-*tert*-butyl phosphite (CAS: 13086-84-5); 2-hydroxybenzyl alcohol is (CAS: 99-90-01); 4-hydroxybenzyl alcohol (CAS: 623-05-2); 4-nitrophenyl chloroformate (CAS: 7693-46-1); 6-bromo-2,2-diemthyl-4H-benzodioxin (CAS: 52113-69-6).

***Tert*-butyl 3-formyl-4-hydroxy-benzoate**



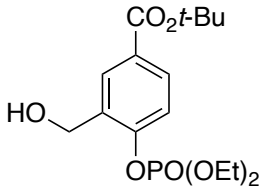

A solution of DCC (13.0 g, 63.2 mmol) in THF (80 mL) was slowly added to a mixture of 3-formyl-4-hydroxybenzoic acid (10 g, 60.2 mmol), 4-dimethylaminopyridine (367 mg, 3.01 mmol) in a combination of tert-butanol (100 mL) and THF (20 mL) under an atmosphere of argon. The reaction mixture was stirred at room temperature for 12 hours and then evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 10–30% ethyl acetate in hexanes) provided the desired product (5.2 g, 39%) as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 11.35 (s, 1H), 9.95 (s, 1H), 8.25 (d, $J$ = 2 Hz, 1H), 8.14 (dd, $J$ = 8.6 and 2 Hz, 1H), 7.01 (d, $J$ = 8.6 Hz) and 1.60 (s, 9H). LRMS (ESI) *m/z* 221.1 $[M - H]^-$.

**_Tert_-butyl 4-hydroxy-3-(hydroxymethyl)benzoate**



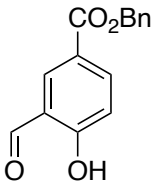

Sodium borohydride (430 mg, 22.4 mmol) was added to a solution of *tert*-butyl 3-formyl-4-hydroxy-benzoate (1.25 g, 5.6 mmol) in THF (10 mL) under an atmosphere of argon. The reaction mixture was stirred at room temperature and allowed to reaction for 3 h. The reaction mixture was quenched by the addition of saturated aq. $NH_4Cl$ and extracted with ethyl acetate, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 5–60% ethyl acetate/hexane) provided the desired product (1.09 g, 87%) as a crystalline white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.89–7.83 (m, 2H), 7.69 (d, *J* = 2.1 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 4.93 (s, 2H), 1.57 (s, 9H). LRMS (ESI) *m/z* 223.0 $[M - H]^-$.

**_Tert_-butyl 4-diethoxyphosphoryloxy-3-(hydroxymethyl)benzoate**




DIPEA (2.80 mL, 16.1 mmol) was added to a cooled (0 ºC) solution of *tert*-butyl 4-hydroxy-3-(hydroxymethyl) benzoate (1.8 g; 8.03 mmol) in dichloromethane (40 mL) under an atmosphere of argon. Diethyl chlorophosphate (1.7 mL, 12.0 mmol) was added slowly to the stirred reaction mixture and then allowed to warm to room temperature over 5 h. The excess acid was quenched by the addition of saturated aq. $NaHCO_3$ solution and the product extracted with ethyl acetate, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 10–80% ethyl acetate in hexanes) to give the desired product (1.0 g, 35%) as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.14–8.08 (m, 1H), 7.95 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.28–7.23 (m, 2H), 4.69 (s, 2H), 4.32–4.14 (m, 4H), 1.59 (s, 9H), 1.39 (t, *J* = 7.1 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 1H). LRMS (ESI) *m/z* 361.0 $[M + H]^+$.

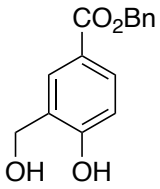
**Benzyl 3-formyl-4-hydroxybenzoate**




DIPEA was added to a solution of benzyl 4-hydroxybenzoate (5 g, 21.9 mmol), magnesium chloride (4.1 g, 43.8 mmol), formaldehyde (1.9 g, 65.7 mmol) in acetonitrile (73 mL) under an atmosphere of argon. The reaction mixture was heated at 70 ºC for 12 h and then cooled to room temperature. The mixture was treated with 1 M HCl solution and extracted with ethyl acetate, dried ($MgSO_4$) and

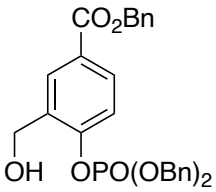
evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 0–15% ethyl acetate in hexanes) gave the desired product (2.2 g, 32%) as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 11.43 (s, 1H), 9.97 (s, 1H), 8.37 (d, *J* = 2.1 Hz, 1H), 8.25 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.49–7.45 (m, 2H), 7.45–7.32 (m, 3H), 7.06 (d, *J* = 8.7 Hz, 1H), 5.40 (s, 2H). LRMS (ESI) *m/z* 255.0 $[M - H]^-$.

**Benzyl 4-hydroxy-3-(hydroxymethyl)benzoate**



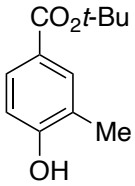

Sodium borohydride (366 mg, 9.68 mmol) was added to a cooled (0 ºC) solution of of benzyl 3-formyl-4-hydroxy-benzoate (1.24 g, 4.84 mmol) in THF (20 mL) under an atmosphere of argon. The reaction mixture was stirred at room temperature for 3 h and then the excess borohydride was quenched by the addition of saturated aq. $NH_4Cl$ solution and diluted with ethyl acetate. The organic phase was separated, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 20–80% ethyl acetate in hexanes) to give the desired product (1.09 g, 87%) as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.78 (d, *J* = 2.1 Hz, 1H), 7.49–7.32 (m, 5H), 6.93 (d, *J* = 8.5 Hz, 1H), 5.34 (s, 2H), 4.94 (s, 2H). LRMS (ESI) *m/z* 259.0 $[M + H]^+$.

**Benzyl 4-dibenzyloxyphosphoryloxy-3-(hydroxymethyl)benzoate**



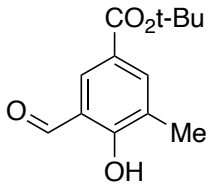

A solution of benzyl 4-hydroxy-3-(hydroxymethyl)benzoate (1.1 g, 4.22 mmol) in acetonitrile (14 mL) was slowly added to a cooled (5 ºC) solution of diisopropylethylamine (2.2 mL, 12.6 mmol), dibenzyl phosphonate (0.94 mL, 4.22 mmol), DMAP (103 mg, 0.84 mmol), carbon tetrachloride (1.63 mL, 16.88 mmol) in acetonitrile (10 mL) under an atmosphere of argon. The reaction mixture was left to stir at room temperature for 6 h and then diluted with ethyl acetate, washed with aqueous 1M HCl solution, brine solution, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 20–80% ethyl acetate in hexanes) provided the desired product (0.78 g, 35%) as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 2.4, 1.0 Hz, 1H), 7.94 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.49–7.25 (m, 16H), 7.25–7.06 (m, 2H), 5.38 (s, 2H), 5.15 (d, *J* = 9.0 Hz, 4H), 4.62 (s, 2H). LRMS (ESI) *m/z* 519.10 $[M + H]^+$.

***Tert*-butyl 4-hydroxy-3-methyl-benzoate**



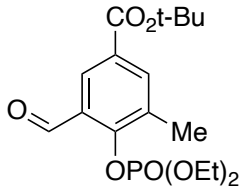

A solution of DCC **(**712 mg, 3.45 mmol) in THF (35 mL) was slowly added to a mixture of **4**-hydroxy-3-methyl-benzoic acid (500 mg, 3.29 mmol), 4-dimethylaminopyridine (150 mg, 1.23 mmol) mmol) in *tert*-butanol (45 mL) under an atmosphere of argon. After stirring for 4 h, the reaction mixture was filtered, and then evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 0–40% ethyl acetate in hexanes) provided the desired product (324 mg, 47%) as a colorless waxy solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.98–7.78 (m, 1H), 7.73–7.64 (m, 2H), 6.70 (d, *J* = 8.3 Hz, 1H), 2.29–2.17 (m, 3H) and 1.51 (s, 9H). LRMS (ESI) *m/z* 207.10 $[M - H]^-$.

***Tert*-butyl-4-hydroxy-3-methyl-5-(hydroxymethyl)-benzoate**



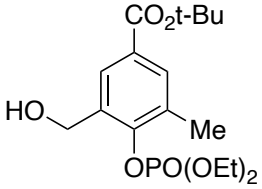

*Tert*-butyl 4-hydroxy-3-methyl-benzoate (2 g, 9.6 mmol) dissolved in THF (12 mL) was added to suspension of magnesium chloride (10 mesh, 1.8 g, 19.2 mmol), paraformaldehyde (864 mg, 28.8 mmol), and triethylamine (2.6 mL, 18.7 mmol) in THF (20 mL) under an atmosphere of argon. The reaction mixture was heated at 65 ºC for 4 h and then cooled to room temperature. The mixture was diluted with water and extracted with ethyl acetate, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The resulting product (1.97 g, 89%) was isolated as a yellow oil was taken through to the next step without further purification $^1$H NMR (500 MHz, $CDCl_3$) δ 11.60 (s, 1H), 9.92 (s, 1H), 8.09 (d, *J* = 2.2 Hz, 1H), 8.00 (d, *J* = 2.1 Hz, 1H), 2.29 (s, 3H), 1.60 (s, 9H). LRMS (ESI) *m/z* 237.0 $[M - H]^-$.

***Tert*-butyl 4-((di-*tert*-butoxyphosphoryl)oxy)-3-(hydroxymethyl)-5-methylbenzoate**



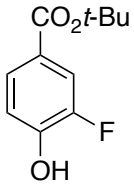

DIPEA (2.2 mL, 12.5 mmol) was added to a cooled (0 ºC) solution of *tert*-butyl 3-formyl-4-hydroxy-5-methyl-benzoate (1.97 g; 8.34 mmol) in dichloromethane (42 mL) under an atmosphere of argon at 0 ºC. diethyl chlorophosphate (1.81 mL, 12.5 mmol) was added slowly to the stirred reaction mixture and it was allowed to warm to room temperature over 20 hours. The excess HCl produced quenched by the addition of saturated aq. $NaHCO_3$ solution. The organic phase was extracted with ethyl acetate, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 10–80% ethyl acetate in hexanes) to give the desired product (2.02 g, 65%) as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.31 (d, *J* = 2.3 Hz, 1H), 8.09 (d, *J* = 2.2 Hz, 1H), 4.30–4.17 (m, 4H), 2.47 (s, 3H), 1.59 (s, 9H), 1.34 (td, *J* = 7.1, 1.1 Hz, 6H). LRMS (ESI) *m/z* 373.10 $[M + H]^+$.

***Tert*-butyl 4-((diethoxyphosphoryl)oxy)-3-(hydroxymethyl)-5-methylbenzoate**




Sodium borohydride (237 mg, 6.51 mmol) was added to a solution of *tert*-butyl 4-diethoxyphosphoryloxy-3-formyl-5-methyl-benzoate (2.02 g, 5.43 mmol) in EtOH (13.5 mL) under an atmosphere of argon. The reaction mixture was stirred at room temperature for 4 h and excess borohydride quenched by the addition of saturated aq. $NH_4Cl$ solution. The organic phase was extracted with ethyl acetate, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 20–70% ethyl acetate in hexanes) to give the desired product (1.11 g, 55%) as a crystalline white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 2.2 Hz, 1H), 7.81 (d, *J* = 2.5 Hz, 1H), 4.62 (s, 2H), 4.30–4.15 (m, 4H), 2.37 (s, 3H), 1.58 (s, 9H), 1.34 (td, *J* = 7.1, 1.2 Hz, 6H). LRMS (ESI) *m/z* 375.1 $[M + H]^+$.

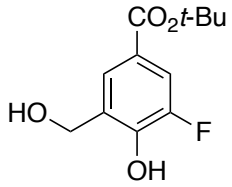
***Tert*-butyl 3-fluoro-4-hydroxy-benzoate**




1,1-Di-*tert*-butoxy-*N,N*-dimethyl-methanamine (5.81 mL, 25.6 mmol) was slowly added to a suspension of 3-fluoro-4-hydroxy-benzoic acid (2.0 g, 12.81 mmol) in toluene (25.6 mL) under an atmosphere of argon. The reaction mixture was heated at 100 ºC for 2 h. The reaction mixture was cooled to room

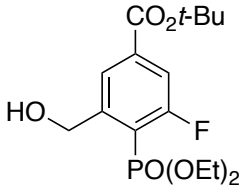
temperature and then evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 0–20% ethyl acetate in hexanes) to give the desired product (270 mg, 19%) as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.83–7.65 (m, 2H), 7.03 (t, *J* = 8.6 Hz, 1H), 1.60 (s, 9H). LRMS (ESI) *m/z* 211.10 [M – H]$^-$.

**_Tert_-butyl 3-fluoro-4-hydroxy-5-(hydroxymethyl)benzoate**



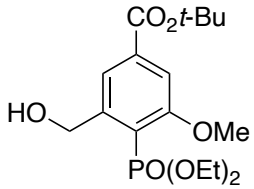

30% Formaldehyde (2.39 mL, 29.5 mmol) was added to a solution containing *tert*-butyl 3-fluoro-4-hydroxy-benzoate (250 mg, 1.18 mmol) in 0.5 M aq. NaOH solution (1 ml) and then heated at 60 ºC for 18 hours. Once cooled, the excess base was quenched by the addition of 1M HCl solution and extracted with ethyl acetate, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 10–50% ethyl acetate in hexanes) gave the desired product (46 mg, 16%) as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.76–7.63 (m, 1H), 7.61 (dd, *J* = 2.1, 1.1 Hz, 1H), 4.91 (s, 2H), 1.59 (s, 9H). LRMS (ESI) *m/z* 241.10 [M – H]$^-$.

***Tert*-butyl 4-diethoxyphosphoryloxy-3-fluoro-5-(hydroxymethyl)benzoate**



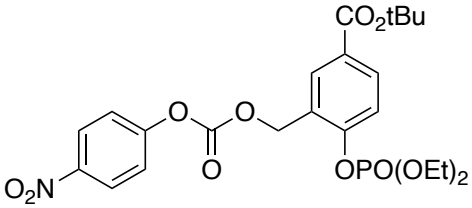

DIPEA (2.93 mL, 16.84 mmol) was added to a cooled (0 ºC) solution of *tert*-butyl 3-fluoro-4-hydroxy-5-(hydroxymethyl)benzoate (1.36 g, 5.61 mmol) in dichloromethane (18.7 mL) under an atmosphere of argon. The reaction was left to stir for 10 minutes and then diethyl chlorophosphate (1.2 mL, 8.42 mmol) was added dropwise. The reaction was warmed to room temperature over 3 h and then quenched by the addition of saturated aq. $NaHCO_3$ solution, extracted with dichloromethane, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 10–60% ethyl acetate in hexanes) gave the desired product (1.05 g, 49%) as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.93–7.92 (m, 1H), 7.76–7.72 (m, 1H), 4.69 (s, 2H), 4.37–4.24 (m, 4H), 1.61 (s, 9H) and 1.45–1.36 (m, 6H). LRMS (ESI) *m/z* 379.10 $[M + H]^+$.

***Tert*-butyl 3-chloro-4-(diethoxyphosphoryl)-5-(hydroxymethyl)benzoate**



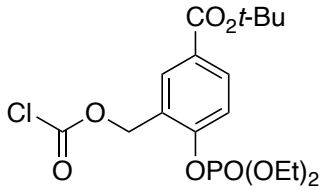

DIPEA (2.0 mL, 11.37 mmol) was added to a cooled (0 ºC) solution of *tert*-butyl 3-chloro-4-hydroxy-5-(hydroxymethyl)benzoate (1.7 g, 6.69 mmol) in dichloromethane (19 mL) under an atmosphere of argon. The reaction was left to stir for 10 minutes and then diethyl chlorophosphite (1.7 mL, 11.37 mmol) was added dropwise. The reaction was warmed to room temperature over 9 h and then quenched by the addition of saturated aq. $NaHCO_3$ solution, extracted with dichloromethane, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 10–60% ethyl acetate in hexanes) provided the desired product (2.1 g, 54%) as a colorless oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.71 (d, $J$ = 2.0 Hz, 1H), 7.45 (dd, $J$ = 4.6, 2.1 Hz, 1H), 5.22–5.12 (m, 2H), 4.23–4.08 (m, 4H), 3.89 (s, 3H), 1.55 (t, $J$ = 1.7 Hz, 9H), 1.36–1.15 (m, 6H). LRMS (ESI) *m/z* 391.10 $[M+H]^+$.

***Tert*-butyl 4-((diethoxyphosphoryl)oxy)-3-((((4 nitrophenoxy)carbonyl)oxy)methyl)benzoate**



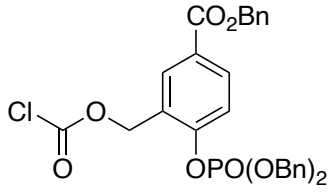

DIPEA (0.29 mL, 1.69 mmol) was added dropwise to a cooled (0 ºC) solution of *tert*-butyl 4-diethoxyphosphoryloxy-3-(hydroxymethyl)benzoate (304 mg, 84 mmol) and 4-nitrophenyl) carbonochloridate (290 mg, 1.43 mmol) in dichloromethane (4.2 mL) under an atmosphere of argon. The reaction was warmed to room temperature and stirred for 16 h. It was then quenched by the addition of saturated aq. $NaHCO_3$ solution, extracted with dichloromethane, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 10–60% ethyl acetate in hexanes) provided the desired product (342 mg, 66%) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.29 (d, *J* = 9.1 Hz, 2H), 8.11 (dd, *J* = 2.2, 1.0 Hz, 1H), 8.01 (dd, *J* = 8.6, 2.2 Hz, 1 H), 7.5 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.41 (d, *J* = 9.1 Hz, 2H), 4.26 (dqd, *J* = 8.5, 7.0, 4.3 Hz, 4H), 1.60 (s, 9H), 1.37 (td, *J* = 7.1, 1.0 Hz, 6H). LRMS (ESI) *m/z* 526.1 $[M + H]^+$.

***Tert*-butyl 3-(((chlorocarbonyl)oxy)methyl)-4-((diethoxyphosphoryl)oxy)benzoate**



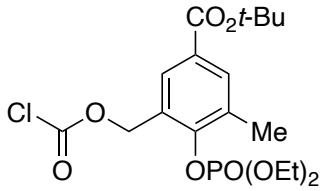

DIPEA (2.3 mL, 13.4 mmol) was added dropwise to a cooled (0 ºC) solution of *tert*-butyl 4-diethoxyphosphoryloxy-3-(hydroxymethyl)benzoate (2.41 g, 6.69 mmol) and triphosgene (2.0 g, 6.69 mmol) in THF (26.7 mL) under an atmosphere of argon. The reaction mixture was allowed to warm to room temperature over 2.5 h and then diluted with water and extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and then evaporated to dryness under reduced pressure to yield the desired product (2.71 g, 96%) as a clear oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.10–7.83 (m, 2H), 7.45 (dd, *J* = 8.6, 0.9 Hz, 1H), 5.34 (s, 2H), 4.34–4.18 (m, 4H), 1.53 (s, 9H), 1.29 (td, *J* = 7.1, 1.1 Hz, 6H).

**Benzyl 4-((bis(benzyloxy)phosphoryl)oxy)-3-(((chlorocarbonyl)oxy)methyl)benzoate**



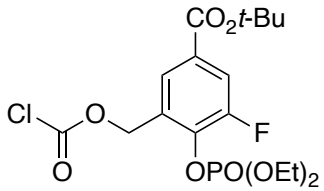

DIPEA (0.23 mL, 1.30 mmol) was added dropwise to a cooled (0 ºC) solution of dibenzyl [4-dibenzyloxyphosphoryl-2-(hydroxymethyl)phenyl] phosphate (672 mg, 1.30 mmol) and triphosgene (384 mg, 1.30 mmol) in THF (6.5 mL) under an atmosphere of argon. The reaction mixture was allowed to warm to room temperature over 2.5 h and then diluted with water and extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and then evaporated to dryness under reduced pressure to yield the desired product (741 mg, 98%) as a gold oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.07 (t, *J* = 1.8 Hz, 1H), 8.02 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.46–7.35 (m, 6H), 7.32–7.29 (m, 10H), 5.36 (s, 2H), 5.23 (s, 2H), 5.14 (s, 2H), 5.12 (s, 2H).

***Tert*-butyl 3-(((chlorocarbonyl)oxy)methyl)-4-((diethoxyphosphoryl)oxy)-5-methylbenzoate**



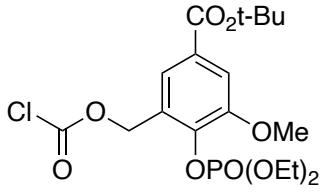

Synthesized in a similar manner to *tert*-butyl 3-(((chlorocarbonyl)oxy)methyl)-4-((diethoxyphosphoryl)oxy)benzoate. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 2H), 5.51 (s, 2H), 4.32–4.16 (m, 4H), 2.43 (s, 3H), 1.59 (s, 9H), 1.35 (t, *J* = 7.1 Hz, 6H).

***Tert*-butyl 3-(((chlorocarbonyl)oxy)methyl)-4-((diethoxyphosphoryl)oxy)-5-fluorobenzoate**



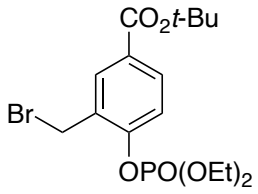

Synthesized in a similar manner to *tert*-butyl 3-(((chlorocarbonyl)oxy)methyl)-4-((diethoxyphosphoryl)oxy)benzoate. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 1.9 Hz, 1H), 7.73 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.42 (s, 2H), 4.29–4.13 (m, 4H), 1.52 (s, 9H), 1.32 (t, J = 7.1 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

***Tert*-butyl 3-(((chlorocarbonyl)oxy)methyl)-4-((diethoxyphosphoryl)oxy)-5-methoxybenzoate**



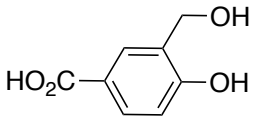
Synthesized in a similar manner to *tert*-butyl 3-(((chlorocarbonyl)oxy)methyl)-4-((diethoxyphosphoryl)oxy)benzoate. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 1.8 Hz, 2H), 5.45 (s, 2H), 4.31–4.21 (m, 4H), 3.93 (s, 3H), 1.59 (s, 9H), 1.37 (td, *J* = 7.0, 1.2 Hz, 6H).

**Synthesis of *tert*-butyl 3-(bromomethyl)-4-((diethoxyphosphoryl)oxy)benzoate**



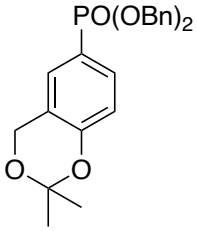

$PPh_3$ (291 mg, 1.11 mmol) was added to a cooled (0 ºC) solution of *tert*-butyl 4-diethoxyphosphoryloxy-3-(hydroxymethyl) benzoate (200 mg, 0.56 mmol) in dichloromethane (1.9 mL) under an atmosphere of argon. $CBr_4$ (368 mg, 1.11 mmol) was slowly added to the stirred reaction mixture and then allowed to warm to room temperature over 4.5 h. The reaction mixture was diluted by the addition of water and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and then evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 10–60% ethyl acetate in hexanes) provided the desired product (140 mg, 54%) as a colorless oil. $^1$H NMR (500 MHz, methanol-$d_4$) δ 8.02 (d, *J* = 1.8 Hz, 1H), 7.93 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 4.55 (s, 2H), 4.34–4.22 (m, 4H), 1.59 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H).

**4-Hydroxy-3-(hydroxymethyl)benzoic acid 9**



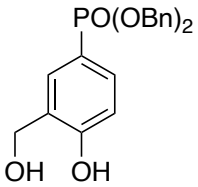

Trifluoroacetic acid (0.08 ml, 0.44 mmol) in dichloromethane (1.1 mL) was added to *tert*-butyl 4-hydroxy-3-(hydroxymethyl)benzoate (100 mg, 0.4459 mmol). The reaction was stirred at room temperature for 1 hr and then evaporated to dryness under reduced pressure. The residue was dissolved in THF (1.1 mL) and treated with aqueous 1M $NaHCO_3$ solution (0.44 mL). The resulting solution was added dropwise to the reaction solution and then concentrated under reduced pressure. Chromatography (C-18; 0–50% acetonitrile in water) provided the desired product (35 mg, 44%) as a white solid. $^1$H NMR (500 MHz, DMSO) δ 7.41–7.38 (m, 2H), 7.35 (br s, 1H), 4.51 (s, 2H). LRMS (ESI) *m/z* 166.9 $[M - H]^-$.

**6-Dibenzyloxyphosphoryl-2,2-dimethyl-4H-1,3-benzodioxine**



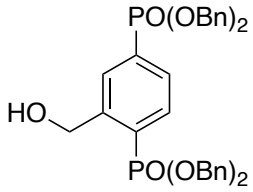

A mixture of 6-bromo-2,2-dimethyl-4H-1,3-benzodioxine (100 mg, 0.41 mmol), palladium tetrakis (47 mg, 0.04 mmol) and benzyloxyphosphonoyloxymethylbenzene (0.1 mL, 0.41 mmol) and triethylamine (0.07 mL, 0.49mmol) in THF (2 mL) was heated in a microwave reactor for 10 min at 120 ºC. The reaction was filtered, washing with dichloromethane and evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 10–50% ethyl acetate in hexanes) provided the desired product (84 mg, 48%) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.60 (ddd, *J* = 12.9, 8.4, 1.9 Hz, 1H), 7.43 (dd, *J* = 13.6, 1.8 Hz, 1H), 7.34 (d, *J* = 3.6 Hz, 10H), 6.87 (dd, *J* = 8.4, 3.8 Hz, 1H), 5.14–5.02 (m, 4H), 4.82 (s, 2H), 1.56 (s, 6H). LRMS (ESI) *m/z* 425.1 $[M + H]^+$.

**4-dibenzyloxyphosphoryl-2-(hydroxymethyl)phenol**



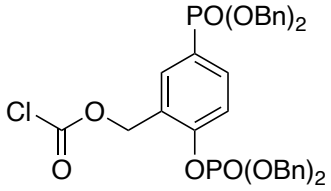

6-Dibenzyloxyphosphoryl-2,2-dimethyl-4H-1,3-benzodioxine (408 mg, 0.96 mmol) was dissolved in acetone (1 mL) and 1M aq. HCl solution (1 mL). The mixture was left to stir at room temperature for 24 h and then diluted with ethyl acetate, dried ($MgSO_4$), and evaporated to dryness under reduced pressure to give the desired product (330 mg, 80%) as a white solid. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.76 (ddt, *J* = 13.3, 2.1, 1.0 Hz, 1H), 7.48 (ddd, *J* = 12.8, 8.2, 2.1 Hz, 1H), 7.39–7.29 (m, 10H), 6.91 (dd, *J* = 8.2, 3.8 Hz, 1H), 5.04–4.94 (m, 4H), 4.52–4.45 (m, 2H). LRMS (ESI) *m/z* 385.0 $[M + H]^+$.

**Tetra-benzyl (2-(hydroxymethyl)-1,4-phenylene)bis(phosphonate)**



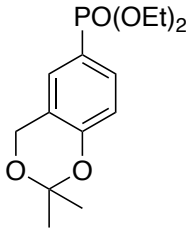

4-Dibenzyloxyphosphoryl-2-(hydroxymethyl)phenol (1.96 g, 5.10 mmol) in acetonitrile (50 mL) was added dropwise to a cooled (−10 ºC) flask containing 4-DMAP (cat.), Dibenzyl phosphite (1.5 mL, 6.63 mmol), DIPEA (2.0 mL, 15.30 mmol), and $CCl_4$ (2.0 mL, 20.40 mmol) under an atmosphere of argon. The resulting solution was allowed to warm to ambient temperature over 18 h, diluted with ethyl acetate, washed with 1M aq. HCl solution, brine solution, dried ($Na_2SO_4$) and evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 0–75% ethyl acetate in hexanes) gave the desired product (1.11 g, 34%) as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$) δ $^1$H NMR (500 MHz, methanol-$d_4$) δ 7.90 (dt, *J* = 13.6, 1.6 Hz, 1H), 7.60 (ddd, *J* = 13.2, 8.3, 2.0 Hz, 1H), 7.35–7.30 (m, 21 H), 5.48 (s, 4H), 5.16 (d, *J* = 9.5 Hz, 2H), 5.09–5.03 (m, 4H). LRMS (ESI) *m/z* 645.2 $[M + H]^+$.

**5-(Bis(benzyloxy)phosphoryl)-2-((bis(benzyloxy)phosphoryl)oxy)benzyl carbonochloridate**



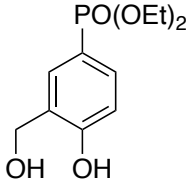

DIPEA (0.1 mL, 0.58 mmol) was added dropwise over 10 minutes to a cooled (0 ºC) solution of dibenzyl [4-dibenzyloxyphosphoryl-2-(hydroxymethyl)phenyl] phosphate (310 mg, 0.48 mmol) and triphosgene (160 mg, 0.53 mmol) in THF (6.5 mL) under an atmosphere of argon. The reaction was warmed to room temperature over 3 hours and then the excess triphosgene quenched by the addition of water. The organic phase was extracted with ethyl acetate, dried ($MgSO_4$) and evaporated to dryness under reduced pressure to yield the desired product (310 mg, 87%) as a clear oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.77–7.66 (m, 2H), 7.46–7.39 (m, 1H), 7.36–7.28 (m, 20H), 5.16 (d, *J*= 2.6 Hz, 2H), 5.15–5.11 (m, 4H), 5.11–5.00 (m, 4H).

**Diethyl (2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)phosphonate**



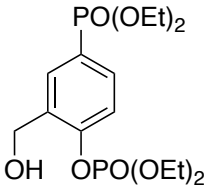

*n*-Butyllithium (1.6 M in hexanes, 16.0 mL) was added to a cooled solution (-78 ºC) of 6-bromo-2,2-dimethyl-4H-1,3-benzodioxine (5.68 g, 23.4 mmol) in THF (117 mL) under an atmosphere of argon. The mixture was allowed to stir at this temperature for 1.5 h before the dropwise addition of diethyl chlorophosphate (6.05 g, 35.1 mmol) in THF (16.0 mL). The mixture was allowed to stir at −78 ºC for 3 minutes before the cold bath was removed, and the reaction mixture was allowed to warm to room temperature. The reaction mixture was quenched with saturated aq. $NH_4Cl$, diluted with water, and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and then evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 30–60% ethyl acetate in hexanes) provided the desired product (5.10 g, 73%) as a pale-yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.56 (ddd, *J* = 12.6, 8.4, 1.8 Hz, 1H), 7.47 (dd, *J* = 13.2, 1.9 Hz, 1H), 6.87 (dd, *J* = 8.4, 3.7 Hz, 1H), 4.86 (s, 2H), 4.18 – 3.99 (m, 4H), 1.55 (s, 6H), 1.31 (t, *J* = 7.1 Hz, 6H). LRMS (ESI) *m/z* 301.1 $[M + H]^+$.

**Diethyl (4-hydroxy-3-(hydroxymethyl)phenyl)phosphonate**



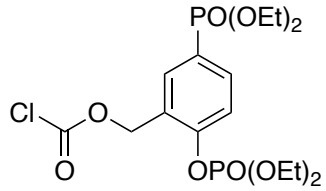
6-Diethoxyphosphoryl-2,2-dimethyl-4H-1,3-benzodioxine (1.55g, 5.16 mmol) was dissolved in THF (25 mL) and 1M aq. HCl solution (25 mL). The mixture was left to stir at room temperature for 24 h and then diluted with ethyl acetate, dried ($MgSO_4$), and evaporated to dryness under reduced pressure to give the desired product (1.3 g, 82%) as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 12.8, 8.4 Hz, 1H), 7.47 (d, *J* = 13.0 Hz, 1H), 6.97 (dd, *J* = 8.3, 3.8 Hz, 1H), 4.89 (s, 2H), 4.17–4.09 (m, 4H), 1.39–1.35 (m, 6H). LRMS (ESI) *m/z* 261.0 $[M + H]^+$.

**4-(Diethoxyphosphoryl)-2-(hydroxymethyl)phenyl diethyl phosphate**



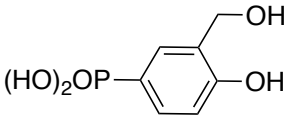

DIPEA (3.2 mL, 17.9 mmol) was added to a cooled (0 ºC) solution of 4-diethoxyphosphoryl-2-(hydroxymethyl)phenol (2.33 g, 8.95 mmol) in dichloromethane (45 mL) under an atmosphere of argon. The reaction was left to stir for 10 minutes and then diethyl chlorophosphate (2.2 mL, 15.2 mmol) was added dropwise. The reaction was warmed to room temperature over 18 h and then quenched by the addition of saturated aq. $NaHCO_3$ solution, extracted with dichloromethane, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 0–15% dichloromethane in MeOH) provided the desired product (5.2 g, 68%) as a golden oil. $^1$H NMR (500 MHz, CDCl3) δ 7.63–7.54 (m, 3H), 4.69 (s, 2H), 4.23 (dt, *J* = 8.2, 7.0 Hz, 4H), 4.16–3.92 (m, 4H), 1.39–1.33 (m, 6H), 1.31 (t, *J* = 7.1 Hz, 6H). LRMS (ESI) *m/z* 397.0 $[M + H]^+$.

**5-(Diethoxyphosphoryl)-2-((diethoxyphosphoryl)oxy)benzyl carbonochloridate**



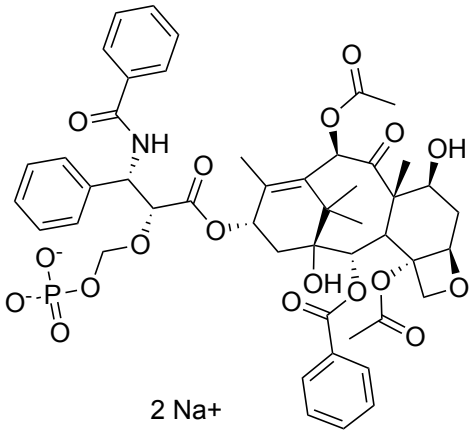

Synthesized in a similar manner to *tert*-butyl 3-(((chlorocarbonyl)oxy)methyl)-4-((diethoxyphosphoryl)oxy)benzoate. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 13.3 Hz, 1H), 7.76 (ddd, *J* = 12.9, 8.4, 2.0 Hz, 1H), 7.52 (dd, *J* = 8.4, 3.5 Hz, 1H), 4.66 (s, 2H), 4.32 – 4.21 (m, 4H), 4.19 – 4.04 (m, 4H), 1.38 (t, *J* = 7.1 Hz, 6H), 1.33 (t, *J* = 7.1 Hz, 6H).

**4-hydroxy-3-(hydroxymethyl)phenyl]phosphonic acid 10**




Bromotrimethylsilane (3.8 mL, 28.82 mmol) was added to a solution of 4-diethoxyphosphoryl-2-(hydroxymethyl)phenol (500 mg, 1.92 mmol) in dichloromethane (19 mL). Once complete, the reaction mixture was heated at 45 ºC for 72 hrs. The mixture was cooled to room temperature and the excess TMSBr quenched by the addition of methanol (30 mL) and then evaporated to dryness under reduced pressure. Chromatography (C-18; 0–20% acetonitrile in water) followed by lyophilization provided the desired product (135 mg, 34%) as a white solid. $^1$H NMR (500 MHz, $D_2O$) δ 7.57 (dd, *J* = 13.4, 2.0 Hz, 1H), 7.50 (ddd, *J* = 13.1, 8.3, 2.1 Hz, 1H), 6.88 (dd, *J* = 8.3, 3.4 Hz, 1H), 4.56 (s, 2H). LRMS (ESI) *m/z* 202.8 $[M - H]^-$.

**[(1R)-1-[(S)-benzamido(phenyl)methyl]-2-[[(1S,2S,4S,7R,9S,10S,12R,15S)-4,12-diacetoxy-2-benzoyloxy-1,9-dihydroxy-10,14,17,17-tetramethyl-11-oxo-6-oxatetracyclo[11.3.1.03,10.04,7]heptadec-13-en-15-yl]oxy]-2-oxo-ethoxy]methyl phosphate 8vii**.[3]

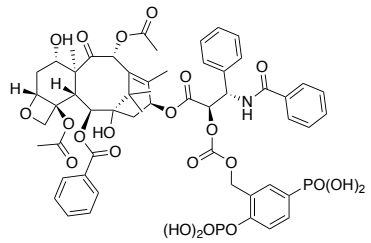


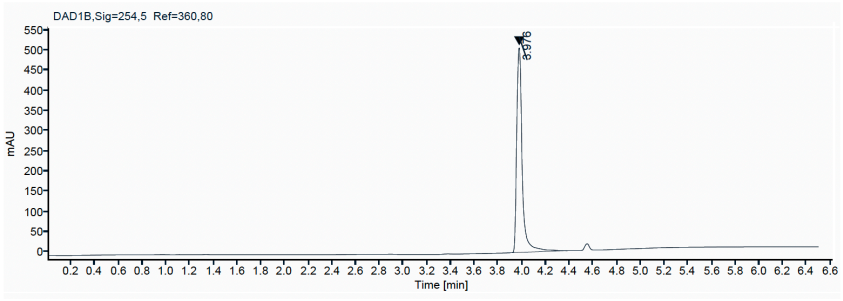

(1S,2S,4S,7R,9S,10S,12R,15S)-4,12-diacetoxy-15-[(2R,3S)-3-benzamido-2-hydroxy-3-phenyl-propanoyl]oxy-1,9-dihydroxy-10,14,17,17-tetramethyl-11-oxo-6-oxatetracyclo[11.3.1.03,10.04,7]heptadec-13-en-2-yl] benzoate (1 g, 1.2 mmol) was suspended in acetonitrile (6 mL) and cooled to 0 ºC under argon. Dimethylsulfide (0.69 mL, 9.4 mmol) was added, followed by benzoyl peroxide (1.13 g, 4.68 mmol) portion wise over 20 minutes and the reaction was allowed to stir at 0 ºC for 2h. The reaction mixture was diluted with ether (100 ml), washed with 1N NaOH (25 ml) and brine (25 ml), dried ($MgSO_4$) and evaporated to dryness under reduced pressure. Chromatography ($SiO_2$; 10–50% ethyl acetate in hexanes) provided [(1S,2S,4S,7R,9S,10S,12R,15S)-4,12-diacetoxy-15-[(2R,3S)-3-benzamido-2-(methylsulfanylmethoxy)-3-phenyl-propanoyl]oxy-1,9-dihydroxy-10,14,17,17-tetramethyl-11-oxo-6-oxatetracyclo[11.3.1.03,10.04,7]heptadec-13-en-2-yl] benzoate (620 mg, 58%). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.14–8.09 (m, 2H), 7.8–7.70 (m, 2H), 7.69–7.56 (m, 1H), 7.56–7.45 (m, 6H), 7.45–7.39 (m, 4H), 7.39–7.32 (m, 1H), 7.06 (d, *J* = 8.9 Hz, 1H), 6.51 (s, 1H), 6.20 (td, *J* = 8.9, 1.6 Hz, 1H), 5.80 (dd, *J* = 9.0, 2.6 Hz, 1H), 5.68 (d, *J* = 6.9 Hz, 1H), 4.94 (dd, *J* = 9.7, 2.0 Hz, 1H), 4.80 (d, *J* = 2.6 Hz, 1H), 4.66 (d, *J* = 2.0 Hz, 2H), 4.35–4.24 (m, 2H), 4.20 (dd, *J* = 8.4, 1.1 Hz, 1H), 3.86 (dd, *J* = 6.9, 1.0 Hz, 1H), 2.80 (ddd, *J* = 14.4, 9.8, 6.8 Hz, 1H), 2.38 (s, 3H), 2.35–2.28 (m, 2H), 2.18 (s, 3H), 2.12 (s, 3H), 1.94 (s, 3H), 1.90–1.82 (m, 2H), 1.76 (s, 6H), 1.22 (s, 3H), 1.19 (s, 3H). LRMS (ESI) *m/z* 914.3 $[M + H]^+$.

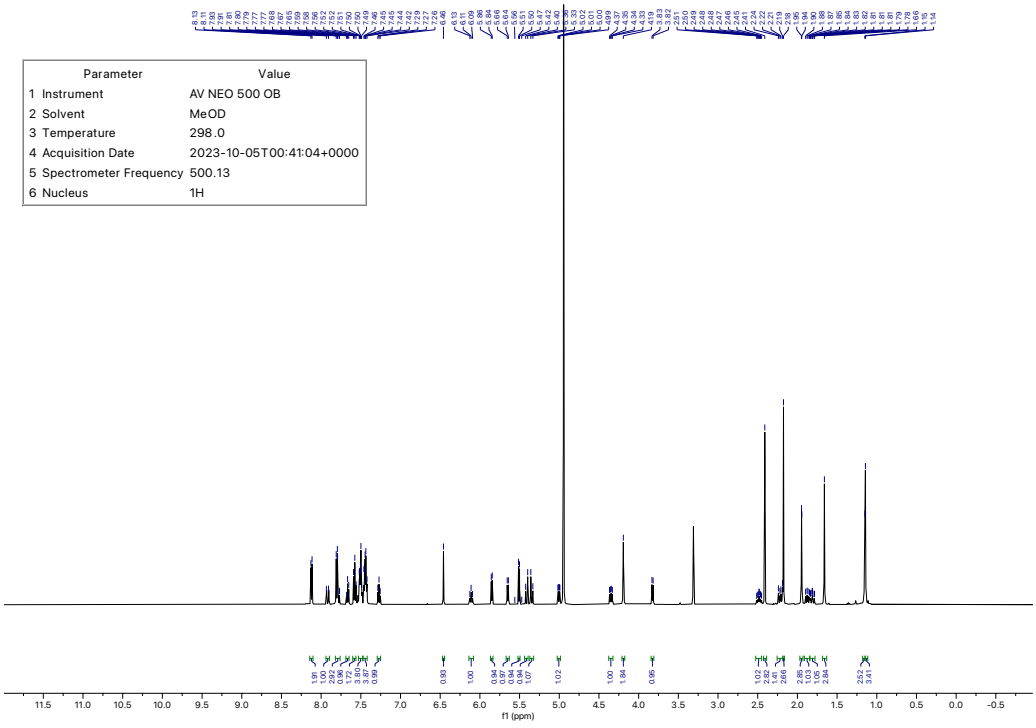
Phosphoric acid (926 mg, 9.45 mmol) was slowly added to a solution of [(1S,2S,4S,7R,9S,10S,12R,15S)-4,12-diacetoxy-15-[(2R,3S)-3-benzamido-2-(methylsulfanylmethoxy)-3-phenyl-propanoyl]oxy-1,9-dihydroxy-10,14,17,17-tetramethyl-11-oxo-6-oxatetracyclo[11.3.1.03,10.04,7]heptadec-13-en-2-yl] benzoate (720 mg, 0.79 mmol) and 4Å molecular sieves (1.5 g) in THF (4 mL). The reaction mixture was allowed to stir for 15 minutes at room temperature. Upon conclusion of the time interval, the reaction was placed in an ice water bath (0 ºC) and NIS (265 mg, 1.18 mmol) was added in one portion. The reaction mixture was allowed to gradually warm to room temperature over 2.5 h. The reaction mixture was quenched by the addition of 10% aq. solution of $Na_2S_2O_3$, basified with saturated aq. $NaHCO_3$ solution until pH 14 was reached. The reaction

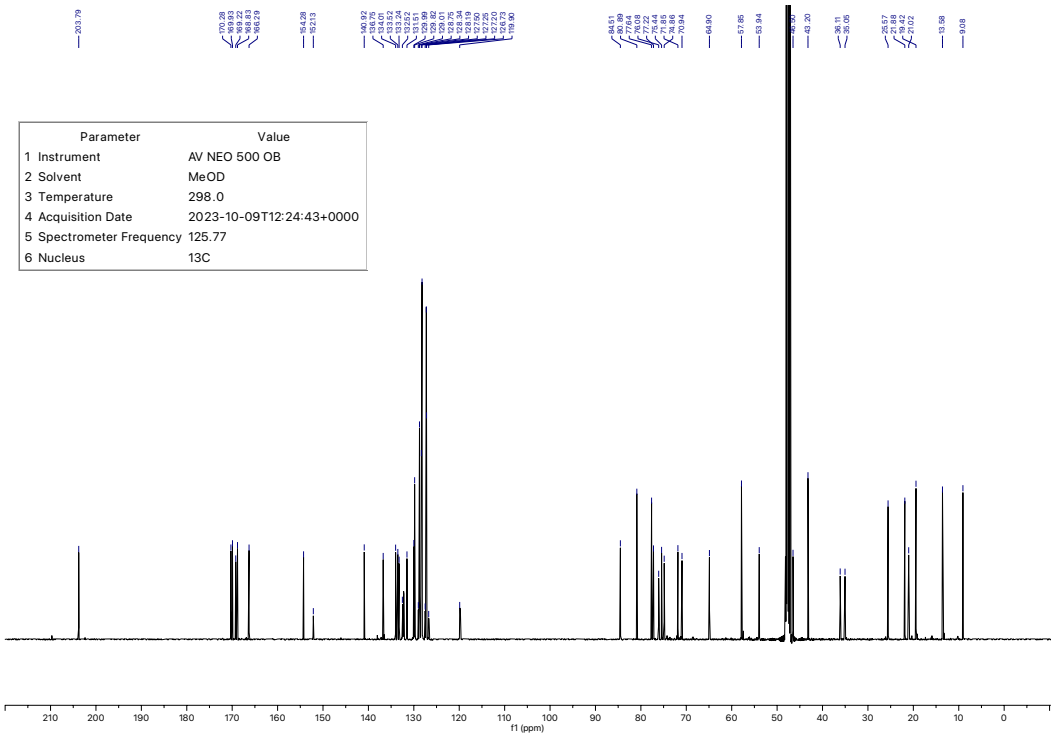
mixture was then diluted by the addition of MeOH (50 mL), filtered and evaporated to dryness under reduced pressure. Chromatography (C-18; 0–50% acetonitrile in water) followed by lyophilization provided **8vii** (470 mg, 59%) as a white solid. $^1$H NMR (500 MHz, $D_2O$) δ 8.08–7.88 (m, 2H), 7.75–7.66 (m, 3H), 7.61 (t, *J* = 7.9 Hz, 2H), 7.58–7.50 (m, 1H), 7.50–7.30 (m, 6H), 7.26–7.17 (m, 1H), 6.27 (s, 1H), 6.08–5.91 (m, 1H), 5.48 (d, *J* = 7.3 Hz, 1H), 5.37 (d, *J* = 7.4 Hz, 1H), 5.14–5.02 (m, 1H), 4.98 (t, *J* = 5.9 Hz, 1H), 4.86–4.75 (m, 2H), 4.27 (d, *J* = 8.7 Hz, 1H), 4.16 (d, *J* = 8.7 Hz, 1H), 4.10 (dd, *J* = 10.8, 6.7 Hz, 1H), 3.68 (d, *J* = 7.3 Hz, 1H), 2.91 (ddd, *J* = 16.1, 10.0, 6.6 Hz, 1H), 2.27 (s, 3H), 2.17 (s, 3H), 1.93–1.84 (m, 2H), 1.82 (d, *J* = 1.5 Hz, 3H), 1.61 (s, 4H), 1.09 (s, 3H), 1.03 (s, 3H). LRMS (ESI) *m/z* 962.3 $[M - H]^-$.

**Supplementary Fig. 2. HPLC, $^{1}H$, $^{13}C$ and $^{31}P$ NMR spectra for Sol-paclitaxel 8vi.**



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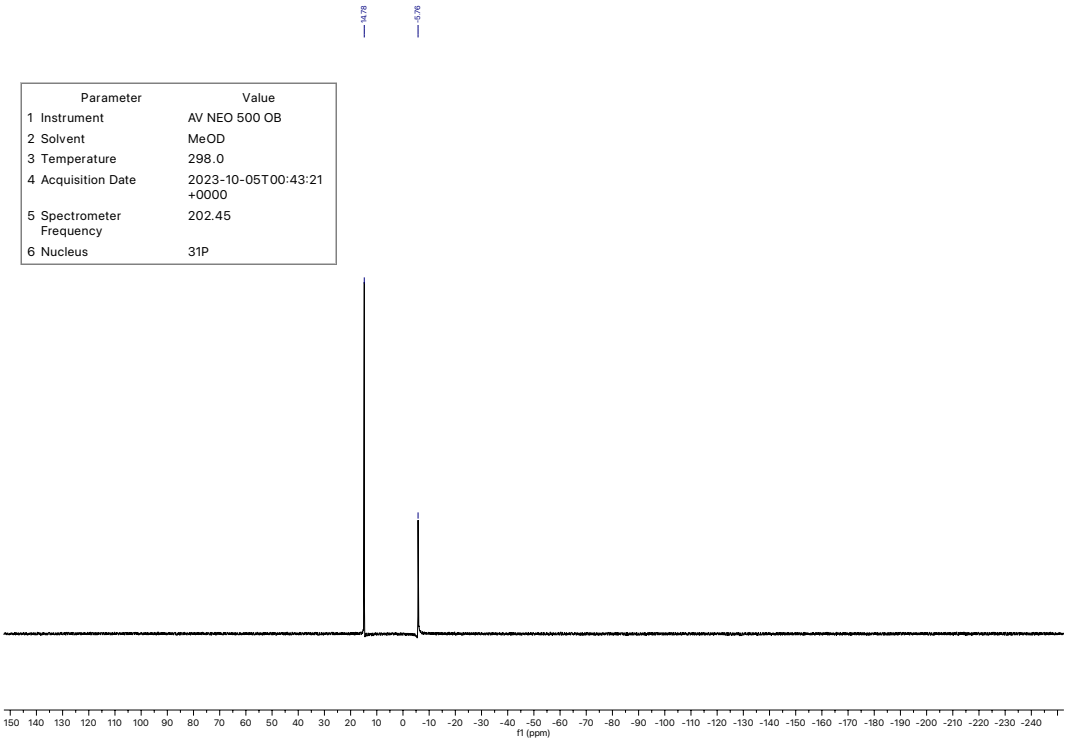
| 4 Acquisition Date | 2023-10-09T12:24:43+0000 |
| 5 Spectrometer Frequency | 125.77 |
| 6 Nucleus | 13C |

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| 5 Spectrometer Frequency | 202.45 |
| 6 Nucleus | 31P |

**Stability in simulated gastric fluid (SGF) and Hank's balanced salt solution (HBSS).**

10 μM of test compound was placed in 500 μL of either SGF or HBSS and incubated for 2 hours at 37 ºC. Aliquots of 25 μL were removed at 0, 60, and 120 min. 300 μL of acetonitrile was added along with an internal standard. The sample was vortexed for 3 minutes and then Sol-moiety-drug conjugate and released drug concentrations were measured by LC-MS/MS. The percentage of compound (Sol-moiety-drug conjugate) remaining as well as released drug was measured for each time point.

**Supplementary Table 1.** Stability of Sol-moiety-drug conjugates tested in SGF and HBSS.

| Compound | SGF (pH 1.2) $t_{1/2}$ min | HBSS (pH 6.5) $t_{1/2}$ min |
|---|---|---|
| **1i** | >120 | >120 |
| **2i** | >120 | >120 |
| **3ii** | >120 | >120 |
| **4i** | >120 | >120 |
| **5i** | >120 | >120 |
| **6i** | >120 | >120 |
| **7ii** | >120 | >120 |
| **8i** | >120 | >120 |
| **8vi** | >120 | >120 |
| **8vii** | >120 | >120 |

**Solubility study using simulated gastric fluid (SGF) and Hank's balanced salt solution (HBSS).** 10 mg/mL samples of each Sol-moiety-drug conjugate were prepared in Hank's balanced salt solution (HBSS) at a pH of 6.5. A series of dilutions were then performed to obtain concentrations of 8, 6, 4, and 2 mg/mL. A standard curve was generated using the peak area at each concentration by HPLC analysis. Λmax was measured for each prodrug utilizing UV-spec. Saturated solutions were prepared by dissolved prodrugs (1 mg) in HBSS (20 µL) or Simulated Gastric Fluid (SGF) (100 µL). The slurries were sonicated for 30 seconds and then centrifuged at 14,000 RPM for 10 min to pellet the insoluble prodrug. The supernatant was analyzed on HPLC, and the product peaks were integrated and compared to calibration curves to quantify the level of prodrug in solution.

**Supplementary Table 2.** Solubility of Sol-moiety-drug conjugates tested in SGF and HBSS.

| Compound | Solubility (mg/mL) in SGF (pH 1.2) | Solubility (mg/mL) in HBSS (pH 6.5) |
|---|---|---|
| **1i** | 0.45 | 47[a] |
| **1iii** | 0.22 | 44[a] |
| **1iv** | 0.40 | 29 |
| **1v** | 0.24 | >49[a] |
| **2i** | 0.080 | 29 |
| **2vi** | 0.66 | 37 |
| **3ii** | 0.35 | >49[a] |
| **4i** | 0.24 | 43 |
| **5i** | 0.23 | >49[a] |
| **6i** | 1.7 | 45 |
| **7ii** | 1.69 | >49[a] |
| **8i** | 0.022 | 0.1 |
| **8vi** | 0.66 | >49[a] |
| **8vii** | 0.024 | 0.1 |

[a] Maximum solubility was not determined due to limited supply of material.

**Hydrolysis in human placental alkaline phosphatase solution.** Human placental ALP (Sigma, 524604) (0.5 unit/mL) was incubated with prodrug (100 μM) in Tris Buffer (50 mM, pH 7.6) at 37 ºC in a final volume of 1 mL. The prodrug in buffer was preincubated at 37 ºC for 5 minutes and reactions were initiated with the addition of 100× enzyme. Aliquots (50 μL) were taken at 0 (immediately after mixing), 2, 4, 8, 16, 32, and 64 minutes and quenched in an equal volume acetonitrile + 0.1% formic acid. Disappearance of the prodrug and appearance of the parent drug were monitored utilizing low-resolution mass spectra on an Agilent LCMS iQ instrument and compared to standard curves for individual parent drugs. The hydrolysis and product formation rates were calculated from the slope of the linear portion of the plotted regression curve of product and converted to picomoles of parent drug available versus time. A control sample was incubated without enzyme and analyzed at the final timepoint.

**Supplementary Table 3.** Hydrolysis rates of Sol-moiety-drug conjugates using human placental alkaline phosphatase (0.5 units/mL).

| Compound | Drug formation rate (pmol/min) |
|---|---|
| **1i** | 4.16 |
| **1iii** | 2.97 |
| **1iv** | 3.43 |
| **1v** | 1.81 |
| **2i** | 0.64 |
| **2vi** | 1.15 |
| **3ii** | 1.26 |
| **4i** | 1.65 |
| **5i** | 2.11 |
| **6i** | 2.24 |
| **7ii** | 1.53 |
| **8i** | 2.13 |
| **8vi** | 1.44 |
| **8vii** | 2.03 |

**Supplementary References**


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2. Appel, R. Tertiary Phosphane/Tetrachloromethane, a Versatile Reagent for Chlorination, Dehydration, and P–N Linkage. *Angew. Chem. Int. Ed.,* **14**, 801–811 (1975).

3. Golik, J. et al. Synthesis and Antitumor Evaluation of Paclitaxel Phosphonooxymethyl Ethers: A Novel Class of Water Soluble Paclitaxel Pro-drugs. *Bioorg. Med. Chem*., **6**, 1837–184 (1996).