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The C-H coupling of arene with diazo-methylene-diphosphonates enables efficient synthesis of new diphosphonates, which exhibit dual MBL and SBL inhibition.

Rh(III)-Catalyzed Directed C-H Carbenoid Coupling Reveals Aromatic Bisphosphonates Inhibiting Metallo- and Serine- β -Lactamases

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Herein, we report the highly efficient and scalable Rh(III)-catalyzed C-H coupling of arenes with diazo-methylene-diphosphonates to give structurally diverse aromatic bisphosphonates in good to excellent yields. These bisphosphonates are one of very few classes of inhibitors acting against the mechanistically distinct metallo- β -lactamases and serine- β -lactamases and thus represent good starting points for the development of broad spectrum β -lactamase inhibitors.

Bisphosphonates were first synthesized in the 19th century and were developed as therapeutic drugs for disorders of bone metabolism in the 1960s.¹ To date, there are at least 10 clinically useful bisphosphonates (Fig. S1),² which are widely used to treat skeletal disorders, including osteoporosis, Paget's disease, osteogenesis imperfecta, and metastatic bone diseases.^{2, 3} Substantial evidence reveals bisphosphonates are also effective against multiple myeloma and bone metastasis, and are beneficial in relieving complex regional pain syndrome.⁴⁻⁶

The broad spectrum of the pharmacological properties and unique pharmacophore features of bisphosphonates has motivated efforts to develop new types of bisphosphonates and exploit them in new clinical applications. In particular, aromatic bisphosphonates have attracted attention because of their potential applications in biology, catalysis, and material sciences.⁷⁻¹⁰ However, traditional methods for preparation of aromatic bisphosphonates are based on nucleophilic substitution, which suffer from drawbacks, including low yield, tedious experimental procedures, and limited potential for functional group diversity.^{11, 12} Thus, the development of efficient methods to construct structurally diverse aromatic

Figure 1. Directed C-H bond functionalization with diazo compounds.

bisphosphonates is desirable. Transition metal-catalyzed carbenoid insertion into C-H bonds to build C-C bonds is a versatile, atom-economical synthetic strategy, which is attracting increased attention. For example, in 2012, Yu's group reported ortho-alkylation of Rh(III)-catalyzed directing-group-containing arene C-H bonds with diazomalonates to prepare aromatic malonic acids (Figure 1);¹³ more recently, Glorius,¹⁴ Wang,¹⁵ Li,¹⁶ and others^{17, 18} expanded and enriched this C-H functionalization method. We proposed that the transition metal-catalyzed directed C-H coupling with bisphosphonate carbenoid might be a promising strategy to synthesize new aromatic bisphosphonates, which we had identified as potential β -lactamase inhibitors on the basis of computational screens.

We describe how highly efficient and scalable Rh(III)-catalyzed directed methylene-diphosphonates carbenoid insertion into aromatic C-H bonds enables the one-step synthesis of aromatic bisphosphonates (Figure 1). Using this approach, we obtained a set of chemically diverse aromatic bisphosphonates in good to excellent yields. We used IFPTarget,¹⁹ a virtual target identification tool, to predict possible binding targets for the aromatic bisphosphonates. The results led to the identification of aromatic bisphosphonates as potential inhibitors of the New Delhi Metallo- β -lactamase (MBL) (NDM)-1 and Verona Integron-encoded MBL (VIM)-2,

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predictions, which were validated by enzymatic inhibition and biophysical assays. NDM-1 and VIM-2 are clinically relevant representatives of MBLs, which can hydrolyze almost all β -lactam antibiotics including carbapenems (*i.e.*, “last resort” antibiotics).²⁰⁻²²

Interestingly, some aromatic bisphosphonates also displayed potent inhibition of the clinically relevant serine- β -lactamase (SBL) TEM-1,^{23, 24} which is structurally and mechanistically distinct from the MBLs. Although a number of SBL and MBL inhibitors have been reported (Figure S2),^{20, 25-30} there is a lack of dual MBL/SBL inhibitors.^{21, 31} aromatic bisphosphonates presented here are good starting points for the development of broad spectrum β -lactamase inhibitors.

We began by attempting reactions of 2-phenylpyridine **1a** (0.2 mmol) with tetraethyl diazo-methylene-diphosphonate **2a** (0.24 mmol) in the presence of [Cp*RhCl₂]₂ (5.0 mol%) and AgSbF₆ (10.0mol%) at 80 °C in 1,2-dichloroethane (DCE, 2ml) for 24 h. The desired target product **3aa** was obtained in 81% yield under these initial conditions. We then used the reaction of **1a** with **2a** as a model for reaction optimization (Supplementary Table S1). The effect of metal catalysts, Ag salts, reaction time, solvent and temperature on reaction efficiency were investigated. Accordingly, the reaction conditions are optimized as follows: 5mol% [Cp*RhCl₂]₂, 10mol% Ag₂SO₄ in DCE at 80°C for 12 h gave an excellent isolated yield of 93%.

With the optimized conditions in hand, we then investigated the substrate scope of 2-phenylpyridines and their analogues in the C-H coupling with diazo-methylene-diphosphonate esters (Scheme 1). First, 2-phenylpyridines with various substituents were tested with **2a** as the diazo reagent. 2-Phenylpyridines with electron-donating substituents at different positions (ortho-, para-, or meta-position) of the 2-phenyl ring (e.g., Me, OMe, Ph, and t-Bu) gave the desired products in excellent yields (90–96%, Scheme 1), whereas electron-withdrawing groups containing 2-phenylpyridines (e.g., NO₂, CF₃, and COOMe) resulted in slightly lower respective yields of 78% and 84% (Scheme 1). These results indicate that the coupling efficiency is to some extent influenced by the electron density of the aromatic ring. We then investigated the coupling efficiency of **2a** with 2-phenylpyridine analogues, including benzo[h]quinolone, 2-(1-naphthalenyl)-pyridine, 2-(2-naphthalenyl)-pyridine, and 3-phenylisoquinoline (Scheme 1). Except for benzo[h]quinolone (**3pa**, 52% yield, Scheme 1), these substrates showed high reactivity in this transformation (**3qa-3ta**, Scheme 1). Notably, the reaction of **2a** with 3-(benzo[d][1,3]dioxol-5-yl)-7,8-dimethoxyisoquinoline (**1t**) produced two regioisomers **3ta** (40%) and **3ta**¹ (38%). Finally, *n*-butyl and benzyl diazo esters were also tested; the corresponding products **3ab** and **3ac** were obtained.

We next investigated the scope of the aromatic substrates with different directing groups in this C-H bond insertion reaction (Scheme 2). The tested substrates included 2-phenyl-pyrimidine, *N*-(2-pyrimidinyl)-indole, 1-phenylpyrazole, oximes, and azobenzene. The 2-phenylpyrimidines bearing electron-releasing and -withdrawing substituents were observed to be as effective substrates, giving the desired products **5a-5d** in

Scheme 1. Rh(III)-catalyzed directed C-H coupling of 2-phenylpyridines **1** with diazo-methylene-diphosphonates **2**. ^a Conditions: **1** (0.3mmol), **2** (0.36mmol), [Cp*RhCl₂]₂ (5mol%), Ag₂SO₄(10mol%), DCE (3 mL), 80 °C, 12 h, under an air atmosphere; Isolated yields are shown. ^b Reaction time extended to 24h.

65–93% yield (Scheme 2). When the amount of **2a** was increased to 2.4 equiv, the reactions with non-/para-substituted 2-phenylpyrimidines afforded di-alkylated products **5e** (90% yield) and **5f** (74% yield). The reaction of **2a** with *N*-(2-pyrimidinyl)-indole gave C-2 alkylated product **5g** in 67% yield. When AgNTf₂ was used as the Ag salt instead of Ag₂SO₄, 1-phenylpyrazole and azobenzene afforded the corresponding products **5h** (82% yield) and **5j** (92% yield). For acetophenone oxime **4i**, it was necessary to increase the reaction temperature to 120 °C to obtain the product **5i** in reasonable yield (52%, Scheme 2). Together, these results lead us to conclude that Rh(III)-catalyzed directed methylene-diphosphonates carbenoid insertion into aromatic C-H bonds is suitable for a wide range of substrates, and is a highly efficient strategy to obtain diverse aromatic bisphosphonates. Based on previous work¹³ and our preliminarily mechanistic experiments(see the Supporting Information), we propose the mechanism shown in Figure S3.

With aim to investigate the potential biological activity of the new aromatic bisphosphonates, we employed IFPTarget,¹⁹ a virtual target identification tool developed by us, to predict possible binding targets for **3aa acid**, the phosphoric acid form of **3aa**. Geranylgeranyl pyrophosphate synthase (GGPS) and farnesyl pyrophosphate synthase (FPPS), known targets of the FDA-approved bisphosphonate drugs,³ were ranked on the top of the retrieved database that contains 2842 unique targets (Table S2),¹⁹ demonstrating the effectiveness of IFPTarget in target identification. We noted that the NDM-1 and VIM-2 di-Zn(II) utilising metallo- β -lactamases (MBLs), which are clinically important targets for antibacterial resistance, were ranked as 37 and 50, respectively, in the IFPTarget derived list (Table S2).

Scheme 2. Scope of the directing group in Rh(III)-catalyzed C-H functionalization. ^a Conditions: **4** (0.3mmol), **2a** (0.36 mmol), [Cp*RhCl₂]₂ (5mol%), Ag₂SO₄(10mmol%), DCE (3 mL), 80 °C, 12 h, air atmosphere; isolated yields are shown. ^b **2a** was improved to 0.72mmol. ^c Using AgNTf₂ (10mmol%) as Ag salt. ^d Using AgNTf₂ (10mmol%) as Ag salt and reaction temperature up to 120 °C.

3aa acid was predicted to likely chelate with the active site zinc ions via one of its phosphonate groups and form key interactions with catalytically important residues of NDM-1 and VIM-2, in a related manner to the crystallographically observed binding modes of the known MBL inhibitors L-

captopril and ML302F

(Figure S4-5).

By using a fluorescence-based assay as described previously,^{22, 29, 30} we observed that **3aa acid** inhibits both NDM-1 and VIM-2 with 50% inhibitory concentrations (IC₅₀) of 32.04 and 11.07 μM (Table S3, Figure S6a-b), respectively; the known MBL inhibitors L-captopril and EDTA exhibited IC₅₀ of 46.38 and 2.07 μM to NDM-1, and 0.74 and 2.35 μM to VIM-2, respectively (Table S3). Encouraged by these results, we then tested whether **3aa acid** inhibits the clinically relevant serine-β-lactamase (SBL) TEM-1 and KPC-2, which are structurally and mechanistically different to NDM-1 and VIM-2, but which can be inhibited by compounds mimicking common intermediates in SBL and MBL catalysis. Surprisingly, **3aa acid** showed inhibition to TEM-1 with IC₅₀ value of 68.39 μM (Table S3, Figure S6c), but only weak inhibitory activity against KPC-2 (Figure S6d). We next tested the inhibitory activities of other aromatic bisphosphonates derived by Rh(III)-catalyzed directed C-H functionalization against NDM-1, VIM-2, TEM-1, and KPC-2. Many of these bisphosphonates displayed inhibition to NDM-1 and VIM-2, with IC₅₀ values ranging from 2.26 μM to 200 μM (Table S3, Figure S7-9); in general, they have lower IC₅₀s to VIM-2 than to NDM-1 (Table S3). In addition, some bisphosphonates, such as **3oa acid**, **3ra acid**, **3sa acid**, and **3ta acid**, showed sub-micromolar potency versus TEM-1 (Table S3). For comparison, we also tested the inhibitory activity of the bisphosphonate ester compounds (**3aa-3ta** and **5a-5j**, Table S4) to the four β-lactamases. Except for **3ta**¹ and **5i**, which showed sub-micromolar inhibition to NDM-1, VIM-2, and TEM-1, most of these compounds only have moderate/weak inhibitory

activities; we cannot rule out partial ester hydrolysis under the incubation conditions.

To investigate the inhibition modes of the aromatic bisphosphonates, we employed isothermal titration calorimetry (ITC) to investigate binding affinities and thermodynamic parameters,³³ using **3qa acid** (as a representative), which manifests IC₅₀ values of 17.11, 3.78, and 1.17 μM to NDM-1, VIM-2, and TEM-1 (Table S3), respectively (Figure 2a-c). The obtained K_d values of **3qa acid** to NDM-1 and VIM-2 are 1.71 μM and 0.893 μM (Figure 2d), respectively, consistent with the corresponding IC₅₀ values for NDM-1 (17.11 μM) and VIM-2 (3.78 μM). The binding affinity of **3qa acid** to TEM-1 is 7.10 μM, which is lower than that to NDM-1 and VIM-2, probably due to its different inhibition modes to NDM-1/VIM-2 (Figure 2d). The ITC analyses revealed that the initial binding of **3qa acid** to NDM-1 and TEM-1 is mainly contributed by entropy, whereas the binding to VIM-2 is more likely partial to the enthalpy contribution.

We then used the jump-dilution method^{30, 34} to examine the reversibility of enzymatic inhibition by **3qa acid**. Comparison of the binding of **3qa acid**, L-captopril, and EDTA to NDM-1 and VIM-2, revealed binding of **3qa acid** and L-captopril is fully reversible; **3qa acid** dissociates slightly quicker than L-captopril (Figure S10). By contrast, EDTA acts *via* sequestering NDM-1/VIM-2 active site zinc ions, manifesting in slow dissociation kinetics (Figure S10). Further kinetic assays revealed that **3qa acid** dose-dependently reduced the catalytic ability of NDM-1 and VIM-2 using assays with a fluorogenic substrate (Figure S11). For VIM-2, **3qa acid** likely binds *via* a substrate-competitive inhibition mode (Figure S11b), while for NDM-1, it appears as though a partially mixed inhibition mode applies (Figure S11a), as supported by molecular docking analyses (Figure S12-13). Interestingly, **3qa acid** manifested substantial time dependent inhibition of TEM-1 (Figure S11c);

Figure 2. The ITC analyses of **3qa acid** with NDM-1, VIM-2, and TEM-1. The curves of molar ratio to thermal effects of **3qa acid** titrating to (a) NDM-1, (b) VIM-2, (c) TEM-1, and (d) the obtained thermodynamic parameters, revealing that the binding of **3qa acid** to NDM-1 and TEM-1 is mainly contributed by entropy, while the binding to VIM-2 is more likely partial to the enthalpy contribution.

docking results indicated that the phosphate group is likely positioned close to the catalytically crucial serine (Ser70) (Figure S14).

We then used the established *E. coli* transsetta strain containing the pET28-lacUV5-VIM-2 plasmid (*E. coli*-VIM-2)³⁵ to preliminarily assess the activity of **3qa acid** in cells as described in Supplementary Experimental Section. Meropenem displayed a minimum inhibitory concentration (MIC) value of 16 µg/mL against the *E. coli*-VIM-2 strain, larger than that against the control *E. coli* strain (MIC < 0.125 µg/mL, Table S5), indicating that the *E. coli*-VIM-2 strain is suitable as a resistant cell model to assess the VIM-2 inhibitors. We observed that the MICs of meropenem in the absence or presence of **3qa acid** revealed that it resulted in 4 fold MIC reduction of meropenem to the *E. coli*-VIM-2 cells (Table S5), which has no visible activity to the *E. coli*-VIM-2 and *E. coli* cells at 100 µM, reflecting that **3qa acid** may inhibit VIM-2 in cells. The similar results were observed for **5g acid** (with IC₅₀ of 5.58 µM to VIM-2, Table S3).

Conclusions

In summary, we report the use of diazo-methylene-diphosphonates as reactants in the Rh(III)-catalyzed carbenoid ortho C-H coupling reaction to assemble aromatic bisphosphonates. This methodology is additional to existing transition metal-catalyzed carbenoid ortho C-H coupling reactions,¹³⁻¹⁸ and enables the efficient synthesis of structurally diverse aromatic bisphosphonates. The utility of the synthetic methodology for aromatic bisphosphonates is exemplified by computational and experimental assays, which reveal them as broad-spectrum inhibitors of clinically relevant MBLs and SBLs, which pose a serious threat to public health.^{21, 36} Since there are few reports of dual MBL/SBL inhibitors, partly due to the mechanistic and structural differences between them, aromatic bisphosphonates are excellent starting points for development. More generally, our C-H activation methodology for aromatic bisphosphonates will be useful in exploring the structurally unique bisphosphonate class of drugs more widely.

Conflicts of interest

There are no conflicts to declare

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Supplementary Information

Rh(III)-Catalyzed Directed C-H Carbenoid Coupling Reveals Aromatic Bisphosphonates Inhibiting Metallo- and Serine- β -Lactamases

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Supplementary Experimental Section

SE. 1. Chemical Synthesis.

1.1 General Information

Unless otherwise noted, all reactions were carried out in reaction vessels in sealed tubes. Reactions were carried out without any precautions to extrude moisture or air unless otherwise noted. Solvents used were of analytical purity. All reactions were monitored by thin-layer chromatography (TLC) and were visualized using UV light. Product purification was done using silica gel column chromatography. Thin layer chromatography (TLC) characterization was performed with precoated silica gel GF254 (0.2mm), while column chromatography characterization was performed with silica gel (100-200mesh). ^1H and ^{13}C spectra were recorded with tetramethylsilane as the internal standard. ^{13}C and ^{31}P spectra were recorded with broadband ^1H decoupling model. ^1H NMR spectra were recorded at 400 or 600 MHz, ^{13}C NMR spectra were recorded at 100 or 150 MHz and ^{31}P NMR spectra were recorded at 162 MHz. Chemical shifts (δ) were reported as parts per million (ppm) downfield from tetramethylsilane and the following abbreviations were used to identify the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad and all combinations thereof can be explained by their integral parts. HRMS spectra were recorded on a Waters Q-TOF Premier. Commercial reagents were from Best-reagent (Homepage: <http://www.best-reagent.com>) or Astatech Chemical Technology Co, Ltd. (Homepage: <http://www.astabio-chem.com>). All reagents were used without further purification.

1.2 Preparation of Substrates

2-Arylpyridine derivatives **1a-1r** were prepared via Suzuki coupling of the corresponding boronic acids and 2-bromopyridine using a reported procedure^{S1}. 2-phenylpyrimidine derivatives **1q, 1u-1y** and 3-phenylisoquinoline derivatives **1t, 1z** were prepared according to reported procedures^{S2-S4}. Substrate **1p** was commercially available and used without further purification. All substrates are shown in Scheme S1.

Preparation of 2-phenylpyridine^{S1}

To a solution of 2-bromopyridine (0.32 g, 2.0 mmol) in toluene (7 mL), ethanol (3.5

mL), and H₂O (7 mL) was added Na₂CO₃ (1.6 g, 15 mmol) followed by Pd(PPh₃)₄ (0.069 g, 0.060 mmol) and arylboronic acid (2.6 mmol) under argon in a 50 mL two-necked flask. The reaction mixture was refluxed for 5 h, then cooled to room temperature. To the reaction mixture was added aqueous NH₄Cl (15 mL); the mixture was then extracted with EtOAc three times; the organic extracts were dried over MgSO₄, then evaporated in vacuo to afford the crude product, which was purified by flash chromatography on silica gel to provide the desired products.

Preparation of 2-phenylpyrimidine^{S2}

To a 50 ml Schlenk tube was added Pd(PPh₃)₂Cl₂ (84 mg, 3.0 mol%), Na₂CO₃ (6.36 g, 60 mmol), phenylboronic acid (1.76 g, 14.4 mmol), 2-chloropyrimidine (1.36 g, 12 mmol), toluene (7 mL), ethanol (3.5 mL), and H₂O (7 mL). The reaction was heated to 105 °C and stirred for 5 h. After completion, the solvent was removed under reduced pressure and ethyl acetate was added which was washed with water and brine respectively. The combined organic layer was dried over anhydrous sodium sulfate and purified by silica gel column chromatography to afford the desired product.

Preparation of 3-phenylisoquinoline

Step 1: To a mixture of Pd(PPh₃)₂Cl₂ (379 mg, 5 mol %) and 2-bromobenzaldehyde (2.0 g, 10.8 mmol) in THF (77 ml) was added triethylamine (4.5 ml, 32.4 mmol). After being stirred for 10 min at room temperature, phenylacetylene (1.7 g, 16.2 mmol) and copper iodide (5 mol %) were added to the reaction mixture. The mixture was stirred at room temperature for 12h under argon. The reaction mixture was quenched with saturated aq. NH₄Cl, extracted with EtOAc three times, and washed with brine. The organic layers were dried over Na₂SO₄ and concentrated under reduced pressure after filtration. The crude mixture was purified by silica-gel column chromatography to provide the desired products^{S3-S4}.

Step 2: *t*-BuOH (47 ml) was added to a mixture of AgNO₃ (0.57 mmol, 0.1 equiv.), ammonium acetate (8.55 mmol, 1.5 equiv.) and 2-(phenylethynyl)-benzaldehyde (5.70 mmol, 1 equiv.) under argon atmosphere. The resulting mixture was stirred at room temperature; the reaction was monitored by TLC. After completion, the reaction was quenched by the addition of NaHCO₃ (0.48 mmol, 4 equiv.) at room temperature and

stirring was continued for additional 4 h. The mixture was then filtered through a cotton plug, washed with EtOAc (5–10 mL), then dried over anhydrous Na₂SO₄. The filtrate was evaporated under reduced pressure and the residue was purified through silica gel column chromatography to obtain the pure isoquinoline derivative ^{S5}.

Preparation of diazo-diphosphonates 2

Step 1: A mixture of 17.6g (0.1 mol) of bis-(dihydroxyphosphiny)-1-methane, and 40.0 g. (0.1 mol) of methane-diphosphonic acid tetraethyl ester was strongly heated to effect dissolution. PCl₅ (166 g, 0.8 mole) was added, with stirring, over a period of about half an hour to a cooled solution of the acid. During most of the addition of the PCl₅ in an ice-bath was employed. The mixture was heated several minutes to dissolve the last traces of PCl₅, then transferred to a larger vessel; 400 ml. of petroleum ether was added and crystallization was induced. The product was cooled in an ice-bath, filtered, and washed with 200 ml. of petroleum ether ^{S6}.

Step 2¹: A suspension of methylene bis-(phosphonic dichloride) (5.00 g, 20.0 mmol) was stirred rapidly in dry toluene (20 mL) at 0 °C. A mixture of dry benzyl alcohol (8.66 mL, 83.0 mmol) and dry pyridine (6.15 mL, 76.1 mmol) was added dropwise via an addition funnel over a 2-hour period, while the temperature was maintained at 0 °C. After the addition was complete, the reaction was allowed to reach 20 °C and stirred for a further 3 h. The solids were removed by filtration and washed twice with toluene (2 × 20 mL). The filtrate was washed twice with 2 M NaOH (2 × 15 mL) and water (15 mL), dried (MgSO₄), and concentrated in vacuo. Removal of benzyl alcohol impurity by distillation (120 °C, 1 mmHg) gave product as a colorless oil ^{S7}.

Step 2²: Methylene bis-(phosphonic dichloride) (5.00 g, 20.0 mmol) and 1H-tetrazole

(0.2 g, 3.5 mmol) were dissolved in 20 mL dry toluene, with vigorous stirring (under nitrogen). When the dissolution was complete, a solution of the alcohol (64.0 mmol) and diisopropylethylamine (6.12 mL, 70.4 mmol) in 20 mL of toluene was added dropwise through an addition funnel over a 2 hour period. After stirring the reaction overnight (about 16-18 hours) at room temperature under a nitrogen atmosphere, the solvent was removed in vacuo. The resulting residue was dissolved in hexane and the diisopropylammonium and tetrazonium salts were removed by filtration using a Hirsch funnel. The solution was concentrated in vacuo and the resulting crude product, a light yellow oil, was purified by flash chromatography (10:90 v/v acetone/hexane; first band)^{S8}.

Step 3: To a stirred solution of 60% NaH (1.8g, 4.5 mmol) in 100 ml dry THF was added methanediphosphonic acid tetra-ester (10.0g, 3.5 mmol) dropwise at 0°C under N₂. After 10 min stirring, Ts-N₃ (6.8 g, 3.5 mmol) was added dropwise. The resulting mixture was stirred at rt for 30 min. The reaction was quenched with water (10 mL), and the product was extracted with EtOAc (100 mL x 3). The combined organic layer was dried over MgSO₄ and evaporated. The crude compound was purified by column chromatography to get 6.0 g product as pale yellow oil^{S9}.

Scheme S1. Substrate Scope.

1.3 Experimental Procedures and Characterizations

1.3.1 General procedure for the synthesis of 3 (taking 3a as an example):

To a 15 ml tube was added **1a** (0.3 mmol, 46.56 mg), **2a** (0.36 mmol, 113.1 mg), [Cp*RhCl₂]₂ (9.20 mg 5mol%), Ag₂SO₄ (10.14 mg 10 mol%) in DCE (3.0 mL). The tube was sealed and stirred at 80°C for 12 h. After completion, the reaction mixture was concentrated in vacuo and purified by silica gel column chromatography (80:1 DCM/MeOH) to provide the product **3aa** (pale brown oil) in 93% yield.

1.3.2 Characterizations

Tetraethyl ((2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3aa). Yield 93%, pale brown oil, ¹H NMR (400 MHz, CDCl₃) δ 8.69 (d, *J* = 4.4 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.77 (td, *J* = 7.6, 1.4 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.48 – 7.34 (m, 3H), 7.32 – 7.20 (m, 1H), 5.09 (t, *J* = 25.6 Hz, 1H), 4.29 – 3.87 (m, 8H), 1.21 (t, *J* = 7.2 Hz, 6H), 1.15 (t, *J* = 7.2 Hz, 6H). ¹³C NMR (150 MHz, CDCl₃) δ 159.09, 149.10, 140.62, 136.57, 131.20, 130.36, 128.31, 128.07, 127.66, 124.55, 121.94, 63.31, 63.26, 62.74, 62.69, 39.78 (t, *J* = 130.5 Hz), 16.25, 16.21, 16.17, 16.13; ³¹P NMR (162 MHz, CDCl₃) δ 19.45; HRMS (ESI): *m/z* calculated for C₂₀H₂₉NO₆P₂ [M+Na⁺]: 464.1362, found: 464.1366.

Tetraethyl ((3-methyl-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ba).

Yield 72%, pale yellow oil, ^1H NMR (400 MHz, CDCl_3) δ 8.71 (d, $J = 4.4$ Hz, 1H), 7.82 (d, $J = 7.6$ Hz, 1H), 7.75 (t, $J = 7.6$ Hz, 1H), 7.39 (d, $J = 7.6$ Hz, 1H), 7.34 – 7.28 (m, 2H), 7.21 (d, $J = 7.6$ Hz, 1H), 4.10 – 3.94, (m, 8H), 3.72 (t, $J = 25.2$ Hz, 1H), 2.02 (s, 3H), 1.24 (t, $J = 6.8$ Hz, 6H), 1.18 (t, $J = 6.8$ Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 158.25, 149.60, 136.73, 136.12, 129.48, 127.83, 127.77, 127.74, 125.57, 122.14, 112.47, 63.38, 63.30, 62.79, 62.74, 41.45 (t, $J = 130.5$ Hz), 20.77, 16.30, 16.26, 16.24, 16.20; ^3P NMR (162 MHz, CDCl_3) δ 19.12 18.79; HRMS (ESI): m/z calculated for $\text{C}_{21}\text{H}_{31}\text{NO}_6\text{P}_2$ $[\text{M}+\text{Na}]^+$: 478.1519, found: 478.1513.

Tetraethyl ((3-methoxy-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ca).

Yield 68%, pale yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.65 (d, $J = 4.4$ Hz, 1H), 7.85 (t, $J = 7.6$ Hz, 1H), 7.44 – 7.31 (m, 4H), 7.08 (d, $J = 7.6$ Hz, 1H), 3.99 – 3.74 (m, 9H), 3.67 (s, 3H), 1.12 (t, $J = 6.8$ Hz, 6H), 1.02 (t, $J = 6.8$ Hz, 6H); ^{13}C NMR 126.15, 122.17, 119.23, 110.29, 63.39, 62.78, 55.76, 40.89 (t, $J = 137.0$ Hz), 16.32; ^{31}P NMR (162 MHz, $\text{DMSO}-d_6$) δ 18.69; HRMS (ESI): m/z calculated for $\text{C}_{21}\text{H}_{31}\text{NO}_7\text{P}_2$ $[\text{M}+\text{Na}]^+$: 494.1468, found: 494.1463.

Tetraethyl ((4-methyl-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3da).

Yield 96%, pale yellow oil, ^1H NMR (400 MHz, CDCl_3) δ 8.66 (d, $J = 4.4$ Hz, 1H), 7.82 (s, 1H), 7.75 (t, $J = 7.6$ Hz, 1H), 7.53 (d, $J = 7.6$ Hz, 1H), 7.33 (d, $J = 7.6$ Hz, 1H), 7.24 (dd, $J = 7.6, 5.6$ Hz, 1H), 7.19 (d, $J = 7.6$ Hz, 1H), 5.14 (t, $J = 26.0$ Hz, 1H), 4.15 – 3.97 (m, 8H), 2.42 (s, 3H), 1.21 (t, $J = 7.2$ Hz, 6H), 1.15 (t, $J = 7.2$ Hz, 6H); ^{13}C 130.24, 128.49, 127.79, 124.58, 121.70, 63.21, 63.17, 62.67, 62.63, 39.57 (t, $J =$

130.5 Hz), 21.36, 16.27, 16.23, 16.15, 16.11; ^{31}P NMR (162 MHz, CDCl_3) δ 19.58; HRMS (ESI): m/z calculated for $\text{C}_{21}\text{H}_{31}\text{NO}_6\text{P}_2$ $[\text{M}+\text{Na}^+]$: 478.1519, found: 478.1513.

Tetraethyl ((4-methoxy-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ea).

Yield 83%, yellow oil, ^1H NMR (400 MHz, CDCl_3) δ 8.68 (d, $J = 4.4$ Hz, 1H), 7.94 (d, $J = 8.0$ Hz, 1H), 7.77 (td, $J = 8.0, 1.3$ Hz, 1H), 7.56 (d, $J = 8.0$ Hz, 1H), 7.267 (d, $J = 8.0$ Hz, 1H), 7.00 – 6.95 (m, 2H), 4.89 (t, $J = 26.0$ Hz, 1H), 4.16 – 3.93 (m, 8H), 3.84 (s, 3H), 1.22 (t, $J = 7.2$ Hz, 6H), 1.17 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 158.90, 158.74, 149.12, 141.88, 136.58, 132.38, 124.47, 122.05, 119.82, 115.73, 113.99, 63.19, 62.62, 55.29, 39.06 (t, $J = 130.5$ Hz), 16.24; ^{31}P NMR (162 MHz, CDCl_3) δ 19.73; HRMS (ESI): m/z calculated for $\text{C}_{21}\text{H}_{31}\text{NO}_7\text{P}_2$ $[\text{M}+\text{Na}^+]$: 494.1468, found: 494.1462.

Tetraethyl ((4-chloro-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3fa).

Yield 78%, yellow oil, ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 8.69 (d, $J = 4.4$ Hz, 1H), 7.97 (t, $J = 7.6$ Hz, 1H), 7.85 (d, $J = 8.4$ Hz, 1H), 7.64 (d, $J = 7.6$ Hz, 1H), 7.56 (d, $J = 8.4$ Hz, 1H), 7.54 (s, 1H), 7.48 – 7.42 (m, 1H), 5.21 (t, $J = 25.2$ Hz, 1H), 3.98 – 3.82 (m, 8H), 1.11 (t, $J = 7.2$ Hz, 6H), 1.01 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.72, 149.18, 142.03, 136.71, 133.49, 132.52, 130.16, 128.24, 126.96, 124.39, 122.34, 63.21, 62.71, 39.35 (t, $J = 130.0$ Hz), 16.14; ^{31}P NMR (162 MHz, $\text{DMSO}-d_6$) δ 18.75; HRMS (ESI): m/z calculated for $\text{C}_{20}\text{H}_{28}\text{ClNO}_6\text{P}_2$ $[\text{M}+\text{Na}^+]$: 498.0973, found: 498.0976.

Tetraethyl ((4-nitro-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ga). Yield

78%, yellow oil, ^1H NMR (600 MHz, DMSO- d_6) δ 8.74 (d, $J = 4.4$ Hz, 1H), 8.36 (d, $J = 8.4$ Hz, 1H), 8.27 (s, 1H), 8.10 (d, $J = 8.4$ Hz, 1H), 8.04 (t, $J = 7.8$ Hz, 1H), 7.74 (d, $J = 7.8$ Hz, 1H), 7.55 – 7.48 (m, 1H), 5.40 (t, $J = 24.6$ Hz, 1H), 4.14 – 3.70 (m, 8H), 1.12 (t, $J = 7.2$ Hz, 6H), 1.02 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 157.01, 149.39, 147.00, 141.68, 137.22, 136.47, 132.50, 125.14, 124.61, 122.95, 122.73, 63.45, 63.41, 63.16, 63.12, 40.29 (t, $J = 130.5$ Hz), 16.27, 16.23, 16.22, 16.18; ^{31}P NMR (162 MHz, DMSO- d_6) δ 17.85; HRMS (ESI): m/z calculated for $\text{C}_{20}\text{H}_{28}\text{NO}_8\text{P}_2$ [$\text{M}+\text{Na}^+$]: 509.1213, found: 509.1217.

Tetraethyl ((2-(pyridin-2-yl)-4-(trifluoromethyl)phenyl)methylene)bis(phosphonate) (3ha). Yield 56%, yellow oil, ^1H NMR (600 MHz, DMSO- d_6) δ 8.72 (d, $J = 4.4$ Hz, 1H), 8.06 (d, $J = 7.8$ Hz, 1H), 8.00 (t, $J = 7.8$ Hz, 1H), 7.87 (d, $J = 8.4$ Hz, 1H), 7.79 (s, 1H), 7.68 (d, $J = 7.8$ Hz, 1H), 7.51 – 7.45 (m, 1H), 5.30 (t, $J = 25.2$ Hz, 1H), 4.02 – 3.83 (m, 8H), 1.12 (t, $J = 7.2$ Hz, 6H), 1.00 (t, $J = 7.2$ Hz, 6H). ^{13}C NMR (150 MHz, CDCl_3) δ 157.78, 149.28, 141.14, 136.86, 132.73, 131.74, 129.74 (q, $J = 32.4$ Hz), 128.76, 127.08, 124.78, 124.57, 122.51, 63.32, 63.27, 62.93, 62.89, 40.02 (t, $J = 130.5$ Hz), 16.23, 16.18, 16.15, 16.11; ^{31}P NMR (162 MHz, DMSO- d_6) δ 18.36; HRMS (ESI): m/z calculated for $\text{C}_{21}\text{H}_{28}\text{F}_3\text{NO}_6\text{P}_2$ [$\text{M}+\text{Na}^+$]: 532.1236, found: 532.1233.

Methyl 4-(bis(diethoxyphosphoryl)methyl)-3-(pyridin-2-yl)benzoate (3ia). Yield 63%, yellow oil, ^1H NMR (600 MHz, DMSO- d_6) δ 8.71 (d, $J = 4.4$ Hz, 1H), 8.10 – 7.94 (m, 4H), 7.64 (d, $J = 7.8$ Hz, 1H), 7.50 – 7.44 (m, 1H), 5.29 (t, $J = 25.2$ Hz, 1H), 4.10 – 3.66 (m, 11H), 1.11 (t, $J = 7.2$ Hz, 6H), 0.99 (t, $J = 7.2$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 158.16, 149.02, 140.55, 136.81, 133.68, 131.37, 130.73, 129.22, 128.97, 128.68, 124.57, 122.29, 63.27, 62.79, 40.04 (t, $J = 130.2$ Hz), 16.13; ^{31}P NMR (162 MHz, DMSO- d_6) δ 18.34; HRMS (ESI): m/z calculated for $\text{C}_{22}\text{H}_{31}\text{NO}_8\text{P}_2$ [$\text{M}+\text{Na}^+$]: 522.1417, found: 522.1412.

Tetraethyl ((5-methyl-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ja).

Yield 96%, yellow solid, mp 145-147 °C, ^1H NMR (400 MHz, CDCl_3) δ 8.68 (d, J = 4.4 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.25 (s, 2H), 7.23 (s, 1H), 4.91 (t, J = 25.6 Hz, 1H), 4.11 – 3.96 (m, 8H), 2.38 (s, 3H), 1.21 (t, J = 7.2 Hz, 6H), 1.16 (t, J = 7.2 Hz, 6H). ^{13}C NMR (150 MHz, CDCl_3) δ

121.88, 63.24, 62.63, 39.56 (t, J = 130.0 Hz), 21.06, 16.24; ^{31}P NMR (162 MHz, CDCl_3) δ 19.59; HRMS (ESI): m/z calculated for $\text{C}_{21}\text{H}_{31}\text{NO}_6\text{P}_2$ $[\text{M}+\text{Na}^+]$: 478.1519, found: 478.1513.

Tetraethyl ((5-(tert-butyl)-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ka).

Yield 96%, yellow oil, ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 8.66 (d, J = 4.4 Hz, 1H), 7.98 – 7.89 (m, 2H), 7.57 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 7.8 Hz, 2H), 7.40 – 7.36 (m, 1H), 5.40 (t, J = 25.2 Hz, 1H), 4.01 – 3.74 (m, 8H), 1.32 (s, 9H), 1.08 (t, J = 7.2 Hz, 6H), 0.98 (t, J = 7.2 Hz, 6H). ^{13}C NMR (150 MHz, CDCl_3) δ 158.68, 151.23, 148.57, 137.05, 130.08, 128.80, 127.52, 124.67, 124.44, 121.85, 63.24, 63.20, 62.60, 62.55, 39.95 (t, J = 132.0 Hz), 34.69, 31.09, 16.27, 16.23, 16.18, 16.14; ^{31}P NMR (162 MHz, $\text{DMSO}-d_6$) δ 19.46; HRMS (ESI): m/z calculated for $\text{C}_{24}\text{H}_{37}\text{NO}_6\text{P}_2$ $[\text{M}+\text{Na}^+]$: 520.1988, found: 520.1981.

Tetraethyl ((5-fluoro-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3la).

Yield 67%, yellow solid, mp 112-114 °C, ^1H NMR (600 MHz, DMSO- d_6) δ 8.66 (d, J = 4.4 Hz, 1H), 7.94 (t, J = 7.8 Hz, 1H), 7.60 (d, J = 10.2 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.28 (t, J = 7.8 Hz, 1H), 5.31 (t, J = 25.2 Hz, 1H), 3.98 – 3.80 (m, 8H), 1.10 (t, J = 7.2 Hz, 6H), 0.99 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, CDCl₃) δ 162.06 (d, J = 246.0 Hz), 158.17, 149.04, 136.74, 131.88 (d, J = 8.0 Hz), 130.84 (dd, J = 16.0, 8.0 Hz), 124.53, 122.02, 118.10 (d, J = 23.0 Hz), 114.71 (d, J = 21.0 Hz), 63.24, 63.92, 39.93 (t, J = 131.0 Hz), 16.16; ^{31}P NMR (162 MHz, DMSO) δ 18.58; HRMS (ESI): m/z calculated for C₂₀H₂₈FNO₆P₂ [M+Na⁺]: 482.1268, found: 482.1263.

Tetraethyl ((5-chloro-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ma).

Yield 87%, pale yellow solid, mp 147-148 °C, ^1H NMR (600 MHz, DMSO- d) δ 8.67 (d, J = 4.4 Hz, 1H), 7.95 (t, J = 7.8 Hz, 1H), 7.85 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.42 (dd, J = 7.8, 1.8 Hz, 1H), 5.32 (t, J = 25.2 Hz, 1H), 4.00 – 3.81 (m, 8H), 1.11 (t, J = 7.2 Hz, 6H), 0.99 (t, J = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, CDCl₃) δ 158.08, 149.14, 138.95, 136.74, 134.16, 131.46, 131.12, 130.42, 127.77, 124.51, 122.17, 63.33, 63.28, 62.85, 62.81, 39.79 (t, J = 132.0 Hz), 16.23, 16.19, 16.15, 16.11; ^{31}P NMR (162 MHz, DMSO- d) δ 18.55; HRMS (ESI): m/z calculated for C₂₀H₂₈ClNO₆P₂ [M+Na⁺]: 498.0973, found: 498.0980.

Tetraethyl ((5-acetyl-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3na).

Yield 84%, pale yellow oil, ^1H NMR (600 MHz, DMSO- d_6) δ 8.70 (d, J = 4.8 Hz, 1H), 8.44 (d, J = 1.8 Hz, 1H), 7.98 (t, J = 8.4 Hz, 2H), 7.63 (d, J = 7.8 Hz, 2H), 7.45 (dd, J = 7.8, 4.8 Hz, 1H), 5.33 (t, J = 25.2 Hz, 1H), 3.97 – 3.83 (m, 8H), 2.60 (s, 3H), 1.09 (t, J = 7.2 Hz, 6H), 1.00 (t, J = 7.2 Hz, 6H), ^{13}C NMR (100 MHz, CDCl₃) δ 197.56, 158.02, 149.16, 144.61, 136.79, 136.40, 131.91, 130.66, 129.05, 126.85, 124.55, 122.50, 63.21, 62.83, 39.55 (t, J = 131.0 Hz), 26.66, 16.17; ^{31}P NMR (162

506.1468, found: 506.1468.

Tetraethyl ((4-(pyridin-2-yl)-[1,1'-biphenyl]-3-yl)methylene)bis(phosphonate) (3oa).

Yield 96%, pale brown oil, ^1H NMR (600 MHz, $\text{DMSO-}d_6$) δ 8.69 (d, $J = 4.2$ Hz, 1H), 8.19 (s, 1H), 7.96 (t, $J = 7.8$ Hz, 1H), 7.73 (d, $J = 7.8$ Hz, 1H), 7.68 (d, $J = 7.8$ Hz, 2H), 7.63 (d, $J = 7.8$ Hz, 1H), 7.59 (d, $J = 7.8$ Hz, 1H), 7.52 (t, $J = 7.8$ Hz, 2H), 7.41 (d, $J = 7.8$, 2H), 5.43 (t, $J = 25.2$ Hz, 1H), 3.99 – 3.81 (m, 8H), 1.11 (t, $J = 7.2$ Hz, 6H), 0.96 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.80, 149.07, 140.49, 139.93, 139.35, 136.52, 130.73, 129.88, 128.72, 128.64, 127.49, 126.91, 125.93, 124.41, 121.85, 63.19, 62.64, 39.78 (t, $J = 133.0$ Hz), 16.14; ^{31}P NMR (162 MHz, $\text{DMSO-}d_6$) δ 19.27; HRMS (ESI): m/z calculated for $\text{C}_{26}\text{H}_{33}\text{NO}_6\text{P}_2$ [$\text{M}+\text{Na}^+$]: 540.1675, found: 540.1671.

Tetraethyl (benzo[h]quinolin-10-ylmethylene)bis(phosphonate) (3pa). Yield 52%, pale brown solid, mp 88-90 °C, ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.35 (t, $J = 26.4$ Hz, 1H), 9.01 (d, $J = 3.2$ Hz, 1H), 8.49 (d, $J = 8.0$ Hz, 1H), 8.19 (d, $J = 8.0$ Hz, 1H), 8.04 (d, $J = 8.0$ Hz, 1H), 7.99 (d, $J = 8.8$ Hz, 1H), 7.89 (d, $J = 8.8$ Hz, 1H), 7.78 – 7.69 (m, 2H), 4.10 – 3.96 (m, 4H), 3.82 – 3.68 (m, 4H), 1.12 (t, $J = 7.2$ Hz, 6H), 0.78 (t, $J = 7.2$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 148.11, 146.29, 136.27, 135.40, 132.74, 129.83, 129.29, 128.73, 127.67, 127.26, 125.39, 121.19, 62.67, 62.51, 39.50 (t, $J = 130.0$ Hz), 16.19, 16.00; ^{31}P NMR (162 MHz, $\text{DMSO-}d_6$) δ 20.59; HRMS (ESI): m/z calculated for $\text{C}_{22}\text{H}_{29}\text{NO}_6\text{P}_2$ [$\text{M}+\text{Na}^+$]: 488.1362, found: 488.1365.

Tetraethyl ((3-(pyridin-2-yl)naphthalen-2-yl)methylene)bis(phosphonate) (3qa).

Yield 91%, pale yellow oil, ^1H NMR (600 MHz, DMSO- d_6) δ 8.70 (d, $J = 4.4$ Hz, 1H), 8.35 (s, 1H), 8.06 (s, 1H), 7.98 (dd, $J = 7.2, 1.2$ Hz, 2H), 7.91 (d, $J = 7.8$ Hz, 1H), 7.71 (d, $J = 7.8$ Hz, 1H), 7.59 – 7.54 (m, 2H), 7.46 – 7.42 (m, 1H), 5.44 (t, $J = 25.8$ Hz, 1H), 4.00 – 3.90 (m, 4H), 3.88 – 3.78 (m, 4H), 1.11 (t, $J = 7.2$ Hz, 6H), 0.94 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.04, 148.81, 136.91, 132.76, 132.26, 130.92, 129.97, 128.06, 127.75, 126.71, 126.60, 125.66, 124.99, 122.03, 119.24, 63.31, 62.74, 39.53 (t, $J = 129.0$ Hz), 16.21; ^{31}P NMR (162 MHz, DMSO- d_6) δ 19.24. HRMS (ESI): m/z calculated for $\text{C}_{24}\text{H}_{31}\text{NO}_6\text{P}_2$ [$\text{M}+\text{Na}^+$]: 514.1519, found: 514.1513.

Tetraethyl ((1-(pyridin-2-yl)naphthalen-2-yl)methylene)bis(phosphonate) (3ra).

Yield 90%, pale brown oil, ^1H NMR (600 MHz, DMSO- d_6) δ 8.80 (d, $J = 4.2$ Hz, 1H), 8.02 – 8.00 (m, 2H), 7.96 (t, $J = 7.8$ Hz, 2H), 7.53 – 7.51 (m, 2H), 7.44 (d, $J = 7.8$ Hz, 1H), 7.42 – 7.39 (m, 1H), 7.16 (d, $J = 8.4$ Hz, 1H), 3.97 – 3.77 (m, 9H), 1.13 (dt, $J = 14.4, 7.2$ Hz, 6H), 0.98 (dt, $J = 14.4, 7.2$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.27, 149.72, 138.52, 136.10, 132.67, 132.50, 128.10, 127.84, 127.27, 126.60, 126.29, 126.13, 125.87, 122.47, 63.15, 62.73, 42.04 (t, $J = 132.0$ Hz), 16.15; ^{31}P NMR (162 MHz, DMSO- d_6) δ 18.71, 18.15; HRMS (ESI): m/z calculated for $\text{C}_{24}\text{H}_{31}\text{NO}_6\text{P}_2$ [$\text{M}+\text{Na}^+$]: 514.1519, found: 514.1517.

Tetraethyl ((2-(isoquinolin-3-yl)phenyl)methylene)bis(phosphonate) (3sa). Yield 90%, pale brown oil, ^1H NMR (600 MHz, DMSO- d_6) δ 8.80 (d, J = 4.2 Hz, 1H), 8.02 – 8.00 (m, 2H), 7.96 (t, J = 7.8 Hz, 2H), 7.53 – 7.51 (m, 2H), 7.44 (d, J = 7.8 Hz, 1H), 7.42 – 7.39 (m, 1H), 7.16 (d, J = 8.4 Hz, 1H), 3.97 – 3.77 (m, 9H), 1.13 (dt, J = 14.4, 7.2 Hz, 6H), 0.98 (dt, J = 14.4, 7.2 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.27, 149.72, 138.52, 136.10, 132.67, 132.50, 128.10, 127.84, 127.27, 126.60, 126.29, 126.13, 125.87, 122.47, 63.15, 62.73, 42.04 (t, J = 132.0 Hz), 16.15; ^{31}P NMR (162 MHz, DMSO- d_6) δ 18.71, 18.15; HRMS (ESI): m/z calculated for $\text{C}_{24}\text{H}_{31}\text{NO}_6\text{P}_2$ $[\text{M}+\text{Na}^+]$: 491.1627, found: 491.1622.

Tetraethyl ((6-(7,8-dimethoxyisoquinolin-3-yl)benzo[d][1,3]dioxol-5-yl)methylene)bis(phosphonate) (3ta). Yield 40%, yellow oil, ^1H NMR (400 MHz, DMSO- d_6) δ 9.44 (s, 1H), 7.91 (s, 1H), 7.78 (q, J = 9.0 Hz, 2H), 7.35 (s, 1H), 7.12 (s, 1H), 6.13 (s, 2H), 5.17 (t, J = 25.6 Hz, 1H), 4.02 (s, 3H), 3.99 (s, 3H), 3.97 – 3.83 (m, 8H), 1.10 (t, J = 7.2 Hz, 6H), 1.02 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.40, 148.87, 147.22, 147.12, 146.78, 143.79, 132.02, 122.76, 122.60, 121.60, 120.37, 120.15, 110.89, 110.59, 101.34, 63.13, 62.67, 61.60, 56.99, 56.95, 39.95 (t, J = 133.0 Hz), 16.18; ^{31}P NMR (162 MHz, DMSO- d_6) δ 19.39; HRMS (ESI): m/z calculated for $\text{C}_{27}\text{H}_{35}\text{NO}_{10}\text{P}_2$ $[\text{M}+\text{Na}^+]$: 618.1628, found: 618.1625.

Tetraethyl((5-(7,8-dimethoxyisoquinolin-3-yl)benzo[d][1,3]dioxol-4-yl)-methylene)-bis(phosphonate) (3ta^I). Yield 38%, pale yellow oil, ^1H NMR (400 MHz, DMSO- d_6) δ 9.39 (s, 1H), 7.87 (s, 1H), 7.79 (s, 2H), 7.00 (q, J = 8.0 Hz, 2H), 6.08 (s, 2H), 5.47 (t, J = 27.2 Hz, 1H), 4.01 – 3.80 (m, 14H), 1.08 (t, J = 6.8 Hz, 6H), 1.02 (t, J = 6.8 Hz,

6H); ^{13}C NMR (101 MHz, CDCl_3) δ 152.51, 150.96, 148.77, 147.47, 146.35, 132.27, 124.43, 122.65, 122.55, 120.33, 120.19, 117.15, 110.33, 107.56, 101.17, 62.99, 62.44, 61.62, 57.01, 56.96, 38.28 (t, $J = 132.0$ Hz), 16.21; ^1P NMR (162 MHz, $\text{DMSO}-d_6$) δ 18.87; HRMS (ESI): m/z calculated for $\text{C}_{27}\text{H}_{35}\text{NO}_{10}\text{P}_2$ $[\text{M}+\text{Na}]^+$: 618.1628, found:

Tetrabutyl ((2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ab). Yield 50%, pale yellow oil, ^1H NMR (600 MHz, CDCl_3) δ 8.69 (d, $J = 4.8$ Hz, 1H), 8.02 (d, $J = 6.6$ Hz, 1H), 7.78 (t, $J = 6.6$ Hz, 1H), 7.55 (d, $J = 7.8$ Hz, 1H), 7.44 (t, $J = 7.8$ Hz, 2H), 7.41 (d, $J = 7.8$ Hz, 1H), 7.39 (s, 1H), 5.12 (t, $J = 25.8$ Hz, 1H), 4.93 – 3.93 (m, 8H), 1.57 – 1.53 (m, 4H), 1.52 – 1.47 (m, 4H), 1.30 – 1.25 (m, 8H), 0.86 (dt, $J = 15.0$, 7.2 Hz, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.09, 148.97, 140.43, 136.48, 131.28, 130.27, 128.30, 128.17, 127.49, 124.44, 121.83, 66.70, 66.31, 39.64 (t, $J = 132.0$ Hz), 32.33, 18.50, 13.51; ^{31}P NMR (162 MHz, $\text{DMSO}-d_6$) δ 19.31; HRMS (ESI): m/z calculated for $\text{C}_{28}\text{H}_{45}\text{NO}_6\text{P}_2$ $[\text{M}+\text{Na}]^+$: 576.2614, found: 576.2617.

Tetrabenzyl ((2-(pyridin-2-yl)phenyl)methylene)bis(phosphonate) (3ac). Yield 82%, pale yellow oil, ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 8.64 (d, $J = 4.2$ Hz, 1H), 7.97 (d, $J = 7.2$ Hz, 1H), 7.79 (t, $J = 7.2$ Hz, 1H), 7.48 – 7.43 (m, 3H), 7.37 – 7.34 (m, 1H), 7.34 – 7.21 (m, 13H), 7.18 (d, $J = 7.2$ Hz, 4H), 7.06 (d, $J = 7.2$ Hz, 4H), 5.74 (t, $J = 27.0$, 1H), 4.98 – 4.80 (m, 8H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.96, 148.78, 140.56, 136.72, 136.25, 131.60, 130.51, 128.55, 128.34, 128.30, 128.12, 128.03, 127.99, 127.85, 127.77, 124.54, 121.92, 68.39, 68.17, 40.10 (t, $J = 131.0$ Hz); ^{31}P NMR (162 MHz, $\text{DMSO}-d_6$) δ 20.04. HRMS (ESI): m/z calculated for $\text{C}_{40}\text{H}_{37}\text{NO}_6\text{P}_2$ $[\text{M}+\text{Na}]^+$: 712.1988, found: 712.1984.

Tetraethyl ((3-methyl-2-(pyrimidin-2-yl)phenyl)methylene)bis(phosphonate) (5a).

Yield 65%, pale yellow oil, ^1H NMR (600 MHz, DMSO- d_6) δ 8.97 (d, J = 4.8 Hz, 2H), 7.66 (d, J = 7.8 Hz, 1H), 7.51 (t, J = 4.8 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.26 (d, J = 7.8 Hz, 1H), 4.06 (t, J = 25.2 Hz, 1H), 3.95 – 3.73 (m, 8H), 2.05 (s, 3H), 1.10 (t, J = 6.6 Hz, 6H), 1.00 (t, J = 6.6 Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 166.96, 156.93, 139.26, 136.75, 129.75, 128.38, 128.27, 128.11, 118.97, 63.41, 63.37, 62.75, 62.70, 41.02 (t, J = 130.5 Hz), 20.81, 16.24; ^{31}P NMR (162 MHz, DMSO- d_6) δ 18.78; HRMS (ESI): m/z calculated for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_6\text{P}_2$ [$\text{M}+\text{Na}^+$]: 479.1471, found: 479.1478.

Tetraethyl ((4-methyl-2-(pyrimidin-2-yl)phenyl)methylene)bis(phosphonate) (5b).

Yield 93%, pale yellow oil, ^1H NMR (600 MHz, DMSO- d_6) δ 8.94 (d, J = 4.8 Hz, 2H), 7.81 (s, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.48 (t, J = 4.8 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 6.23 (t, J = 25.8 Hz, 1H), 3.96 – 3.77 (m, 8H), 2.36 (s, 3H), 1.08 (t, J = 7.2 Hz, 6H), 0.95 (t, J = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 166.73, 156.90, 137.36, 137.12, 132.01, 131.71, 130.55, 126.43, 118.62, 63.09, 62.52, 38.86 (t, J = 130.5 Hz), 21.07, 16.17; ^{31}P NMR (162 MHz, DMSO- d_6) δ 19.63; HRMS (ESI): m/z calculated for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_6\text{P}_2$ [$\text{M}+\text{Na}^+$]: 479.1471, found: 479.1473.

Tetraethyl ((4-methoxy-2-(pyrimidin-2-yl)phenyl)methylene)bis(phosphonate) (5c).

Yield 82%, pale yellow oil, ^1H NMR (400 MHz, DMSO- d_6) δ 8.97 (d, J = 4.8 Hz, 2H), 7.79 (d, J = 8.8 Hz, 1H), 7.54 (s, 1H), 7.50 (t, J = 4.8 Hz, 1H), 7.11 (dd, J = 8.8, 2.4 Hz, 1H), 6.20 (t, J = 26.0 Hz, 1H), 3.96 – 3.88 (m, 4H), 3.88 – 3.76 (m, 8H), 1.10 (t, J = 6.8 Hz, 6H), 0.96 (t, J = 6.8 Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 166.32, 158.76, 156.87, 138.38, 133.01, 121.35, 118.77, 116.32, 115.85, 63.05, 62.46, 55.28, 38.40 (t, J = 130.5 Hz), 16.13; ^{31}P NMR (162 MHz, DMSO- d_6) δ 19.76; HRMS

(ESI): m/z calculated for $C_{20}H_{30}N_2O_7P_2$ $[M+Na]^+$: 495.1420, found: 495.1423.

Methyl 4-(bis(diethoxyphosphoryl)methyl)-3-(pyrimidin-2-yl)benzoate (5d). Yield 91%, pale yellow oil, 1H NMR (600 MHz, $DMSO-d_6$) δ 9.03 (d, $J = 4.8$ Hz, 2H), 8.65 (s, 1H), 8.08 (d, $J = 8.4$ Hz, 1H), 8.03 (d, $J = 8.4$ Hz, 1H), 7.57 (t, $J = 4.8$ Hz, 1H), 6.48 (t, $J = 25.8$ Hz, 1H), 4.03 – 3.93 (m, 4H), 3.92 – 3.82 (m, 7H), 1.10 (t, $J = 7.2$ Hz, 6H), 0.97 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.46, 165.76, 157.04, 137.53, 134.96, 132.76, 132.02, 130.19, 129.41, 119.05, 63.28, 63.24, 62.76, 62.72, 52.17, 39.65 (t, $J = 130.5$ Hz), 16.15; ^{31}P NMR (162 MHz, $DMSO-d_6$) δ 18.58; HRMS (ESI): m/z calculated for $C_{21}H_{30}N_2O_8P_2$ $[M+Na]^+$: 523.1370, found: 523.1375.

Octaethyl((2-(pyrimidin-2-yl)-1,3-phenylene)bis(methanetriyl))tetrakis(phosphonate) (5e). Yield 90%, pale yellow oil, 1H NMR (400 MHz, $DMSO-d_6$) δ 9.04 (d, $J = 4.8$ Hz, 2H), 7.83 (d, $J = 8.0$ Hz, 2H), 7.56 (t, $J = 4.8$ Hz, 1H), 7.50 (t, $J = 8.0$ Hz, 1H), 4.41 (t, $J = 25.6$ Hz, 2H), 3.93 – 3.79 (m, 16H), 1.11 (t, $J = 6.8$ Hz, 12H), 1.01 (t, $J = 6.8$ Hz, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.75, 156.93, 130.56, 129.43, 128.24, 119.18, 63.26, 62.68, 41.16 (t, $J = 130.5$ Hz), 16.21; ^{31}P NMR (162 MHz, $DMSO-d_6$) δ 18.70; HRMS (ESI): m/z calculated for $C_{28}H_{48}N_2O_{12}P_4$ $[M+Na]^+$: 751.2050, found: 751.2053.

Octaethyl((5-methyl-2-(pyrimidin-2-yl)-1,3-phenylene)bis(methanetriyl))tetrakis(phosphonate) (5f). Yield 74%, pale yellow solid, mp 71–73 °C, 1H NMR (400 MHz,

DMSO-*d*₆) δ 9.02 (d, *J* = 4.8 Hz, 2H), 7.65 (s, 2H), 7.54 (t, *J* = 4.8 Hz, 1H), 4.48 (t, *J* = 25.6 Hz, 2H), 3.94 – 3.77 (m, 16H), 2.36 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 12H), 1.01 (t, *J* = 7.2 Hz, 12H); ¹³C NMR (150 MHz, CDCl₃) δ 165.89, 156.84, 137.98, 136.46, 131.23, 129.14, 118.96, 63.19, 62.62, 40.91 (t, *J* = 130.5 Hz), 21.55, 16.21; ³¹P NMR (162 MHz, DMSO-*d*₆) δ 18.79; HRMS (ESI): *m/z* calculated for C₂₉H₅₀N₂O₁₂P₄ [M+Na⁺]: 765.2206, found: 765.2203.

Tetraethyl ((1-(pyrimidin-2-yl)-1H-indol-2-yl)methylene)bis(phosphonate) (5g).

Yield 67%, pale yellow solid, mp 167-169 °C, ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.99 (d, *J* = 4.8 Hz, 2H), 8.18 (d, *J* = 7.2 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 4.8 Hz, 1H), 7.22 (dt, *J* = 21.2, 7.2 Hz, 2H), 7.06 (s, 1H), 6.13 (t, *J* = 26.0 Hz, 1H), 4.02 – 3.85 (m, 8H), 1.13 (t, *J* = 6.8 Hz, 6H), 1.02 (t, *J* = 6.8 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 158.07, 136.79, 128.60, 128.05, 123.43, 122.06, 120.61, 119.21, 117.14, 114.40, 110.87, 63.53, 62.84, 37.27 (t, *J* = 131.0 Hz), 16.23; ³¹P NMR (162 MHz, DMSO-*d*₆) δ 17.28; HRMS (ESI): *m/z* calculated for C₂₁H₂₉N₃O₆P₂ [M+Na⁺]: 504.1424, found: 504.1425.

Tetraethyl ((2-(1H-pyrazol-1-yl)phenyl)methylene)bis(phosphonate) (5h).

Yield 82%, pale solid, mp 75-78 °C ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.02 (s, 1H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.82 (s, 1H), 7.52 – 7.45 (m, 2H), 7.41 (d, *J* = 7.2 Hz, 1H), 6.55 (d, *J* = 1.8 Hz, 1H), 4.69 (t, *J* = 25.2 Hz, 1H), 4.00 – 3.91 (m, 4H), 3.90 – 3.80 (m, 4H), 1.15 (t, *J* = 7.2 Hz, 6H), 1.01 (t, *J* = 7.2 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 140.91, 139.95, 131.51, 131.49, 128.32, 128.25, 126.61, 126.25, 106.64, 63.33, 62.86, 38.30 (t, *J* = 126.0 Hz), 16.23, 16.16, 16.13, 16.01; ³¹P NMR (162 MHz, DMSO-*d*₆) δ 18.33; HRMS (ESI): *m/z* calculated for C₁₈H₂₈N₂O₆P₂ [M+Na⁺]: 453.1315, found: 453.1317.

Tetraethyl

((2-((methoxyimino)methyl)-4-methylphenyl)methylene)(E)-bis(phosphonate) (5i).

Yield 52%, pale yellow oil, ^1H NMR (400 MHz, DMSO- d_6) δ 8.46 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.43 (s, 1H), 7.23 (d, J = 8.0 Hz, 1H), 5.13 (t, J = 26.0 Hz, 1H), 4.07 – 4.00 (m, 4H), 3.90 – 3.80 (m, 7H), 2.30 (s, 3H), 1.20 (t, J = 7.2 Hz, 6H), 1.02 (t, J = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, CDCl $_3$) δ 148.59, 137.86, 131.24, 130.53, 130.36, 129.70, 125.27, 63.70, 63.23, 62.09, 39.46 (t, J = 132.0 Hz), 20.92, 16.23, 16.19, 16.11, 16.07; ^{31}P NMR (162 MHz, DMSO- d_6) δ 18.82; HRMS (ESI): m/z calculated for C $_{18}$ H $_{31}$ NO $_7$ P $_2$ [M+Na $^+$]: 458.1468, found: 458.1468.

Tetraethyl ((3-methyl-2-(o-tolyldiazenyl)phenyl)methylene)(E)-bis(phosphonate) (5j). Yield 92%, pale yellow oil, ^1H NMR (600 MHz, CDCl $_3$) δ 7.93 (d, J = 7.2 Hz,

= 7.2 Hz, 1H), 5.27 (t, J = 25.2 Hz, 1H), 4.14 – 3.99 (m, 8H), 2.71 (s, 3H), 2.43 (s, 3H), 1.23 (t, J = 7.2 Hz, 6H), 1.15 (t, J = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, DMSO- d_6) δ 151.08, 149.49, 138.31, 132.28, 132.12, 132.07, 129.46, 129.22, 127.79, 127.33, 114.70, 63.04, 63.00, 62.78, 62.76, 20.81, 17.85, 16.54, 16.50, 16.32, 16.30; ^{31}P NMR (162 MHz, DMSO- d_6) δ 18.68; HRMS (ESI): m/z calculated for C $_{23}$ H $_{34}$ N $_2$ O $_6$ P $_2$ [M+Na $^+$]: 519.1784, found: 519.1788.

1.3.2 General procedure for the synthesis of acid (taking 3aa acid as an example):

To a solution of **3aa** (30.0 mg, 0.068 mmol) in 5 mL of dry CH₂Cl₂, trimethylsilyl - bromide (62.5mg, 0.41 mmol) was added and the reaction mixture was stirred under a nitrogen flow. The reaction was monitored by TLC. After 4 h, the reaction was quenched with 10 mL of H₂O and the aqueous layer was evaporated in vacuo to obtain **3aa acid** as a microcrystalline powder in 96% yield.

((2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (**3aa acid**). Yield 96%, yellow powder, ¹H NMR (400 MHz, D₂O) δ 8.65 (d, *J* = 5.2 Hz, 1H), 8.51 (td, *J* = 8.0, 1.2 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.90 (t, *J* = 7.2 Hz, 2H), 7.57 – 7.48 (m, 1H), 7.44 – 7.38 (m, 2H), 3.41 (t, *J* = 23.6 Hz, 1H); ¹³C NMR (150 MHz, D₂O) δ 152.15, 146.90, 141.03, 132.14, 131.41, 131.25, 130.60, 128.71, 127.77, 125.77, 112.52; ³¹P NMR (162 MHz, D₂O) δ 16.69; HRMS (ESI): *m/z* calculated for

((3-methyl-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (**3ba acid**). Yield 95%, yellow powder, ¹H NMR (400 MHz, D₂O) δ 8.81 (s, 1H), 8.64 (s, 1H), 8.04 (d, *J* = 7.2Hz, 2H), 7.75 (s, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 3.11 (s, 1H), 1.99 (s, 3H); ¹³C NMR (150 MHz, D₂O) δ 158.22, 149.65, 136.72, 136.09, 129.41, 127.88, 127.77, 127.74, 125.57, 122.14, 112.51, 20.77; ³¹P NMR (162 MHz, D₂O) δ 14.87; HRMS (ESI): *m/z* calculated for C₁₃H₁₅NO₆P₂ [M+Na⁺]: 366.0267, found: 366.0263.

((4-methyl-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (**3da acid**). Yield 97%, yellow powder, ¹H NMR (400 MHz, D₂O) δ 8.63 (s, 1H), 8.49 (s, 1H), 8.02 (s,

1H), 7.88 (s, 1H), 7.70 (s, 1H), 7.30 (d, $J = 7.6$ Hz, 1H), 7.23 (d, $J = 7.6$ Hz, 1H), 3.85 (t, $J = 23.2$ Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100MHz, D_2O) δ 152.26, 146.94, 146.89, 142.50, 141.08, 131.48, 131.21, 129.06, 128.70, 128.65, 125.62, 20.67; ^{31}P NMR (162 MHz, D_2O) δ 17.32; HRMS (ESI): m/z calculated for $\text{C}_{13}\text{H}_{15}\text{NO}_6\text{P}_2$ $[\text{M}+\text{Na}^+]$: 366.0267, found: 366.0261.

((4-methoxy-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (3ea acid).

Yield 96%, pale yellow powder, ^1H NMR (400 MHz, D_2O) δ 8.66 (s, 1H), 8.52 (t, $J = 7.6$ Hz, 1H), 8.04 (d, $J = 7.6$ Hz, 1H), 7.93 (s, 1H), 7.79 (d, $J = 7.6$ Hz, 1H), 7.21 – 7.06 (m, 1H), 6.99 (d, $J = 2.4$ Hz, 1H), 3.73 (s, 3H), 3.37 (t, $J = 23.2$ Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 158.19, 151.65, 147.05, 141.28, 133.06, 132.01, 128.73, 126.10, 123.83, 117.35, 116.41, 55.67; ^{31}P NMR (162 MHz, D_2O) δ 16.11; HRMS (ESI): m/z calculated for $\text{C}_{13}\text{H}_{15}\text{NO}_7\text{P}_2$ $[\text{M}+\text{Na}^+]$: 382.0216, found: 382.0217.

((4-nitro-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (3ga acid). Yield 97%, yellow powder, ^1H NMR (400 MHz, D_2O) δ 8.83 (d, $J = 4.8$ Hz, 1H), 8.68 (t, $J = 7.2$ Hz, 1H), 8.42 (s, 2H), 8.22 (d, $J = 7.2$ Hz, 2H), 8.10 (d, $J = 7.2$ Hz, 1H), 3.64 (t, $J = 23.2$ Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 149.84, 147.39, 146.44, 141.84, 140.84, 133.12, 132.07, 129.06, 126.83, 126.33, 125.77; ^{31}P NMR (162 MHz, D_2O) δ 13.77; HRMS (ESI): m/z calculated for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_8\text{P}_2$ $[\text{M}+\text{Na}^+]$: 396.9961, found:

((2-(pyridin-2-yl)-4-(trifluoromethyl)phenyl)methylene)bis(phosphonic acid) (3ha acid). Yield 97%, yellow powder, ^1H NMR (400 MHz, D_2O) δ 8.80 (d, J = 4.8 Hz, 1H), 8.65 (td, J = 8.0, 1.5 Hz, 1H), 8.24 – 8.12 (m, 2H), 8.10 – 8.02 (m, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.87 (s, 1H), 3.58 (t, J = 23.6 Hz, 1H); ^{13}C NMR (150 MHz, D_2O) δ 157.78, 149.32, 141.12, 136.83, 132.79, 131.71, 129.69 (q, J = 54.0 Hz, 1H), 128.69, 127.08, 124.80, 124.50, 122.47; ^{31}P NMR (162 MHz, D_2O) δ 14.88; HRMS (ESI): m/z calculated for $\text{C}_{13}\text{H}_{12}\text{F}_3\text{NO}_6\text{P}_2$ [$\text{M}+\text{Na}$]: 366.0267, found: 366.0261.

((5-methyl-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (3ja acid). Yield 98%, pale yellow powder, ^1H NMR (400 MHz, D_2O) δ 8.64 (s, 1H), 8.50 (t, J = 7.6 Hz, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.90 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.24 (s, 1H), 3.42 (t, J = 24.0 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ 152.19, 146.96, 141.16, 138.51, 132.24, 131.88, 131.62, 130.46, 128.66, 128.39, 125.83, 42.85 (t, J = 123.0 Hz), 19.97; ^{31}P NMR (162 MHz, D_2O) δ 15.93; HRMS (ESI): m/z calculated for $\text{C}_{13}\text{H}_{15}\text{NO}_6\text{P}_2$ [$\text{M}+\text{Na}^+$]: 366.0267, found: 366.0265.

((5-(tert-butyl)-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (3ka acid). Yield 97%, yellow powder, ^1H NMR (600 MHz, D_2O) δ 8.67 (s, 1H), 8.52 (s, 1H), 8.14 – 7.97 (m, 2H), 7.92 (s, 1H), 7.51 (s, 1H), 7.40 (s, 1H), 3.52 (t, J = 21.6 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, D_2O) δ 157.72, 154.64, 154.59, 149.36, 143.56, 18.48; HRMS (ESI): m/z calculated for $\text{C}_{16}\text{H}_{21}\text{NO}_6\text{P}_2$ [$\text{M}+\text{Na}^+$]: 408.0736, found:

((5-fluoro-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (3la acid). Yield 97%, pale yellow powder, ^1H NMR (400 MHz, D_2O) δ 8.83 (d, $J = 5.2$ Hz, 1H), 8.69 (t, $J = 8.0$ Hz, 1H), 8.22 (d, $J = 8.0$ Hz, 1H), 8.15 – 8.04 (m, 1H), 7.83 (d, $J = 10.0$ Hz, 1H), 7.63 (dd, $J = 8.4, 6.0$ Hz, 1H), 7.33 (t, $J = 8.4$ Hz, 1H), 3.59 (t, $J = 22.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.00 (d, $J = 246.0$ Hz), 158.07, 149.01, 136.74, 131.88 (d, $J = 8.4$ Hz), 130.84 (dd, $J = 16.0, 8.0$ Hz), 124.71, 122.02, 118.07 (d, $J = 23.0$ Hz), 114.67 (d, $J = 21.0$ Hz); ^{31}P NMR (162 MHz, D_2O) δ 15.66; HRMS (ESI):

((5-acetyl-2-(pyridin-2-yl)phenyl)methylene)bis(phosphonic acid) (3na acid). Yield 95%, pale yellow powder, ^1H NMR (400 MHz, D_2O) δ 8.77 (s, 1H), 8.61 (s, 1H), 8.52 (s, 1H), 8.15 (d, $J = 7.8$ Hz, 1H), 8.07 – 7.94 (m, 2H), 7.61 (d, $J = 7.8$ Hz, 1H), 3.56 (t, $J = 23.6$ Hz, 1H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ 202.70, 150.88, 147.17, 141.60, 138.40, 136.37, 133.14, 131.78, 130.78, 128.79, 127.19, 126.50, 43.42 (t, $J = 125.0$ Hz), 26.55; ^{31}P NMR (162 MHz, D_2O) δ 14.99; HRMS (ESI): m/z calculated for $\text{C}_{13}\text{H}_{15}\text{NO}_6\text{P}_2$ $[\text{M} + \text{Na}^+]$: 394.0216, found: 394.0213.

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4 **((4-(pyridin-2-yl)-[1,1'-biphenyl]-3-yl)methylene)bis(phosphonic acid) (3oa acid).**

5 Yield 98%, pale yellow powder, ^1H NMR (600 MHz, D_2O) δ 8.70 (d, $J = 4.8$ Hz, 1H),
6 8.55 (t, $J = 7.2$ Hz, 1H), 8.20 (s, 1H), 8.11 (d, $J = 7.8$ Hz, 1H), 7.95 (s, 1H), 7.70 (d, J
7 $= 7.2$ Hz, 3H), 7.52 (d, $J = 7.8$ Hz, 1H), 7.45 (t, $J = 7.2$ Hz, 2H), 7.41 – 7.34 (m, 1H),
8 3.58 (t, $J = 24.0$ Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 158.81, 149.07, 140.49,
9 139.93, 139.35, 136.52, 130.73, 129.88, 128.72, 128.64, 127.49, 126.91, 125.93,
10 124.41, 121.85; ^{31}P NMR (162 MHz, D_2O) δ 15.78; HRMS (ESI): m/z calculated for
11 $\text{C}_{13}\text{H}_{15}\text{NO}_6\text{P}_2$ $[\text{M}+\text{Na}^+]$: 428.0423, found: 428.0421.
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23 **(benzo[h]quinolin-10-ylmethylene)bis(phosphonic acid) (3pa acid).** Yield 95%,
24 yellow powder, ^1H NMR (400 MHz, D_2O) δ 8.87 (d, $J = 3.6$ Hz, 2H), 7.78 (d, $J =$
25 7.2 Hz, 1H), 7.64 (d, $J = 7.2$ Hz, 1H), 7.44 (s, 1H), 7.32 – 7.00 (m, 2H); ^{13}C NMR
26 (100 MHz, D_2O) δ 159.33, 136.36, 126.64, 123.43, 122.21, 120.58, 119.17,
27 112.53; ^{31}P NMR (162 MHz, D_2O) δ 15.94; HRMS (ESI): m/z calculated for
28 $\text{C}_{14}\text{H}_{13}\text{NO}_6\text{P}_2$ $[\text{M}+\text{Na}^+]$: 376.0110, found: 376.0112.
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41 **((3-(pyridin-2-yl)naphthalen-2-yl)methylene)bis(phosphonic acid) (3qa acid).** Yield
42 96%, yellow powder, ^1H NMR (600 MHz, D_2O) δ 8.70 (d, $J = 4.8$ Hz, 1H), 8.55 (t, J
43 $= 7.2$ Hz, 1H), 8.20 (s, 1H), 8.11 (d, $J = 7.8$ Hz, 1H), 7.95 (s, 1H), 7.70 (d, $J = 7.2$ Hz,
44 3H), 7.52 (d, $J = 7.8$ Hz, 1H), 7.45 (t, $J = 7.2$ Hz, 2H), 7.41 – 7.34 (m, 1H), 3.58 (t, J
45 $= 24.0$ Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 159.02, 148.81, 136.96, 132.71, 132.26,
46 131.00, 129.99, 128.06, 127.75, 126.75, 126.60, 125.61, 125.08, 124.99, 122.03; ^{31}P
47 NMR (162 MHz, D_2O) δ 16.35; HRMS (ESI): m/z calculated for $\text{C}_{16}\text{H}_{15}\text{NO}_6\text{P}_2$
48 $[\text{M}+\text{Na}^+]$: 402.0267, found: 402.0263.
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((1-(pyridin-2-yl)naphthalen-2-yl)methylene)bis(phosphonic acid) (3ra acid). Yield 96%, yellow powder, ^1H NMR (400 MHz, D_2O) δ 8.81 (s, 1H), 8.63 (t, $J = 7.2$ Hz, 1H), 8.05 (t, $J = 8.4$ Hz, 3H), 8.01 – 7.89 (m, 2H), 7.48 (t, $J = 7.2$ Hz, 1H), 7.38 (t, $J = 8.4$ Hz, 1H), 7.02 (d, $J = 8.4$ Hz, 1H), 3.26 (t, $J = 24.8$ Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 150.36, 147.36, 142.31, 131.96, 131.62, 131.34, 130.58, 128.44, 127.98, 126.86, 126.69, 124.22, 123.31; ^{31}P NMR (162 MHz, D_2O) δ 15.33; HRMS (ESI): m/z calculated for $\text{C}_{16}\text{H}_{15}\text{NO}_6\text{P}_2$ [$\text{M}+\text{Na}$] $^+$: 402.0267, found: 402.0265.

((2-(isoquinolin-3-yl)phenyl)methylene)bis(phosphonic acid) (3sa acid). Yield 96%, yellow powder, ^1H NMR (600 MHz, D_2O) δ 9.54 (d, $J = 7.2$ Hz, 1H), 8.42 (d, $J = 11.4$ Hz, 1H), 8.37 (d, $J = 7.8$ Hz, 1H), 8.18 (d, $J = 7.8$ Hz, 1H), 8.11 (t, $J = 6.6$ Hz, 1H), 7.92 (d, $J = 6.6$ Hz, 1H), 7.55 (t, $J = 7.2$ Hz, 1H), 7.50 (d, $J = 7.2$ Hz, 1H), 7.44 (t, $J = 7.2$ Hz, 1H), 3.53 (t, $J = 22.8$ Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 152.51, 151.87, 127.16, 126.65, 120.86; ^{31}P NMR (162 MHz, D_2O) δ 16.16; HRMS (ESI): m/z

((6-(7,8-dimethoxyisoquinolin-3-yl)benzo[d][1,3]dioxol-5-yl)methylene)bis(phosphonic acid) (3ta acid). Yield 98%, pale yellow powder, ^1H NMR (600 MHz, D_2O) δ 9.54 (d, $J = 7.2$ Hz, 1H), 8.22 (d, $J = 15.0$ Hz, 1H), 7.98 (d, $J = 8.8$ Hz, 1H), 7.91 (d, $J = 8.8$ Hz, 1H), 7.36 (s, 1H), 6.87 (s, 1H), 5.95 (s, 2H), 3.99 (s, 6H), 3.41 (t, $J = 23.4$ Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 150.95, 149.47, 147.40, 144.63, 142.08,

140.21, 133.59, 126.51, 125.38, 123.34, 122.30, 112.48, 110.76, 110.38, 102.20, 61.13, 56.19; ^{31}P NMR (162 MHz, D_2O) δ 16.16; HRMS (ESI): m/z calculated for $\text{C}_{19}\text{H}_{19}\text{NO}_{10}\text{P}_2$ [$\text{M}+\text{Na}^+$]: 506.0376, found: 506.0371.

((1-(pyrimidin-2-yl)-1H-indol-2-yl)methylene)bis(phosphonic acid) (5g acid). Yield 98%, yellow powder, ^1H NMR (600 MHz, D_2O) δ 8.82 (d, $J = 4.8$ Hz, 2H), 7.74 (d, $J = 7.8$ Hz, 1H), 7.59 (d, $J = 7.8$ Hz, 1H), 7.39 (d, $J = 4.8$ Hz, 1H), 7.25 – 7.11 (m, 2H), 7.00 (s, 1H), 5.02 (t, $J = 25.2$ Hz, 1H); ^{13}C NMR (150 MHz, D_2O) δ 159.27, 155.74, 136.38, 129.84, 128.16, 123.49, 122.21, 120.56, 119.13, 112.51, 38.15 (t, $J=121.5\text{Hz}$); ^{31}P NMR (162 MHz, D_2O) δ 18.20; HRMS (ESI): m/z calculated for

((2-(1H-pyrazol-1-yl)phenyl)methylene)bis(phosphonic acid) (5h acid). Yield 98%, pale powder ^1H NMR (400 MHz, D_2O) δ 7.99 (s, 1H), 7.91 (dd, $J = 20.4, 7.2\text{Hz}$, 2H), 7.52 (d, $J = 7.2\text{Hz}$, 1H), 7.43 (t, $J = 7.2$, 1H), 7.37 (d, $J = 7.2\text{Hz}$, 1H), 6.65 (s, 1H), 3.76 (t, $J = 23.4$ Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 139.36, 137.37, 134.17, 133.01, 130.64, 130.24, 128.54, 127.44; ^{31}P NMR (162 MHz, D_2O) δ 15.91; HRMS (ESI): m/z calculated for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_6\text{P}_2$ [$\text{M}+\text{Na}^+$]: 318.0171, found: 318.0178.

1.4 Mechanistic studies

1.4.1 Synthesis of 2-(pentadeuteriophenyl)pyridine(1a-d₅)

Step1: A two-neck 25 mL flask fitted with magnetic stirring bar, and low-temperature thermometer was charged with bromobenzene- D_5 (0.5 mL, 4.8 mmol) under argon

atmosphere. Dry THF (12 mL) was added, and the solution was cooled to -78°C . To this solution was added *n*-butyllithium (3.6 mL, 1.6 M, 5.7 mmol) drop wise using slow addition pump over 30 minutes. The solution was stirred at -78°C for 2 h whereupon triisopropyl borate (1.3 g, 7.1 mmol) dissolved in 1.2 mL of dry THF was added drop wise to the reaction system. The solution was allowed to warm to room temperature overnight. After that the reaction was quenched with dilute HCl (20%, 8.4 mL), and the reaction mixture was stirred for 3 h at room temperature. The resulted biphasic solution was extracted with Et_2O (3 X 6 mL). The ether solution was washed twice with H_2O and concentrated by rotary evaporation. To the crude product, hexane 75 ml was added. The white (*d*₅-phenyl)boronic acid solid precipitated in hexane was filtered and dried and used without further purification (409 mg, 67.8%)

S10.

Step2: To a solution of 2-bromopyridine (200 mg, 1.26 mmol) in toluene (5 mL), ethanol (2 mL), and H_2O (5 mL) was added Na_2CO_3 (1.0 g, 9.43 mmol) followed by $\text{Pd}(\text{PPh}_3)_4$ (44mg, 0.038 mmol) and (*d*₅-phenyl)boronic acid (209 mg, 1.65 mmol) under argon in a 25 mL two-necked flask. The reaction mixture was refluxed for 12 h, and then cooled to room temperature. To the reaction mixture was added aqueous NH_4Cl (10 mL), extracted by EtOAc for three times, dried over MgSO_4 , and evaporated in vacuum to afford the crude product, which was purified by flash chromatography on silica gel to provide **1a-d₅** Pale yellow oil (132 mg, 65.4%)^{S1}.

¹H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.67 (d, $J = 4.4$ Hz, 1H), 7.96 (d, $J = 7.6$ Hz, 1H), 7.88 (t, $J = 7.6$ Hz, 1H), 7.39 – 7.31 (m, 1H).

1.4.2 Reversible D/H exchange

To a 15 ml oven-dried tube was added **1a** (0.19 mmol, 30.0 mg), [Cp^{*}RhCl₂]₂ (6.0 mg 5 mol%), Ag₂SO₄ (6.0 mg 10 mol%) in DCE (1.8 mL):CD₃OD (0.2 ml). The tube was sealed and stirred at 80 °C for 1 h. After completion, the reaction mixture was concentrated in vacuo and purified by silica gel column chromatography (50:1 PE/EA) to provide the product **[D_n]-1a** (pale brown oil), which was analyzed by ¹H NMR in DMSO-*d*₆. H/D exchange of **1a** at the ortho-position was observed by ¹H NMR (with 51% D) in the presence of the suggesting reversible C-H activation. ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.67 (d, *J* = 3.8 Hz, 1H), 8.09 (d, *J* = 7.5 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.89 (t, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 6.5 Hz, 2H), 7.47 – 7.41 (m, 1H), 7.36 (d, *J* = 5.5 Hz, 1H).

1.4.3 Determination of intermolecular kinetic isotope effect (KIE)

To a 15 ml oven-dried tube was added **1a** (0.08 mmol, 12.5 mg), **[D₅]-1a** (0.08 mmol, 12.7 mg), **2a** (0.20 mmol, 63.0mg), [Cp*RhCl₂]₂ (5.0 mg 5 mol%), Ag₂SO₄(5.0 mg 10 mol%) in DCE(3ml). The tube was sealed and stirred at 80 °C for 1h. After completion, the reaction mixture was concentrated in vacuo and purified by silica gel column chromatography to afford the mixture of **3aa** and **[D₄]-3aa**, which was analyzed by ¹H NMR in DMSO-*d*₆. ¹H NMR spectra of the **3aa** and **[D₄]-3aa** determined the intramolecular KIE value equal to 1.5.

1.4.4 Competitive Reaction

To a 15 ml oven-dried tube was added **1e** (0.27 mmol, 50.0 mg), **1h** (0.27 mmol, 60.0 mg), **2a** (0.65 mmol, 204.0mg), [Cp*RhCl₂]₂ (16.7 mg 5 mol%), Ag₂SO₄(16.8 mg 10

mol%) in DCE(4ml). The tube was sealed and stirred at 80 °C for 1h. After completion, the reaction mixture was concentrated in vacuo and purified by silica gel column chromatography to afford a mixture of **3ea** and **3ha**, which was analyzed by ¹H NMR in DMSO-*d*₆. ¹H NMR spectra **3ea** and **3ha** were afforded in a ratio of 1:1.25.

1.4.5 Cyclometalated Rh(III) Complex **6**

(a) Synthesis of cyclometalated Rh(III) complex **6**

The cyclorhodated complex was prepared according to the literature procedure^{S11}. A 50 mL Schlenk flask was charged with [Cp*RhCl₂]₂ (50.0 mg, 0.081 mmol), NaOAc (29.1m g, 0.49 mmol), **1q**(41.5g, 0.20 mmol) and CH₂Cl₂ (20 mL). The mixture was stirred at room temperature for 15 h. The solution was filtered through Celite® and concentrated under reduced pressure. The product was then washed with hexane to afford a cyclometallated Rh(III) complex **6** as an orange solid. ¹H NMR (400 MHz, CDCl₃) δ 8.81 (d, *J* = 5.4 Hz, 1H), 8.17 (s, 1H), 8.12 (s, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.82 – 7.74 (m, 3H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.24 – 7.19 (m, 1H), 1.66 (s, 15H).

(b) Complex **6-catalyzed coupling reaction**

Complex **6** (5.0 mol %), **1q** (0.15 mmol, 30 mg), Ag_2SO_4 (10 mol %), **2a** (0.18 mmol, 55.2 mg) and DCE (3 mL) were added to a test tube. The reaction mixture was stirred at 80 °C for 8 h. The solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography using DCM/MEOH (80:1) to afford the title compound **3qa** (52%).

(c) Reaction of complex **6 with **2a****

Complex **6** (0.04 mmol, 20.0 mg), Ag_2SO_4 (0.08 mmol, 24.9 mg), **2a** (0.048 mmol, 16.0 mg) and DCE (3 mL) were added to a test tube. The reaction mixture was stirred at 80 °C for 8 h. After that, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using DCM/MEOH (80:1) to afford the desired compound **3qa** in yield 61%.

SE. 2. Computational Studies.

In order to exploit the potential applications of aromatic bisphosphonates, we employed a virtual target screening system, termed IFPTarget,^{S12} to predict possible binding targets for the representative aromatic bisphosphonate acid **3aa**. The 3D structure of **3aa** acid was prepared as described previously.^{S12-14} Using IFPTarget, **3aa** acid was screened against an established target library,^{S12} which contains 11,863 protein structures covering 2842 unique targets. The possible target hits for **3aa** acid were ranked by a comprehensive index (Cvalue),^{S12} which involves the predicted docking score (Vinascore), interaction fingerprint similarity (IFPscore), and the predicted binding affinity (IDscore).^{S15} The top 1% target “hits” identified by IFPTarget are given in Table S2. Predicted results were analyzed using the Discovery Studio Visualizer. The figures for the predicted binding modes were made using PyMol program.

The molecular docking analyses for **3qa** acid with NDM-1, VIM-2, and TEM-1 were carried out using AutoDock Vina. The complex structures of NDM-1: Cephalosporins (PDB ID: 4RL0),^{S16} VIM-2:2-(2-chloro-6-fluorobenzyl)-3-oxoisoin doline-4-carboxylic acid (compound 16) (PDB ID: 5LE1),^{S14} and TEM-1: (1*R*)-2-Phenylacetamido-2-(3-carboxyphenyl)ethyl boronic acid (PDB ID: 1ERO)^{S17} were used as docking templates. All the water molecules and solvent molecules were removed. Gasteiger-Marsili charges were added to the protein model, and non-polar hydrogens were merged onto their respective heavy atoms. The grid centers were set as coordinates of [x, y, z = 3.0, 16.9, 41.6] for NDM-1, [x, y, z = 111.5, 72.1, 9.8] for VIM-2, and [x, y, z = 41.8, 37.0, 32.9] for TEM-1, and the grid size was as 23Å × 23Å × 23Å. The other parameters for Vina were set as default. The docking results were viewed using PyMol program.

SE. 3. Protein Production.

Recombinant forms of VIM-2 MBL (residues 27-266), NDM-1 MBL (residues 1-270), TEM-1 SBL (residues 24-286), and KPC-2 SBL (residues 26-289) were produced in *E. coli* *Transetta* (DE3) cells (Novagen) at 37 °C using LB medium supplemented with 50 µg/ml ampicillin and 50 µg/ml chloramphenicol. Cells were grown until the OD₆₀₀ reached 0.6-0.7. At this point the temperature was lowered to 30 °C (for VIM-2), 20 °C (for NDM-1), 27 °C (for TEM-1) or 20 °C (for TEM-1), expression was induced with IPTG (0.5 mM final concentration) and the cells were further incubated for 18-20 hours. Cells were harvested by centrifugation (15min, 4000 rpm) and were resuspended in lysis buffer A (20 mM Tris-HCl, pH 8.0, 250 mM NaCl) supplemented with EDTA-free protease-inhibitor, and then lysed using an ultrahigh-pressure homogenizer (JNBIO). The cellular debris was removed by centrifugation of the lysate at 15,000 rpm for 30 min; the supernatant was then loaded

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onto a Ni-NTA column (Roche), followed by extensive washing using buffer B (20 mM Tris-HCl, pH 8.0, 250 mM NaCl, 5 mM imidazole) to remove nonspecifically binding proteins. The target proteins were eluted with buffer C (20 mM Tris-HCl, pH 8.0, 250 mM NaCl, 250 mM imidazole). Fractions containing the purified enzyme were concentrated using Amicon Ultra 10K (Millipore), and then desalted using a HiTrap Desalting column (GE Healthcare) into reaction buffer (VIM-2/NDM-1: 20 mM Tris-HCl, pH 7.5, 200 mM NaCl, 0.5 mM TCEP; TEM-1/KPC-2: 50 mM Phosphate, pH 7.0) for enzyme kinetic analyses. The purified enzymes were concentrated by centrifugal ultrafiltration and stored at -80 °C. All purification steps were identified *via* 12% SDS-PAGE, and the concentrations of the purified proteins were determined through a NanoDrop 2000 spectrophotometer (Thermo Scientific).

SE. 4. Inhibition, Competitive, Reversibility, and Cellular Assays.

Assays were performed using a Thermo microplate reader (Varioskan LUX) and were performed at room temperature (24-25 °C). The assay buffer for VIM-2 and NDM-1 is: 50 mM HEPES-NaOH (~pH 7.2), 1 µg/mL BSA (to minimize the denaturation of the enzyme), 1 µM ZnSO₄, and 0.1% Triton X-100 (to large extent exclude the possibility that compounds form large colloid-like aggregates that sequester and thereby inhibit enzymes). The assay buffer for KPC-2 and TEM-1 is: 50 mM phosphate, pH 7.0, 1 µg/mL BSA, and 0.1% Triton X-100. The activities of VIM-2, NDM-1, KPC-2, and TEM-1 were determined using the fluorescent substrate FC-5^{S14, S18, S19}. Hydrolysis of FC5 was monitored by following the variation in fluorescence at excitation 380 nm and emission at 460 nm, respectively. In all tests, 96 well flat bottom black plates were used. The details are described as follows.

Inhibition Assays.

In the inhibition assays, the final concentration of the substrate FC-5 is 5 µM, and the concentrations of VIM-2, NDM-1, KPC-2, and TEM-1 are 0.2 nM, 0.2 nM, 2 nM, and 10nM, respectively. Except where noted, the compounds for inhibition assays were prepared in 100 mM DMSO stock solutions. For IC₅₀ determination, compounds were 3-fold diluted from 600 µM. The IC₅₀ values (concentration required to affect 50% inhibition of enzyme activity) for all aromatic bisphosphonates were determined by preincubation of the tested compound with the appropriate amount of enzymes in the assay buffer for 10 min (NDM-1 and VIM-2) or 4h (KPC-2 and TEM-1) at room temperature, prior to the initiation of the reactions by the addition of the substrates. The bisphosphonate ester compounds (**3aa-3ta** and **5a-5j**, Scheme 1-2) were initially tested against VIM-2, NDM-1, KPC-2, and TEM-1 at 100 µM; for compounds showing inhibition >50% at 100 µM, the IC₅₀ values were determined. The fluorescence intensity was recorded every 60 seconds. All assays were carried out in triplicates.

Substrate Competitive Assays.

The calibration curve of fluorescence values versus product concentrations (or the FC-5 substrate^{S18,S19}) was first determined. The saturated enzymes were reacted with FC-5 with different concentration (from 100 μ M ~ 0.195 μ M, 2-fold dilutions) for 24 h at 4 °C in the assay buffer to obtain the calibration curve (the fluorescence intensity was obtained every 60 seconds). Then, the catalytic abilities of NDM-1 or VIM-2 in the absence and the presence of **3qa** acid were then determined. For NDM-1, treating with different concentrations of **3qa** acid (0 μ M, 3 μ M, 10 μ M, 30 μ M, and 90 μ M), the enzyme kinetic values were determined using the FC-5 substrate. Similarly, the enzyme kinetic values were determined for VIM-2 at different concentrations of **3qa** acid (0 μ M, 1 μ M, 3 μ M, 10 μ M, and 30 μ M).

The Jump-Dilution Assays.

The jump-dilution method^{S20} was used to determine the reversibility of MBL/SBL inhibition by **3qa** acid. *L*-captopril and EDTA were used as controls. 170 μ M **3qa** acid (10-fold the IC₅₀ value to NDM-1), 25 μ M EDTA (10-fold the IC₅₀ value to NDM-1), or 500 μ M *L*-captopril (10-fold the IC₅₀ value to NDM-1) were preincubated with 10 nM NDM-1 (100-fold the concentration of NDM-1 used in inhibition assays) for 30 min at room temperature (24-25 °C). Similarly, 38 μ M **3qa** acid (10-fold the IC₅₀ value to VIM-2), 25 μ M EDTA (10-fold the IC₅₀ value to VIM-2), or 20 μ M *L*-captopril (10-fold the IC₅₀ value to VIM-2) were preincubated with 10 nM VIM-2 (100-fold the concentration of VIM-2 used in the inhibition assays). The samples are then rapidly diluted 100-fold into an assay solution, and the enzyme activities are measured.

Microdilution Broth Minimum Inhibitory Concentrations (MICs)

Strains of *E. coli* Transetta containing plasmids pET28-lacUV5-VIM-2 (*E. coli*-VIM-2) and pET28-lacUV5 (as control) were used to assess the cellular activities of the inhibitors. The pET28-lacUV5 and pET28-lacUV5-VIM-2 plasmids were obtained by multi-step gene cloning. Single colonies of the *E. coli*-VIM-2 strain on Mueller Hinton (MH) agar plates were transferred to 5 mL of MH liquid medium, and grown at 37 °C to an OD₆₀₀ of ~0.6. The MICs of meropenem in the absence or presence of **3qa acid** and **5g acid** were determined according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. The concentrations of *E. coli*-VIM-2 and *E. coli* strains were diluted to ~10⁷ colony forming units (CFU) per mL in the MH medium, then transferred to the microtiter plates, and treated with meropenem (final concentrations of 64 mg/L to 0.125 mg/L in 2-fold dilution) or/and the inhibitors (final concentrations of 100 μ M, 50 μ M, 25 μ M, and 10 μ M). The microtiter plates were incubated for

16-20 h at 37 °C and visually evaluated for bacterial growth. Each determinate was performed in duplicate.

SE. 5. ITC Analyses.

ITC binding assays were carried out using a MicroCal ITC200 calorimeter (GE Healthcare) at 25 °C. The **3qa** acid (500 µM or 600 µM) was titrated with NDM-1 (60 µM), VIM-2 (50 µM), or TEM-1 (50 µM), separately. In the calorimeter cell and syringe only contained <1% DMSO. The system was equilibrated until the cell temperature reached 25 °C. All titrations were conducted using a preliminary injection of 0.2 µL **3qa** acid (500 µM or 600 µM) and then a series of 19 individual injections of 2 µL at time intervals of 150 s. The titration cell was continuously stirred at 750 rpm. The obtained curves were fitted to a single binding site model using ITC data analysis module of Origin 7.5 (OriginLab).

Supplementary Tables

Table S1. Reaction Optimization^a

Entry	Catalyst	Ag Salt	Solvent	<i>T</i> [°C]	Time[h]	Yield ^b
1	[Cp*RhCl ₂] ₂	AgSbF ₆	DCE	80	24	81%
2	Pd(OAc) ₂	AgSbF ₆	DCE	80	24	N.R.
3	[Ru(<i>p</i> -cymene)Cl ₂] ₂	AgSbF ₆	DCE	80	24	N.R.
4	Cp*Co(CO)I ₂	AgSbF ₆	DCE	80	24	N.R.
5	[Cp*Co(CH ₃ CN) ₃][SbF ₆] ₂	AgSbF ₆	DCE	80	24	N.R.
6	[Cp*IrCl ₂] ₂	AgSbF ₆	DCE	80	24	20%
7	[Cp*RhCl ₂] ₂	AgOAc	DCE	80	24	N.R.
8	[Cp*RhCl ₂] ₂	Ag ₂ SO ₄	DCE	80	24	91%
9	[Cp*RhCl ₂] ₂	AgNO ₃	DCE	80	24	N.R.
10	[Cp*RhCl ₂] ₂	Ag ₂ CO ₃	DCE	80	24	N.R.
11	[Cp*RhCl ₂] ₂	Ag ₂ SO ₄	DCE	80	12	93%
12	[Cp*RhCl ₂] ₂	Ag ₂ SO ₄	DCE	60	12	80%
13	[Cp*RhCl ₂] ₂	Ag ₂ SO ₄	DCE	40	12	56%
14	[Cp*RhCl ₂] ₂	Ag ₂ SO ₄	THF	80	12	45%
15	[Cp*RhCl ₂] ₂	Ag ₂ SO ₄	MeOH	80	12	88%
16	[Cp*RhCl ₂] ₂	Ag ₂ SO ₄	CH ₃ CN	80	12	21%
17	[Cp*RhCl ₂] ₂	Ag ₂ SO ₄	Dioxane	80	12	N.R.

^a Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), [Cp*RhCl₂]₂ (5mol %), AgSO₄ (10mol %), DCE 2ml under air; ^b Isolated yields.

Table S2. The top 1% target ‘hits’ identified by IFPTarget for **3aa** acid. **3aa** acid

Rank	Target Name	PDB	Cvalue	IFPscore	Vinascore	IDscore	No. of IFPs
1	Geranylgeranyl pyrophosphate synthase GGPS	3LDW	16.04	1.00	-7.40	7.17	5
2	Human farnesyl pyrophosphate synthase FPPS	2F9K	15.91	0.98	-8.60	7.09	8
3	HIV-1 reverse transcriptase	1VRU	15.55	1.00	-8.30	5.32	8
4	Polyprotein	2D3Z	15.19	1.00	-6.00	5.75	5
5	Rat phosphodiesterase 10A	3LXG	15.10	1.00	-5.80	5.65	3
6	Coagulation Factor X	4BTT	15.04	1.00	-6.00	5.34	5
7	Bromodomain-containing protein 4 BRD4	4J0S	15.04	1.00	-6.60	4.98	5
8	cAMP-specific 3',5'-cyclic phosphodiesterase PDE7A	3G3N	14.97	1.00	-6.10	5.11	3
9	Bromodomain-containing protein 4 BRD4	3U5L	14.96	1.00	-6.20	5.02	4
10	Bromodomain-containing protein 4 BRD4	3MXF	14.89	1.00	-6.60	4.59	4
11	Glutaminy cyclase	4MHZ	14.87	1.00	-5.30	5.32	4
12	Endo-1,4-beta-xylanase d	1UX7	14.82	1.00	-4.80	5.49	3
13	Bromodomain-containing protein 4 BRD4	4F3I	14.79	1.00	-6.70	4.25	4
14	Bromodomain-containing protein 4 BRD4	4QZS	14.76	1.00	-6.20	4.49	4
15	Bromodomain-containing protein 4 BRD4	4BW1	14.74	1.00	-6.20	4.43	4
16	Mycobacterium tuberculosis	4OWM	14.73	1.00	-6.10	4.47	4
17	Polymerase PA	4AWF	14.70	1.00	-5.50	4.74	4
18	Transthyretin	1E4H	14.67	1.00	-5.60	4.61	3
19	Bromodomain-containing protein 4 BRD4	4MEQ	14.66	1.00	-5.90	4.40	4
20	Mycobacterium tuberculosis	4OWO	14.63	1.00	-5.90	4.31	3

21	Bromodomain testis-specific protein	4FLP	14.62	1.00	-6.30	4.06	4
22	RNA-directed RNA polymerase	4EO6	14.53	1.00	-6.00	3.99	4
23	Integrase	4AH9	14.53	1.00	-6.00	3.98	3
24	Lactoylglutathione lyase	4KYK	14.51	1.00	-5.50	4.23	3
25	N-terminal endonuclease domain of Bunyaviridae RNA Polymerases	2XI7	14.46	0.96	-5.30	5.97	4
26	Human farnesyl pyrophosphate synthase FPPS	2F89	14.43	0.93	-6.50	6.21	10
27	L-lactate dehydrogenase A chain	4I9U	14.41	1.00	-5.40	4.03	4
28	Bromodomain-containing protein 4 BRD4	4O70	14.40	1.00	-5.40	4.00	3
29	PA-I galactophilic lectin	4A6S	14.38	1.00	-5.10	4.13	5
30	CAMP and cAMP-inhibited cGMP 3',5'-cyclic phosphodiesterase 10A, PDE10A	3WS9	14.36	1.00	-5.10	4.08	3
31	Human peroxiredoxin-5	4MMM	14.28	1.00	-5.00	3.93	6
32	Wild type human transthyretin TTR	3NEE	14.26	1.00	-5.60	3.51	4
33	Thrombin alpha	1MU8	14.25	0.93	-6.80	5.75	6
34	Vp39	1B42	14.23	0.90	-7.30	6.61	4
35	Transthyretin	1E5A	14.22	1.00	-4.90	3.83	4
36	Carbonic anhydrase 2	1H4N	14.20	0.94	-7.30	4.65	5
37	Metallo-β-lactamase NDM-1	4EXS	14.17	0.91	-7.10	6.19	3
38	Polymerase protein PA	4E5G	14.06	0.96	-5.40	4.86	4
39	Polymerase protein PA	4AVG	14.02	0.93	-6.30	5.45	7
40	P-30 protein (T89N/E91A)	2GMK	13.99	1.00	-4.20	3.64	4
41	Lactoylglutathione lyase	4KYH	13.98	0.94	-6.40	4.91	5
42	Serum albumin	1GNJ	13.94	0.88	-8.60	6.08	5
43	Human farnesyl pyrophosphate synthase FPPS	2F94	13.92	0.87	-8.00	6.80	9
44	Acetylcholine-binding protein	2XZ5	13.90	0.88	-7.30	6.77	3
45	Leshmaniasis major Farnesyl diphosphate synthase	4K10	13.89	0.94	-6.30	4.42	5
46	Antibody fab fragment	1CT8	13.88	0.86	-8.20	6.83	10
47	Metallo-beta-lactamase CphA	3IOG	13.87	0.95	-6.10	4.27	5
48	PDE4B	2QYL	13.84	0.90	-6.30	6.16	4
49	Transthyretin	4ABV	13.79	1.00	-4.20	3.10	3
50	Metallo-β-lactamase VIM-2	4PVT	13.71	0.89	-8.00	5.18	5

51	Abscisic acid receptor PYL9/RCAR9	3W9R	13.70	0.92	-6.50	4.97	4
52	Beta-lactamase II	1HLK	13.68	0.90	-7.40	5.06	4
53	Dihydroorotase	2EG7	13.66	0.90	-6.70	5.27	8
54	Farnesyl pyrophosphate synthase	4DWB	13.65	0.86	-7.90	6.41	7
55	Nucleotide binding domain of the	3LLM	13.63	0.92	-5.80	5.21	8
56	PEPCK-Mn ²⁺	2RKD	13.62	0.92	-6.10	5.01	6
57	HIV-1 RNase H p15	3HYF	13.62	0.92	-5.60	5.29	6
58	Proto-oncogene tyrosine-transferase src	1O4R	13.61	0.93	-6.40	4.30	9
59	Transferase Ectonucleotide	1C8K	13.61	0.86	-7.70	6.50	5
60	pyrophosphatase/phosphodiesterase family member 2	3WAV	13.52	0.88	-6.70	6.11	3
61	HIV-1 IN core domain	3LPT	13.51	0.90	-6.70	5.05	4
62	Human nicotinamide phosphoribosyltransferase	3DKJ	13.45	0.90	-6.70	5.00	12
63	Proto-oncogene tyrosine-transferase src	1O4O	13.41	1.00	-3.60	2.45	5
64	Fatty acid binding protein, adipocyte	1TOW	13.40	0.88	-8.30	4.82	5
65	Dodecin	2CCC	13.40	0.88	-7.00	5.61	3
66	Cystic fibrosis transmembrane conductance regulator	1R0X	13.37	0.88	-6.60	5.78	7
67	Bromodomain-containing protein 4 BRD4	3P5O	13.37	0.90	-6.30	4.90	4
68	Intracellular B30.2 Domain of BTN3A1	4N7U	13.36	0.94	-5.40	3.86	4
69	HIV-1 reverse transcriptase	3LP0	13.34	0.91	-4.90	5.30	3
70	1-Deoxy-D-xylulose 5-phosphate reductoisomerase	3R0I	13.33	0.91	-5.60	4.83	5
71	Rna polymerase	2HAI	13.33	0.88	-7.30	5.23	5
72	Human BRD4	2YEL	13.32	0.90	-6.50	4.66	4
73	Genome polyprotein	4JU7	13.30	0.90	-6.70	4.49	4
74	X Secretory Phospholipase A2	4UY1	13.29	0.88	-7.60	4.94	3
75	Heparin-binding growth factor 1	3UD7	13.28	0.94	-4.90	3.94	6
76	Polymerase protein PA	4E5F	13.28	0.91	-5.30	4.89	3
77	Hiv-1 reverse transcriptase	1RTI	13.27	0.86	-7.40	5.77	5

78	Bromodomain BRD2	4A9M	13.26	0.90	-6.60	4.44	4
79	<i>Pseudomonas aeruginosa</i> Madelate racemase mutant K166R	1MDL	13.25	0.90	-5.30	5.19	3
80	Interleukin-13 receptor subunit alpha-1	4HWB	13.24	0.90	-6.70	4.33	3
81	Fatty acid-binding protein	1HMT	13.24	0.90	-7.10	4.07	3
82	14-3-3 Protein sigma	4DHP	13.24	0.91	-5.50	4.65	6
83	Soluble epoxide hydrolase 2	3WKD	13.22	0.88	-7.20	5.02	3
84	Dihydroorotase	1XGE	13.22	0.89	-6.40	4.91	6
85	Farnesyl pyrophosphate synthase	4GA3	13.20	0.82	-8.00	6.86	8
86	Succinyl-CoA:acetate coenzyme A transferase	4EU3	13.20	0.92	-5.20	4.42	4
87	14-3-3 Protein sigma	3T0M	13.17	0.93	-5.20	3.83	4
88	Methionine aminopeptidase	2Q93	13.14	0.84	-5.90	6.91	5
89	Glycogen phosphorylase	1GGN	13.14	0.85	-7.20	6.02	7
90	Farnesyl pyrophosphate synthase	4DZW	13.14	0.83	-8.40	6.01	9
91	Conserved hypothetical protein	2GL0	13.13	0.83	-8.20	6.21	8
92	Bromodomain-containing protein 4 BRD4	3U5J	13.13	0.88	-7.10	4.84	3
93	Human Peroxiredoxin-5	4K7I	13.12	0.93	-5.00	3.82	6
94	AmpC β -lactamase	4OKP	13.09	0.92	-5.90	3.70	4
95	14-3-3 Protein sigma	4DHR	13.08	0.90	-5.40	4.67	5
96	Renin	4GJ8	13.06	0.86	-8.10	4.78	5
97	6-Phosphogluconate dehydrogenase	4GWK	13.05	0.92	-4.30	4.56	4
98	Geranylgeranyl pyrophosphate synthetase	2Z50	13.04	0.89	-6.70	4.24	6
99	Botulinum neurotoxin A	4ELC	13.02	0.90	-6.20	4.03	4
100	Replication protein A 70 kDa DNA-binding subunit	4LUV	13.02	0.90	-4.20	5.24	3
101	Ribonucleoside-diphosphate	3RSR	13.01	0.84	-7.20	5.75	7
102	CREB-binding protein	2L84	12.98	0.90	-6.10	4.00	3
103	Glycogen phosphorylase B	8GPB	12.97	0.85	-7.80	5.04	5
104	D-alanyl-D-alanine carboxypeptidase	2Y4A	12.97	0.88	-6.40	4.84	6
105	Human phosphodiesterase 4d	3G58	12.96	0.83	-6.40	6.55	4
106	Fucose-binding lectin PA-IIL (G24N)	2JDU	12.96	0.90	-5.20	4.47	4

107	Transthyretin	3CFT	12.94	0.86	-6.00	5.75	4
108	Human MTH1 protein	4N1T	12.94	0.83	-6.20	6.62	6
109	Dengue virus ns5 RNA dependent RNA polymerase	2J7W	12.94	0.90	-5.00	4.54	6
110	Hiv-1 reverse transcriptase	1IKW	12.93	0.82	-8.30	5.95	7
111	Farnesyl pyrophosphate synthase	4E1E	12.92	0.83	-7.70	6.00	7
112	Ribonuclease 2	1HI3	12.91	0.90	-5.40	4.23	7
113	14-3-3 Protein sigma	4DHN	12.89	0.90	-5.30	4.25	5
114	14-3-3 Protein sigma	4DHO	12.89	0.89	-6.00	4.27	4
115	Integrase	4NYF	12.88	0.90	-5.90	3.85	4
116	Polymerase PA	4MK1	12.88	0.89	-5.60	4.32	5
117	PDE2a catalytic domain	4D09	12.86	0.86	-6.50	5.24	5
118	Hiv-2 protease	6UPJ	12.85	0.88	-6.20	4.64	3

Table S3. The inhibition activity of aromatic bisphosphonates against the clinically relevant β -lactamases NDM-1, VIM-2, TEM-1 and KPC-2.

Cpd ID	Chemical structure	IC ₅₀ (μ M) / pIC ₅₀ / s.e. logIC ₅₀ ^a			
		NDM-1	VIM-2	TEM-1	KPC-2
L-captopril		46.38 / 4.33 / 0.088	0.74 / 6.13 / 0.120	>400 / < 3.40 / ~	>400 / < 3.40 / ~
EDTA		2.07 / 5.68 / 0.06	2.35 / 5.63 / 0.042	>400 / < 3.40 / ~	>400 / < 3.40 / ~
3aa acid		32.04 / 4.49 / 0.025	11.07 / 4.96 / 0.029	68.39 / 4.16 / 0.040	>400 / < 3.40 / ~
3ba acid		>400 / < 3.40 / ~	7.65 / 5.12 / 0.074	126.30 / 3.90 / 0.065	>400 / < 3.40 / ~
3da acid		117.4 / 3.93 / 0.11	8.89 / 5.05 / 0.059	>400 / < 3.40 / ~	>400 / < 3.40 / ~
3ea acid		75.59 / 4.12 / 0.045	14.58 / 4.84 / 0.047	>400 / < 3.40 / ~	>400 / < 3.40 / ~
3ga acid		78.31 / 4.11 / 0.036	14.08 / 4.85 / 0.065	>400 / < 3.40 / ~	>400 / < 3.40 / ~
3ha acid		97.08 / 4.01 / 0.032	4.32 / 5.36 / 0.096	137.0 / 3.86 / 0.04	>400 / < 3.40 / ~
3ja acid		91.13 / 4.04 / 0.038	8.63 / 5.06 / 0.068	>400 / < 3.40 / ~	>400 / < 3.40 / ~

3ka acid		>400 / <3.40 / ~	7.86 / 5.10 / 0.041	>400 / <3.40 / ~	>400 / <3.40 / ~
3la acid		123.8 / 3.91 / 0.037	2.26 / 5.65 / 0.032	>400 / <3.40 / ~	>400 / <3.40 / ~
3na acid		179.8 / 3.75 / 0.087	5.10 / 5.29 / 0.036	>400 / <3.40 / ~	>400 / <3.40 / ~
3oa acid		55.64 / 4.26 / 0.021	36.53 / 7.44 / 0.062	0.93 / 6.03 / 0.056	>400 / <3.40 / ~
3pa acid		268.3 / 3.57 / 0.18	19.84 / 4.70 / 0.072	145.50 / 3.84 / 0.061	>400 / <3.40 / ~
3qa acid		17.11 / 4.77 / 0.044	3.78 / 5.42 / 0.041	1.73 / 5.76 / 0.055	>400 / <3.40 / ~
3ra acid		120.6 / 3.92 / 0.076	4.57 / 5.34 / 0.053	1.18 / 5.93 / 0.24	>400 / <3.40 / ~
3sa acid		16.24 / 4.79 / 0.036	2.47 / 5.61 / 0.077	38.9 / 4.41 / 1.46	>400 / <3.40 / ~
3ta acid		17.23 / 4.76 / 0.045	5.36 / 5.27 / 0.045	1.72 / 5.77 / 0.16	>400 / <3.40 / ~
5g acid		15.00 / 4.82 / 0.030	5.58 / 5.25 / 0.043	11.52 / 4.94 / 0.040	>400 / <3.40 / ~

5h acid		>400 / <3.40 / ~	3.92 / 5.41 / 0.070	86.39 / 4.06 / 0.59	>400 / <3.40 / ~
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^a The method for measuring IC₅₀/pIC₅₀ (n=3) values is described in Experimental Section; IC₅₀ curves are given in Fig. S5-7.

Table S4. The inhibitory activities of aromatic bisphosphonates **3aa-5ja** against NDM-1, VIM-2, TEM-1 and KPC-2.

ID	Chemical Structure	Inhibition% @ 100 μ M (IC ₅₀ (μ M) / pIC ₅₀ / s.e pIC ₅₀) ^a			
		NDM-1 MBL	VIM-2 MBL	TEM-1 SBL	KPC-2 SBL
3aa		30.32 $\pm$ 0.70	26.49 $\pm$ 23.69	2.23 $\pm$ 1.58	24 $\pm$ 1.60
3ba		18.78 $\pm$ 0.04	32.05 $\pm$ 12.05	65.22 $\pm$ 2.89 (79.5 / 4.10 / 0.152)	30.56 $\pm$ 6.15
3ca		53.74 $\pm$ 1.05 (>100)	16.01 $\pm$ 10.72	36.63 $\pm$ 8.49	41.11 $\pm$ 8.78
3da		25.5 $\pm$ 1.00	44 $\pm$ 0.39	3.65 $\pm$ 0.15	45.47 $\pm$ 7.16
3ea		32.18 $\pm$ 0.29	47.6 $\pm$ 27.67	39 $\pm$ 9.67	48 $\pm$ 0.06
3fa		33.65 $\pm$ 0.14	52.16 $\pm$ 1.48	21.37 $\pm$ 2.30	40.77 $\pm$ 8.30
3ga		33.88 $\pm$ 0.73	26.5 $\pm$ 26.54	10.72 $\pm$ 8.90	60.11 $\pm$ 2.80
3ha		16 $\pm$ 2.22	41.6 $\pm$ 0.05	9.15 $\pm$ 11.72	29.92 $\pm$ 7.38

3ia		46±1.58	33.53±20.67	64.41±10.60 (>100)	9.46±7.65
3ja		8.81±0.54	13.08±2.8	45.83±0.94	5.79±6.80
3ka		48.95±1.19	42.99±5.09	19.31±1.21	42.32±3.05
3la		16.05±0.79	34.48±3.06	27.36±12.62	42.07±8.60
3ma		56.04±1.95	39.33±25.8	3.40±0.07	42.48±4.99
3na		22.08±0.34	38.6±0.04	47.13±8.80	26±0.32
3oa		37.32±1.99	5.21±2.31	95.22±1.46 (133 / 3.876 / 0.209)	38.35±7.45
3pa		39.3±7.47	28.6±0.01	56.26±8.42 (>100)	49.31±1.94
3qa		19.55±6.67	7.5±9.90	45.73±6.34	47.36±2.63
3ra		33.16±5.43	47.00±0.09	27.53±1.05	15.35±2.85

3sa		47.58±3.56	60.66±3.26	47.57±12.04	45±2.65
3ta		46.6±11.10	45.25±14.41	39.87±14.02	3.5±0.89
3ta¹		72.67 ± 0.52 (42.2 / 4.37 / 0.044)	98.02±0.31 (7.94 / 5.1 / 0.082)	96.32±2.19 (1.10 / 5.96 / 0.068)	18±0.27
3ba		39.96±4.68	25.3±23.2	76.3±4.59 (119 / 3.92 / 0.064)	15±9.38
3ca		36.93±6.04	54.17±10.37	37.7±7.51	60.61±0.07 (>100)
5a		44.14±1.75	28.16±3.13	9.6±6.08	13.36±11.92
5b		46.47±10.71	8.71±6.83	58.42±9.70	36±0.60
5c		36.87±4.19	29.6±0.01	24.21±12.27	34.5±22.00
5d		48.93±4.26	44.96±4.03	19.19±8.41	47.2±0.84
5e		52.32 ± 6.64 (>100)	78.12±3.92	30.6±14.00	15.33±5.75

5f		58 ± 3.17 (>100)	83.51±2.68 (>100)	94.92±10.43 (>100)	16.8±5.46
5g		39.92±5.01	62.3±6.49	8.68±8.66	21.4±0.66
5h		26.93±2.33	39.18±22.43	18.98±3.60	26.16±2.03
5i		85.4±0.15 (7.13 / 5.15 / 0.036)	86.49±5.98 (6.58 / 5.18 / 0.025)	96.82±6.85 (3.75 / 5.42 / 0.115)	37.57±24.84
5j		9.27±4.36	39.87±9.83	30.7±0.74	17.83±6.84

^aThe method for measuring mean ± SD (n=3) values is described in the Supplementary Methods.

Table S5. MICs of meropenem in the absence or presence of **3qa acid** and **5g acid** against VIM-2-producing *E. coli* transetta strain.

Assay No.	Inhibitor (Concentration)	Meropenem	MIC (µg/mL)	
			<i>E. coli</i> -VIM-2	<i>E. coli</i>
1	-	+	16	<0.125
2	3qa acid (100 µM)	-	>64	>64
3	5g acid (100 µM)	-	>64	>64
4	3qa acid (100 µM)	+	4	<0.125
5	3qa acid (50 µM)	+	4	<0.125
6	3qa acid (25 µM)	+	16	<0.125
7	3qa acid (10 µM)	+	16	<0.125
8	5g acid (100 µM)	+	4	<0.125
9	5g acid (50 µM)	+	4	<0.125
10	5g acid (25 µM)	+	16	<0.125
11	5g acid (10 µM)	+	16	<0.125

Supplementary Figures

Figure S1. Chemical structures of representative clinically useful bisphosphonates.

Figure S2. The clinically useful SBL inhibitors, representative MBL inhibitors and MBL/SBL dual inhibitors.

Figure S3. Proposed mechanism for the insertion reaction.

Figure S4. Comparison of the predicted binding mode of **3aa** acid based on an NDM-1:L-captopril (PDB ID: 4EXS)^{S21} complex structure, revealing that **3aa** acid likely has a similar binding mode to that of L-captopril.

Figure S5. Comparison of the predicted binding mode of **3aa** acid based on an VIM-2:ML302F (PDB ID: 4PVT)^{S22} complex structure, revealing that **3aa** acid likely has a similar binding mode to that of ML302F.

Figure S6. The IC_{50} curves of **3aa acid** with (a) NDM-1, (b) VIM-2, (c) TEM-1, and (d) KPC-2.

Figure S7. The IC_{50} curves of all the compounds in Table 1 with NDM-1.

Figure S8. The IC_{50} curves of all the compounds in Table 1 with VIM-2.

Figure S9. The IC_{50} curves of all the compounds in Table 1 with the TEM-1 SBL.

Figure S10. Testing the reversibility of **3qa** acid inhibiting (a) NDM-1 and (b) VIM-2. *L*-captopril and EDTA were used as controls (the details please see Supplementary Experimental Section SE.4). The samples of inhibitors and NDM-1/VIM-2 were preincubated for 30 min at room temperature, then rapidly diluted 100-fold into an assay solution, and finally determined the enzyme activities.

Figure S11. Testing how **3qa acid** affects the activity of NDM-1, VIM-2, and TEM-1. (a) The results reveal that **3qa acid** inhibits NDM-1 probably through the partially mixed inhibition type, but which inhibits VIM-2 probably in a substrate-competitive manner. (b) The inhibitory activities were tested after preincubation of **3qa acid** with TEM-1 for 10 min, 1 hour, 4 hours, and 24 hours, respectively. The results revealed that **3qa acid** manifests time-dependent inhibition with TEM-1.

Figure S12. The predicted binding mode of **3qa** acid with NDM-1.

Figure S13. The predicted binding mode of **3qa** acid with VIM-2.

Figure S14. The predicted binding mode of **3qa** acid with TEM-1.

^1H NMR, ^{13}C NMR, ^{31}P NMR of Compounds

Compound 3aa

ZC-170331-2_H1_CDCl3_2017-3-31
ZC-170331-2_H1_CDCl3_2017-3-31

OVL-170331-2-CDCl3-C13-2017-4-15
OVL-170331-2-CDCl3-C13-2017-4-15

0YL-170331-2

19.448

Compound 3ba

ZC-170331-3_H1_CDC13_2017-3-31
ZC-170331-3_H1_CDC13_2017-3-31

0.000

OVL-170331-3-CDCL3-C13-2017-4-15
OVL-170331-3-CDCL3-C13-2017-4-15

138.252

149.596

136.735

136.117

129.478

127.829

127.766

127.735

125.569

122.141

112.470

63.379

63.300

62.786

62.741

42.314

41.446

40.571

20.749

16.304

16.364

16.342

16.202

OVL-170331-3

19.441
18.791

Compound 3ca

ZC-170619-01_H1_DMSO_2017-6-19
ZC-170619-01_H1_DMSO_2017-6-19

ZC-170705-C3-CDCl3-C13-2017-7-8
ZC-170705-C3-CDCl3-C13-2017-7-8

0YL-170619-01

Compound 3da

ZC-170331-5_H1_CDCl3_2017-3-31
ZC-170331-5_H1_CDCl3_2017-3-31

OYL-170331-5-CDCL3-C13-2017-4-15
OYL-170331-5-CDCL3-C13-2017-4-15

159.155
148.924
138.072
137.664
136.564
131.825
128.441
128.400
127.789
124.579
121.701
63.208
63.165
62.669
62.650
40.454
39.571
38.700
21.339
16.209
16.277
16.115
16.109

OYL-170331-5

19.579

Compound 3ea

0YL-170331-4

19.727

Compound 3fa

ZC-170406-1_H1_DMSO_2017-4-6
ZC-170406-1_H1_DMSO_2017-4-6

ZC-170710-C2-CDCl3-C13-2017-7-16
ZC-170710-C2-CDCl3-C13-2017-7-16

157.723
149.180
142.085
139.712
133.866
132.824
130.159
128.244
126.561
124.394
122.335

63.215
62.712

40.671
39.328
38.046

16.143

OVL-170406-1

18.747

A (g)
18.75
H

Compound 3ga

ZC-170406-2_H1_DMSO_2017-4-6
ZC-170406-2_H1_DMSO_2017-4-6

2017-08-08 zhanghailong-ZC170802C

0YL-170406-2

— 17.848

Compound 3ha

ZC-170406-3_H1_DMSO_2017-4-6
ZC-170406-3_H1_DMSO_2017-4-6

8.723, 8.716, 8.066, 8.053, 8.012, 7.999, 7.987, 7.882, 7.868, 7.852, 7.838, 7.689, 7.676, 7.491, 7.482, 7.471, 5.339, 5.327, 5.325, 5.305, 5.282, 5.279, 5.255, 5.235, 5.215, 5.195, 5.175, 5.155, 5.135, 5.115, 5.095, 5.075, 5.055, 5.035, 5.015, 4.995, 4.975, 4.955, 4.935, 4.915, 4.895, 4.875, 4.855, 4.835, 4.815, 4.795, 4.775, 4.755, 4.735, 4.715, 4.695, 4.675, 4.655, 4.635, 4.615, 4.595, 4.575, 4.555, 4.535, 4.515, 4.495, 4.475, 4.455, 4.435, 4.415, 4.395, 4.375, 4.355, 4.335, 4.315, 4.295, 4.275, 4.255, 4.235, 4.215, 4.195, 4.175, 4.155, 4.135, 4.115, 4.095, 4.075, 4.055, 4.035, 4.015, 3.995, 3.975, 3.955, 3.935, 3.915, 3.895, 3.875, 3.855, 3.835, 3.815, 3.795, 3.775, 3.755, 3.735, 3.715, 3.695, 3.675, 3.655, 3.635, 3.615, 3.595, 3.575, 3.555, 3.535, 3.515, 3.495, 3.475, 3.455, 3.435, 3.415, 3.395, 3.375, 3.355, 3.335, 3.315, 3.295, 3.275, 3.255, 3.235, 3.215, 3.195, 3.175, 3.155, 3.135, 3.115, 3.095, 3.075, 3.055, 3.035, 3.015, 2.995, 2.975, 2.955, 2.935, 2.915, 2.895, 2.875, 2.855, 2.835, 2.815, 2.795, 2.775, 2.755, 2.735, 2.715, 2.695, 2.675, 2.655, 2.635, 2.615, 2.595, 2.575, 2.555, 2.535, 2.515, 2.495, 2.475, 2.455, 2.435, 2.415, 2.395, 2.375, 2.355, 2.335, 2.315, 2.295, 2.275, 2.255, 2.235, 2.215, 2.195, 2.175, 2.155, 2.135, 2.115, 2.095, 2.075, 2.055, 2.035, 2.015, 1.995, 1.975, 1.955, 1.935, 1.915, 1.895, 1.875, 1.855, 1.835, 1.815, 1.795, 1.775, 1.755, 1.735, 1.715, 1.695, 1.675, 1.655, 1.635, 1.615, 1.595, 1.575, 1.555, 1.535, 1.515, 1.495, 1.475, 1.455, 1.435, 1.415, 1.395, 1.375, 1.355, 1.335, 1.315, 1.295, 1.275, 1.255, 1.235, 1.215, 1.195, 1.175, 1.155, 1.135, 1.115, 1.095, 1.075, 1.055, 1.035, 1.015, 0.995, 0.975, 0.955, 0.935, 0.915, 0.895, 0.875, 0.855, 0.835, 0.815, 0.795, 0.775, 0.755, 0.735, 0.715, 0.695, 0.675, 0.655, 0.635, 0.615, 0.595, 0.575, 0.555, 0.535, 0.515, 0.495, 0.475, 0.455, 0.435, 0.415, 0.395, 0.375, 0.355, 0.335, 0.315, 0.295, 0.275, 0.255, 0.235, 0.215, 0.195, 0.175, 0.155, 0.135, 0.115, 0.095, 0.075, 0.055, 0.035, 0.015, 0.000

ZC-170710-C3-CDCl3-C13-2017-7-14
ZC-170710-C3-CDCl3-C13-2017-7-14

157.782
149.277
141.144
136.860
132.754
131.740
130.066
129.888
129.414
128.759
127.079
124.777
124.573
122.507

63.319
63.273
62.933
62.887

40.893
40.021
39.151

16.225
16.183
16.148
16.105

OYL-170406-3

18.357

Compound 3ia

ZC-170406-4_H1_DMSO_2017-4-6
ZC-170406-4 H1 DMSO 2017-4-6

8.715, 8.708, 8.039, 8.025, 8.002, 7.995, 7.984, 7.651, 7.638, 7.621, 7.468, 7.455, 5.327, 5.285, 5.244, 3.981, 3.965, 3.953, 3.942, 3.919, 3.905, 3.892, 3.875, 3.859, 3.847, 3.834, 3.820, 1.124, 1.112, 1.100, 1.001, 0.997, 0.990, 0.979

ZC-170719-C7-CDCL3-C13-2017-7-22
ZC-170719-C7-CDCL3-C13-2017-7-22

158.159, 149.015, 140.589, 138.285, 137.079, 133.373, 130.731, 129.222, 128.970, 128.680, 124.570, 122.286, 63.271, 62.789, 41.342, 40.040, 38.695, 16.125

0YL-170406-4

Compound **3ja**

ZC-170331-6_H1_CDC13_2017-3-31
ZC-170331-6 H1 CDC13 2017-3-31

0VL-170331-6-CDCL3-C13-2017-4-15
 0VL-170331-6-CDCL3-C13-2017-4-15

0VL-170331-6

Compound 3ka

ZC-170406-5_H1_DMSO_2017-4-6
ZC-170406-5_H1_DMSO_2017-4-6

ZC-170710-C1-CDCl3-C13-2017-7-14
ZC-170710-C1-CDCl3-C13-2017-7-14

0YL-170406-5

-19.464

Compound 3la

ZC-170414-1_H1_DMSO_2017-4-16
ZC-170414-1_H1_DMSO_2017-4-16

8.667 8.660 7.955 7.943 7.930 7.607 7.590 7.569 7.556 7.544 7.531 7.418 7.409 7.397 7.297 7.283 7.270 5.350 5.308 5.266 3.976 3.971 3.964 3.960 3.950 3.948 3.936 3.925 3.912 3.910 3.897 3.881 3.875 3.865 3.855 3.850 3.837 3.824 3.812 3.809 1.116 1.104 1.093 1.002 0.990 0.978

Compound 3ma

ZC-170414-5_H1_DMSO_2017-4-16
ZC-170414-5 H1 DMSO 2017-4-16

8.676
8.669
7.967
7.954
7.941
7.851
7.867
7.574
7.527
7.515
7.372
7.488
7.434
7.425
7.422
7.413
5.359
5.317
5.275
3.979
3.973
3.966
3.962
3.950
3.938
3.923
3.908
3.896
3.879
3.877
3.854
3.841
3.828
3.824
1.118
1.106
1.094
1.095
1.083

ZC-170710-C5_C13_CDCl3_2017-7-12
ZC-170710-C5 C13 CDCl3 2017-7-12

138.477
149.141
38.953
36.740
34.159
31.455
31.119
30.417
27.773
24.459
22.169
63.325
63.279
62.852
62.805
40.660
39.789
38.915
16.230
16.185
16.132
16.108

0YL-170414-5

—18.537

Compound 3na

ZC-170414-4_H1_DMSO_2017-4-16
ZC-170414-4_H1_DMSO_2017-4-16

8.706
8.698
8.442
8.439
7.997
7.983
7.969
7.636
7.621
7.465
7.457
7.453
7.444
5.376
5.374
5.291
3.963
3.951
3.946
3.939
3.935
3.923
3.911
3.897
3.885
3.873
3.862
3.850
3.838
1.105
1.093
1.082
1.070
0.999
0.987

ZC-170705-C6-CDC13-C13-2017-7-8
ZC-170705-C6-CDC13-C13-2017-7-8

OVL-170414-4

Compound 30a

ZC-170414-3_H1_DMSO_2017-4-16
ZC-170414-3 H1 DMSO 2017-4-16

ZC-170710-C4-CDCL3-C13-2017-7-14
ZC-170710-C4-CDCL3-C13-2017-7-14

0YL-170414-3

— 19.265

Compound 3pa

ZC-170505-04_H1_DMSO_2017-5-5
ZC17050504 H1 DMSO 2017-5-5

ZC-170629-C5-CDCl3-C13-2017-7-1
ZC-170629-C5-CDCl3-C13-2017-7-1

148.114
146.280
136.274
135.404
132.739
129.829
129.288
128.726
127.668
125.393
121.192

62.673
62.512

40.803
39.500
38.208

16.189
15.996

0VL-170505-04

20.592

Compound 3qa

0YL-170414-2

19.241

Compound 3ra

ZC-170426-03_H1_DMSO_2017-4-26
ZC-170426-03_H1_DMSO_2017-4-26

ZC-170719-C3-CDCl3-C13-2017-7-22
ZC-170719-C3-CDCl3-C13-2017-7-22

157.269
149.724
138.520
136.097
132.669
132.497
128.181
127.982
127.965
126.600
126.285
126.131
125.869
122.473

63.151
62.728

43.357
42.044
40.705

16.147

OVL-170426-03

18.709
18.146

Compound 3sa

0YL-170619-06

—19.330

Compound 3ta

ZC-170626-4_H1_DMSO_2017-6-26
ZC-170626-4_H1_DMSO_2017-6-26

9.435

7.915

7.814

7.791

7.778

7.755

7.345

7.119

6.130

5.237

5.173

5.110

4.016

3.993

3.967

3.960

3.941

3.923

3.915

3.886

3.878

3.861

3.844

3.826

1.117

1.099

1.082

1.035

1.017

1.000

ZC-170626-C2-CDCl3-C13-2017-6-28
ZC-170626-C2-CDCl3-C13-2017-6-28

150.396
148.874
147.224
147.115
146.779
145.790
132.018
122.764
122.600
121.603
120.968
120.151
110.888
110.588
101.339
63.131
62.672
61.603
56.988
56.948
41.275
39.948
38.622
16.183

OVL-170626-4

19.387

Compound **3ta**¹

—18.872

2017-08-08 zhanghailong-ZC1708024

ZC-170705-C1-CDCL3-C13-2017-7-8
ZC-170705-C1-CDCL3-C13-2017-7-8

—159.091

—148.957

—140.433

—136.479

—131.275

—130.265

—128.296

—128.165

—127.885

—124.440

—121.829

—66.703

—66.306

—40.936

—39.629

—38.337

—32.331

—18.503

—13.512

OVL-170705

—19.312

Compound 3ac

ZC-170510-01_H1_DMSO_2017-5-10
ZC-170510-01_H1_DMSO_2017-5-10

ZC-170705-C2-CDCl3-2017-7-13
ZC-170705-C2-CDCl3-2017-7-13

0YL-170510-01

-20.043

Compound 5a

ZC-170426-01_H1_DMSO_2017-4-26
ZC-170426-01_H1_DMSO_2017-4-26

Compound **5b**

ZC-170426-02_H1_DMSO_2017-4-26
ZC-170426-02_H1_DMSO_2017-4-26

ZC-170703-C2-CDCL3-C13-2017-7-8
ZC-170703-C2-CDCL3-C13-2017-7-8

0YL-170426-02

Compound 5c

ZC-170505-05_H1_DMSO_2017-5-5
ZC17050505 H1 DMSO 2017-5-5

ZC-170626-C1_C13_CDCl3_2017-6-27
ZC-170626-C1 C13 CDCl3 2017-6-27

138.377
133.011
121.340
118.766
116.325
115.848

63.048
62.461
55.278

39.280
38.402
37.526

16.126

OVL-170510-05

19.762

Compound 5d

ZC-170510-02_H1_DMSO_2017-5-10
ZC-170510-02_H1_DMSO_2017-5-10

9.033
8.653
8.091
8.077
8.053
8.006
7.579
7.571
7.563
6.522
6.479
6.456

4.008
3.992
3.980
3.968
3.900
3.887
3.874
3.862
3.850
3.837
3.825
3.812
3.800
3.787
3.775
3.762
3.750
3.737
3.725
3.712
3.700
3.687
3.675
3.662
3.650
3.637
3.625
3.612
3.600
3.587
3.575
3.562
3.550
3.537
3.525
3.512
3.500
3.487
3.475
3.462
3.450
3.437
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ZC-170703-C3-CDCL3-C13-2017-1-18
ZC-170703-C3-CDCL3-C13-2017-1-18

166.538
165.718
157.039
137.528
134.557
132.053
132.025
130.193
129.413
119.053
112.489
63.284
63.239
62.764
62.718
52.168
40.520
39.651
38.768
16.149

OYL-170510-02

-18.584

Compound 5e

ZC-170505-03_H1_DMSO_2017-5-5
ZC17050503 H1 DMSO 2017-5-5

ZC-170703-C1-CDCl3-C13-2017-7-8
ZC-170703-C1-CDCl3-C13-2017-7-8

OVL-170805-03

Compound **5f**

ZC-170505-01_H1_DMSO_2017-5-5
ZC17050501: H1 DMSO 2017-5-5

ZC-170703-C5-CDCL3-C13-2017-5-8
ZC-170703-C5-CDCL3-C13-2017-5-8

0YL-170505-01

— 18.787

Compound 5g

ZC-170505-02_H1_DMSO_2017-5-5
ZC17050502 H1 DMSO 2017-5-5

Compound **5h**

ZC-170510-03_H1_DMSO_2017-5-10
ZC-170510-03_H1_DMSO_2017-5-10

8.000, 7.895, 7.883, 7.845, 7.534, 7.492, 7.481, 7.470, 7.458, 7.419, 7.407, 6.553, 4.734, 4.692, 4.690, 3.973, 3.963, 3.952, 3.940, 3.926, 3.883, 3.871, 3.860, 3.850, 3.838, 3.825, 1.157, 1.145, 1.134, 1.022, 1.010, 0.999

ZC-170629-C2-CDCl3-C13-2017-7-1
ZC-170629-C2-CDCl3-C13-2017-7-1

140.915, 139.954, 139.514, 131.487, 128.319, 128.248, 126.607, 126.249, 106.644, 63.327, 62.802, 39.539, 38.330, 36.995, 16.230, 16.164, 16.125, 16.038

0YL-170510-03

-18.327

Compound 5i

ZC-170619-04_H1_DMSO_2017-6-19
ZC-170619-04_H1_DMSO_2017-6-19

Compound 5j

0YL-170726

18.078

Compound 3aa acid

YST-HLY-2

Compound 3ba acid

Compound 3da acid

YST-HLT-3da

152.262
146.840
146.832
145.497
141.082
131.476
131.205
128.696
128.646
125.622

20.667

17.319

Compound 3ea acid

YST-HLY-3ea

16.112

Compound 3ga acid

YST-HLY-3ja

YST-HL1-3 ja

149.541
147.393
146.418
141.839
140.845
133.118
132.073
129.088
126.828
126.326
125.766

13.765

Compound 3ha acid

Compound **3ja acid**

YSY-HLY-3ga

YSY-HLY-3 ga

152.188
146.959
141.155
138.907
132.242
131.616
130.457
128.665
128.387
125.853

44.080
42.837
41.617

19.973

YSY-HLY-3 ga

15.929

Compound 3ka acid

Compound 3la acid

2017-08-24 zhanghailong-ZC-3na

Compound 3oa acid

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Compound 3pa acid

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Chemical structure of 10: O=P(O)(O)C1=C(C2=CC=CC=C2)C3=CC=CC=C3N1C4=CC=CC=C4

¹H NMR spectrum (DMSO-d₆):

Chemical Shift (ppm)	Integration
8.65, 8.62, 8.58, 8.55, 8.52, 8.48, 8.45, 8.42, 8.38, 8.35, 8.32, 8.28, 8.25, 8.22, 8.18, 8.15, 8.12, 8.08, 8.05, 8.02, 7.98, 7.95, 7.92, 7.88, 7.85, 7.82, 7.78, 7.75, 7.72, 7.68, 7.65, 7.62, 7.58, 7.55, 7.52	1.00, 0.99, 1.03, 3.08, 1.06, 1.00
3.59	1.19

Compound 3ra acid

Compound 3sa acid

Compound **3ta acid**

— 16.163

Compound **5g acid**

ZC-5g_H1_D2O_2017-8-28-2
ZC-5g_H1_D2O_2017-8-28-2

7.750
7.737
7.701
7.689
7.397
7.390
7.198
7.187
7.171
7.157
7.145
6.996

5.069
5.018
4.976

ZC-5g-D2O-C13-2017-9-15
ZC-5g-D2O-C13-2017-9-15

HQ-ZC5G

Compound 5h acid

2017-08-24 zhanghailong-ZC-Sha

15.905

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