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Supporting Information

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Supporting Information

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# SUPPORTING INFORMATION

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## S1. Materials and Methods

Starting materials for GMP and metal-organic layer (MOL) synthesis and other reagents were purchased from Sigma-Aldrich and Thermo Fisher Scientific (USA) unless otherwise noted and used without further purification. Transmission electron microscopy (TEM) was performed on a TECNAI Spirit microscope. Atomic force microscopy was performed on a Bruker V/Multimode 8 instrument. Powder X-ray diffraction (PXRD) patterns were acquired on a Bruker D8 Venture diffractometer using a Cu Kα radiation source (λ = 1.54178 Å) and processed with PowderX software. UV-Vis spectra were obtained with a Shimadzu UV-2600 UV-Vis spectrophotometer. Dynamic light scattering (DLS) and ζ-potential were measured on a Malvern Zetasizer Nano ZS instrument. $^{1}$H-NMR and $^{31}$P-NMR spectra were collected on a Bruker NMR 400 DRX spectrometer at 400 MHz and 161.6 MHz, respectively. Solid-state $^{31}$P-NMR was performed on a Bruker Avance III HD 400 MHz solid nmr system (Hg400) at 161.815 MHz at Integrated Molecular Structure Education and Research Center (IMSERC) at Northwestern University. Isothermal titration calorimetry (ITC) was performed on a MicroCal iTC200 system (Malvern Instruments). X-ray photoelectron spectroscopy (XPS) was performed on the KRATOS AXIS NOVA X-ray Photoelectron Spectrometer, based on a monochromatic Al Kα X-ray source at X-ray Research Facilities of University of Chicago. Raman spectra were taken on a LabRAM HR Evolution Raman Spectrometer (HORIBA Scientific). The concentrations of phenylphosphonic acid (PPA), diphenylphosphinic acid (DPPA), and GMP were quantified by LC-MS on an Agilent 6540 Q-tof system with Agilent ZORBAX Extend-C18 Column (2.1 mm × 50 mm, 3.5 *μ*m). Flow cytometry data were recorded on an LSR-Fortessa 4-15 (BD Biosciences, USA) and analyzed by FlowJo software (Tree Star, USA). Confocal laser scanning microscope (CLSM) images were collected on a Leica Stellaris 8 laser scanning confocal microscope at the University of Chicago Integrated Light Microscopy Facility and analyzed with ImageJ software (NIH, USA). The histological slides were scanned on a CRi Pannoramic SCAN 40× whole slide scanner by Integrated Light Microscopy Core at the University of Chicago and analyzed with the QuPath-0.2.3 and ImageJ.[1] The absorbance in MTS assays was measured by a BioTek Synergy HTX microplate reader.

For X-ray irradiation in test tubes and *in vitro* experiments, an RT250 orthovoltage X-ray machine model (Philips, USA) with a fixed setting at 250 kVp, 15 mA, and a built-in 1 mm Cu filter was used. For animal irradiations and computerized tomography (CT) scans, an X-RAD 225 image-guided biological irradiator (Precision X-ray Inc., USA) was used with voltage at 225 kVp, current at 13 mA, a 0.3 mm Cu filter, and a 15 mm collimator. The X-ray dose rate of X-RAD 225 was 0.04167 Gy/second. The X-ray dosimetry of both instruments was calibrated with an ionization chamber regularly by the Department of Radiation Oncology at the University of Chicago.

Gemcitabine was purchased from Medkoo Biosciences. Phosphate-buffered saline (PBS) was purchased from Thermo Fisher Scientific. Trypsin-EDTA solution was purchased from ATCC. The murine colorectal carcinoma CT26 cell was purchased from the American Type Culture Collection (ATCC, Rockville, MD) and cultured in RPMI-1640 (Corning, USA) (Gibco, USA) supplemented with 10% fetal bovine serum (FBS) (VWR, USA), 100 U/ml penicillin G sodium and 100 *μ*g/ml streptomycin

sulphate. The murine colorectal carcinoma MC38 cell was kindly provided by Dr. Ralph R. Weichselbaum at the University of Chicago and cultured in DMEM (4.5 g/L glucose, Corning, USA) supplemented with 10% fetal bovine serum (VWR, USA, filtered), 1% MEM non-essential amino acids solution (100X), sodium pyruvate solution (100 mM stock), 1% Hepes solution (1 M), and 1% Pen/Strep 100X solution. The cells were kept in a humidified atmosphere with 5% $CO_2$ at 37°C. BALB/c breeders were obtained from Charles River Laboratories (USA) and bred in-house at the animal facility at the University of Chicago. BALB/c mice aged 6-8 weeks were used for in vivo experiments. The Institutional Animal Care and Use Committee (IACUC) at the University of Chicago reviewed and approved the study protocol, D16-00322 (A3523-01). The Human Tissue Resource Center at the University of Chicago provided histology-related services.

## S2. Synthesis and Characterization

### S2.1 Synthesis and characterization of gemcitabine 5'-monophosphate (GMP)

1.58 g of gemcitabine (6 mmol, 1 eq) was added portion-wise to a solution of $POCl_3$ (60 mmol, 10 eq) in 40.0 mL of $PO(OMe)_3$ for 10 minutes in an ice-water bath. The reaction mixture was stirred for 5 minutes at 5 °C followed by 2 hours at room temperature. The mixture was carefully added to a mixture of deionized water (140 mL) and $Et_2O$ (300 mL) while chilled in an ice-water bath. The aqueous layer was collected and washed with extra $Et_2O$ (2 × 200 mL), and the pH was adjusted to 7 using concentrated $NH_4OH$ while keeping the mixture chilled. The aqueous layer was then washed with more $Et_2O$ (200 mL) and concentrated at a temperature lower than 30 °C to obtain a white slurry, which was stirred with MeOH (250 mL) at room temperature for 4 hours, filtered, and then concentrated to a slurry. Absolute EtOH (800 mL) was added to this slurry, stirred for another 4 hours, and filtered, and the resulting solid was dispersed and stirred in 400 mL of EtOH for 2 hours. The crude product was then dried and ground into a powder, which was recrystallized from MeOH to yield GMP as an ammonium salt (white solid, 1.8 g, 79.5%).$^1$H-NMR (400 MHz, $D_2O$) δ 8.13 (d, J = 8.0 Hz, 1H), 6.32 (d, J = 8.0 Hz, 1H), 6.30 – 6.23 (m, 1H), 4.59 – 4.46 (m, 1H), 4.28 (m, 2H), 4.15 (m, 1H). HRMS: m/z=344.0440 (expected 344.0460 for $[M+H]^+$).

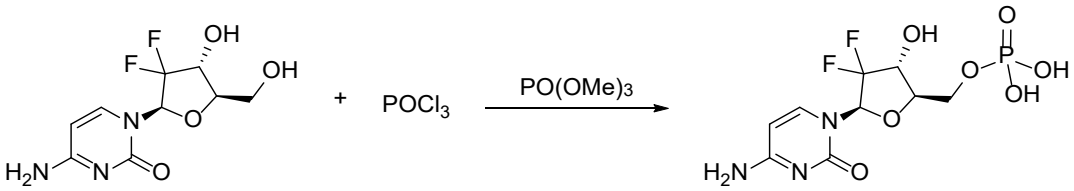


**Figure S1**. Synthesis of GMP.

### S2.2 Synthesis and characterization of MOL, DPPA/MOL, PPA/MOL, and GMP/MOL

Ir(DBB)[dF)$CF_3$)ppy]$^{2+}$ [$H_2$DBB-Ir-F, DBB = 4,4'-di(4-benzoato)-2,2'-bipyridine; dF($CF_3$)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine] and $Hf_{12}$-Ir MOL were synthesized according to the literature reports.[2] For $Hf_{12}$-Ir MOL, 500 $\mu$L of $HfCl_4$ solution [2.0 mg/mL in *N,N*-dimethylformamide

(DMF)], 500 $\mu$L of $H_2$DBB-Ir-F solution (4.0 mg/mL in DMF), 2 $\mu$L of trifluoroacetic acid (TFA), and 5 $\mu$L of water were added to a 1-dram glass vial. The mixture was sonicated and heated in an 80 °C oven for 24 h. The yellow suspension was collected by centrifugation and washed with DMF and ethanol. The final product $Hf_{12}$-Ir MOL was dispersed in ethanol for storage. To prepare DPPA/MOL and PPA/MOL, the $Hf_{12}$-Ir MOL was dispersed in ethanol at an equivalent Hf concentration of 2 mM, and an equivalent volume of DPPA and PPA solution (0.33 mM in ethanol) was added to the MOL suspension. The mixture was vortexed for 15-35 minutes to afford the conjugated MOL. To prepare GMP/MOL, 0.17 mM GMP was dissolved in water and then added to $Hf_{12}$-Ir and vortexed as above.

400 $\mu$L of bare MOL or conjugated MOL solution was centrifuged and dried under vacuum and then digested in a solution of 400 $\mu$L $D_6$-DMSO, 50 $\mu$L $D_2O$, and 50 $\mu$L $D_3PO_4$ by sonication for 10 minutes. The mixture was then analyzed by $^1$H-NMR and $^{31}$P-NMR. After digestion of three conjugated MOLs in $D_3PO_4$/ $D_6$-DMSO, the peaks of the three organophosphorus molecules reappeared in $^1$H-NMR and $^{31}$P-NMR spectra because the structure of MOLs is disrupted, allowing the release of organophosphorus molecules.

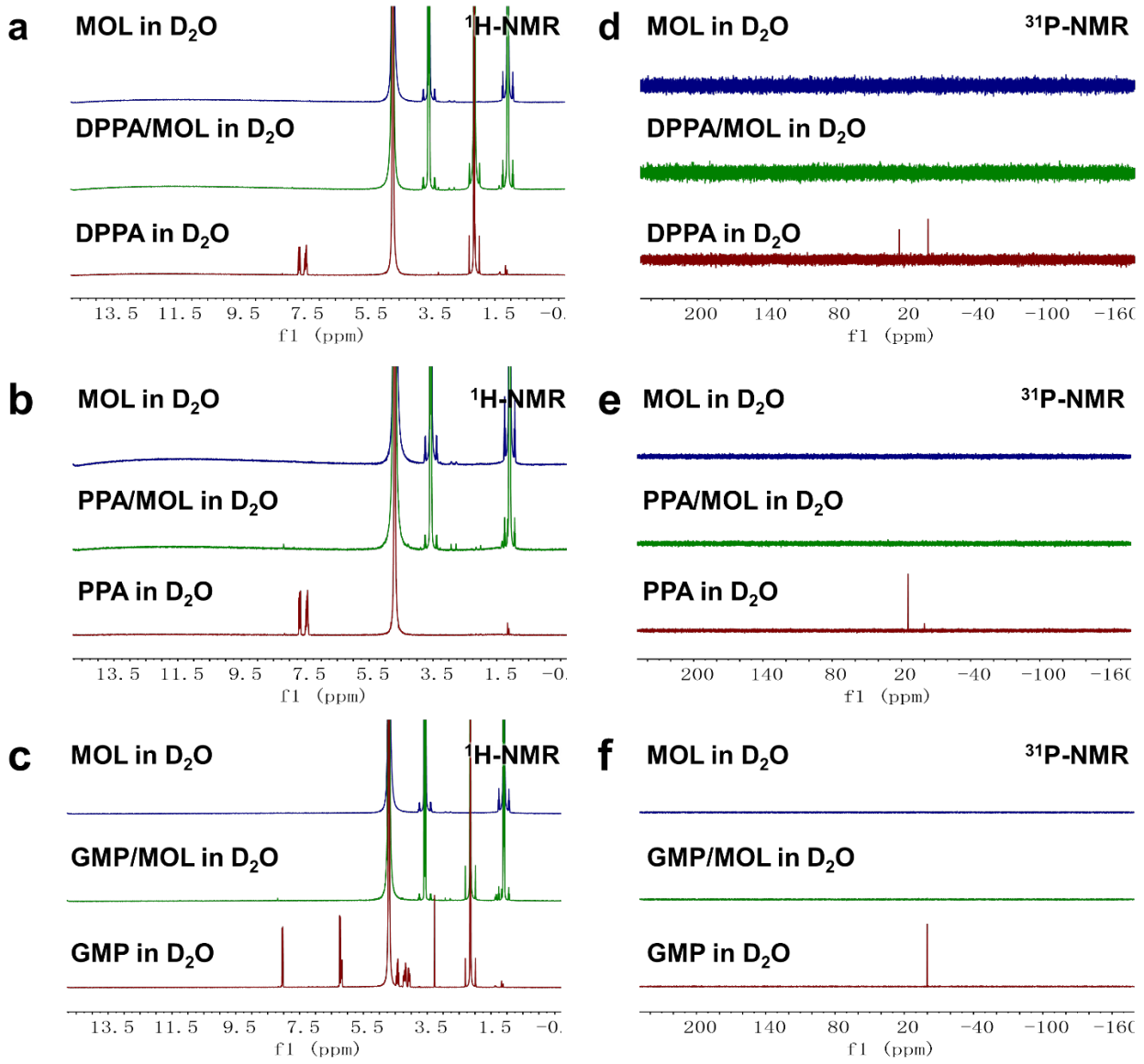


**Figure S2**. (a-c) $^{1}$H-NMR of (a) DPPA and DPPA/MOL, (b) PPA and PPA/MOL, and (c) GMP and GMP/MOL in $D_2O$. (d-f) $^{31}$P-NMR of (d) DPPA and DPPA/MOL, (e) PPA and PPA/MOL, and (f) GMP and GMP/MOL in $D_2O$.

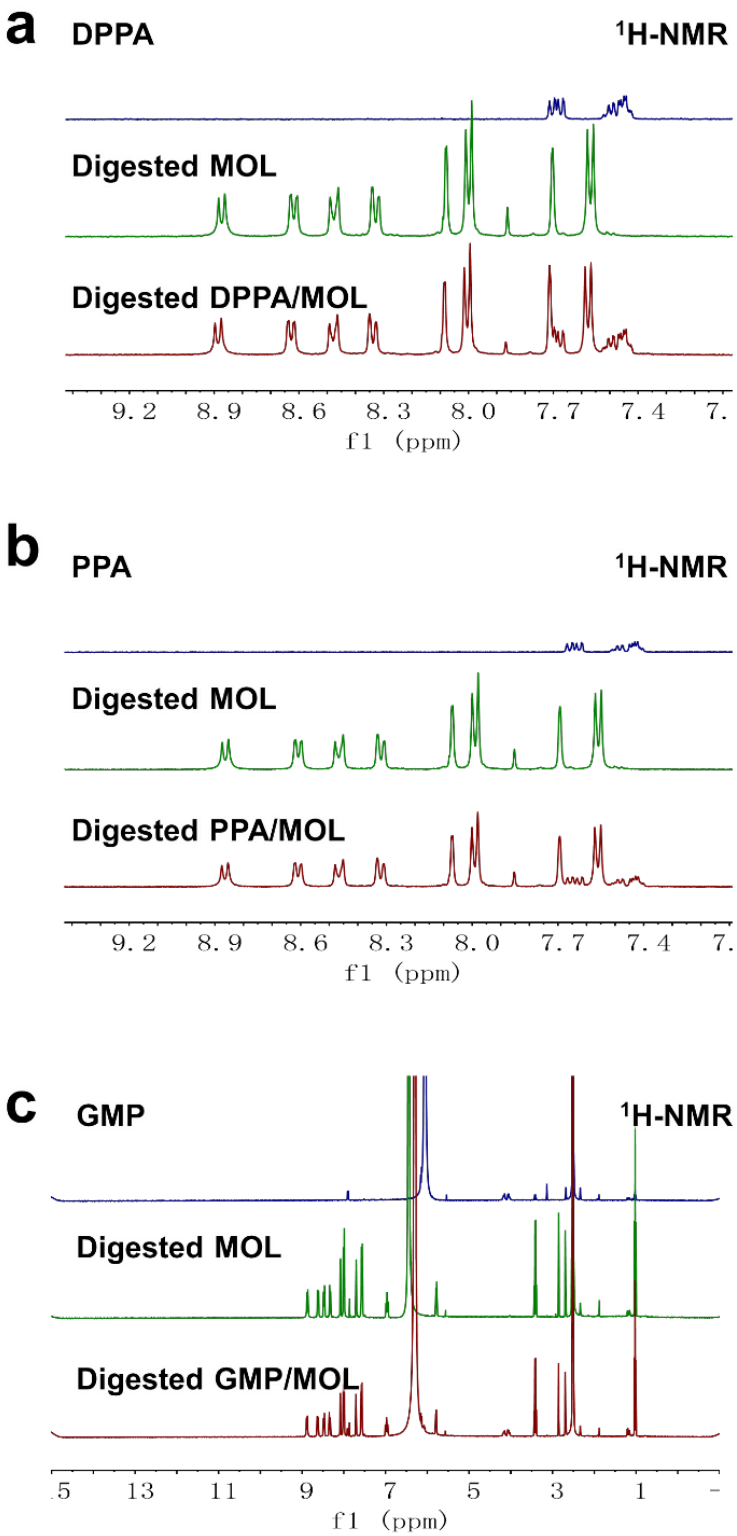


**Figure S3**. $^1$H-NMR of (a) DPPA and digested DPPA/MOL, (b) PPA and digested PPA/MOL, and (c) GMP and digested GMP/MOL in $D_6$-DMSO and $D_3PO_4$.

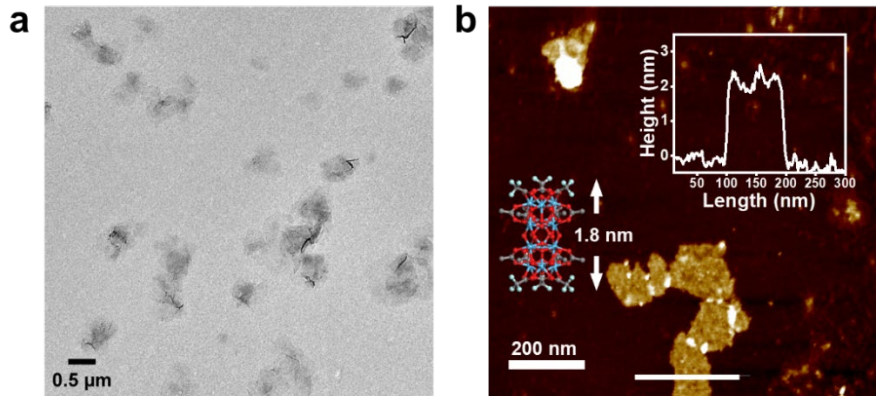


**Figure S4**. (a) TEM and (b) AFM images of $Hf_{12}$-Ir MOL.

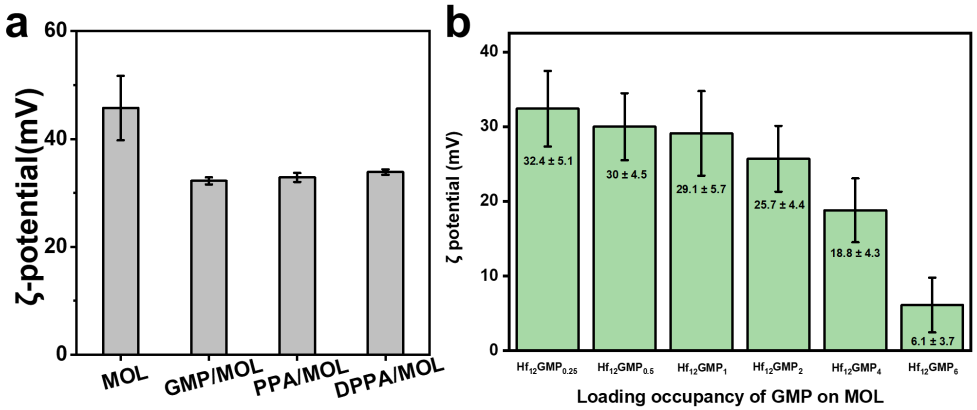


**Figure S5**. (a) ζ-potentials of MOL, DPPA/MOL, PPA/MOL, and GMP/MOL in water. (b) ζ-potentials of GMP/MOL with different loading percentages.

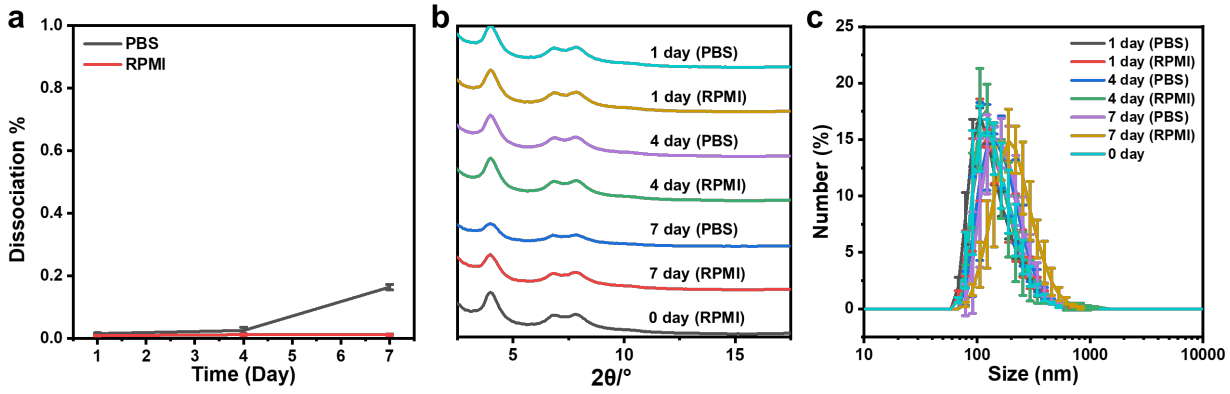


**Figure S6**. (a) Time-dependent Hf leaching from MOL in 1 mM PBS and RPMI-1640 medium measured by ICP-MS (n=3). (b) PXRD patterns of MOL after dispersing in 1 mM PBS and RPMI-1640 medium for 7 days. (c) Number-averaged sizes of MOL after dispersing in 1 mM PBS and RPMI-1640 medium for 7 days.

**Table S1.** Number-averaged sizes of MOL after incubation with 1 mM PBS and RPMI medium for different periods of time.

| Days | Number-averaged size (nm) |
|---|---|
| 0 day | 232.49±4.85 |
| 1 day (PBS) | 229.82±2.91 |
| 1 day (RPMI) | 236.84±12.18 |
| 4 days (PBS) | 232.34±5.87 |
| 4 days (RPMI) | 232.73±6.56 |
| 7 days (PBS) | 243.64±12.67 |
| 7 days (RPMI) | 271.2±8.6 |

### S2.3 Isothermal titration calorimetry

The interaction between organophosphorus and MOL was measured and analyzed by ITC on a MicroCal $iTC_{200}$ system (Malvern Instruments) equipped with reference and sample cells (V = 400 $\mu$L). All titrations were carried out using a 40 $\mu$L syringe at 298.15 K with a stirring rate of 250 rpm. 900 $\mu$M MOL (based on SBU) water solution was titrated with 3 mM DPPA, PPA, or GMP water solution. The first injection of 0.4 $\mu$L was followed by 20 injections of 2 $\mu$L at intervals of 150 s. The same organophosphorus samples were used to titrate $H_2O$ to subtract background noise. Data analysis was performed using the MicroCal $iTC_{200}$ software, and all data were fitted to an independent single-site model.

### S2.4 Loading capacity

The loading capacity of MOLs was tested by gradually increasing the ratio of DPPA, PPA, or GMP to MOL. Considering that both sides of MOL could conjugate molecules, the ratio of DPPA/PPA/GMP to binding sites on the SBU was defined as 1 when 6 molecules were coordinated with one SBU (three on each side). When the ratio was ≤1/3 (on average less than one drug on each side of one SBU), all three model compounds afforded complete loading. DPPA and PPA exhibited a >97% loading efficiency when reaching the maximal loading quantity. In comparison, GMP showed a loading of 85% when reaching the maximal loading quantity, indicating that spatial hindrance might negatively impact the loading efficiency.

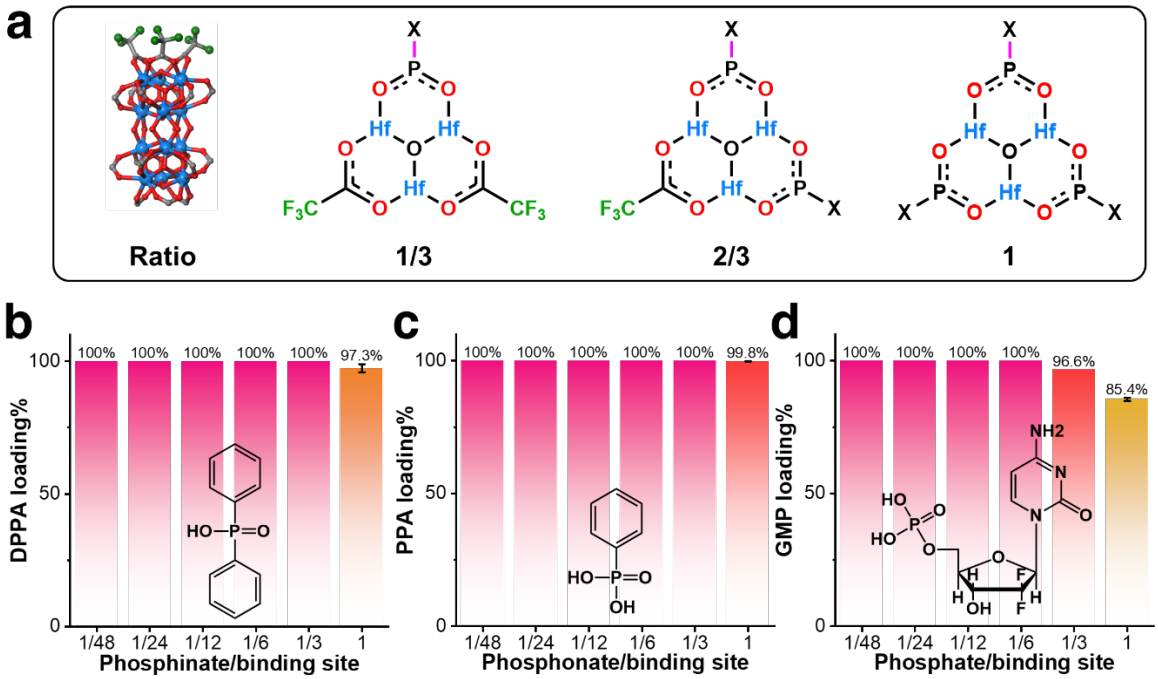


**Figure S7**. (a) Schematic showing loading ratios of DPPA, PPA, or GMP onto SBUs. (b-d) Loading percentages of (b) DPPA, (c) PPA, and (d) GMP from binding ratios of 1/48 to 1 (*n*=3).

**Table S2.** Loading ratios of DPPA, PPA, GMP to MOL presented by molar ratio of loaded molecules to SBUs, molar ratio of loaded molecules to binding sites on SBUs, molar ratio of loaded molecules to Hf atoms, and weight percentage(w/w) of loaded molecules to MOL.

| | Molar ratio of loaded molecules to $Hf_{12}$ SBUs | Molar ratio of loaded molecules to binding sites on SBUs | Molar ratio of loaded molecules to Hf | Weight percentage of loaded molecules to MOL |
|---|---|---|---|---|
| DPPA/MOL | **1** | **1/6** | **1/12** | **2.15%** |
| PPA/MOL | **1** | **1/6** | **1/12** | **1.57%** |
| GMP/MOL | **1** | **1/6** | **1/12** | **3.35%** |

### S2.5 XPS

XPS spectra of GMP, GMP/MOL and MOL were obtained with reference to the C 1s peak at 284.8 eV. Hf 4f, Ir 4f, and P 2p signals were observed in the XPS spectra (Figure S8). The Hf 4f signal in the GMP/MOL spectra is broadened compared to the Hf 4f signal in MOL (Figure S9 and S10). The Hf peaks in GMP/MOL slightly shifted to higher binding energies, suggesting a decrease in the electron density of Hf upon GMP coordination onto $Hf_{12}$ SBU. However, due to the low abundance of phosphorous in GMP/MOL (atomic ratio ~0.25%), the P 2p peak shows noisy signals but we did find a shift of the signal to a lower binding energy after GMP loading.

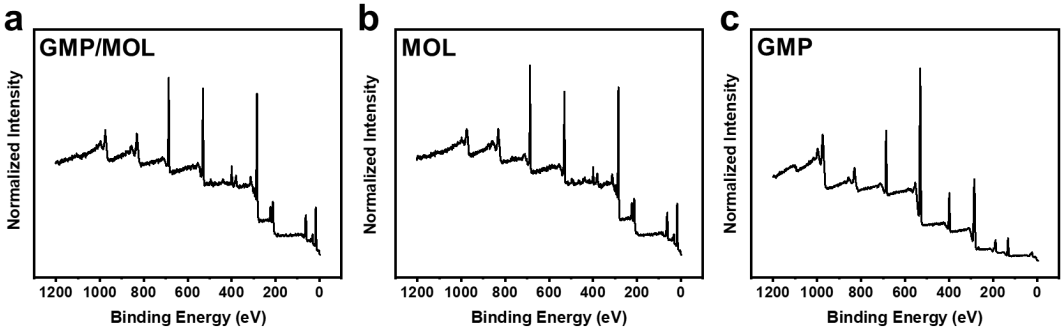


**Figure S8.** XPS spectra of (a) GMP/MOL, (b) MOL, and (c) GMP.

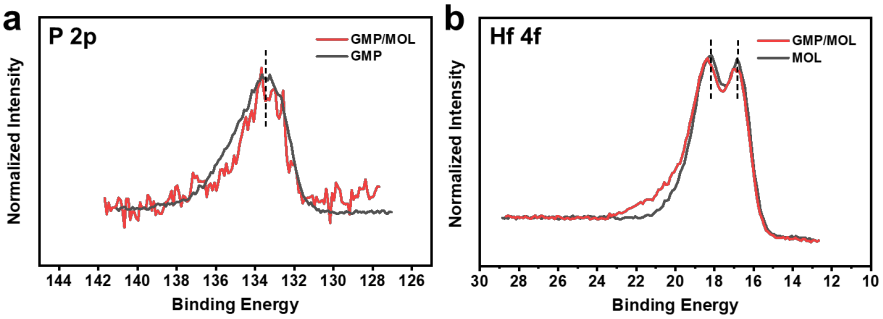


**Figure S9.** Comparison of (a) P 2p signals between GMP and GMP/MOL and (b) Hf 4f signals between MOL and GMP/MOL.

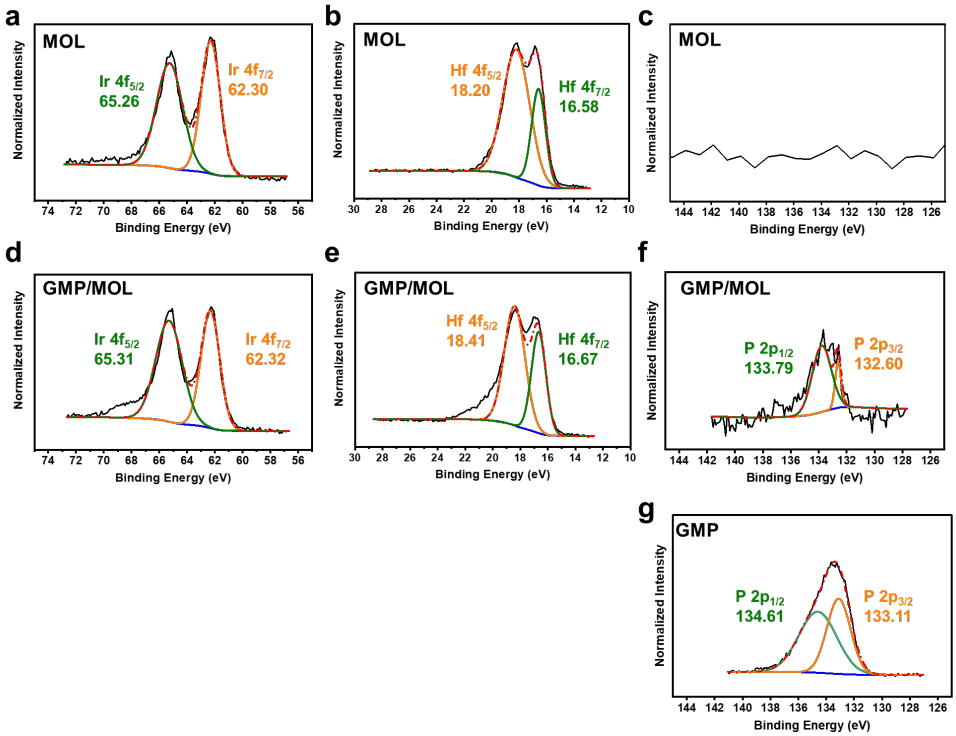

**Figure S10.** Peak fitting for (a) Ir 4f, (b) Hf 4f, and (c) P 2p of MOL. Peak fitting for (d) Ir 4f, (e) Hf 4f, and (f) P 2p of GMP/MOL. (g) Peak fitting for P 2p of GMP. As expected, MOL does not show any P 2p signal.

### S2.6 Raman spectroscopy

The vibrational modes of GMP/MOL were measured by Raman spectroscopy. The GMP, MOL, and GMP/MOL samples were cast onto a Si substrate and dried in vacuum to form thin layers of the samples. A laser at 633 nm was used to excite the samples. GMP alone exhibits two characteristic peaks of C-O-C stretching and C-N stretching at 781.314 $cm^{-1}$ and 1253.17 $cm^{-1}$, respectively. A shift of C-O-C stretching of GMP to a lower frequency of 775.56 $cm^{-1}$ was observed after its loading onto MOL, indicating changes in the molecular environment after coordination. The changes in C-N stretching of GMP cannot be observed due to overlap with the signals of MOL (possibly from the C-N stretching of $H_2$DBB-Ir ligands).

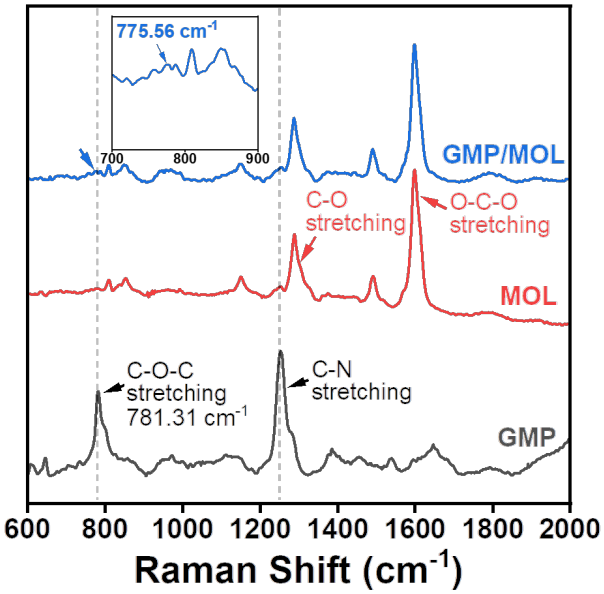


**Figure S11**. Raman spectra of GMP, MOL, and GMP/MOL.

### S3. DFT Calculations

DFT calculations were performed with Gaussian 16 software, Revision A.03.[3] To reduce the computational cost, we used the $Hf_6$ cluster as a substitute for the $Hf_{12}$ cluster and acetates to replace DBB-Ir linkers. Both approximations do not affect the binding interaction between the organophosphorus molecules and the SBUs. The structures of PA ($HPO_4^{2-}$), $Hf_6$-SBU, GMP, PPA, DPPA, and the conjugates were fully optimized using the B3LYP-D3(BJ) functional.[4] The 6-31G(d) basis set was used for C, H, O, N, P, and F, and the SDD basis set was used for Hf. The single-point energy calculation was based on the Def2TZVP basis set to ensure accuracy, and the corresponding thermal correction calculation was based on the 6-31G(d) basis set. The solvation effect (in $H_2O$) was calculated using the SMD solvation model.[5] The XYZ coordinates of optimized geometries were listed in S8. DFT calculations showed that the substitution of GMP, PPA, and DPPA by phosphate on SBUs yielded a ΔG of 15.6 kcal·$mol^{-1}$, 2.4 kcal·$mol^{-1}$, and -1.1 kcal·$mol^{-1}$, respectively (**Figure**

**S6**). From DPPA to PPA to GMP, the free energy change for the substitution reaction gradually increases. This calculation result supports that the release of DPPA is the easiest, while the release of GMP molecules from SBUs is the most difficult.

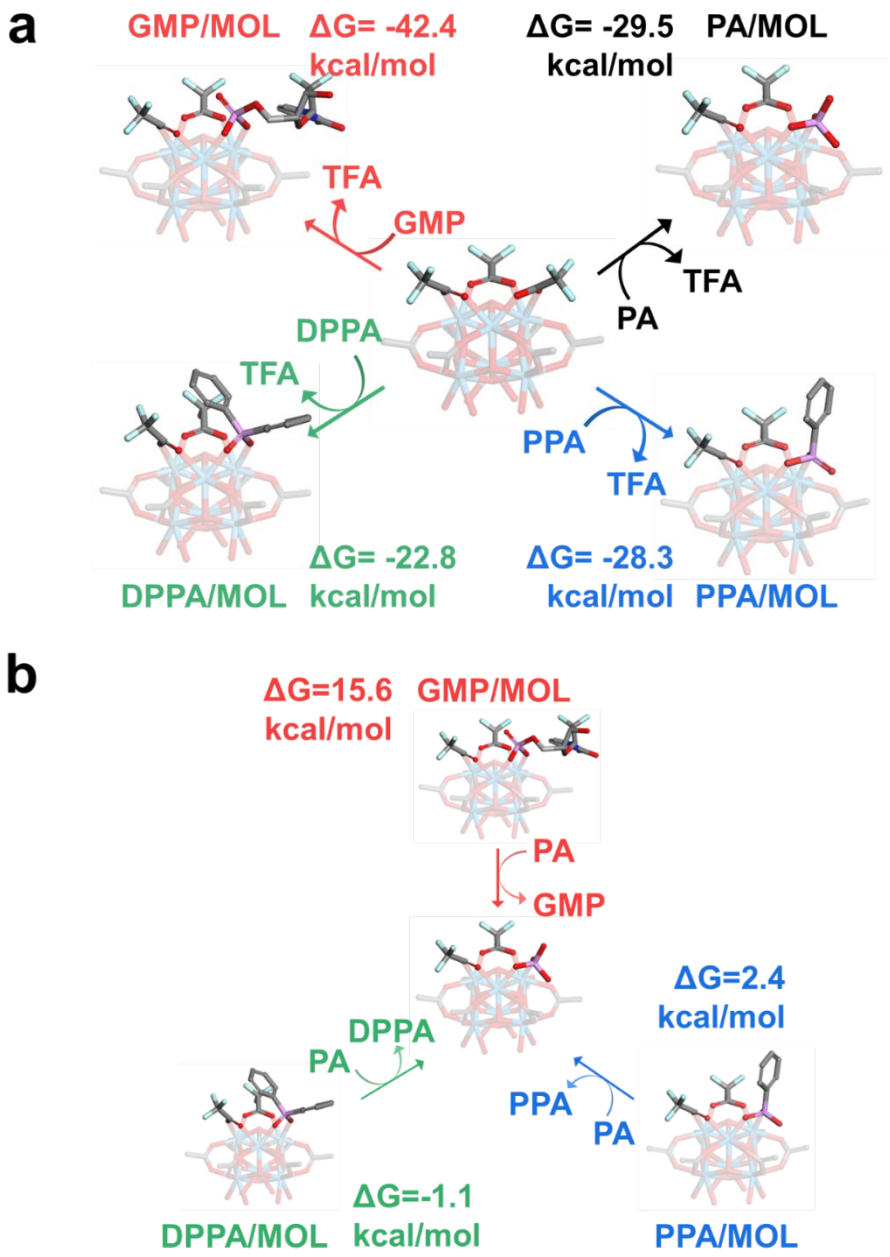


**Figure S12**. (a) Free energy changes of substitution reactions of TFA on SBUs by PA (phosphate), GMP, PPA, and DPPA. (b) Free energy changes of substitution reactions of GMP, PPA, and GMP on SBUs by PA.

### S4. Loading Efficiency and Release Profiles

LC-MS quantification of DPPA, PPA, and GMP was achieved by an Agilent 6540 Q-Tof system with Agilent ZORBAX Extend-C18 Column (2.1 mm × 50 mm, 3.5 $\mu$m). Mobile phase A (0.1% TFA in water [v/v]) and mobile phase B (0.1% TFA in acetonitrile [v/v]) were operated with a fixed elution at a flow rate of 0.5 mL/min as 5% B for 5 min. The column temperature and sample temperature were both room temperature. The injection volume was 5 $\mu$L. For loading efficiency, different ratios of DPPA, PPA, or GMP were mixed with MOL as described in S2.2. The mixture was centrifuged at 14,000 rpm for 15 minutes, and the supernatant was directly subjected to LC-MS to quantify the concentrations of unconjugated molecules.

For release profiles, DPPA/MOL, PPA/MOL, or GMP/MOL was freshly prepared and redispersed in 1× PBS or 0.1× PBS (200 $\mu$L/tube) in 1.5 mL Eppendorf tubes ($n$ = 3), respectively. The EP tubes were transferred to a 37 °C incubator. The supernatants (100 $\mu$L/tube) were collected at 0 h, 0.5 h, 1 h, 2h, 4 h, 8 h, and 24 h by centrifugation at 14,000 rpm and directly subjected to LC-MS quantification. The release profiles were fitted by the Hill function in OriginLab software.

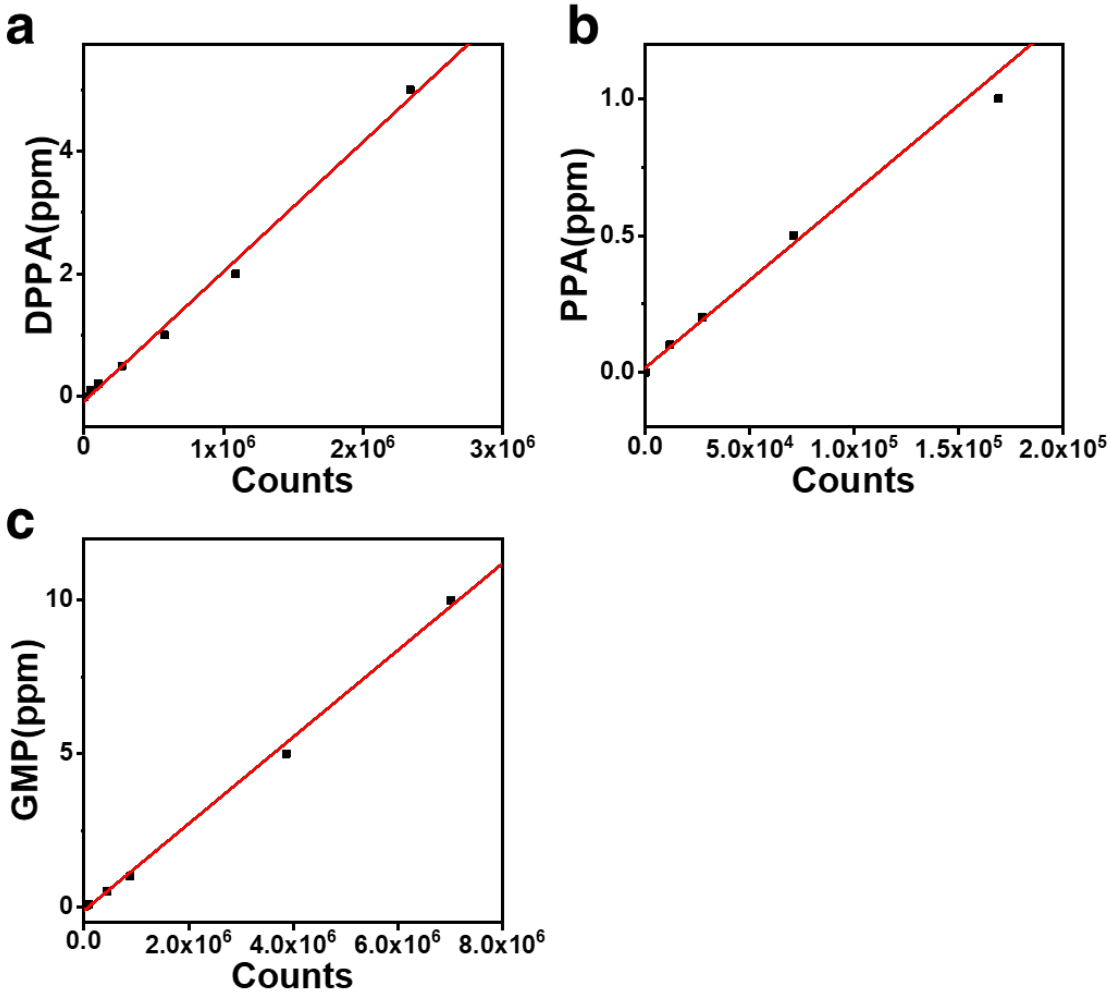


**Figure S13**. LC-MS standard curves of (a) DPPA, (b) PPA, and (c) GMP.

## S5. In Vitro Studies

### S5.1. Cellular uptake

CT26 cells were seeded in 6-well plates at a density of 2 × $10^5$/well and incubated overnight. MOL or GMP/MOL was added at an equivalent Hf dose of 20 $\mu$M ($n$ = 3). The cells were incubated at 37 ℃ for 1, 4, 8, and 12 hours. At each time point, the medium was aspirated, and the cells were washed with PBS three times, trypsinized, and collected by centrifugation at 1,800 rpm for 3 minutes. The cell pellets were digested with 1 mL of concentrated $HNO_3$ with 1% HF in 1.5 mL Eppendorf tubes for 48 hours. The Hf concentration was determined by ICP-MS after dilution.

### S5.2. Cell viability assay

The cytotoxicity of GMP, MOL, and GMP/MOL was evaluated in CT26 cells by CellTiter 96 $AQ_{ueous}$ One Solution Cell Proliferation Assay (MTS assay, Promega, USA). The cells were seeded in 96-well plates at a density of 1,500 cells/well and cultured overnight. GMP or GMP/MOL was added at an equivalent GMP concentration of 0, 0.02, 0.2, 0.5, 1, 2, 5, 10, 20, 50, and 100 $\mu$M, and the cells were further incubated for 2 days. The cell viability was determined by MTS assay ($n$ = 3). The toxicity of GMP/MOL to HEK293T, splenocytes, and bone marrow derived dendritic cells (BMDCs) were evluated in a similar way by MTS assay except the cells were plated at a density of 10,000 cells/well ($n$ = 3). $IC_{50}$ values of all treatment groups were fitted with the dose-response curves in Origin Lab software.

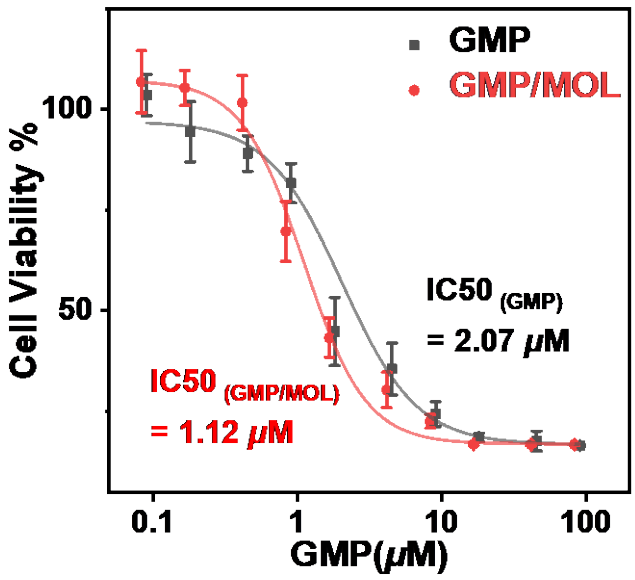


**Figure S14**. Cell viability curves of GMP and GMP/MOL in MC38 cells by MTS assays ($n$ = 3).

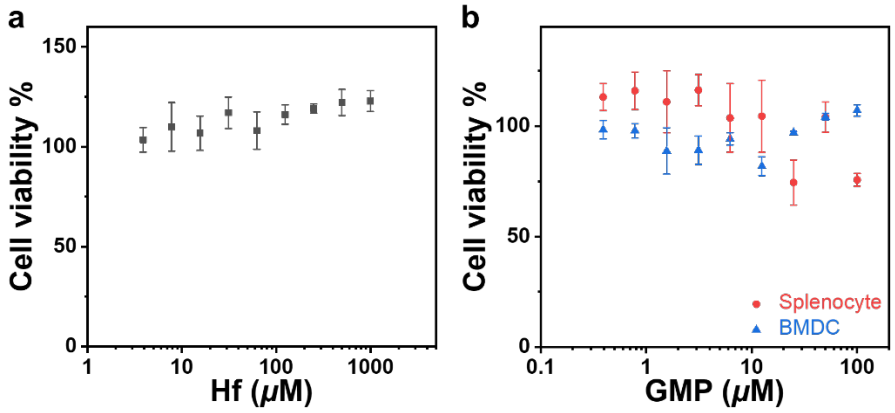


**Figure S15**. (a) Cytotoxicity of MOL in CT26 cells by the MTS assay ($n$ = 3). (b) Cell viability of splenocytes and bone marrow-derived dendritic cells (BMDCs) treated with GMP/MOL ($n$ = 3).

**Table S3**. $IC_{50}$ values of GMP and GMP/MOL in CT26 and MC38 cells.

| Treatment | $IC_{50}$(CT26) | $IC_{50}$(MC38) |
|---|---|---|
| GMP | **1.16±0.27** | **2.07±0.50** |
| GMP/MOL | **0.62±0.17** | **1.12±0.21** |

### S5.3. Growth rate inhibition assay

$1\times10^5$ cells/mL of CT26 cells were seeded in 6-well plates with or without coverslip in 2 mL of culture medium and cultured overnight for CLSM or flow cytometry, respectively. GMP or GMP/MOL was added at a GMP concentration of 1.67 μM and incubated for 8 hours. The cells were irradiated by 2 Gy X-ray and immediately trypsinized to afford single-cell suspensions. The cells were then counted, diluted to 1000~2000 cells/mL, and reseeded in 24-well plates. The plates were put in IncuCyte S3 live imaging system and continuously observed by a 10× objective in phase contrast mode. The phase contrast images were collected and analyzed with IncuCyte 2021A software to obtain a time-dependent confluence in each well (25 tiles per well, triplicates for each treatment group). The first derivative was calculated based on a time-dependent growth curve to give a growth rate ($k_t$). The time point where the $k$ of the control group (PBS, 0 Gy) reached a maximum ($t_{max}$) was selected as the time to define the growth rate inhibition index ($GRI$). The $GRI$ in the radiosensitization experiment was defined using the equation below[6]:

$$GRI(D, t_{max}) = 2^{k(D,t_{\max})/k(0)} - 1$$

Where $D$ was the radiation dose and $k(0)$ was the growth rate of the control group at $t_{max}$. $GRI$ data could be fitted linearly with GRI in log scale:

$$\log\left[GRI(D)\right] = \alpha D + \beta$$

Then the relative growth inhibition factor at $GRI = 10\%$ ($GIF_{10\%}$) was defined based on the fitting curve of $GRI(D)$ to quantify the radiosensitizing effects:

$$GIF_{10\%} = \frac{D_{treatment\ A}}{D_{treatment\ B}}$$

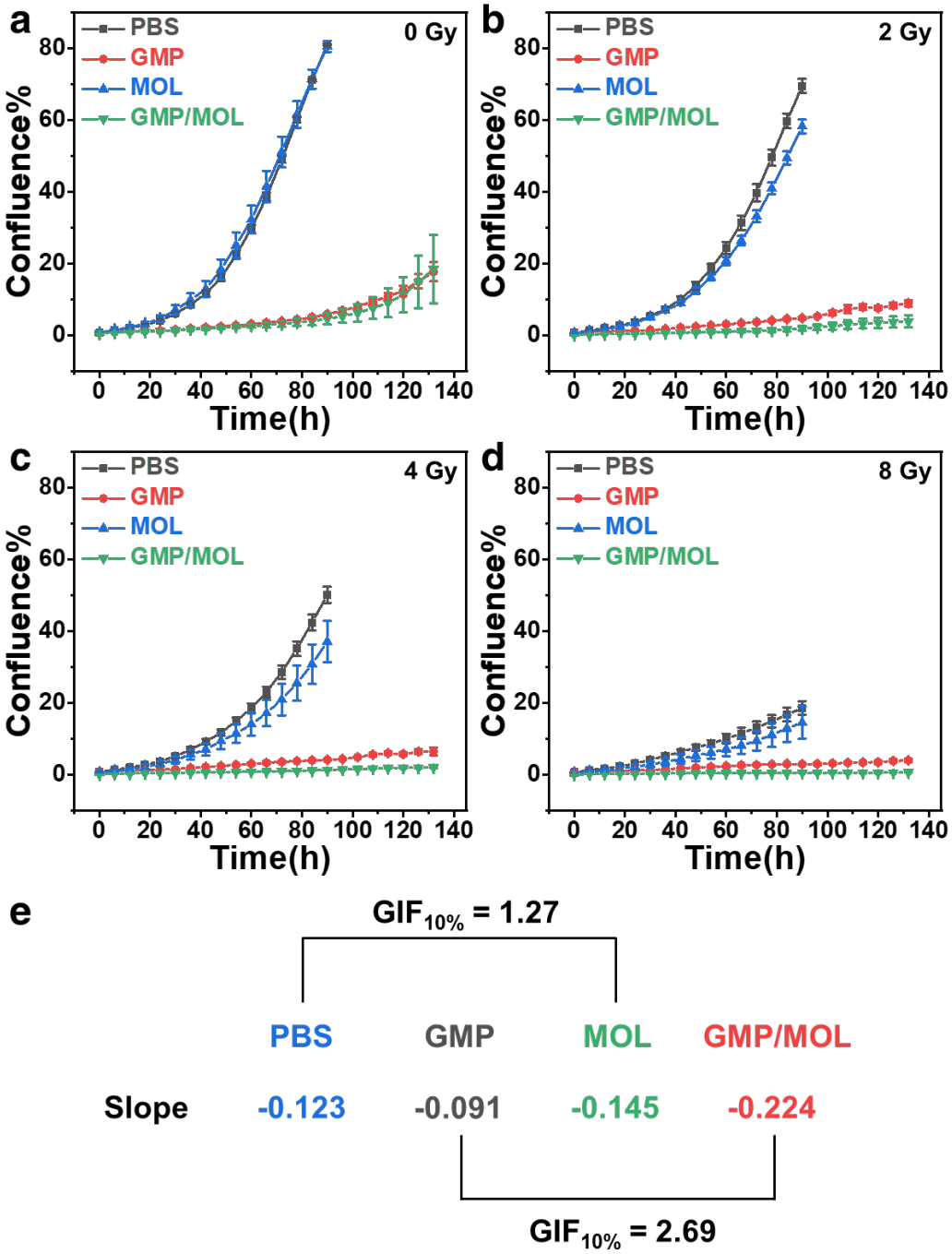


**Figure S16**. Time-dependent confluence curves of cells irradiated by (a) 0 Gy, (b) 2 Gy, (c) 4 Gy, and (d) 8 Gy. (e) Relative $GIF_{10\%}$ values of PBS to MOL and GMP to GMP/MOL.

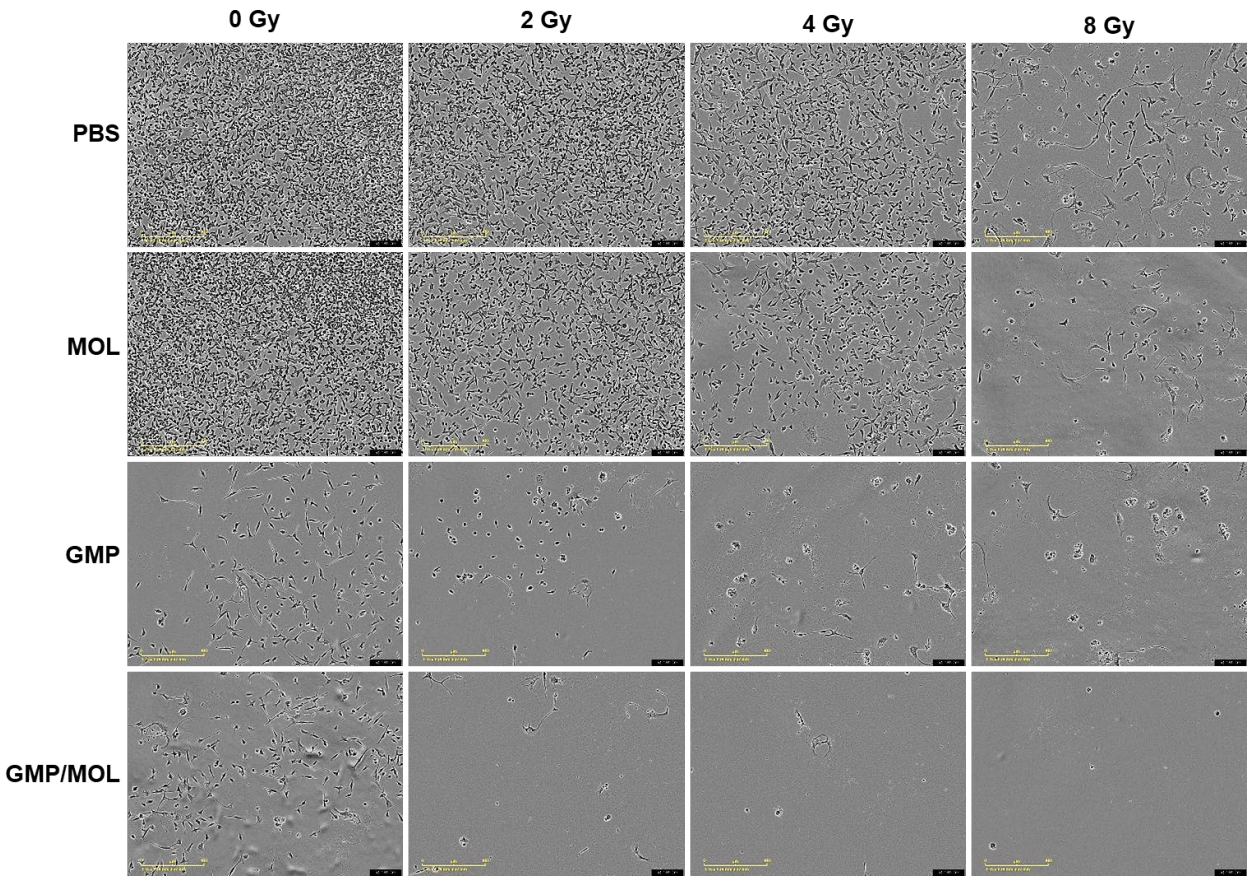


**Figure S17**. Representative phase contrast images of CT26 cells in GRI assay 3 days 18 hours after treatment. (scale bar = 400 $\mu$m)

### S5.4. γ-H2AX staining

$1\times10^5$ cells/mL of CT26 cells were seeded in 6-well plates with or without coverslip in 2 mL of culture medium and cultured overnight for CLSM or flow cytometry, respectively. The cells were treated the same way as GR assays and incubated for another 24 hours. For CLSM, the cells were fixed with 4% paraformaldehyde (pH = 7.2) at room temperature for 20 minutes. The cells were washed with PBS, blocked, and permeabilized by 5% FBS + 0.3% Triton-X in PBS at room temperature for 1 hour. After blocking, the cells were incubated with primary antibodies in 1% BSA + 0.3% Triton-X in PBS at 4°C overnight (phospho-histone H2A.X (Ser139) (20E3) rabbit mAb #9718, 1:400). The cells were then washed by PBS and incubated with secondary antibodies in 1% BSA + 0.3% Triton-X in PBS at room temperature for 1 hour (anti-rabbit IgG (H+L), F(ab')2 fragment (Alexa Fluor® 647 conjugate) #4414, 1:1000). After staining, cells were washed by PBS and further incubated with 1:500 Acti-stain™ 488 and 1:3000 Hoechst 33342 in PBS for 30 minutes. After washing with PBS, the coverslips were mounted on glass slides with ProLong™ glass antifade mountant, cured at room temperature overnight, sealed by nail polish, and observed on a Leica Stellaris 8 confocal microscope. The images were processed and analyzed by Fiji ImageJ (NIH). For flow cytometry, the cells were collected as single-cell suspensions, fixed, blocked, and permeabilized in the same way as above, but stained only

with primary and secondary antibodies. The cells were finally suspended in 0.5% BSA in PBS for flow cytometry analysis.

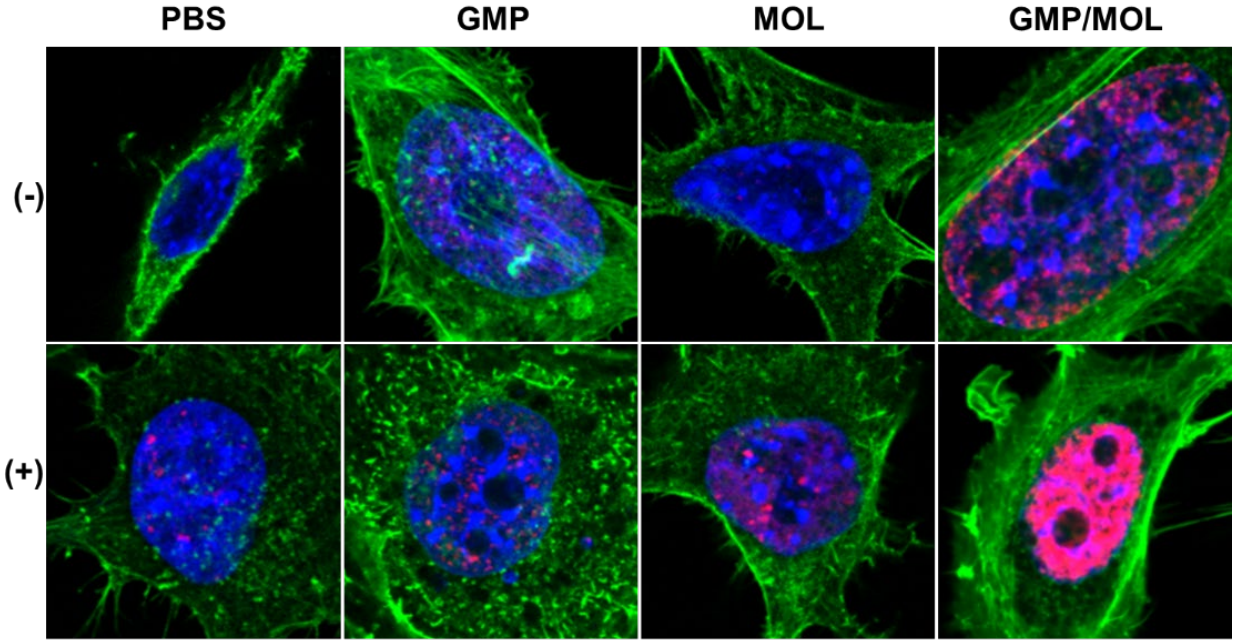


**Figure S18**. Representative CLSM images of DNA damage after different treatments. Nuclei were blued by Hoechst 33342. Cytoskeletons were green by Phalloidin. DNA damage was red by γ-H2AX. Frame length = 29.09 $\mu$m.

## S6. In Vivo Studies

### S6.1. Intratumoral retention and pharmacokinetics (PK) of GMP/MOL

To evaluate intratumoral retention and PK of GMP/MOL, a subcutaneous CT26 model was established in BALB/c mice by inoculating $2\times10^6$ cells/mouse subcutaneously. At day 7, GMP or GMP/MOL was injected intratumorally with an equivalent Hf dose of 1 $\mu$mol (GMP dose 1/12 $\mu$mol) ($n$ = 3). Three control mice without treatment served as the blank control to calculate the detection limit and the recovery rate of the GMP extraction method. At each time point, the mice were anesthetized, and the blood was drawn by retro-orbital bleeding. The tumors were excised and kept on ice, and the mice were euthanized.

The whole blood was immediately centrifuged at 2,000 g for 15 minutes, and the clear top layer was collected as plasma. For LC-MS of GMP, samples were diluted 5-fold by PBS (40 $\mu$L + 160 $\mu$L) and centrifuged by Centrifree centrifugal filters (Merck, Millipore) to obtain LC-MS samples (Swinging bucket, 1,000 g, RT, 20 minutes). For ICP-MS of Hf, 20 $\mu$L of plasma samples were diluted into 1 mL concentrated $HNO_3$ in 15 mL ep tubes and heated in a 60 °C oven for 2 hours. The samples were digested overnight, filtered, and diluted 35-fold with MilliQ water before ICP-MS.

Meanwhile, the tumors were excised and immersed in 15 mL ep tubes filled with 2 mL 5% $H_3PO_4$ (on ice). The tumor tissues were then homogenized with a probe sonicator (500 W, 20 kHz) with 30% power for 1 minute on ice. The mixture was centrifuged at 2,000 g RT for 15 minutes to remove all the solid residues, and 500 $\mu$L of supernatants were collected. For LC-MS of GMP, the tumor lysis was first diluted 5-fold by PBS and transferred 200 $\mu$L of supernatant into Centrifree centrifugal filters (Merck, Millipore) to obtain LC-MS samples (Swinging bucket, 1,000 g, RT, 20 minutes). For ICP-MS of Hf, 100 $\mu$L of tumor lysis was transferred into 1 mL concentrated $HNO_3$ and processed the same way as plasma samples for ICP-MS.

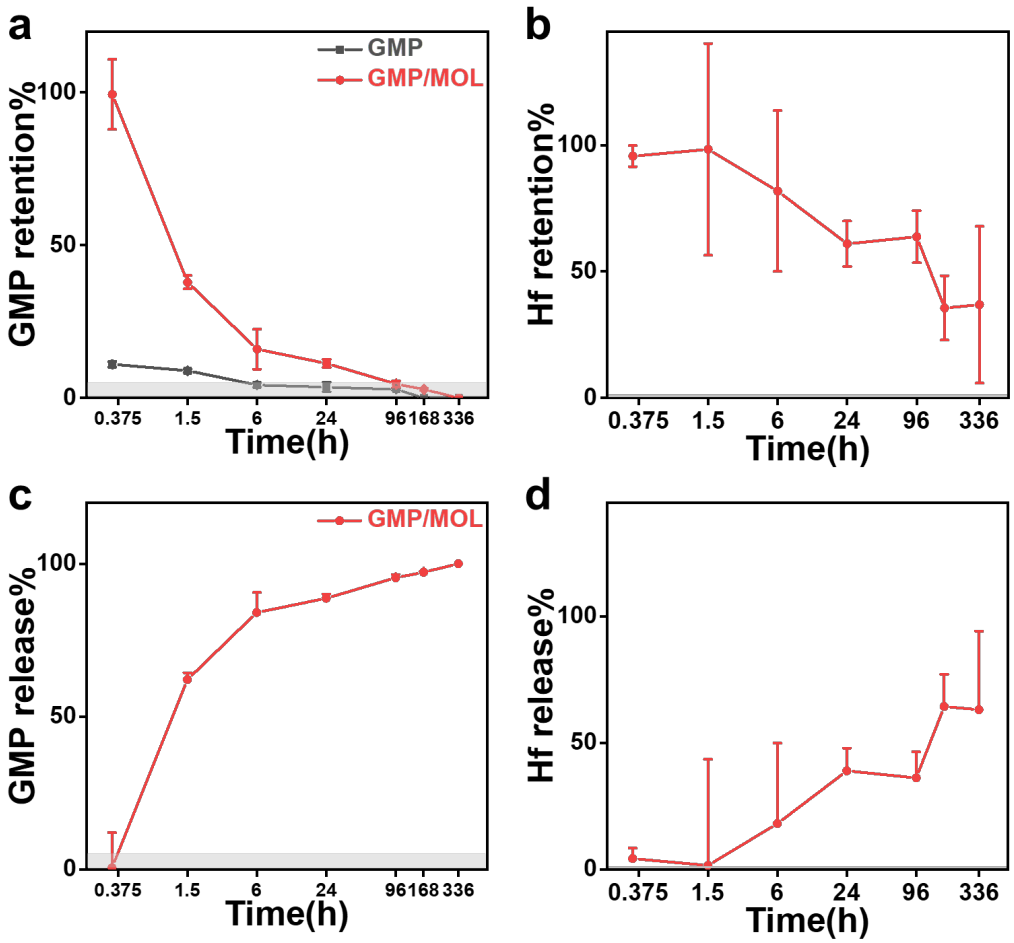


**Figure S19**. Tumor retention over 21 days of (a) GMP (31.4 $\mu$g/mouse) and (b) Hf (1 $\mu$mol/mouse) after i.t. injection of free GMP or GMP/MOL into subcutaneous CT26 tumors ($n$ = 3). The corresponding release percentage of (c) GMP and (d) Hf in vivo over 21 days.

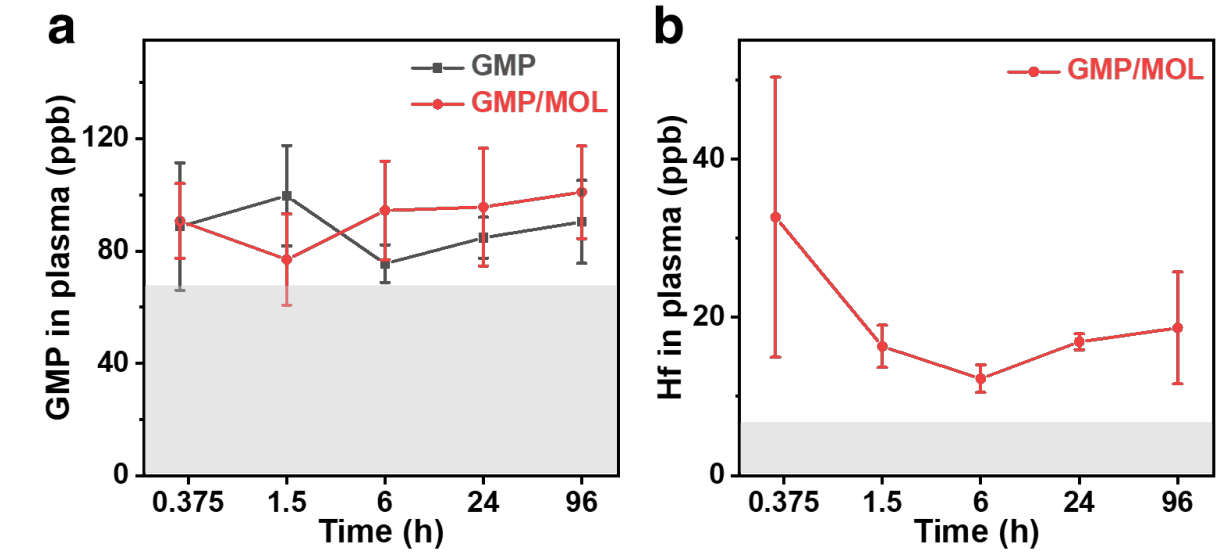


**Figure S20**. (a) GMP and (b) Hf concentrations in plasma after intratumoral injection of GMP or GMP/MOL. Grey bars indicate the detection limit.

### S6.2. In vivo anti-cancer efficacy

To evaluate in vivo chemoradiotherapy efficacy of GMP/MOL, a subcutaneous CT26 model was established in BALB/c mice by inoculating $2\times10^6$ cells/mouse subcutaneously. At day 7, the mice with tumor volumes around 75 $mm^3$ were randomized for treatment. PBS, GMP, MOL, or GMP/MOL was injected intratumorally with an equivalent Hf dose of 1 $\mu$mol (GMP dose 1/12 $\mu$mol) ($n$ = 6). Eight hours later, the mice were anesthetized with 2.5% (V/V) isoflurane/$O_2$ and irradiated by 2 Gy X-ray. Tumor sizes were measured with an electronic caliper (tumor volume = length×width$^2$/2), and body weight was monitored with an electronic scale. On day 22, the mice were euthanized, and the tumors were excised and weighed. Major organs were sectioned for H&E staining to evaluate general toxicity. The tumor growth inhibition index (TGI) was defined as the equation below:

$$TGI = 1 - \frac{\frac{T_e}{T_s} \Big/ \frac{C_e}{C_s}}{1 - \frac{C_s}{C_e}} \times 100\%$$

where $T_e$, $T_s$, $C_e$, and $C_s$ represent average tumor volumes of treated mice at the endpoint, treated mice at the starting point, control mice at the endpoint, and control mice at the starting point, respectively.

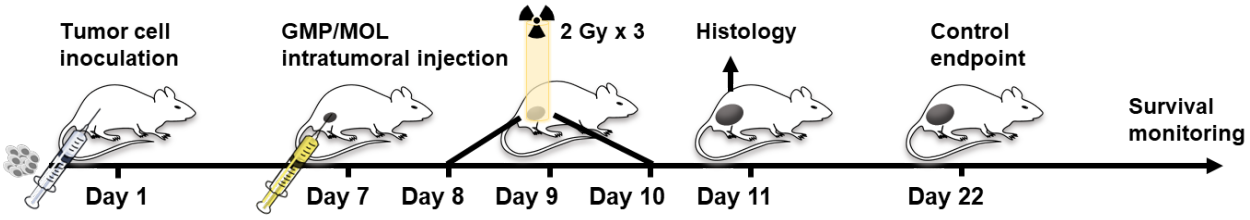


**Figure S21**. Treatment schedules for efficacy, histology, and survival studies in CT26-bearing BALB/c mice.

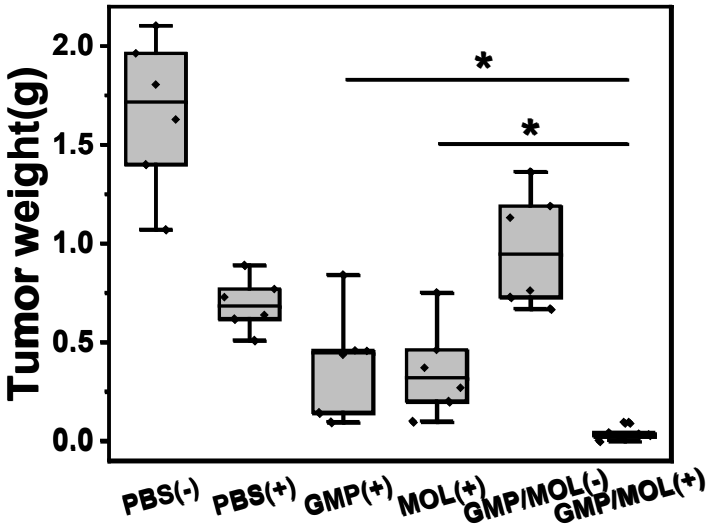


**Figure S22**. Excised tumor weights of CT26-bearing BALB/c mice (*n* = 6). (+) indicates irradiation treatment, and (-) indicates no irradiation.

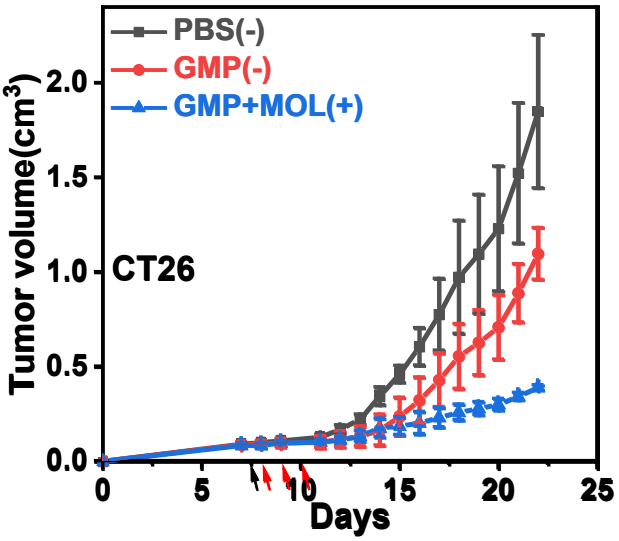


**Figure S23.** Tumor volumes of CT26 tumor-bearing BALB/c mice after different treatments (*n* = 5, the black arrow indicates *i.t.* injection, and the red arrow indicates X-ray irradiation of 2 Gy for 3 fractions). GMP+MOL(+) group refers to the treatment of i.t. injection of GMP first followed by i.t injection of MOL and radiation 24 hours later.

**Table S4**. TGI values of CT26-bearing BALB/c mice at day 22.

| Treatment | TGI(CT26) |
|---|---|

| | |
|---|---|
| PBS(+) | **0.59** |
| GMP(-) | **0.35** |
| GMP(+) | **0.75** |
| MOL(+) | **0.77** |
| GMP/MOL(-) | **0.50** |
| GMP+MOL(+) | **0.76** |
| GMP/MOL(+) | **0.98** |

**Table S5**. Median survival of CT26-bearing BALB/c mice.

| Treatment | Median Survival |
|---|---|
| PBS(-) | **21.5 d** |
| PBS(+) | **29.5 d** |
| GMP(+) | **36.5 d** |
| MOL(+) | **38.0 d** |
| GMP/MOL(-) | **27.5 d** |
| GMP/MOL(+) | **N/A** |

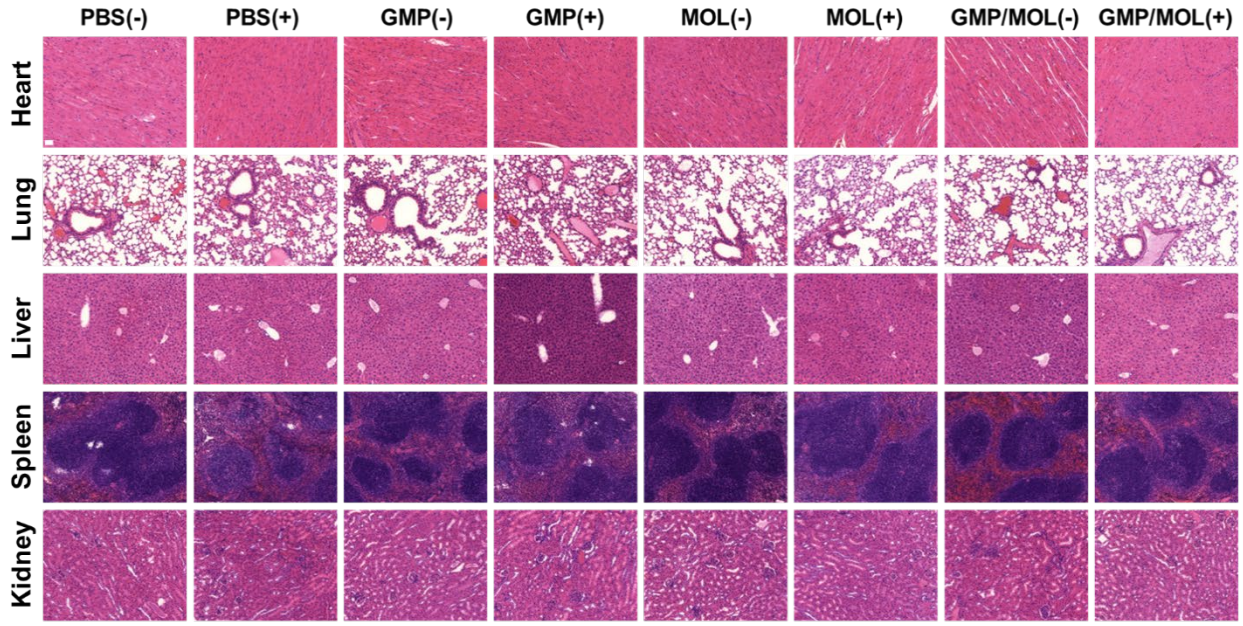


**Figure S24**. H&E staining of major organs of CT26-bearing BALB/c mice.

### S6.3. Immunohistochemistry staining and analysis

One day after the last X-ray irradiation on day 11, the mice were euthanized, and the tumors were excised. Tumor tissues were fixed in 4% PFA for 1 day and 70% ethanol for 1 day. Tissues were embedded in paraffin, sectioned, and stained for γ-H2AX, Ki67, and TUNEL by the Human Tissue Resource Center at the University of Chicago.[7] The slides were sealed and scanned on a CRi Panoramic SCAN 40x whole slide scanner by Integrated Light Microscopy Core at the University of Chicago. The images were viewed and analyzed by QuPath-0.4.2 software.[1]

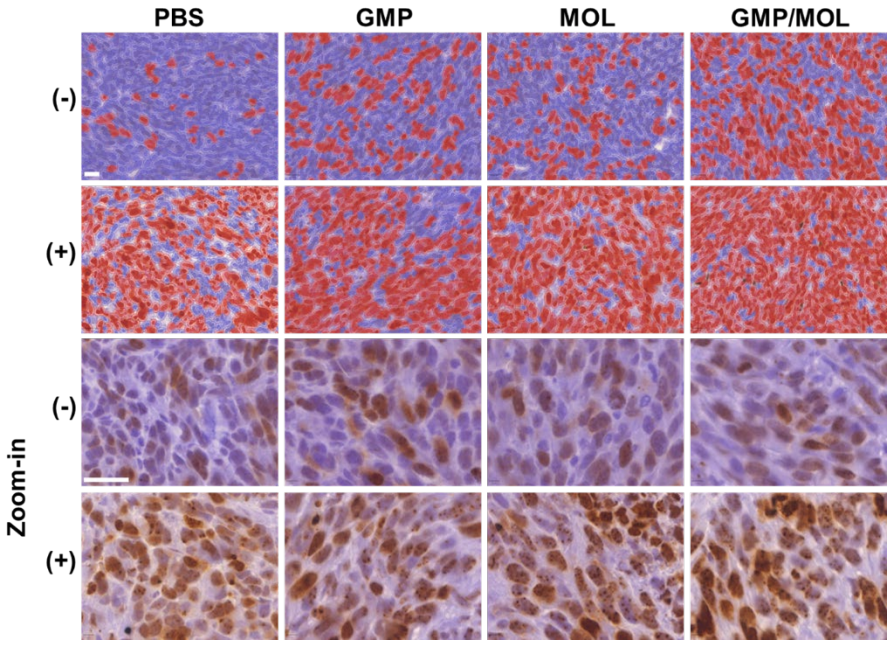


**Figure S25**. Representative images with positive cell detection of γ-H2AX staining in CT26 tumors treated by PBS, GMP, MOL, and GMP/MOL with or without RT, respectively. The zoom-in figures show the γ-H2AX foci after different treatments. (Scale bar = 20 $\mu$m; the DAB-positive cells were marked with red masks, and the negative cells were marked with blue masks).

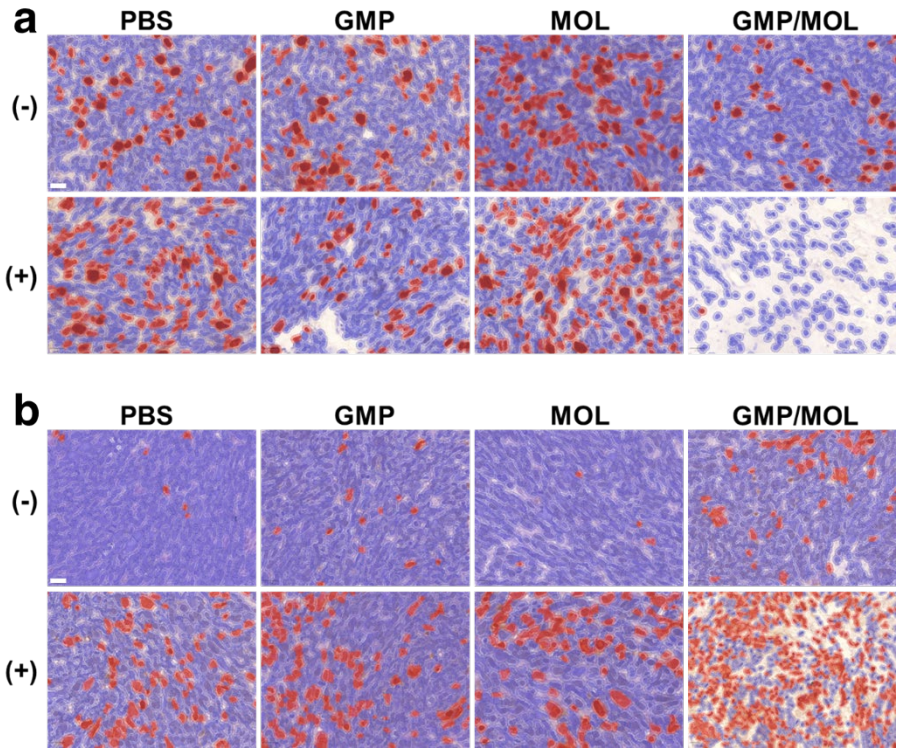


**Figure S26**. Representative images with positive cell detection of (a) Ki67 and (b) TUNEL staining in CT26 tumors treated by PBS, GMP, MOL, and GMP/MOL with or without RT, respectively. (Scale bar

= 20 $\mu$m; the DAB-positive cells were marked with red masks, and the negative cells were marked with blue masks).

### S6.4. Biodistribution of MOL

To evaluate biodistribution of MOL, a subcutaneous CT26 model was established in BALB/c mice by inoculating $2\times10^6$ cells/mouse subcutaneously. At day 7, MOL was injected intratumorally with an equivalent Hf dose of 1 $\mu$mol ($n$ = 3). At day 14 and day 21, the mice were anesthetized, and the major organs were excised and digested by concentrated $HNO_3$ as described in S6.1. The Hf content was measured by ICP-MS after proper dilutions.

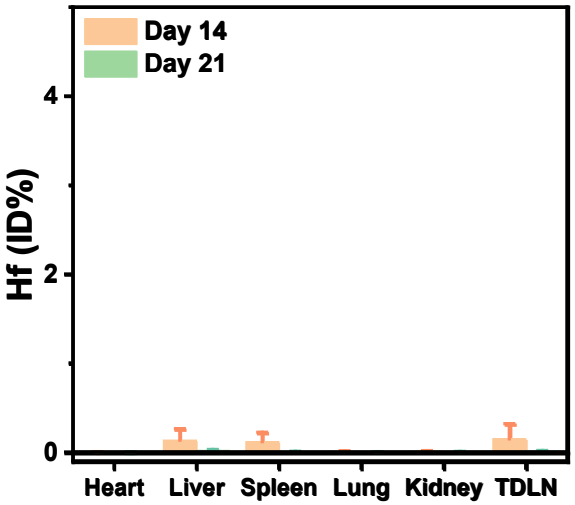


**Figure S27**. Biodistribution of GMP/MOL in the heart, liver, spleen, lung, kidney, and tumor draining lymph node (TDLN). The Hf content is measured by ICP-MS and presented by injection dose (ID) percentage ($n$ = 3).

**S7. Cartesian Coordinates Calculated by DFT**

**Table S6.** XYZ coordinates of optimized $Hf_6$-TFA

---

| | | | |
|---|---|---|---|
| H | -0.00070900 | 0.00033000 | 2.89168200 |
| H | -3.46468400 | -1.04722300 | -3.70416400 |
| H | 2.64035300 | -2.47949000 | -3.70012900 |
| H | 0.83066500 | 3.52434400 | -3.70098900 |
| H | -2.16793800 | 0.66392600 | -3.90731600 |
| H | 1.66577500 | 1.54618900 | -3.90505600 |
| H | 0.51148300 | -2.21602300 | -3.90344100 |
| H | 2.26879700 | 2.28282900 | -1.65778900 |
| H | 0.84297700 | -3.10780900 | -1.65667400 |
| H | -3.11131800 | 0.82210700 | -1.66190200 |
| C | -1.31566000 | -4.28633400 | -0.39086600 |
| C | 4.36990200 | 1.00472300 | -0.39202900 |
| C | -3.05530800 | 3.28072800 | -0.39903000 |
| C | 1.00170600 | 4.37612000 | -0.33130300 |
| C | 3.28992300 | -3.05491700 | -0.32833400 |
| C | -4.29048900 | -1.32052600 | -0.33232500 |
| C | 2.71050400 | -0.71759600 | 2.90641700 |
| C | -1.98024700 | -1.98690400 | 2.90368300 |
| C | -0.73570100 | 2.70915900 | 2.90256800 |
| O | 1.96248700 | -1.69400900 | 2.65214800 |
| O | -3.62181100 | -1.73007800 | -1.32805100 |
| O | 0.48376700 | 2.54914000 | 2.64866500 |
| O | 3.30881000 | -2.27582700 | -1.32803800 |
| O | -2.45198800 | -0.85165700 | 2.64672000 |
| O | 0.31901300 | 4.00259300 | -1.33162300 |
| O | -3.18429300 | 2.32690200 | 0.43323600 |
| O | 3.60671600 | 1.59330300 | 0.43885700 |
| O | -0.42453900 | -3.91968700 | 0.44038900 |
| O | -3.92486200 | -0.40077000 | 0.46991000 |
| O | 2.31073600 | -3.19672200 | 0.47449000 |
| O | 1.61289900 | 3.59919000 | 0.47264900 |
| O | 2.55219600 | 0.50182000 | 2.64584300 |
| O | -2.26794600 | 3.27974300 | -1.39480900 |
| O | -0.84480600 | -2.45960200 | 2.64470000 |
| O | 3.97756800 | 0.32696900 | -1.39125100 |
| O | -1.71302200 | 1.96352200 | 2.64011200 |
| O | -1.70339500 | -3.60940600 | -1.39240400 |
| O | 0.00118200 | -0.00149800 | -2.38964800 |
| O | 1.66479000 | -0.44833300 | 0.10323100 |
| O | -1.21857300 | -1.21568400 | 0.10066600 |
| O | -0.44295500 | 1.66397700 | 0.10023100 |
| O | -0.00099000 | 0.00069000 | 1.92454700 |
| O | -2.21897100 | 0.58042200 | -1.37757600 |
| O | 0.60697000 | -2.21317800 | -1.37450800 |
| O | 1.61313600 | 1.63024100 | -1.37513700 |
| O | 0.44611100 | 2.63581200 | -3.74775600 |
| O | -2.50275800 | -0.93631200 | -3.74859600 |
| O | 2.06129100 | -1.70352700 | -3.74644100 |
| O | -0.45522500 | -2.50755900 | -3.79851500 |
| O | -1.93724400 | 1.64664100 | -3.80308200 |
| O | 2.40037000 | 0.85413000 | -3.79914200 |
| Hf | -1.45556300 | -1.47843000 | -1.97214100 |

| | | | |
|---|---|---|---|
| Hf | 1.44970100 | 1.44834900 | 0.90990300 |
| Hf | 2.00868200 | -0.52415300 | -1.97045500 |
| Hf | -1.98025200 | 0.53259300 | 0.90725900 |
| Hf | -0.54850300 | 1.99885100 | -1.97323700 |
| Hf | 0.52906500 | -1.97968600 | 0.91085300 |
| C | 5.85385000 | 1.10699300 | -0.14233200 |
| H | 6.42205900 | 0.80931200 | -1.02482400 |
| H | 6.11613500 | 2.12109600 | 0.17012600 |
| H | 6.09854400 | 0.43377100 | 0.68830000 |
| C | 1.09075500 | 5.85386300 | -0.03785700 |
| H | 2.10499300 | 6.11933700 | 0.27188800 |
| H | 0.77622400 | 6.44658200 | -0.89832100 |
| H | 0.42368100 | 6.06489300 | 0.80668000 |
| C | -3.88879100 | 4.51376400 | -0.15460900 |
| H | -3.91577800 | 5.15107500 | -1.03971600 |
| H | -4.89792600 | 4.23308900 | 0.15796000 |
| H | -3.42981200 | 5.06688200 | 0.67401500 |
| C | -5.61723800 | -1.97840100 | -0.04164700 |
| H | -6.35697900 | -1.22807200 | 0.24980500 |
| H | -5.96530000 | -2.55941000 | -0.89714900 |
| H | -5.47496800 | -2.64871300 | 0.81461600 |
| C | -1.97459200 | -5.61936500 | -0.13825400 |
| H | -2.50256100 | -5.97054900 | -1.02614300 |
| H | -1.23472100 | -6.35169600 | 0.19468000 |
| H | -2.69484100 | -5.48434600 | 0.67807100 |
| C | 4.52436600 | -3.87209800 | -0.03484100 |
| H | 4.24631000 | -4.88778200 | 0.25885500 |
| H | 5.20240100 | -3.88348700 | -0.88967700 |
| H | 5.03180500 | -3.41021200 | 0.82069800 |
| C | -2.97306800 | -2.98012900 | 3.54683900 |
| C | -1.10096700 | 4.06473300 | 3.54653900 |
| C | 4.06812000 | -1.07912900 | 3.54825200 |
| F | -1.34419500 | 4.93780600 | 2.52913400 |
| F | -0.10510400 | 4.56313800 | 4.28619800 |
| F | -2.20388100 | 3.99180700 | 4.29864500 |
| F | -3.61787000 | -3.61634600 | 2.52877500 |
| F | -3.89377500 | -2.36682700 | 4.29752600 |
| F | 4.00067400 | -2.18611300 | 4.29497300 |
| F | -2.35919200 | -3.90786100 | 4.28807900 |
| F | 4.56172100 | -0.08424800 | 4.29233700 |
| F | 4.94180200 | -1.31359000 | 2.52910600 |
| H | -0.98648700 | -2.11290100 | -4.51569300 |
| H | -1.32636000 | 1.90762900 | -4.51797800 |
| H | 2.32149300 | 0.19467600 | -4.51424400 |

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**Table S7.** XYZ coordinates of optimized $Hf_6$-DPPA

---

| | | | |
|---|---|---|---|
| H | 2.14245000 | 1.35805000 | -0.00046100 |
| H | -5.08931400 | 0.96994500 | 1.91252500 |
| H | -2.21949000 | -4.59499300 | 1.69677800 |
| H | -3.74040300 | -1.65591500 | -3.61739900 |
| H | -4.90622600 | 0.15524600 | -0.07670100 |
| H | -3.31885500 | -2.91986800 | -1.92153400 |
| H | -3.37570700 | -2.80321300 | 2.00073900 |
| H | -1.14626800 | -2.25223500 | -2.79193500 |
| H | -1.13015100 | -2.27789700 | 2.77353500 |
| H | -3.36032400 | 2.03175100 | 0.01804000 |
| C | -0.82533600 | -0.16016600 | 4.49635700 |
| C | 1.02740200 | -3.77705600 | -2.14637600 |
| C | -2.52484800 | 3.14325700 | -2.35417000 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| C | -0.77812700 | -0.09610900 | -4.49886800 | O | -1.10153600 | -1.70212800 | -1.99799500 |
| C | 1.10141300 | -3.75919500 | 2.11655100 | O | -3.84913000 | -1.55076300 | -2.66014200 |
| C | -2.43828200 | 3.16027500 | 2.39193200 | O | -4.72194500 | 0.14731300 | 1.55521000 |
| C | 1.63692000 | 2.56185300 | 2.35270000 | O | -2.61251500 | -3.93741600 | 1.10316300 |
| C | 1.63112100 | 2.57638300 | -2.34572600 | O | -3.67594900 | -1.99649100 | 2.53996600 |
| O | 3.00034100 | -0.85999500 | 1.32174400 | O | -4.83216100 | 0.23601600 | -1.08534500 |
| O | -2.97704900 | 2.03503300 | 2.61563600 | O | -2.81686900 | -3.66433400 | -1.45004800 |
| O | 1.81132800 | 1.36965400 | -2.62822900 | Hf | -2.60977800 | -0.06215000 | 1.80397900 |
| O | 0.15163400 | -4.04665400 | 1.32607900 | Hf | 0.89658400 | -0.55640700 | -1.79028700 |
| O | 0.98461500 | 3.08446000 | 1.41451000 | Hf | -1.18863000 | -2.80162700 | -0.01979300 |
| O | -1.91800400 | -0.02203600 | -3.95035500 | Hf | -0.53223700 | 2.16783400 | -0.00046200 |
| O | -1.70068400 | 3.41165600 | -1.42411200 | Hf | -2.62579700 | -0.03231300 | -1.78498300 |
| O | 1.36315800 | -2.61364000 | -2.52474000 | Hf | 0.89733900 | -0.55846500 | 1.78775000 |
| O | 0.27405800 | -0.42016100 | 3.91351700 | C | 1.85206900 | -4.93136300 | -2.66566100 |
| O | -1.66663500 | 3.42944300 | 1.41592400 | H | 1.30828400 | -5.87320300 | -2.57442600 |
| O | 1.38984800 | -2.59414400 | 2.53171100 | H | 2.15103100 | -4.74991600 | -3.70104200 |
| O | 0.30720600 | -0.40959900 | -3.91254200 | H | 2.76599200 | -4.99043500 | -2.06127400 |
| O | 2.99979600 | -0.86050700 | -1.33993500 | C | -0.67763000 | 0.22353500 | -5.97265400 |
| O | -3.04448400 | 2.00529300 | -2.57102800 | H | -0.02905300 | -0.50127900 | -6.47238000 |
| O | 1.81107400 | 1.35369700 | 2.63671600 | H | -1.66427000 | 0.24835200 | -6.43812800 |
| O | 0.07259200 | -4.04714400 | -1.35267200 | H | -0.20723300 | 1.20873400 | -6.07718600 |
| O | 0.96872100 | 3.09687800 | -1.41220700 | C | -2.89397800 | 4.27220900 | -3.28664200 |
| O | -1.95942000 | -0.08693600 | 3.93113900 | H | -3.82742300 | 4.05648700 | -3.80932400 |
| O | -2.52420400 | -1.16075100 | -0.00019400 | H | -2.96035600 | 5.21356000 | -2.73574700 |
| O | 0.48445300 | -1.52949300 | -0.00112700 | H | -2.09131600 | 4.37802400 | -4.02706900 |
| O | -0.70357800 | 0.74540600 | 1.48804000 | C | -2.71106600 | 4.28641700 | 3.36179100 |
| O | -0.70443100 | 0.74517200 | -1.48975900 | H | -2.92055900 | 5.21088000 | 2.81641500 |
| O | 1.32481300 | 0.83787200 | -0.00163700 | H | -3.53314100 | 4.03709100 | 4.03455000 |
| O | -2.67725200 | 1.34734000 | 0.01722000 | H | -1.80108100 | 4.45555300 | 3.95026100 |
| O | -1.08643800 | -1.72850600 | 1.97907600 | C | -0.76567800 | 0.10300900 | 5.98238400 |

| | | | |
|---|---|---|---|
| H | -1.74613800 | -0.03474600 | 6.44154200 |
| H | -0.01797300 | -0.54012900 | 6.45284600 |
| H | -0.45030700 | 1.14311700 | 6.13186400 |
| C | 1.98435600 | -4.88615900 | 2.60263700 |
| H | 2.17349300 | -4.78167500 | 3.67475900 |
| H | 1.54242400 | -5.85869800 | 2.37986100 |
| H | 2.95085600 | -4.80343400 | 2.09041400 |
| C | 2.27471100 | 3.56880500 | 3.33472700 |
| C | 2.27490300 | 3.58636300 | -3.32091200 |
| F | 1.35873000 | 3.92142900 | -4.25880300 |
| F | 3.34113300 | 3.06499100 | -3.95394500 |
| F | 2.66722400 | 4.70562000 | -2.69789200 |
| F | 1.35351000 | 3.89635600 | 4.27111200 |
| F | 2.66469600 | 4.69271100 | 2.71873600 |
| F | 3.34060500 | 3.04826900 | 3.96840100 |
| H | -4.59166600 | -1.76925700 | 2.29030400 |
| H | -5.21281800 | -0.56272400 | -1.49761400 |
| H | -3.40033800 | -4.06522000 | -0.77781000 |
| P | 3.77605200 | -0.72195900 | -0.00873600 |
| C | 4.48651300 | 0.94530400 | -0.00733200 |
| C | 4.71191700 | 1.61422100 | -1.22075200 |
| C | 4.70975600 | 1.60932200 | 1.20942200 |
| C | 5.14973900 | 2.93867300 | -1.21404100 |
| H | 4.50110800 | 1.11092100 | -2.15776100 |
| C | 5.14709300 | 2.93385500 | 1.20930900 |
| H | 4.49798200 | 1.10174500 | 2.14393200 |
| C | 5.36506800 | 3.59728700 | -0.00082900 |
| H | 5.29592400 | 3.46106900 | -2.15351800 |
| H | 5.29127700 | 3.45227900 | 2.15135900 |
| H | 5.68936100 | 4.63380900 | 0.00154300 |
| C | 5.03783300 | -2.00585000 | -0.00645900 |
| C | 5.52955200 | -2.50592100 | -1.21997700 |
| C | 5.50434300 | -2.52284800 | 1.21012300 |
| C | 6.49078200 | -3.51634400 | -1.21330900 |
| H | 5.13865300 | -2.11841900 | -2.15549300 |
| C | 6.46546100 | -3.53349400 | 1.20937400 |
| H | 5.09443200 | -2.14690700 | 2.14218300 |
| C | 6.95943100 | -4.02770900 | -0.00049500 |
| H | 6.86953900 | -3.90877700 | -2.15268700 |
| H | 6.82485900 | -3.93888500 | 2.15088400 |
| H | 7.70677000 | -4.81617200 | 0.00170200 |

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**Table S8.** XYZ coordinates of optimized $Hf_6$-PPA

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| | | | |
|---|---|---|---|
| H | 2.27047600 | 0.03613400 | 1.41766400 |
| H | -4.93617500 | -1.88531400 | 0.58788500 |
| H | -1.58903400 | -1.82630900 | -4.66921500 |
| H | -3.33638000 | 3.56321400 | -2.04832300 |
| H | -4.69698400 | 0.07265100 | -0.28069100 |
| H | -2.84720300 | 1.82572000 | -3.22903300 |
| H | -2.90604600 | -2.08236500 | -3.00845700 |
| H | -0.70189700 | 2.72667300 | -2.37500800 |
| H | -0.68571500 | -2.82859200 | -2.25393400 |
| H | -3.33737900 | 0.03105900 | 1.74722900 |
| C | -0.59651500 | -4.48197900 | -0.00501800 |
| C | 1.63458800 | 1.95628700 | -3.65618900 |
| C | -2.60182400 | 2.44791200 | 2.86486100 |
| C | -0.56529900 | 4.48125700 | -0.18444800 |
| C | 1.67399500 | -2.12920600 | -3.54331200 |
| C | -2.54999700 | -2.31924600 | 3.01401500 |

| | | | |
|---|---|---|---|
| C | 1.43821900 | -2.36896500 | 2.80619100 |
| C | 1.42403900 | 2.49897700 | 2.70099400 |
| O | 3.21050000 | -1.28518700 | -0.45441700 |
| O | -2.98762500 | -2.57278200 | 1.85159900 |
| O | 1.83330100 | 2.68894800 | 1.53709600 |
| O | 0.69113700 | -1.43141700 | -3.95491000 |
| O | 0.82996000 | -1.36589100 | 3.26181400 |
| O | -1.71667600 | 3.95191400 | -0.25962800 |
| O | -1.85662900 | 1.49411400 | 3.24655900 |
| O | 1.75890400 | 2.47922000 | -2.50671800 |
| O | 0.51285000 | -3.92202900 | -0.25154500 |
| O | -1.83024100 | -1.32435700 | 3.33879400 |
| O | 1.78553800 | -2.59942500 | -2.36902500 |
| O | 0.53764800 | 3.90621000 | -0.43007600 |
| O | 3.20667600 | 1.28169300 | -0.52245200 |
| O | -3.03565200 | 2.62583500 | 1.68563500 |
| O | 1.83817800 | -2.61758500 | 1.64931900 |
| O | 0.64412900 | 1.24270100 | -4.02413800 |
| O | 0.81402600 | 1.51793400 | 3.20233700 |
| O | -1.74350100 | -3.94432600 | -0.10895700 |
| O | -2.22494800 | -0.03468300 | -1.36028600 |
| O | 0.81189500 | -0.03450400 | -1.46056800 |
| O | -0.58172800 | -1.48240200 | 0.76566600 |
| O | -0.58381900 | 1.51843400 | 0.69242000 |
| O | 1.39854400 | 0.02618200 | 0.99655400 |
| O | -2.60138700 | 0.01041600 | 1.12129400 |
| O | -0.73872300 | -2.01756800 | -1.73074700 |
| O | -0.75840600 | 1.94538700 | -1.80854300 |
| O | -3.51044300 | 2.61769300 | -1.92597700 |
| O | -4.52490300 | -1.56388500 | -0.22860700 |
| O | -2.07144900 | -1.20841000 | -4.09874000 |
| O | -3.28967700 | -2.61282500 | -2.22915700 |
| O | -4.65009400 | 1.08343400 | -0.20785000 |
| O | -2.29185900 | 1.34650900 | -3.92580400 |
| Hf | -2.38304200 | -1.80976500 | -0.22655600 |
| Hf | 1.16888800 | 1.76564200 | -0.48319900 |
| Hf | -0.72398300 | -0.05123300 | -2.87132800 |
| Hf | -0.53895900 | 0.05110400 | 2.14020800 |
| Hf | -2.40449700 | 1.77382600 | -0.28689200 |
| Hf | 1.17358200 | -1.78333100 | -0.39969500 |
| C | 2.75849800 | 2.16674400 | -4.63224200 |
| H | 2.44553700 | 1.94903700 | -5.65541700 |
| H | 3.16088500 | 3.17970700 | -4.54605200 |
| H | 3.53725300 | 1.46001800 | -4.31509800 |
| C | -0.48386600 | 5.92410100 | 0.26657600 |
| H | 0.27834100 | 6.45952600 | -0.30586800 |
| H | -1.45370800 | 6.41929100 | 0.18714000 |
| H | -0.16754100 | 5.92166800 | 1.31684200 |
| C | -2.97630500 | 3.47246000 | 3.91308200 |
| H | -3.80992900 | 4.09229800 | 3.57792000 |
| H | -3.21165900 | 2.97762500 | 4.85933600 |
| H | -2.09862200 | 4.10768800 | 4.08268700 |
| C | -2.88507300 | -3.29270100 | 4.12383700 |
| H | -3.13423500 | -2.75172800 | 5.04096500 |
| H | -3.69684900 | -3.96172100 | 3.83176700 |
| H | -1.98476400 | -3.88530700 | 4.32520400 |
| C | -0.53817900 | -5.91109500 | 0.48826300 |
| H | -1.51271100 | -6.39630000 | 0.40756200 |
| H | 0.22544500 | -6.47060400 | -0.05857600 |
| H | -0.23600400 | -5.88297400 | 1.54246900 |

| | | | |
|---|---|---|---|
| C | 2.80640300 | -2.39456100 | -4.49703900 |
| H | 3.20915600 | -3.40046900 | -4.35071600 |
| H | 2.50244600 | -2.23479200 | -5.53376000 |
| H | 3.58126800 | -1.66897000 | -4.21525500 |
| C | 1.64323900 | -3.51521900 | 3.82239900 |
| C | 1.61525900 | 3.69532500 | 3.66063500 |
| F | 0.52622000 | 4.50805900 | 3.53792600 |
| F | 2.69887600 | 4.42643000 | 3.36342900 |
| F | 1.69810900 | 3.32302200 | 4.94606900 |
| F | 0.56849500 | -4.35090500 | 3.73272500 |
| F | 1.71181000 | -3.08106300 | 5.08914300 |
| F | 2.74076100 | -4.24100800 | 3.56615700 |
| H | -4.20850300 | -2.32359700 | -2.07024500 |
| H | -4.91499800 | 1.47818700 | -1.06096400 |
| H | -2.82436500 | 0.62800100 | -4.31896700 |
| P | 3.90504700 | -0.01756500 | -1.10994600 |
| C | 5.54291000 | 0.00502300 | -0.32054500 |
| C | 6.18526800 | 1.22139100 | -0.05479000 |
| C | 6.19422900 | -1.19578200 | -0.00934700 |
| C | 7.46228500 | 1.23634000 | 0.50765300 |
| H | 5.66816200 | 2.14977000 | -0.27767200 |
| C | 7.47119400 | -1.18029500 | 0.55292500 |
| H | 5.68395000 | -2.13573600 | -0.19672500 |
| C | 8.10856100 | 0.03568400 | 0.81062800 |
| H | 7.95123400 | 2.18519800 | 0.71565000 |
| H | 7.96707100 | -2.11703600 | 0.79641700 |
| H | 9.10237800 | 0.04762000 | 1.25196200 |
| O | 4.00447100 | -0.05694600 | -2.61420300 |
| H | 0.02144900 | 1.01046100 | 2.74603900 |
| H | -1.85941900 | 1.31730900 | -4.52531900 |
| H | -1.80800200 | -4.39565300 | -2.02910600 |
| H | 3.58625600 | -1.52270600 | -3.31548600 |
| H | 0.10057700 | 0.43119700 | -4.40593300 |
| H | 1.85246200 | -2.76085400 | -3.02106900 |
| H | -2.06684800 | -2.53661900 | -3.07547400 |
| H | 2.73734200 | -2.23798800 | -0.77960300 |
| H | -2.82780200 | -2.12245400 | -0.77799900 |
| H | 0.05004300 | 2.22664600 | -2.74976600 |
| C | -4.47968800 | 0.07092200 | -0.33616800 |
| C | 2.08602200 | -3.90799500 | 1.23218900 |
| C | 2.46125200 | 3.21619000 | -1.83924700 |
| C | 4.48435900 | -0.11475900 | -0.27879400 |
| C | -2.27579100 | -3.78826800 | 1.28123400 |
| C | -2.30406200 | 3.35645900 | -1.79721800 |
| C | -2.38458100 | 2.54185700 | 2.09905800 |
| C | 2.49487300 | 2.43702400 | 2.09997100 |
| O | -1.29051400 | -0.97433200 | 3.35435300 |
| O | -2.55589500 | 2.27317900 | -2.40702100 |
| O | 2.68167900 | 1.22472500 | 2.33034200 |
| O | -1.45090400 | -4.03859900 | 0.34200600 |
| O | -1.37177700 | 3.08402900 | 1.58465600 |
| O | 3.95878900 | -0.00864700 | -1.43031400 |
| O | 1.50357500 | 3.47703200 | -1.04893700 |
| O | 2.50977700 | -2.77797800 | 1.61092700 |
| O | -3.92501800 | -0.33630700 | 0.72703100 |
| O | -1.31718100 | 3.56274100 | -1.02554500 |
| O | -2.65443700 | -2.63282500 | 1.63406300 |

**Table S9.** XYZ coordinates of optimized $Hf_6$-PA

| | | | |
|---|---|---|---|
| O | 3.90267400 | -0.52696200 | 0.76949500 |
| O | 1.24949300 | -1.04152200 | 3.35387000 |
| O | 2.64458900 | 2.11510400 | -2.44438400 |
| O | -2.62981700 | 1.33831900 | 2.32455000 |
| O | 1.24720500 | -4.10132100 | 0.28985700 |
| O | 1.51143700 | 3.02498200 | 1.57684200 |
| O | -3.93127200 | 0.14518800 | -1.48136900 |
| O | -0.02226100 | -1.01530900 | -2.12504800 |
| O | -0.04075800 | -1.62841500 | 0.88482900 |
| O | -1.47149100 | 0.82532100 | -0.18345200 |
| O | 1.51347300 | 0.75187400 | -0.17965300 |
| O | 0.01776700 | 0.74912300 | 1.81264900 |
| O | 0.02540400 | 1.49462100 | -2.11939500 |
| O | -2.00869400 | -1.61213400 | -0.72744200 |
| O | 1.94505400 | -1.68643800 | -0.73574900 |
| O | 2.63915400 | -1.38080900 | -3.46406400 |
| O | -1.53396400 | 0.45182900 | -4.23514300 |
| O | -1.19172700 | -3.74888100 | -2.40518000 |
| O | -2.59409400 | -1.70722700 | -3.33099300 |
| O | 1.11112300 | 0.49312000 | -4.33959400 |
| O | 1.36587000 | -3.53482400 | -2.58341200 |
| Hf | -1.79688700 | 0.13375400 | -2.11834000 |
| Hf | 1.76153000 | -0.66848700 | 1.37959000 |
| Hf | -0.04781700 | -2.73569000 | -0.88841900 |
| Hf | 0.05359200 | 2.18630500 | 0.07841100 |
| Hf | 1.78920800 | 0.07569700 | -2.12832100 |
| Hf | -1.79313700 | -0.58370100 | 1.37753300 |
| C | 2.57390400 | -5.11786100 | 1.98894500 |
| H | 2.45139000 | -6.02849300 | 1.39906600 |
| H | 3.61329600 | -4.98175800 | 2.29749200 |
| H | 1.95986400 | -5.18763200 | 2.89509500 |
| C | 5.92783700 | 0.31179400 | -0.12329900 |
| H | 6.45762700 | -0.37425700 | 0.54292100 |
| H | 6.42652100 | 0.38203000 | -1.09197700 |
| H | 5.92738200 | 1.29991700 | 0.35263100 |
| C | 3.48334400 | 4.31096300 | -2.04863700 |
| H | 4.10061900 | 4.11035900 | -2.92617400 |
| H | 2.98717700 | 5.28172200 | -2.13150800 |
| H | 4.12145700 | 4.34144100 | -1.15729200 |
| C | -3.26969300 | 4.50795000 | -1.97473500 |
| H | -2.72388100 | 5.45121800 | -2.06364200 |
| H | -3.92002000 | 4.34902600 | -2.83705700 |
| H | -3.88290100 | 4.56572400 | -1.06765700 |
| C | -5.91352000 | 0.53709300 | -0.21765400 |
| H | -6.38978100 | 0.60012000 | -1.19781500 |
| H | -6.47309500 | -0.12381700 | 0.44956000 |
| H | -5.89837200 | 1.53352200 | 0.24073100 |
| C | -2.81476700 | -4.95555000 | 2.07113700 |
| H | -3.85159600 | -4.77318800 | 2.36455400 |
| H | -2.71931200 | -5.89018900 | 1.51433700 |
| H | -2.21124600 | -5.01587200 | 2.98485200 |
| C | -3.54730100 | 3.51010700 | 2.41320500 |
| C | 3.69784500 | 3.35334600 | 2.41845700 |
| F | 4.50879900 | 3.36814500 | 1.31989700 |
| F | 4.42572900 | 2.90981600 | 3.45116000 |
| F | 3.33557100 | 4.61940100 | 2.66809300 |
| F | -4.35725900 | 3.55314200 | 1.31467800 |
| F | -3.13178700 | 4.76114800 | 2.65585800 |
| F | -4.29279900 | 3.10332200 | 3.44843300 |
| H | -2.29392700 | -1.39844000 | -4.20776100 |

| | | | |
|---|---|---|---|
| H | 1.50659800 | -0.30904800 | -4.73156900 |
| H | 0.65877500 | -3.84554100 | -3.18115100 |
| P | -0.03987200 | -1.72029400 | 3.99975800 |
| O | -0.07833900 | -3.22767000 | 3.32228700 |
| H | -0.07038500 | -3.09940700 | 2.35558200 |
| O | -0.04215200 | -1.81972900 | 5.47990200 |

**Table S10.** XYZ coordinates of optimized $Hf_6$-GMP

| | | | |
|---|---|---|---|
| H | 0.56154000 | -0.62412900 | 2.43026500 |
| H | -5.69313500 | 0.73116300 | -1.45996800 |
| H | -1.26330100 | -2.17427000 | -4.74151700 |
| H | -0.69248500 | 3.88771500 | -3.46755600 |
| H | -4.17824500 | 2.05142200 | -2.24322400 |
| H | -0.79937800 | 1.87191800 | -4.19885800 |
| H | -2.99181600 | -1.34389700 | -3.79356200 |
| H | 1.02779200 | 1.92154700 | -2.55620400 |
| H | -1.95233300 | -2.77771500 | -2.11612700 |
| H | -3.82831300 | 1.95021900 | 0.16917600 |
| C | -3.47612400 | -3.61249300 | 0.04117300 |
| C | 2.91037700 | 0.00305800 | -2.70681600 |
| C | -2.34390500 | 3.97087600 | 1.35303200 |
| C | 1.32295700 | 3.92567900 | -0.66057800 |
| C | 0.64933700 | -3.66284900 | -2.32912600 |
| C | -4.88856400 | -0.06017900 | 1.78390200 |
| C | -1.74493200 | -1.93765800 | 3.35994100 |
| C | 0.89492500 | 2.10343100 | 2.95383600 |
| O | -4.96978600 | -0.38970900 | 0.56136700 |
| O | 1.69045500 | 1.76356200 | 2.05078900 |
| O | 0.47080900 | -2.69189700 | -3.13064900 |
| O | -1.85064000 | -0.68488900 | 3.43012400 |
| O | 0.17327200 | 3.97156500 | -1.20058400 |
| O | -2.40947100 | 2.92771300 | 2.07287600 |
| O | 2.88721700 | 0.55108000 | -1.56361600 |
| O | -2.23028500 | -3.71260500 | 0.25703800 |
| O | -3.91968500 | 0.55583000 | 2.32516200 |
| O | 0.21463400 | -3.74256600 | -1.14479600 |
| O | 1.94578300 | 2.87539400 | -0.32344500 |
| O | -2.18844400 | 3.99509600 | 0.09378200 |
| O | -1.22798000 | -2.65877400 | 2.48131200 |
| O | 1.88580200 | -0.41228900 | -3.34150000 |
| O | -0.28691700 | 1.74339100 | 3.18063100 |
| O | -4.05191400 | -2.66056200 | -0.57202800 |
| O | -1.94233900 | 0.52773600 | -2.13992500 |
| O | 0.42686400 | -0.87039900 | -0.89182700 |
| O | -2.15772400 | -0.85197700 | 0.56837600 |
| O | -0.54088800 | 1.66169800 | 0.32287600 |
| O | 0.08917000 | -0.41144500 | 1.59096300 |
| O | -3.05418100 | 1.42598300 | -0.07570000 |
| O | -1.70375300 | -1.93739500 | -1.70898300 |
| O | 0.40364000 | 1.41445900 | -2.02019800 |
| O | -1.35386000 | 3.18536800 | -3.37431600 |
| O | -4.92262600 | 0.59545200 | -2.03191700 |
| O | -1.50792700 | -1.28079000 | -4.45672200 |
| O | -3.83554700 | -1.40862500 | -3.22825100 |
| O | -3.63026000 | 2.90434500 | -2.21726900 |
| O | -0.37458100 | 1.02073800 | -4.54922200 |
| Hf | -3.39066300 | -0.58668400 | -1.08315200 |
| Hf | 1.34287800 | 0.74231400 | 0.03141600 |
| Hf | -0.26731100 | -0.57611900 | -2.83221600 |

| | | | |
|---|---|---|---|
| Hf | -1.77526400 | 0.80597300 | 1.73914600 |
| Hf | -1.49234700 | 2.43902200 | -1.35850700 |
| Hf | -0.56482700 | -2.22168600 | 0.32927300 |
| C | 4.26091100 | -0.18035200 | -3.35258100 |
| H | 4.15803700 | -0.41574900 | -4.41348900 |
| H | 4.88209300 | 0.70709500 | -3.20811000 |
| H | 4.76478200 | -1.00388800 | -2.83537900 |
| C | 2.00940100 | 5.24181000 | -0.36981000 |
| H | 3.07977700 | 5.15857600 | -0.57394300 |
| H | 1.55439500 | 6.05623300 | -0.93719100 |
| H | 1.88737900 | 5.44697600 | 0.70174400 |
| C | -2.42959000 | 5.29640700 | 2.07662500 |
| H | -2.62317800 | 6.11390300 | 1.37982500 |
| H | -3.19668900 | 5.25441300 | 2.85465900 |
| H | -1.46618300 | 5.46510300 | 2.57334700 |
| C | -6.02885100 | -0.45092200 | 2.69897600 |
| H | -6.26340200 | 0.36852900 | 3.38410300 |
| H | -6.91091900 | -0.74823400 | 2.12861700 |
| H | -5.68787500 | -1.29847900 | 3.30567800 |
| C | -4.34935600 | -4.71632000 | 0.59476300 |
| H | -5.33463900 | -4.71246000 | 0.12481600 |
| H | -3.85946900 | -5.68602100 | 0.47347600 |
| H | -4.46407700 | -4.53653800 | 1.67106600 |
| C | 1.48317800 | -4.82158900 | -2.83696000 |
| H | 1.22940000 | -5.74245100 | -2.30763500 |
| H | 1.36529900 | -4.94279800 | -3.91654600 |
| H | 2.53696300 | -4.58923400 | -2.63818800 |
| C | -2.46284900 | -2.71059100 | 4.48761200 |
| C | 1.42155000 | 3.22892600 | 3.87028600 |
| F | 1.10321100 | 4.42194700 | 3.28844800 |
| F | 2.75888500 | 3.19694800 | 4.00456600 |
| F | 0.87444200 | 3.21328200 | 5.09069600 |
| F | -3.73444500 | -2.97392300 | 4.06342500 |
| F | -2.55499800 | -2.00747300 | 5.62428600 |
| F | -1.87947700 | -3.88439000 | 4.76091500 |
| H | -4.45098100 | -0.69906800 | -3.49593200 |
| H | -3.33352300 | 3.11991500 | -3.12281100 |
| H | -1.02814200 | 0.54145000 | -5.09508700 |
| P | 2.39022800 | -1.90309000 | 1.79280700 |
| O | 2.66675100 | -0.66717500 | 0.85569100 |
| O | 3.75696700 | -2.80404500 | 1.69493800 |
| C | 4.00956000 | -3.50520600 | 0.47941200 |
| H | 3.20942200 | -3.33725200 | -0.24641000 |
| H | 4.04300200 | -4.57937600 | 0.70260600 |
| C | 5.33595800 | -3.08652500 | -0.12673000 |
| H | 5.55082400 | -3.74147100 | -0.98244100 |
| O | 5.23471600 | -1.72852400 | -0.58290200 |
| C | 6.39825700 | -0.99024600 | -0.24802100 |
| H | 7.15711100 | -1.04770000 | -1.03216400 |
| C | 6.55071500 | -3.16379100 | 0.81837300 |
| H | 6.30204900 | -3.61408200 | 1.78702100 |
| C | 6.93458200 | -1.69156400 | 1.01103500 |
| O | 1.29346800 | -2.80415200 | 1.11147100 |
| O | 2.10168800 | -1.52075300 | 3.21500400 |
| O | 7.58591800 | -3.86184000 | 0.14809900 |
| H | 8.42087000 | -3.60594200 | 0.57275800 |
| F | 8.29566700 | -1.53824100 | 1.12479000 |
| F | 6.39073800 | -1.20629300 | 2.15974900 |
| C | 5.14502900 | 0.81518300 | 0.80489600 |
| C | 6.69783900 | 1.33585100 | -1.01282300 |

| | | | |
|---|---|---|---|
| C | 4.85222800 | 2.13105200 | 0.95479900 |
| H | 4.61727100 | 0.04343100 | 1.33862900 |
| C | 5.56544200 | 3.03578200 | 0.11112300 |
| H | 4.07749300 | 2.44996600 | 1.63965600 |
| N | 6.08735500 | 0.40722000 | -0.09735600 |
| N | 6.42618900 | 2.66016300 | -0.81815900 |
| N | 5.34263100 | 4.38262200 | 0.23406600 |
| H | 6.02096200 | 4.97936200 | -0.21989400 |
| H | 4.93698300 | 4.72048200 | 1.09450200 |
| O | 7.43362200 | 0.90491300 | -1.89548800 |

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