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Drug Delivery

Copper-free Click-Chemistry Platform to Functionalize Cisplatin Prodrugs

Rakesh K. Pathak,[a] Christopher D. McNitt,[b] Vladimir V. Popik,[b] and Shanta Dhar*[a]

Abstract: The ability to rationally design and construct a platform technology to develop new platinum(IV) [Pt^{IV}] prodrugs with functionalities for installation of targeting moieties, delivery systems, fluorescent reporters from a single precursor with the ability to release biologically active cisplatin by using well-defined chemistry is critical for discovering new platinum-based therapeutics. With limited numbers of possibilities considering the sensitivity of Pt^{IV} centers, we used a strain-promoted azide–alkyne cycloaddition approach to provide a platform, in which new functionalities can easily be installed on cisplatin prodrugs from a single Pt^{IV} precursor. The ability of this platform to be incorporated in nanodelivery vehicle and conjugation to fluorescent reporters were also investigated.

The discovery of *cis*-diamminedichlorido-platinum(II) or cisplatin[1] and its huge success in the treatment of a variety of tumors led the exploration of new platinum compounds. The need for new platinum complexes with remarkable anticancer properties and selectivity to reduce side effects and overcome resistance shown by cisplatin demand the ability to install targeting moieties, delivery systems, and a second therapeutic on the platinum center.[2] The biological activity of cisplatin begins with aquation inside cell with the loss of one or both chloride ligands to generate highly electrophilic platinum(II) aqua complexes, which readily react with biological nucleophiles including the N7 position of purine DNA bases resulting intra and interstrand cross-links with nuclear DNA.[3] This series of biological activities imposes limitation on the strategies to synthesize new Pt^{II} complexes. The nonleaving group ligands, which stay bound to the Pt^{II} center upon DNA binding, offer only limited modifications without affecting the biological activity.[2] The requirement of good leaving group for aquation introduces further limitation to incorporate new functionalities on the Pt^{II} centers.

The kinetically "inert" Pt^{IV} prodrugs with two available axial sites can be an attractive way to introduce new functionalities on platinum. Pt^{IV} compounds show biological activities, which involve reduction to Pt^{II} prior to DNA binding.[4] The ability to rationally design and construct a platform technology to develop new platinum(IV) prodrugs by using well-defined synthetic chemistry from a single precursor can be of enormous benefit for discovering new therapeutics. Anhydrides are widely used as electrophiles for installation of new functionalities on relatively weak nucleophilic Pt^{IV}–OH center.[5] However, all anhydrides are not stable, and a large number of molecules of interest lack acid functionality for transformation to anhydrides. Click chemistry can be a convenient way to introduce a variety of ligands.[6] However, possibility of Pt^{IV} reduction by copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction conditions and cytotoxicity of remaining copper are limiting factors for utility of CuAAC click reactions for synthesis of new multifunctional Pt^{IV} prodrugs. Thus, only a limited number of examples documented CuAAC click reaction on Pt^{IV} compounds with poor yields.[7] With such issues in mind, we describe a platform technology by using strain-promoted azide–alkyne cyclo-

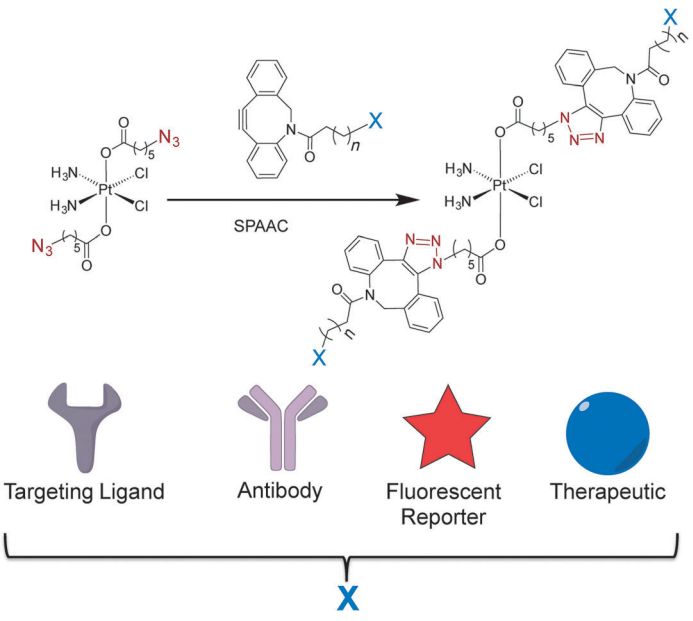

Figure 1. SPAAC-based platform to Pt^{IV} prodrugs from a single platinum precursor.

[a] *Dr. R. K. Pathak, Prof. Dr. S. Dhar*
NanoTherapeutics Research Laboratory, Department of Chemistry
University of Georgia, Athens, GA 30602 (USA)
Fax: (+1) 706-542-9454
E-mail: shanta@uga.edu
Homepage: http://shanta.chem.uga.edu

[b] *C. D. McNitt, Prof. Dr. V. V. Popik*
Department of Chemistry, University of Georgia
Athens, GA 30602 (USA).

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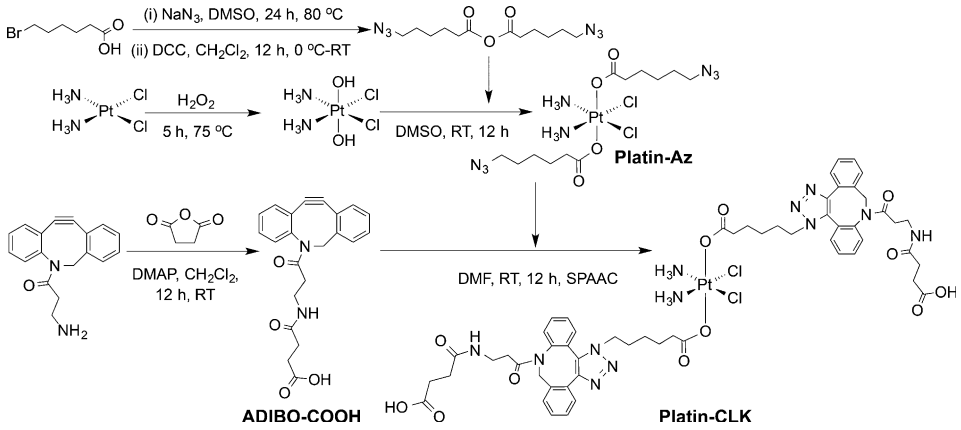
addition (SPAAC) approach,[8] a single Pt^{IV} precursor Platin-Az, and functionalized azadibenzocyclooctyne (ADIBO) derivatives for easy installation of new functionalities on Pt^{IV} centers in a single step (Figure 1).

ADIBO-based cycloaddition probes are excellent for introducing new functionalities and to increase lipophilic properties of molecules of interest for their biological activities.[9] A new terminal-azide-appended Pt^{IV} compound, Platin-Az was synthesized (Scheme 1, Figures S1–S6 in the Supporting Information) as a precursor, which can be used in a variety of SPAAC reaction with functionalized ADIBO-X derivatives (Figure 1). To demonstrate the effectiveness of this platform, an acid-functionalized ADIBO–COOH was synthesized by reacting ADIBO–NH_2 with succinic anhydride (Scheme 1, Figures S7 and S8 in the Supporting Information). Reaction of Platin-Az with ADIBO–COOH resulted in Platin-CLK in a single step in an efficient manner (Scheme 1, Figures S9–S13 in the Supporting Information). The success in performing SPAAC reaction on Pt^{IV} prodrug indicated that this technology in conjunction with Platin-Az can be used to introduce numerous functionalities when one uses suitably functionalized ADIBO derivatives for incorporation, for example, a second therapeutic, targeting moiety, fluorescent reporter, drug-delivery system. A comparison of redox potentials of Platin-Az and Platin-CLK at two different pH values of 6.0 and 7.4 demonstrated that introduction of ADIBO functionality does not change the redox behavior of the prodrug; favorable redox parameters required for cellular reduction of Platin-CLK to cisplatin were noted (Figure S14 in the Supporting Information). DNA binding ability of cisplatin produced upon reduction of Platin-CLK with sodium ascorbate followed by reaction with 2′-deoxyguanosine 5′-monophosphate sodium salt hydrate (5′-dGMP) as a truncated version of DNA was investigated. Product analysis by matrix-assisted laser desorption/ionization (MALDI) time-of-flight (TOF) mass spectrometry (MS) analysis confirmed formation of Pt^{II}-5′-dGMP-bisadduct, $[Pt(NH_3)_2(5'\text{-dGMP-N7})_2]$, ($m/z = 922$, Figure S15 in the Supporting Information) suggesting that cisplatin released upon reduction of Platin-CLK forms the desired DNA adduct.



Scheme 1. Construction of precursors for SPAAC reaction and synthesis of Platin-CLK in a single step by click reaction. DMAP = 4-dimethylaminopyridine; DCC = *N*,*N*′-dicyclohexylcarbodiimide.

The antiproliferative properties of the newly synthesized Pt^{IV} complexes, Platin-Az and Platin-CLK were tested in prostate cancer (PCa) PC3 and DU145 cell lines. Cisplatin and ADIBO–COOH were used as controls. Incubation of PC3 and DU145 cells with different concentrations of Platin-Az and Platin-CLK for 72 h followed by cell-survival analyses by using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay demonstrated that these complexes show efficient cell-killing behavior (Figure 2A, Table S1 and Figure S16 in the Supporting Information). The relative nontoxic behavior of ADIBO–COOH indicated that functionalized ADIBO-based derivatives could be used to introduce variety of functionalities on platinum center. Platin-Az, the precursor for SPAAC, was found to be more efficient in killing PCa cells and its activity was better than cisplatin and Platin-CLK. We believe that this enhanced activity is due to the presence of terminal azide groups. This is supported by the fact that *cis,cis,trans*-$[Pt(NH_3)_2Cl_2\{OOC(CH_2)_2CH_3\}_2]$ or butyroplatin, a Pt^{IV} compound devoid of such terminal azide group showed less cytotoxicity in these cells (Table S1 and Figure S16 in the Supporting Information). Butyroplatin was synthesized by following a modified literature reported method (Figures S17–S19 in the Supporting Information).[10] We would like to stress that an enhanced toxicity of Platin-Az will not be a problem, because the SPAAC will be carried out in vitro for installation of other moieties on to Pt^{IV}. Comparable cytotoxicity of the clicked product, Platin-CLK and butyroplatin indicated that installation of ADIBO did not cause any additional toxicity, thus, the SPAAC approach will serve as a versatile platform to install other biomolecules effectively on to Pt^{IV} prodrugs.

The ability to install a robust near-infrared fluorescent reporter such as Cy5.5 on Platin-Az using SPAAC was investigated. A Cy5.5-functionalized ADIBO derivative, ADIBO-Cy5.5, was used to construct Platin-Cy5.5 from Platin-Az (Figure 2B, Figures S20 and S21 in the Supporting Information). Live-cell imaging of Platin-Cy5.5 treated PC3 cells provided insight into the cellular-uptake properties of this series of Pt^{IV} prodrugs (Figure 2C). Analysis of the treated cells by using confocal microscopy indicated significant cellular internalization of this prodrug. Construction of Platin-Cy5.5 from Platin-Az and ADIBO-Cy5.5 by using SPAAC and its cellular uptake by imaging studies demonstrated the ability to install a fluorescent reporter in this platform for possible use in theranostics. The fluorescence quenching of fluorophores upon conjugation to heavy platinum center[11] is often viewed as a problem to un-

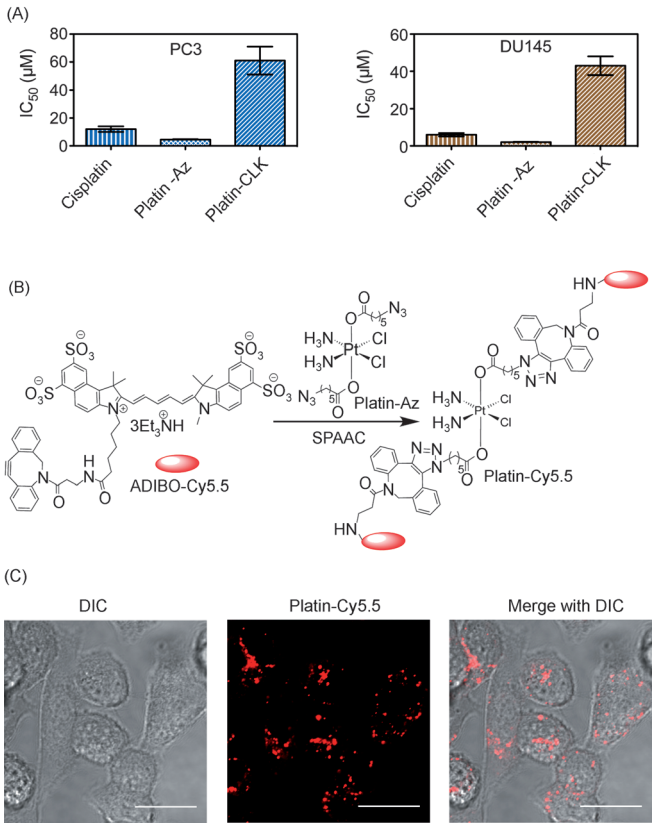


Figure 2. A) Cytotoxicity of Platin-Az, Platin-CLK, and cisplatin in PC3 and DU145 cells. B) Installation of a Cy5.5 fluorescent reporter to Pt^{IV} by using Platin-Az and ADIBO-Cy5.5 in a single step SPAAC. C) Live-cell imaging of PC3 cells in presence of Platin-Cy5.5. Scale bar = 25 μm; DIC = differential interference contrast.

derstand biodistribution (bioD) and biotransformation of such compounds. Because fluorescence quenching by Pt through the heavy-atom effect depends on the spatial separation between the fluorophore and the metal center, the ability of ADIBO-based ligand to install the fluorophore at a long distance from the Pt center will be an additional feature of the current platform for possible uses in theranostics.

Clinical translation of small molecule-based therapies face tremendous challenges due to their poor bioD and pharmacokinetic (PK) properties, rapid clearance, and marked toxicity. Nanoparticles (NPs) due to their large size compared to small molecules hold promise as carriers.[12] Inclusion of platinum-based compounds into NP delivery vehicles have obvious benefits, which include better selectivity and lesser side effects.[13] Controlled release polymers have tremendous potential for fabrication of drug-encapsulated NPs.[14] The plethora of NP platforms available, in addition to the various methods in hand to combine them with drugs, allows researchers to fine-tune the pharmacological profile of the drugs to infinity. Polymeric NPs of poly(lactide-*co*-glycolide)-*b*-polyethyleneglycol (PLGA-*b*-PEG) are especially promising as drug-delivery vehicles.[15] The use of PLGA and PEG polymers in the Food and Drug Administration (FDA) approved products makes these biomaterials ideal for development of therapeutic NPs. PLGA-*b*-PEG-NPs with the advantages of controlled release, extended blood-circulation half-life, ability to carry a large drug payload, and high therapeutic index are now in clinical trials.[16] PLGA-*b*-PEG-NPs can be used as delivery vehicles for Pt^{IV}-based compounds.[15c,17] However, successful engineering of polymeric NPs loaded with Pt^{IV} compounds depends on the hydrophilicity/hydrophobicity of the molecule of interest. Most Pt^{IV} compounds show very low loadings without compromising suitable NP sizes required for tumor accumulation.[10,17a,b] We investigated the ability of Platin-CLK-based prodrugs to be encapsulated in PLGA-*b*-PEG-based NPs. The interior of PLGA-*b*-PEG-NPs is more hydrophobic than their surface, and the presence of hydrophobic ADIBO moieties increased the lipophilic character of Platin-CLK making it convenient for NP-based delivery approaches to manage PK and bioD properties of such Pt complexes. PLGA-COOH and OH-PEG-OH polymers were used to prepare PLGA-*b*-PEG-OH copolymer (Figures S22–S24 in the Supporting Information).[18] We used a nanoprecipitation method[18] to encapsulate Platin-CLK, and the NPs were characterized by dynamic light scattering (DLS) to give the size, polydispersity, and zeta potential of each preparation (Figure 3, Table S2, and Figure S25 in the Supporting Information). Morphology of these NPs was checked by using transmission electron microscopy (TEM; Figure 3). The loading and encapsulation efficiency (EE) of Platin-CLK at various added weight-percentage values of Pt^{IV} to polymer are shown in Figure 3. In comparison, our effort to encapsulate the precursor Platin-Az lacking the hydrophobic ADIBO moieties in PLGA-*b*-PEG-NPs under the same conditions resulted in significantly lower loading and EE (Figure 3, Figure S26, and Table S3 in the Supporting Information). The ability to load Platin-CLK inside PLGA-*b*-PEG-NPs without compromising the size of the NPs further demonstrated the usefulness of this platform to be incorporated in a nanoformulation (Figure 3). The octahedral Pt^{IV} prodrugs are generally substitution inert.[19] However, the incorporation of kinetically "inert" Pt^{IV} prodrugs into delivery vehicles produce formulations, which often lacks enough long-term stability for making a prac-

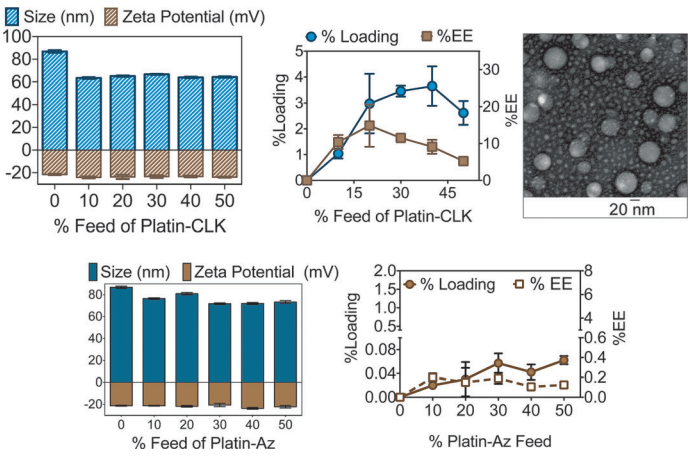


Figure 3. Size, zeta potential, loading, EE, and morphology of Platin-CLK-loaded PLGA-*b*-PEG-NPs and a comparison with Platin-Az loading in similar NPs.

tical drug.[13,20] Our current approach of making a prodrug with such easiness and their rapid modular assembly by using polymeric NPs prior to administration can be beneficial for potential clinical translation.

In conclusion, we developed a platform technology for construction of Pt^{IV} complexes containing functionalities, such as cell-receptor targeting moiety, a delivery system, other therapeutics, or fluorescent reporters with easiness and high efficacy. A versatile Pt^{IV} prodrug Platin-Az was synthesized to be used as a universal precursor in SPAAC reaction. By using this precursor, we demonstrated the utility of SPAAC reaction in presence of ADIBO-X to introduce new functionalities with easiness and high efficacy. We demonstrated the ability of these complexes to be entrapped in the hydrophobic core of PLGA-*b*-PEG-based NPs. Unique ability of this platform for easy installation of a fluorescent cell reporter, such as Cy5.5 was performed for tracking Pt^{IV} prodrugs in live cells. These new Pt^{IV} compounds demonstrated favorable redox and antiproliferative properties. The modular designing of this platform and the huge scope to introduce multiple functionalities with high efficiency by using well-defined synthetic chemistry make this work a key platform for discovering new platinum-based therapeutic agents.

Experimental Section

Synthesis of Platin-Az

A mixture of *cis,cis,trans*-$[PtCl_2(NH_3)_2(OH)_2]$ (0.54 g, 1.60 mmol) and 6-azidohexanoic anhydride (1.7 g, 5.6 mmol) in DMSO (5 mL) was stirred for 12 h. The solvent was then removed by multiple washes with diethyl ether. The crude product was purified by dissolving in acetonitrile and precipitated with diethyl ether to get a light yellow solid. Yield 0.63 g (64%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.50$ (m, 6H), 3.27 (t, 4H), 2.19 (t, 4H), 1.28–1.45 ppm (m, 12H; see Figure S3 in the Supporting Information); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.13$, 51.02, 35.92, 28.43, 26.15, 25.37 ppm (see Figure S4 in the Supporting Information); ^{195}Pt ($[D_6]$DMSO, 107.6 MHz): $\delta =$ 1215.33 ppm (see Figure S5 in the Supporting Information); HRMS: *m/z* calcd for $C_{12}H_{27}Cl_2N_8O_4Pt$: $[M+H]^+$ 612.1180; found 612.1159 (Figure S6 in the Supporting Information); elemental analysis calcd (%) for $C_{12}H_{26}Cl_2N_8O_4Pt$: C 23.54, H 4.28, N 18.30; found: C 23.36, H 4.57, N 18.75.

Synthesis of Platin-CLK

A solution of Platin-Az (80 mg, 0.13 mmol) and ADIBO–COOH (103 mg, 0.27 mmol) in dry DMF (5 mL) was stirred at RT for 12 h. The solvent was evaporated under reduced pressure (note that the temperature during rotor evaporation should be kept below 40 °C). The crude product was suspended in CH_2Cl_2 and acetonitrile (1:2) and precipitated upon addition of diethyl ether (6×). Finally, the product was isolated by precipitating with CH_2Cl_2/diethyl ether (2:8) to get an off white solid. Yield: 141 mg (79%); ^{1}H NMR ($[D_6]$DMSO, 400 MHz): $\delta = 12.02$ (broad s, 2H), 7.26–7.72 (m, 18H), 6.53 (broad, 6H), 5.84–5.97 (m, 2H), 4.35–4.46 (m, 4H), 4.22 (m, 2H), 2.98 (t, 4H), 2.87 (m, 2H), 2.33 (t, 4H), 2.19 (m, 8H), 1.82–1.94 (m, 4H), 1.35–1.64 (m, 10H), 1.01–1.10 ppm (m, 2H; see Figure S9 in the Supporting Information and gradient-selected COSY in Figure S10 in the Supporting Information); ^{13}C NMR ($[D_6]$DMSO, 100 MHz): $\delta = 181.17$, 181.14, 181.12, 174.31, 174.29, 171.40, 171.24, 170.17, 169.76, 144.18, 143.27, 142.63, 141.37, 140.47, 135.81, 134.27, 134.20, 132.68, 132.38, 132.02, 131.17, 130.27, 130.20, 129.96, 129.71, 129.60, 129.12, 128.79, 128.74, 127.91, 127.32, 127.29, 124.71, 52.27, 50.93, 48.90, 48.17, 35.91, 35.70, 35.23, 35.19, 33.84, 33.78, 30.29, 30.25, 29.67, 29.52, 29.49, 29.46, 26.27, 25.55, 25.36, 25.19 ppm (see Figure S11 in the Supporting Information). Note that ADIBO triazole is known to exhibit different isomers, and this phenomenon is reflected in the ^{13}C NMR peaks. ^{195}Pt NMR ($[D_6]$DMSO, 107.6 MHz): $\delta = 1213.97$ ppm (see Figure S12 in the Supporting Information); HRMS *m/z* calcd for $C_{56}H_{67}Cl_2N_{12}O_{12}Pt$: $[M+H^+]$ 1364.4026; found 1364.4027 (see Figure S13 in the Supporting Information); elemental analysis calcd (%) for $C_{56}H_{66}Cl_2N_{12}O_{12}Pt{\cdot}CH_3CN{\cdot}CH_2Cl_2$: C 47.52, H 4.80, N 12.21; found: C 47.10, H 5.09, N 12.24.

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Drug Delivery

*R. K. Pathak, C. D. McNitt, V. V. Popik, S. Dhar**

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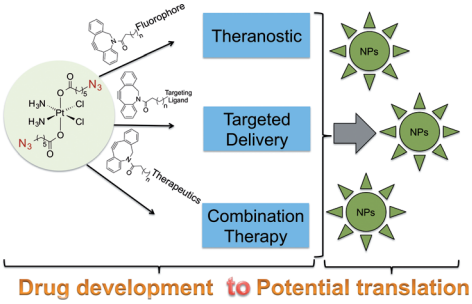
Copper-free Click-Chemistry Platform to Functionalize Cisplatin Prodrugs



Clicking into platinum: A platform technology employing copper-free click chemistry to construct platinum(IV) prodrugs with numerous functionalities to release the active drug cisplatin was devised. This technology allows easy construction of highly functionalized Pt^{IV} prodrugs from a single azide precursor and suitably functionalized strained alkyne with high efficiency and purity in a single step. Application of this new methodology can be in combination therapy, targeted drug delivery, and in theranostics (see scheme).