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Highly cytotoxic palladium(II) complexes of 1,2,4-triazole derived carbenes

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1. Synthesis of the compounds

General Considerations. All the synthetic experiments were conducted in atmospheric condition unless otherwise stated. Solvents for syntheses and spectroscopic measurements were used as received. The triazolium salts **tz-Mes**·HBr and **tz-Dipp**·HBr were synthesized follow the procedure reported previously.

*Synthesis of trans-[PdBr$_2$(tz-Mes)] (**1**).* A mixture of tz-Mes·HBr (178 mg, 0.5 mmol), silver(I) oxide (58 mg, 0.25 mmol) and palladium(II) bromide (67 mg, 0.25 mmol) in dichloromethane (20 mL) was stirred in the dark for 14 h. The precipitate was filtered off and the volatile solvent was removed under reduced pressure. The obtained solid was subjected to silicagel column chromatoghraphy using dichloromethane as eluent. The title compound was isolated as a pale yellow solid. Yield 189 mg (0.23 mmol, 92%). trans- syn (syn:anti molar ratio = 1.5:1): ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 7.74 (s, 1 H, NCHN), 7.34–7.29 (m, 5 H, Ar-H), 6.92 (s, 2 H, Ar-H), 5.86 (s, NCH_2), 2.48 (s, 3 H, CH_3), 1.97 (s, 6 H, CH_3). ^{13}C-NMR ($CDCl_3$, 125.7 MHz): δ = 172.8 (CNHC), 143.9 (NCHN), 138.9, 135.9, 135.5, 131.7, 129.4, 128.9, 128.8, 128.2 (Ar-C), 57.1 (NCH_2), 21.4, 19.5 (CH_3). trans-anti: ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 7.79 (s, 1 H, NCHN), 7.56–7.54 (m, 3 H, Ar-H), 7.43–7.41 (m, 2 H, Ar-H), 6.87 (s, 2 H, Ar-H), 5.64 (s, 2 H, NCH_2), 2.23 (s, 3 H, CH_3), 2.22 (s, 6 H, CH_3). ^{13}C-NMR ($CDCl_3$, 125.7 MHz): δ = 172.7 (CNHC), 143.9 (CNCHN), 143.7, 136.1, 135.1, 131.9, 129.3, 129.1, 128.6, 128.2 (Ar-C), 56.9 (NCH_2), 24.1, 19.8 (CH_3). Anal. Calcd for $C_{36}H_{38}Br_2N_6Pd$: C, 52.67; H, 4.67; N, 10.24. Found: C, 52.36; H, 4.81; N, 10.50. MS (ESI) Calcd. for $[M + H_2O]^+$, $C_{36}H_{40}Br_2N_6OPd$: m/z 838.0645 Found: m/z 838.1132.

Synthesis of PdBr$_2$(**tazy-Dipp**)$_2$ (**2**). The complex was prepared in a similar manner with that of **1**, starting from **tz-Dipp**·HBr (200 mg, 0.5 mmol), silver(I) oxide (58 mg, 0.25 mmol) and palladium(II) bromide (67 mg, 0.25 mmol). The product was isolated as a pale yellow solid. Yield: 195 mg (0.22 mmol, 86%). trans- syn (syn:anti = 2:1): ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 7.78 (s, 1 H, NCHN), 7.60 (d, 2 H, Ar-H), 7.36–7.33 (m, 4 H, Ar-H), 7.14 (d, 2 H, Ar-H), 6.02 (s, 2 H, NCH_2), 2.71 (sept., $^3J_{H\text{-}H}$ = 6.7 Hz, 2 H, C*H*(CH_3)$_2$), 0.95 (d, $^3J_{H\text{-}H}$ = 7 Hz, 6 H, CH_3), 0.90 (d, $^3J_{H\text{-}H}$ = 7 Hz, 6 H, CH_3). ^{13}C-NMR ($CDCl_3$, 125.7 MHz): δ = 173.4 (C_{NHC}), 146.7 (NCHN), 135.1, 131.1, 130.5, 129.2, 128.7, 128.3, 124.2 (2 C) (Ar-C), 57.3 (NCH_2), 28.3 (*C*H(CH_3)$_2$, 26.3, 22.9 (CH_3). trans- anti: ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 7.86 (s, 1 H, C_{NHC}), 7.44–7.25 (m, 8 H, Ar-H), 5.63 (s, 2 H, NCH_2), 2.98 (sept, $^3J_{H\text{-}H}$ = 7 Hz, 2 H, C*H*(CH_3)$_2$), 1.33 (d, $^3J_{H\text{-}H}$ = 7 Hz, 6 H, CH_3), 0.94 (d, $^3J_{H\text{-}H}$ = 7 Hz, 6 H, CH_3). ^{13}C-NMR ($CDCl_3$, 125.7 MHz): δ = 173.5 (C_{NHC}), 147.1, 144.7, 134.6, 131.4, 130.8, 129.6, 128.6, 128.2 (2 C), (Ar-C), 123.9 (NCH_2), 28.6 (*C*H(CH_3)$_2$), 26.6, 22.8 (CH_3). Anal. Calcd for $C_{42}H_{50}Br_2N_6Pd$: C, 55.73; H, 5.57; N, 9.29. Found: C, 55.89; H, 5.81; N, 9.05. MS (ESI) Calcd for $[M + H_2O]^+$, C42H52Br2N6OPd: *m/z* 922.1584. Found: *m/z* 922.2080.

2. Structural Analysis.

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of the complexes were recorded on a Bruker Avance III 500 MHz instrument in deuterated chloroform - $CDCl_3$. Spectra were calibrated by referencing the solvent residual signal to 7.26 ppm (^{1}H-NMR) and 77.16 ppm (^{13}C NMR). ESI-MS spectra were collected using a SCIEX X500 QTOF system. Elemental analyses were performed using a Thermo Scientific FlashSmart Elemental Analyzer.

3. X-ray Crystallography.

Single-crystal X-ray diffraction were collected on a Bruker D8 QUEST instrument at 298 K with Mo Kα radiation (λ = 0.71073 Å) using a TRIUMPH monochromator. Standard procedures were applied for data reduction and absorption correction.[1,2] Structure solution and refinement were performed with the SHELXT and SHELXL 2014/7 programs.[3,4] Hydrogen atoms were calculated for idealized positions using OLEX2.[5] The representation of molecular structures was ploted using the program OLEX2-1.2. The .cif files for the structures have been deposited to CCDC library under CCDC No. 2156068 (**1**) and 2156071 (**2**).

4. Cytotoxicity assay

The cells were maintained in 75 cm^2 tissue culture flasks containing Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (Invitrogen, Carlsbad, CA, USA), 1% non-essential amino acids and 1% antibiotics (Sigma, St. Louis, MO, USA) at 37 °C in a humidified 5% CO_2 atmosphere. The cell proliferation was then determined using Sulforhodamine B colorimetric assay.[6,7]

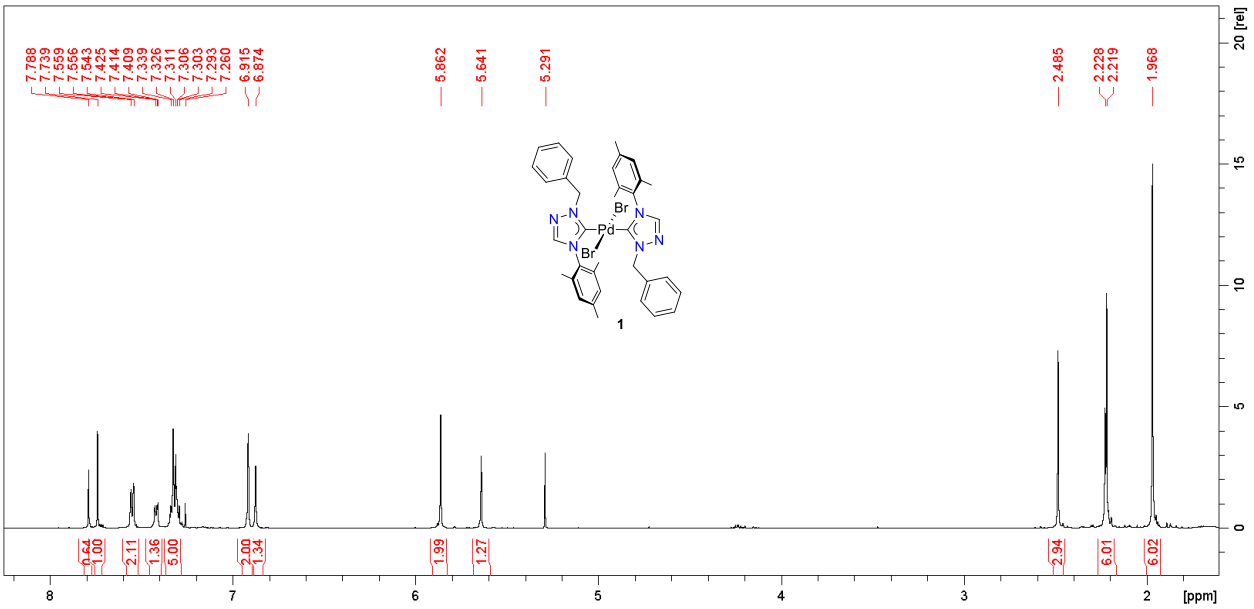

Figure S1. ^{1}H NMR spectrum of **1** in $CDCl_3$.

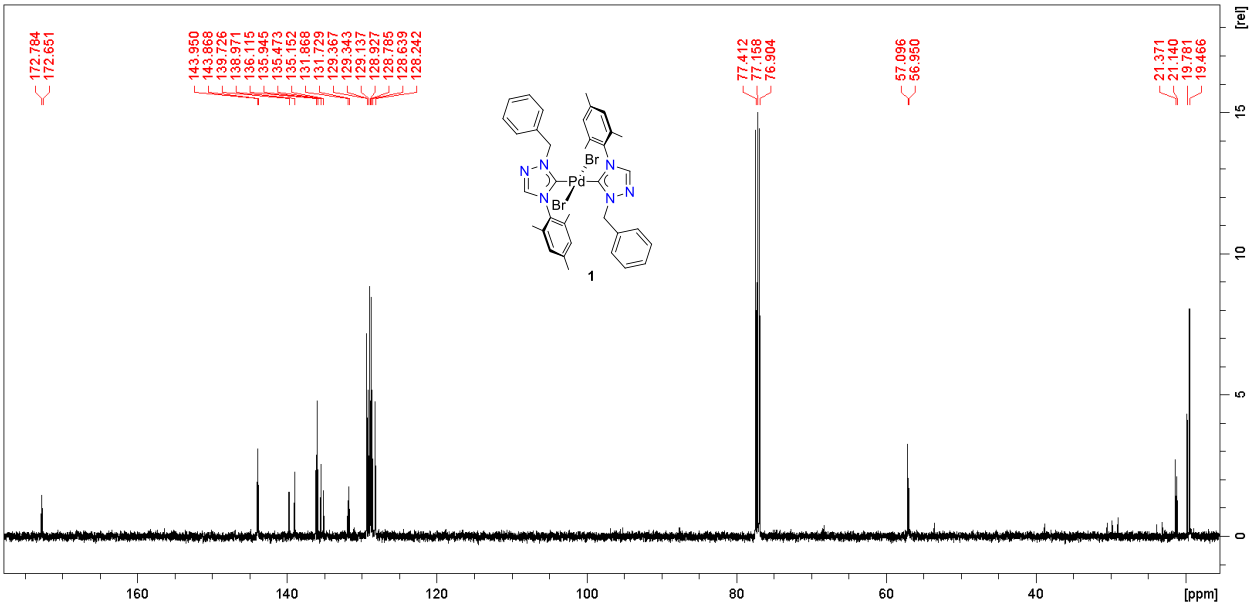

Figure S2. ^{13}C NMR spectrum of **1** in $CDCl_3$.

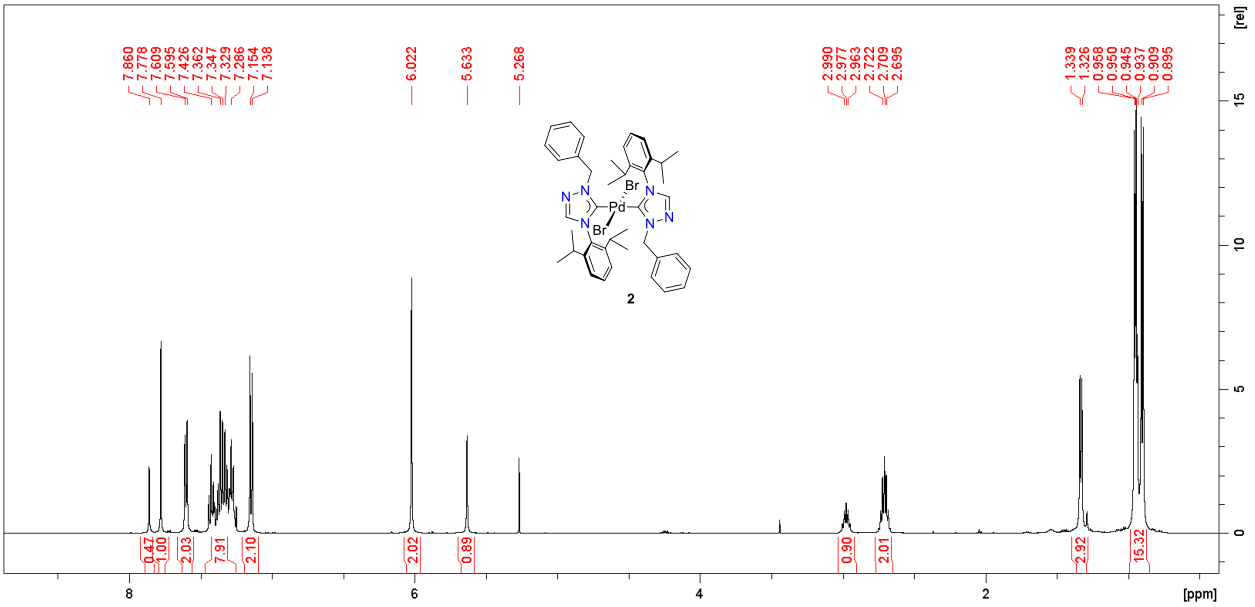

Figure S3. ^{1}H NMR spectrum of **2** in $CDCl_3$.

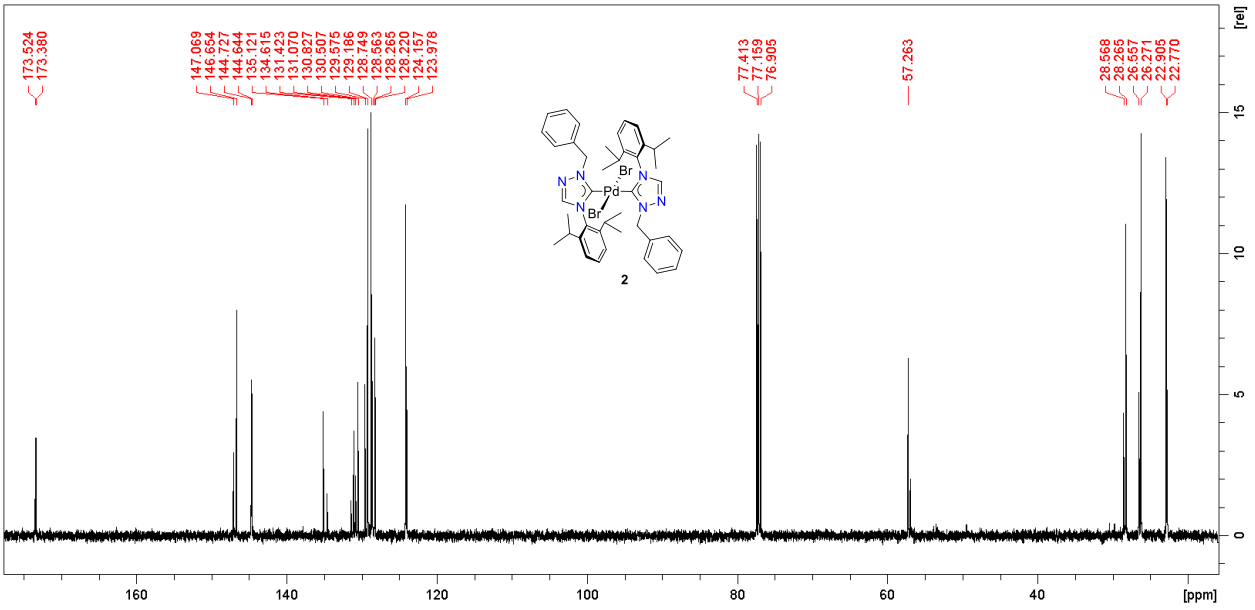

Figure S4. ^{13}C NMR spectrum of **2** in $CDCl_3$.

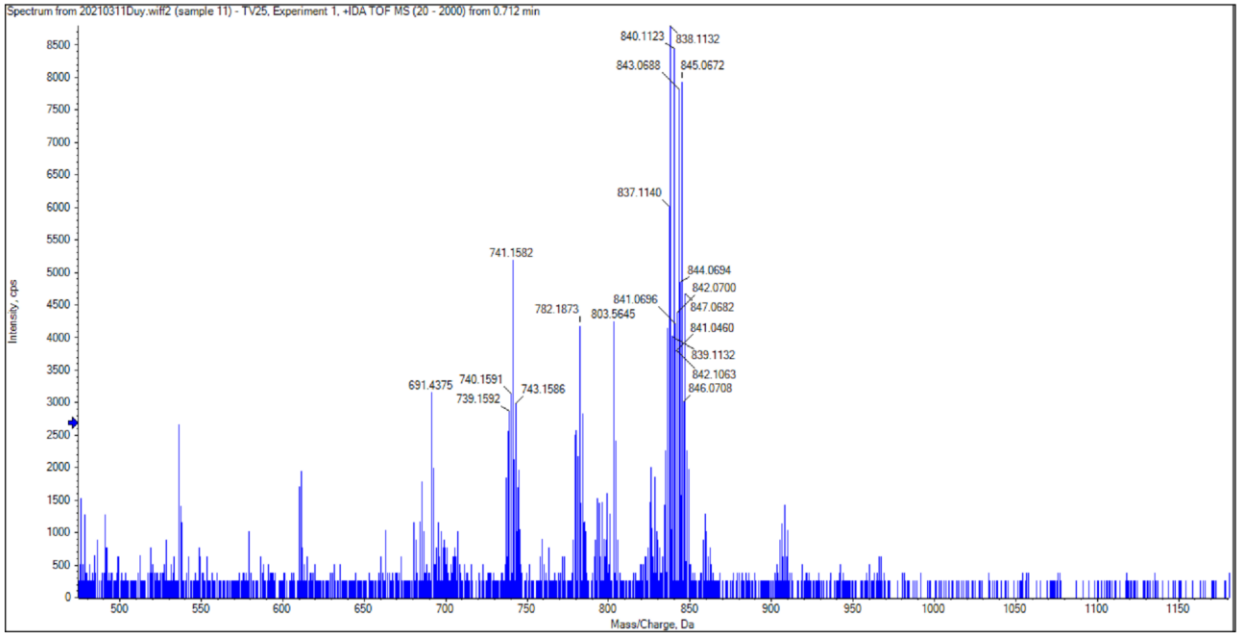

Figure S6. ESI-MS spectrum of **1**.

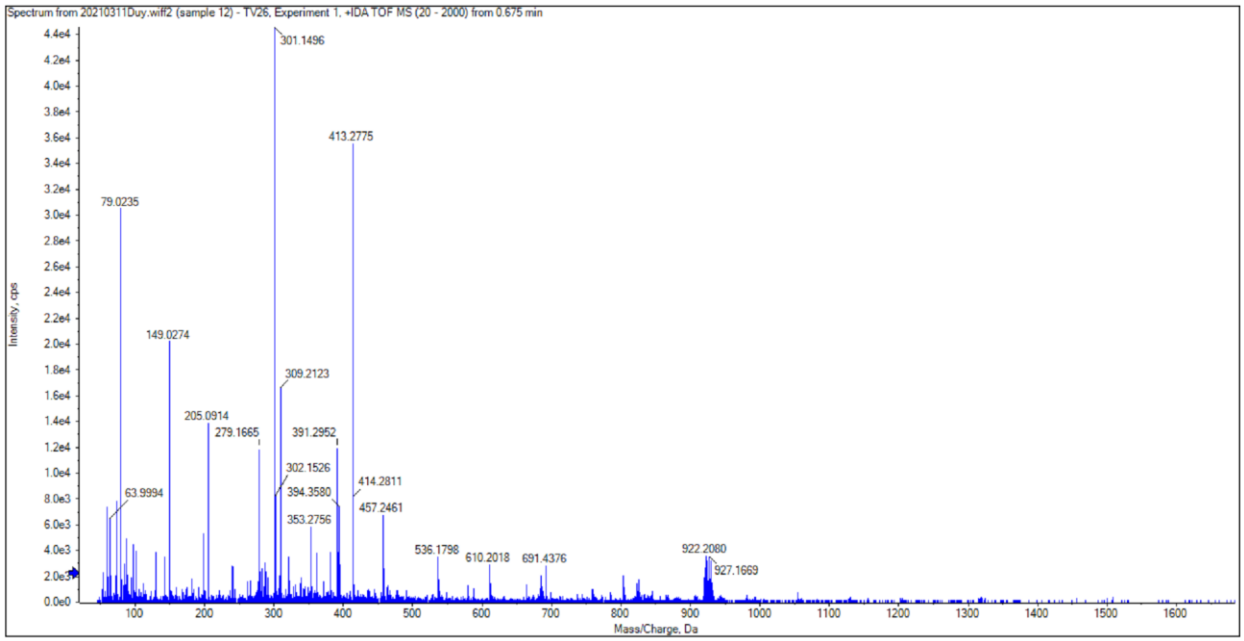

Figure S7. ESI-MS spectrum of **2**.

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