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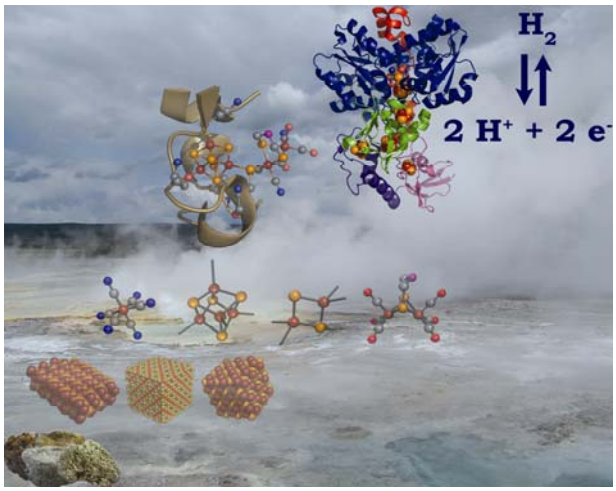

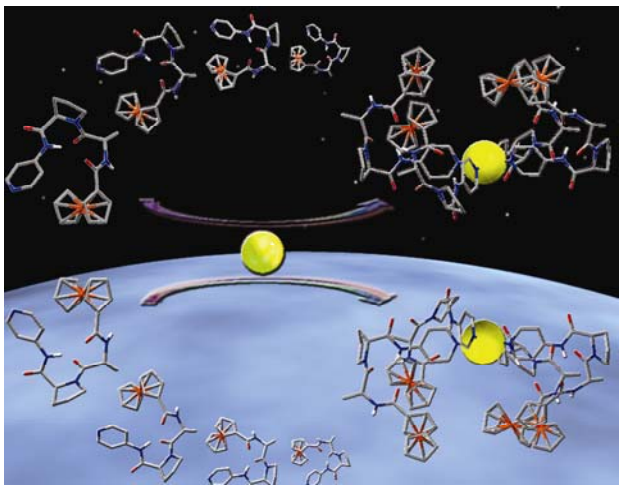

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Synthesis of a 1,4-benzodiazepine containing palladacycle with *in vitro* anticancer and cathepsin B activity†

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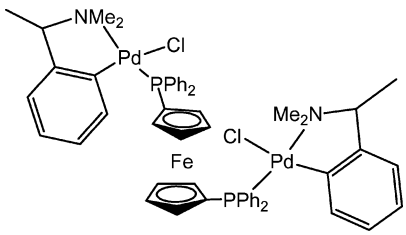
The reaction of the five-membered C,N-palladacycle $[(L)PdCl]_2$, where LH = 1-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one, with 1,2-ethane*bis*(diphenylphosphine), dppe, leads to the formation of the bridged palladacycle. $[Pd_2L_2(\mu\text{-dppe})Cl_2]$ **3**, which was characterised in solution by ^1H and ^{31}P NMR spectroscopy and in the solid state by X-ray crystallography. Complex **3** was tested *in vitro* against a number of cell lines. For example, it inhibited K562 leukaemia cells with an IC_{50} value of 4.3 μM (1 h exposure) and displayed cathepsin B inhibitory action with an IC_{50} value of 3 μM.

Introduction

Historically transition metals have played an important role in medicinal chemistry.[1] Many have anticancer activity due to their cytotoxic action and a number are now marketed as drugs or in advanced clinical trials.[2] New generation complexes are currently being developed whereby the metal can act as an inert scaffold and many enable binding modes and geometries that are not accessible to traditional organic, carbon-based, chemistry.[3]

We have a long-standing interest in palladium chemistry, especially palladacycles, which are molecules containing a C–Pd bond stabilised intramolecularly by a dative bond (*e.g.* N-, S-, O-, P-, Se- donor).[4] A number of palladacycles have been evaluated for cytotoxic activity but have yet to make sufficient progress to clinical trials for evaluation as drugs.[5] Nevertheless, a recent breakthrough from Caires' group has shown that a dimeric dppf bridged C,N-palladacycle **1** (dppf = 1,1′-*bis*(diphenylphosphine)-ferrocene) has promising non-cytotoxic anticancer activity; *in vivo* animal studies with **1** have shown that significant tumour shrinkage can be achieved and that very little toxicity is observed, even at high doses. Compounds **1** can be synthesised from either (*R*)- or (*S*)-dmpa, (*N,N*-dimethyl-1-phenethylamine) and have notable cathepsin B inhibitory activity, with the potential to treat metastatic cancer (Fig. 1).[6]

The promising results derived from **1** have prompted us to investigate the reaction of the benzodiazepine containing palladacycle **2** with bidentate phosphine ligands in order to generate compounds for biological evaluation.[7] The premise for such a study stems from the modular nature, *i.e.* ease of synthesis of analogues for structure activity studies (SAR), of the benzodiazepine ligand and the druglikeness of the benzodiazepine scaffold, which may lead to favourable properties in the resulting palladacycle complex.[8]



(S) and *(R)*-**1**

Fig. 1 Non-cytotoxic palladacycles.

Results and discussion

The dimeric palladacycle **2** reacted with an equivalent of dppe to afford an ash coloured solid. Analysis by ^{31}P NMR spectroscopy showed the appearance of a major signal at 40.4 ppm (s), corresponding to the dppe bridged dimer **3**, as well as a trace amount of a product displaying doublets centred at 43.9 and 61.1 ppm, which was attributed to **4** (Scheme 1).[9] The structure of **3**, which could be isolated in pure form by recrystallisation, was corroborated by ^1H NMR spectroscopy and elemental analysis as well as by single crystal X-ray analysis (*vide infra*), which confirmed the presence of chloroform solvates (Fig. 2).

Complex **3** has been characterised in the solid phase by a single crystal X-ray diffraction study. The centre of mass of the palladium dimer lies on an inversion centre (see Fig. 2), such that only half of the molecule is crystallographically unique. The $Pd(1)\cdots Pd(1)^i$ distance is 7.55 (1) Å, showing that the two metal atoms in the dimer are not bonded. The structure contains four molecules of chloroform per palladium dimer. The geometry about the palladium atom is distorted square planar, with the maximum deviation from the least squares plane through atoms Pd(1), Cl(1), P(1), N(2) and C(15) being 0.08 Å for atom N(2). The bond angle at Pd(1) involving the bidentate ligand, N(2)–Pd(1)–C(15) = 80.5 (3)°, is smaller than the other three bond angles at the palladium

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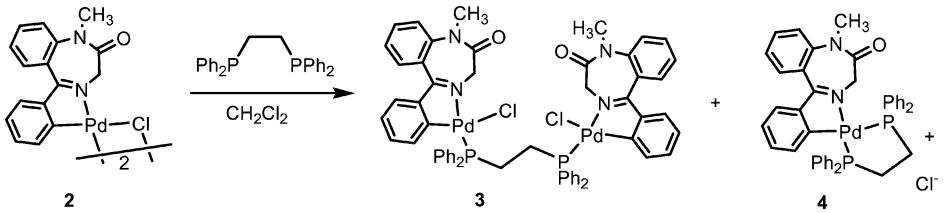
† CCDC reference number 706386 for **3**. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b819061e



Scheme 1 Synthesis of a dppe bridged palladacycle.

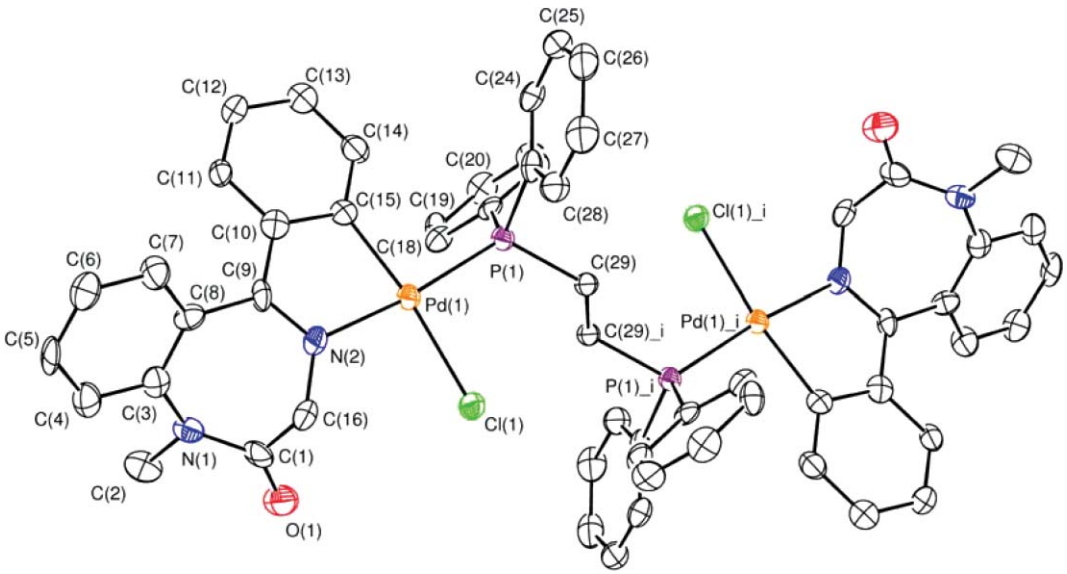


Fig. 2 Ortep diagram for complex **3** with ellipsoids drawn at the 50% probability level. Hydrogen atoms and chloroform molecules have been omitted for clarity. The centre of mass of the dimeric molecule lies on an inversion centre. The symmetry transformation used to generate equivalent atoms is: (i) $-x, -y, -z$. Selected bond lengths (Å), and angles (°): Pd(1)–Cl(1) 2.381 (2), Pd(1)–P(1) 2.259 (2), Pd(1)–N(2) 2.099 (8), Pd(1)–C(15) 2.016 (9), P(1)–C(29) 1.833 (9), C(29)–C(29)^{i} 1.543 (17), N(2)–Pd(1)–C(15) 80.5 (3), C(15)–Pd(1)–P(1) 93.7 (3), P(1)–Pd(1)–Cl(1) 93.43 (8), Cl(1)–Pd(1)–N(2) 92.5 (2), P(1)–Pd(1)–N(2) 172.4 (2), Cl(1)–Pd(1)–C(15) 172.7 (3), Pd(1)–P(1)–C(29) 118.8 (3), P(1)–C(29)–C(29)^{i} 114.2 (8), Pd(1)–N(2)–C(9) 114.7 (6), Pd(1)–N(2)–C(16) 126.3 (6), Pd(1)–N(2)–C(9)–C(10) 4.3 (10), Pd(1)–C(15)–C(10)–C(9) 0.1 (10), P(1)–Pd(1)–C(15)–C(14) 9.6 (8).

centre, the average of which is 93.2 (1–3)° (See Fig. 2). The five-membered ring formed by the bonding of the bidentate ligand to the metal centre, Pd(1), N(2), C(9), C(10) and C(15), is planar with the maximum deviation from the least squares plane through the atoms being 0.03 Å for atom N(2). The larger group C(8)–C(16), Pd(1), Cl(1), N(2) and P(1) is also close to being planar with the maximum deviation from the least squares plane through all the atoms being 0.20 Å for atom P(1). There is a twist in this group, with the torsion angle P(1)–Pd(1)–C(15)–C(14) being 10 (1)°.

Complex **3** was tested for *in vitro* anticancer activity against a K562 human leukaemic cell line *via* a medium throughput screen. For comparison, a number of palladacycles **1** and **5** were synthesised and tested (Table 1). Both (*R*)- and (*S*)-**1** have very weak cytotoxic action (Entries 1–2), confirming Caires' findings,[6] and most of the benzodiazepine palladacycle analogues **5** display poor activity, as does the commercially available coordination complex dppfPdCl$_2$ (Entries 4–11). However, complex **3** displays good *in vitro* activity, with an IC$_{50}$ of 4.3 μM (Entry 3).

Having established **3** as a "hit" from this primary screen, we have evaluated it in other immortal cell lines namely B16 (Murine Melanoma) and Vero (African Green Monkey Kidney Epithelia).[10] Preliminary data show **3** to have submicromolar activity (Fig. 3 and 4).

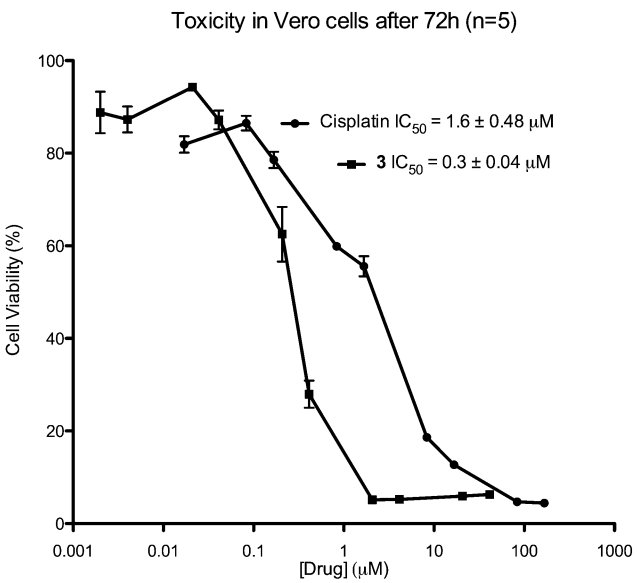
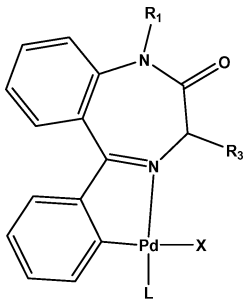


Fig. 3 Toxicity of palladacycle **3** and cisplatin against Vero cell lines.

Furthermore, compound **3** has been tested for cathepsin B inhibitory activity[11] and registered an IC$_{50}$ value of 2.98 μM, which is in the same range as that of **1** (Fig. 5).

Table 1 *In vitro* activity of palladacycles against a K562 cell line



5

Entry	Compound	R_1	R_3	L	X	$IC_{50}/\mu M^a$
1	(*R*)-**1**[b]	—	—	—	—	400
2	(*S*)-**1**[b]	—	—	—	—	300
3	**3**	—	—	—	—	4.3
4	dppfPdCl_2	—	—	—	—	>1000
5	**5a**[c]	Me	H	PPh_3	Cl	550
6	**5b**[c]	Me	H	pyr	Cl	>1000
7	**5c**[c]	Me	H	PPh_3	OAc	>1000
8	**5d**[c]	Me	*i*-Pr	PPh_3	OAc	>1000
9	**5e**[c]	Me	*i*-Pr	pyr	OAc	>1000
10	**5f**[c]	Bn	H	pyr	Cl	1000
11	**5g**[c]	Bn	H	PPh_3	Cl	200

[a] MTT assay from DMSO stock solution on human leukaemic K562 cells (1 h exposure). [b] From ref. 6. [c] From ref. 7.

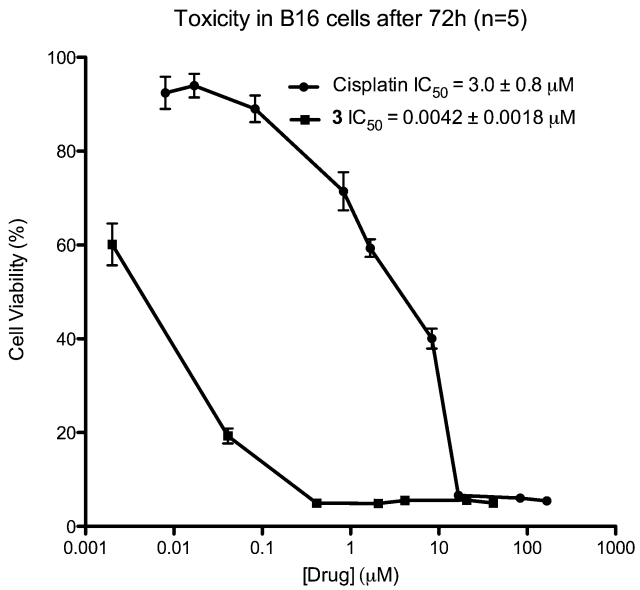


Fig. 4 Toxicity of palladacycle **3** and cisplatin against B16 cell lines.

Conclusion

Palladacycle **3** is cytotoxic and inhibits cathepsin B with IC_{50} values in the low μM range. Current studies are aiming to address some remaining questions including (i) whether **3** displays selectivity towards cancer over normal cells, (ii) if the cathepsin B inhibitory action of **3** is exhibited by other related benzodiazepine containing palladacycles, which preferably display lower toxicity than **3** to cancer cell lines, (iii) if complexes **3** can be used as biological probes for proteins and biomolecules *e.g.* cysteine, selenocysteine proteases.[12] All these exciting aspects of palladacycle chemistry will be divulged in due course.

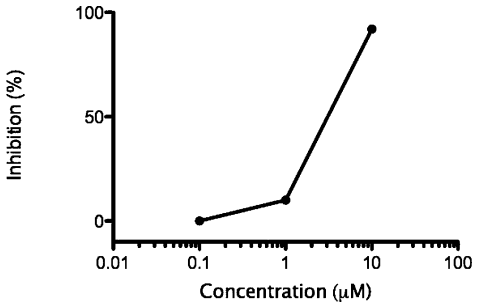


Fig. 5 Inhibitory action of **3** towards (human liver) cathepsin B.

Experimental

General

Starting materials and commercial grade solvents were purchased from Sigma-Aldrich or Alfa Aesar and used without further purification. Reactions were carried out under argon. NMR spectra were measured on a Jeol EX270 spectrometer at 270 MHz (^{1}H), 109.4 MHz (^{31}P) and 68 MHz (^{13}C) in $CDCl_3$. Elemental analysis was performed on a CE Instruments Eager 300 apparatus. Unless otherwise stated all cell culture reagents were from Invitrogen. Vero cells were from the American Tissue Culture Collection (ATCC-CCL-81). The B16 cells were kindly donated by Professor I. Hart (St Thomas' Hospital). Compounds **1** were synthesised according to ref. 6, compounds **2**, **5a–g** were synthesised according to ref. 7.

Palladacycle 3. Complex **2** (0.668 g, 0.85 mmol of dimer) was stirred with dppe (0.338 g, 0.85 mmol) in dichloromethane (10 cm^3) for 2 h. The reaction mixture was filtered over Celite and the filter cake was washed with further dichloromethane (20 ml). Thereafter the resulting combined filtrates were evaporated to nearly dryness and hexane was added to afford an ash colour precipitate. The latter was collected by filtration and dried *in vacuo.* Yellow crystals were obtained from $CHCl_3$–hexane (0.945 g, 94%). NMR ($CDCl_3$) δ_H 8.16–7.90 (8H, m, aryl), 7.64 (4H, m, aryl), 7.38–7.24 (16H, m, aryl), 6.98 (2H, d, $J = 7.7$ Hz, aryl), 6.77 (2H, t, $J = 6.8$ Hz, aryl), 6.53 (4H, m, aryl), 6.01 (2H, d, $J = 11.0$ Hz, CH_2), 3.72 (2H, d, $J = 11.0$ Hz, CH_2), 3.31 (6H, s, CH_3), 2.92 (4H, brs, CH_2): δ_P 40.40 (s): δ_C 175.6, 164.1, 153.6, 153.5, 141.5, 137.9, 129.4 (overlapping carbons), 126.4, 125.0 (overlapping carbons), 122.6 (overlapping carbons), 118.3, 117.5, 115.7, 47.8, 28.9, 21.2 (m). Found C, 58.1; H, 4.3; N, 4.2. $C_{58}H_{50}Cl_2N_4O_2P_2Pd_2$ 0.25 $CHCl_3$ requires C, 57.8; H, 4.2; N, 4.6.

Cell culture. B16 and Vero cells were maintained in an atmosphere of 5% (v/v) CO_2 at 37 °C. IC_{50} values were obtained using published methodologies. Briefly, 5×10^3 cells/well were used to seed 96 well cell culture treated plates (Sigma). Compounds were dissolved at 5 mg ml^{-1} in sterile DMSO and further diluted with the appropriate complete cell culture medium. After 72 h cell viability was assessed using MTT (Sigma) also following published protocols.[10]

Growth inhibitory activity against the human K562 cell line. K562 human chronic myeloid leukemia cells were maintained in

RPM1 1640 medium supplemented with 10% fetal calf serum and 2 mM glutamine at 37 °C in a humidified atmosphere containing 5% CO_2 and were incubated with a specified dose of test agent for 1 h at 37 °C in the dark. The incubation was terminated by centrifugation (5 min, 300 g) and the cells were washed once with drug-free medium. Following the appropriate drug treatment, the cells were transferred to 96-well microtitre plates. Plates were then kept in the dark at 37 °C in a humidified atmosphere containing 5% CO_2. The assay is based in the ability of viable cells to reduce a yellow soluble tetrazolium salt, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT, Sigma Chemical Co.) to an insoluble purple formazan precipitate. The optical density was then read at a wavelength of 550 nm on a plate reader, and a dose-response curve was constructed. For each curve, an IC_{50} value was read as the dose required to reduce the final optical density to 50% of the control value.

X-Ray crystallography†

A suitable crystal was selected and a dataset for **3** was measured on a Bruker APEXII CCD diffractometer at the window of a Bruker FR591 rotating anode ($\lambda_{Mo\,K\alpha}$ = 0.71073 Å) at 120 K (Table 2). The data collection was driven by COLLECT[13] and processed by DENZO.[14] An absorption correction was applied using SADABS.[15] The structure was solved in SIR2004[16] and was refined by a full-matrix least-squares procedure on F^2 in SHELXL-97.[17] All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on the equivalent isotropic displacement parameter (U_{eq}) of the parent atom. The highest difference electron density peak, 1.870 e Å^{-3}, is located at 0.98 Å from Pd(1) and the deepest hole, –0.826 e Å^{-3}, is located at 0.89 Å from Cl(13). Figures were produced using ORTEP3 for Windows[18] while structural analysis was carried out in PARST.[19]

Table 2 X-Ray crystallography experimental data

Empirical formula	$C_{58}H_{50}Cl_2N_4O_2P_2Pd_2$, 4($CHCl_3$)
Formula weight	1658.13
Temperature/K	120 (2)
Crystal size/mm	0.1 × 0.07 × 0.02
Crystal system	Monoclinic
Space group	$P2_1/c$
a; *b*; *c*/Å	11.3456(5); 10.9170(4); 27.5717(11)
α; β; γ/°	90; 97.760(2); 90
V/Å^3	3383.8(2)
Z; *Z*′	2; 0.5
Density (calculated)/Mg m^{-3}	1.627
Absorption coefficient Mo Kα/mm^{-1}	1.178
Max. and min. transmission	0.9768 and 0.8913
F(000)	1660
θ Range for data collection/°	3.12–25.03
Index ranges	$-13 \le h \le 13$, $-12 \le k \le 12$, $-32 \le l \le 32$
Reflections collected	21908
Independent reflections	5894 [R_{int} = 0.0744]
Measured reflections with $I \ge 2\sigma(I)$	4287
Completeness to θ_{max}	98.6
Data/restraints/parameters	5894/0/389
Goodness-of-fit on F^2	1.091
Final *R* indices (observed data)	R_1 = 0.0856, wR_2 = 0.1567
Final *R* indices (all data)	R_1 = 0.1260, wR_2 = 0.1796
Largest diff. peak; hole/e Å^{-3}	1.870; –0.826

Acknowledgements

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