Effect of charge and surface area on the cytotoxicity of cationic metallointercalation reagents[1]

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Abstract: Reaction of a series of nitrogen donor ligands (1-phenylpyrazoles, 2-phenylpyridine, benzo[*h*]quinoline, 1-(2′-pyridyl)indole, 1-phenylindazole, and 2-phenylindazole) with palladium(II) and platinum(II) salts gave complexes where ortho-metallation had occurred resulting in bidentate binding to the metal centres through N and C atoms. These cyclometallated products were isolated as μ-chloro dimers. Subsequent treatment of these μ-chloro dimers with chelating diamines such as 1,2-ethanediamine converted them into 14 cationic (1+) complexes. Analogous coordination mixed ligand complexes (charge 2+) were prepared by reaction of dichloro(1,2-ethanediamine-*N*,*N*′)palladium(II) with aromatic diamines such as 2-(1′-pyrazolyl)pyridine, 2,2′-bipyridine, and 1,10-phenanthroline. The complexes exhibited growth inhibitory activity against L1210 mouse leukæmia cells in vitro over a wide concentration range; in general, the cyclometallated complexes were more active than the mixed ligand complexes, although one cyclometallated organoplatinum complex was less active than the mixed ligand analogue. Substitution around the periphery of the aromatic ligands also resulted in increased activity. One complex, derived from 1-(2′-pyridyl)indole, was tested in vivo and showed no significant antitumour inhibition against P388 leukæmia at doses below toxic levels.

Key words: anticancer, metallointercalator, cyclometallation, palladium, platinum, cytotoxicity.

Résumé : La réaction d'une série de ligands donneurs d'azote (1-phénylpyrazoles, 2-phénylpyridine, benzo[*h*]quinoléine, 1-(2′-pyridyl)indole, 1-phénylindazole et 2-phénylindazole) avec des sels de palladium(II) et de platine(II) conduit à la formation de complexes dans lesquels il s'est produit une ortho-métallation qui résulte en une liaison bidentate avec les centres métalliques par le biais des atomes de N et de C. On a isolé ces produits sous la forme de dimères μ-chloro et un traitement subséquent de ces dimères avec des diamines qui peuvent agir comme agent chélatant, telles l'éthane-1,2-diamine, a permis de les transformer en quatorze complexes cationiques (1+). On a préparé des complexes analogues avec des ligands à coordination mixte (charge 2+) en faisant réagir du dichloro(éthane-1,2-diamine-*N*,*N*′)palladium(II) avec des diamines aromatiques, telle la 2-(1′-pyrazolyl)pyridine, la 2,2′-bipyridine et la 1,10-phénanthroline. Dans des essais in vitro, ces complexes présentent, sur large plage de concentration, une activité inhibitrice de la croissance des cellules de la lignée L1210 de la leucémie de la souris; en général, les complexes cyclométallés sont plus actifs que les complexes de ligands mixtes, même si un complexe organique cyclométallé du platine est moins actif que l'analogue avec un ligand mixte. Une substitution autour de la périphérie des ligands aromatiques conduit aussi à une augmentation de l'activité. Un complexe, celui dérivé du 1-(2′-pyridyl)indole, a été évalué in vivo et, à des doses inférieures aux niveaux toxiques, il ne présente aucune activité d'inhibition antitumorale contre la leucémie P388.

Mots clés : anticancéreux, intercalation métallique, cyclométallation, palladium, platine, cytotoxicité.

[Traduit par la Rédaction]

Introduction

Cancer, as a group of diseases, ultimately kills one-quarter of the human population. The quest for new and effective chemotherapeutic agents to combat cancers has led to tremendous activity; however, until relatively recently, the use of heavy metals has attracted only sporadic interest. The serendipitous discovery by Rosenberg et al. (1) that *cis*-

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It is a pleasure to honour Howard Alper's very significant contributions both to chemistry and to the chemical profession.

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Table 1. Products of cyclometallation reactions.

Ligand	Abbreviation	Metal	Complex	Yield (%)
1-Phenylpyrazole (**1**)	Hpzph	Pd	**3**	99
2-Phenylpyridine (**2**)	Hpyph	Pd	**4**	96
2-Phenylpyridine (**2**)	Hpyph	Pt	**5**	65
1-(2′-pyridyl)indole (**6**)	Hpyin	Pd	**10**	97
1-Phenyl-1*H*-indazole (**7**)	H-1phiz	Pd	**11**	99
2-Phenyl-2*H*-indazole (**8**)	H-2phiz	Pd	**12**	98
Benzo[*h*]quinoline (**9**)	Hbq	Pd	**13**	92
3,5-Dimethyl-1-phenylpyrazole (**14**)	Hdmpzph	Pd	**15**	45

diamminedichloroplatinum(II) (cisplatin) inhibited cell division in *Escherichia coli*, and the subsequent establishment that a range of platinum complexes inhibited the development of sarcoma 180 and leukæmia L1210 in mice (2), led not only to the introduction of cisplatin as a clinically efficacious agent against testicular and ovarian cancers in 1978 (3), but also to the rekindling of interest in metal-based therapies (4, 5). While the clinical effectiveness of cisplatin against human malignancies, both as a single agent and in combination therapy, has had a major impact on cancer treatment, its therapeutic usefulness has been offset by a range of toxic side effects. The combination of good activity, dose-limiting side effects, and the disadvantage that some tumours acquire resistance to the drug, has stimulated research into second and third generation platinum drugs (6, 7).

While the anticancer activity of cisplatin has been attributed to the formation of bifunctional adducts with DNA, especially guanine–guanine crosslinks (6), pioneering work initiated by Lippard and co-workers (8) utilized another aspect of the chemistry of platinum(II) — its ability to act as a square-planar template to impart planarity on ligands such as 2,2′-bipyridine (bpy). While these complexes would have been predicted to have negligible anticancer activity based on observations gleaned from cisplatin and its analogues, the synthesis of planar, kinetically inert metal complexes provided a new mechanism of action namely, intercalation. In particular, Lippard used platinum(II) as a framework to force the aromatic rings of ligands such as bpy and 2,2′:6′,2″-terpyridine (terpy) into a coplanar arrangement, providing a flat aromatic surface capable of intercalation into DNA. However, despite extensive studies on the interactions of these materials with isolated nucleic acids or synthetic polynucleotides (9, 10), until recently there have been relatively few reports of the biological activity of square-planar platinum(II) or palladium(II) metallointercalators (11, 12).

The work initiated by Lippard and co-workers (8) provided the basis for the design of a range of complexes as potential new anticancer agents. Based on the metallointercalation model, a potential intercalator (13) should incorporate a kinetically inert metal with square-planar geometry, and it should fix aromatic, multidentate ligands in a coplanar array. Central to our strategy was the use of bidentate, nonlabile cyclometallated ligands to stabilize the complex and suppress dissociation of the intercalating aromatic ligand from the metal centre in vivo. Analogous mixed ligand coordination compounds with nitrogen donor ligands would provide contrasts to determine the importance of intercalator charge. Most metal complexes with anticancer activity are based on platinum, and to date analogous palladium complexes have shown marginal in vivo activity at best. While some palladium complexes have shown promising activity in vitro (12) or in animal models (6), they have not made a successful transition to clinical usefulness; the poor activity could be attributed to the higher reactivity of palladium species towards ligand displacement reactions. In this study drugs were designed where covalent binding to DNA is not expected and, as the coordination chemistries of platinum(II) and palladium(II) are similar, both metals should provide suitable frameworks upon which to build intercalating complexes. In a following paper we report the activity of a range of monofunctional cyclometallated platinum(II) and palladium(II) complexes (14).

Results and discussion

Cyclometallation reactions

Reactions of nitrogen donor ligands such as 1-phenylpyrazole (Hpzph) (**1**) (15) and 2-phenylpyridine (Hpyph) (**2**) (16) with palladium(II) salts to give cyclometallated complexes (referred to herein as cyclopalladated complexes) have been well-documented. While we have previously shown that the cyclopalladation of these ligands occurs readily providing products **3** and **4** in near-quantitative yields (Table 1), the analogous reaction of **2** with a platinum(II) salt (cycloplatination) requires more forcing conditions and gives only a moderate (65%) yield of the μ-chloro dimer **5** (17) (Fig. 1). Although the dimeric complexes are insoluble or very sparingly soluble in most solvents, they dissolve with reaction in dimethyl sulfoxide. An examination of the ^{1}H NMR spectra recorded in ($^2H_6$)dimethyl sulfoxide ($(CD_3)_2SO$) indicated the loss of one aryl proton, in agreement with the cyclometallated structures. An alternative confirmation that cyclometallation had taken place was obtained in many cases by addition of one drop of ($^2H_5$)pyridine (py-d_5) to a suspension of the dimers in $CDCl_3$; the complexes dissolved with reaction to give monomers where loss of one proton was evident and shielding of the proton ortho to the site of metallation was observed as a result of its proximity to the pyridine ligand (Fig. 1) (17).

Variation of the aromatic ligand could provide increased surface area for the planar intercalator possibly resulting in enhanced DNA binding, and it was shown that 1-(2′-pyridyl)indole (Hpyin) (**6**), 1-phenylindazole (H-1phiz) (**7**), 2-phenylindazole (H-2phiz) (**8**) (18), and benzo[*h*]quinoline (Hbq) (**9**) (19) could be cyclopalladated with $Na_2[PdCl_4]$ in near-quantitative yields giving μ-chloro dimers **10**–**13** on heating of the reaction mixtures for up to 24 h (Table 1,

Fig. 1. Cyclometallation reaction and product of bridge cleavage with py-d_5.

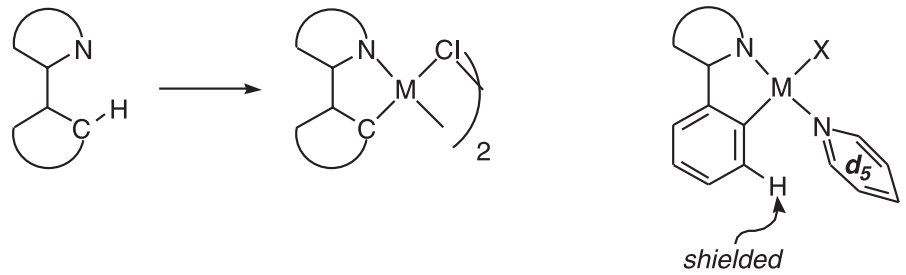


Fig. 2. Ligands and abbreviations with positions of metallation indicated.

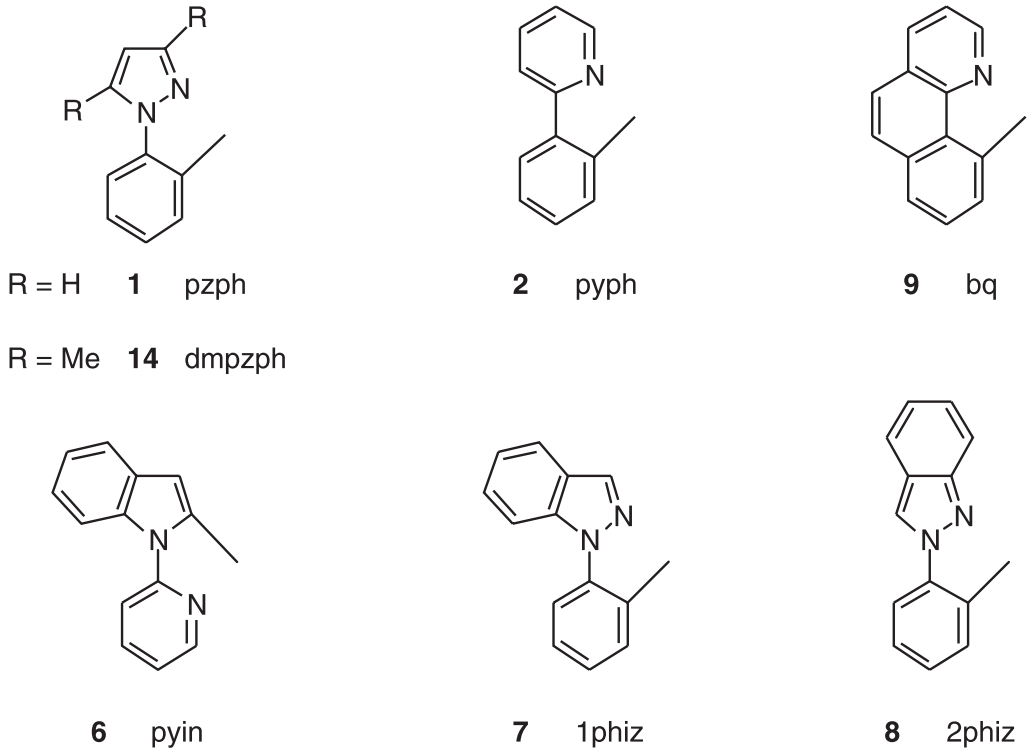


Fig. 2). Nonoyama and Nakajima (20) have recently reported the cyclometallation of **6** in moderate yield with palladium(II) acetate in boiling acetonitrile. Attempted cyclometallation of **6** with $Na_2[PdCl_4]$ at room temperature gave a mixture of the cyclometallated dimer **10** and a non-metallated coordination complex, as shown by a complex ^{1}H NMR spectrum in $(CD_3)_2SO$, where evidence for non-metallated ligand (indole H3 was noted as a doublet at δ 6.76 ppm, J = 3.5 Hz) was observed. A terminal ν(Pd–Cl) corresponding to the coordination complex was also observed at 343 cm^{-1} in the far-IR region, suggesting trans stereochemistry. No attempt was made to separate the mixture into its components. In several cases throughout this work, metathesis of the complexes with LiBr in acetone or dimethyl sulfoxide assisted interpretation of the far-IR spectra (17).

Cyclometallation of 3,5-dimethyl-1-phenylpyrazole (Hdmpzph) (**14**) using $K_2[PdCl_4]$ in boiling aqueous methanol gave a mixture of cyclometallated product **15** and coordination complex **16** (Fig. 3), at variance with earlier reports by Trofimenko and Vaughan (21) that cyclometallation was achieved quantitatively. Extended heating only increased the yield of the desired product **15** marginally. The products could be separated by extraction of coordination complex **16** into boiling dichloromethane. While the insoluble cyclometallated dimer **15** was contaminated with a small amount of palladium metal, it was of sufficient purity for further use. Analytically pure material could be obtained by precipitation of the dimer from a filtered solution of *N*,*N*-dimethylformamide (DMF) by the addition of methanol. Coordination complex **16** was identified as the cis stereoisomer by observation of two terminal ν(Pd–Cl) bands in the far-IR spectrum at 362 and 321 cm^{-1}; while approximately 10% of a second component was observed in the ^{1}H NMR spectrum, it was not determined whether this was due to a small amount of the trans isomer, or restricted rotation of the pyrazole ligands within the complex on the ^{1}H NMR timescale resulting in detection of syn and anti rotamers of complex **16**. All attempts to convert coordination complex **16** into cyclometallated dimer **15** were unsuccessful.

The ligand 1-methyl-3,5-diphenylpyrazole (**17**) is potentially able to form a five-membered chelate ring by metal-

Fig. 3. Products from cyclometallation of 3,5-dimethyl-1-phenylpyrazole (**14**).

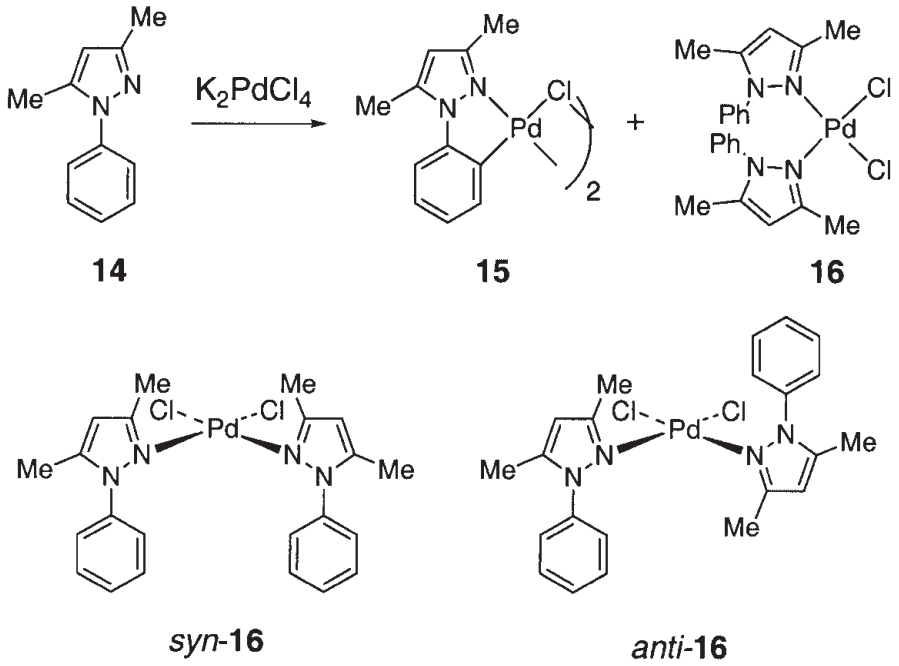
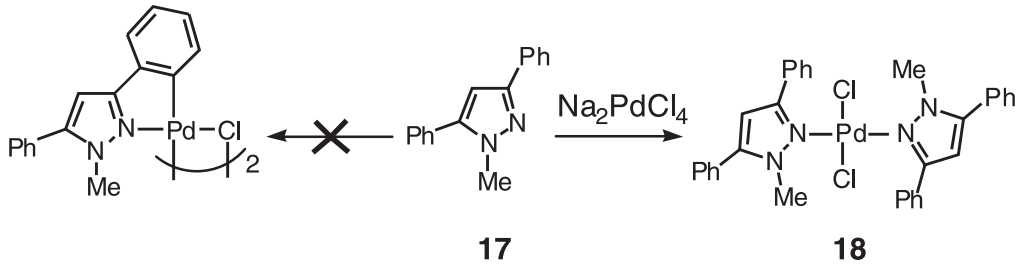


Fig. 4. Attempt to cyclometallate 1-methyl-3,5-diphenylpyrazole (**17**).



lation onto an ortho carbon of the 3-phenyl ring; this would provide an intercalator of comparable size but different geometry to other phenylpyrazoles (Fig. 4). Heating the ligand with $Na_2[PdCl_4]$ in methanol only gave the coordination complex $PdCl_2L_2$ (**18**) (22); a single ν(Pd–Cl) was observed in the far-IR spectrum at 349 cm^{-1} suggesting formation of the trans stereoisomer, and the ^1H NMR spectrum indicated that the product was a 15:1 mixture of two components, which Alonso et al. (22) have suggested results from restricted rotation about the Pd—N bonds. It is noteworthy that pyrazole **17** gives the trans stereoisomer **18**, whereas pyrazole **14** gives mainly the cis isomer **16**, despite both reaction mixtures being heated for comparable periods.

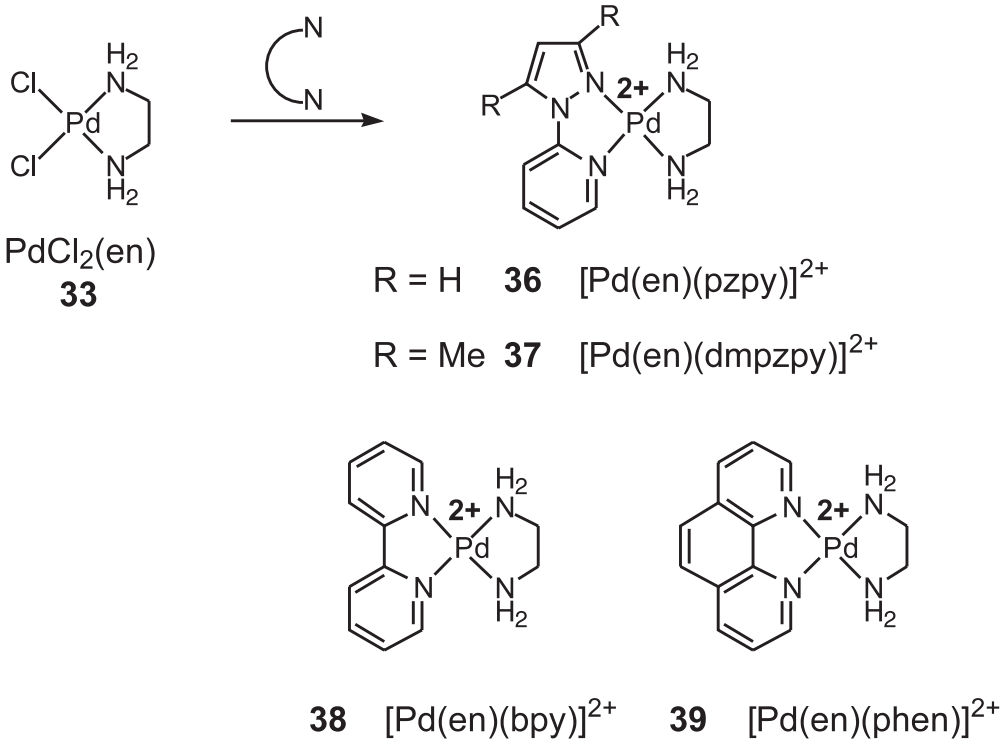
Preparation of cationic complexes

Addition of a bidentate diamine to the appropriate μ-chloro dimers gave the desired cationic complexes as water- and alcohol-soluble products (Table 2), which could be purified by precipitation of the complexes from alcoholic or aqueous alcoholic solution by the addition of ether. Diamine ligands chosen for study included 1,2-ethanediamine (en), 1,3-propanediamine (trimethylenediamine, tn), and *cis*- and *trans*-cyclohexanediamine (chxn). Biological and clinical studies of platinum complexes of chxn have been extensive (6, 7); in general, complexes of *trans*-chxn are more active than their *cis*-chxn analogues (6, 23), and complexes prepared from *R*,*R*-chxn are more active than those containing *S*,*S*-chxn (23). The oxalate-containing complex oxaliplatin ($Pt(C_2O_4)$(*R*,*R*-chxn)) in combination with 5-fluorouracil is emerging as a major therapy for colorectal cancer (24). In

Table 2. Cationic cyclometallated complexes.

Cyclometallated ligand	Metal	Diamine	Compound	Yield (%)
pzph	Pd	en	**19**	59
pzph	Pd	*cis*-chxn	**20**	65
pzph	Pd	*trans*-chxn	**21**	67
pyph	Pd	en	**22**	85
pyph	Pd	tn	**23**	79
pyph	Pd	*cis*-chxn	**24**	62
pyph	Pd	*trans*-chxn	**25**	80
pyph	Pt	en	**26**	75
dmpzph	Pd	en	**27**	70
dmpzph	Pd	tn	**28**	74
bq	Pd	en	**29**	69
pyin	Pd	en	**30**	67
1phiz	Pd	en	**31**	80
2phiz	Pd	en	**32**	78

Fig. 5. Mixed ligand complexes isolated as dichloride salts.



this study, complexes of *cis*- and racemic *trans*-chxn were prepared for biological testing.

Several of the complexes were isolated as hydrates; attempted drying at elevated temperature led to partial decomposition and drying at ambient temperature failed to remove the water of crystallization. In general, while the IR spectra of the complexes usually showed several absorptions of medium to strong intensity in the range 3000–3300 cm^{-1}, which could be attributed to the N–H stretching frequencies of the coordinated diamine ligands; absorptions at higher frequencies (3300–3500 cm^{-1}) were only observed for the hydrated complexes and were assigned to water of crystallization. Examination of the far-IR spectra of the complexes supported the assigned chelate structures as no strong absorptions between 240 and 360 cm^{-1}, which might be attributed to ν(M-Cl), were observed.

In the ^1H NMR spectra of the complexes, two distinct NH_2 signals were observed that can be attributed to a nonequivalence of the NH_2 groups as a result of the different trans carbon and nitrogen ligands. It is interesting that, for the platinum complex **26**, $^2J_{Pt,H}$ was only resolved in the signal for the downfield (6.15 ppm) NH_2 group; mere broadening of the other signal (5.44 ppm) was observed. The poly(methylene) bridges in the en and tn complexes were observed as broad signals. Coordination of chxn to a metal constrains the ligand to adopt specific conformations and, as a result, further resolution of the cyclohexyl amine protons was observed. The rigidity of the chelate ring constrains the protons on each nitrogen to lie in pseudoaxial and pseudoequatorial environments; as a result, up to four distinct exchangeable signals were observed for the chxn complexes.

The cyclometallation reaction gives complexes with anionic carbon σ-donor ligands and the overall charge on the resulting cationic complexes is therefore one less than the corresponding Pt(II) complexes $[Pt(en)(bpy)]^{2+}$ and $[Pt(en)(phen)]^{2+}$. A range of nonmetallated, cationic complexes analogous to these classical coordination compounds was also prepared to determine the relationship of intercalator charge to biological activity. Comparison of the activities of the palladium(II) complexes with those reported for the corresponding platinum(II) complexes could allow an assessment of the relationship between metal and activity.

Synthesis of the mixed complexes was achieved by reaction of $PdCl_2(en)$ **33** with the appropriate bidentate aromatic ligand (pyrazolylpyridines **34** and **35**, bpy, and phen) by an adaptation of the method of Watt and Carter (25); the mixed ligand complexes **36–39** (Fig. 5) were isolated in moderate to good yields. The alternative approach, where en was added to Pd complexes of the bidentate aromatic ligands, led to partial displacement of the ligand from the metal with $[Pd(en)_2]Cl_2$ being isolated instead. Some hydration of the mixed ligand complexes was evident from the microanalytical data, and this was confirmed by observation of ν(O-H) in the range 3300–3500 cm^{-1}, as described previously. The ^1H NMR spectra of the complexes were unremarkable; whereas two signals for the coordinated NH_2 groups were observed for the cyclometallated complexes, the symmetry or pseudosymmetry of the coordination complexes caused the NH_2 groups to be chemical-shift equivalent.

In vitro and in vivo testing

The complexes were subjected to an in vitro screen for growth inhibitory activity against the murine leukæmia cell line L1210. While these tests do not discriminate between cytotoxic and cytostatic activity, they provide valuable infor-

Table 3. Growth inhibition of L1210 cells in culture.

Complex	Aromatic ligand	Diamine	Metal	Charge	IC_{50} (μmol/L)
19	pzph	en	Pd	1	63
20	pzph	*cis*-chxn	Pd	1	24
21	pzph	*trans*-chxn	Pd	1	43
22	pyph	en	Pd	1	34
23	pyph	tn	Pd	1	18
24	pyph	*cis*-chxn	Pd	1	11.5
25	pyph	*trans*-chxn	Pd	1	20.5
26	pyph	en	Pt	1	300
27	dmpzph	en	Pd	1	11
28	dmpzph	tn	Pd	1	14
29	bq	en	Pd	1	16
30	pyin	en	Pd	1	14
31	1phiz	en	Pd	1	18
32	2phiz	en	Pd	1	17
36	pzpy	en	Pd	2	230
37	dmpzpy	en	Pd	2	>200
38	bpy	en	Pd	2	60
39	phen	en	Pd	2	13
	bpy	en	Pt	2	33 (11)
	phen	en	Pt	2	2 (11)

mation about whether the complexes can affect the rate at which cells grow and divide. The complexes (drugs) were dissolved in sterile water or ethanol (for the chxn complexes) and growth inhibition experiments were conducted for a 48 h period against L1210 cell cultures, providing drug concentrations that caused a 50% inhibition of cell growth (IC_{50}) (Table 3). For comparison, it should be noted that cisplatin has an IC_{50} of 0.9 μmol/L under similar conditions.

The cationic planar complexes reported in this study caused 50% growth inhibition over a wide range of concentrations. The cyclometallated complexes (formal charge 1+) generally were more active than the dipositive coordination analogues (compare **19** with **36**, **27** with **37**, and **22** with **38**), but it should be noted that the phenanthroline complex **39** had a similar IC_{50} value (13 μmol/L) to that of the benzo[*h*]quinolinyl complex **29** (16 μmol/L). Although a variation of the intercalator charge might influence the biological activity, especially in electrostatic stabilization of an initial drug–DNA complex, the relative stabilities of the organometallic drugs in the presence of a wide range of biological ligands could also explain the observed differences. As described above, in the preparation of the cationic complexes, addition of diamines to the cyclometallated μ-chloro dimers gave the desired products cleanly, whereas addition of en to palladium complexes of bidentate heterocyclic ligands resulted in at least partial displacement of the aromatic ligand. Thus, it is proposed that the presence of the palladium–carbon σ bond appears to increase the stability of the complexes, and therefore the cyclometallated complexes would be more likely to reach their biological target intact. It is possible that the increased stability of the phenanthroline complex with respect to displacement of the ligand from the metal centre meant that its stability was similar to that of the benzo[*h*]quinolinyl complex under biological conditions, hence its activity was likewise similar.

Table 4. Antitumour testing for complex **30** against P388 leukæmia.

Dose (mg/kg/injection)	%T/C
0 (control)	100
2	110
4	111
8	110
16	0
32	0
50 (5-fluorouracil: standard)	158

In this study, a single organoplatinum cyclometallated complex $[Pt(pyph)(en)]^+$ (**26**) was prepared and its biological activity was measured (IC_{50} = 300 μmol/L); somewhat surprisingly it was almost an order of magnitude less active than $[Pt(en)(bpy)]^{2+}$ (IC_{50} = 33 μmol/L) (11). This suggests that there might be no firm correlation between platinum and palladium metallointercalators as the analogous organopalladium complex **22** $[Pd(pyph)(en)]^+$ (IC_{50} = 34 μmol/L) was *more* active than the coordination analogue **38** $[Pd(en)(bpy)]^{2+}$ (IC_{50} = 60 μmol/L).

Increased biological activity is observed with increased substitution on the planar organometallic ligand. Substitution with methyl groups or fusion of an extra benzene ring onto the planar aromatic structure, led to lower IC_{50} values. The methyl substituents may provide a steric barrier to dislodgement of an intercalated drug, accounting for the increased activity. The position of fusion of an extra aromatic ring did not seem to affect the activity greatly (compare: 1phiz **31** (18 μmol/L) and 2phiz **32** (17 μmol/L) complexes). Additional aromatic rings give a larger surface area to intercalate between the base pairs in a drug–DNA complex, and the extra aromatic ring could lead to a more stable complex as a result of an enhanced π-orbital overlap. The weakest drug–DNA complexes would be expected for complexes such as the 2-(2-pyridyl)phenyl and 1-(pyrazolyl)phenyl complexes, which have only two coplanar aromatic rings, and stronger drug–DNA adducts would be expected for larger cationic complexes. However, it is noteworthy that McFadyen et al. (11) found that a series of structurally related, cationic complexes exerted their biological activities in different ways, and it is possible that structurally similar complexes here might likewise be inhibiting cell growth by different mechanisms.

Variation of the diamine ligand also resulted in a change in biological activity. Increased bulk (chxn vs. en or tn) tended to give more active complexes, and a consistent effect was noted for the chxn complexes, where lower IC_{50} values for the *cis*-chxn complexes **20** and **24** than their trans analogues **21** and **25** were measured.

One of the more active complexes (the 1-(2-pyridyl)indolyl complex **30**) was selected for further study. Potential antitumour activity against P388 leukæmia in mice was evaluated over a range of dose levels up to a maximum tolerated dose, with results expressed (%T/C) as a ratio of mean survival times of treated animals (T) relative to control animals (C); significant antitumour activity requires %T/C values greater than 125%, and values of 0% indicate that no treated animals survived the drug regime at these dose levels. Results obtained in this screening (Table 4) indicated that the

metallointercalator showed no significant antitumour activity in vivo at doses below toxic levels.

Experimental

General procedure

Elemental analyses were performed by the Microanalytical Service, School of Chemistry, University of New South Wales. IR spectra were measured with a PerkinElmer 180 Grating IR spectrophotometer with a far-IR option, and refer to paraffin mulls of solids, measured between KBr plates (4200–380 cm^{-1}) and between polyethylene discs (550–100 cm^{-1}). Only absorptions of strong to medium intensity are reported herein. ^1H NMR spectra were recorded at 90 MHz (Bruker WH90 spectrometer), 200 MHz (Bruker AC200 spectrometer), or 300 MHz (Bruker AM300 spectrometer). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (δ 0.00 ppm, referenced to $CHCl_3$ impurity in $CDCl_3$). Addition of one drop of py-d_5 to $CDCl_3$ suspensions of dimers **10**, **11**, **12**, **15**, and **18** converted the insoluble dimers into soluble monomeric complexes, which gave well-resolved spectra that integrated cleanly, providing excellent evidence for cyclometallation. Hbq (**9**), phen, bpy, *trans*-1,2-cyclohexanediamine (*trans*-chxn), en, and trimethylenediamine (tn) were obtained from the Aldrich Chemical Company and were recrystallized or distilled prior to use. *cis*-1,2-Cyclohexanediamine (*cis*-chxn) was separated from a mixture of isomers by the method of Saito and Kidani (26). 1-Phenylpyrazole (**1**) and **14** were prepared by the method of Finar and Hurlock (27). 1-(2′-Pyridyl)indole (**6**) was prepared by the method of Khan and Polya (28). 1-Phenyl-indazole (H-1phiz) (**7**) was prepared by the method of Pozharskii et al. (29), and **8** was prepared by the method of Cadogan and Mackie (30). 2-(1′-Pyrazolyl)pyridine (**34**) and 2-(3′,5′-dimethyl-1′-pyrazolyl)pyridine (**35**) were prepared by the general method of Khan and Pinto (31). Cyclopalladations of **1** to give **3** (15), of **2** to give **4** (16, 32), and of **9** to give **13** (19), and cycloplatination of **2** to give **5** (17), were carried out according to published procedures. Dichloro(1,2-ethanediamine-*N*,*N*′)palladium(II) ($PdCl_2$(en)) (**33**) was prepared by the method of McCormick et al. (33). Mixed ligand complex $[Pd(en)(phen)]Cl_2$ (**39**) (9) was prepared by the method described for complex **36** in the following section.

Preparations

Di-μ-chlorobis[1-(2′-pyridyl)indol-2-yl)-N′,C]dipalladium (10)

1-(2′-Pyridyl)indole (**6**) (1.50 g, 7.7 mmol) in methanol (20 mL) was added to a stirred solution of $Na_2[PdCl_4]$ (1.96 g, 6.7 mmol) in methanol (60 mL) under a nitrogen atmosphere. The mixture was heated under reflux for 24 h, and the resultant yellow precipitate was filtered off and washed successively with methanol and ether. A suspension of the crude product in dichloromethane (30 mL) was heated under reflux for 2 h, and then cooled to room temperature. The sparingly soluble solid was collected, washed with dichloromethane and then ether, and dried to give the μ-chloro dimer **10** as a yellow powder (2.16 g, 97%), mp 228–230 °C (dec.). A sample was recrystallized from DMF–methanol for microanalysis. IR (cm^{-1}): 1613, 1510, 1489, 1318, 1288, 1253, 1185, 745, 734, 418, 319 (Pd–Cl), 290, 240 (Pd–Cl). ^1H NMR (90 MHz, $CDCl_3$ – one drop of py-d_5) δ: 9.22 (dd, J = 5.9, 1.2 Hz, 1H, pyridyl H6), 7.91–7.07 (m, 6H, aryl), 6.89 (ddd, J = 7.4, 5.9, 1.4 Hz, 1H, pyridyl H5), 5.58 (d, J = 0.5 Hz, 1H, indolyl H3). Elemental anal. calcd. for $C_{26}H_{18}Cl_2N_4Pd_2$ (%): C 46.6, H 2.7, N 8.4; found: C 46.6, H 2.55, N 8.2.

Di-μ-chlorobis[2-(1′H-indazol-1′-yl)phenyl-N′,C]dipalladium (11)

The title compound **11** was prepared by a similar method to **10**, from **7** (0.62 g, 3.2 mmol) and $Na_2[PdCl_4]$ (0.75 g, 2.6 mmol), as a yellow powder (0.84 g, 99%), mp > 300 °C. A sample was recrystallized from DMF–methanol for microanalysis. IR (cm^{-1}): 1215, 1100, 836, 735, 722, 615, 421, 306 (Pd–Cl), 279, 230 (Pd–Cl). ^1H NMR (300 MHz, $CDCl_3$ – one drop of py-d_5) δ: 8.83 (s, 1H, indazolyl H3), 7.98 (dd, J = 8.7, 0.6 Hz, 1H, indazolyl H7), 7.79 (d, J = 8.1 Hz, 1H, aryl), 7.59 (ddd, J = 8.7, 7.1, 1.2 Hz, 1H, indazolyl H6), 7.54 (dd, J = 8.0, 1.0 Hz, 1H, aryl), 7.30 (t, J = 7.1 Hz, 1H, indazolyl H5), 7.17 (td, J = 7.7, 1.2 Hz, 1H, aryl), 6.80 (td, J = 7.6, 1.0 Hz, 1H, aryl), 6.33 (dd, J = 7.6, 1.1 Hz, 1H, phenyl H6). Elemental anal. calcd. for $C_{26}H_{18}Cl_2N_4Pd_2$ (%): C 46.6, H 2.7, N 8.4; found: C 46.5, H 2.5, N 8.45.

Di-μ-chlorobis[2-(2′H-indazol-2′-yl)phenyl-N′,C]dipalladium (12)

The title compound **12** was prepared by a similar method to **10**, from **8** (0.62 g, 3.2 mmol) and $Na_2[PdCl_4]$ (0.75 g, 2.6 mmol), as a yellow powder (0.83 g, 98%), mp > 300 °C (lit. value (18) mp > 300 °C). A sample was recrystallized from DMF–methanol for microanalysis. IR (cm^{-1}): 1627, 1519, 1489, 1352, 1071, 792, 784, 753, 745, 739, 437, 330 (Pd–Cl), 246 (Pd–Cl). ^1H NMR (300 MHz, $CDCl_3$ – one drop of py-d_5) δ: 9.01 (d, J = 8.9 Hz, 1H, indazolyl H7), 8.44 (s, 1H, indazolyl H3), 7.58 (d, J = 8.5 Hz, 1H, indazolyl H4), 7.34 (t, J = 7.4 Hz, 1H, aryl), 7.30 (dd, J = 7.9, 0.9 Hz, 1H, phenyl H3), 7.09 (t, J = 7.9 Hz, 1H, aryl), 7.03 (t, J = 7.5 Hz, 1H, aryl), 6.79 (t, J = 7.5 Hz, 1H, aryl), 6.08 (d, J = 7.6 Hz, 1H, phenyl H6). Elemental anal. calcd. for $C_{26}H_{18}Cl_2N_4Pd_2$ (%): C 46.6, H 2.7, N 8.4; found: C 46.5, H 2.7, N 8.4.

Di-μ-chlorobis[2-(3′,5′-dimethyl-1′-pyrazolyl)phenyl-N′,C]dipalladium (15)

A mixture of $K_2[PdCl_4]$ (1.50 g, 4.6 mmol) and **14** (1.00 g, 5.8 mmol) in aqueous dioxan (60 mL of 50% *v*/*v*) was stirred under a nitrogen atmosphere. A yellow precipitate separated and the mixture was stirred at room temperature for 18 h, and then heated under reflux for 36 h. The precipitate was filtered off, washed successively with methanol and ether, and dried. The product was suspended in dichloromethane (60 mL) and the suspension was heated under reflux for 6 h. The sparingly soluble solid was collected, washed with dichloromethane and ether, and dried to give the μ-chloro complex **15** as a yellow powder (0.65 g, 45% based on Pd), mp 337–339 °C (dec.). A sample was recrystallized from DMF–methanol for microanalysis. IR (cm^{-1}): 1552, 1443, 1438, 743, 738, 341 (Pd–Cl), 283, 265 (Pd–Cl). ^1H NMR (90 MHz, $(CD_3)_2SO$) δ: 7.64 (d br, J = 7.0 Hz, 1H, phenyl), 7.31–6.70 (m, 3H, phenyl), 6.21 (s, 1H,

pyrazolyl H4), 2.63 (s, 3H, Me), 2.33 (s, 3H, Me). Elemental anal. calcd. for $C_{22}H_{22}Cl_2N_4Pd_2$ (%): C 42.2, H 3.5, N 8.95; found: C 42.3, H 3.5, N 8.9.

The filtrate was evaporated to dryness and the residue was dissolved in dichloromethane and the solution filtered. On addition of hexane, dichlorobis(3,5-dimethyl-1-phenylpyrazole-N^2)palladium (**16**) separated as orange needles (0.98 g, 41% based on Pd), mp 315–317 °C (dec.) IR (cm^{-1}): 1595, 1555, 1503, 1418, 1399, 808, 764, 760, 696, 692, 565, 362 (Pd–Cl), 321 (Pd–Cl). ^{1}H NMR (90 MHz, $CDCl_3$) (major: minor components, 10:1) δ: 7.84–7.58 (m, 10H major + 10H minor, phenyl), 6.02 (s, 2H minor, H4′), 5.91 (s, 2H major, H4′), 3.05 (s, 6H minor, Me), 2.21 (s, 6H major, Me), 2.09 (s, 6H major, Me), 1.97 (s, 6H minor, Me). Elemental anal. calcd. for $C_{22}H_{24}Cl_2N_4Pd$ (%): C 50.6, H 4.6, N 10.7; found: C 50.7, H 4.6, N 10.7.

Dichlorobis(1-methyl-3,5-diphenylpyrazole-N^2)palladium (18)

1-Methyl-3,5-diphenylpyrazole (**17**) (0.22 g, 0.94 mmol) in methanol (10 mL) was added to a stirred solution of $Li_2[PdCl_4]$ (prepared from $PdCl_2$ (0.14 g, 0.79 mmol) and LiCl (0.20 g, 4.7 mmol)) in methanol (40 mL). A yellow solid separated, and the mixture was heated under reflux for 40 h under a nitrogen atmosphere. The product was filtered off and dissolved in dichloromethane, and the solution was filtered. On addition of hexane the palladium complex **18** separated as small yellow needles (0.19 g, 63%), mp 280–282 °C (dec.) (lit. value (22) mp 290–293 °C). IR (cm^{-1}): 3085, 1437, 1428, 1296, 838, 775, 766, 751, 703, 694, 681, 349 (Pd–Cl). ^{1}H NMR (300 MHz, $CDCl_3$) (major:minor components, 15:1) δ: 8.43–8.33 (m, 2H major + 2H minor, phenyl), 7.59–7.45 (m, 8H major + 8H minor, phenyl), 6.43 (s, 1H major + 1H minor, pyrazole H4), 4.80 (s, 3H minor, NMe), 4.36 (s, 3H major, NMe). Elemental anal. calcd. for $C_{32}H_{28}Cl_2N_4Pd$ (%): C 59.5, H 4.4, N 8.7; found: C 59.2, H 4.2, N 8.6.

(1,2-Ethanediamine-N,N′)[2-(1′-pyrazolyl)phenyl-N′,C]palladium(1+) chloride (19)

1,2-Ethanediamine (60 mg, 1.0 mmol) in chloroform (5 mL) was added to a stirred suspension of μ-chloro dimer **3** (0.233 g, 0.41 mmol) in chloroform (10 mL). A white powder slowly formed, and the mixture was stirred at room temperature for 12 h. The solid was filtered off, washed with chloroform, and dried. Recrystallization of the crude product from methanol–dichloromethane gave the title compound **19** as a white powder (0.166 g, 59%), mp 230 °C (dec.) (lit. value (15) mp 195 °C (dec.)). IR (cm^{-1}): 3295 (br), 3170 (br), 3105 (br), 1589, 1416, 1344, 1181, 1113, 1057, 1031, 755, 750, 612, 492, 406, 244, 192. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ: 8.77 (d, J = 2.7 Hz, 1H, pyrazolyl H5), 7.95 (d, J = 2.2 Hz, 1H, pyrazolyl H3), 7.56 (d, J = 7.5 Hz, 1H, phenyl), 7.20–7.12 (m, 2H, phenyl), 7.00 (td, J = 7.4, 1.0 Hz, 1H, phenyl), 6.70 (t, J = 2.5 Hz, 1H, pyrazolyl H4), 5.40 (s br exch, 2H, NH_2), 4.59 (s br exch, 2H, NH_2), 2.71 (s br, C 4H, H_2CH_2). Elemental anal. calcd. for $C_{11}H_{15}ClN_4Pd$ (%): C 38.3, H 4.4, N 16.2; found: C 38.2, H 4.4, N 16.2.

(cis-1,2-Cyclohexanediamine-N,N′)[2-(1′-pyrazolyl)phenyl-N′,C]palladium(1+) chloride (20)

Freshly distilled *cis*-chxn (10 drops) was added to a stirred suspension of **3** (0.201 g, 0.35 mmol) in methanol (20 mL) and water (10 mL). The reaction mixture was warmed for 10 min and then stirred at room temperature overnight. Evaporation of the solvents gave a pale yellow solid that was recrystallized from methanol–ether to give the title compound **20** as fine colourless needles (0.183 g, 65%), mp 276–278 °C (dec.). IR (cm^{-1}): 3200, 3170 (br), 3135, 3095, 1600, 1511, 1412, 1210, 1093, 1070, 1059, 750, 741, 737, 364. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ: 8.78 (d, J = 2.9 Hz, 1H, pyrazolyl H5), 7.93 (d, J = 2.2 Hz, 1H, pyrazolyl H3), 7.56 (dd, J = 7.8, 1.0 Hz, 1H, phenyl), 7.22 (dd, J = 7.5, 1.0 Hz, 1H, phenyl), 7.17 (td, J = 7.6, 1.0 Hz, 1H, phenyl), 7.00 (td, J = 7.4, 1.0 Hz, 1H, phenyl), 6.70 (t, J = 2.5 Hz, 1H, pyrazolyl H4), 5.59 (d br, J = 6 Hz, 1H, NH), 4.90 (dd br, J = 11, 7 Hz, 1H, NH), 4.82 (d br, J = 7 Hz, 1H, NH), 4.41 (dd br, J = 11, 7 Hz, 1H, NH), 3.04 (s br, 2H, C*H*NH_2), 1.78–1.57 (m, 6H, cyclohexyl), 1.32 (s br, 2H, cyclohexyl). Elemental anal. calcd. for $C_{15}H_{21}ClN_4Pd$ (%): C 45.1, H 5.3, N 14.0; found: C 44.9, H 5.4, N 14.0.

(trans-1,2-Cyclohexanediamine-N,N′)[2-(1′-pyrazolyl)phenyl-N′,C]palladium(1+) chloride (21)

Freshly distilled *trans*-chxn (15 drops) was added to a stirred, boiling suspension of μ-chloro dimer **3** (0.560 g, 0.95 mmol) in ethanol (70 mL) under a nitrogen atmosphere. The mixture was heated under reflux for 2 h, during which time the μ-chloro dimer dissolved. The resultant solution was filtered while hot, cooled to room temperature, and slowly diluted with ether to give the crude product. Recrystallization (twice) from ethanol–ether gave the title compound **21** as fine colourless needles (0.458 g, 67%), mp 287 to 288 °C (dec.). IR (cm^{-1}): 3195, 3150 (br), 3110, 3065, 1601, 1514, 1413, 1073, 1064, 1057, 755, 745, 738, 606, 363. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ: 8.78 (d, J = 2.7 Hz, 1H, pyrazolyl H5), 7.96 (d, J = 2.2 Hz, 1H, pyrazolyl H3), 7.57 (dd, J = 7.3, 1.2 Hz, 1H, phenyl), 7.19–7.15 (m, 2H, phenyl), 7.01 (t, J = 7.3 Hz, 1H, phenyl), 6.70 (t, J = 2.5 Hz, 1H, pyrazolyl H4), 5.44 (d exch, J = 7 Hz, 1H, NH), 5.17 (t exch, J = 10.5 Hz, 1H, NH), 4.95 (d exch, J = 7 Hz, 1H, NH), 4.18 (t exch, J = 10.5 Hz, 1H, NH), 2.43–2.31 (m, 2H, C*H*NH_2), 1.99 (t, J = 14.7 Hz, 2H, cyclohexyl), 1.63 (d br, J = 7.6 Hz, 2H, cyclohexyl), 1.32 (sextet br, J = 10.7 Hz, 2H, cyclohexyl), 1.10 (t br, J = 10 Hz, 2H, cyclohexyl). Elemental anal. calcd. for $C_{15}H_{21}ClN_4Pd$ (%): C 45.1, H 5.3, N 14.0; found: C 45.0, H 5.3, N 13.8.

(1,2-Ethanediamine-N,N′)[2-(2′-pyridyl)phenyl-N′,C]palladium(1+) chloride (22)

This compound was prepared by the same method as complex **21** from the μ-chloro dimer **4** (0.258 g, 0.44 mmol) and 1,2-ethanediamine (0.06 g, 1.0 mmol) in methanol (10 mL). Recrystallization of the crude product from methanol–ether gave the title compound **22** as fine, pale yellow needles (0.263 g, 85%), mp 245 to 246 °C (dec.). IR (cm^{-1}): 3260 (br), 3185 (br), 3115 (br), 3090 (br), 1605, 1578, 1438, 1160, 1058, 753, 744, 341. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ: 8.39 (d, J = 5.6 Hz, 1H, pyridyl H6), 8.10–8.06 (m, 2H, pyridyl), 7.74–7.72 (m, 1H, phenyl), 7.42–7.37 (m, 1H, aryl), 7.16–7.09 (m, 3H, aryl), 5.27 (s br exch, 2H, NH_2), 4.55 (s br exch, 2H, NH_2), 2.72 (m br, 4H, CH_2CH_2). Elemental anal. calcd. for $C_{13}H_{16}ClN_3Pd$ (%): C 43.8, H 4.5, N 11.8; found: C 43.9, H 4.6, N 11.8.

(1,3-Propanediamine*-N,N′*)[2-(2′-pyridyl)phenyl*-N′,C*]palladium(1+) chloride monohydrate (23)

This compound was prepared by the same method as complex **21** from **4** (0.217 g, 0.37 mmol) and 1,3-propanediamine (10 drops) in methanol (10 mL). Recrystallization of the crude product from methanol–ether gave the title compound **23** as pale yellow needles (0.224 g, 79%), mp 210 to 211 °C (dec.). IR (cm^{-1}): 3450 (br), 3365 (br), 3325 (br), 3240 (br), 3115 (br), 1607, 1582, 1433, 1191, 1150, 1037, 902, 755, 735. ^{1}H NMR (90 MHz, $(CD_3)_2SO$) δ: 8.41 (d, J = 5.6 Hz, 1H, pyridyl H6), 8.18–7.97 (m, 2H, aryl), 7.74–7.11 (m, 5H, aryl), 4.89 (s br exch, 2H, NH_2), 4.22 (s br exch, 2H, NH_2), 2.88–2.66 (m br, 4H, 2 × CH_2N), 1.76–1.55 (m, 2H, CH_2). Elemental anal. calcd. for $C_{14}H_{20}ClN_3OPd$ (%): C 43.3, H 5.2, N 10.8; found: C 43.3, H 5.1, N 10.8.

(*cis*-1,2-Cyclohexanediamine*-N,N′*)[2-(2′-pyridyl)phenyl*-N′,C*]palladium(1+) chloride (24)

This compound was prepared by the same method as complex **20** from **4** (0.357 g, 0.60 mmol) and *cis*-chxn (10 drops). Recrystallization of the crude product from ethanol–ether gave the title compound **24** as fine, pale yellow needles (0.308 g, 62%), mp 292 to 293 °C (dec.). IR (cm^{-1}): 3205 (br), 3175 (br), 3135, 3095 (br), 1602, 1578, 1434, 1093, 750, 730, 627, 407, 363. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ: 8.36 (d br, J = 4.9 Hz, 1H, pyridyl H6), 8.08 (s br, 2H, aryl), 7.73 (d br, J = 6.9 Hz, 1H, aryl), 7.44–7.36 (m, 1H, aryl), 7.18–7.08 (m, 3H, aryl), 5.42 (s br exch, 1H, NH), 4.72–4.61 (m br exch, 2H, 2 × NH), 4.23 (s br exch, 1H, NH), 3.02 (s br, 2H, C*H*NH_2), 1.82–1.57 (m, 6H, cyclohexyl), 1.42–1.26 (m br, 2H, cyclohexyl). Elemental anal. calcd. for $C_{17}H_{22}ClN_3Pd$ (%): C 49.8, H 5.4, N 10.2; found: C 49.7, H 5.6, N 10.35.

(*trans*-1,2-Cyclohexanediamine*-N,N′*)[2-(2′-pyridyl)phenyl*-N′,C*]palladium(1+) chloride (25)

This compound was prepared by the same method as complex **21** from **4** (0.560 g, 0.95 mmol) and *trans*-chxn (15 drops). Recrystallization of the crude product from ethanol–ether gave the title compound **25** as fine, pale yellow needles (0.622 g, 80%), mp 350–352 °C (dec.). IR (cm^{-1}): 3210, 3175, 3085 (br), 3050 (br), 1608, 1601, 1579, 1434, 752, 732, 627, 364. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ: 8.37 (d, J = 5.5 Hz, 1H, pyridyl H6), 8.10–8.07 (m, 2H, aryl), 7.75–7.72 (m, 1H, aryl), 7.44–7.37 (m, 1H, aryl), 7.17–7.11 (m, 3H, aryl), 5.25 (d exch, J = 6.2 Hz, 1H, NH), 5.04 (t exch, J = 10.6 Hz, 1H, NH), 4.79 (d exch, J = 6.9 Hz, 1H, NH), 4.14 (t exch, J = 10.2 Hz, 1H, NH), 2.43–2.28 (m, 2H, C*H*NH_2), 1.99 (t, J = 14.6 Hz, 2H, cyclohexyl), 1.63 (d br, J = 7.0 Hz, 2H, cyclohexyl), 1.30 (sextet br, J = 12.6 Hz, 2H, cyclohexyl), 1.11 (t br, J = 10.6 Hz, 2H, cyclohexyl). Elemental anal. calcd. for $C_{17}H_{22}ClN_3Pd$ (%): C 49.8, H 5.4, N 10.2; found: C 49.5, H 5.5, N 10.1.

(1,2-Ethanediamine*-N,N′*)[2-(2′-pyridyl)phenyl*-N′,C*]platinum(1+) chloride (26)

This compound was prepared by the same method as complex **21** from the μ-chloro dimer **5** (0.250 g, 0.32 mmol) and 1,2-ethanediamine (10 drops) in methanol (50 mL). Recrystallization of the crude product from methanol–ether gave the title compound **26** as fine yellow needles (0.216 g, 75%), mp 297 to 298 °C (dec.). IR (cm^{-1}): 3245 (br), 3170 (br), 3095 (br), 3060 (br), 1611, 1584, 1428, 1424, 1160, 1152, 1125, 1061, 754, 730, 414, 252. ^{1}H NMR (200 MHz, $(CD_3)_2SO$) δ: 8.69 (d with satellites, J = 5.6 Hz, $J_{Pt,H}$ = 27 Hz, 1H, pyridyl H6), 8.14–8.02 (m, 2H, aryl), 7.72–7.68 (m, 1H, aryl), 7.38–7.25 (m, 2H, aryl), 7.15–7.08 (m, 2H, aryl), 6.15 (s br with satellites, exch, $J_{Pt,H}$ = 46 Hz, 2H, NH_2), 5.44 (s br exch, 2H, NH_2), 2.67 (m br, 4H, CH_2CH_2). Elemental anal. calcd. for $C_{13}H_{16}ClN_3Pt$ (%): C 35.1, H 3.6, N 9.45; found: C 35.2, H 3.7, N 9.2.

[2-(3′,5′-Dimethyl-1′-pyrazolyl)phenyl*-N′,C*](1,2-ethanediamine*-N,N′*)palladium(1+) chloride monohydrate (27)

This compound was prepared by the same method as complex **21** from **15** (0.23 g, 0.37 mmol) and 1,2-ethanediamine (45 mg, 0.75 mmol) in methanol (10 mL). Recrystallization of the crude product from methanol–ether gave the title compound **27** as fine colourless needles (0.20 g, 70%), mp 250 °C (dec.). IR (cm^{-1}): 3420 (br), 3310, 3290, 3210 (br), 3160, 3120 (br), 3085 (br), 3030, 1554, 1440, 1424, 1184, 1164, 1136, 1102, 1083, 1061, 776, 484, 411, 238, 186. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ: 7.37 (dd, J = 7.3, 0.8 Hz, 1H, phenyl), 7.15 (td, J = 7.6, 1.3 Hz, 1H, phenyl), 7.07 (dd, J = 7.6, 1.3 Hz, 1H, phenyl), 6.97 (td, J = 7.4, 0.8 Hz, 1H, phenyl), 6.27 (s, 1H, pyrazolyl H4), 5.34 (s br exch, 2H, NH_2), 4.52 (s br exch, 2H, NH_2), 2.67 (s br, 4H, CH_2CH_2), 2.66 (s, 3H, 5′-Me), 2.22 (s, 3H, 3′-Me). Elemental anal. calcd. for $C_{13}H_{21}ClN_4OPd$ (%): C 39.9, H 5.4, N 14.3; found: C 39.5, H 5.5, N 14.2.

[2-(3′,5′-Dimethyl-1′-pyrazolyl)phenyl*-N′,C*](1,3-propanediamine*-N,N′*)palladium(1+) chloride hemihydrate (28)

This compound was prepared by the same method as complex **21** from **15** (0.158 g, 0.25 mmol) and 1,3-propanediamine (10 drops) in methanol (10 mL). Recrystallization of the crude product from ethanol–ether gave the title compound **28** as fine colourless needles (0.148 g, 74%), mp 201 to 202 °C (dec.). IR (cm^{-1}): 3440 (br), 3270 (br), 3240 (br), 3165, 3145, 3050, 1550, 1440, 1422, 1186, 1175, 1165, 1160, 1037, 1028, 927, 794, 746, 479. ^{1}H NMR (90 MHz, $(CD_3)_2SO$) δ: 7.42–7.06 (m, 4H, phenyl), 6.25 (s, 1H, pyrazolyl H4), 4.90 (s br exch, 2H, NH_2), 4.07 (s br exch, 2H, NH_2), 2.75 (s br, 4H, 2 × CH_2N), 2.65 (s, 3H, 5′-Me), 2.33 (s, 3H, 3′-Me), 1.78–1.58 (m, 2H, CH_2). Elemental anal. calcd. for $C_{14}H_{22}ClN_4O_{0.5}Pd$ (%): C 42.4, H 5.6, N 14.1; found: C 42.5, H 5.6, N 14.1.

(Benzo[*h*]quinolin-10-yl*-N′,C*)(1,2-ethanediamine*-N,N′*)palladium(1+) chloride (29)

This compound was prepared by the same method as complex **21** from the μ-chloro dimer **13** (0.157 g, 0.25 mmol) and 1,2-ethanediamine (5 drops) in methanol (10 mL). Recrystallization of the crude product from methanol–ether gave the title compound **29** as small yellow prisms (0.128 g, 69%), mp 215–220 °C (dec.). IR (cm^{-1}): 3205 (br), 3165 (br), 3120, 3080, 1405, 1058, 848, 714, 482. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ: 8.75 (dd, J = 5.2, 0.9 Hz, 1H, H2), 8.69 (d, J = 8.1 Hz, 1H, H4), 7.92 (d, J = 8.8 Hz, 1H, aryl), 7.84 (d, J = 8.8 Hz, 1H, aryl), 7.78 (dd, J = 8.1, 5.2 Hz, 1H, H3), 7.72 (d, J = 7.8 Hz, 1H, aryl), 7.50 (t, J = 7.5 Hz, 1H, H8), 7.36 (d, J = 7.0 Hz, 1H, aryl), 5.49 (s br exch, 2H, NH_2), 4.69 (s br exch, 2H, NH_2), 2.82–2.78 (m br, 4H,

CH_2CH_2). Elemental anal. calcd. for $C_{15}H_{16}ClN_3Pd$ (%): C 47.4, H 4.2, N 11.05; found: C 47.3, H 4.2, N 11.0.

(1,2-Ethanediamine-*N,N′*)(1-(2′-pyridyl)indol-2-yl-*N′,C*)palladium(1+) chloride dihydrate (30)

This compound was prepared by the same method as complex **21** from the μ-chloro dimer **10** (0.244 g, 0.36 mmol) and 1,2-ethanediamine (5 drops) in ethanol (15 mL) and water (4 mL). Recrystallization by slow addition of ether to a solution of the crude product in ethanol–water (90% *v*/*v*) gave the title compound **30** as cream-coloured needles (0.211 g, 67%), mp 223–225 °C (dec.). IR (cm^{-1}): 3460 (br), 3355 (br), 3295 (br), 3230 (br), 3140 (br), 1611, 1595, 1510, 1490, 1146, 1061, 777, 754, 731, 420. ^1H NMR (300 MHz, $(CD_3)_2SO$) δ: 8.31 (d, *J* = 5.6 Hz, 1H, pyridyl H6), 8.19–8.15 (m, 2H, aryl), 8.01–7.98 (m, 1H, aryl), 7.49–7.46 (m, 1H, aryl), 7.25–7.13 (m, 3H, aryl), 6.35 (s, 1H, indolyl H3), 5.46 (s br exch, 2H, NH_2), 4.80 (s br exch, 2H, NH_2), 2.78 (s br, 2H, CH_2), 2.70 (s br, 2H, CH_2). Elemental anal. calcd. for $C_{15}H_{21}ClN_4O_2Pd$ (%): C 41.8, H 4.9, N 13.0; found: C 41.8, H 4.6, N 13.05.

(1,2-Ethanediamine-*N,N′*)(2-(1′*H*-indazol-1′-yl)phenyl-*N′,C*)palladium(1+) chloride sesquihydrate (31)

This compound was prepared by the same method as complex **21** from the μ-chloro dimer **11** (0.127 g, 0.19 mmol) and 1,2-ethanediamine (10 drops) in methanol (10 mL). Recrystallization of the crude product from ethanol–ether gave the title compound **31** as colourless microcrystals (0.128 g, 80%), mp 242 °C (dec.). IR: A satisfactory paraffin mull could not be prepared. ^1H NMR (300 MHz, $(CD_3)_2SO$) δ: 8.76 (s, 1H, indazolyl H3), 8.41 (d, *J* = 8.6 Hz, 1H, aryl), 8.05 (d, *J* = 8.2 Hz, 1H, aryl), 7.90 (d, *J* = 7.7 Hz, 1H, aryl), 7.76–7.72 (m, 1H, aryl), 7.43 (t, *J* = 7.5 Hz, 1H, aryl), 7.26 (td, *J* = 7.7, 1.1 Hz, 1H, aryl), 7.20 (dd, *J* = 7.5, 1.1 Hz, 1H, aryl), 7.01 (t, *J* = 7.4 Hz, 1H, aryl), 5.49 (s br exch, 2H, NH_2), 4.72 (s br exch, 2H, NH_2), 2.77 (s br, 4H, CH_2CH_2). Elemental anal. calcd. for $C_{15}H_{20}ClN_4O_{1.5}Pd$ (%): C 42.7, H 4.8, N 13.3; found: C 42.65, H 4.6, N 13.4.

(1,2-Ethanediamine-*N,N′*)(2-(2′*H*-indazol-2′-yl)phenyl-*N′,C*)palladium(1+) chloride monohydrate (32)

This compound was prepared by the same method as complex **21** from the μ-chloro dimer **12** (0.120 g, 0.18 mmol) and 1,2-ethanediamine (10 drops) in methanol (10 mL). Recrystallization of the crude product from ethanol–ether gave the title compound **32** as fine, off-white needles (0.115 g, 78%), mp 271 to 272 °C (dec.). IR: 3460 (br), 3330 (br), 3245 (br), 3200, 3105 (br), 3070, 1929, 1520, 1444, 1282, 1056, 1050, 748, 729. ^1H NMR (300 MHz, $(CD_3)_2SO$) δ: 9.51 (s, 1H, indazolyl H3), 7.89 (d, *J* = 8.4 Hz, 1H, aryl), 7.87 (d, *J* = 7.7 Hz, 1H, aryl), 7.56–7.51 (m, 1H, aryl), 7.42 (d, *J* = 8.8 Hz, 1H, aryl), 7.30–7.25 (m, 2H, aryl), 7.22 (d, *J* = 7.2 Hz, 1H, aryl), 7.14 (t, *J* = 7.3 Hz, 1H, aryl), 5.54 (s br exch, 2H, NH_2), 5.00 (s br exch, 2H, NH_2), 2.75 (s br, 4H, CH_2CH_2). Elemental anal. calcd. for $C_{15}H_{19}ClN_4OPd$ (%): C 43.6, H 4.6, N 13.6; found: C 43.6, H 4.5, N 13.8.

(1,2-Ethanediamine-*N,N′*)[2-(1′-pyrazolyl)pyridine-*N,N′*]palladium(2+) dichloride dihydrate (36)

2-(1′-Pyrazolyl)pyridine (**34**) (0.37 g, 2.5 mmol) in methanol (40 mL) was added to a stirred suspension of $PdCl_2$(en) (0.60 g, 2.5 mmol) in water (50 mL) and the reaction mixture was heated under reflux for 24 h. During this time the orange solid dissolved to give a pale yellow solution. After being cooled to room temperature, the solution was filtered and the solvent removed. The crude product was dissolved in water (5 mL) and the solution was filtered and diluted with ethanol. On the addition of ether, the title compound **36** separated as fine, pale yellow needles (0.62 g, 59%), mp 328 °C (dec.). IR (cm^{-1}): 3420 (br), 3185, 3110, 3060, 1609, 1591, 1493, 1407, 1136, 1074, 1053, 784, 596. ^1H NMR (90 MHz, $(CD_3)_2SO$) δ: 8.62 (dd, *J* = 2.5, 0.5 Hz, 1H, pyrazolyl H5), 8.48 (dt, *J* = 4.9, 1.8 Hz, 1H, pyridyl H6), 8.03–7.94 (m, 2H, pyridyl H3 and H4), 7.83 (dd, *J* = 1.8, 0.5 Hz, 1H, pyrazolyl H3), 7.36 (ddd, *J* = 6.2, 4.9, 2.3 Hz, 1H, pyridyl H5), 6.58 (dd, *J* = 2.5, 1.8 Hz, 1H, pyrazolyl H4), 4.89 (s br exch, 4H, 2 × NH_2), 2.34 (s br, 4H, CH_2CH_2). Elemental anal. calcd. for $C_{10}H_{19}Cl_2N_5O_2Pd$ (%): C 28.7, H 4.6, N 16.7; found: C 28.5, H 4.4, N 17.1.

Heating a mixture of 1,2-ethanediamine (2.5 mL of a 0.03 g/mL solution in methanol, 1.2 mmol) and dichloro[2-(1′-pyrazolyl)pyridine-*N*,*N*′]palladium (34) (0.21 g, 0.7 mmol) in methanol (20 mL) and water (5 mL) gave, on addition of ether, a white solid that was identified as bis(1,2-ethanediamine-*N*,*N*′)palladium(2+) dichloride (35) (0.129 g, 69%), mp 245 °C (dec.). IR (cm^{-1}): 3195, 3150, 3060, 3020, 1606, 1599, 1318, 1274, 1136, 1126, 1058, 468, 370, 290. ^1H NMR (90 MHz, D_2O) δ: 2.75 (s br, 8H, CH_2CH_2).

[2-(3′,5′-Dimethyl-1′-pyrazolyl)pyridine-*N,N′*](1,2-ethanediamine-*N,N′*)palladium(2+) dichloride dihydrate (37)

This compound was prepared from 2-(3′,5′-dimethyl-1′-pyrazolyl)pyridine (**35**) (0.100 g, 0.58 mmol) in methanol (10 mL) and $PdCl_2$(en) (0.139 g, 0.59 mmol) in water (10 mL) as described for compound **36**. The crude product was dissolved in methanol–water (85% *v*/*v*) and ether was added slowly to give the title compound **37** as fine, pale yellow needles (0.182 g, 71%); mp 301 to 302 °C (dec.). IR (cm^{-1}): 3420 (br), 3370 (br), 3210, 3125, 3060, 1610, 1560, 1491, 1420, 1139, 1067, 1064, 773, 590. ^1H NMR (300 MHz, $(CD_3)_2SO$) δ: 8.44 (ddd, *J* = 4.9, 1.5, 0.8 Hz, 1H, pyridyl H6), 7.93 (ddd, *J* = 8.5, 7.1, 1.5 Hz, 1H, pyridyl H4), 7.79 (dd, *J* = 8.5, 0.9 Hz, 1H, pyridyl H3), 7.30 (ddd, *J* = 7.1, 4.9, 0.9 Hz, 1H, pyridyl H5), 6.11 (s, 1H, pyrazolyl H4), 4.89 (s br exch, 4H, 2 × NH_2), 2.57 (s, 3H, 5′-Me), 2.32 (s br, 4H, CH_2CH_2), 2.20 (s, 3H, 3′-Me). Elemental anal. calcd. for $C_{12}H_{23}Cl_2N_5O_2Pd$ (%): C 32.3, H 5.2, N 15.7; found: C 32.35, H 4.95, N 15.8.

(2,2′-Bipyridine-*N,N′*)(1,2-ethanediamine-*N,N′*)palladium(2+) dichloride sesquihydrate (38)

This compound was prepared from 2,2′-bipyridine (0.228 g, 1.5 mmol) in methanol (15 mL) and $PdCl_2$(en) (0.283 g, 1.2 mmol) in water (5 mL) as described for compound **36**. The crude product was dissolved in methanol and dichloromethane was added slowly to give the title compound **38** as small, pale yellow needles (0.388 g, 77%); mp > 270 °C (dec.). A sample was recrystallized from ethanol (95%) for microanalysis. IR (cm^{-1}): 3420 (br), 3150 (br), 3115, 3080, 3050, 3020, 1607, 1601, 1560, 1473, 1172, 770, 722, 580. ^1H NMR (300 MHz, $(CD_3)_2SO$) δ: 8.70 (d, *J* = 8.1 Hz, 2H, 2 × pyridyl H3), 8.53 (d, *J* = 5.6 Hz, 2H, 2 × pyridyl H6), 8.45 (t, *J* = 7.8 Hz, 2H, 2 × pyridyl H4), 7.89

(t, J = 6.6 Hz, 2H, 2 × pyridyl H5), 6.47 (s br exch, 4H, 2 × NH_2), 2.78 (s br, 4H, CH_2CH_2). Elemental anal. calcd. for $C_{12}H_{19}Cl_2N_4O_{1.5}Pd$ (%): C 34.3, H 4.55, N 13.3; found: C 34.25, H 4.3, N 13.3.

Growth inhibition of murine leukæmia L1210 cells in vitro (continuous exposure)

This procedure was adapted from the method of McFadyen et al. (11). Mouse lymphoid leukæmia L1210 cells in in vitro culture were grown on Minimum Essential Medium (Flow Laboratories, USA) supplemented with 15% foetal calf serum, glutamine (2 mmol/L), and gentamycin (2 mg/100 mL). Cells were incubated without agitation in a 5% O_2 – 10% CO_2 atmosphere at 37 °C and, under these conditions, the average doubling time was approximately 12 h. The drugs were dissolved in the appropriate sterile solvent (water or ethanol) and serial dilutions of the stock solution were made using the same solvent. Aliquots of the drug solutions (40 μL) were dispensed into 2 mL of medium containing approximately 5×10^4 cells/mL. Control cultures received the same volume of sterile solvent, and assays were conducted in duplicate for each drug concentration. After incubation at 37 °C for 48 h, cells were counted using a Coulter particle counter (Model ZM, Coulter Electronics Ltd., Luton, UK) with the lower (10) and upper (99) thresholds set to include all particles above 8 μm in diameter (the normal L1210 cell diameter is approximately 11 μm). Cell growth as a percentage of control cultures was plotted against drug concentration and the IC_{50} concentration (the concentration of drug required to effect 50% growth inhibition) was determined. Assays were repeated at least once and IC_{50} values quoted are the means of these determinations.

Antitumour testing was carried out by the method described by McFadyen et al. (11).

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