of an equal volume of water gave an off-white precipitate which was collected by filtration. Crystallization from ethanol yielded 64 mg (72%) of 2.

Enzyme Isolation and Assay. The thymidine kinases from HSV1- and HSV2-infected HeLa cells were isolated by the use of a thymidine 3′-(*p*-aminophenylphosphate) affinity column as described previously.[5] The enzymes were assayed with limiting concentrations of [^{3}H]thymidine as described.[2] Stock solutions of inhibitors in dimethyl sulfoxide were diluted into assay mixtures; control assays contained an identical concentration of the compound solvent.

Calculations. Derivation of equations and statistical analyses were done on a IBM PC using a BASIC program written by one of the authors (J.G.).

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DNA-Directed Alkylating Agents. 5. Acridinecarboxamide Derivatives of (1,2-Diaminoethane)dichloroplatinum(II)

Ho H. Lee,† Brian D. Palmer,† Bruce C. Baguley,† Michael Chin,† W. David McFadyen,‡ Geoffrey Wickham,§ Deborah Thorsbourne-Palmer,§ Laurence P. G. Wakelin,∥ and William A. Denny*,†

Cancer Research Laboratory, University of Auckland School of Medicine, Private Bag, Auckland, New Zealand, School of Science and Mathematics Education, Institute of Education, University of Melbourne, Parkville, Australia 3052, and Department of Medicinal Chemistry, Victorian College of Pharmacy, 381 Royal Parade, Parkville, Australia 3052.
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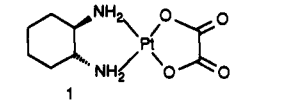
A series of acridine-2- and -4-carboxamide-linked analogues of $PtenCl_2$ has been prepared and evaluated for biological activity against several tumor cell lines in vitro and in vivo. The platinum complexes were generally more cytotoxic than the corresponding ligands against wild-type P388 leukemia cells in vitro, with acridine-4-carboxamide complexes being the more effective. In contrast to cisplatin and $PtenCl_2$, the complexes were equally active in vitro against both wild-type and cisplatin-resistant P388 lines. The 4-carboxamide complexes showed high levels of in vivo activity (ILS >100%) against wild-type P388 using a single-dose protocol, and one compound was also significantly active in vivo in a cisplatin-resistant line, against which cisplatin and $PtenCl_2$ are inactive.

One focus of work on developing analogues of cisplatin (*cis*-diamminedichloroplatinum(II)) is to improve activity against cell lines which are (for a variety of reasons) resistant to cisplatin itself. Novel examples are the DACH compounds (e.g. 1-OHP; 1)[1] and the bis-cisplatin derivatives (e.g. 2).[2] Members of these classes show almost equal cytotoxicity in cisplatin-sensitive and -resistant lines, probably (in the case of the DACH compounds) by providing DNA adducts of enhanced lethality.[3]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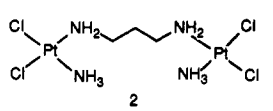
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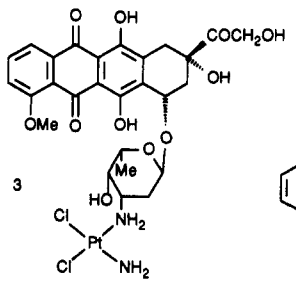
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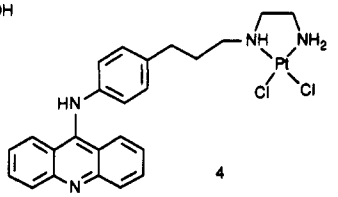
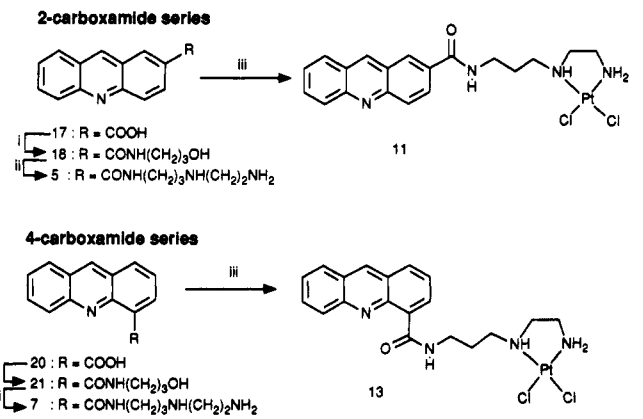

4

Another way of providing platinum–DNA adducts of high cytotoxicity is to "target" the platinum moiety to DNA by attachment to a suitable carrier ligand. This general concept has been discussed in detail,[4-6] and demonstrable effects with targeted aniline mustards include altered regiospecificity and sequence-specificity of DNA alkylation,[6,7] together with increased cytotoxicity and improved in vivo antitumor activity compared with the

Scheme I[a]



[a] (i) 1,1′-Carbonyldiimidazole/DMF/50 °C; $NH_2(CH_2)_nOH$; (ii) MsCl/py; excess $NH_2(CH_2)_2NH_2$; (iii) aqueous Na_2CO_3; K_2PtCl_4/20 °C/20 h; aqueous KCl.

† Cancer Research Laboratory.
‡ University of Melbourne.
§ Victorian College of Pharmacy.
∥ Present address: St. Luke's Cancer Research Fund, Highfield Rd., Rathgar, Dublin 6, Ireland.

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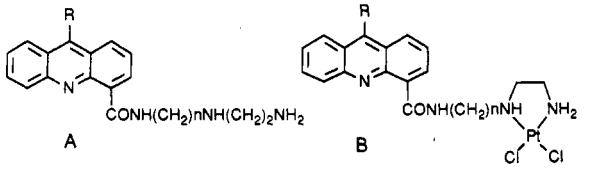
Table I. Physicochemical and Biological Properties of (Acridinecarboxamide)-Pt(II) Complexes and Ligands



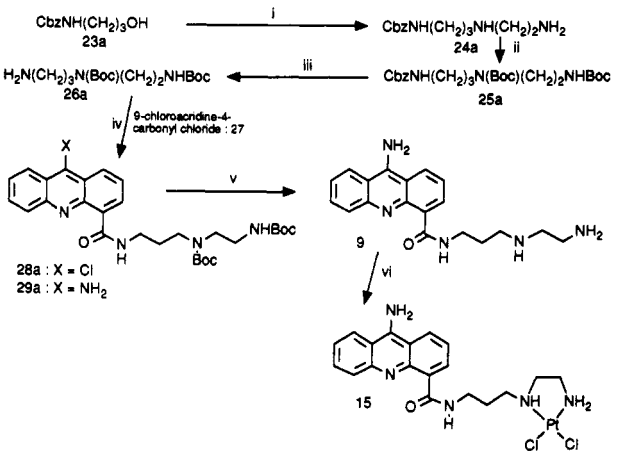
no.	form	R	side chain	n	mp (°C)	formula	analyses	growth inhibiton: IC_{50} (μM)[a] P388/W	P388/AMSA	P33/CP	P388/W in vivo OD[b]	P388/W in vivo ILS[c]	P388/CP in vivo OD[b]	P388/CP in vivo ILS[c]
5	A	H	2	3	235–237	$C_{19}H_{22}N_4O{\cdot}3HCl$	C,H,N,Cl	3.8	–	4.9	100	NA[d]		
6	A	H	2	6	244–246	$C_{22}H_{28}N_4O{\cdot}3HCl{\cdot}^1/_2H_2O$	C,H,N,Cl	3.6	–	3.8	100	NA		
7	A	H	4	3	234–236	$C_{19}H_{22}N_4O{\cdot}3HClH_2O$	C,H,N	0.74	1.6	0.59	30	64		
8	A	H	4	6	198–200	$C_{22}H_{28}N_4O{\cdot}3HCl{\cdot}^1/_2H_2O$	C,H,N,Cl	0.51	1.1	0.35	20	23		
9	A	NH_2	4	3	282–284	$C_{19}H_{23}N_5O{\cdot}3HCl$	C,H,N,Cl	3.1	0.87	2.6	45	45		
10	A	NH_2	4	6	252 dec	$C_{22}H_{29}N_5O{\cdot}3HCl{\cdot}8H_2O$	C,H,N,Cl	5.2	–	2.3	65	NA		
11	B	H	2	3	261–263	$C_{19}H_{22}Cl_2N_4OPt{\cdot}H_2O$	C,H,N,Pt	5.9	–	9.1	65	32		
12	B	H	2	6	266–269	$C_{22}H_{29}Cl_2N_4OPt{\cdot}H_2O$	C,H,N,Pt	0.3	–	0.4	45	NA		
13	B	H	4	3	240 dec	$C_{19}H_{22}Cl_2N_4OPt$	C,H,N,Pt	0.06	0.43	0.4	45	103	45	25
14	B	H	4	6	206 dec	$C_{22}H_{29}Cl_2N_4OPt$	C,H,N	0.05	0.50	0.04	30	105	30	24
15	B	NH_2	4	3	291 dec	$C_{19}H_{23}N_5Cl_2OPt{\cdot}3H_2O$	C,H,N	0.56	0.58	1.1	20	86	20	47
16	B	NH_2	4	6	283 dec	$C_{22}H_{29}Cl_2N_5OPt{\cdot}HCl{\cdot}2H_2O$	C,H,N,Cl	0.67	–	0.70	150	38		
PtenCl$_2$								0.30	–	1.03	13.3	70	13.3	NA
cisplatin								1.2	5.5	5.3	5.3	120	5.5	NA

[a] IC_{50}: the concentration of drug (μM) to inhibit cell growth in the various cell lines by 50%, measured in 96-well cultures as described in ref 23. All measurements were done in triplicate, with a typical standard error of 10%. [b] OD: optimal dose of drug in milligrams/kilogram, administered intraperitoneally as a solution in 0.1 mL of 30% v/v ethanol/water (ligands) or 0.1 mL of 1:1:2 DMA/glycerol/water (Pt complexes), on days 1, 5, and 9 after intraperitoneal inoculation of 10^6 P388/W leukemia cells. [c] ILS: percentage increase in life span of treated animals (when treated at the optimal dose), compared with tumor-bearing control animals. Values are the mean of at least two determinations. Average life span of control animals was 11 days. [d] Compound inactive (ILS < 20) at all dose levels.

corresponding untargeted alkylators.[5] Similar targeting of platinum species might also serve to minimize exposure to inactivating agents such as thiols, desirable since overexpression of thiols and thiol-transferring enzymes is a recognized mechanism of cellular resistance to cisplatin.[8,9]

Examples of putative DNA-targeted platinum drugs which show improved selectivity with respect to cisplatin-resistant cell lines include the doxorubicin analogue **3**[10,11] and the 9-anilinoacridine compound **4**.[12,13] Although these compounds did show improved differential toxicity between wild-type and platinum-resistant cell lines, the differentials were no greater than those shown by the unplatinated ligands themselves, and it was not possible to decide the role of the 9-anilinoacridine carrier moiety. The complexes showed only minimal in vivo activity, possibly because they were very insoluble.[12] In the present paper we report studies on a further series of platinum compounds (**11–16**) linked to a more water-soluble acridinecarboxamide DNA-targeting carrier.

Scheme II[a]



[a] (i) MsCl/py/20 °C/1 h; excess $NH_2(CH_2)_2NH_2$; (ii) $(t\text{-}BuO)_2CO$; (iii) $H_2/Pd/C$; (iv) phenol/NH_3/120 °C; (v) concentrated HCl/MeOH/CH_2Cl_2; (vi) aqueous Na_2CO_3; K_2PtCl_4/20 °C/20 h; aqueous KCl.

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Chemistry

Synthesis of the acridinecarboxamide ligands required for complexes 11–14 (Table I) was straightforward, and is shown in Scheme I. The acridine-2- and -4-carboxylic acids 17 and 20 were coupled selectively with 3-aminopropanol via the imidazolides,[14] and the resulting alcohols 18 and 21 were activated with methanesulfonyl chloride and treated with excess 1,2-diaminoethane to give the desired diamines 5 and 7. Similar reactions using 6-aminohexanol provided the diamines 6 and 8 (Table I).

However, synthesis of the 9-aminoacridinecarboxamide ligands 15 and 16 required prior construction of the side chain, as shown in Scheme II. 3-Aminopropanol was N-protected with benzyloxycarbonyl groups, and the alcohol group of the resulting compound (23) was activated with methanesulfonyl chloride and reacted with excess 1,2-diaminoethane. The newly-formed amine groups of the triamine derivative 24 was then protected with Boc groups to give the differentially-protected triamine derivative 25. Selective deblocking of the N-Cbz group gave the unstable amine 26, which was reacted selectively with 9-chloroacridine-4-carbonyl chloride (27)[15] to give the 9-chloro compound 28. This was converted in situ to the 9-phenoxy compound and then treated with dry ammonia at 120 °C to give the 9-aminoacridine 9, the precursor ligand for the desired platinum complexes (15). An identical sequence beginning with 6-aminohexanol gave the ligand 10, precursor of the platinum complex 16 (Table I).

The ligands 5–10 reacted readily with K_2PtCl_4 in the dark at 25 °C to form the corresponding platinum complexes 11–16. The coordination state of the platinum in the complexes was confirmed by ^{195}Pt NMR spectroscopy, with all complexes exhibiting a single signal in the range δ −2338 to −2344 ppm. This is similar to the ^{195}Pt resonance positions in the 9-anilinoacridine Pt complexes reported earlier (e.g., 4: δ −2344 ppm) and in $PtenCl_2$ itself (δ −2312 ppm).[12] For the 9-aminoacridinecarboxamide complexes 15 and 16 this distinguishes between alternative coordination modes via the 9-amino group, since the ^{195}Pt resonances of such compounds occur at lower fields (e.g. for *cis*-[$Pt(NH_3)_2(N^9$-9-aminoacridine)Cl](NO_3), δ −2206 ppm).[16]

Results and Discussion

Since previous studies[12,13] have shown that 9-anilinoacridine-linked platinum complexes (e.g., 4) are very insoluble, the compounds studied here use more water-soluble carriers. Compounds 11 and 12 place the complex off the long axis of an acridinecarboxamide intercalator (position 2), while the corresponding compounds 13 and 14 have this appended off the short axis (position 4). Compounds 15 and 16 use the more tightly DNA-binding and even more water-soluble 9-aminoacridinecarboxamide chromophore.

DNA Binding. The interaction of selected complexes with DNA has been studied in several ways. The kinetics of the alkylation of DNA by 12 and 14 were similar to those of $PtenCl_2$ itself ($t_{1/2}$ = 5.5, 3.7, and 2.1 h, respectively).[13] However, they unwound closed circular supercoiled DNA as efficiently as 9-aminoacridine, and formed interstrand DNA cross-links more effectively than $PtenCl_2$ as determined using nondenaturing agarose gels and linearized pBR 322 plasmid DNA[13] (12–14 achieve complete cross-linking at a drug/base-pair ratio of 0.013, compared with a ratio of 0.038 for $PtenCl_2$). The sequence specificity of adduct formation of selected compounds has been studied using the *taq* DNA polymerase linear amplification method,[17] and shown to be subtly different from that for $PtenCl_2$.

In Vitro Cytotoxicity. IC_{50}s for continuous exposure (72 h) were measured in 96-well cultures as described previously,[18] and are given in Table I. The cell lines used were the drug-sensitive wild-type P388 (P388/W), a subline (P388/AMSA) resistant to the topoisomerase II agent amsacrine by its expression of a topoisomerase II isozyme,[19] and a subline (P388/CP) which shows ca. 5-fold resistance to cisplatin (Table I). The unplatinated acridine-2-carboxamide carrier ligands 5 and 6 had similar IC_{50} values (3–5 μM) in both the wild-type and CP-resistant lines, while the isomeric 4-carboxamide ligands 7 and 8 were considerably more cytotoxic (0.4–0.7 μM). Selected ligands also evaluated against P388/AMSA (Table I) were found to be up to 10-fold less effective, ratios typical for DNA topoisomerase II inhibitors,[20] and suggest that the cytotoxicity of the ligands is mediated, at least to some extent, by inhibition of topoisomerase II. With the exception of compound 11, the platinum complexes 11–16 were considerably more cytotoxic (on average 10-fold) than the corresponding ligands, but their comparative activity in the different cell lines was similar. Compounds 13 and 14 showed significantly higher cytotoxicity than $PtenCl_2$ itself against P388/W, but all the complexes were equally active against the wild-type and CP-resistant lines.

In Vivo Activity. The 2-carboxamide ligands 5 and 6 were not active against P388/W in vivo, but the 4-carboxamide ligands 7–10 did show moderate activity, with the C3 analogues being more active than the C6 analogues in each case. This agrees with the known SAR for acridinecarboxamides.[21] While the complexes showed no dramatic increase in potency compared with the ligands, they did show higher activity. The preferred side-chain orientation was clearly at the 4-position, with the nature of the chromophore (9-H or 9-amino) being less critical.

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The 4-carboxamide complexes **13** and **14** showed low in vivo activity (ILS 25%) against P388/CP (both cisplatin and $PtenCl_2$ are inactive), but the 9-amino derivative **15** was considerably more effective, with an ILS of 47%.

Conclusions

Previous work[17,22] has shown that the attachment of platinum moieties (specifically $PtenCl_2$) to DNA-intercalating ligands does alter the nature of the interaction of the metal complex with DNA, although there is little effect on the rates of covalent adduct formation. The acridinecarboxamide complexes evaluated here showed little increase in either in vitro cytotoxicity or in vivo activity against P388/W cells compared with $PtenCl_2$, but did have improved activity in the P388/CP platinum-resistant line. One compound, the 9-aminoacridine-4-carboxamide complex **15**, also showed significant in vivo activity against the cisplatin-resistant line.

Experimental Section

Where elemental analyses are indicated by the symbols of the elements, results were within ±0.4% of theoretical values. Melting points were determined on an Electrothermal apparatus using the supplied stem-corrected thermometer and are as read. ^1H NMR spectra were measured on a Bruker AM-400 spectrometer. ^{195}Pt NMR spectra were determined at 86.0 MHz for solutions (ca. 1.5×10^{-2} M) in DMF, with an external D_2O lock. Spectra were collected by using a 10-μs pulse width and acquisition times from 0.123 to 0.4 s, with spectral widths from 11 to 33 kHz. Shifts are referenced to Na_2PtCl_6 in H_2O as 0 ppm. Platinum determinations were carried out on a Perkin-Elmer 3030 atomic absorption spectrometer.

Acridine Ligands: Preparation of *N*-[3-[(2-Aminoethyl)amino]propyl]acridine-4-carboxamide (7). Example of General Method of Scheme I. Acridine-4-carboxylic acid (**20**) (2.39 g, 10.1 mmol) was suspended in dry DMF (20 mL), 1,1'-carbonyldiimidazole (2.5 g, 15 mmol) was added, and the mixture was warmed to 50 °C until all solids dissolved and gas evolution ceased. The mixture was cooled to 20 °C, 3-aminopropanol (2 g, 30 mmol) was added, and the solution was kept at 20 °C for 45 min. Water was then added, and the solvents were removed under reduced pressure. The residue was partitioned between ice-cold 1 N Na_2CO_3 and EtOAc, and the organic layer was washed with water, dried, and evaporated to give crude *N*-(3-hydroxypropyl)acridine-4-carboxamide (**21**) (2.75 g, 98%), pure by TLC and suitable for direct use. A sample was recrystallized from EtOAc/petroleum ether as needles: mp 120–122 °C; ^1H NMR ($CDCl_3$) δ 9.05 (br s, 1 H, ArH-3), 8.93 (s, 1 H, ArH-9), 8.25–7.60 (m, 6 H, acridine protons), 3.86 (t, J = 5.8 Hz, 2 H, CH_2OH), 3.79 (t, J = 5.8 Hz, 2 H, $NHCH_2$), 1.95 (quintet, J_{app} = 5.8 Hz, $CH_2CH_2CH_2$). Anal. ($C_{17}H_{16}N_2O_2$) C, H, N.

The above crude alcohol **21** (2.7 g, 9.6 mmol) was dissolved in dry pyridine (50 mL) and treated with methanesulfonyl chloride (0.85 mL, 11 mmol) at 20 °C for 30 min. Water (1 mL) was then added, followed after 5 min by ethane-1,2-diamine (25 mL). The mixture was stirred for 20 h, and volatiles were removed under reduced pressure. The residue was partitioned between CH_2Cl_2 and dilute Na_2CO_3, and the organic layer was washed with water, dried, and evaporated. The residue was dissolved in 1 N HCl and extracted with CH_2Cl_2, and the aqueous layer was then evaporated to dryness under reduced pressure to give a yellow solid. Crystallization from aqueous MeOH gave the trihydrochloride salt of *N*-[3-[(2-aminoethyl)amino]propyl]acridine-4-carboxamide (**7**) (2.9 g, 70% yield): mp 234–236 °C dec; ^1H NMR (CD_3SOCD_3) δ 9.5–7.75 (m, 8 H, acridine protons), 3.78 (q, J = 6 Hz [converted to t after D_2O exch], 2 H, $CONHCH_2$), 3.28 (br s, 4 H, CH_2NHCH_2), 3.15 (br s, 2 H, CH_2NH_2), 2.15 (m, 2 H, $CH_2CH_2CH_2$). Anal. in Table I.

Similar treatment of acridine-4-carboxylic acid (**20**) with 6-aminohexanol gave *N*-(6-hydroxyhexyl)acridine-4-carboxamide (**22**): mp ($EtOAc/CH_2Cl_2$) 112–113 °C; ^1H NMR ($CDCl_3$) δ 9.00 (d, J = 5.4 Hz, 1 H, ArH-3), 8.90 (s, 1 H, ArH-9), 8.20–7.55 (m, 6 H, acridine protons), 3.71 (t, J = 6.9 Hz, 2 H, CH_2OH), 3.65 (t, J = 6.4 Hz, 2 H, $NHCH_2$), 1.9–1.5 (m, 10 H, [8 H after D_2O exchange] $-(CH_2)_4-$, NH and OH). Anal. ($C_{20}H_{22}N_2O_2$) C, H, N. Reaction of this with methanesulfonyl chloride followed by ethane-1,2-diamine as above gave the trihydrochloride of triamine **8**: mp 198–200 °C (dec); ^1H NMR (CD_3SOCD_3) δ 9.5–7.7 (m, 8 H, acridine H), 3.60 (q, J = 6.1 Hz, 2 H, became t after D_2O exch, $CONHCH_2$), 3.23 (br s, 4 H, CH_2NHCH_2), 2.97 (br s, 2 H, CH_2NH_2), 1.8–1.4 (m, 8 H, $-(CH_2)_4-$). Anal. in Table I.

Similar treatment of acridine-2-carboxylic acid (**17**) with 3-aminopropanol gave *N*-(3-hydroxypropyl)acridine-2-carboxamide (**18**): mp (EtOAc) 150–152 °C; ^1H NMR (CD_3SOCD_3) δ 9.26 (s, 1 H, ArH-1), 8.68 (s, 1 H, ArH-9), 8.3–7.7 (m, 6 H, acridine protons), 3.56 (t, J = 6.6 Hz, 2 H, CH_2OH), 3.42 (t, J = 6.6 Hz, 2 H, $NHCH_2$), 1.80 (quintet, J_{app} = 6.6 Hz, 2 H, $CH_2CH_2CH_2$). Anal. ($C_{17}H_{16}N_2O_2$) C, H, N. This in turn yielded the trihydrochloride of triamine (**5**): mp 235–237 °C dec; ^1H NMR (CD_3SOCD_3) δ 9.82 (s, 1 H, H-9), 9.00 (s, 1 H, H-1), 8.60–7.85 (m, 6 H, acridine H), 3.50 (q, J = 6.7 Hz, became t after D_2O exch, $CONHCH_2$), 3.25 (br s, 4 H, became 2 × t, J = 5.4 and 5.4 Hz after D_2O exch, $NHCH_2CH_2NH_2$), 3.10 (br s, 2 H, became a t, J = 7.4 Hz after D_2O exch, CH_2NHCH_2), 2.02 (m, 2 H, $CH_2CH_2CH_2$). Anal. in Table I.

Similar treatment of acridine-2-carboxylic acid (**17**) with 6-aminohexanol gave *N*-(6-hydroxyhexyl)acridine-2-carboxamide (**19**) [mp (EtOAc/MeOH) 150.5–151.5 °C; ^1H NMR (CD_3SOCD_3) δ 9.25 (s, 1 H, ArH-1), 8.70 (s, 1 H, ArH-9), 8.4–7.6 (m, 6 H, acridine protons), 3.40 (m, 4 H, $NHCH_2$ and CH_2OH), 1.7–1.2 (m, 8 H, $-(CH_2)_4-$). Anal. ($C_{20}H_{22}N_2O_2$) C, H, N.], which in turn gave the trihydrochloride of triamine (**6**) [mp (aqueous MeOH) 244–246 °C (dec); ^1H NMR (CD_3SOCD_3) δ 9.83 (s, 1 H, H-1), 8.93 (s, 1 H, H-9), 8.55–7.85 (m, 6 H, acridine protons), 3.37 (q, J = 6.5 Hz, 2 H, became t on D_2O exch, $CONHCH_2$), 3.20 (br s, 4 H, CH_2NHCH_2), 1.75–1.35 (m, 8 H, $-(CH_2)_4-$). Anal. in Table I.]

9-Aminoacridine Ligands: Preparation of *N*-[3-[(2-aminoethyl)amino]propyl]-9-aminoacridine-4-carboxamide Trihydrochloride (9). Example of the General Method. Benzyl chloroformate (22.9 g, 19.1 mL, 0.134 mol) was added dropwise to a stirred homogeneous mixture of 3-amino-1-propanol (10.0 g, 0.134 mol) and $NaHCO_3$ (16.9 g, 0.201 mol) in H_2O (250 mL) at 20 °C, and the reaction was stirred for a further 1.5 h at 20 °C. Extraction with CH_2Cl_2 and usual workup gave 3-[(benzyloxycarbonyl)amino]-1-propanol (**23a**) (23.9 g, 86%) as a colorless solid: mp (EtOAc/petroleum ether) 49–50 °C; ^1H NMR ($CDCl_3$) δ 7.36 (m, 5 H, C_6H_5), 5.12 (s, 2 H, $C_6H_5CH_2$), 5.06 (br s, 1 H, exch with D_2O, NH), 3.67 (q, J = 6.0 Hz, 2 H, collapsing to t after D_2O, CH_2OH), 3.36 (q, J = 6.0 Hz, 2 H, collapsing to t after D_2O, $NHCH_2$), 2.58 (t, J = 6.0 Hz, exch with D_2O, OH), 1.71 (quintet, J = 6.0 Hz, 2 H, $CH_2CH_2CH_2$). Anal. ($C_{17}H_{15}NO_3$) C, H, N.

A solution of the above alcohol **23a** (21.7 g, 0.104 mol) in pyridine (90 mL) was treated at 15–20 °C with methanesulfonyl chloride (12.5 mL, 1.65 mol) for 1 h. The solution was then cooled to 0 °C and water (2.4 mL) was added, followed by 1,2-diaminoethane (90 mL). After stirring at 0 °C for 2 h and then at 20 °C for 20 h, most of the solvents were removed under reduced pressure at ca. 40 °C, and the residue was partitioned between CH_2Cl_2 and aqueous 0.5 N Na_2CO_3. The organic extract was worked up as usual to give the crude triamine **24a** (22.5 g, 86%) as a dark green oil, which was used immediately: ^1H NMR ($CDCl_3/D_2O$) δ 7.30 (m, 5 H, C_6H_5), 5.10 (s, 2 H, $C_6H_5CH_2$), 3.27 (t, J = 6.4 Hz, 2 H, $CONHCH_2$), 2.75 (t, J = 5.8 Hz, 2 H, $NHCH_2CH_2NH_2$), 2.66 (t, J = 6.4 Hz, 2 H, $CH_2CH_2CH_2NHCH_2$), 2.62 (t, J = 5.8 Hz, 2 H, CH_2NH_2), 1.66 (quintet, J = 6.4 Hz, 2 H, $CH_2CH_2CH_2$).

A solution of di-*tert*-butyl dicarbonate (24.4 g, 0.112 mol) was added dropwise to a solution of triamine **24a** (25.5 g, 0.102 mol)

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in dry CH_2Cl_2 (200 mL) over 70 min, and the mixture was stirred for a further 24 h at 20 °C. The mixture was then partitioned between CH_2Cl_2 and aqueous 0.5 N Na_2CO_3, and the organic layer was worked up as usual. The resulting solid was chromatographed on SiO_2, elution with EtOAc/petroleum ether (1:5) affording pure *N,N'*-bis(*tert*-butoxycarbonyl)-*N*-[3'-[(benzoxycarbonyl)amino]-propyl]ethane-1,2-diamine (**25a**) (16.0 g, 35%) as a pale yellow solid: mp (EtOAc/petroleum ether) 62–64 °C; ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 5 H, C_6H_5), 5.10 (s, 2 H, $C_6H_5CH_2$), 3.24 (m, 8 H, $CH_2CH_2CH_2$ and CH_2CH_2), 1.73 (m, 2 H, $CH_2CH_2CH_2$), 1.46 (s, 9 H, 3 × CH_3), 1.42 (s, 9 H, 3 × CH_3). Anal. ($C_{23}H_{37}N_3O_6$) C, H, N.

The above protected triamine **25a** (5.00 g, 11.1 mmol) was dissolved in MeOH/EtOAc (1:1) and hydrogenolyzed over 5% Pd/C to give the crude amine **26a**, which was immediately dissolved in a mixture of dry CH_2Cl_2 (70 mL) and Et_3N (15 mL) and added dropwise to solid 9-chloroacridine-4-carbonyl chloride (**27**) (3.94 g, 14.3 mmol, freshly prepared from 9-oxoacridan-4-carboxylic acid).[15] The reaction was stirred at 20 °C for 2 h and was then diluted with CH_2Cl_2 (200 mL) and washed with aqueous 0.5 N Na_2CO_3 (200 mL). The CH_2Cl_2 layer was separated and worked up as usual to give a residue which was azeotroped with dry toluene (2 × 50 mL) to give the crude 9-chloro amide **28a** as a brown oil. This was dissolved in dry benzene (60 mL), phenol (24 g) was added, and the mixture was heated in an open flask until the internal temperature reached 90 °C. It was then cooled to 40 °C, and anhydrous NH_3 gas was bubbled through the mixture, which was brought to 120 °C and held there for 10 min. The cooled mixture was then partitioned between CH_2Cl_2 and 2 N NaOH, and the organic layer was worked up as usual. The residue was chromatographed on SiO_2 and eluted with EtOAc/MeOH (10:1) to afford *N*-[3-[*N,N'*-bis(*tert*-butoxycarbonyl)-ethylenediamino]propyl]-9-aminoacridine-4-carboxamide (**29a**) (3.84 g, 64%) as a bright yellow solid: mp (CH_2Cl_2/MeOH) 207–209 °C; ^{1}H NMR ($CDCl_3$) δ 12.60 (br s, 1 H, exch with D_2O, N*H*), 9.00–7.02 (m, 7 H, aromatic protons), 6.00 (br s, 3 H, exch with D_2O, N*H*), 3.67 (q, *J* = 6.0 Hz, 2 H, collapsing to t after D_2O, $NHCH_2CH_2CH_2$), 3.58–3.24 (m, 6 H, $CH_2NCH_2CH_2NH$), 2.04 (quintet, *J* = 6.0 Hz, 2 H, $CH_2CH_2CH_2$), 1.54 and 1.43 (2 s, 18 H, 6 × CH_3). Anal. ($C_{29}H_{39}N_5O_5$) C, H, N.

This compound (3.67 g, 6.83 mmol) was dissolved in a mixture of CH_2Cl_2/MeOH (10:1, 110 mL) and concentrated HCl (5 mL) and the reaction was stirred vigorously at 20 °C for 30 min. Solvents were removed under reduced pressure at 45 °C, and the residue was taken up in 1 N HCl and washed with CH_2Cl_2 (3 × 30 mL). Evaporation of the aqueous layer left a bright yellow solid, which was recrystallized from CH_2Cl_2/MeOH to afford the desired *N*-[3-[(2-aminoethyl)amino]propyl]-9-aminoacridine-4-carboxamide trihydrochloride (**9**) (2.81 g, 92%): mp 282–284 °C dec; ^{1}H NMR (CD_3SOCD_3) δ 13.80 (br s, 1 H, exch with D_2O, *H*Cl), 10.45 (br s, 2 H, exch with D_2O, 2 *H*Cl), 9.70 (br s, 3 H, exch with D_2O, N*H*), 9.10–7.60 (m, 7 H, aromatic protons), 8.45 (br s, 3 H, exch with D_2O, N*H*), 3.52 (q, *J* = 7.0 Hz, 2 H, collapsing to t after D_2O, $CONHCH_2CH_2CH_2$), 3.23 (br s, $W_{1/2}$ = 5 Hz, 4 H, $NHCH_2CH_2NH_2$), 3.09 (t, *J* = 7.0 Hz, 2 H, $CONHCH_2CH_2CH_2$), 2.05 (quintet, *J* = 7.0 Hz, 2 H, $CH_2CH_2CH_2$). Anal. in Table I.

Similar treatment of 6-aminohexanol and collection of the precipitated product by filtration gave 6-[(benzyloxycarbonyl)-amino]-1-hexanol (**23b**) in 60% yield: mp (EtOAc/petroleum ether) 79–81 °C; ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 5 H, C_6H_5), 5.13 (br s, 1 H, exchangeable with D_2O, N*H*), 4.77 (br s, 1 H, exch with D_2O, O*H*), 3.63 (q, *J* = 6.4 Hz, 2 H, collapsing to t after D_2O, CH_2OH), 3.20 (q, *J* = 6.6 Hz, 2 H, collapsing to t after D_2O, $NHCH_2$), 1.62–1.32 (m, 8 H, 4 × CH_2). Anal. ($C_{14}H_{21}NO_3$) C, H, N.

This was then treated as above to give the protected triamine **24b**, which was reacted with di-*tert*-butyl dicarbonate as above to afford *N,N'*-bis(*tert*-butoxycarbonyl)-*N*-[6-[(benzyloxy-carbonyl)amino]hexyl]ethane-1,2-diamine (**25b**) in 91% yield as a pale yellow viscous oil: ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 5 H, C_6H_5), 5.10 (s, 2 H, $C_6H_5CH_2$), 3.22 (m, 8 H, $CH_2(CH_2)CH_2$; CH_2CH_2), 1.56–1.24 (m, 8 H, $CH_2(CH_2)_4CH_2$), 1.46 and 1.44 (2 s, 18 H, 6 × CH_3).

The fully-protected triamine **11** was then selectively deprotected and reacted with **27** as above via the intermediates **26b** and **28b** to give *N*-[6-[*N,N'*-bis(*tert*-butoxycarbonyl)amino]hexyl]-9-aminoacridine-4-carboxamide (**29b**) in an overall yield of 41%: mp (CH_2Cl_2/MeOH) 198–200 °C; ^{1}H NMR ($CDCl_3$) δ 8.94–7.50 (m, 7 H, aromatic protons), 3.65 (br q, *J* = 6 Hz, 2 H, collapsing to t after D_2O, $CONHCH_2(CH_2)_5$), 3.23 (m, 6 H, $CONH(CH_2)_5CH_2NCH_2CH_2NH$), 1.86–1.20 (m, 8 H, $CH_2(CH_2)_4CH_2$), 1.44 (s, 18 H, 6 × CH_3). Anal. ($C_{32}H_{45}N_5O_5 \cdot 0.5H_2O$) C, H, N.

Finally, deprotection of **29b** as above gave a 96% yield of *N*-[6-[(2-aminoethyl)amino]hexyl]-9-aminoacridine-4-carboxamide trihydrochloride (**10**), after recrystallization from MeOH/CH_2Cl_2: mp 251 °C dec; ^{1}H NMR (CD_3SOCD_3) δ 13.90 (s, 1 H, exch with D_2O, *H*Cl), 10.50 (s, 1 H, exch with D_2O, *H*Cl), 10.40 (s, 1 H, exch with D_2O, *H*Cl), 9.55 (s, 2 H, exch with D_2O, N*H*), 9.45 (s, 1 H, exch with D_2O, N*H*), 9.05–7.60 (m, 7 H, aromatic protons), 8.40 (s, 3 H, exch with D_2O, N*H*), 3.44 (t, *J* = 7 Hz, 2 H, $CONHCH_2$), 3.21 (m, 4 H, $NHCH_2CH_2NH_2$), 3.00 (t, *J* = 7.6 Hz, 2 H, $CH_2NH(CH_2)_2NH_2$), 1.66 (m, 4 H, $NHCH_2CH_2(CH_2)_2CH_2CH_2NH$), 1.43 (m, 4 H, $NH(CH_2)_2(CH_2)_2(CH_2)_2NH$). Anal. in Table I.

Typical Platination Procedure: Synthesis of 12. The trihydrochloride **6** (48 mg, 0.1 mmol) was dissolved in water (2 mL), and 2 N aqueous Na_2CO_3 was added until the solution was just basic. A solution of K_2PtCl_4 (42 mg, 0.1 mmol) in water (1 mL) was added, and the mixture was stirred at 20 °C in the dark for 25 h. A solution of 5% aqueous KCl (10 mL) was then added, and the mixture was stirred for a further 90 min. The resulting pale yellow precipitate was collected, washed several times with deionized water, and dried to give pure [*N*-[6-[(2-aminoethyl)-amino)hexyl]acridine-2-carboxamide]dichloroplatinum(II) (**12**) (54 mg, 86% yield): mp 266–269 °C; ^{195}Pt NMR (DMF) δ −2339. Anal. ($C_{22}H_{29}Cl_2N_4OPt$) in Table I.

Similar reactions gave **11** [73%; mp 261–263 °C dec; ^{195}Pt NMR (DMF) δ −2344. Anal. in Table I.], **13** [72%; mp 240–243 °C dec; ^{195}Pt NMR (DMF) δ −2339. Anal. in Table I.], and **14** [88%; mp 206 °C dec; ^{195}Pt NMR (DMF) δ −2339. Anal. in Table I.].

A similar procedure carried out using **9**, but with the pH of the ligand solution adjusted to 8–9 before mixing, afforded [*N*-[3-[(2-aminoethyl)amino]propyl]-9-aminoacridine-4-carboxamide]dichloroplatinum(II) (**15**) (90%): mp 291 °C dec; ^{195}Pt NMR (DMF) δ −2339. Anal. in Table I. Likewise, ligand **10** gave complex **16** (87%) as the monohydrochloride: mp 283 °C dec; ^{195}Pt NMR (DMF) δ −2338. Anal. in Table I.

The platinum complexes were formulated for biological testing by suspending the free bases in dimethylacetamide and adding an equal volume of glycerol to give a homogeneous solution. Water was then added to make up the required concentration.

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