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Click Chelators for Platinum-Based Anticancer Drugs

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Triazoles from "click chemistry" are convenient ligands for the formation of platinum complexes bearing combined triazole–amine or triazole–carboxylate moieties. Striking differences in the chelation modes are observed between the two series. One of the triazole–amine platinum complexes exhibits selective cytotoxicity against breast cancer cells lines.

Introduction

Platinum anticancer drugs have enjoyed a long history since the discovery of *cisplatin* by Rosenberg et al. in the 1960s.[1] Most of the well-known platinum based anticancer compounds share the general formula *cis*-$[PtX_2(NH_2R)_2]$ or *cis*-$[PtX_2(NHR_2)_2]$, in which R is an organic fragment and X is a leaving group such as chloride. Some other antitumour Pt^{II} compounds have appeared recently, as exemplified by the trinuclear (**1**),[2] binuclear (**2**)[3] and mononuclear (**3**)[4] complexes (Figure 1).

Flexible polynuclear compounds **1** were found to chelate at the N7 site of DNA guanines in long-range inter- and intrastrand crosslinks.[5] Binuclear azoles **2** (pyrazole and triazole) are able to create intrastrand crosslinks that cause a minor kink in the DNA double helix.[6] AMD473 (**3**) is a sterically hindered Pt^{II} complex designed to overcome the resistance caused by thiols such as gluthatione and metallothionein[4c,4d] that entered clinical trials in 1997.

With the exception of the seminal work of Reedijk et al., who reported metal–peptide and metal–oligonucleotide solid-phase synthesis,[7] the production of biologically active platinum complexes has remained within the confines of inorganic and organometallic chemistry. Modern approaches for drug discovery − such as parallel and combinatorial syntheses − have not yet been applied to transition-metal complexes.

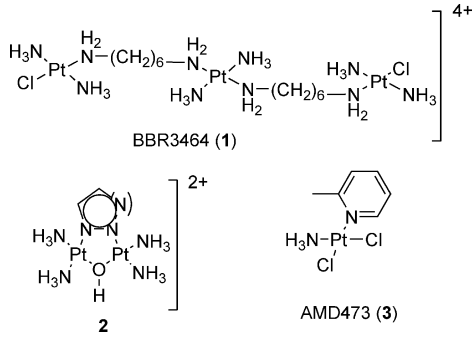

Figure 1. Recently developed anticancer complexes **1**–**3**.

The recent emergence of "click chemistry" as a new paradigm for organic synthesis invokes only simple, high-yielding and easily workable transformations. It has facilitated an extraordinary expansion in the number of molecules available for medicinal chemistry.[8] Among these click reactions, the copper-catalysed Huisgen [2+3] cycloaddition has received unrivalled attention and has furnished an impressive array of new biologically relevant compounds.[8c,8d] The technique has been used to facilitate in situ target-guided selection of lead drug compounds.[9] Other recent developments include the formation of palladium ligands for Suzuki–Miyaura coupling, Tsuji–Trost allylation or amination of aryl chlorides.[10] In general, triazole has proven itself useful for metal binding and it is not surprising that multidentate N,N and N,P ligands find use in metal-based catalysis.[11] A very recent publication relates the behaviour of 1,4-

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disubstituted 1,2,3-triazoles as chelators of rhenium and technetium for the radiolabelling of biomolecules.[12]

Prompted by the interest in azole structures **2**, we decided to investigate the copper-catalysed Huisgen [2+3] cycloaddition reaction with the intention to generate a small library of 1,2,3-triazole ligands for platinum complexes. It is of note that most of the synthesis of Pt^{II} N,N or N,O complexes of biological interest are conducted in water. Indeed, most of the criteria relevant to click chemistry apply to the preparation of such compounds: complex formation is modular and has a large scope, whereas reactions take place in ecologically benign solvents such as water and generate inoffensive byproducts. Moreover, product isolation is usually simple (e.g., by filtration), processes are insensitive to oxygen and yields are usually good. Thus, we consider that not only triazole formation but also metal complexation fall within the confines of click chemistry.

The targeted structures, depicted in Figure 2, are Pt^{II} chelates that coordinate through one triazole nitrogen atom and one exocyclic functionality (amine or carboxylate). The ligands can be classified into two categories: "regular" click ligands, in which the C4 substituent chain participates with N3 for chelation, and the isomeric counterparts, "inverse" click ligands, in which the chelation involves N2 and the substituent chain at N1. The regular and inverse ligands are expected to form five- and six-membered complexes, respectively.

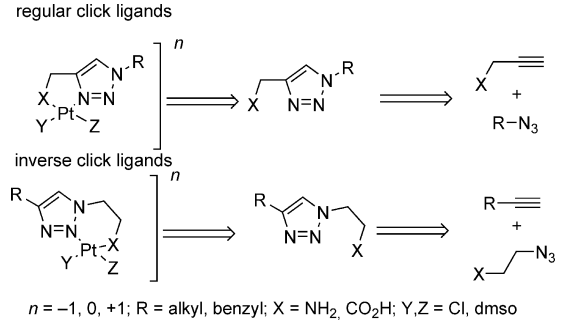
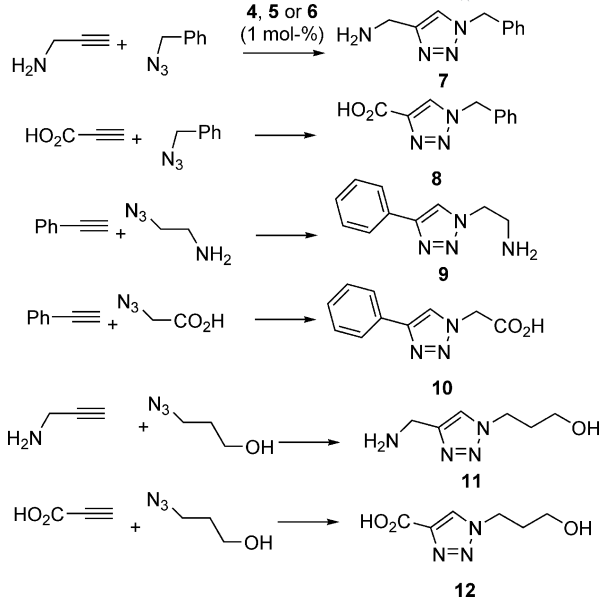


Figure 2. Retrosynthetic analysis for target triazoles and complexes.

Results and Discussion

Synthesis of the Ligands

We began by screening several catalyst systems for the preparation of the library of target triazole ligands by using the Huisgen [2+3] cycloaddition reaction (Scheme 1). The catalysts examined were: the known $CuSO_4$/TBAT (**4**)/ascorbic acid;[13] $CuSO_4$/hydrosoluble ligand **5**/ascorbic acid;[13] and the newly-reported N-heterocyclic carbene (NHC) copper(I) complex [(SIMes)CuBr] (**6**)[14] (Figure 3).



Scheme 1. Triazole ligands **7**–**12** synthesised in this work.

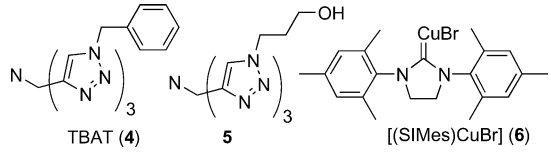


Figure 3. Selected click catalysts.

An aqueous stock solution of the precatalyst $CuSO_4$/**5** (0.10 M) was prepared (this solution is stable for months at room temperature), and the active species was generated in situ by adding ascorbic acid. NHC–copper(I) catalyst **6** presents two advantages: (1) it is a stable copper(I) species that does not require a reducing reagent to generate the active species and (2) its activity is conserved in neat conditions if the components of the reaction are liquids.

Results of ligand syntheses are shown in Table 1. We were pleased to find that catalysts **4** and **5** behaved equally well and produced the expected triazoles in good yields and high purities (>95%). The activity of NHC–copper(I) catalyst **6** was comparable for alkynes functionalised by amines and acids under neat conditions (Table 1, Entries 3 and 6) and gave the same regioisomeric product as that obtained in the reactions involving **4** and **5**, which provides evidence for a catalysed process.[15] In contrast, the catalytic activity of **6** was not retained with amine- and acid-functionalised azides (Table 1, Entries 9 and 12); it was restored, however, with 3-azidopropanol (Table 1, Entries 15 and 18). Coordination of the azide to copper is known to be one of the key steps of the catalytic process.[16] A bifunctional coordinative ligand such as azido–acetic acid or azido–ethylamine might form a "copper clamp" that saturates the coordination sphere of the copper centre and thus blocks its catalyst activity. In the case of 3-azidopropanol, a "clamp" does not form because the alcohol has a weaker coordinating capacity; thus, the catalytic activity is retained.

Table 1. Synthesis of triazoles **7**–**12** by using three different catalytic systems.

Entry	Compound	Catalyst[a]	Yield [%]
1	**7**[b]	**4**	75
2	**7**[b]	**5**	85
3	**7**[b]	**6**	90
4	**8**	**4**	60
5	**8**	**5**	67
6	**8**	**6**	68
7	**9**[b]	**4**	57
8	**9**[b]	**5**	55
9	**9**[b]	**6**	0
10	**10**	**4**	78
11	**10**	**5**	83
12	**10**	**6**	0
13	**11**[b]	**4**	78
14	**11**[b]	**5**	74
15	**11**[b]	**6**	91
16	**12**	**4**	97
17	**12**	**5**	99
18	**12**	**6**	95

[a] Loading of 1 mol-%. [b] Isolated as its hydrochloride salt.

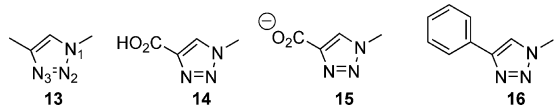
Overall, this reaction allowed us to build a representative selection of regular ligands classified as N,N (**7** and **11**) and N,O (**8** and **12**) chelators and two inverse ligands classified as N,N (**9**) and N,O (**10**) chelators.

DFT Calculations

The designation of regular and inverse ligand chelation modes depends on which triazole nitrogen atom is involved in metal bonding. Among the regulars, N,O ligands constitute a subset, in which the conjugation of the carboxylate functionality can influence the electron density at N2 and N3. It is noteworthy that previous DFT calculations suggested that the highest electron density in the triazole is at the N3 position and consequently regular click ligands are reported to be better chelators.[12] To delineate the influence of the substitution pattern, calculations were carried out by using density functional theory (DFT, Gaussian 03) at the B3LYP/6-311G(d,p) level of theory.[17] The geometries of the model compounds 1,4-dimethyl-1,2,3-triazole, (**13**), 1-methyl-1,2,3-triazole-4-carboxylic acid, (**14**), 1-methyl-1,2,3-triazole-4-carboxylate, (**15**) and 1-methyl-4-phenyl-1,2,3-triazole (**16**) were optimised, and the NPA electron density around the triazole heterocycle was calculated (Table 2).

These calculations revealed that N3 possesses the highest electron density, regardless of the nature of the substituents. Compound **13**, as a model for the regular N,N ligands, displays the highest electron density at N3, which is the position expected to be involved in chelation. Compounds **14** and **15**, as models for the N,O regular ligands, also displayed high electron density at N3, although in the case of conjugate base **15**, the electron density also increased at N2. In contrast, **16**, which is a model for inverse ligands, is poorly populated at the N2 position. This phenomenon was recently suggested as the reason for weak inverse ligand chelation to technetium.[12]

Table 2. Structures subjected to natural population analysis (NPA).



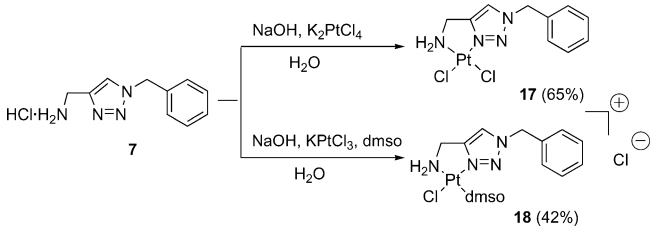
Atom	**13**	**14**	**15**	**16**
N1	–0.206	–0.204	–0.236	–0.201
N2	–0.077	–0.067	–0.133	–0.071
N3	–0.278	–0.216	–0.254	–0.264
C4	0.090	–0.042	0.012	0.078
C5	–0.067	0.014	–0.050	–0.041

Complex Formation

We selected two platinum sources, K_2PtCl_4 and $KPtCl_3$·dmso (Kukushkin's salt),[18] for the formation of metal complexes. The anion of the latter reagent is known to exhibit a strong *trans* effect, and the presence of the dmso ligand offers convenient stoichiometry determination of the platinum complexes formed therefrom through simple ^1H NMR spectroscopic signal integration.[19]

Behaviour of Five-Membered Regular Chelate Ligands

Complexation of regular N,N ligand **7** with the two selected platinum sources in aqueous solution gave a five-membered chelate in each case, as illustrated in Scheme 2. The presence of base to release the amine was necessary; blank experiments in the absence of NaOH showed that no precipitation occurred. Neutral and cationic complexes **17** and **18** were obtained in average yields. Their structures were supported by ^{195}Pt NMR spectroscopy: **17** resonated at δ = –2143 ppm (N_2Cl_2 coordination) and **18** at δ = –2835 ppm (typical of a N_2ClS coordination).[20] Only one of the two possible *cis* and *trans* isomers of **18** was obtained, as shown by the ^1H, ^{13}C, and ^{195}Pt NMR spectra, but we were not able to determine its exact structure by X-ray diffraction as a result of unsatisfactory crystals.



Scheme 2. Synthesis of regular N,N complexes.

A single crystal of **17** suitable for X-ray diffraction was grown by slow diffusion of ethanol into a saturated dmf solution of the complex over one week at 35 °C. Figure 4 presents a perspective view of the molecule.

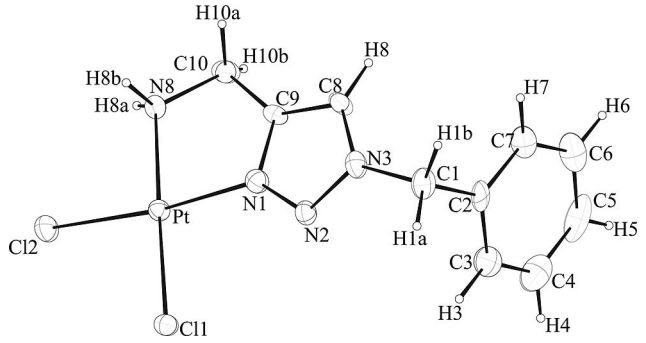


Figure 4. CAMERON plot (50% thermal probability ellipsoids) of **17**.

The X-ray structure proved unambiguously the formation of a five-membered chelate. Bond lengths and angles of interest are summarised in Table 3. The Pt^{II} centre presents a square-planar geometry, and the metal centre bond lengths and angles fall into their usual ranges. The diagonal bonds are not equivalent, however, as N1–Pt is shorter than N8–Pt [1.999(5) and 2.042(4) Å, respectively] and Pt–Cl2 is shorter than Pt–Cl1 [2.277(2) and 2.306(1) Å, respectively].

Table 3. Selected bonds lengths and angles of **17**.

Distances [Å]			
N1–Pt	1.999(5)	Cl1–Pt	2.306(1)
N8–Pt	2.042(4)	Cl2–Pt	2.277(2)
Angles [°]			
N8–Pt–Cl2	90.8(1)	N1–Pt–Cl1	96.4(1)
N8–Pt–Cl1	177.1(1)	N1–Pt–Cl2	172.1(1)
N8–Pt–N1	81.4(2)	Cl1–Pt–Cl2	91.40(6)
Torsions [°]			
N1–C9–C10–N8	15.1(7)	N8–Pt–N1–C9	–3.7(4)
C9–C10–N8–Pt	–17.3(6)	Pt–N1–C9–C10	–5.7(7)
C10–N8–Pt–N1	12.2(4)		

A comparison with related heterocyclic platinum complexes is interesting (Figure 5). As a result of the strain effect, **17** differs significantly from AMD473 (**3**); the picoline plane with respect to the Pt square plane is tilted by 50° in the latter, whereas for **17** the triazole is almost coplanar with the metal centre (angle between the two planes is 3.7°). Thus, the geometrical structure of **17** is closer to *cis*-Cl_2Pt(amp) [amp = 2-pyridylmethylamine] and *cis*-Cl_2Pt(pea) [pea = 2-pyridylmethylamine], in which the pyridine rings lie at an angle of about 8° from the metal coordination plane.[21a] Interestingly, *cis*-Cl_2Pt(amp) displays cytotoxicity in the cisplatin range against the hormone-independent human mammary carcinoma cell line MDA-MB 231.[21b]

The behaviour of regular N,O ligand **8** was rather different, as shown in Scheme 3. Complexation of an equimolar ratio of **8** and K_2PtCl_4 in water afforded neutral product **19** in low yield (12%). By using a 2:1 ratio of **8**/K_2PtCl_4, the yield of **19** increased to 43%. The L_2Pt stoichiometry was confirmed by ^{195}Pt NMR spectroscopy (δ = –1416 ppm, typical for N_2O_2 coordination) and mass spectrometry. Inspection of the ^{1}H and ^{13}C NMR spectra revealed a mixture of *cis*/*trans* isomers (ratio 3:1, presumably in favour of *trans*-**19** for steric and thermodynamic reasons, according to Farrell[22]). Reaction of **8** with Kukushkin's salt afforded **20**, as only one of the two possible *cis* or *trans* isomers, in average yield. ^{195}Pt NMR spectroscopy (δ = –3001 ppm, NOSCl coordination) and mass spectrometry confirmed the structure but here again we were not able to determine its exact structure by X-ray diffraction because of unsatisfactory crystals.

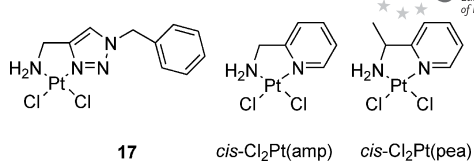
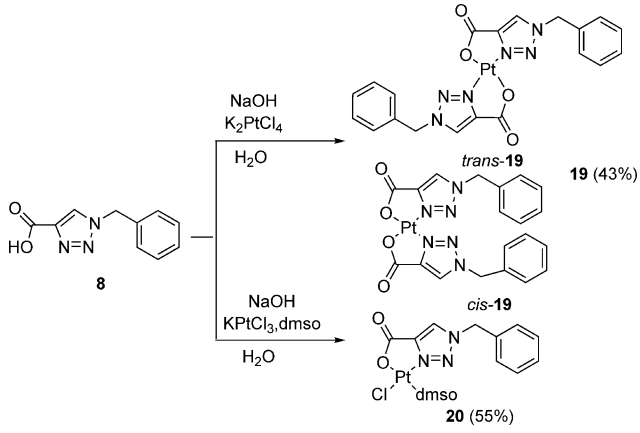
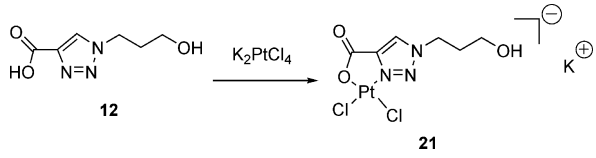


Figure 5. New compound **17** and some related platinum–heterocyclic complexes.



Scheme 3. Synthesis of regular N,O complexes.

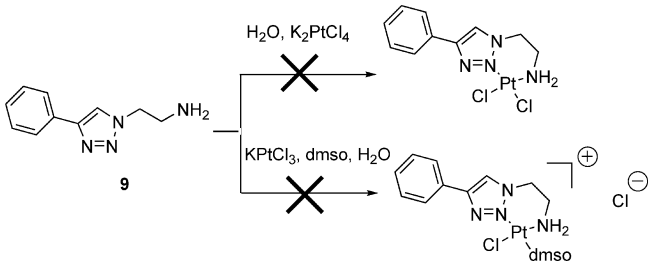
To gain more information about the reasons for the formation of L_2Pt-type complexes **19**, we took advantage of the aqueous solubility of ligand **12**. A mixture of **12**, K_2PtCl_4 and NaOH (1:1:1 in water) afforded a solution, in which only one ^{195}Pt NMR signal was detected at δ = –1626 ppm, which is typical for a $NOCl_2$ coordination sphere. In the ^{1}H NMR spectrum, the H5 signal of free ligand **12** (sodium salt) in D_2O appeared at δ = 8.35 ppm. A 1:1 ratio of **12**/K_2PtCl_4 showed a shift of H5 to 8.41 ppm and a broadening of the signal, whereas a 2:1 ratio of **12**/K_2PtCl_4 showed two sharp signals at δ = 8.21 and 7.65 ppm (ratio 75:25, respectively). On the basis of the ^{195}Pt NMR signal, structure **21** was proposed for the main product (Scheme 4). Thus, we concluded that the formation of bis(ligand) complexes **19** (Scheme 3) was accelerated by their precipitation from the reaction medium.



Scheme 4. A water-soluble regular N,O complex.

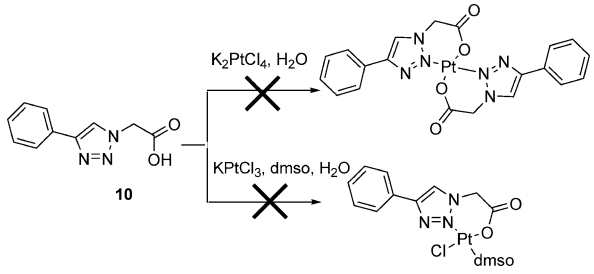
Behaviour of Six-Membered Inverse Chelate Ligands

Efforts to coordinate ligand **9** with each of the two platinum sources in aqueous solution are summarised in Scheme 5. The complexation of **9** with K_2PtCl_4 was unsuccessful: only small amount of an undefined white material was formed after 5 h at 60 °C. Reaction with Kukushkin's salt also failed to give an identifiable complex.



Scheme 5. Attempted syntheses of inverse N,N complexes.

Similarly, we were unable to obtain any tractable product from the reaction of **10** with either of the platinum sources, even after an extended reaction time or by increasing the reaction temperature (Scheme 6).



Scheme 6. Attempted syntheses of inverse N,O click complexes.

Cytotoxicity

Four platinum complexes were submitted to prescreening at 50 and 25 μm concentrations on three cancer cells lines (MCF7: breast, PA1: ovarian and A549: lung) and a fibroblast lane as a blank. To evaluate the influence of the ligand, the platinum complexes selected were: N_2Cl_2 (**17**), N_2SCl (**18**), N_2O_2 (**19**) and NOSCl (**20**).

Addition of the test compound to the cellular medium was performed from a dmf stock solution, rather than dmso because of the chelating properties of the latter. The final concentration of dmf did do not exceed 0.05% v/v owing to the inherent cytotoxicity of this solvent.

The results of this prescreening (Table 4) show that the complexes containing N_2SCl (**18**), N_2O_2 (**19**) and NOSCl (**20**) coordinations displayed no interesting activity, which is in accordance with the accepted structure–activity relationships of platinum drugs.[23] In contrast, N_2Cl_2 coordination complex **17** displayed significant cytotoxicitiy toward PA1 and MCF7 line cells.

The IC_{50} values of **17** and of cisplatin against all four cell lines are given in Table 5. The neutral *cis* dichloro diamino complex **17** exhibited cytotoxicity against the MCF7 breast carcinoma cell line comparable to that of cisplatin. In contrast, it is less active than cisplatin against PA1 ovarian carcinoma and poorly active against the A549 nonsmall cell lung cancer. Interestingly, it is almost inactive against normal fibroblast, an argument supporting a favourable therapeutic index in vivo.

Table 5. IC_{50} values (μM) values of **17** and cisplatin against different cell lines.

Compound	PA1	MCF7	A549	Fibroblast
17	6.7	27.0	>50	>50
Cisplatin	0.4	16.5	5.6	23.9

Conclusions

We showed that click chemistry is a useful tool for the facile construction of a series of potentially chelating triazole ligands for platinum. Among these, only regular ligands give good complexation through the formation of five-membered chelates. Complex **17** displays an interesting cytotoxicity against breast cancer cells, which is comparable to cisplatin. Extension of the synthetic methodology to more structurally diverse motifs is currently under investigation.

Experimental Section

General Methods

Chemistry: The following general procedures were used in all reactions unless otherwise noted. Reactions were stirred with a Teflon-covered magnetic stirring bar. Solvents were removed with a Buchi rotary evaporator (water bath 40 °C). All commercially available reagents were used as received, unless otherwise indicated. TLC was performed with 250-μm silica gel 60 plates with 254 nm fluorescent indicator.

Spectroscopy: Solution NMR spectra were recorded in Fourier Transform mode at 25 °C with a Bruker AVANCE 400 (^{1}H at

Table 4. Percentage of inhibition of cell growth at 50 and 25 μM concentrations of **17**, **18**, **19** and **20** in comparison to that of cisplatin.

	PA1		MCF7		A549		Fibroblast	
	50 μM	25 μM	50 μM	25 μM	50 μM	25 μM	50 μM	25 μM
17	100	98	80	76	45	40	40	35
18	95	75	45	20	35	35	25	20
19	50	40	20	0	23	17	20	10
20	40	40	15	5	30	27	10	5
Cisplatin	100	100	95	75	100	100	95	92

400 MHz, ^{13}C at 100 MHz) or a Bruker AV 500 (^{195}Pt at 107 MHz) spectrometer. Data are reported as chemical shifts (δ) in ppm with respect to the standard reference compounds tetramethylsilane (^{1}H, ^{13}C) or Na_2PtCl_6 (^{195}Pt). Spin multiplicity is described by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets and br. = broad. Coupling constants (J) are reported in Hz. IR spectra were obtained as solid KBr pellets with a Paragon 500 Perkin–Elmer FTIR and data are reported in cm^{-1}. High-resolution mass spectra were recorded with a Q-TOF micro apparatus (Waters). Samples were dissolved in dmf (2 mg·mL^{-1}), 10 or 20 μL of the dmf solution were diluted, respectively, in 990 or 980 μL of water and injected by syringe at a flow rate of 5 μL·min^{-1}. The high-resolution measurements were obtained with a lock mass: leucine–enkephalin (m/z = 556.2771).

Electron Density Calculations: All calculations were conducted by using density functional theory (DFT) as implemented in the Gaussian 03 program.[17] Geometry optimisations and vibrational frequency calculations were performed by using the restricted B3LYP exchange and correlation functional and the triple-ζ 6-311G(d,p) basis sets for all atoms. Harmonic frequency analysis based on analytical second derivatives was used to characterise the optimised geometries as local minima.

Cell-Growth Inhibition Assay: Normal human fibroblasts were purchased from Promocell (Heidelberg, Germany). Breast cancer adenocarcinoma (MCF7), lung nonsmall cell carcinoma (A549) and ovary adenocarcinoma (PA1) human cell lines were purchased from the European Collection of Cell Cultures (ECACC; Salisbury, UK). Stock cell cultures were maintained as a monolayer in 75 cm^2 culture flasks in Glutamax Eagle's Minimum Essential Medium with Earle's salts (MEM; Invitrogen, Cergy–Pontoise, France) supplemented with 10% fetal calf serum (Sigma, St Quentin Fallavier, France), 1 mM sodium pyruvate (Invitrogen), 1X vitamins solution (Invitrogen), 1X nonessential amino acids solution (Invitrogen) and 4 μg·mL^{-1} of gentamicine (Invitrogen). Cells were grown at 37 °C in a humidified atmosphere containing 5% CO_2. Cells were plated at a density of 5×10^3 cells per well in 96-well microplates (Nunclon, Nunc, Roskilde, Denmark) in 150 μL of culture medium and were allowed to adhere for 16 h before treatment with the test compound. Stock solution of each compound was prepared in dimethylformamide (dmf) and kept at –20 °C until use. The percentage of dmf was kept at 0.05% (v/v) regardless of the concentration tested; this quantity of dmf did not modify cellular growth. 50 μL of a 4X solution in MEM was then added and a 48 h continuous drug exposure protocol was used. After this time, the cytotoxic effect of compounds on tumour cells was assessed by using a resazurin reduction assay.[24] Briefly, plates were rinsed by 200 μL PBS (37 °C, Invitrogen) by using a multichannel dispenser (Labsystems, Helsinki, Finland) and emptied by overturning on absorbent towelling. 150 μL of a 25 μg·mL^{-1} solution of resazurin in MEM (without SVF nor phenol red) was added to each well. The plates were incubated 1 h at 37 °C in a humidified atmosphere with 5% of CO_2 for fluorescence development by living cells. Fluorescence was then measured on the automated 96-well plate reader Fluoroskan Ascent FL (Labsystems) by using an excitation wavelength of 530 nm and an emission wavelength of 590 nm. Fluorescence is proportional to the number of living cells in the well and IC_{50} values (drug concentration required to decrease final cell population by 50%) were calculated from the curve of concentration-dependent cell number decrease, defined as the fluorescence in experimental wells as a percentage of that in control wells, with blank values subtracted.

General Procedure for the Synthesis of Azides: Unless otherwise specified, the alkyl or benzyl chloride or bromide (1.0 equiv.) was suspended in water at a concentration of 1.5 M. Sodium azide (1.05 equiv.) and ammonium chloride (2.0 equiv.) were added, and the reaction was heated at 70 °C for 48 h with vigorous stirring. The aqueous layer was extracted with diethyl ether, dried with $MgSO_4$ and the solvent was evaporated to yield pure azide. Benzyl azide: 97%; 3-azido-propane-1-ol: 93%; azido–acetic acid: quantitative after 48 h at room temperature followed by acidification (conc. HCl) to give pH = 2, then extraction with diethyl ether.

General Procedure for the Synthesis of Ligands by Using Catalyst 4 or 5: To a solution of azide (3.76 mmol) and alkyne (3.76 mmol) in H_2O/tBuOH (1:1, 10 mL) was added **4** (20 mg, 38 μmol, 1.0 mol-%) and $CuSO_4 \cdot 7H_2O$ (11 mg, 38 μmol, 1.0 mol-%) or precatalyst **5** (0.1 M, 380 μL, 38 μmol, 1.0 mol-%) and a fresh solution of ascorbic acid (0.1 M, 1.14 mL, 0.114 mmol, 3 mol-%). The solution was stirred at room temperature for 10 h. When the 1,2,3-triazole product had precipitated from the reaction medium, the solid was filtered, washed with diethyl ether and dried in air. In other cases, the 1,2,3-triazole was extracted from the medium with EtOAc, and the extract solution was dried with $MgSO_4$ and evaporated.

General Procedure for the Synthesis of Ligands by Using Catalyst 6: In a screw-capped vial, neat alkyne (2.0 mmol, 1.0 equiv.), neat azide (2.0 mmol, 1.0 equiv.) and **6** (9.0 mg, 0.02 mmol, 1 mol-%) were mixed. The resulting mixture was stirred for 1 h at room temperature to give a solid that was filtered, washed with hexane or ether (2 mL) and dried in air.

(1-Benzyl-1*H*-[1,2,3]triazol-4-yl)methylammonium Chloride (7·HCl): A minimum amount of cold ethanol was used to dissolve the crude reaction product and a few drops of conc. HCl (12 M) were added. A white precipitate formed immediately. The suspension was cooled to 0 °C for 1 h and was filtered and washed with ice-cold ethanol and diethyl ether. The white solid was dried in air. M.p. 229–230 °C. ^{1}H NMR (400 MHz, D_2O): δ = 4.31 (s, 2 H), 5.65 (s, 2 H), 7.35–7.38 (m, 2 H), 7.42–7.45 (m, 3 H), 8.13 (s, 1 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 34.0, 54.0, 125.4, 128.1, 128.8, 129.2, 134.7, 139.9 ppm. IR (KBr): $\tilde{\nu}$ = 3469 (br.), 3069, 3001, 2568, 2364, 1587, 1496, 1458, 1225, 1177, 1141, 1087, 1054, 1028, 967, 872, 717, 694 cm^{-1}. $C_{10}H_{13}ClN_4$ (224.69): calcd. C 53.46, H 5.83, N 24.95; found C 53.90, H 5.84, N 24.47.

1-Benzyl-1*H*-[1,2,3]triazole-4-carboxylic Acid (8): M.p. 177–179 °C. ^{1}H NMR (400 MHz, [D_6]dmso): δ = 5.64 (s, 2 H), 7.33–7.38 (m, 5 H), 8.77 (s, 1 H), 13.10 (s, 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]-dmso): δ = 57.4, 128.1, 123.3, 128.0, 128.8, 135.6, 139.9, 161.7 ppm. IR (KBr): $\tilde{\nu}$ = 3413, 3116, 1683, 1546, 1430, 1341, 1236, 1049, 945, 895, 785, 716, 688, 554 cm^{-1}. $C_{10}H_9N_3O_2$ (203.20): calcd. C 59.11, H 4.46, N 20.68; found C 58.98, H 4.61, N 20.79.

2-(4-Phenyl-1*H*-[1,2,3]triazol-1-yl)ethylammonium Chloride (9·HCl): A mixture of 2-chloroethylammonium chloride (2.00 g, 17 mmol) and sodium azide (1.17 g, 18 mmol) in water (17 mL) was heated at 80 °C for 2 d to provide a 1.0 M solution of 2-azidoethylammonium chloride. The evolution and completion of the reaction was followed by sampling the reaction mixture, adding a few drops of D_2O then recording the ^{13}C NMR spectrum [product data: ^{13}C NMR (D_2O): δ = 48.1, 38.9 ppm]. As the azide intermediate is unstable in neat conditions, the 1.0 M stock solution was used directly. To the stock solution (2.0 mL, 2.0 mmol, 1.0 equiv.) was added *tert*-butyl alcohol (2.0 mL), phenyl acetylene (214 mg, 2.1 mmol, 1.05 equiv.), precatalyst **5** (0.1 M, 200 μL, 20 μmol, 1.0 mol–%) and a fresh solution of ascorbic acid (0.1 M, 600 μL, 0.60 mmol, 3 mol-%). The reaction was left overnight, and then the solvent was evaporated. Water (5 mL) was added, and the aqueous solution was extracted with diethyl ether. The aqueous layer was evaporated to yield 206 mg of a white powder. (55%). ^{1}H NMR (400 MHz, D_2O):

δ = 3.04 (t, J = 5.8 Hz, 2 H), 4.36 (t, J = 5.8 Hz, 2 H), 7.4–7.3 (m, 3 H), 7.63 (d, J = 7.0 Hz, 2 H), 8.10 (s, 1 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 40.5, 52.3, 122.2, 125.5, 128.7, 129.1, 129.4, 143.4 ppm. IR (KBr): $\tilde{\nu}$ = 3500–2500 (br.), 1603.9, 1508.4, 767.7, 691.3 cm^{-1}. $C_{10}H_{13}ClN_4$ (224.69): calcd. C 53.46, H 5.83, N 24.95; found C 53.65, H 6.02, N 25.21.

2-(4-Phenyl-1*H*-[1,2,3]triazolyl)acetic Acid (10): M.p. 198–200 °C. ^{1}H NMR (400 MHz, [D_6]dmso): δ = 5.38 (s, 2 H), 7.34 (s, 1 H), 7.40 (s, 2 H), 7.88 (m, 2 H), 8.57 (s, 1 H), 13.01 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]dmso): δ = 50.7, 122.7, 125.1, 127.9, 128.8, 130.6, 146.4, 168.6 ppm. IR (KBr): $\tilde{\nu}$ = 1734, 1102 cm^{-1}. $C_{10}H_9N_3O_2$ (203.20): calcd. C 59.11, H 4.46, N 20.68; found C 59.14, H 4.54, N 20.7.

1-(3-Hydroxypropyl)-1*H*-[1,2,3]triazol-4-ylmethylammonium Chloride (11·HCl): M.p. 130–132 °C. ^{1}H NMR (400 MHz, [D_6]dmso): δ = 1.93 (q, J = 7.8 Hz, 2 H), 3.39 (t, J = 7.2 Hz, 2 H), 4.01 (br. s, 2 H), 4.44 (t, J = 7.2 Hz, 2 H), 8.23 (s, 1 H), 8.64 (br. s, 3 H) ppm. ^{13}C NMR (100 MHz, [D_6]dmso): δ = 30.9, 31.7, 44.6, 55.1, 122.5, 137.9 ppm. IR (KBr): $\tilde{\nu}$ = 3500–2500 (br.), 1591.9, 1485.3, 1117.1, 879.4, 710.2, 701.2, 534.4 cm^{-1}. $C_6H_{13}ClN_4O$ (192.65): calcd. C 37.41, H 6.80, N 29.08; found C 37.22, H 7.12, N 29.34.

1-(3-Hydroxypropyl)-1*H*-[1,2,3]triazole-4-carboxylic Acid (12): M.p. 149–151 °C. ^{1}H NMR (400 MHz, [D_6]dmso): δ = 2.00 (t, J = 6.5 Hz, 2 H), 3.40–3.34 (m, 2 H), 4.45 (t, J = 6.5 Hz, 2 H), 4.60 (br. s, 1 H), 8.66 (s, 1 H), 13.00 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]dmso): δ = 32.5, 47.0, 57.3, 128.9, 139.5, 161.7 ppm. IR (KBr): $\tilde{\nu}$ = 3700–3200 (br.), 1705, 1558, 1433, 1242, 1048, 759 cm^{-1}. $C_6H_9N_3O_3$ (171.15): calcd. C 42.10, H 5.30, N 24.55; found C 42.05, H 5.41, N 24.89.

Platinum Complexes

17: To a solution of **7·HCl** (50.0 mg, 0.22 mmol, 1.0 equiv.) in water (600 μL) was added KOH (1.0 M, 220 μL, 0.22 mmol) and K_2PtCl_4 (92.0 mg, 0.22 mmol, 1.0 equiv.) in water (1 mL). The solution was stirred 12 h at room temperature in the dark. The precipitate was filtered and washed with water (2 mL), ethanol (2 mL) and diethyl ether (2 mL) to give 65.5 mg of a pale yellow solid (0.14 mmol, 65%). M.p. >230 °C. ^{1}H NMR (400 MHz, [D_7]dmf): δ = 3.53 (s, 2 H), 5.80 (s, 2 H), 7.35–7.50 (m, 5 H), 8.46 (s, 2 H) ppm. ^{13}C NMR (100 MHz, [D_7]dmf): δ = 43.7, 56.2, 123.6, 129.6, 129.8, 130.1, 136.0 ppm. ^{195}Pt NMR (107 MHz, [D_7]dmf): δ = –2143 ppm. IR (KBr): $\tilde{\nu}$ = 3470, 3204, 3112, 1576, 1451, 1256, 1143, 710 cm^{-1}. $C_{10}H_{12}Cl_2N_4Pt$ (454.21): calcd. C 26.44, H 2.66, N 12.33; found C 26.66, H 2.72, N 12.33.

18: To a solution of **7·HCl** (50.0 mg, 0.21 mmol, 1.0 equiv.) in water (760 μL) was added KOH (1.0 M, 213 μL, 0.21 mmol) and $KPtCl_3$·dmso (89.0 mg, 0.21 mmol, 1.0 equiv.) in water (1.8 mL). The solution was stirred 12 h at room temperature in the dark. The precipitate was filtered and washed with water (2 mL), ethanol (2 mL) and diethyl ether (2 mL) to give 47.9 mg of a white solid (90 μmol, 42%). M.p. >230 °C. ^{1}H NMR (400 MHz, [D_7]dmf): δ = 3.36 (s, 6 H), 3.51 (s, 2 H), 5.79 (s, 2 H), 7.40–7.50 (m, 5 H), 8.42 (s, 2 H) ppm. ^{13}C NMR (100 MHz, [D_7]dmf): δ = 31.0, 43.7, 57.0, 123.6, 129.6, 129.8, 130.1, 136.0, 154.6 ppm. ^{195}Pt NMR (107 MHz, [D_7]dmf): δ = –2964 ppm. IR (KBr): $\tilde{\nu}$ = 3470, 3204, 3112, 1576, 1451, 1256, 1143, 710 cm^{-1}. HRMS (ES): calcd. for $C_{12}H_{18}Cl_2N_4OPtS$ 495.0516; found 495.0435.

***cis*/*trans*-19:** To a solution of **8** (97.0 mg, 0.48 mmol, 2.0 equiv.) in water (1 mL) was added NaOH (1.0 M, 500 μL, 0.50 mmol) and K_2PtCl_4 (100.0 mg, 0.24 mmol, 1.0 equiv.) in water (1.0 mL). The solution was heated at 60 °C for 4 h. The solution was stirred overnight at room temperature and a precipitate appeared. The precipitate was filtered and washed with water (2 mL), methanol (1 mL) and diethyl ether (2 mL) to give 73.0 mg (0.12 mmol, 50%) of a green solid. M.p. >230 °C. ^{1}H NMR (400 MHz, [D_6]dmso): δ = 5.61 (s, 1.33 H, minor isomer), 5.77 (s, 0.6 H, major isomer), 7.50–5.0 (m, 10 H), 8.60 (s, 0.6 H, minor isomer), 9.0 (s, 1.33 H, major isomer) ppm. ^{13}C NMR (100 MHz, [D_6]dmso): δ = 55.3, 55.4, 127.9, 128.3, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 133.9, 134.0, 166.9 ppm (carbonyl not found). ^{195}Pt NMR (107 MHz, [D_7]dmf): δ = –1416 ppm. IR (KBr): $\tilde{\nu}$ = 3406, 1599, 1404, 1288, 1048, 810, 534 cm^{-1}. HRMS (ES): calcd. for $C_{20}H_{16}N_6O_4Pt$ 599.0938; found 599.0818.

20: To a solution of **8** (50.0 mg, 0.25 mmol, 1.0 equiv.) in water (300 μL) was added KOH (1.0 M, 250 μL, 0.25 mmol) and $KPtCl_3$·dmso (100.0 mg, 0.25 mmol, 1.0 equiv.) in water (1.2 mL). The solution was stirred at room temperature for 12 h. A precipitate appeared during this time; it was filtered and washed with water (2 mL), ethanol (1 mL) and diethyl ether (2 mL) to give 69.4 mg (0.14 mmol, 55%) of a white solid. M.p. 177–178 °C. ^{1}H NMR (400 MHz, [D_7]dmf): δ = 3.71 (s, 6 H), 5.94 (s, 2 H), 7.44 (m, 3 H), 7.55 (m, 2 H), 9.04 (s, 1 H) ppm. ^{13}C NMR (100 MHz, [D_7]dmf): δ = 46.0, 57.0, 129.3, 129.8, 130.1, 130.1, 135.2, 143.4, 166.7 ppm. ^{195}Pt NMR (107 MHz, [D_7]dmf): δ = –2838 ppm. IR (KBr): $\tilde{\nu}$ = 3462, 3015, 1705, 1560, 1267, 1165, 1034, 723 cm^{-1}. HRMS (ES): calcd. for $C_{12}H_{14}Cl_2N_3PtO_3S$ 510.0156; found 510.1056. $C_{12}H_{14}Cl_2N_3O_3PtS$ (510.85): calcd. C 28.21, H 2.76, N 8.23, S 6.28; found C 28.41, H 2.72, N 8.27, S 5.98.

X-ray Crystallographic Study of Compound 17: Diffraction intensity data were collected at T = 293 K with an Oxford-Diffraction XCALIBUR diffractometer [Mo-K_α radiation (λ = 0.7107 Å)] with data collection and reduction by using the CrysAlis program package.[25] Data were corrected for Lorentz-polarisation effects and empirical absorption corrections by using SCALE3 ABSPACK.[26] The structure was solved by direct methods with SIR-92[27] and refined by least-squares methods on F^2 with SHELXL-97[28] incorporated in the WinGX package.[29] Hydrogen atoms were inserted at calculated positions with isotropic thermal parameters constrained to be 1.2 times the U_{eq} of the carrier atoms. The molecule was drawn by using CAMERON.[30] Crystal data, data collection parameters and convergence results are listed in Table 6. CCDC-647393 contains

Table 6. Crystal data and structure refinement for **17**.

Empirical formula	$C_{10}H_{12}Cl_2N_4Pt$
M_w	454.23
Crystal system	monoclinic
Space group	$P12_1/a$ 1
a [Å]	10.732(1)
b [Å]	9.415(1)
c [Å]	12.696(1)
β [°]	95.49(1)
V [Å^3]	1276.9(1)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	2.363
$F(000)$	848
μ [mm^{-1}]	11.389
θ range [°]	2.88/32.19
Measured reflections	13597
Independent reflections	4252
Observed reflections	2327
Selection criterion	$I > 2\sigma(I)$
R_1	0.035
wR_2	0.057
Goodness-of-fit	0.836
Residual electron density [e Å^{-3}]	–1.46 and 2.93

the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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