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Synthesis, characterization and anticancer evaluation of phosphinogold (I) thiocarbohydrate complexes

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ABSTRACT

Several novel thiocarbohydrate phosphinogold(I) complexes were prepared *via* the reaction of *n*-gluconamidoalkyl thiol (**L1**–**L7**) {where **L1–L4** = *n*-gluconamidoalkyl thiol (*n* = 1–4), **L5–L7** = acetylated *n*-gluconamidoalkyl thiol (*n* = 1–3)} with the gold precursors [AuCl(PPh_3)], [Au_2Cl_2(dppe)], [Au_2Cl_2(dppp)] and [Au_2Cl_2(dppb)], leading to the new gold(I) complexes [Au(**L1**)(PPh_3)] (**1**–**4**), [Au(**L5**)(PPh_3)] (**5**–**7**), [Au_2(**L1**)$_2$(dppe)] (**8**–**11**), [Au_2(**L5**)$_2$(dppx)] (**12**–**14**), [(Au_2(**L6**)$_2$)(dppx)] (**15**–**17**), [Au_2(**L7**)$_2$(dppx)] (**18**–**20**), {where dppe = 1,2-bis(diphenylphosphino)ethane (x = e), dppp = 1,3-bis(diphenylphosphino)propane (x = p) and dppb = 1,4-bis-(diphenylphosphino)butane (x = b)}. These gold complexes were characterized by a combination of NMR and infrared spectroscopy, microanalysis and mass spectrometry. Complexes **8**, **12**, **14**–**16** (IC_{50} values between 0.003 and 1.8 μM) are all active against MCF7, HCT116 and PC3 cells. Complex **8** recorded the highest IC_{50} value of 0.003 μM against PC3. Complex **14** was found to be selective towards both MCF7 and PC3 cells with a TS value of 142.1, while compounds **15** and **16** were highly selective toward PC3 cells with TS values of 970.0 and 937.5, respectively.

1. Introduction

Therapeutic applications of gold have been explored throughout the history of civilization dating back to 2500 BC when gold was used for the treatment of skin ulcers, smallpox and measles [1–3]. Later in the 19th century a number of gold complexes, such as gold cyanide for the treatment of tuberculosis [4,5], aurothiomalate, aurothioglucose and auranofin as disease modifying antirheumatic drugs (DMARDs), were developed [6–14]. Recent reports of their anticancer [15,16,7,17] and anti-HIV [18] properties have attracted attention in medicinal chemistry. However, the use of gold complexes in medical applications [19] is usually hampered by the toxicity of the ligands and their lack of biocompatibility [20]. Thus, the enhanced therapeutic activity of gold based compounds coupled with the problem associated with ligands that are toxic to the human body raises considerable interest in developing novel gold complexes with non-toxic ligands.

In view of the above mentioned drawbacks of the therapeutic applications of gold, several reports have focused on ligand modification to reduce toxicity and improve bioavailability of phosphinogold(I) compounds. Raubenheimer and co-workers [21] have reported a heterobimetallic *N*-heterocyclic carbene (NHC) complex of gold conjugatively attached to a ferrocenyl moiety. This phosphine-free 'complex of a complex' was found to be tumor specific (TS = 6.98) against the HeLa and Jurkat cancer cell lines. Exocyclic imine complexation of azol-2-ylideneamine ligands with $[(Ph_3P)Au]^+$ increases their anticancer as well as antimalarial activity [22]. As a follow up to eliminate delay toxicity and resistance of the phosphinogold(I) compounds, Raubenheimer and co-workers [23] developed dinuclear diphosphinogold(I) complexes having an *N*-heterocyclic ligand [24,25] and the complexes were active against selected cancer cells. The activity was modulated by the length of the aliphatic carbon chain between the two phosphorus donor atoms, with an optimum length of five or six carbons having the highest tumor specificity of ~25. Recently, our group reported phosphinogold(I) dithiocarbamate complexes which demonstrated excellent anticancer activity and tumor specificity as an improvement to that reported by Raubenheimer et al. [21]. The diphenylphosphinoalkyl ligands with alkyl chains longer than ethyl were found to be active against several cancer cells. Compounds with a hexyl chain were found to be the most active and extremely selective (TS = 70.5) [26]. Although such compounds with a hexyl chain exhibited excellent activity and tumor selectivity, their *in vivo* activity was poor. The above examples demonstrate the importance of ancillary ligands in the development of

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anticancer drugs, such as di(phosphino)-alkanegold(I) compounds. Herein, we report the use of biofriendly thiocarbohydrates as ligands in the synthesis of mononuclear and binuclear gold(I) complexes and their anticancer activities against three cancer cell lines (MCF7, HCT116 and PC3 cells). Our choice of thiocarbohydrates as ancillary ligands is based on their biocompatibility, non-toxicity and water solubility.

2. Material and methods

2.1. Materials and instrumentation

All chemicals: tetrahydrothiophene, hydrogen tetrachloroaurate, triethylamine and potassium carbonate were purchased from Sigma–Aldrich and used as received unless otherwise specified. Toluene, dichloromethane and methanol were dried using SP-1 standalone solvent purifier. 2-Gluconamidoethyl thiol (**L1**), 3-gluconamidopropyl thiol (**L2**), 4-gluconamidobutyl thiol (**L3**), 5-gluconamidopentyl thiol (**L4**), acetylated 2-gluconamidoethyl thiol (**L5**), acetylated 3-gluconamidopropyl thiol (**L6**) and acetylated 4-gluconamidobutyl thiol (**L7**) were prepared in house as reported in our previous work [34]. [AuCl(PPh_3)], [Au_2Cl_2(dppe)], [Au_2Cl_2(dppp)] and [Au_2Cl_2(dppb)] were prepared following literature reported protocols [39–42].

All the nuclear magnetic resonance (^1H and $^{13}C\{^1H\}$) spectra were recorded either in D_2O or $CDCl_3$ on a Bruker Ultra shield (400 MHz) spectrometer at room temperature. The ^1H and ^{13}C chemical shifts are referenced to the residual signals of the protons or carbon atoms of the NMR solvents and are quoted in ppm: D_2O at δ 4.65 ppm for ^1H and $CDCl_3$ at δ 7.24 and 77.00 ppm for ^1H and ^{13}C spectra, respectively. The infrared spectra were recorded on a Bruker tensor 27 fitted with an ATP-IR probe and Perkin Elmer FT-IR spectrum BX. Elemental analysis was performed on a Vario Elementar III microcube CHNS analyzer at Rhodes University, South Africa. ESI-MS spectra were recorded on a waters API quattro micro spectrophotometer at the University of Stellenbosch, South Africa. Melting point determination was performed using a Q600 series™ Differential Scanning Calorimeter (DSC). MCF7 (breast cancer), HCT116 (colon cancer) and PC3 (prostate cancer) were obtained from NCI in the framework a collaborative research program between CSIR and NCI South Africa. The WI-38 cell line (Normal Human Fetal Lung Fibroblast) and HCT116 were obtained from ECACC.

2.2. Synthesis of the n-gluconamidoethyl (triphenylphosphino)gold(I) thiolate complexes

2.2.1. Triphenylphosphino((2-((2S,3S,4R)-2,3,4,5,6-pentahydroxyhexanamido)ethyl) thio)gold(I) complex (**1**)

2-Gluconamidoethyl thiol (**L1**) (0.05 g, 0.19 mmol) in water (5 mL) and [AuCl(PPh_3)] (0.09 g, 0.19 mmol) in dichloromethane (5 mL) were mixed together, followed by the addition of triethylamine (30 μL). The reaction mixture was allowed to stir for 1 h at ambient temperature. A yellow precipitate formed, which was isolated by suction filtration and washed several times with dichloromethane to provide the title complex. Yield: 0.12 g (86%). ^1H NMR (DMSO-*d6*, 400 MHz) δ_H, ppm: 7.61–7.50 (m, 15H, P*Ph*$_3$); 5.37 (s, 1H, N—H); 4.52 (s, 1H, O—H); 4.47 (s, 1H, O—H); 4.40 (d, 1H, *J* = 6.4 Hz, O—H); 4.32 (s, 1H, O—H); 3.96 (s, 1H, O—H), 3.91 (s, 1H, H-5); 3.58 (d, 1H, *J* = 10.0 Hz, H-4); 3.72 (s, 1H, H-3); 3.41 (s, 1H, H-2); 3.37 (t, 2H, *J* = 12.8 Hz, CH_2); 2.95 (t, 1H, *J* = 7.6 Hz, H-6). $^{13}C\{^1H\}$ NMR (DMSO-*d6*, 100 MHz) δ_C, ppm: 172.7 (*C*═O); 134.3 (P*Ph*); 134.2 (P*Ph*); 132.5 (P*Ph*); 130.1 (P*Ph*); 130.0 (P*Ph*); 74.0 (C-2); 72.8 (C-3); 71.9 (C-4); 70.6 (C-5); 63.8 (C-6); 55.3 (2CH_2). $^{31}P\{^1H\}$ NMR (DMSO-*d6*, 400 MHz) δ_P, ppm: 36.41. FT-IR (neat, cm^{-1}); 3264 *ν*(O—H, broad); 2362 *ν*(P-C); 1636 *ν*(C═O); 1536 *υ*(N—H); 1404 *ν*(CH_2 bend), 1227 *ν*(O—C), 1028 *ν*(C—N). $C_{26}H_{31}AuO_6NPS.3H_2O$ (MW = 713.53 g mol^{-1}) *Anal.* Calc.: C, 40.68; H, 4.86; N, 1.82; S, 4.18. Found: C, 40.62, H, 4.01; N, 1.37; S, 3.27 %. MS(ESI), *m/z* $M^+$and $[M+H]^+$ calcd.: 713.13, 714.53; found: 713.13, 714.13.

A similar method for preparing complex **1** was used to synthesise complexes **2**–**4**, but using the reagents indicated for each complex.

2.2.2. Triphenylphosphino((2-((2S,3S,4R)-2,3,4,5,6-pentahydroxyhexanamido)propyl) thio)gold(I) complex (**2**)

3-Gluconamidopropyl thiol (**L2**) (0.10 g, 0.34 mmol), AuPPh_3Cl (0.18 g, 0.24 mmol) and triethylamine (50 μL). Yield: 0.19 g (70%). ^1H NMR (DMSO, 400 MHz) δ_H, ppm: 7.52 (m, 15H, PPh_3); 5.33 (s, 1H, N—H); 4.51 (s, 1H, O—H); 4.46 (s, 1H, O—H); 4.37 (s, 1H, O—H); 4.31 (s, 1H, O—H); 3.95 (s, 1H, O—H); 3.88 (s, 1H, H-2); 3.54 (s, 1H, H-3); 3.45 (s, 1H, H-4); 2.87 (t, 2H, *J* = 6.8 Hz, CH_2); 1.79 (t, 2H, *J* = 8.0 Hz, CH_2); 0.91 (t, 1H, *J* = 7.2 Hz, CH). $^{31}P\{^1H\}$ NMR (DMSO-*d6*, 400 MHz) δ_P, ppm: 36.77 (PPh_2). $^{13}C\{^1H\}$ NMR (DMSO-*d6*, 100 MHz) δ_C, ppm: 172.7 (*C*═O); 134.3 (P*Ph*); 134.2 (P*Ph*); 132.5(P*Ph*); 130.2 (P*Ph*); 130.1 (P*Ph*); 74.1 (C-2); 73.0 (C-3); 72.0 (C-4); 70.7 (C-5); 63.9 (C-6); 46.2 (—CH_2); 38.2 (—CH_2); 37.9 (—CH_2). FT-IR (neat, cm^{-1}): 1636 *ν*(C═O); 3260 *ν*(O—H); 1638 *υυ*(C═O); 1541 *ν*(N—H); 1434 *ν*(CH_2); 1227 *ν*(O—C); 1028 *ν*(C—N); 741, 692 *ν*(PPh_2). HRMS(ESI), *m/z* $[M+H]^+$ calcd.: 727.5594; found: 727.5537.

2.2.3. Triphenylphosphino((2-((2S,3S,4R)-2,3,4,5,6-pentahydroxyhexanamido)butyl) thio)gold(I) complex (**3**)

4-Gluconamidobutyly thiol (**L3**) (0.10 g, 0.36 mmol), AuPPh_3Cl (0.18 g, 0.36 mmol) and triethylamine (50 μL). Yield: 0.17 g (67%). ^1H NMR (DMSO-*d6*, 400 MHz) δ_H, ppm: 7.60 (m, 15H, PPh_3); 5.37 (t, 1H, *J* = 4.4 Hz, N—H); 4.55 (s, 1H, O—H); 4.49 (s, 1H, O—H); 4.40 (d, 1H, *J* = 6.4 Hz, O—H); 4.40 (d, 1H, *J* = 7.2 Hz, O—H); 4.35 (t, 1H, *J* = 5.6 Hz, O—H); 3.97 (s, 1H, H-2); 3.89 (s, 1H, H-3); 3.58 (s, 1H, H-4); 3.55 (s, 1H, H-5); 3.46 (s, 1H, H-6); 3.44 (s, 1H, H6′); 3.07 (q, 2H, *J* = 6.8 Hz, CH_2); 2.70 (t, 2H, *J* = 6.4 Hz, CH_2); 1.70 (s, 2H, CH_2); 1.58 (t, 1H, *J* = 6.8 Hz, CH); 1.49 (d, 1H, *J* = 7.2 Hz, CH) . $^{31}P\{^1H\}$ NMR (DMSO-*d6*, 400 MHz) δ_P, ppm: 33.29. FT-IR (neat, cm^{-1}): 3056 *ν*(O—H, broad); 1655 *ν*(C═O); 1586 *υυ*(N—H); 1433 *ν*(CH_2 bend); 1211 *ν*(O—C); 1026 *ν*(C—N); 998, 746, 690 *ν*(P(PPh_2). HRMS (ESI), *m/z* [M+Na] calcd.: 764.1588. Found: 764.1564.

2.2.4. Triphenylphosphino((2-((2S,3S,4R)-2,3,4,5,6-pentahydroxyhexanamido)pentyl) thio)gold(I) complex (**4**)

5-Gluconamidopentyl thiol (**L4**) (0.10 g, 0.34 mmol), AuPPh_3Cl (0.17 g, 0.34 mmol) and triethylamine (50 μL). Yield: 0.16 g (62%). ^1H NMR (DMSO-*d6*, 400 MHz) δ_H, ppm: 7.59–7.51 (m, 15H, PPh_3); 5.33 (s, 1H, N—H); 4.46 (s, 4H, 4 x O—H); 3.96 (s, 1H, H—O); 3.88 (s, 1H, H-3); 3.56 (s, 1H, H-4); 3.56 (s, 1H, H-5); 3.46 (s, 1H, H-6); 3.07 (s, 2H, H6); 2.68 (t, 2H, *J* = 6.8 Hz, CH_2); 2.70 (t, 2H, *J* = 6.4 Hz, CH_2); 1.60 (s, 2H, CH_2); 1.50 (s, 2H, CH_2); 1.41 (d, 2H, *J* = 6.0 Hz, CH_2); 1.32 (d, 2H, *J* = 6.2 Hz, CH_2); $^{31}P\{^1H\}$ NMR (DMSO-*d6*, 400 MHz) δ_P, ppm: 33.25; $^{13}C\{^1H\}$ NMR (DMSO-*d6*, 100 MHz) δ_C, ppm: 172.8 (C═O); 134.3; 134.2; 132.8; 130.2; 130.1 (Ar); 74.1 (C-2); 72.9 (C-3); 72.0 (C-4); 70.6 (C-5); 63.8 (C-6); 38.5 (—CH_2); 38.2 (—CH_2); 29.2 (—CH_2); 28.8 (—CH_2); 25.6 (—CH_2); FT-IR (neat, cm^{-1}): 3303 *ν*(O—H); 2923 *ν*(CH_2); 1623 *ν*(C═O); 1545 *υυ*(N—H); 1433 *ν*(CH_2); 1211 *ν*(O—C); 1083 *ν*(C—S); 1029 *ν*(C—N); 861, 748, 692 *ν*(Ar); HR-MS(ESI). *m/z* $[M+H]^+$ calcd.: 756.1778; found: 756.177.

2.3. Synthesis of the acetylated thiocarbohydrate triphenylphosphinogold(I) complexes

2.3.1. Triphenylphosphino((3-((2S,3S,4R)-2,3,4,5,6-pentaacetoxyhexanamido)ethyl)thio)gold(I) complex (**5**)

A mixture of acetylated 2-gluconamidoethyl thiol (**L5**) (0.04 g, 0.08 mmol), $AuPPh_3Cl$ (0.03 g, 0.08 mmol) and triethylamine (10 μL) in toluene (5 mL) was stirred overnight at ambient temperature. The resultant mixture was filtered and the solvent of the filtrate was evaporated using a high vacuum pump, producing a cream solid of the title complex. Yield: 0.05 (72%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H, ppm: 7.49 (m, 15H, J = 2.4 Hz, PPh_3); 6.69 (t, 1H, J = 6.0 Hz N—H); 5.66 (q, 1H, J = 5.1 Hz, H-4); 5.45 (m, 1H, J = 5.4 Hz, H-5); 5.33 (dd, 1H, J = 4.35 and 28.95 Hz, H-2); 5.03 (q, 1H, J = 5.7 Hz, H-3); 4.28 (t, 1H, J = 5.6 Hz, H-6a); 4.11 (q, 1H, J = 5.2 Hz, H-6b); 3.53 (quintet, 1H, J = 6.0 Hz, CH_2); 3.19 (q, 1H, J = 7.2 Hz, CH_2); 2.77 (t, 1H, J = 6.4 Hz, CH_2); 1.35 (t, 1H, J = 7.6, CH_2); 2.18 (s, 3H, —OCOCH_3); 2.09 (s, 3H, —OCOCH_3); 2.06 (s, 3H, —OCOCH_3); 2.04 (s, 3H, —OCOCH_3); 2.02 (s, 3H, —OCOCH_3). ^{31}P {^{1}H} NMR ($CDCl_3$, 400 MHz) δ_P, ppm: 35.134. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ_C, ppm: 170.6 (—O*C*OCH$_3$); 169.9 (—O*C*OCH$_3$); 169.3 (—O*C*OCH$_3$); 169.7 (—O*C*OCH$_3$); 169.6 (—O*C*OCH$_3$); 165.9 (C-1); 75.0 (C-2); 69.0 (C-3); 68.1 (C-4); 667.9 (C-5); 63.6 (C-6); 46.2 (2 × CH_2); 21.5 (—OCO*C*H$_3$); 20.8 (—OCO*C*H$_3$); 20.7 (—OCO*C*H$_3$); 20.6 (—OCO*C*H$_3$); 10.2 (—O*C*OCH$_3$); 137.9 (P*Ph*); 134.2 (P*Ph*); 134.1(P*Ph*); 129.6 (P*Ph*); 129.2 (P*Ph*); 128.2 (P*Ph*); 125.3 (P*Ph*); 121.1 (P*Ph*); 121.0 (P*Ph*). FT-IR (neat, cm^{-1}): 2341 ν(P—C); 1752 ν(C=O); 1685 ν(C=O); 1533 ν(N—H); 3057 ν(CH_2, bands); 1437 ν(CH_2); 1213 ν(O—C); 1028 ν(C—N); 1101 ν(C—C). ($C_{34}H_{39}AuNO_{10}$-SP). *Anal.* Calc.: C, 46.81; H, 4.47; N, 1.52; S, 3.47. Found: C, 46.02; H, 5.18; N, 1.74; S, 3.76%. MS(ESI), m/z [M+Na]$^+$ calcd.: 944.18; Found: 944.12.

Synthesis of complexes **6**–**7** was achieved using the procedure described for complex **5** above, but using the reagents indicated for each complex.

2.3.2. Triphenylphosphino((3-((2S,3S,4R)-2,3,4,5,6-pentaacetoxyhexanamido)propyl)- thio)gold(I) complex (**6**)

Acetylated 3-gluconamidopropyl thiol (**L6**) (0.05 g, 0.11 mmol), $AuPPh_3Cl$ (0.05 g, (0.01 mmol 1 equiv.) and triethylamine (20 μL). Yield: 0.08 (89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H, ppm: 7.46 (m, 15H, P*Ph*$_3$); 6.65 (s, 1H, N—H); 5.67 (t, 1H, J = 5.1 Hz, H-3); 5.45 (t, 1H, J = 4.0 Hz, H-4); 5.36, (dd, 1H, J = 4.40 and 12.01 Hz, H-2); 5.03(q, 1H, J = 5.7 Hz, H-5); 4.27 (dd, 1H, J = 4.4 and 12.0 Hz, H-6a); 4.12 (dd, 1H, J = 5.6 and 12.04 Hz, H-6b); 3.48 (s, 1H, CH_2); 3.04 (t, 1H, J = 6.4 Hz, CH_2); 2.33 (s, 2H, CH_2); 1.88 (t, 1H, J = 6.4 Hz, CH_2); 1.17 (t, 2H, J = 7.2 Hz, CH_2); 2.33 (s, 1H, —OCOCH_3); 2.18 (s, 2H, CH_2); 2.09 (s, 3H, —OCO*C*H$_3$); 2.08 (s, 3H, CHCOC*H*$_3$); 2.06 (s, 3H, —OCO*C*H$_3$); 2.04 (s, 3H, —OCO*C*H$_3$). ^{31}P {^{1}H} NMR ($CDCl_3$, 400 MHz) δ_P, ppm: 37.36 (*P*Ph$_3$). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C, ppm: 170.6 (—O*C*OCH$_3$); 169.9 (—O*C*OCH$_3$); 169.7 (—O*C*OCH$_3$); 169.3 (—O*C*OCH$_3$); 166.3 (C-1); 137.8 (PPh) 134.3 (PPh); 134.2 (PPh); 131.8 (PPh); 131.8 (PPh); 129.4 (PPh); 129.3 (PPh); 71.9 (C-2) 69.8 (C-3); 69.2 (C-4); 68.7 (C-5); 61.4 (PPh); 46.3 (CH_2); 39.4 (CH_2); 38.4 (CH_2); 21.5 (CH_2); 21.0 (—OCO*C*H$_3$); 20.8 (—OCO*C*H$_3$); 20.7 (—OCO*C*H$_3$); 20.5 (—OCO*C*H$_3$). FT-IR (neat, cm^{-1}): 2926 ν(C—H); 2359 ν(P*Ph*$_3$); 2344 ν(P*Ph*$_3$); 1744 ν(C=O); 1676 ν(C=O); 1534 ν(N—H); 1437 ν(CH_2); 1210 ν(O—C); 1046 ν(C—N); 1099 ν(C—C). $C_{55}H_{58}Au_2NO_{11}P_2S$ (Mw = 1396.25) *Anal.* Calc.: C, 47.39; H, 4.62; N, 1.49; S, 3.42. Found: C, 47.26; H, 5.34; N, 1.91; S, 2.87%. HR-MS(ESI), m/z M$^+$ calcd.: 938.1994; Found: 938.2036.

2.3.3. Triphenylphosphino((3-((2S,3S,4R)-2,3,4,5,6-pentaacetoxyhexanamido)butyl)thio) gold(I) complex (**7**)

Acetylated 4-gluconamidobutyl thiol (**L7**) (0.05 g, 0.10 mmol), $AuPPh_3Cl$ (0.05 g, 0.10 mmol) and triethylamine (20 μL). Yield: 0.07 g (72%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H, ppm: 7.46 (m, 15H, P*Ph*$_3$); 6.19 (s, 1H, N—H); 5.65 (t, 1H, J = 5.2 Hz, H-3); 5.43 (q, 1H, J = 5.2 Hz, H-4); 5.29, (dd, 1H, J = 4.80 and 15.2 Hz, H-2); 5.02(q, 1H, J = 5.2 Hz, H-5); 4.28 (dd, 1H, J = 7.6 and 12.0 Hz, H-6a); 4.11 (dd, 1H, J = 5.6 and 12.0 Hz, H-6b); 3.25 (t, 2H, J = 6.4 Hz, CH_2); 3.01 (t, 1H, J = 6.4 Hz, CH_2); 2.64 (t, 1H, J = 6.8 Hz, CH_2); 2.41 (s, 3H, —OCO*C*H$_3$); 2.09 (s, 3H, —OCO*C*H$_3$); 2.07 (s, 3H, —OCO*C*H$_3$); 2.04 (s, 3H, —OCO*C*H$_3$); 2.01 (s, 3H, —OCO*C*H$_3$); 1.67 (t, 2H, J = 7.2 Hz, CH_2); 1.57 (t, 2H, J = 10.4 Hz, CH_2). ^{31}P {^{1}H} NMR ($CDCl_3$, 400 MHz) δ_P, ppm: 34.84 (*P*Ph$_3$). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C, ppm: 171.8 (O*C*OCH$_3$); 169.9 (OCOCH$_3$); 169.7 (OCOCH$_3$); 169.2 (O*C*OCH$_3$); 166.3 (C-1); 134.2 (P*Ph*); 134.1 (P*Ph*); 131.8; 129.4 (P*Ph*); 129.3 (P*Ph*); 129.2 (P*Ph*); 128.9 (P*Ph*); 71.8 (C-2); 69.4 (C-3); 69.1 (C-4); 68.8 (5); 61.8 (C-6); 39.0 (CH_2); 38.1 (CH_2); 28.03 (CH_2); 26.0 (CH_2); 20.7 (3× —OCO*C*H$_3$); 20.68 (2× —OCO*C*H$_3$). FT-IR (neat, cm^{-1}): 3015 ν(N—H); 2968 ν(C—H); 2355 ν(P*Ph*$_3$); 2333 ν(P*Ph*$_3$); 1745 ν(C=O); 1677 ν(C=O); 1537 ν(N—H); 1431.92 ν(CH_2); 1371 ν(O—C); 1216 ν(C-S); 1098 ν(C—N); 1046 ν(C—C). ($C_{37}H_{43}AuNO_{11}SP$). *Anal.* Calc.: C, 47.95; H, 4.77; N, 1.47; S, 3.37. Found: C, 47.60; H, 4.69; N, 1.46; S, 3.44%. HR-MS(ESI), m/z [M]$^+$ and [M+H]$^+$ calcd.: 951.2116 and 952.2150; Found: 951.2136 and 952.2136.

2.4. Synthesis of diphosphinogold(I) glycothiolato complexes

2.4.1. Bis{diphenylphosphino((2-((2S,3S,4R)-2,3,4,5,6-pentahydroxyhexanamido)ethyl) thio)gold(I)} complex (**8**)

To a mixture of 2-gluconamidoethyl thiol (**L1**) (0.10 g, 0.39 mmol, 2 equiv.) in water (5 mL) and [Au_2(dppe)Cl_2] (0.17 g, 0.20 mmol) dissolved in CH_2Cl_2 (10 mL), was added triethylamine (50 μL). The reaction mixture was stirred at ambient temperature for 3 h under nitrogen. The resultant mixture was filtered and the precipitate was washed with water and DCM to afford a light yellow solid of the title complex. Yield: 0.20 g (69%). ^{1}H NMR (DMSO, 400 MHz) δ_H, ppm: 7.78 (s, 4H, —P*Ph*$_2$(CH_2)$_2$P*Ph*$_2$—); 7.53 (s, 4H, —P*Ph*$_2$(CH_2)$_2$P*Ph*$_2$—); 7.34 (d, 2H, —P*Ph*); 7.21 (s, 1H, N—H); 5.43 (s, 1H, OH); 4.57–4.36 (m, 4H, OH); 4.13 (s, 1H, H); 3.94 (d, 2H, J = 21.2 Hz, H-6); 3.15 (s, 3H, H—); 2.91 (s, 4H, (s, 1H, —PPh$_2$(*CH*$_2$)$_2$PPh$_2$—). ^{31}P {^{1}H} NMR (DMSO-*d6*, 400 MHz) δ_P, ppm: 35.1 (*P*Ph$_2$), 21.29 (*P*Ph$_2$). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C, ppm: 172.6 (C=O); 133.7 (*Ph*$_2$P(CH$_2$)$_5$P*Ph*$_2$); 132.4 (P*Ph*$_2$(CH$_2$)$_5$ P*Ph*$_2$); 129.9 (P*Ph*$_2$(CH$_2$)$_5$P*Ph*$_2$); 129.3 (P*Ph*$_2$(CH$_2$)$_5$P*Ph*$_2$); 74.0 (C-2); 72.9 (C-3); 72.0 (C-4); 70.6 (C-5); 63.8 (C-6); 45.2 (N*C*H$_2$CH$_2$ S-); 31.2 (NCH$_2$*C*H$_2$S—); 29.6 (Ph$_2$PCH$_2$*C*H$_2$PPh$_2$); 23.1 (PPh$_2$(*C*H$_2$-CH$_2$PPh$_2$). FT-IR (neat, cm^{-1}): 1637 ν(C=O); 1536 ν(N—H); 1434 ν(CH_2); 1222 ν(C—O); 1025 ν(C—O); 930, 867, 725, 691 ν(P*Ph*$_2$). HR-MS (ESI), *(m/z)* [M+H]$^+$ calcd.: 1300.2081; found: 1300.2428.

A similar method used to prepare complex **8** was followed to synthesize complexes **9**–**11**, but using the reagents indicated.

2.4.2. Bis{diphenylphosphino((2-((2S,3S,4R)-2,3,4,5,6-pentahydroxyhexanamido)propyl)thio)gold(I)} complex (**9**)

3-Gluconamidopropyl thiol (**L2**) (0.11 g, 0.4 mmol, 2 equiv.), [Au_2(dppe)Cl_2] (0.18 g 0.20 mmol, 1 equiv.) and triethylamine (50 μL). Yield: 0.19 g (73%). ^{1}H NMR (DMSO, 400 MHz) δ_H, ppm: 7.70 (s, 4H, —P*Ph*$_2$); 7.45 (s, 4H, —P*Ph*$_2$); 7.38 (d, 2H, —P*Ph*); 7.21 (s, 1H, N—H); 5.42 (s, 1H, OH); 4.47–4.26 (m, 4H, OH); 4.23 (s, 1H, H); 3.91 (s, 2H, H-6); 3.15 (s, 2H, —NCH$_2$); 2.86 (s, 2H,

—CH_2S—); 1.79 (s, 1H, CH_2); 1.56 (s, 4H, —P(CH_2)$_2$P—); ^{31}P{^{1}H} NMR (DMSO-*d6*, 400 MHz) δ_P, ppm: 32.5 (*P*Ph$_2$). ^{13}C {^{1}H} NMR (CDCl$_3$, 100 MHz) δ_C, ppm: 172.6 (C=O); 133.7 (—P*Ph*$_2$); 132.4 (—P*Ph*$_2$); 129.9 (—P*Ph*$_2$); 129.3 (—P*Ph*$_2$); 74.2 (C-2); 73.0 (C-3); 72.0 (C-4); 70.6 (C-5); 63.8 (C-6); 44.9 (NCH_2CH$_2$S—); 31.4 (NCH$_2$CH_2S-); 28.6 (CH_2). FT-IR (neat, cm^{-1}): 1639 *v*(C=O); 1536 *v*(N—H); 1433 *v*(CH$_2$); 1224 *v*(C—O); 1029 *v*(C—O); 930–690 *v*(PPh$_2$). HR-MS (ESI), *m/z* [M+H]$^+$ calcd.: 1328.2394; Found: 1328.2084.

2.4.3. Bis{diphenylphosphino((2-((2S,3S,4R)-2,3,4,5,6-pentahydroxyhexanamido)butyl) thio)gold(I)} complex (**10**)

4-Gluconamidoethyl thiol (**L3**) (0.11 g, 0.4 mmol, 2 equiv.), [Au$_2$(dppe)Cl$_2$] (0.18 g 0.20 mmol, 1 equiv.) and triethylamine (50 μL). Yield: 0.20 g (69%). ^{1}H NMR (DMSO, 400 MHz) δ_H, ppm: 7.73 (s, 4H, —P*Ph*$_2$(CH$_2$)$_2$P*Ph*$_2$—); 7.57 (d, 4H, *J* = 7.2 Hz, —P*Ph*$_2$(CH$_2$)$_2$P*Ph*$_2$—); 7.51 (d, 4H, —P*Ph*); 5.7 (s, 1H, N—H); 5.37 (s, 1H, OH); 4.54–4.38 (m, 4H, OH); 3.96 (s, 1H, H-2); 3.88 (s, 2H, H-3); 3.56 (d, 2H, *J* = 11.2, H-5); 3.08 (t, 2H, *J* = 6.4 Hz, H-6); 2.96 (s, 1H, H-4); 2.71 (d, 4H, *J* = 6.0 Hz, NCH_2CH_2S—) 1.71(NCH$_2$(CH_2)$_2$CH$_2$S—); 1.58 (t, 2H, *J* = 6.4 Hz, —PPh$_2$(CH_2)$_2$PPh$_2$—); 1.49 (t, 2H, *J* = 6.4 Hz, —PPh$_2$(CH_2)$_2$PPh$_2$—). ^{31}P {^{1}H} NMR (DMSO-*d6*, 400 MHz) δ_P, ppm: 30.5 (*P*Ph$_2$). ^{13}C {^{1}H} NMR (CDCl$_3$, 100 MHz) δ_C, ppm: 172.8 (C=O); 133.8 (*Ph*$_2$P(CH$_2$)$_5$P*Ph*$_2$); 133.7 (P*Ph*$_2$(CH$_2$)$_5$P*Ph*$_2$); 132.7 (P*Ph*$_2$(CH$_2$)$_5$P*Ph*$_2$); 129.9 (P*Ph*$_2$(CH$_2$)$_5$P*Ph*$_2$); 74.1 (C-2); 72.8 (C-3); 71.9 (C-4); 70.6 (C-5); 63.8 (C-6); 38.2 (NCH$_2$CH$_2$S—); 37.6 (NCH$_2$CH$_2$S—); 28.4 (Ph$_2$PCH$_2$CH$_2$PPh$_2$); 27.7 (NCH$_{2(}$CH$_2$)$_2$CH2S—); 26.3 (PPh$_2$(CH$_2$)$_2$PPh$_2$). FT-IR (neat, cm^{-1}): 1622 *v*(C=O); 1542 *v* (N—H); 1435 *v*(CH$_2$); 1277 *v*(C—O); 1075 *v*(C—O); 862, 867, 727, 690 *v*(PPh$_2$). HR-MS (ESI), *(m/z)* [M+H]$^+$ calcd.: 1359.2863; Found: 1359.6355.

2.4.4. Bis{diphenylphosphino((2-((2S,3S,4R)-2,3,4,5,6-pentahydroxyhexanamido)pentyl)thio)gold(I)} complex (**11**)

5-Gluconamidopentyl thiol (**L4**) (0.06 g, 0.19 mmol, 2 equiv.), [Au$_2$(dppe)Cl$_2$] (0.10 g, 0.10 mmol, 1 equiv.) and triethylamine (20 μL). Light yellow powder. Yield: 0.11 g (85%). ^{1}H NMR (DMSO-*d6*, 400 MHz) δ_H, ppm: 7.74 (s, 2H, —P*Ph*$_2$(CH$_2$)$_2$P*Ph*$_2$—); 7.58 (s, 2H, —P*Ph*$_2$(CH$_2$)$_2$P*Ph*$_2$—); 7.52 (d, 1H, —P*Ph*); 5.32 (s, 1H, N—H); 4.50 (s, 1H, OH); 4.44 (s, 1H, OH); 4.35 (s, 1H, OH); 4.30 (s, 1H, OH); 3.96 (s, 1H, H5); 3.89 (s, 1H, H4); 3.55 (s, 3H, H3); 3.46 (s, 2H, H6); 3.07 (s, 2H, —PPh$_2$(C*H$_2$*)PPh$_2$—); 2.95 (s, 1H, H2); 2.68 (—PPh$_2$(C*H$_2$*)PPh$_2$—); 1.60 (s, 2H, —NCH$_2$—); 1.42 (s, 2H, —CH$_2$—); 1.32 (s, 2H, —CH$_2$—). ^{31}P {^{1}H} NMR (DMSO-*d6*, 400 MHz) δ_P, ppm: 30.7 (*P*Ph$_2$). ^{13}C {^{1}H} NMR (DMSO-*d6*, 100 MHz) δ_C, ppm: 172.8 (C=O); 133.7 (*Ph*$_2$P(CH$_2$)$_5$P*Ph*$_2$); 132.7 (P*Ph*$_2$(CH$_2$)$_5$P*Ph*$_2$); 129.9 (P*Ph*$_2$(CH$_2$)$_5$P*Ph*$_2$); 74.3 (C-2); 73.1 (C-3); 72.0 (C-4); 70.7 (C-5); 64.0 (C-6); 38.5 (NCH$_2$CH$_2$S—); 38.2 (NCH$_2$CH$_2$S—); 29.2 (Ph$_2$PCH$_2$CH$_2$PPh$_2$); 28.8 (PPh$_2$(*CH$_2$*CH$_2$PPh$_2$); 25.7 (—CH$_2$—); 25.5 (—CH$_2$—). FT-IR (neat, cm^{-1}): 3289 (OH); 2927 (CH$_2$); 1653 *v*(C=O); 1558 *v*(N—H); 1434 *v*(CH$_2$ str.); 1157 (C—S), *v*(C—O); 1085 *v*(C—O); 890, 727, 690 *v*(PPh$_2$). HR-MS (ESI), *m/z* [M+H]$^+$ calcd.: 1385.3053; Found: 1385.3131.

2.4.5. Acetylated gluconamidoethyl bis(diphenylphosphino)ethanegold (I) thiolate complex **12**

To a mixture of acetylated gluconamidoethyl thiol (**L5**) (0.11 g, 0.23 mmol) and [Au$_2$(dppe)Cl$_2$] (0.1 g, 0.12 mmol) (2:1 mol ratio respectively) dissolved in CH$_2$Cl$_2$ (10 mL), excess K$_2$CO$_3$ (0.15 g) was added. The reaction mixture was stirred at ambient temperature for 2 days and the resultant mixture filtered and the filtrate reduced to half of the volume. The product was precipitated in diethyl ether to form a white solid. The precipitate was filtered and washed twice with 10 mL diethyl ether to afford a white solid which was dried under high *vacuo*. Yield: 0.15 g (75%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H, ppm: 7.57 (s, 8H, (—P*Ph*$_2$(CH$_2$)$_2$P*Ph*$_2$—); 7.40 (s, 12H, (—P*Ph*$_2$(CH$_2$)$_2$P*Ph*$_2$—); 7.15 (s, 1H, N—H); 5.66 (d, 1H, *J* = 4.4 Hz, H-3); 5.47 (t, 1H, *J* = 5.6 Hz, H-4); 5.36 (s, 1H, H-2); 5.04 (q, 1H, *J* = 5.2 Hz, H-5); 4.27 (dd, 1H, *J* = 4.4 and 2.4 Hz, H-6a); 4.12 (dd, 1H, *J* = 5.6 and 12.4 Hz, H-6b); 3.55 (s, 2H, —N(CH$_2$)$_2$-S—); 3.20 (s, 2H, —N(CH$_2$)$_2$S—); 2.74 (s, 1H, —Ph$_2$P(C*H$_2$*)$_2$PPh$_2$—); 2.22 (s, 3H, —OCOCH$_3$); 2.07 (s, 3H, —OCOCH$_3$); 2.05 (s, 3H, —OCOCH$_3$); 2.04 (s, 3H, —OCOCH$_3$); 2.01 (s, 3H, —OCOCH$_3$); 1.63 (s, 2H, —PPh$_2$(CH$_2$)$_2$PPh$_2$—). ^{31}P {^{1}H} NMR (CDCl$_3$, 400 MHz) δ_P, ppm: 36.85 (*P*Ph$_2$). ^{13}C {^{1}H} NMR (CDCl$_3$, 100 MHz) δ_C, ppm: 170.6 (—OCOCH$_3$); 169.9 (—OCOCH$_3$); 169.8 (—OCOCH$_3$); 169.4 (—OCOCH$_3$); 166.3 (C-1); 133.4 (PPh$_2$(C*H$_2$*)$_3$PPh$_2$—); 133.3 (—P*Ph*$_2$(CH$_2$)$_3$P*Ph*$_2$—); 132.3 (P*Ph*$_2$(CH$_2$)$_3$P*Ph*$_2$—); 129.6 (P*Ph*$_2$(CH$_2$)$_3$P*Ph*$_2$—); 72.1 (C-2); 69.8 (C-3); 69.1 (C-4); 68.7 (C-5); 61.5 (C-6); 29.6 (—N(C*H$_2$*)$_2$S—); 24.2 (—Ph$_2$P(C*H$_2$*)$_3$PPh$_2$—); 23.9 (—Ph$_2$P(C*H$_2$*)$_3$PPh$_2$—); 23.8 (—Ph$_2$P(C*H$_2$*)$_3$PPh$_2$—); 21.0 (—OCOCH$_3$); 20.8 (—OCOCH$_3$); 20.7 (—OCOCH$_3$); 20.6 (—OCOCH$_3$); 20.6 (—OCOCH$_3$). FT-IR (neat, cm^{-1}): 1742 *v*(C=O); 1676 *v*(C=O); 1526 *v*(N—H); 1437 *v*(CH$_2$); 1213 *v* (C—O); 1036 *v*(CH$_3$C—O); 959, 773, 729, 693 *v*(PPh$_2$). HR-MS(ESI), *(m/z)* [M+H]$^+$ calcd.: 1721.3171; Found: 1721.2787.

Synthesis of complexes **13**–**14** was achieved using the procedure described for complex **12** above, but using the reagents indicated for each complex.

2.4.6. Acetylated gluconamidoethyl bis(diphenylphosphino) propanegold(I) thiolate complex **13**

[Au$_2$(dppp)Cl$_2$] (0.10 g, 0.11 mmol), acetylated gluconamidoethyl thiol (**L5**) (0.11 g, 0.23 mmol, 2 equiv.) and K$_2$CO$_3$ (0.12 g). Yield: 0.13 g (67%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H, ppm: 7.62 (m, 8H, —P*Ph*$_2$(CH$_2$)$_3$P*Ph*$_2$—); 7.46 (m,12H, —*Ph*$_2$P(CH$_2$)$_3$P*Ph*$_2$—); 7.18 (s, 1H, N—H); 6.49 (t, 1H, N—H); 5.67 (t, 1H, *J* = 4.8 Hz, H-3); 5.47 (t, 1H, *J* = 6.0 Hz, H-4); 5.36 (d, 2H, *J* = 4.0, H-2); 5. 04 (q, 1H, *J* = 5.6 Hz, H-5); 4.28 (dd, 1H, *J* = 4.4 and 12.0 Hz, H-6a); 4.12 (dd, 1H, *J* = 5.6 and 12.0 Hz, H-6b); 3.39 (q, 2H, *J* = 6.0 Hz, —N(C*H$_2$*)$_2$S—); 3.04 (q, 2H, *J* = 6.0 Hz, —N(C*H$_2$*)$_2$S—); 2.82 (d, 2H, *J* = 8.0 Hz, —PPh$_2$(C*H$_2$*)$_3$PPh$_2$—); 2.19 (s, 3H, —OCOCH$_3$); 2.09 (s, 3H, —OCOCH$_3$); 2.08 (s, 3H, —OCOCH$_3$); 2.06 (s, 3H, —OCOCH$_3$); 2.04 (s, 3H, —OCOCH$_3$); 1.94 (m, 2H, —PPh$_2$(C*H$_2$*)$_3$PPh$_2$—); 1.63 (s, 2H, —PPh$_2$-P(C*H$_2$*)$_3$PPh$_2$—). ^{31}P {^{1}H} NMR (CDCl$_3$, 400 MHz) δ_P, ppm: 29.88 (*P*Ph$_2$). ^{13}C {^{1}H} NMR (CDCl$_3$, 100 MHz) δ_C, ppm: 170.5 (—OCOCH$_3$); 169.8 (—OCOCH$_3$); 169.7 (—OCOCH$_3$); 169.3 (—OCOCH$_3$); 166.1 (C-1); 133.4 (P*Ph*$_2$(CH$_2$)$_3$P*Ph*$_2$—); 133.3 (—P*Ph*$_2$(CH$_2$)$_3$P*Ph*$_2$—); 132.0 (P*Ph*$_2$(CH$_2$)$_3$P*Ph*$_2$—); 129.5 (P*Ph*$_2$(CH$_2$)$_3$P*Ph*$_2$—); 72.0 (C-2); 69.70 (C-3); 69.2 (C-4); 68.8 (C-5); 61.5 (C-6); 44.6 (—N(C*H$_2$*)$_2$S—); 29.9 (—Ph$_2$P(C*H$_2$*)$_3$PPh$_2$—); 29.8 (—Ph$_2$P(C*H$_2$*)$_3$PPh$_2$—); 28.5 (—Ph$_2$P(C*H$_2$*)$_3$PPh$_2$—); 20.8 (—OCOC*H$_3$*); 20.8 (—OCOC*H$_3$*); 20.7 (—OCOC*H$_3$*); 20.6 (—OCOC*H$_3$*); 20.5 (—OCOC*H$_3$*). FT-IR (neat, cm^{-1}): 1747 *v*(C=O); 1675.72 *v* (C=O); 1213 *v*(C—N). (C$_{63}$H$_{78}$Au$_2$N$_2$O$_{22}$P$_2$S$_2$ 1.5CH$_2$Cl$_2$), *Anal.* Calc.: C, 40.98; H, 4.34; N, 1.47; S, 3.37. Found: C, 41.08; H, 4.45; N, 1.70; S, 2.71%. HR-MS(ESI), *(m/z)* [M+H]$^+$ calcd. 1735.3327; Found: 1735.3378.

2.4.7. Acetylated gluconamidoethyl bis(diphenylphosphino)butanegold (I) thiolate complex **14**

Acetylated gluconamidoethyl thiol (**L5**) (0.10 g, 0.22 mmol), [Au$_2$(dppb)Cl$_2$] (0.10 g, 0.11 mmol) and K$_2$CO$_3$ (0.25 g). Yield: 0.132 g (67%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H, ppm: 7.59 (t, 8H, *J* = 7.2, Hz, —*Ph*$_2$P(CH$_2$)$_4$P*Ph*$_2$—); 7.41 (t, 12H, *J* = 5.6 Hz, —*Ph*$_2$P(CH$_2$)$_4$P*Ph*$_2$—); 7.13 (s, 1H, N—H); 5.66 (t, 1H, *J* = 4.4 Hz, H-3); 5.47 (t, 1H, *J* = 6.0 Hz, H-4); 5.35 (d, 1H, *J* = 3.2 Hz, H-2); 5.04 (t, 1H, *J* = 5.2 Hz, H-5); 4.27 (dd, 1H, *J* = 4.4 and 12.4 Hz, H-6a); 4.12 (dd, 1H, *J* = 5.6 and 12.4 Hz, H-6b); 3.56 (s, 2H, —N(CH$_2$)$_2$S—); 3.23 (s, 2H, —N(CH$_2$)$_2$S—); 2.46 (s, 3H, —Ph$_2$P(C*H$_2$*)$_4$PPh$_2$—); 2.21 (s, 3H, —OCOCH$_3$); 2.07 (s, 3H, —OCOCH$_3$); 2.05 (s, 3H, —OCOCH$_3$); 2.04 (s, 3H, —OCOCH$_3$); 2.01 (s, 3H, —OCOCH$_3$); 1.73 (s, 5H, —Ph$_2$P(C*H$_2$*)$_4$PPh$_2$—). ^{31}P {^{1}H} NMR (CDCl$_3$, 400 MHz) δ_P, ppm: 32.54 (PPh$_2$). ^{13}C{^{1}H} NMR (CDCl$_3$, 100 MHz) δ_C, ppm: 170.51

(—OCOCH$_3$); 169.8 (—OCOCH$_3$); 169.7 (—OCOCH$_3$); 169.7 (—OCOCH$_3$); 169.4 (—OCOCH$_3$); 167.0 (C-1); 133.3 (—P*Ph*$_2$(CH$_2$)$_4$-P*Ph*$_2$—); 133.2 (—P*Ph*$_2$(CH$_2$)$_4$P*Ph*$_2$—); 133.2 (—P*Ph*$_2$(CH$_2$)$_4$P*Ph*$_2$—); 131.8 (—*Ph*$_2$P (CH$_2$)$_4$P*Ph*$_2$—); 129.4 (—*Ph*$_2$P(CH$_2$)$_4$P*Ph*$_2$—); 129.3 (—*Ph*$_2$P(CH$_2$)$_4$P*Ph*$_2$—); 72.1 (C-2); 69.7 (C-3); 69.1 (C-4); 68.8 (C-5); 61.5 (C-6); 31.6 (—N(*C*H$_2$)$_2$S—); 29.1 (—Ph$_2$P(*C*H$_2$)$_4$PPh$_2$—); 28.9 (—Ph$_2$P (*C*H$_2$)$_4$PPh$_2$—); 28.0 (—Ph$_2$P(*C*H$_2$)$_4$PPh$_2$—); 22.6 (—OCO*C*H$_3$); 21.0 (—OCO*C*H$_3$); 20.8 (—OCO*C*H$_3$); 20.7 (—OCO*C*H$_3$); 20.6 (—OCO*C*H$_3$). FT-IR (neat, cm^{-1}): 1744 *ν*(C=O); 1676 *ν*(C=O); 1522 *ν*(N—H); 1437 *ν*(CH$_2$ str.); 1370, 1212 *ν*(C—O); 1046 *ν* (C—N); 957, 746, 693 *ν*(PPh$_2$). (C$_{64}$H$_{80}$Au$_2$N$_2$O$_{22}$P$_2$S$_2$ 2CH$_2$Cl$_2$), *Anal.* Calc.: C, 40.15; H, 4.33; N, 1.40; S, 3.20. Found: C, 40.91; H, 3.05; N, 1.80; S, 3.93%. HR-MS(ESI), *m/z* M$^+$and [M+Na]$^+$ calcd. 1748.3450 and 1771.3450; Found: 1748.3214 and 1771.3378.

Complexes **15**–**17** were prepared using the procedure described for complex **12** above, but using the reagents indicated for each complex.

2.5. Synthesis of acetyl gluconamidopropyl diphosphinogold(I) thiolate complexes 15–17

*2.5.1. Acetylated 3-gluconamidopropyl bis(diphenylphosphino) ethanegold(I) thiolate complex **15***

[Au$_2$(dppe)Cl$_2$] (0.09 g, 0.10 mmol), **L6** (0.10 g, 0.21 mmol) and K$_2$CO$_3$ (0.12 g, 0.87 mmol). Yield: 0.15 g (82%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H, ppm: 7.60 (t, 8H, *J* = 5.6 Hz —P*Ph*$_2$(CH$_2$)$_2$P*Ph*$_2$—); 7.47 (m, 12H, —P*Ph*$_2$(CH$_2$)$_2$P*Ph*$_2$—); 7.10 (s, 1H, N—H); 5.68 (t, 1H, *J* = 4.8 Hz, H-3); 5.47 (t, 1H, *J* = 6.0 Hz, H-4); 5.34 (d, 1H, *J* = 4.4 Hz, H-2); 5.03 (q, 1H, *J* = 5.6 Hz, H-5); 4.29 (dd, 1H, *J* = 4.0 and 12.0 Hz, H-6a); 4.11 (dd, 1H, *J* = 5.6 and 12.0 Hz, H-6b); 3.45 (q, 2H, *J* = 6.8 Hz, —N(*C*H$_2$)$_3$S—); 3.06 (s, 2H, —N(*C*H$_2$)$_3$S—); 2.73 (s, 2H, —N(*C*H$_2$)$_3$S—); 2.17 (s, 3H, —OCO*C*H$_3$); 2.06 (s, 3H, —OCO*C*H$_3$); 2.05 (s, 3H, —OCO*C*H$_3$); 2.01 (s, 3H, —OCO*C*H$_3$); 2.00 (s, 3H, —OCO*C*H$_3$); 1.84 (quintet, 4H, *J* = 6.4 Hz, — Ph$_2$P(*C*H$_2$)$_2$PPh$_2$-—). ^{31}P {^{1}H} NMR (CDCl$_3$, 400 MHz) δ_P, ppm: 34.80 (*P*Ph$_2$). ^{13}C {^{1}H} NMR (CDCl$_3$, 100 MHz) δ_C, ppm: 170.7 (—O*C*OCH$_3$); 169.8 (—O*C*OCH$_3$); 169.8 (—O*C*OCH$_3$); 169.7 (—O*C*OCH$_3$); 169.24 (—O*C*OCH$_3$); 166.2 (C-1); 133.3 (—*Ph*$_2$P(CH$_2$)$_2$P*Ph*$_2$—); 132.3 (—*Ph*$_2$-P(CH$_2$)$_2$P*Ph*$_2$—); 129.6 (—*Ph*$_2$P(CH$_2$)$_2$P*Ph*$_2$—); 128.7 (—*Ph*$_2$P (CH$_2$)$_2$-P*Ph*$_2$—); 71.9 (C-2); 69.7 (C-3); 69.2 (C-4); 68.8 (C-5); 61.5 (C-6); 38.7 (—N(CH$_2$)$_3$S—); 35.7 (—N(CH$_2$)$_3$S—); 29.5 (—N(CH$_2$)$_3$S—); 28.7 (Ph$_2$P(CH$_2$)$_2$PPh$_2$—); 24.2 (—Ph$_2$P(*C*H$_2$)$_2$PPh$_2$—); 21.0 (—OCO*C*H$_3$); 20.8 (—OCO*C*H$_3$); 20.7 (—OCO*C*H$_3$); 20.6 (—OCO*C*H$_3$); 20.5 (—OCO*C*H$_3$). FT-IR (neat, cm^{-1}): 1747 *ν*(C=O); 1664 *ν*(C=O); 1528 *ν*(N—H); 1436 *ν*(CH$_2$); 1371, 1213 *ν*(C—O); 1045 *ν*(C—N); 960, 746, 693 *ν*(PPh$_2$). HR-MS(ESI), (*m/z*) M$^+$and [M+H]$^+$ calcd.: 1748.3450 and 1749.3484; Found: 1748.2982 and 1749.3475.

*2.5.2. Acetylated 3-gluconamidopropyl bis(diphenylphosphino) propanegold(I) thiolate complex **16***

[Au$_2$(dppp)Cl$_2$] (0.09 g, 0.10 mmol), **L6** (0.10 g, 0.21 mmol) and K$_2$CO$_3$ (0.12 g, 0.87 mmol). Yield: 0.14 g (77%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H, ppm: 7.62 (d, 8H, *J* = 8.4 Hz, —*Ph*$_2$P(CH$_2$)$_3$P*Ph*$_2$—); 7.44 (s, 12H, —*Ph*$_2$P(CH$_2$)$_3$P*Ph*$_2$—); 7.06 (s, 1H, N—H); 5.67 (t, 1H, *J* = 4.4 Hz, H-3); 5.46 (t, 1H, *J* = 5.6 Hz, H-4); 5.34 (d, 1H, *J* = 4.0 Hz, H-2); 5.04 (q, 1H, *J* = 5.6 Hz, H-5); 4.28 (dd, 1H, *J* = 4.0 and 12.0 Hz, H-6a); 4.12 (dd, 1H, *J* = 5.6 and 12.0 Hz, H-6b); 3.40 (d, 2H, *J* = 5.2 Hz, —N(CH$_2$)$_3$S—); 3.04 (s, 2H, —N(CH$_2$)$_3$S—); 2.86 (s, 2H, —N(CH$_2$)$_3$S—); 2.2 (s, 3H, —OCOCH$_3$); 2.07 (s, 3H, —OCOCH$_3$); 2.06 (s, 3H, —OCOCH$_3$); 2.02 (s, 3H, —OCOCH$_3$); 2.00 (s, 3H, —OCOCH$_3$); 1.90 (m, 4H, —Ph$_2$P(*C*H$_2$)$_3$PPh$_2$—) 1.64 (s, 2H, —Ph$_2$P(*C*H$_2$)$_2$PPh$_2$—). ^{31}P{^{1}H} NMR (CDCl$_3$) δ_P, ppm: 30.54 (*P*Ph$_2$). ^{13}C{^{1}H} NMR (CDCl$_3$, 100 MHz) δ_C, ppm: 170.7 (—O*C*OCH$_3$); 169.8 (—O*C*OCH$_3$); 169.8 (—O*C*OCH$_3$); 169.7 (—O*C*OCH$_3$); 166.0 (C-1); 133.4 (—P*Ph*$_2$(CH$_2$)$_3$P*Ph*$_2$—); 131.9 (—*Ph*$_2$P(CH$_2$)$_3$P*Ph*$_2$—); 129.5 (—*Ph*$_2$P(CH$_2$)$_3$P*Ph*$_2$—); 129.3 (—*Ph*$_2$P(CH$_2$)$_3$P*Ph*$_2$—); 71.8 (C-2); 69.7 (C-3); 69.3 (C-4); 68.8 (C-5); 61.5 (C-5); 39.2 (—N(CH$_2$)$_3$S—); 35.6 (—N(CH$_2$)$_3$S—); 29.9 (—Ph$_2$P(*C*H$_2$)$_3$PPh$_2$—); 29.9 (—PPh$_2$(CH$_2$)$_3$PPh$_2$-—); 28.5 (—Ph$_2$P (*C*H$_2$)$_3$PPh$_2$—); 20.9 (—OCO*C*H$_3$); 20.8 (—OCO*C*H$_3$); 20.7 (—OCO*C*H$_3$); 20.5 (—OCO*C*H$_3$); 20.5 (—OCO*C*H$_3$). FT-IR (neat, cm^{-1}): 1746 *ν*(C=O); 1676 *ν*(C=O); 1530 *ν*(N—H); 1436 *ν*(CH$_2$); 1371, 1211 *ν*(C—O); 1045 *ν*(C—N); 960, 746, 693 *ν*(PPh$_2$). HR-MS (ESI), *m/z* [M]$^+$ and [M+Na]$^+$ calcd.: 1762.3607 and 1785.36; Found: 1762.8674 and 1785.2944.

*2.5.3. Acetylated 3-gluconamidopropyl bis(diphenylphosphino) butanegold(I) thiolate complex **17***

[Au$_2$(dppb)Cl$_2$] (0.09 g, 0.11 mmol), **L6** (0.10 g, 0.21 mmol) and K$_2$CO$_3$ (0.12 g, 0.87 mmol). Yield: 0.17 g (85%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H, ppm: 7.63 (q, 8H, *J* = 7.6 Hz, —*Ph*$_2$P(CH$_2$)$_4$P*Ph*$_2$—); 7.46 (quintet, 12H, *J* = 8.0 Hz, —*Ph*$_2$P(CH$_2$)$_4$P*Ph*$_2$—); 7.29 (s, 1H, N—H); 5.68 (t, 1H, *J* = 4.8 Hz, H-3); 5.46 (t, 1H, *J* = 6.0 Hz, H-4); 5.35 (d, 1H, *J* = 4.4 Hz, H-2); 5.03 (q, 1H, *J* = 4.8 Hz, H-5); 4.29 (dd, 1H, *J* = 4.0 and 12.0 Hz, H-6a); 4.21 (dd, 1H, *J* = 5.6 and 12.0 Hz, H-6b); 3.47 (t, 2H, *J* = 6.4 Hz, —N(CH$_2$)$_3$S—); 3.09 (q, 2H, *J* = 6.4 Hz, —N(CH$_2$)$_3$S—); 2.53 (t, 2H, *J* = 4.4 Hz, N(CH$_2$)$_3$S—); 2.19 (s, 3H, —OCO*C*H$_3$); 2.07 (s, 3H, —OCO*C*H$_3$); 2.05 (s, 3H, —OCO*C*H$_3$); 2.04 (s, 3H, —OCO*C*H$_3$); 2.03 (s, 3H, —OCO*C*H$_3$); 1.86 (m, 4H, —Ph$_2$P (*C*H$_2$)$_4$PPh$_2$—); 1.78 (s, 2H, —Ph$_2$P(*C*H$_2$)$_4$PPh$_2$—); 1.64 (s, 2H, — Ph$_2$P(*C*H$_2$)$_4$PPh$_2$—). ^{31}P{^{1}H} NMR (CDCl$_3$, 400 MHz) δ_P, ppm: 32.48 (*P*Ph$_2$). ^{13}C{^{1}H} NMR (CDCl$_3$, 100 MHz) δ_C, ppm: 170.4 (—O*C*OCH$_3$); 169.8 (—O*C*OCH$_3$); 169.8 (—O*C*OCH$_3$); 169.7 (—O*C*OCH$_3$); 169.4 (—O*C*OCH$_3$); 168.5 (C-1); 133.3 (—PPh$_2$(*C*H$_2$)$_4$ PPh$_2$—); 133.2 (—PPh$_2$(*C*H$_2$)$_4$PPh$_2$—); 131.8 (—PPh$_2$(*C*H$_2$)$_4$PPh$_2$—); 131.0 (—PPh$_2$(*C*H$_2$)$_4$PPh$_2$—); 72.1 (C-2); 69.7 (C-3); 69.1 (C-4); 68.7 (C-5); 61.5 (C-5); 31.5 (—N(CH$_2$)$_3$S—); 29.9 (—N(CH$_2$)$_3$S—); 29.0 (—N(CH$_2$)$_3$S—); 20.9 (—OCO*C*H$_3$); 20.8 (—OCO*C*H$_3$); 20.7 (—OCO*C*H$_3$); 20.6 (—OCO*C*H$_3$). FT-IR (neat, cm^{-1}): 1747 *ν*(C=O); 1664 *ν*(C=O); 1528 *ν*(N—H); 1436 *ν*(CH$_2$); 1371, 1213 *ν*(C—O); 1045 *ν*(C—N); 960, 725, 693 *ν*(PPh$_2$). HR-MS(ESI), *m/z* M$^+$and [M +H]$^+$ calcd.: 1776.3763 and 1777.3797; Found: 1776.3735 and 1777.3776.

Complexes **18**–**20** were prepared using the procedure described for complex **12** above, but using the reagents indicated for each complex.

2.6. Synthesis of acetylated 4-gluconamidobutyl diphosphinogold(I) complexes 18–20

*2.6.1. Acetylated 4-gluconamidobutyl bis(diphenylphosphino) ethanegold(I) thiolate complex **18***

[Au$_2$(dppe)Cl$_2$] (0.10 g, 0.12 mmol), **L7** (0.11 g, 0.23 mmol) and K$_2$CO$_3$ (0.12 g). Yield: 0.09 g (45%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H, ppm: 7.63 (q, 8H, *J* = 7.6 Hz, Ar); 7.47 (t, 12H, *J* = 13.6 Hz, Ar); 7.13 (s, 1H, N—H); 5.68 (t, 1H, *J* = 4.8 Hz, H-3); 5.45 (t, 1H, *J* = 5.2 Hz, H-4); 5.32 (d, 1H, *J* = = 4.0 Hz, H-2); 5.03 (q, 1H, *J* = 4.4 Hz, H-5); 4.30 (dd, 1H, *J* = 3.6 and 12.0 Hz, H6a); 4.12 (q, 1H, *J* = 6.0, H-6b); 3.19 (m, 4H, -N(CH$_2$)$_2$-); 2.49 (q, 2H, *J* = 7.2 Hz, -CH$_2$S-); 2.19 (s, 3H, -COCH$_3$); 2.09 (s, 3H, —OCO*C*H$_3$); 2.07 (s, 3H, —OCO*C*H$_3$); 2.06 (s, 3H, —OCO*C*H$_3$); 2.05 (s, 3H, —OCO*C*H$_3$); 1.92 (d, 2H, *J* = 4.0 Hz, —CH$_2$—); 1.60 (m, 4H, —PCH$_2$CH$_2$P-). ^{31}P {^{1}H} NMR (CDCl$_3$, 400 MHz) δ_P, ppm: 34.52 (PPh$_2$). ^{13}C{^{1}H} NMR (CDCl$_3$, 100 MHz) δ_C, ppm: 170.6, 169.9, 169.7, 169.4, 169.3 (—OCOCH$_3$); 166.1 (C-1); 133.3, 133.2, 132.0, 129.4, 129.3 (Ar); 71.6 (C-2); 69.4 (C-3); 69.3 (C-4); 68.9 (C-5); 61.6 (C-6); 39.0 (—NCH$_2$—); 38.1 (—CH$_2$S—); 31.6 (—CH$_2$S—); 28.2 (—CH$_2$—); 27.6 (—P(CH$_2$)P—); 24.7 (—P(CH$_2$)P—); 22.6, 20.9, 20.7, 20.6, 20.5 (—OCO*C*H$_3$). FT-IR (neat, cm^{-1}): 1744 *ν*(COCH$_3$); 1672 *ν*(C=O); 1533 *ν*(N—H); 1436 *ν*(CH$_2$); 1370, 1213 *ν*(C—O); 1044 *ν*(C—N); 958–693 *ν*(Ar). HR-MS(ESI), *m/z* [M+H]$^+$ calcd. 1776.3797; Found: 1776.3763.

*2.6.2. Acetylated 4-gluconamidobutyl bis(diphenylphosphino) propanegold(I) thiolate complex **19***

[Au_2(dppp)Cl_2] (0.10 g, 0.12 mmol), **L7** (0.11 g, 0.23 mmol) and K_2CO_3 (0.12 g). Yield: 0.07 g (33%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H, ppm: 7.63 (q, 8H, J = 7.6 Hz, Ar); 7.45 (m, 12H, Ar); 6.85 (s, 1H, N—H); 5.67 (t, 1H, J = 4.8 Hz, H-3); 5.45 (t, 1H, J = 5.2 Hz, H-3); 5.31 (d, 1H, J = 4.0 Hz, H-4); 5.03 (q, 1H, J = 4.4 Hz, H-2); 4.29 (dd, 1H, J = 3.6 and 12.0 Hz, H-6a); 4.12 (q, 1H, J = 6.0, H-6b); 3.17 (t, 2H, J = 4.8 Hz, —NCH_2—); 2.88 (t, 4H, J = 6.0 Hz, —CH_2S—); 2.18 (s, 3H, —OCOCH_3); 2.08 (s, 3H, —OCOCH_3); 2.06 (s, 3H, —OCOCH_3); 2.05 (s, 3H, —OCOCH_3); 2.04 (s, 3H, —OCOCH_3); 1.75 (m, 6H, —P$(CH_2)_3$P—). ^{31}P{^{1}H} NMR ($CDCl_3$, 400 MHz) δ_P, ppm: 29.02 (PPh_2). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C, ppm: 170.6, 169.9, 169.84, 169.8, 169.3 (—O*C*OCH$_3$); 166.2 (C-1); 133.4, 132.1, 129.5, 129.4 (Ar); 71.9 (C-2); 69.7 (C-3); 69.3 (C-4); 68.8 (C-5); 61.6 (C-6); 39.2 (—NCH_2—); 34.4 (—CH_2S—); 31.6 (—CH_2—); 28.6 (—CH_2—); 28.5 (—P$(CH_2)_2$P—); 28.2 (—CH_2—); 20.9, 20.8, 20.7, 20.5 (—OCO*C*H$_3$). FT-IR (neat, cm^{-1}): 1744 ν(COCH$_3$); 1672 ν(C=O); 1533 ν(N—H), 1436 ν(CH_2); 1370, 1213 ν(C—O); 1044 ν(C—N); 958–693 ν(Ar). HR-MS(ESI), m/z [M+H]$^+$ calcd. 1791.3953; Found: 1791.3357.

*2.6.3. Acetylated 4-gluconamidobutyl bis(diphenylphosphino) butanegold(I) thiolate complex **20***

[Au_2(dppb)Cl_2] (0.10 g, 0.11 mmol), **L7** (0.11 g, 0.22 mmol) and K_2CO_3 (0.12 g). Yield: 0.08 g (40%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H, ppm: 7.63 (q, 8H, J = 7.6 Hz, Ar); 7.47 (t, 12H, J = 13.6 Hz, Ar); 7.13 (s, 1H, N—H); 5.68 (t, 1H, J = 4.8 Hz, H-3); 5.45 (t, 1H, J = 5.2 Hz, H-4); 5.32 (d, 1H, J = 4.0 Hz, H-2); 5.03 (q, 1H, J = 4.4 Hz, H-5); 4.30 (dd, 1H, J = 3.6 and 12.0 Hz, H-6a); 4.12 (q, 1H, J = 6.0, H-6b); 3.19 (m, 4H, —NCH_2—); 2.49 (q, 2H, J = 7.2 Hz, —CH_2S—); 2.19 (s, 3H, —OCOCH_3); 2.09 (s, 3H, —OCOCH_3); 2.07 (s, 3H, —OCOCH_3); 206 (s, 3H, —OCOCH_3); 2.05 (s, 3H, —OCOCH_3); 1.92 (d, 2H, J = 4.0 Hz, —CH_2—); 1.69 (d, 8H, —P$(CH_2)_4$P—). ^{31}P {^{1}H} NMR ($CDCl_3$, 400 MHz) δ_P, ppm: 31.05 (PPh_2). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C, ppm: 170.6, 169.9, 169.9, 169.7, 169.4, 169.3 (—O*C*OCH$_3$); 166.1 (C-1); 133.3; 133.2, 132.0, 129.4, 129.3 (Ar); 71.9 (C-2); 69.7 (C-3); 69.3 (C-4); 68.8 (C-5); 61.5 (C-6); 39.0 (—NCH_2—); 38.1 (—CH_2S—); 28.2 (—*C*H_2—); 28.1 (—CH_2—); 28.0 (—$Ph_2CH_2CH_2Ph_2$—); 27.6 (—CH_2—); 24.7 (—CH_2—); 20.9, 20.8, 20.7, 20.5, 20.45 (—OCO*C*H$_3$). FT-IR (neat, cm^{-1}): 1744 ν(—COCH$_3$); 1672 ν(C=O); 1533 ν(N—H); 1436 ν(CH_2); 1370, 1213 ν(C—O); 1044 ν(C—N); 958–693 ν(Ar). HR-MS(ESI), m/z [M+Na]$^+$ calcd.: 1827.3276; Found: 1827.3258.

2.7. In vitro anticancer screening

Cell culture. The human cancer cells lines MCF7 (breast cancer), HCT116(colon cancer) and PC3(prostate cancer) lines were routinely maintained as a monolayer cell culture at 37 °C, 5% CO_2, 95% air and 100% relative humidity in RPMI containing 5% fetal bovine serum, 2 mM L-glutamine and 50 μg/ml gentamicin. The WI-38 cell line-normal Human Fetal Lung Fibroblast from ECACC was routinely maintained as a monolayer cell culture at 37 °C, 5% CO_2, 95% air and 100% relative humidity in EMEM containing 10% fetal bovine serum, 2 mM L-glutamine and 50 μg/ml gentamicin.

2.7.1. Anti-cancer activity screening of the compounds

The growth inhibitory effects of the compounds were tested in the 3-cell line panel consisting of MCF7 (breast cancer), HCT116 (colon cancer) and PC3 (prostate cancer) by a Sulforhodamine B (SRB) assay [43,44]. Its principle is based on the ability of the protein dye Sulforhodamine B (Acid Red 52) to bind electrostatically in a pH-dependent manner to protein basic amino acid residues of trichloroacetic acid-fixed cells. Under mild acidic conditions it binds to the fixed cellular protein, while under mild basic conditions it can be extracted from cells and solubilised for measurement. The SRB assay was performed at CSIR in accordance with the protocol of the Drug Evaluation Branch, NCI, and the assay has been adopted for this screen. For the screening experiment, the cells (3–19 passages) were inoculated in 96-well microtiter plates at plating densities of 7–10 000 cells/well and were incubated for 24 h. After 24 h, one plate was fixed with TCA to represent a measurement of the cell population for each cell line at the time of drug addition (T_0). The other plates with cells were treated with the experimental drugs which were previously dissolved in DMSO and diluted in medium to produce 5 concentrations (6.25–100 μg/ml or 0.01–100 μM). Cells without drug addition served as a control. The blank contains complete medium without cells. Parthenolide was used as a reference standard. The plates were incubated for 48 h after addition of the compounds. Viable cells were fixed to the bottom of each well with cold 50% trichloroacetic acid, washed, dried and dyed by SRB. Unbound dye was removed and protein-bound dye was extracted with 10 mM Tris base for optical density determination at a wavelength of 540 nm using a multiwell spectrophotometer. Data analysis was performed using GraphPad Prism software. 50% of cell growth inhibition (IC_{50}) was determined by non-linear regression.

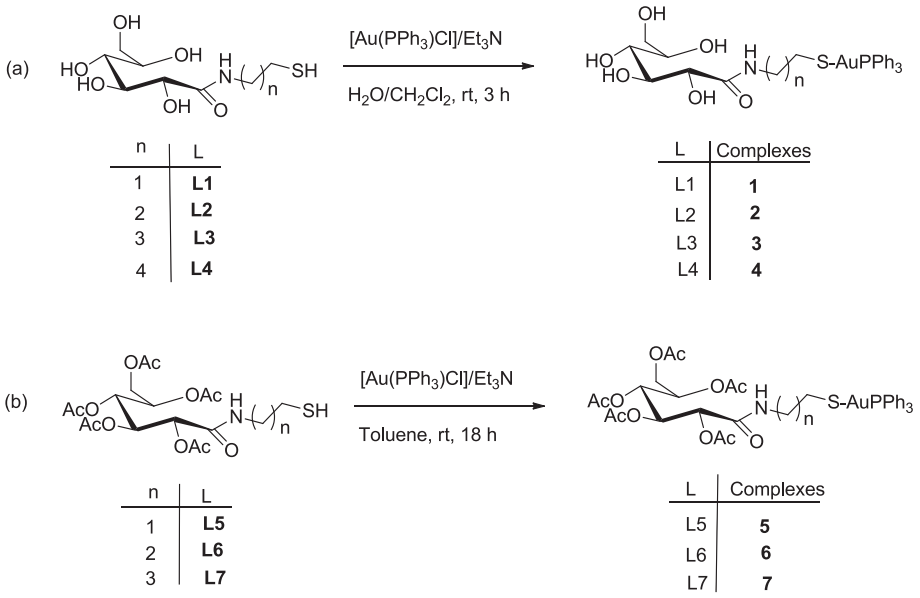
2.7.2. Cytotoxicity evaluation of active gold(1) complexes

The *in vitro* cytotoxicity of the active complexes was tested against the WI-38 normal human cell line by a Sulforhodamine B (SRB) assay [41,42]. For the screening experiment, the cells (21–50 passages) were inoculated in 96-well microtiter plates at plating densities of 10 000 cells/well and were incubated for 24 h. After 24 h the cells were treated with the experimental drugs which were previously dissolved in DMSO and diluted in medium to produce 5 concentrations. Cells without drug addition served as a control. The blank contains complete medium without cells. Parthenolide was used as a standard. The plates were incubated for 48 h after addition of the compounds. Viable cells were fixed to the bottom of each well with cold 50% trichloroacetic acid, washed, dried and dyed by SRB. Unbound dye was removed and protein-bound dye was extracted with 10 mM Tris base for optical density determination at a wavelength of 540 nm using a multiwell spectrophotometer. Data analysis was performed using GraphPad Prism software. 50% of cell growth inhibition (IC_{50}) was determined by non-linear regression.

3. Results and discussion

3.1. Synthesis of the gold(I) gluconamidoalkylthiolate complexes

The triphenyl phosphinogold(I) complexes [Au(**L1**)(PPh_3)] (**1**); [Au(**L2**)(PPh_3)] (**2**); [Au(**L3**)(PPh_3)] (**3**) and [Au(**L4**)(PPh_3)] (**4**) were synthesized from the reaction of [AuCl(PPh_3)] and the respective glycothiols **L1**-**L4**, in a biphasic medium of water and dichloromethane, as shown in Scheme 1a. All the complexes were isolated as pale yellow solids. The complexes were characterized using spectroscopic techniques, mass spectrometry and microanalysis. The ^{1}H NMR spectrum of complex **1** showed characteristic signals at 5.37 (singlet), 2.95 (triplet) and 3.47 (singlet), which were assigned to the amine (NH), —CH_2S— and —NCH_2— protons of the amino ethyl thiol linker respectively (Fig. S1 Supplementary information). The introduction of a triphenyl phosphine moiety was confirmed by the presence of multiplets in the aromatic region, integrating for a total of 15 protons due to aromatic protons of the triphenyl phosphine ligand. The ^{31}P {^{1}H} NMR spectra of complexes **1**–**4** displayed a single peak in each case, which resonated downfield at 33.29–36.77 ppm compared with the precursor [AuCl(PPh_3)] at 31.74 ppm (Fig. S1a).



Scheme 1. General synthesis of the thiocarbohydrate mono phosphinogold(I) complexes **1**–**7**.

The ^{13}C NMR spectrum of complex **1** showed, in addition to signals between 134.3 and 130.0 ppm for the aromatic carbons of the PPh_3 ligands, 172.7 for C═O and 55.3 ppm for CH_2S of the amino ethyl thiol linker. The IR absorption bands at 3264 and 1636 cm^{-1} correspond to the OH and C═O stretching vibrations in the complex. The weak absorption bands at 2362 cm^{-1} are also unambiguously assigned to the P-C stretching vibrations of the phenyl ring, and the stronger bands at 1536 and 1404 cm^{-1} are attributed to the stretching vibrations of the N—H and methyl groups bend. The mass spectra of complexes **1**–**4** showed molecular ion peaks comparable to the calculated values which confirmed the complexation (Fig. S1b). For example, the mass spectrum of complex **1** showed a molecular ion peak at *m/z* 714.13, which corresponds to the $[Au(\mathbf{2c})(PPh_3) + H]^+$ fragment (the calculated *m/z* value is 714.13 for $[Au(\mathbf{2c})(PPh_3) + H]^+$) and the *m/z* peak at 735.2065 corresponds to the sodium adduct ($[Au(\mathbf{2c})(PPh_3) + Na]^+$). All the complexes showed a typical fragmentation pattern. For example, in the HRMS of complex **1** the most characteristic signals observed at high *m/z* values represent fragments formed by the formation of the salt $[M+Na]^+$ and the formation of the most stable olefinic gold(I) intermediate fragment at *m/z* 646.1999 (Fig. S1a and Scheme S1) via the loss of four hydroxyl radical units $[M-4OH]^+$. Elemental analysis also confirmed the structure of **1**. Similar NMR spectral patterns, FTIR and mass spectroscopy results were observed for complexes **2**, **3** and **4**, but with different chemical shifts, as presented in detail in the experimental section.

Since lipophilicity seems to enhance anticancer activity [27], the acetylated forms of the glyco gold(I) complexes, $[Au(\mathbf{L5})(PPh_3)]$ (**5**), $[Au(\mathbf{L6})(PPh_3)]$ (**6**) and $[Au(\mathbf{L7})(PPh_3)]$ (**7**), were also obtained from the reaction of $[AuCl(PPh_3)]$ and acetylated gluconamidoalkyl thiol ligands **L5**-**L7** and these complexes were isolated as light yellow solids, as shown in Scheme 1b. Complexes **5**–**7** are soluble in organic solvents (CH_2Cl_2, DMSO, methanol etc.), show excellent stability at room temperature and also upon exposure to air. The downfield shifts obtained for the resonances of the ethylene protons upon complexation confirmed coordination to gold. The disappearance of the thiol (—SH) signal in the range 1.43–1.33 ppm in the ^1H NMR spectra of the complexes further confirmed the formation of the proposed products (Fig. S2a). There was also a significant downfield shift of the ethylene linker carbon peaks observed for complexes **5**–**7** in the ^{13}C NMR spectra. For example, in complex **6** the carbon atom close to the amide (—NCH_2—) group resonates at 46 ppm, compared to that of ligand **L6** at *ca.* 38 ppm. The carbon atom bonded to the sulfur atom and the middle carbon atom (—CH_2CH_2S) are also significantly shifted upfield from 29 and 36 ppm in **L6** to 38 and 39 ppm in complex **6**, respectively. The ^{13}C NMR spectrum of complex **5** showed, in addition to the signals between 134.3–130.0 ppm for the aromatic carbon atoms, 165.9 ppm for the amide carbonyl C═O group and 46.2 ppm for the CH_2S group of the amino ethyl thiol linker, confirming both the ligand and the gold(I) phosphines are intact after the complexation has taken place. The $^{31}P\{^1H\}$ NMR spectra of complexes **5**–**7**, measured at room temperature, exhibit only one resonance with a downfield shift between 35.13 and 37.36 ppm compared to the precursor $[Au(PPh_3)Cl]$ at 33.74 ppm. High resolution mass spectral data support the formation of complexes **5**–**7**, having the general formula $[Au(\mathbf{L})PPh_3]$, and their purity was established by microanalysis (Figs. S2a and S2b). HRMS of complex **5** showed a peak at *m/z* 944.12, which corresponds to the $[Au(\mathbf{L5})(PPh_3)+Na]^+$ fragment (the calculated *m/z* value is 944.18 for $[M+Na]^+$). Elemental analysis also confirmed the structure of **5**. In the case of complexes **6** and **7**, HRMS of these complexes showed, among other peaks, a peak at *m/z* 938.2030, analogous to the $[Au(\mathbf{L6})(PPh_3)]^+$ fragment (the calculated *m/z* value is 938.1993 for $[Au(\mathbf{L6})(PPh_3)]^+$) (Fig. S2a), Similarly, a peak at *m/z* 953.2227 in the spectrum of complex **7** is correlated to the $[Au(\mathbf{L7})(PPh_3) + H]^+$ fragment (the calculated *m/z* value is 953.2228 for $[Au(\mathbf{L7})(PPh_3) + H]^+$). Surprisingly, the fragmentation patterns of **6** and **7** showed most stable molecular ion peaks at *m/z* 1396.2537 (Fig. S2b) and 1411.2684, which correspond to the two gold(I) triphenyl phosphine conjugates of **L6** $[Au_2(\mathbf{L6})(PPh_3)_2]^+$ and **L7** $[Au_2(\mathbf{L7})(PPh_3)_2]^+$, respectively. This suggests an Au–Au interaction between the gold(I) triphenyl phosphine and the glyco gold(I) complex comparable to that which has been reported in the literature by Raubenheimer et al. [21] and Keter et al. [26]. This result was supported by elemental analysis of complex **6**, which agrees very well with the two bi-triphenyl phosphine gold(I) conjugates of **L6** $[Au_2(\mathbf{L6})(PPh_3)_2]$ and **L7** $[Au_2(\mathbf{L7})(PPh_3)_2]^+$ reported in the experimental section. This observation is not common to the shorter chain ($n = 1$) complex **5**, as confirmed in the mass spectrum (Fig. S2a), which may be due to steric hindrance caused by the closeness of phenyl and acetyl groups of the thiocarbohydrate

moiety. Additional evidence of this was detected in the IR spectrum, with a distinct shift to 1752 ν(C═O), 1685 ν(C═O) and 1533 cm^{-1} ν(N—H).

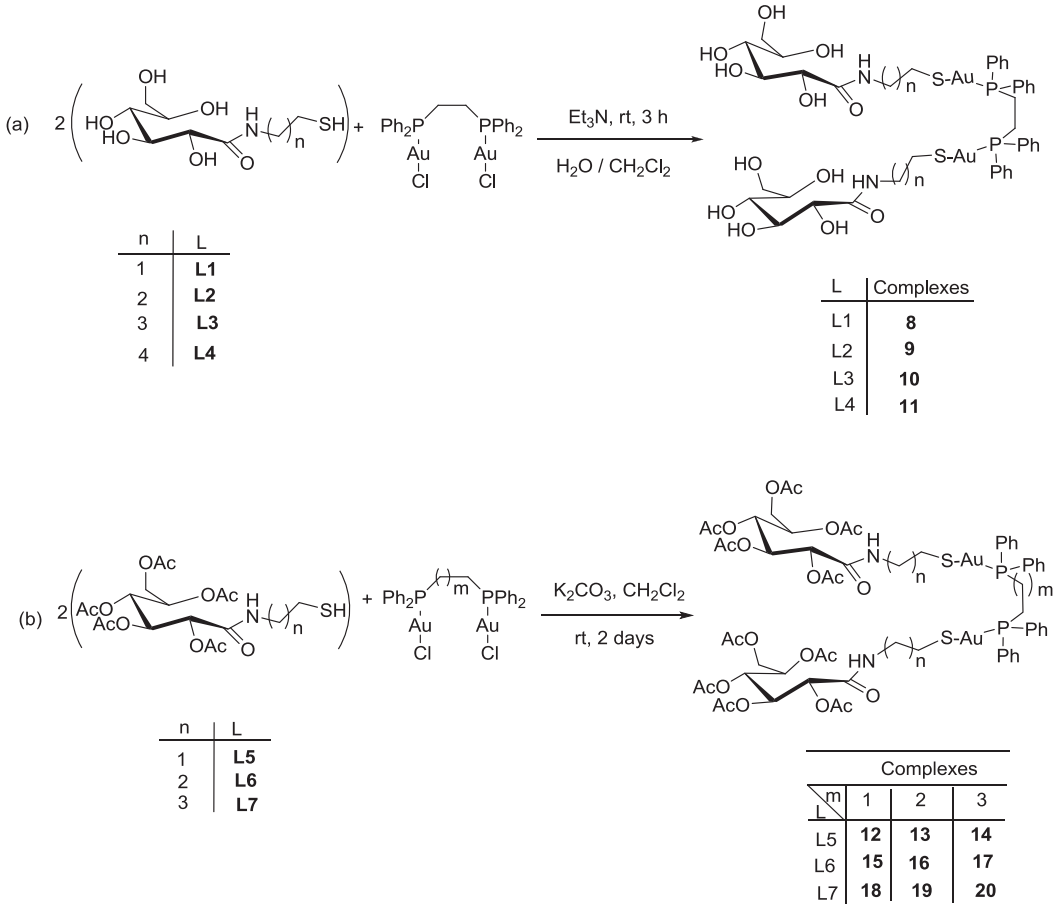
3.2. Synthesis of the binuclear gold(I) gluconamidoalkyl thiolate complexes

After the successful synthesis of the mononuclear gold(I) complexes having non-toxic thiocarbohydrate ligands, our attention turned to the synthesis of binuclear gold(I) complexes using the same ligand system, as shown in Scheme 2a. The complexes [Au(**L1**)(dppe)] (**8**), [Au(**L2**)(dppe)] (**9**), [Au(**L3**)(dppe)] (**10**) and [Au(**L4**)(dppe)] (**11**) [dppe = bis(diphenylphosphino)ethane] where prepared by reacting $[Au_2(dppe)Cl_2]$ and two molar equivalents of each of the ligands **L1–L4** in a biphasic medium (DCM/H_2O), as described for complexes **1–4** (Scheme 2a). This is to allow the study of the effect of the chain length of the linker on the anticancer properties of these complexes. The complexes were isolated as pale yellow solids in moderate yields. The general pattern of ^1H and $^{13}C\{^1H\}$ NMR spectra of the complexes is similar to the free ligands, although broadening and slight downfield shift of the methylene signals were observed. The ^1H NMR spectrum of (Au(**L2**)(dppe)] (**8**) in DMSO-*d6* displayed similar spectral patterns to that of complexes **1–4**, except for the fact that complex **8** showed two different aromatic signals at δ 7.78 and 7.53 ppm, integrating to a total of 5 protons, each due to aromatic protons of the biphenyl phosphine groups. This is supported by the ^{31}P NMR spectrum, which exhibited two phosphine signals at 35.19 and 21.29 ppm (Fig. S3b as inset). The two signals revealed that the two phosphorus atoms are in different environments, which is presumably due to steric interactions between adjacent phenyl rings because of the short chain of the ethyl linker of the diphosphine [32]. In the case of complexes **9–11**, where the alkyl length of the sugar linker was extended, a singlet peak at δ_P 32.5, 30.5 and 30.7 ppm, respectively, was observed, showing the equivalence of the two phosphorus atoms in accordance with a binuclear ring structure.

The ^{13}C NMR spectrum of complex **8** showed signals at 133.7–129.3 ppm for the aromatic carbon atoms, 172.6 ppm for the C═O group, 45.2 and 31.2 ppm for the CH_2S unit of the amino ethyl thiol linker, and 29.6 and 23.1 ppm for the CH_2 unit of the dppe groups. The HRMS of complex **8** showed a signal at *m/z* 1301.2428, which corresponds to the $[M+H]^+$ fragment (the calculated *m/z* value is 1301.24 for $[M+H]^+$) (Fig. S3c). Complex **9** showed a peak at *m/z* 1328.2084, which is also assigned to the $[M+H]^+$ fragment (the calculated *m/z* value is 1328.2394 for $[M+H]^+$), whilst complexes **10** and **11** gave *m/z* values of 1359.6355, and 1385.3131 respectively, signifying binuclear complexes of the thiocarbohydrate gold(I) complexes. The FTIR signals of structures **8–11** were similar to those of structures **1–4**.

Consequently, nine different forms of acetylated glyco binuclear gold(I) complexes were synthesized by mixing dichloromethane solutions of $[Au_2(dppx)Cl_2]$ (x = alkyl chain between the phosphines) with two molar equivalents of the ligands **L5-L7** (Scheme 2b).

The binuclear gold(I) complexes $[Au_2(\mathbf{L5})_2(dppe)]$ (**12**), $[Au_2(\mathbf{L5})_2(dppp)]$ (**13**), $[Au_2(\mathbf{L5})_2(dppb)]$ (**14**), $[Au_2(\mathbf{L6})_2(dppe)]$ (**15**), $[Au_2(\mathbf{L6})_2(dppp)]$ (**16**), $[Au_2(\mathbf{L6})_2(dppb)]$ (**17**), $[Au_2(\mathbf{L7})_2(dppe)]$ (**18**), $[Au_2(\mathbf{L7})_2(dppp)]$ (**19**) and $[Au_2(\mathbf{L7})_2(dppb)]$ (**20**) [dppe = bis(diphenylphosphino)ethane, dppp = bis(diphenylphosphino) propane and dppb = bis(diphenylphosphino)butane] were thus prepared.



n	L
1	**L1**
2	**L2**
3	**L3**
4	**L4**

L	Complexes
L1	**8**
L2	**9**
L3	**10**
L4	**11**

n	L
1	**L5**
2	**L6**
3	**L7**

	Complexes		
L \ m	1	2	3
L5	**12**	**13**	**14**
L6	**15**	**16**	**17**
L7	**18**	**19**	**20**

Scheme 2. Synthesis of the thiocarbohydrate binuclear phosphinogold(I) complexes.

All the complexes were isolated as pale yellow solids in moderate yields. Subsequently, complexes **12**–**20** were characterized by a combination of IR, NMR spectroscopy (Figs. S3a–S5a), microanalysis and mass spectrometry (Figs. S3b-S5b). The significant downfield shift of the NH protons after complex formation appearing between 7.15 and 7.18 ppm of complexes **12**–**14** compared to that of ligand **L5** at 6.64 ppm was an indication of complexation (Fig. S5a). The broadness of the peaks for the CH_2 protons of dppe and amino alkyl thiol linker of the ligand is probably due to unresolved ^{31}P–H coupling or/and fluxional behaviour of the protons at room temperature [28]. However, a temperature variation NMR experiment performed at room temperature to −50 °C did not show any difference in the broadness of these peaks. This is comparable to unpublished work by our group on the development of a dithiocarbamate binuclear gold(I) complex as an anticancer agent [28]. The ^{31}P{^{1}H} NMR spectra of complexes **12**–**20** measured at room temperature exhibit a significant downfield shift trend, but with different chemical shift values and only one resonance (Fig. S5b). The ^{31}P{^{1}H} NMR spectra obtained for these complexes is characteristic of compounds with a P–Au–S motif [29–31]. The appearance of only one phosphorus peak in these complexes also confirms the equivalence of the two phosphorus atoms, in accordance with a binuclear ring structure [32]. High resolution mass spectra of complexes **12**–**20** (Figs. S4 and S5b) showed molecular ion peaks corresponding to the binuclear complexes. All the complexes showed a typical fragmentation pattern (Fig. S4 and S5b). For example, in the HRMS of **12**, the most characteristic signals observed at high *m/z* values represent fragments formed by the loss of one acetyl radical unit: [M−Ac]+ and the formation of the most stable salt [M−Ac + Na]+ fragment at *m/z* 1654.3025 (Fig. S4). FTIR vibration signals of these sets of complexes were also typical, being similar to those of complexes **5**–**7**.

3.3. In vitro anticancer studies

Seven ligands and twenty novel compounds, namely seven mononuclear glyco gold(I) and thirteen binuclear glyco gold(I) complexes, were subjected to *in vitro* cytotoxicity evaluation against MCF7 (breast cancer), HCT116 (colon cancer) and PC3 (prostate cancer) cell lines, as well as the WI-38 non-cancer cell (Normal Human Fetal Lung Fibroblast) by a Sulforhodamine B (SRB) assay, using Parthenolide as the reference drug [33]. This is to enable us to evaluate the effect of: (i) hydrogen bonding using the protected and unprotected carbohydrate moiety, (ii) P–Au–S (mononuclear) and S-Au-P-$(CH_2)_2$-P-Au-S (binuclear) motifs and (iii) the length of the carbon bridge between the two phosphorus atoms (m) and the amino alkyl thiol linker (*n*).

The percent inhibition of viability for each concentration of the compounds was calculated with respect to the control and 50% cell growth inhibition (IC_{50}) values were estimated with the GraphPad Prism software *via* non-linear regression. Each experiment was repeated three times and the results are summarized in Tables 1 and 2. In order to establish the activities of the complexes, we first established the activities of the ligands towards the three cancer cell lines, and they were found to be non-toxic to all the three human cancer cell lines reported in our previous work [34]. However, the activities improved significantly with the mononuclear and dinuclear gold(I) complexes of the same ligands. Mononuclear complexes **1**–**7** exhibited weak to very active activities against all the three cancer cell lines, with IC_{50} values ranging between 1.94 and 52.71 μM (Table 1 and Fig. S6).

In order to investigate whether the activity is the result of the Au–S or P–Au–S motifs, gold nanoparticles using the same ligand system were prepared and evaluated for their anticancer activities against the three cancer lines [34]. In comparison to the IC_{50} values of the gold nanoparticles, the IC_{50} values of the gold complexes were far lower, suggesting that the observed activity could be due to the P–Au–S moiety, given the fact that the ligands and nanoparticles possessing Au-S motifs were relatively inactive [23,34,35,27].

This is believed to be the result of associative ligand exchange reactions between the thiolate ligand and the membrane-localized biological thiols to form intermediates with Au–P–S motifs [36–38]. Indisputably, from these above reports, the nature of the di(phosphino)-alkanegold(I) and the subsidiary ligand bound to the gold(I) centre is important in determining the anticancer activity and tumor selectivity of these compounds.

The unprotected mononuclear complexes **1**–**4** showed weak to very active activities as the amino alkyl chain length (n) increases. Complexes **2** (*n* = 2) and **3** (*n* = 3) were active against HCT-116 and PC-3 cancer cells (the TS values are 8.8 and 7.3 for **2** and 1.6 and 2.1 for **3**, respectively). Complexes **1** and **4** (*n* = 4) were found to be inactive and moderately active against all three cancer cell lines, respectively. The inactivity of complex **1** is attributed to the insoluble nature of the complex.

The effect of protecting group was investigated. The per-acetylated complexes **5**–**7** were found to inhibit the growth (IC_{50} = 1.94–6.75 μM) of all the cancer cell lines compared to their corresponding unprotected complexes **1**–**4** (IC_{50} = 5.71–52.71 μM). The enhanced activities of the mononuclear complexes **5**–**7** having per-acetylated thiocarbohydrate ligands compared to the corresponding complexes **1**–**4** with an unprotected ligand could be attributed to the increased lipophilicity/reduced hydrogen bonding, suggesting the importance of the balance between the hydrophilicity and lipophilicity of the complexes (**5**–**7**) [23]. In this set of complexes, the activity and tumor selectivity depended on the amino alkyl thiol linker. The longer amino alkyl thiol linker (*n* = 3) showed a greater tumor selectivity and inhibition activity compared to shorter chains (**5** versus **7**). This implies that toxicity to normal cell was reduced significantly as the chain length was

Table 1
In vitro cytotoxicity (IC_{50}, μM)[a] and tumor specificity (TS) [35] of the mononuclear gold(I) compounds against human cancer cell lines.

Complexes	WI-38	MCF7		HCT116		PC3	
	IC_{50} (μM)[a]	IC_{50} (μM)[a]	TS[b]	IC_{50} (μM)[a]	TS[b]	IC_{50} (μM)[a]	TS[b]
Parthenolide	24.40	6.38	3.82	16.09	1.52	18.42	1.32
1	–	44.84	–	52.71	–	33.78	–
2	50.50	15.10	3.34	5.71	8.84	6.88	7.34
3	12.5	26.88	0.47	7.76	1.61	6.10	2.05
4	12.00	29.75	0.40	36.80	0.33	20.30	0.59
5	6.64	1.94	3.42	6.62	1.00	2.20	3.02
6	2.35	2.30	1.02	3.80	0.62	2.21	1.06
7	33.20	2.63	12.62	6.75	4.92	4.81	6.90

[a] IC_{50} is the drug concentration effective in inhibiting 50% of cell growth, measured by the SRB assay after 48 h drug exposure. (–) = not determined.
[b] $TS = \frac{[IC_{50} \text{ of WI-38}]}{[IC_{50} \text{of the cancer cells}]}$.

Table 2
In vitro cytotoxicity (IC_{50}, μM)[a] and tumor specificity of the binuclear gold(I) compounds against human tumor cell lines.

Complexes	WI-38	MCF7		HCT116		PC3	
	IC_{50} ($^{\mu M}$)[a]	IC_{50} (μM)[a]	TS[b]	IC_{50} (μM)[a]	TS[b]	IC_{50}(μM)[a]	TS[b]
Parthenolide	24.40	6.38	3.82	16.09	1.52	18.42	1.32
8	–	3.85	–	20.56	–	0.003	–
10	1.89	3.85	0.49	0.90	2.1	0.08	23.63
11	11.57	2.84	4.07	0.63	18.37	0.22	52.59
12	0.56	0.24	2.33	0.79	0.71	0.008	70
13	1.39	0.70	2.00	0.25	5.56	0.03	46.33
14	19.90	0.14	142.14	0.84	23.70	0.14	142.14
15	3.92	0.17	23.06	1.18	3.32	0.004	980.00
16	3.75	0.12	31.25	0.77	4.87	0.004	937.50
17	3.43	2.28	1.50	0.27	12.70	0.03	114.33
18	1.51	1.81	0.83	0.39	3.87	0.04	37.75
19	1.29	2.16	0.60	0.28	4.61	0.03	43.00
20	3.63	0.97	3.74	0.74	4.91	0.56	6.48

[a] IC_{50} is the drug concentration effective in inhibiting 50% of the cell growth measured by the SRB assay after 48 h drug exposure. (–) = not determined.
[b] $TS = \frac{[IC_{50} \text{ of WI-38}]}{[IC_{50} \text{of the cancer cells}]}$.

increased (Table 1). The cytotoxicities of complexes **6** and **7** might be attributed to Au-Au interactions, in agreement to the literature report [23,26].

The dinuclear gold(I) complexes **8**–**20** inhibited the growth of all the cancer cells significantly compared to their mononuclear analogues **1**–**7** (Tables 1 and 2, Figs. S6–S7). Complex **8** (an unprotected dinuclear gold(I) complex with n and $m = 1$) exhibited the highest growth inhibitory activity against the prostate cancer cell lines, with an IC_{50} value of 0.003 μM, which is 6140-fold more potent than the positive control parthenolide (with an IC_{50} value of 18.42 μM). Similar to the mononuclear gold(I) complexes, the activities and tumor specificities of these dinuclear complexes improved significantly as the aminoalkyl chain increased. For example, complex **11** ($n = 4$) inhibited growth of all the three cancer cells with IC_{50} = 0.22–2.84 μM and TS values of 4.07, 18.4 and 52.6 for MCF7, HCT116 and PC-3, respectively, as against the inhibitory activity of complex **10** ($n = 3$) (IC_{50} = 0.80–3.85 μM) with TS values of 0.5, 2.1 and 23.6, respectively. Similar high activities as observed for the per-acetylated mononuclear complexes was also observed in the per-acetylated dinuclear gold(I) complexes **12**–**20**.

Binuclear gold(I) complexes **8**–**20** exhibited the highest anticancer activities, even higher than that of cisplatin reported in the literature [23], as well as high tumor specificities (Table 2) against breast, colon and prostate cancer cells. The novel binuclear complexes were more specific towards prostate and breast cancer cell lines with TS values between 70–980 and 23–142, respectively (Table 2). A general trend in the TS values observed was that the length of the carbon bridge between the two phosphorus atoms (m) and the amino alkyl thiols (n) significantly influences the TS value. Thus the longer the carbon chain, the higher the TS factor. For instance, complex **12**, which is comprised of aminoethyl thiol and dppe, exhibited TS values: 2.33, 0.71 and 70 against MCF7, HCT116 and PC3 cell lines, respectively. The TS values were significantly improved to *ca.* 142, 24 and 142, respectively, when the carbon bridge between the two phosphorus atoms was extended to four (dppb) (**14**). These results are in agreement with findings by Mirabelli et al. [35,27].

The tumor selectivity of the complexes depended mostly on the cell line type, with prostate cancer being the most significantly affected followed by breast cancer. An interesting trend of the TS values is that the two alkyl chain lengths (n and m) affect the cell line type selectivity. For example, the extended amino alkyl chain length gold(I) complexes **15** ($n = 2$) and **16** ($n = 2$) selectively inhibited prostate cancer cell better than the other two cells, while complex **14**, with an extended length of carbon bridge between the two phosphorus atoms ($m = 3$), selectively inhibited breast and prostate cancer cells. Overall, the length of the carbon bridge between the two phosphorus atoms (m) has a more significant effect over the amino alkyl chain linker (n) in terms of its ability to inhibit the growth of different cancer cell lines (**12** versus **15**–**16**).

Complexes **14**–**20** and their analogues with longer alkyl chains, such as **10** and **11** discussed above, may be the most promising of the new compounds, exhibiting good tumor specificities and activities. All the complexes showed a moderate selectivity against colon cancer cells, except complex **14** with a good TS value of *ca.* 24. The dinuclear complexes are more active and selective toward cancer cells than the mononuclear complexes. The mechanism of action of these complexes is not yet known, however, further investigation into their mode of action is part of our future work.

4. Conclusion

In summary, twenty thiocarbohydrate gold(I) complexes, namely seven mononuclear and thirteen binuclear gold(I) complexes, were synthesized and evaluated against three human cancer cells. The reaction of non-acetylated and per-acetylated gluconamidoalkyl thiols (**L1–L4** and **L5–L7**) with [AuCl(PPh_3)], [Au_2(dppe)Cl_2], [Au_2(dppp)Cl_2], [Au_2(dppb)Cl_2] and [Au_2(dpppt)Cl_2] led to the successful isolation of mononuclear and binuclear phosphinogold(I) complexes. The anticancer evaluation showed that this class of compounds generally exhibited good activities against breast, colon and prostate cancer cell lines. The nature of the phosphine had a great influence on the anticancer activity against these cancer cell lines. The mononuclear phosphinogold (I) complexes generally are less active than their diphosphinogold(I) counterparts, but also compounds that have hydroxylated thiocarbohydrate ligands are less active than their corresponding acetylated thiocarbohydrate counterparts. The most active anticancer agents from this study against all the three cancer cells lines are complexes **10**–**20**, signifying the importance of the acetyl group in the growth inhibition process. Activity against the cancer cells improved as the carbon chain lengths in both the diphosphino and the aminoalkyl thiol linker in the carbohydrate thiolate ligands increased. Tumor specificity values of complexes **15** and **16** are the highest, *ca* 980 and 938 respectively, against PC3 cell lines and amply demonstrated the efficacy of these complexes as excellent PC3 anticancer agents. To the best of our knowledge these two are the most tumor specific gold compounds to date.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.poly.2017.09.010.

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