Polyhedron 138 (2017) 57–67

Contents lists available at ScienceDirect

Polyhedron

journal homepage: www.elsevier.com/locate/poly

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

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ARTICLE INFO

Article history:
Received 29 May 2017
Accepted 5 September 2017
Available online 21 September 2017

Keywords:
n-Gluconamidoalkyl thiol
Thiocarbohydrate phosphinogold(I) complex
SRB assay
Cytotoxicity
Tumor-specificity

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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https://doi.org/10.1016/j.poly.2017.09.010
0277-5387/

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.