Coordination Chemistry Reviews 316 (2016) 36–67

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

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

Review

Comprehensive review on tumour active palladium compounds and structure–activity relationships

Md Nur Alam, Fazlul Huq*

Discipline of Biomedical Science, University of Sydney, Cumberland Campus, C42, East Street, Lidcombe, NSW 1825, Australia

Contents

ARTICLE INFO

Article history:
Received 28 October 2015
Accepted 5 February 2016
Available online 26 February 2016

Keywords:
Anticancer
Palladium
IC_{50}
Structure–activity-relationship

ABSTRACT

This article provides a comprehensive review of palladium compounds that have been evaluated for anticancer activity *in vivo* or *in vitro* from the era of discovery of cisplatin up to 2015. In total, 847 compounds have been discussed into three categories namely (1) potent palladium compounds, (2) palladium compounds with comparable activity and (3) palladium compounds with insignificant activity. Structure activity relationships are proposed that may aid in the design of new palladium compounds with greater antitumour activity.

1. Introduction

Platinum based anticancer drugs cisplatin, carboplatin and oxaliplatin are among the most widely used chemotherapeutics prescribed for 50–70% of all cancer patients with more than US$ 2 billion sales every year [1]. However, use of the drugs is also limited by dose-limiting side-effects such as neurotoxicity, hepatotoxicity and nephrotoxicity [2–4] and the problem of intrinsic and/or acquired resistance [5]. Thus, much research effort has been directed at developing new platinum drugs and elucidating cellular response, with the aim of overcoming the limitations [6,7]. The search has also been extended to compounds of other metal ions including palladium (II), gallium (III), ruthenium (II) and ruthenium (III), gold (I) and gold (III), bismuth (III), rhenium (I), copper (II) and tin (IV). Some of the designed complexes possess greater *in vitro* and *in vivo* antitumour activity than cisplatin [8].

Since palladium (II) is a d^8 system similar to platinum (II), a number of analogous Pd (II) complexes were synthesized and tested at an early stage of structure activity studies on platinum complexes [9–12]. However none of the studies resulted in a Pd (II) complex with significant antitumour activity possibly due to the higher lability of Pd (II) compounds [13].

More promising results for tumour active palladium complexes were found in the late 1970s and 1980s giving new impetus to search anew for tumour active palladium compounds.

Palladium complexes are among the most widely investigated metal compounds being the fifth after those of platinum, copper, gold and ruthenium. Many designed palladium complexes show significant antitumour activity with some of them greater than cisplatin or other clinically used drugs. The objective of the present study is to provide a comprehensive review on palladium complexes relating to their antitumour activity and particularly highlighting the structure activity relationships.

* Corresponding author. Tel.: +61 2 93519522.
E-mail address: fazlul.huq@sydney.edu.au (F. Huq).

http://dx.doi.org/10.1016/j.ccr.2016.02.001
0010-8545/

To date six reviews have been published on tumour active palladium complexes. These were by Caires in 2007, Abu Surrah et al. in 2008, Gao et al. in 2009, Bakalova in 2013, Zhang et al. in 2014 and Kapdi and Fairlamb in 2014 [14–19]. But none of the studies provided a comprehensive review of the subject. Caires considered only important results from 2002 to 2007 while Abu Surrah covered studies from 1998 to 2008. Bakalova described very few potential complexes whereas Zhang reported only 118 compounds. Kapdi and Fairlamb claimed to have provided an up to date account of advances made over the past several decades but limited the review to only 180 compounds, which is less than one fourth of total (847) reported compounds. The present study aims to provide a more comprehensive account of tumour active palladium complexes. These are divided into three categories namely 'potent palladium compounds', 'palladium compounds with comparable activity' and 'palladium compounds with insignificant activity'. A brief account of 26 most remarkable palladium complexes along with their structures (denoted as Complexes A to Z) is also given with special focus on structure activity relationship if there is any.

2. Potent palladium compounds

Each of the papers included in this section (Table 1) has described at least one palladium compound with activity greater than cisplatin or any other clinically used drug. However, some findings of patent publications, *e.g.* WO 2004/019924 A1, WO 2004018043 A1, US 4584316, US 8030299 B2 could not be included.

The first palladium compound reported to have a greater antitumour activity greater than cisplatin against sarcoma 180J cells was $[Pd(bpy)(ONO_2)_2]$ [20]. However, the compound was inactive against leukemic P388 cells as well as Sarcoma 180 cells [131]. In 1989 Mital et al. synthesized $[Pd(bipy)(ddtc)]NO_3{\cdot}H_2O$ and $[Pd(phen)(ddtc)]NO_3{\cdot}H_2O$ that were much more active than cisplatin (about 10 times greater), being attributed to the presence of planar ligands and suitable solubility properties of the α-diimines. It is thought that planar rings present might promote intercalation with DNA [132].

In 1998, Navarro-Ranninger and Quiroga et al. made a number of palladium complexes containing thiosemicarbazone ligands (Fig. 1: Complex A, Complex B and Complex C), endowed with significant anticancer activity in a variety of cell lines including cisplatin-resistant cell lines [29–31]. Moreover, the compounds were more active than cisplatin, adriamycin and etoposide against cisplatin-resistant PAM-ras cell line. Against glioma cell lines the palladium compounds had better or comparable activity compared with etoposide which is the clinically used drug for treating brain tumours. However, the ligands itself and their corresponding platinum analogues also displayed high cytotoxicity and in some cases even greater than palladium compounds.

Zhao et al. in 1998 described the synthesis and cytotoxicity of five palladium complexes using ligand N,N′-dialkyl-1,10-phenanthroline-2,9-dimathanamine among which three exhibited greater activity than cisplatin in L1210 and Bel7402 cell lines. Changing the alkyl groups in the complex caused changes in its cytotoxicity. The greater the lipophilicity of the alkyl groups, the greater was the cytotoxicity [32]. The same group also described two dinuclear palladium complexes having about 13 times and 4 times greater activity against HCT8 cell lines. The higher activity of the selenide complex than sulphide complex could be attributed to the presence of selenium instead of sulphur. But both the complexes displayed lower cytotoxicity than cisplatin against L1210 cell line.

First *trans*-palladium complex showing greater antitumour activity was described by Al-Allaf et al. in 1998 that had 2 to 54 times lower IC_{50} values than cisplatin against three different cell lines (P_{388}, L_{1210}, K_{562}). The complex *trans*-$[Pd(DMSO)(Harmine)Cl_2]$ (Fig. 1: Complex D) showed even greater activity over carboplatin and 5-fluorouracil [34]. Matesanz et al. 1999 described the cytotoxicity of a compound with better therapeutic index and greater cytotoxicity than cisplatin, etoposide and adriamycin against three different cancer cell lines (HeLa, Vero, cisplatin resistant Pam-*ras*) [35].

During the first decade of twenty-first century our group published a number of research articles describing a range of promising *trans*-palladium compounds [43,46,50,53,85]. Most of the complexes displayed greater activity in cisplatin resistant cancer cell lines (*e.g.* $A2780^{cisR}$ & $A2780^{ZD0473R}$) than in sensitive cell lines (A2780). In terms of IC_{50} values some of the complexes displayed 16, 45 and even 78 times greater activity than cisplatin. Complex E & Complex F (Fig. 2) are contribution from our group resulting from the search of novel palladium based anticancer drugs.

In 2007, Ray et al. discovered the potentiality of using novel palladium complexes having N-heterocyclic carbene ligands in cancer therapy. Complex G (Fig. 2) exhibited 2 to 20 times greater cytotoxicity compared with cisplatin in three different cancer cell lines (HeLa, MCF-7 and HCT 116). The high cytotoxicity of the compound may be attributed to the high electron density at the metal centre. However, corresponding gold and silver complexes did not show any activity [54]. In the same year Rocha et al. described another encouraging result from Complex H (Fig. 2) that was proved to be effective during *in vitro* and *in vivo* model study using Ehrlich ascites tumour (EAT) cells. The greater activity of Complex H than $[\{Pd(N,C\text{-}dmba)\}_2(\mu\text{-}NCS)_2]$ could be due to the presence of the ligand dppp {1,3-cis(diphenylphosphino)propane} or the number of metal centre [55]. The success of exploring palladium complex with highest *in vitro* anticancer activity in a wide range of cancer cell lines (breast, colon, ovary and lung cancer) is credited to Kovala-Demertzi et al. in 2007. Using thiosemicarbazone ligand (HAc4Et) the authors synthesized Complex I (Fig. 2) that is characterized by potent growth inhibitory activity (IC_{50}s in the nM range and 5600 times lower than cisplatin). Against A2780/$A2780^{cisR}$ and 41M/$41M^{cisR}$ cell lines, the palladium complex showed resistant factors <1.5 in both cases whereas for cisplatin the values were 16 and 4.5 respectively. The high antitumour activity of the complex may be due to the presence of the ligand (HAc4Et), which itself also showed high activity (with mean IC_{50} values in nM range) greater than the palladium complex in some cell lines. In fact, the mean IC_{50} values for Complex I against tested twelve cell lines is lower than its parallel platinum complex and the ligand itself as well [57].

Ruiz et al. in 2008 described the potentiality of Complex J (Fig. 2) as an anticancer agent which had lower IC_{50} values than cisplatin against HL-60 cell line for both 24 h and 72 h periods of incubation. Cationic nature of the Complex J may be responsible for enhanced DNA interaction leading to greater activity compared with other two palladium complexes tested in the study [60].

Use of diphenylphosphine (dppe) ligand for designing more effective anticancer palladium compounds was introduced by Spencer et al. in 2009. The authors described Complex K (Fig. 3) with very low IC_{50} values compared with cisplatin against different cell lines (K562, Vero and B16) [70]. Research group of Amin Badsha described Complex L (Fig. 3) with significant cytotoxicity against DU145 human prostate carcinoma (HTB-81) cells and attributed this to the presence of electron donating tricyclohexyl group in organophosphine ligand. The Pd—P bond is expected to be stronger owing to the electron donating ability of tricyclohexylphosphine and the complex is expected to remain intact, giving a greater chance to reach the target DNA [78]. Using proflavine (3,6-diaminoacridine) Polyanskaya et al. in 2010 described activity of $[Pd(terpy)(proflavine)](NO_3)(HSO_4){\cdot}3H_2O$ & $[Pd(proflavineH)Cl_2](SO_4)_{0.5}{\cdot}H_2O$ complexes in cisplatin resistant cancers. The complexes had very low IC_{50} values (0.75–2.7 μM) in human breast cancer (SK-BR-3; MCF-HER-2-6) cell lines whereas cisplatin gave a value of >1000 μM. Due to high variation in data