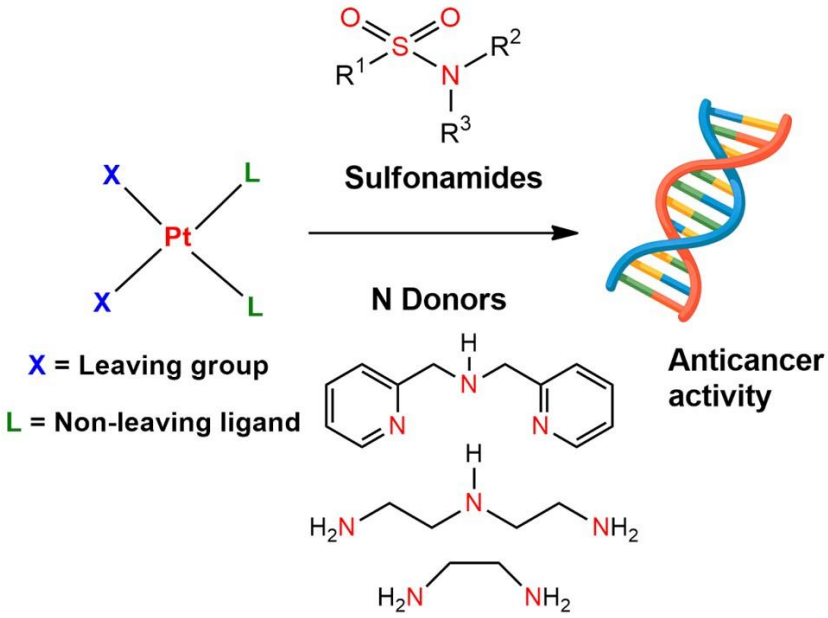
Platinum complexes of N-donor ligands bearing sulfonamide groups as anti-cancer agents: A review

K. W. G. K. P. Yasarathna[1,2] and N. T. Perera[1*]

[1]*Department of Chemistry, Faculty of Applied Sciences, University of Sri Jayewardenepura, Nugegoda, Sri Lanka*
[2]*Department of Pharmacy, Faculty of Allied Health Sciences, University of Ruhuna, Galle, Sri Lanka*

Date Received: 04-10-2025 Date Accepted: 25-12-2025



Abstract

Cancer has become a major health problem globally, and the trend of developing metal-based anticancer agents has evolved due to the greater cytotoxicity displayed by the metal complexes studied recently, including platinum and other transition metals. Different groups of anticancer drugs are employed in a clinical setting to treat different types of cancers. Platinum complexes, particularly cisplatin, is mostly utilized to treat various cancers worldwide. Nitrogen donors such as diethylenetriamine, dipicolylamine, ethylenediamine, etc. have been widely employed in the synthesis of many of the ligands which in turn are used to synthesize the relevant metal complexes possessing various biological properties. Furthermore, sulfonamide group and derivatives of sulfonamide have been incorporated into these metal complexes due to the variety of pharmacological properties it possesses, such as antibacterial, anti-carbonic anhydrase, antiprotease activities, etc. Most of these novel sulfonamide derivatives possess *in vivo* and *in vitro* anticancer activities. Platinum complexes bearing sulfonamide groups that have been studied recently have demonstrated significant anticancer activity *in vitro*. The therapeutic application of these platinum complexes will depend on pharmacokinetic, pharmacodynamic and safety profile data obtained through the clinical trials. Most of the platinum complexes used in oncotherapy contain amines as ligands in their general formula. More research is needed for the development of the field by identifying the opportunities present in various aspects to discover more metal-based compounds to curb cancer worldwide.

Keywords: *Anticancer, Dipicolylamine, N donor ligands, Sulfonamides, Pt complexes*

*Correspondence: theshi@sjp.ac.lk

Introduction

Availability of *d* electrons in valence shells of transition metals imparts unique biological, chemical and physical properties to these metals (Ndagi et al., 2017). Transition metal-based complexes have been utilized in the treatment of various diseases such as psoriasis (Tapio and Grosche, 2006), rheumatoid diseases (Jungwirth et al., 2011), syphilis (Dilda and Hogg, 2007), etc. from ancient time and there has been a rising trend in developing metal complexes as anti-tumor agents. This trend may be attributed both to the growing global burden of cancer and to the enhanced *in vitro* cytotoxicity demonstrated by recently synthesized metal complexes (Adhikari et al., 2024; Kostova, 2006; Ndagi et al., 2017).

Platinum complexes, particularly cisplatin, is used to treat cervical, ovarian, breast, prostate, testicular and lung cancers. The disadvantages associated with cisplatin, such as severe side effects can be overcome by using platinum prodrugs with promising pharmacological properties (Bruijnincx and Sadler, 2008; Kostova, 2006). Common platinum complexes with anticancer properties usually bear the molecular formula *cis*-$[PtX_2(NHR_2)_2]$, where a leaving group (carboxylate or chloride) is denoted by X and an organic fragment is denoted by R (Kostova, 2006). Generally, clinically established platinum based anticancer drugs contain N-donor ligands, which are bound to the platinum metal center with robust interactions and they are not released as platinum compounds exert their mode of action (Yasser, 2015).

In addition to platinum, treating tridentate amine ligands with some other metals such as rhenium has produced several metal-based complexes. Most of these complexes can be used as analogues of radiopharmaceuticals while some may serve as therapeutic agents (Perera et al., 2010). Nitrogen donor compounds including dipicolylamine, diethylenetriamine, N,N,N-trimethyldiethylenetriamine, N,N-dimethyldiethylenetriamine, N-methyl-2,2-diaminodiethylamine, N-ethylethylenediamine, etc. have been used to synthesize most of the ligand derivatives which have been utilized in the synthesis of relevant metal complexes possessing different biological properties (Aglin, 2018; Christoforou et al., 2006; Christoforou et al., 2007; Perera et al., 2010; N. Thushara et al., 2021).

Due to the presence of various biological properties, sulfonamides have been used as an important class of drugs to treat various disease conditions. Furthermore, recent drug discovery processes have been more focused on developing metal complexes bearing sulfonamide groups and other sulfonamide derivatives which are of biological relevance as radiopharmaceuticals (Perera et al., 2012) and anticancer agents (Casini et al., 2002). Some of the novel derivatives that contain a sulfonamide moiety have shown both *in vivo* and *in vitro* anticancer activity (Owa and Nagasu, 2000; N. Thushara et al., 2021).

Exploring platinum-based compounds with anticancer properties may contribute meaningfully to the development of new anticancer agents in the battle against cancer. Incorporation of a sulfonamide moiety with nitrogen donors enhances the therapeutic potential of these metal complexes. We thus discuss here some of the important aspects of platinum complexes derived from nitrogen donor ligands with sulfonamide groups as anticancer agents.

Prevalence of cancer

According to the need of the human body, cells grow, divide and multiply to form new cells replacing old and damaged cells. In some cases, this normal process breaks and cells become abnormal. In this situation, damaged and old cells remain alive and new cells are formed when there is no need for new cells. These extra cells grow continuously which leads to formation of cancers (World Cancer Research Fund, 2018). It is a genetic disorder results by the changes in genes that are responsible for normal cell functions of human body (Gao, 2023).

Cancer has become the second main cause of death in the world and thus has been recognized as a major health problem worldwide (Wu et al., 2024). According to the current estimations, one in six demises occur due to cancer and nearly 70% of demises with cancer occur in low- and middle-

*Correspondence: theshi@sjp.ac.lk

income countries (Murray et al., 2025). Skin, colorectal, prostate, lung and breast cancers are considered as common cancers (Murray et al., 2025). It has been estimated that new cases of cancer in elderly may rise from 12.4 million in the year 2020 to 20.7 million by 2040 in the world. (Li et al., 2024).

Similar to the global scenario, cancer is a prevalent disease in Sri Lanka as well. In Sri Lanka, 23,530 cases of cancer have been reported in 2018 and majority of them are females (53%) (The Global Cancer Observatory, 2019). According to the latest data from Global Cancer Observatory, 33,243 of new cancer cases has been reported in Sri Lanka in 2022 with 19,145 number of cancer deaths. Lip/oral cavity, lung, colorectum, esophagus and prostate cancers are the top five most frequent cancers (Global Cancer Observatory, 2022).

Treatment modalities for cancer

Chemotherapy or the treatment of diseases with chemicals, was first introduced by Paul Ehrlich, who was a German chemist and immunologist (Buczkowska, 2011). Cytotoxic chemotherapy medicines inhibit cell proliferation. Drug groups including platinum drugs, antimetabolites, alkylating agents, topoisomerase inhibitors, etc. are used to treat various types of cancers (Figure 1). Platinum drugs such as cisplatin, oxaliplatin, carboplatin exert their mechanism by cross linking the DNA (Kostova, 2006). Moreover, alkylating agents including nitrogen mustard, ethyleneimines, alkyl sulfonates, nitrosoureas and triazines cause to transfer alkyl groups to DNA during cell division (Bennett and Brown, 2003). They affect the functions and integrity of DNA and induce cell death in rapidly multiplying tissues (Goodman and Gilman, 2005).

Antimetabolites act by inhibiting DNA and RNA function in different ways. Purine base analogues inhibit the formation of vital precursors of DNA. Other analogues including adenosine nucleoside analogues block DNA elongation and its function by incorporating to DNA (Goodman and Gilman, 2005).

Metal based drugs have been used to treat numerous types of cancers. Arsenic trioxide was one of the first metallodrugs which was used as an anticancer agent. Arsenic trioxide was used mainly to treat leukemia (Jungwirth et al., 2011).

Discovery of the platinum(II) complex, cisplatin, was a turning point in the development of anticancer agents in the modern era. It is the most commonly used antineoplastic agent with a broad anticancer activity against many cancers. The success of cisplatin led to the development of other metal compounds incorporating ruthenium, titanium, copper, cobalt, etc. with anticancer properties and some of them are in pre-clinical evaluation (Adhikari et al., 2024; Jungwirth et al., 2011). Although cisplatin is one of the most successful anticancer drugs reported to-date, it causes serious adverse effects including neurotoxicity, renal impairment and ototoxicity as it lacks selectivity to cancer cells or tumor tissues. Therefore, novel anticancer agents have been developed to overcome these side effects (Kostova, 2006). Thus, scientists have stepped forward with the discovery of new chemical entities possessing successful antitumor activities with no/ little harm to the patients.

Role of sulfonamides

Sulfonamides are being considered as a major group of drugs as they possess important pharmacological properties such as antibacterial, diuretic, anti-carbonic anhydrase and antiprotease activities. Sulfanilamide, which is the lead compound of sulfonamide group provided the foundation for the development of pharmaceuticals with these various biological properties (Casini et al., 2002). Apart from that, several sulfonamide derivatives possessing *in vivo* and *in vitro* anticancer activities have been reported recently (Casini et al., 2002). Tertiary sulfonamides derived from dipicolylamine have also been identified as an important mode to conjugate biological targets of interest and thus, new tridentate ligands of dipicolylamine, bearing sulfonamide groups ($N(SO_2R)$dpa) have been synthesized as a novel approach in radiopharmaceutical bioconjugation (Perera et al., 2012). Furthermore, it was

*Correspondence: theshi@sjp.ac.lk

concluded that, tertiary sulfonamides bind with the metal through N, when the N atom is in a compatible geometry (sp^3 hybridization) to form a strong bond (Perera et al., 2012).

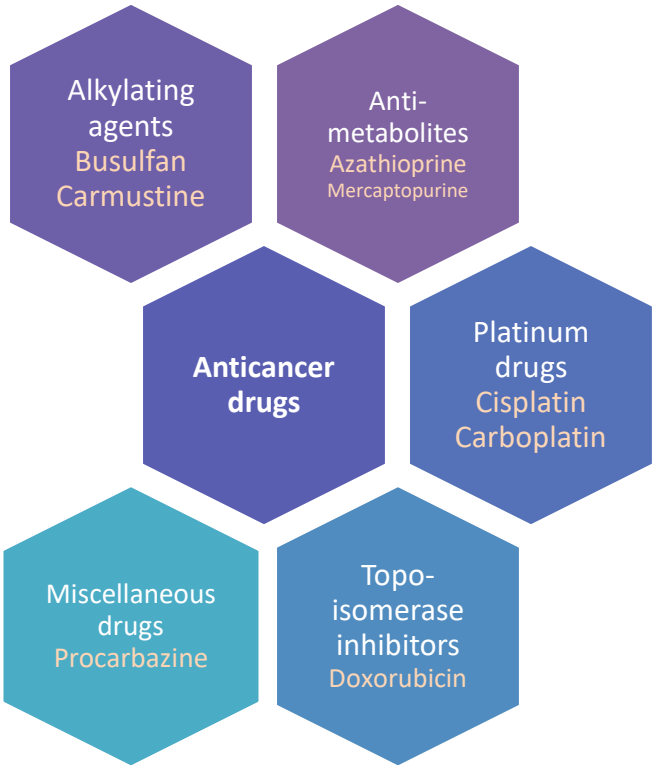


Figure 1: Current anticancer drug groups

N-sulfonamides

N-Sulfonamides (N-alkyl or N-aryl sulfonamides) are a group of sulfonamides ($-SO_2NH_2$) where the N atom is substituted with an alkyl or aryl group (Babalola and Suleiman, 2024). N-sulfonamides are widely used in medicinal chemistry and antibacterial activity was the first reported biological activity of these sulfa drugs (Solar et al., 2013). Furthermore, N-sulfonamides have been used as agents in PET (Positron Emission Tomography) scan in the diagnosis of different types of cancers (Solar et al., 2013). Although sulfonamides have diverse uses in medicinal chemistry, their utility in platinum-based complexes have not been studied extensively (Rozbicki and Branowska, 2025). New *trans*-N-sulfonamide platinum complexes have been synthesized using two synthetic steps from commercially available precursors (Solar et al., 2013). It was found that N-sulfonamides platinum complexes with chloride, dansyl sulfonamide and *trans*-cyclohexyldiamine ligands exhibit excellent antiproliferative activity (Solar et al., 2013). Another set of novel *trans*-N-sulfonamide platinum compounds have been studied by Perez *et.al* (Pérez et al., 2014) where mono-sulfonamide platinum compounds were reported to possess excellent anticancer properties against various tumor cell lines. Furthermore, it has been suggested that, regarding structure activity relationship, small differences in the ligand (such as changing the configurations; *cis* and *trans*) could give rise to a major change in biological activity which provide a new rationale for the invention of novel platinum-based anticancer drugs (Pérez et al., 2014).

*Correspondence: theshi@sjp.ac.lk

N-donors for ligand synthesis

Clinically established platinum anticancer drugs are bound with nitrogen donor ligands and the antitumor activity of these complexes depend on the properties of these nitrogen donor ligands allowing them to be used in the treatment of various cancer types (Yasser, 2015). Furthermore, N donor groups possess enhanced ability to form the metal complex (Re, Pt) with the ligand than carboxylate O donor groups (Perera et al., 2010).

Symmetrical linear tridentate ligands prevent formation of racemic mixtures or diastereoiosmeric mixtures and form symmetrical metal complexes, and are thus suitable candidate for these synthetic procedures. Compounds with tridentate ligands are more robust and possess good pharmacokinetic properties compared to compounds containing bidentate ligands (Abhayawardhana et al., 2014; Kothari et al., 2003; Perera et al., 2012).

Dipicolylamine, diethylenetriamine, ethylenediamine, N,N-dimethyldiethylenetriamine, N-methyl-2,2-diaminodiethylamine, N,N,N-trimethyldiethylenetriamine, N-ethylethylenediamine, etc (Figure 2) have been used as N donors in many studies to synthesize various types of ligands.

Recently, much attention has been focused on metal complexes bearing dipicolylamine derivatives. Dipicolylamine is a secondary amine with two picolyl substituents (Figure 2a) which can be used as a bidentate or tridentate ligand in coordination chemistry (Ngo et al., 2012; Sakamoto et al., 2009). The presence of three nitrogen donors in di-(2-picolyl)amine facilitates the modulation of the lipophilicity by derivatization with different groups at the central nitrogen. Di-(2-picolyl)amine appended sulfonamide ligand; ($N(SO_2pip)dpa$) and the corresponding rhenium complex; ($[Re(CO)_3(N(SO_2pip)dpa)]^+$) have been synthesized by Subasinghe *et al* and their anticancer property has been evaluated against human breast cancer cells (Subasinghe et al., 2016). These compounds have shown comparatively low IC_{50} values, showing promise to be investigated further to confirm their effective therapeutic application as anticancer agents (Subasinghe et al., 2016).

In coordination chemistry, diethylenetriamine can also serve as a tridentate ligand in the synthesis of various metal complexes. According to Christoforou *et al*., diethylenetriamine with dansyl sulfonamide moiety can act as a tridentate or bidentate ligand (Christoforou et al., 2006). Christoforou *et al.* have also synthesized asymmetrical tridentate N donor ligands with diethylenetriamine (N(H)dien), which forms a sulfonamide linkage between an aromatic moiety and the terminal nitrogen. These tridentate ligands may also be utilized to synthesize radiopharmaceuticals using a $^{99m}Tc(CO)_3$ core (Christoforou et al., 2007)(Christoforou et al., 2008).

Ethylenediamine is a powerful basic amine which is commonly used as a good precursor in coordination chemistry and is usually abbreviated as 'en'. Due to the presence of two amine groups, ethylenediamine can act as a bidentate ligand by donating the lone pairs of electrons in the two N atoms. Novel *trans*-N-sulfonamide platinum complexes have been synthesized using ethylenediamine as the N donor ligand in some studies (Pérez et al., 2014; Solar et al., 2013).

Platinum complexes with anticancer activity

Therapeutic application of metal complexes in cancer treatment depends on specific characteristic features of metals such as reactivity with the organic substrate, flexible coordination patterns and redox activity. As mentioned previously, cisplatin is the most commonly used platinum-based drug for the treatment of different cancers. However, resistance to cisplatin created an urgent need for finding alternate anticancer agents with enhanced pharmacokinetic properties and anticancer activity (Ndagi et al., 2017). Carboplatin (diamine[1,1-cyclobutanedicarboxylate(2-)]-O,O′-platinum (II)), a second-generation anticancer agent, was introduced as a result of this. Chloride groups of cisplatin were replaced by a cyclobutanedicarboxylate ligand and it was reported to reduce the nephrotoxicity without affecting the antitumor activity (Kostova, 2006).

After the successful transition of a few generations of platinum anticancer drugs (carboplatin, nedaplatin, oxaliplatin, picoplatin, lobaplatin, etc.) (Figure 3), various platinum complexes have been reported recently (lipoplatin, $NHC(PtX_2)$–amine complexes) which have demonstrated good

*Correspondence: theshi@sjp.ac.lk

cytotoxicity and better pharmacokinetic profiles. The therapeutic use of these compounds will depend on the pharmacokinetic, pharmacodynamic and safety profile data obtained through the clinical trials. Due to the lack of superior anticancer activity or inherent toxicity, some of them may have been discontinued from these clinical trials (Ndagi et al., 2017).

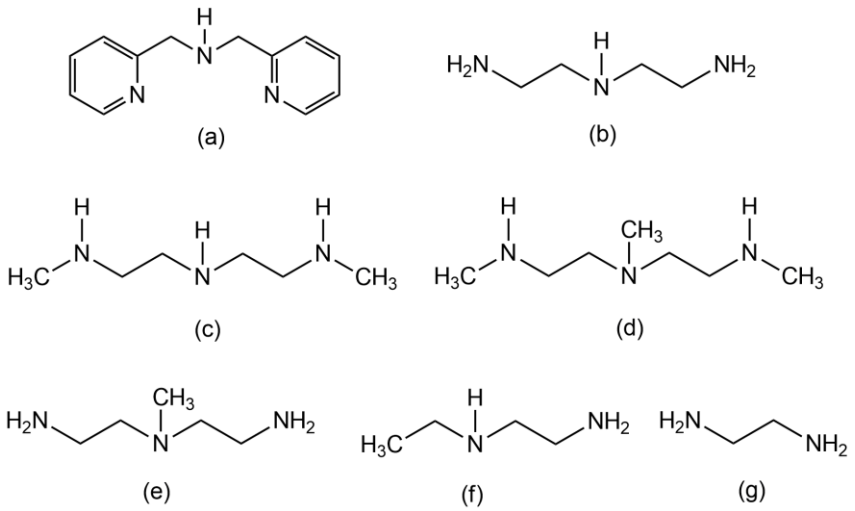


Figure 2: Line diagram of (a) dipicolylamine, (b) diethylenetriamine, (c) N,N-dimethyldiethylenetriamine, (d) N,N,N-trimethyldiethylenetriamine, (e) N-methyl-2,2-diaminodiethylamine, (f) N-ethylethylenediamine and (g) ethylenediamine

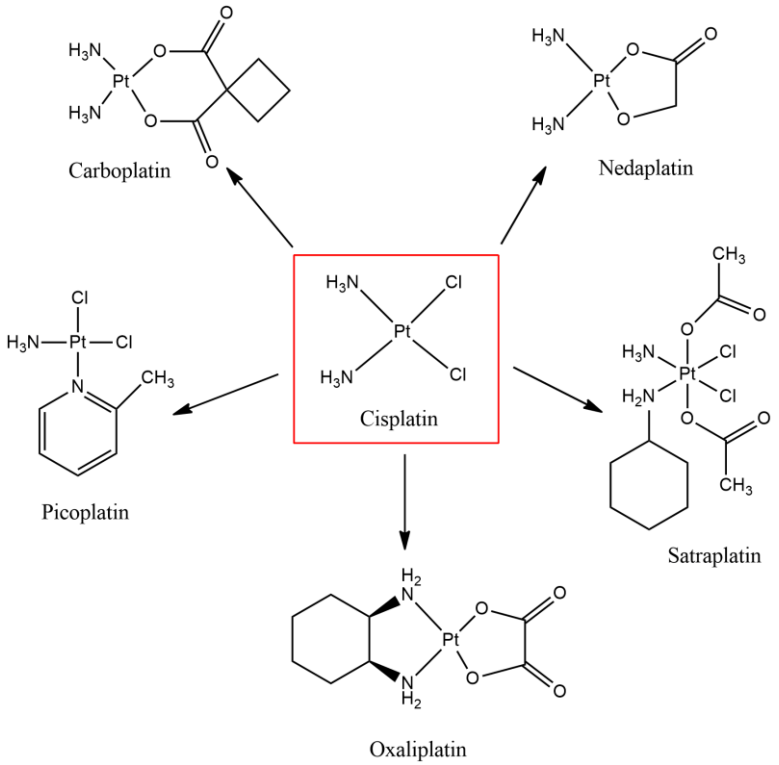


Figure 3: Second- and third-generation platinum(II) complexes derived from cisplatin

*Correspondence: theshi@sjp.ac.lk

Reported structure-activity relationship data indicate that, only the platinum complexes having *cis* configuration may exhibit inhibitory properties on cell growth (Kostova, 2006). Furthermore, most of the platinum complexes used in the treatment of cancer contain amine ligands. Platinum(II) complexes with amine substituents exhibit effective antitumor activity in mammals as they can easily bind with anionic macromolecular groups in cellular environment (Kostova, 2006).

A series of new platinum complexes; $[PtCl_2(NH_2CH_2)_2CHOR)]$ (R = CH_2CH_3 (1), $(CH_2)_3CH_3$ (2), $(CH_2)_7CH_3$ (3), CH_2Ph (4)) and $[PtCl_2(NH_2CH_2CH_2OR)_2]$ (R = CH_2CH_3 (5), $(CH_2)_3CH_3$ (6)) has been synthesized and their *in vitro* anticancer activity has been evaluated using four tumor cell lines including T lymphocytic, leukaemia (HL-60), colorectal (HCT116) and breast (MCF-7) cancers (Freire et al., 2017). The results showed that five complexes (2 – 6) possess anticancer properties against at least one cancer cell line and two complexes (3 and 6) have showed antitumor activity against all the tumor cell lines that were tested at micromolar concentrations (Freire et al., 2017).

Novel platinum complexes; $Pt(NH_3)_2Cl_2(CO_2C_6H_4R)_2$ (R = H, p-methoxy, p-vinyl, p-cyano, p-iodo or o-carboxyl) containing functionalized aromatic carboxylate ligand groups have been synthesized and characterized by different spectroscopic analysis (Ang et al., 2005). Furthermore, their ability of inhibition of cell proliferation and cellular uptake have been studied against breast, colon and lung cancer cell lines where results showed that these complexes possess antitumor activities (Ang et al., 2005). It has been reported that octahedral Pt complexes with the two extra coordination sites provide flexible synthetic pathways and those complexes also possess anticancer properties comparable to square planar complexes (Ang et al., 2005).

Exploring the bioconjugation of Pt metal, two novel platinum complexes; $[PtCl_2(N(SO_2pip)dpa)]$ and $[PtCl_2(N(SO_2(2\text{-}nap)dpa)]$ derived from two sulfonamide ligands; $N(SO_2pip)dpa$ and $N(SO_2(2\text{-}nap)dpa$ containing a dipicolylamine group have been synthesized and characterized by Thushara *et al*. Results revealed that these two ligands and two Pt complexes possess anticancer properties against breast cancer cells (MCF-7). Furthermore, the IC_{50} values reported for the ligand; $N(SO_2(2\text{-}nap))dpa$ and its corresponding platinum complex; $[PtCl_2(N(SO_2(2\text{-}nap)dpa)]$ were 34.88 mg/L and 0.1810 mg/L, respectively (N. Thushara et al., 2021; Thushara and Perera, 2018). 1-4 benzodioxane (non-rigid) based and 4-methylbiphenyl (rigid) based sulfonamide ligands derived from dipicolylamine and their corresponding Pt complexes have been synthesized recently. These ligands and complexes have shown an outstanding *in vitro* anticancer properties against non-small cell lung cancer cells (NCI-H292) with highest cytotoxicity in $[PtCl_2(N(SO_2)(4\text{-}Mebip)\ dpa)]\cdot CH_3CN$ complex with IC_{50} 62.26 µg/mL (Kaluthanthiri et al., 2024).

Furthermore, four diethylenetriamine based sulfonamide ligands derived from benzodioxane, methylbiphenyl and naphthalene moieties and their corresponding platinum complexes have also been reported by Kaluthanthiri *et al*. The cytotoxicity of these compounds has been evaluated using non-small cell lung tumor cell line (NCI-H292). Among these compounds, higher level of anticancer activity has been demonstrated by methylbiphenyl incorporated ligand (<10 µg/mL) followed by its corresponding platinum complex (<25 µg/mL) (Kaluthanthiri et al., 2023).

Two novel Pt complexes of quinoline and azobenzene based dipicolylamine appended sulfonamide ligands have been reported (Maladeniya et al., 2022). The synthesized Pt complexes have demonstrated significant cytotoxicity against human lung cancer cells (NCI-H292) compared to that of their corresponding ligands with IC_{50} values of 9.01 µg/mL and 12.13 µg/mL after 72 hours of incubation. Furthermore, $[PtCl_2(N(SO_2quin)dpa)]$ has displayed ~6-fold higher anticancer activity compared to its ligand (Maladeniya et al., 2022).

Four novel trans-platinum complexes of N-sulfonamides; one complex with linear alkyl group and three complexes with cyclic hexyldiamine groups have been reported for the first time by Aleman *et al*. *In vitro* anticancer activity of these complexes has been evaluated against five tumor cell lines (colon, non-small cell lung, endometrial, cervix and breast). The finding revealed that, cyclic complexes exhibit increased cytotoxicity against all the tested cell lines with GI_{50} values of 1.7 – 3.5 µM (Aleman et al., 2011).

*Correspondence: theshi@sjp.ac.lk

Anticancer properties of a platinum complex derived from a bidentate sulfonamide ligand have been studied recently (Izuchukwu and Conradie, 2023). This complex has shown a good cytotoxicity against A549 (IC_{50} = 7.32 μM) and HCT-116 (IC_{50} = 6.88 μM) cell lines where the control drug, cisplatin has shown IC_{50} values of 17.23 and 14.68 μM, respectively.

Based on the findings of the reported literature (Ang et al., 2005; Kaluthanthiri et al., 2024, 2023; Maladeniya et al., 2022; Subasinghe et al., 2016; N. Thushara et al., 2021) (Figure 4), platinum-based complexes appear to have a substantial potential to be investigated as anticancer agents. Platinum complexes with *cis* geometry have been studied significantly and tumor cell lines such as leukemia, breast and lung cancer have been employed in most of the investigations. Integration of an amine as the nitrogen donor ligand is important as it stabilizes the platinum compounds in the intracellular environment.

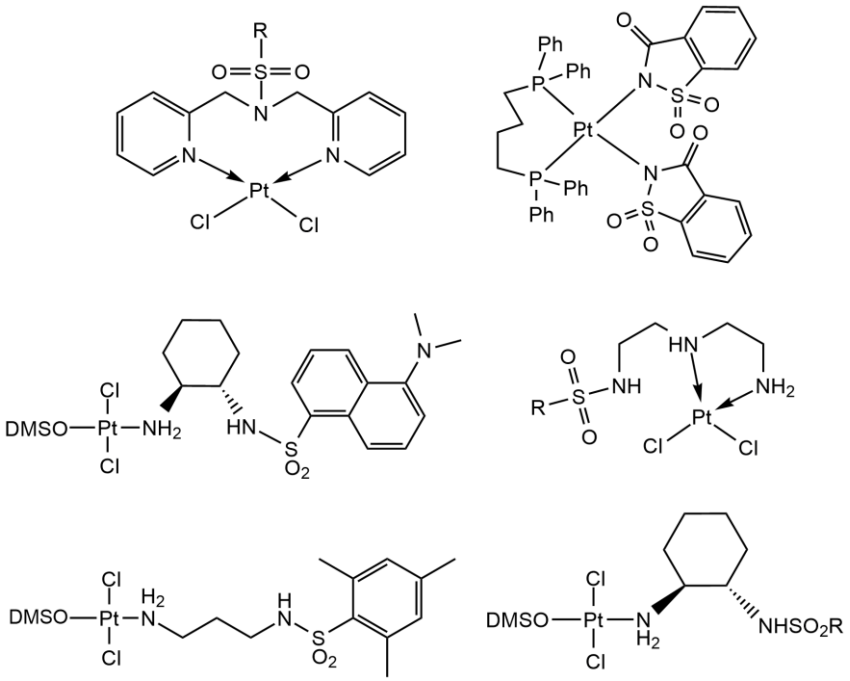


Figure 4: Recently synthesized platinum complexes with anticancer properties

Conclusion

The discovery of cisplatin as a therapeutic agent towards cancer provided the platform for studying and designing novel metal-based compounds with promising anticancer properties. Severe side effects associated with cisplatin fashioned the path of inorganic chemistry to discover new drugs with successful antitumor activities. The above literature provides a glimpse of many novel platinum metal complexes which have been synthesized and investigated in the recent decades for their anticancer properties. This review, in turn would facilitate the novel drug discovery and development process. Cancer is reported as a major cause of death in the world. Thus, the development of anticancer drugs with potential benefits to patients is crucial. Although different groups of anticancer drugs are currently available, this review highlights the fact that platinum-based complexes with sulfonamide groups bearing N donors have demonstrated excellent anticancer activity. Hence, in drug designing perspective, researchers can focus on this fact to discover new metal-based anticancer drugs. Although inorganic medicinal chemistry is a growing trend worldwide, the field is relatively unexplored in Sri Lanka. Being a part of the organometallic research field, more research in coordination chemistry is needed for the development of this field by identifying the opportunities present in various aspect to discover more metal based compounds to curb cancer as well as other diseases.

*Correspondence: theshi@sjp.ac.lk

References

Abhayawardhana, P. L., Marzilli, P. A., Fronczek, F. R., & Marzilli, L. G. (2014). A new series of complexes possessing rare "Tertiary" sulfonamide nitrogen-to-metal bonds of normal length: *fac*-$[Re(CO)_3(N(SO_2R)dien)]PF_6$ Complexes with hydrophilic sulfonamide ligands. *Inorganic Chemistry*, *53*(2), 1144–1155. https://doi.org/10.1021/ic4026987

Adhikari, S., Nath, P., Das, A., Datta, A., Baildya, N., Duttaroy, A. K., & Pathak, S. (2024). A review on metal complexes and its anti-cancer activities : Recent updates from in vivo studies. *Biomedicine & Pharmacotherapy*, *171*, 116211. https://doi.org/10.1016/j.biopha.2024.116211

Aglin, A. A. (2018). Medicinal Effects of Mollugo cerviana - A Review. *International Journal of Scientific Research in Multidisciplinary Studies*, *4*(9), 34–37.

Aleman, J., Solar, V. del, Alvarez-Valdes, A., Rios-Luci, C., M.Padron, J., & Navarro-Ranninger, C. (2011). Novel N-sulfonamide trans-platinum complexes: synthesis, reactivity and in vitro evaluation. *Medicinal Chemistry Communications*, *2*, 789–793. https://doi.org/10.1039/c1md00070e

Ang, W. H., Pilet, S., Scopelliti, R., Bussy, F., Juillerat-jeanneret, L., & Dyson, P. J. (2005). Synthesis and Characterization of Platinum(IV) Anticancer Drugs with Functionalized Aromatic Carboxylate Ligands: Influence of the Ligands on Drug Efficacies and Uptake. *Journal of Medicinal Chemistry*, *48*, 8060–8069. https://doi.org/10.1021/jm0506468

Babalola, I. T., & Suleiman, G. (2024). Design, synthesis, and molecular docking studies of N-substituted sulfonamides as potential anticancer therapeutics. *Journal of Taibah University Medical Sciences*, *19*(1), 175–183. https://doi.org/10.1016/j.jtumed.2023.10.006

Bennett, P. N., & Brown, M. J. (2003). *Clinical Pharmacology* (9th ed.). Churchil Livingstone.

Bruijnincx, P. C. A., & Sadler, P. J. (2008). New trends for metal complexes with anticancer activity. *Current Opinion in Chemical Biology*, *12*, 197–206. https://doi.org/10.1016/j.cbpa.2007.11.013

Buczkowska, M. K. (2011). *Synthesis, characterization, antitumor and antimicrobial activities of heterocyclic transition metal complexes*. https://api.semanticscholar.org/CorpusID:92871307

Casini, A., Scozzafava, A., Mastrolorenzo, A., & Supuran, C. T. (2002). Sulfonamides and Sulfonylated Derivatives as Anticancer Agents. *Current Cancer Drug Targets*, *2*, 55–75. https://doi.org/10.2174/1568009023334060

Christoforou, A. M., Fronczek, F. R., Marzilli, P. A., & Marzilli, L. G. (2007). *fac*-$Re(CO)_3L$ complexes containing tridentate monoanionic ligands (L^-) with a seldom-studied sulfonamido group as one terminal ligating group. *Inorganic Chemistry*, *46*, 6942–6949. https://doi.org/10.1021/ic700594a

Christoforou, A. M., Marzilli, P. A., Fronczek, F. R., & Marzilli, L. G. (2008). *fac*-$[Re(CO)_3L]$ complexes containing tridentate monoanionic ligands (L^-) having a terminal amido and two amine ligating groups. *Journal of Chemical Crystallography*, *38*, 115–121. https://doi.org/10.1007/s10870-007-9274-x

Christoforou, A. M., Marzilli, P. A., & Marzilli, L. G. (2006). The Neglected Pt−N(sulfonamido) Bond in Pt Chemistry. New Fluorophore-Containing Pt(II) Complexes Useful for Assessing Pt(II) Interactions with Biomolecules. *Inorganic Chemistry*, *45*, 6771–6781. https://doi.org/10.1021/ic0606375

Dilda, P. J., & Hogg, P. J. (2007). Arsenical-based cancer drugs. *Cancer Treatment Reviews*, *33*, 542–564. https://doi.org/10.1016/j.ctrv.2007.05.001

Freire, R. L. M., Marques, M. B. D. F., De Souza-Fagundes, E. M., De Oliveira, R. B., & Alves, R. J. (2017). Synthesis and evaluation of platinum complexes with potential antitumor activity. *Brazilian Journal of Pharmaceutical Sciences*, *53*(1), 1–7.

Gao, K. (2023). Brief note on Origin and Formation of Cancer Cells. *Cell & Development Biology*, *12*(1), 266. https://doi.org/10.35248/2168-9296.23.12.266.Citation

Global Cancer Observatory. (2022). https://doi.org/10.1002/ijc.33588.

Goodman, L., & Gilman, A. (2005). *The Pharmacological Basis of Therapeutics* (11th ed.). McGraw-

*Correspondence: theshi@sjp.ac.lk

Hill.

Izuchukwu, D., & Conradie, J. (2023). Anticancer properties of complexes derived from bidentate ligands. *Journal of Inorganic Biochemistry*, *246*(112268), 1–23. https://doi.org/10.1016/j.jinorgbio.2023.112268

Jungwirth, U., Kowol, C. R., Keppler, B. K., Hartinger, C. G., Berger, W., & Heffeter, P. (2011). Anticancer Activity of Metal Complexes : Involvement of Redox Processes. *Antioxidants & Redox Signaling*, *15*(4), 1085–1127. https://doi.org/10.1089/ars.2010.3663.Anticancer

Kaluthanthiri, D., Rajagopalan, U., Fronczek, F. R., Samarakoon, S., Weerasinghe, L., Perera, I. C., & Perera, T. (2024). Synthesis and characterization of sulfonamide appended rigid phenyl-based and non-rigid 1,4-benzodioxan-based ring systems and their Pt(II) complexes towards potential therapeutic targets. *Polyhedron*, *255*, 117131. https://doi.org/10.1016/j.poly.2024.117131

Kaluthanthiri, D., Rajagopalan, U., Samarakoon, S., Perera, I. C., & Perera, T. (2023). Synthesis and Characterization of Novel Diethylenetriamine Based Sulfonamide Ligands and Their Bidentate Platinum(II) Complexes Toward Anticancer Drug Leads. *Current Scientia*, *26*(02), 78–98. https://doi.org/https://doi.org/10.31357/vjs.v26i02.6809

Kostova, I. (2006). Platinum Complexes as Anticancer Agents. *Recent Patents on Anti-Cancer Drug Discovery*, *1*, 1–22. https://doi.org/10.2174/157489206775246458

Kothari, K., Joshi, S., Venkatesh, M., Ramamoorthy, N., & Pillai, M. (2003). Synthesis of $^{99m}Tc(CO)_3$-mebrofenin via $[^{99m}Tc(OH_2)_3(CO)_3]^+$ precursor and comparative pharmacokinetics studies with ^{99m}Tc-mebrofenin. *Journal of Labelled Compounds and Radiopharmaceuticals*, *56*, 633–644. https://doi.org/10.1002/jlcr.704

Li, L., Shan, T., Zhang, D., & Ma, F. (2024). Nowcasting and Forecasting Global Aging and Cancer Burden: Analysis of Data from the GLOBOCAN and Global Burden of Disease Study. *Journal of the National Cancer Center*, *9*(4 (3)), 223–232. https://doi.org/doi: 10.1016/j.jncc.2024.05.002

Maladeniya, C., Darshani, T., Samarakoon, S. R., Fronczek, F. R., Sameera, W. M. C., Perera, I. C., & Perera, T. (2022). Biological Evaluation of Platinum(II) Sulfonamido Complexes: Synthesis, Characterization, Cytotoxicity, and Biological Imaging. *Bioinorganic Chemistry and Applications*, *2022*, 1–13. https://doi.org/https://doi.org/10.1155/2022/7821284

Murray, C. J. L., Vos, T., & Lim, S. S. (2025). The global, regional, and national burden of cancer, 1990–2023, with forecasts to 2050: a systematic analysis for the Global Burden of Disease Study 2023. *The Lancet*, *406*(10512), 1565–1586. https://doi.org/10.1016/S0140-6736(25)01635-6

Ndagi, U., Mhlongo, N., & Solimn, M. E. (2017). Metal complexes in cancer therapy – an update from drug design perspective. *Drug Design, Development and Therapy*, *11*, 599–616. https://doi.org/http://dx.doi.org/10.2147/DDDT.S119488

Ngo, H. T., Liu, X., & Jolliffe, K. A. (2012). Anion recognition and sensing with Zn(II)–dipicolylamine complexes. *Chemical Society Reviews*, *41*, 4928–4965. https://doi.org/https://doi.org/10.1039/C2CS35087D

Owa, T., & Nagasu, T. (2000). Novel sulphonamide derivatives for the treatment of cancer. *Expert Opinion on Therapeutic Patents*, *10*(11), 1725–1740. https://doi.org/10.1517/13543776.10.11.1725

Perera, T., Abhayawardhana, P., Marzilli, P. A., Fronczek, F. R., & Marzilli, L. G. (2012). Formation of a Metal-to-Nitrogen Bond of Normal Length by a Neutral Sufonamide Group within a Tridentate Ligand. A New Approach to Radiopharmaceutical Bioconjugation. *Inorganic Chemistry*, *52*(5), 2412–2421. https://doi.org/10.1021/ic302180t

Perera, T., Marzilli, P. A., Fronczek, F. R., & Marzilli, L. G. (2010). Several Novel N-Donor Tridentate Ligands Formed in Chemical Studies of New *fac*-$Re(CO)_3$ Complexes Relevant to *fac*-$^{99m}Tc(CO)_3$ Radiopharmaceuticals : Attack of a Terminal Amine on Coordinated Acetonitrile. *Inorganic Chemistry*, *49*, 2123–2131. https://doi.org/10.1021/ic901705x

Pérez, C., Díaz-garcía, C. V., Agudo-lópez, A., del Solar, V., Cabrera, S., Agulló-ortuño, M. T., Navarro-ranninger, C., Alemán, J., & López-martín, J. A. (2014). Evaluation of novel trans-

*Correspondence: theshi@sjp.ac.lk

sulfonamide platinum complexes against tumor cell lines. *European Journal of Medicinal Chemistry*, *76*, 360–368. https://doi.org/10.1016/j.ejmech.2014.02.022

Rozbicki, P., & Branowska, D. (2025). A Review on Sulfonamide Complexes with Metals: Their Pharmacological Potential as Anticancer Drugs. *Pharmaceuticals*, *18*(1414), 1–40. https://doi.org/https://doi.org/10.3390/ph18091414

Sakamoto, T., Ojida, A., & Hamachi, I. (2009). Molecular recognition, fluorescence sensing, and biological assay of phosphate anion derivatives using artificial Zn(II)–Dpa complexes. *Chemical Communications*, 141–152. https://doi.org/https://doi.org/10.1039/b812374h

Solar, V. del, Quiñones-lombraña, A., Cabrera, S., Padrón, J. M., Ríos-luci, C., Alvarez-valdés, A., Navarro-ranninger, C., & Alemán, J. (2013). Expanding the synthesis of new trans-sulfonamide platinum complexes: Cytotoxicity, SAR, fluorescent cell assays and stability studies. *Journal of Inorganic Biochemistry*, *127*, 128–140. https://doi.org/10.1016/j.jinorgbio.2013.01.013

Subasinghe, A., Perera, I. C., Pakhomova, S., & Perera, T. (2016). Synthesis, Characterization and Biological Studies of a Piperidinyl Appended Dipicolylamine Ligand and Its Rhenium Tricarbonyl Complex as Potential Therapeutic Agents for Human Breast Cancer. *Bioinorganic Chemistry and Applications*, *2016*, 1–10. https://doi.org/http://dx.doi.org/10.1155/2016/2675937

Tapio, S., & Grosche, B. (2006). Arsenic in the aetiology of cancer. *Mutation Research*, *612*, 215–246. https://doi.org/10.1016/j.mrrev.2006.02.001

The Global Cancer Observatory. (2019).

Thushara, N., Darshani, T., Samarakoon, S. R., Perera, I. C., Fronczek, F. R., Sameera, W. M. C., & Perera, T. (2021). Synthesis, characterization and biological evaluation of dipicolylamine sulfonamide derivatized platinum complexes as potential anticancer agents. *RSC Advances*, *11*(29), 17658–17668. https://doi.org/10.1039/d1ra00842k

Thushara, P. A. N., & Perera, T. (2018). Synthesis, characterization and biological studies of dipicolylamine sulfonamide derivatized platinum complexes as potential anticancer agents. *3rd International Research Symposium on Pure and Applied Sciences, 26th October 2018 - Faculty of Science, University of Kelaniya, Sri Lanka*, *October*, 35.

World Cancer Research Fund. (2018). dietandcancerreport.org

Wu, Z., Xia, F., & Lin, R. (2024). Global burden of cancer and associated risk factors in 204 countries and territories, 1980 – 2021: a systematic analysis for the GBD 2021. *Journal of Hematology & Oncology*, *17*(119), 1–14. https://doi.org/10.1186/s13045-024-01640-8

Yasser, S. O. A. (2015). *Synthesis of New Platinum-Based Anti-Cancer Drugs*. https://scholarworks.wmich.edu/masters_theses/618

*Correspondence: theshi@sjp.ac.lk