Complexes of N, N- and N, N, N- Sulfonamide Ligands as Therapeutic and Diagnostic Agents

Dilmi Witharana[1], Theshini Perera[1*]

[1]*Department of Chemistry, University of Sri Jayewardenepura, Sri Lanka*

Date Received: 29/09/2022 Date Accepted: 26-09-2023

Abstract

Ethylenediamine, diethylenetriamine and dipicolylamine have been used as the carrier ligands to synthesize bidentate (N,N) or tridentate (N,N,N) chelate systems that coordinate with metal centers. The terminal amine groups of ethylenediamine and diethylenetriamine and the central amine group of dipicolylamine can be easily substituted to give sulfonamide ligands having bulky aromatic fragments. In the formation of metal sulfonamides, the sulfonamide nitrogens of primary or secondary sulfonamides deprotonate and coordinate with metal centers forming M-N bonds while the free amines coordinate to metal centers through lone pairs. The reported synthetic approaches and the properties of these complexes and ligands are discussed in this review. The bulky sulfonamide moieties bring about unique biological features to the ligand system while enhancing the fluorescent properties of the ligand. The metal center itself incorporates interesting biological features to the complex. These properties of the metal center and the ligand show a synergistic effect in the complexes that may come in handy when designing therapeutic or diagnostic agents. The increased lipophilicity of the ligands and thereby the complexes will ensure better uptake by target cells making them ideal candidates for biological applications.

Keywords: Sulfonamide, ethylenediamine, diethylenetriamine, dipicolylamine

1. Introduction

The renaissance in Inorganic Medicinal Chemistry began with Rosenburg's serendipitous discovery of the antitumor activity of cisplatin in 1965 (Rosenberg et al., 1965). Ever since there has been an increasing interest in studying the chemistry of coordination complexes for the development of drugs and diagnostic agents. Coordination of organic drugs to metal centers is an efficient way of enhancing the properties of both the ligand and the metal ion. This allows to exploit the unique properties of metal centers which include having several oxidation and coordination numbers, a variety of redox properties, and symmetries providing new approaches for drug design (Zhang and Sadler, 2017), whereas the ligand may play a role the in target recognition, interaction or as a pharmacologically active component (Topală et al., 2019).

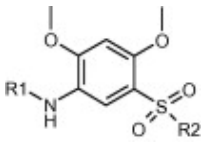
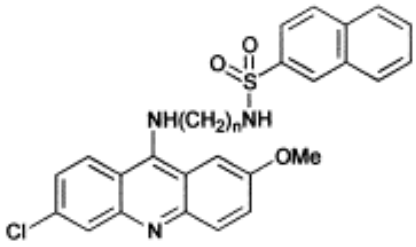
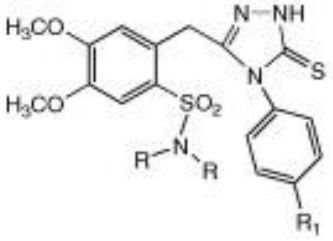
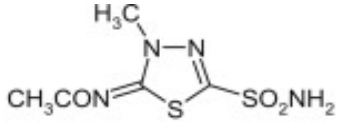
Coordination compounds have been studied extensively in inorganic medicinal chemistry as antimicrobial agents (Obaleye et al., 2012), antidiabetic agents (Sakurai et al., 2002), anticancer agents (Zhang and Sadler, 2017), therapeutic drugs (Zhang and Lippard, 2003), radioprotective agents (Ali and Van Lier, 1999), enzyme inhibitors (Louie et al., 1999) and diagnostic agents (Gielen and Tiekink, 2005,

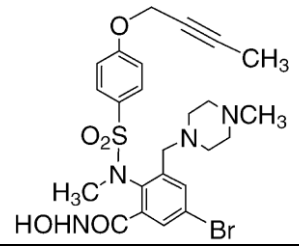
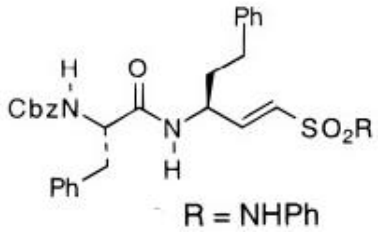
**Correspondence: theshi@sjp.ac.lk*

Gaynor and Griffith, 2012). The focus of this review is to explore the properties of ethylenediamine (en), diethylenetriamine (dien) and dipicolylamine (dpa) ligands containing a sulfonamide moiety which are coordinated to metal centers through N,N or N,N,N type donor atoms. Ethylenediamine is a well-known bidentate ligand (N,N donor) whereas diethylenetriamine and dipicolylamine are known to bind in bidentate (N,N) or tridentate (N,N,N) fashion.

Sulfonamides, commonly known as sulfa drugs were the first antibiotics systematically used to treat bacterial infections in humans (Taylor and Hansch, 1990). Since the start of WWII, sulfonamides have been clinically used as antimicrobial agents due to their antibacterial (Stokes et al., 2012), antiprotozoal (Chibale et al., 2001), antiviral (Ogden and Flexner, 2001), and antifungal (Ezabadi et al., 2008) properties. Other applications of sulfonamide derivatives (**Table 1**) include anti-inflammatory (Kennedy and Thorley, 1999), anticancer (Ma et al., 2012) and carbonic anhydrase inhibitor (Vullo et al., 2013) properties. They are also used as treatments for urinary and intestinal infections (Wilson et al., 2004) as well as diseases like rheumatoid arthritis (Levin et al., 2002) and Alzheimer's disease (Roush et al., 1998). The Lewis acidity of sulfonamides increase once deprotonated therefore, unlike the typical amides, the sulfonamides are poor electron donors. Moreover, the sulfonamide links are capable of resisting conditions prone to hydrolysis, reduction and oxidation and thereby are considered exceptionally stable (Diltz et al., 1997). It has been observed that upon coordination with a metal center, the sulfonamides show enhanced toxicological and pharmacological properties (Chohan, 2008).

Table 1: Sulfonamide compounds and their biological properties

Type of compound	Biological Property	Source
	Antibacterial activity	Stokes et al., 2012
	Antiprotozoal activity	Chibale et al., 2001
	Antifungal activity	Ezabadi et al., 2008
	Carbonic anhydrase inhibitor	Vullo et al., 2013

	Selective inhibitor of TACE	Levin et al., 2002
	Excellent inhibitor of cruzain	Roush et al., 1998

This review elaborates the synthetic pathways of sulfonamide ligands by using bulky aromatic sulfonyl chlorides and primary or secondary amine groups of ethylenediamine, diethylenetriamine and dipicolylamine ligands, the structural and biological properties exhibited by these ligands followed by the synthesis of complexes of *d*-block metals coordinated to the sulfonamide ligands, with a comparison of the properties of the free ligand versus their corresponding complexes.

2. N-sulfonamide ligands

Attaching dangling groups having fluorescent or targeting moieties to carrier ligands is an efficient way by which novel properties can be introduced into metal centers such as enhanced fluorescence, improved targeting ability, high anticancer/antitumor activity or new bioconjugation chemistry (Ranasinghe et al., 2018). Ethylenediamine is a well-known bidentate chelating ligand and diethylenetriamine is a renowned tridentate chelating ligand whose nitrogen atoms donate the lone pairs to bind with metal centers. Once the amine group undergoes sulfonylation forming the sulfonamide, then the sulfonamide nitrogen can be deprotonated allowing the anionic sulfonamide to bind with the metal center. The ethylenediamine and diethylenetriamine sulfonamides show amphipathic properties where the amine incorporates hydrophilic properties, while the bulky aromatic sulfonyl fragment imparts a lipophilic nature to the ligand. These properties are of great value in terms of chemotherapeutic agents and the uptake of synthesized drugs by target cells.

On the other hand, dipicolylamine (dpa) ligands are neutral secondary amines which contain two pyridyl rings. Dpa is a tridentate symmetrical ligand which can be used as a linker group to attach sulfonamide fragments to metal centers. The central nitrogen of dpa can undergo sulfonylation to give symmetric N,N,N or N,N type sulfonamide ligands depending on the metal center to which it coordinates.

**Correspondence: theshi@sjp.ac.lk*

2.1 Synthesis of N-sulfonamide ligands

The most commonly used method of synthesizing sulfonamides is the sulfonylation of ammonia, primary or secondary amines with sulfonyl chlorides in the presence of a base (**Figure 1**). The base abstracts the proton released during the nucleophilic attack on the amine by the sulfonyl chloride. Due to the moisture-sensitive nature of sulfonyl chlorides, solid sodium bicarbonate can be used as a base (Zhao et al., 2021). Using a solvent such as pyridine can serve dual purposes as the solvent and as the base that abstracts the proton. This is favorable as the reagents used for the synthesis can be minimized. The above method of using a basic solvent is practiced in the synthesis of disubstituted ethylenediamine sulfonamide ligands (**Figure 2**) (Sánchez-Piso et al., 2002, Bodoki et al., 2009).

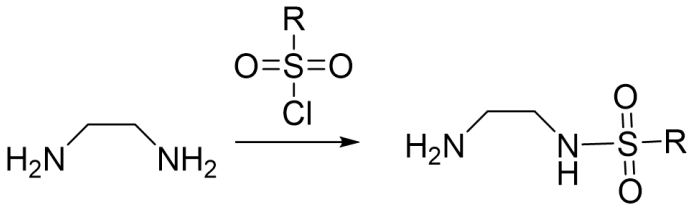


Figure1: The typical process for the synthesis of ethylenediamine sulfonamides

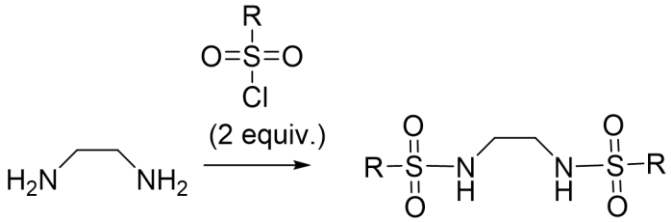


Figure 2: The typical process for the synthesis of disubstituted ethylenediamine sulfonamides

When it comes to monosubstituted ethylenediamine and diethylenetriamine ligands the amine is no longer the limiting reagent as excess ethylenediamine or diethylenetriamine is used to facilitate the monosubstitution (2020, Darshani et al., 2020a, Feng et al., 2017). Here the excess amine can serve as a base to abstract the proton released during sulfonylation.

In diethylenetriamine, the sulfonyl fragment tends to connect to one of the terminal amine groups (**Figure 3**) but the sulfonylation of the central carbon can be achieved by employing a protecting group for terminal amines such as tert-butyloxycarbonyl (Boc) groups (Abhayawardhana et al., 2014) (**Figure 04**).

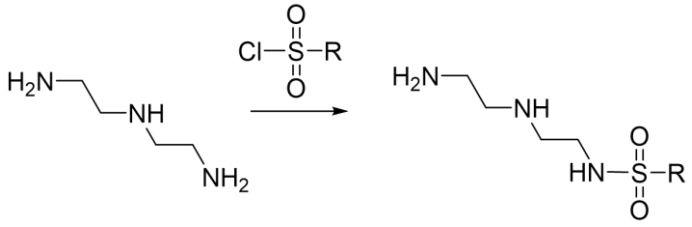


Figure 3: Scheme for the synthesis of N(SO_2R)dien ligands

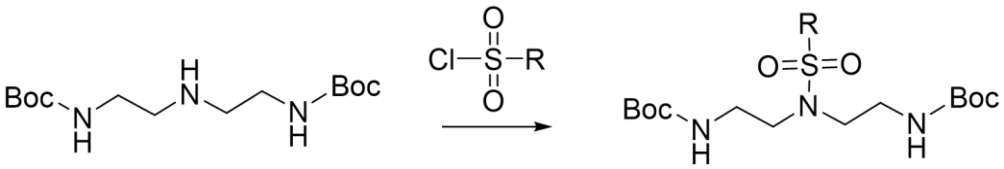


Figure 4: Scheme for the sylfonylation of the central N of dien

However, dipicolylamine ligands always bind to the sulfonyl groups at the central donor nitrogen forming symmetrical sulfonamide ligands with a tertiary sulfonamide nitrogen (**Figure 5**).

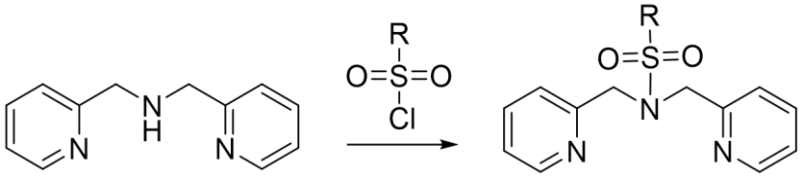


Figure 5: Scheme for the synthesis of N(SO_2R)dpa ligands

3. Metal-N(sulfonamido) complexes

As a result of the resonance stabilization of the sulfonamide group, the lone pair on the secondary sulfonamide nitrogen is not available to coordinate with the metal center, therefore, the sulfonamide nitrogen deprotonates upon binding to the metal center. N(SO_2R)dien-type ligands (**Figure 6**) such as tmbSO_2-N,N-Me$_2$dienH, tmbSO_2-N′-MedienH, tmbSO_2-dienH (tmb = trimethylbenzene) coordinate in a tridentate approach through the donation of the lone pair of free amino groups and the deprotonation of the anionic nitrogen of the sulfonamide group (Christoforou, 2007). Ethylenediamine sulfonamides where both the nitrogens are sulfonalated, bind to the metal center as anionic chelates by deprotonating the two sulfonamide nitrogens (Bodoki et al., 2009, Sánchez-Piso et al., 2002). Conventionally, tertiary sulfonamides such as the central nitrogen of N(SO2R)dpa-type ligands do not bind to metal centers due to their inability to deprotonate. The few complexes that are reported where the tertiary sulfonamide coordinates to a metal center show that it is possible only when the sulfonamide group is a part of macrocyclic ligands (Perera et al., 2013). However, N(SO_2R)dpa and N(SO_2R)dien type ligands with tertiary sulfonamide moiety at the center have been found to bind with metals such as rhenium in tridentate fashion. This requires the energy of the M-N bond to be favorable enough to change the hybridization of the sulfonamide nitrogen from resonance stabilized sp^2 to sp^3 which is stabilized by the metal-nitrogen bond (Ranasinghe et al., 2018). The first examples of structurally characterized metal complexes with the sulfonamide as part of a noncyclic linear tridentate ligand having a normal metal−N(sulfonamide) bond length (∼2.2 Å) are *fac*-[Re(CO)$_3$(N(SO_2R)dpa)]PF_6 (Perera et al., 2013) and *fac*-[Re-(CO)$_3$(N(SO_2R)dien)]PF_6 (Abhayawardhana et al., 2014) (**Figure 7**).

**Correspondence: theshi@sjp.ac.lk*

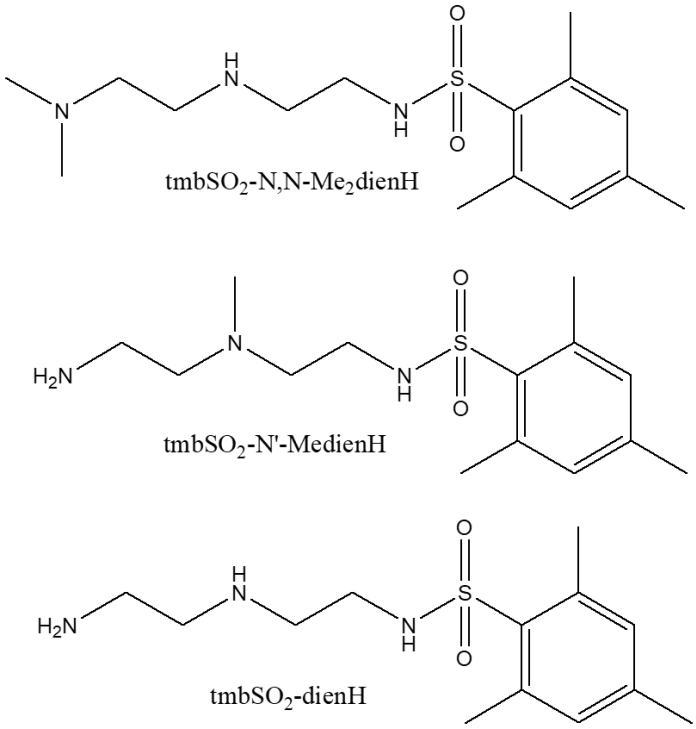


Figure 6: Structures of $N(SO_2R)$dien-type ligands

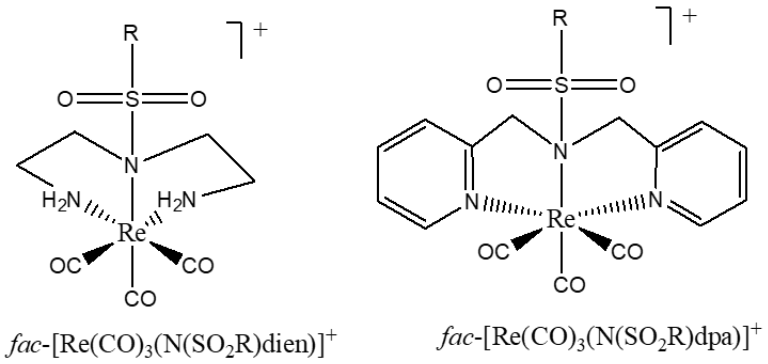


Figure 7: Structures of metal complexes with tridentate sulfonamide ligands

3.1 Synthesis of metal-N(sulfonamido) complexes

Either of two different methods are employed for the synthesis of metal sulfonamide complexes. One is to react a solution of the ligand with a solution of the metal precursor and / or heat the mixture at reflux until the limiting reagent is fully consumed (Bodoki et al., 2009, Perera et al., 2013, Darshani et al., 2020b, Darshani et al., 2020a). The other is to utilize an electrochemical procedure to obtain the complex.

For this, a solution of the ligand and a current carrier such as tetramethylammonium perchlorate is used along with a platinum wire as the cathode and the relevant metal plate as the sacrificial anode. Once the required voltage is applied electrolysis will take place and the emission of hydrogen gas at the cathode and /or a change in the color of the solution may be witnessed. The solid complex is collected at the bottom of the cell (Sánchez-Piso et al., 2002). The features of the reported complexes of different metals and their synthetic procedures are discussed separately in section 3.2

3.2 Properties of metal-N(sulfonamido) complexes

3.2.1 Platinum

Platinum is a soft metal that prefers soft donors such as nitrogen, thus both ethylenediamine and diethylenetriamine fit the role as suitable ligand systems for platinum complexes. Platinum(II) is widely used in many inorganic medicinal agents targeted at diseases like cancer. In fact, platinum-based drugs are known to be the best single type of anticancer drug active against a broad range of cancers (Lippert, 1999). In order for a platinum(II) complex to show anti-cancer activity it should have square planar geometry, be of neutral charge and contain two cis ammine ligands and two cis anionic ligands. Therefore, en and dien ligands can be used to make platinum complexes as it has been found that the ammine ligands can be replaced by a chelating diamine ligand (Johnstone et al., 2014). Even though many complexes with Pt-dien backbone have been studied (Monroe et al., 2018, Ndinguri et al., 2010, Carlone et al., 2000, Carlone et al., 2004), the Pt-N(sulfonamido) chemistry is scarcely explored. Therefore, the compounds having a sulfonamide moiety provide the opportunity to incorporate a fluorophore into the complex and to investigate the properties of the complexes with small biomolecules. The DNSH-dienH (Christoforou et al., 2006) ligand where DNSH is 5-(dimethylamino)naphthalene-1-sulfonamide) (Christoforou et al., 2006) has the ability to bind with platinum (II) in bidentate, tridentate, or quadridentate fashion. The complexes [Pt(DNSH-dienH)Cl_2], [Pt(DNSH-dien)Cl], [Pt(DNS-dien)] synthesized by Christoforou et al. show quenched fluorescence intensities compared to the ligand and they also indicate that the quenching is less when the fluorophore is further away from Pt(II) (Christoforou et al., 2006). The quenching or enhancement of the fluorescent intensity of complexes has a correlation to the capability of the fluorophore of the ligand to make a π contact with the metal center (Deems et al., 2020).

The [$PtCl_2$($N(SO_2R)$dpa)] complexes where the R group represents 1-napthyl, 2-napthyl and piperidinyl moieties show that dpa sulfonamides coordinate to the Pt(II) center in a bidentate manner forming a rare eight membered chelate ring such that the central sulfonamide nitrogen is not bound to the metal center (Thushara et al., 2021) (**Figure 8)**.

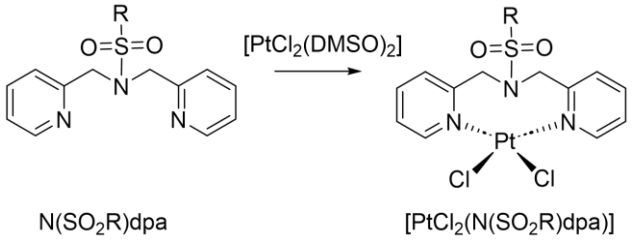


Figure 8: Scheme for the synthesis of [$PtCl_2$($N(SO_2R)$dpa)] complexes

**Correspondence: theshi@sjp.ac.lk*

3.2.2 Copper

In recent years there has been a significant demand for chemotherapeutic research on essential metalloelements (Sorenson, 1992) such as copper and zinc to overcome the limitations caused by platinum-based drugs such as toxicity, side effects and development of resistance by cells (Liguori et al., 2010). The Cu-N(sulfonamido) complexes where the N-sulfonamido ligand is derived by substituting both the nitogens of ethylenediamine with bulky sulfonamide fragments, are synthesized by incorporating a neutral ligand such as phenanthroline to obtain overall a neutral charge. $[CuL(phen)_2]$ complex, electrochemically synthesized by Sánchez-Piso et al. in 2002, where L is the dianionic ligand N,N'-bis(p-toluenesulfonyl)ethylenediamide (Sánchez-Piso et al., 2002) is crystallographically characterized to have an octahedral structure with the longer Cu-N distances associated with the axial nitrogen atoms. The equatorial plane consists of the two sulfonamide nitrogen atoms of L and two other nitrogen atoms, one from each phenanthroline molecule whereas the axial positions are occupied by the remaining nitrogen atoms of each phenanthroline.

[CuL(phen)] complexes (**Figure 9**) synthesized by Bodoki et al. in a non-electrochemical manner show distorted square planar geometry) and the distortion is due to the coordination to two bidentate ligands. The crystal structures of these complexes show π-π stacking interactions, which is a result of intermolecular parallel π-π stacking between the phenanthroline rings belonging to adjacent complex molecules and the chelate rings formed at the copper center (Bodoki et al., 2009).

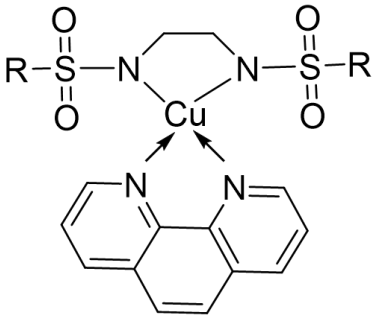


Figure 9: Structure of [CuL(phen)] complexes

3.2.3 Rhenium

Even though analogous *fac*-$Re(CO)_3$ complexes have been largely studied during the previous decades as model systems for $^{99m}Tc(CO)_3$ diagnostic agents (He et al., 2007), more recently rhenium complexes are being explored for their potential to serve as anticancer agents (Knopf et al., 2017, Simpson et al., 2017). Having a long lifetime, kinetic inertness and a large Stoke's shift are the reasons why rhenium complexes are favored over other metals (Guo et al., 1997, Stephenson et al., 2004). It is also noted that tridentate ligands are better than bidentate ones in terms of robustness and pharmacokinetics of pharmaceutical agents of the type *fac*-$[^{99m}Tc(CO)_3L]^+$ (Schibli et al., 2000). A comparative study by Christoforou et al. of *fac*-$[Re(CO)_3L]$ complexes where L= tmbCOdienH and tmbSO_2-dienH (**Figure 10**) with monoanionic tridentate diethylenetriamine ligands with a dangling bulky aromatic group connected via two different linker groups; an amido bond (N-CO) and a sulfonamido bond (N-SO_2) shows that the sulfonamido group is more flexible whereas the amido bond restricted the rotation of the dangling pendant group. It is also noted that the linker component and the position of the pendant group affect the overall shape of the complex (Christoforou et al., 2008). Tridentate ligands which are linear and symmetrical

with linkage at the center donor are suitable as radiopharmaceuticals as they do not form racemic or diastereoisomeric mixtures (Perera et al., 2013). $[Re(CO)_3(N(SO_2R)dpa)]PF_6$ complexes (**Figure 7**) synthesized by Perera et al. were the first structurally characterized complexes with normal length metal-nitrogen bond for a tertiary sulfonamide (Perera et al., 2013).

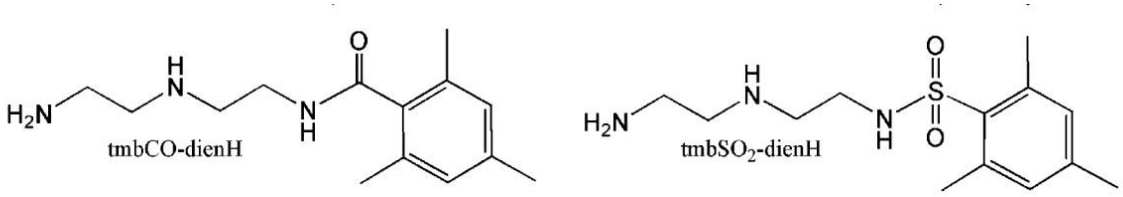


Figure 10: The structures of tmbCOdienH and $tmbSO_2$-dienH ligands

$[Re(CO)_3(N(SO_2R)dien)]PF_6$ complexes (**Figure 7**) synthesized by Abhayawardhana et al. shows that the tertiary sulfonamide coordinates with the metal center forming a normal length M-N bond by rehybridizing the sulfonamide nitrogen from sp^2 to sp^3 despite dien being a flexible moiety unlike dpa which is rigid ligand (Abhayawardhana et al., 2014). Thus, the coordination of the tertiary sulfonamide of dien to Re(I) proves that the coordination is not influenced by the rigidity of the chelate ring. Furthermore, the dien framework being small is an added advantage in constructing biocongugates (Abhayawardhana et al., 2014).

3.2.4 Other d-block metals

Even though the deprotonation of an amide proton by a metal is not an easy task, in the case of sulfonamides, deprotonation is favored upon coordination to metal centers due to the electron withdrawing nature of the sulfonyl group (Otter et al., 1998). This paves way for the electrochemical synthesis of metal complexes with sulfonamide ligands. Metal complexes of general formula $[ML(phen)_2]$ synthesized by Sánchez-Piso and coworkers are examples for such electrochemical synthetic methods. These complexes are synthesized through electrochemical oxidation of anodic metal (nickel, copper, zinc and cadmium) in acetonitrile solutions containing N,N'-bis[(4 methylphenyl)sulfonyl]ethylenediamine (Sánchez-Piso et al., 2002) as the sulfonamide ligand (L) in the presence of a another nitrogen co-ligand which is neutral, such as 1,10-phenanthroline. Crystals of all four complexes $[NiL(phen)_2]$, $[CuL(phen)_2]$, $[ZnL(phen)_2]$ and $[CdL(phen)_2]$ (Sánchez-Piso et al., 2002) show distorted octahedral geometry around the metal atom (MN_6).

The $[Zn(N(SO_2Rdpa)Cl_2]$ complexes reported by Darshani el al. (Darshani et al., 2020b) in 2020 are the first structurally characterized Zn complexes coordinated to sulfonamide derivatized dpa ligands. Here similar to the $[PtCl_2(N(SO_2R)dpa)]$ (Thushara et al., 2021) complexes mentioned above (**Figure 8**), the pyridyl nitrogens of dpa coordinate to Zn in a bidentate mode where the sulfonamide nitrogen refrains from binding to the metal center. The crystal structures of the complexes and the downward shift of the νC=N band in FTIR spectra further validate the coordination of the pyridyl nitrogens to the metal center. The complexes show distorted tetrahedron geometry around the Zn center (Darshani et al., 2020b). Quenched fluorescence intensities of the Zn complexes are observed in comparison to that of the free

**Correspondence: theshi@sjp.ac.lk*

ligand. This reduction in fluorescence intensity upon coordination could be due to metal binding induced fluorescence.

4. Biological applications

The study of coordination complexes as chemotherapeutic agents flourished following Rosenburg's discovery (Rosenberg et al., 1965) of the therapeutic potential of cis-diamminedichloroplatinum(II) (cisplatin) in the early 1960s. Since then, the cytotoxicity of different platinum complexes has been studied which later extended to other metal ions as well. Budzisz, 2019 discusses thepromising potential in different metal ions and their complexes as drugs with antimicrobial, antiviral, and antifungal properties as well as for neurodegenerative disorders and as chemotherapeutic agents. The sulfonamide ligand itself can show interesting biological properties such as antitumor, antibacterial, antiviral, anti-inflammatory, anticonvulsant, and analgesic activity depending on the bulky sulfonamide moiety (Table 1) that is attached to the carrier ligand. The bulky aromatic fragment is also responsible for the fluorescence exhibited by the ligands and the complexes. Thus, these biological properties exhibited by the ligands and the metal ions play a synergistic role to give unique and valuable features to the metal complexes.

Thermal denaturation studies conducted by Budoki et al., 2009 show that [CuL(phen)] complexes (**Figure 9**) where L stands for ethylenediamine sulfonamide ligands, interact strongly with CT-DNA stabilizing the original structure of DNA, whereas the free sulfonamide ligands do not show any significant interactions with DNA. The ability of these complexes to cleave DNA using gel electrophoresis and the results demonstrate that the above copper complexes possess nuclease activity, and that the efficacy of the nuclease activity is more at higher concentrations. Thus, the results of the study of Budoki et al. suggest that these compounds have the potential to be used as chemotherapeutic agents.

Darshani et al. explored the *in vitro* cytotoxicity of diethylenetriamine sulfonamide ligands and their rhenium complexes (**Figure 11**) which shows that the metal complexes show higher cytotoxicity than their corresponding sulfonamide ligands (Darshani et al., 2020a). The complexes were found to be more potent than the reported values for cisplatin. The comparative study of the above complexes with non-small cell lung cancer cells (NCI-H-292) and human normal lung fibroblast cells (MRC-5) depicts that the [$Re(CO)_3(N(SO_2)$(1-nap)dien)] complex (**Figure 11**) shows higher toxicity towards cancer cell lines (Darshani et al., 2020a). This selective toxicity towards lung cancer cells can be exploited in further studies as a potential anticancer drug lead.

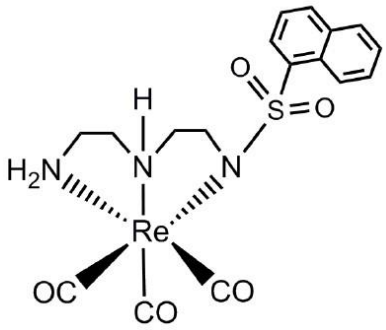


Figure 11: The structure of [$Re(CO)_3(N(SO_2)$(1-nap)dien)] complex

Bio assays investigated by Thushara et al. present a comparative study of the antiproliferative activity of dipicolylamine sulfonamide ligands and their platinum complexes in human breast cancer cells and normal breast cells (Thushara et al., 2021). The dpa sulfonamide ligands containing napthyl and piperidinyl moieties have demonstrated a selectively high toxicity towards the cancer cell lines. However, the study depicts that the platinum complexes of the above ligands show different behavior towards the cell lines than their corresponding ligands. [$PtCl_2$(N(SO_2(1-nap))dpa)] (**Figure 12**) shows higher toxicity towards the normal cell lines than towards the cancer cell lines (Thushara et al., 2021), which demonstrates that coordination to platinum may transform the behavior of the ligands towards the cell lines. The high antiproliferative activity shown by these compounds implies that they could be potential leads for anticancer drugs due to their efficacy at lower concentrations which would decrease the possible side effects during treatments.

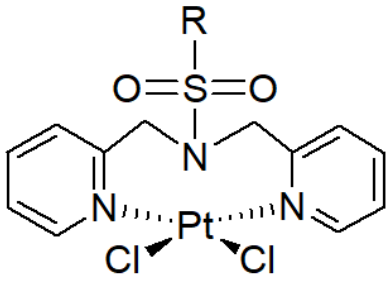


Figure 12: The structure of [$PtCl_2$(N(SO_2(1-nap))dpa)] complex

Even though the [Zn(N(SO_2Rdpa)Cl_2] complexes (Darshani et al., 2020b) show quenching of fluorescence compared to their corresponding free ligands, the fact that the complexes are fluorescent makes them potential candidates for applications as fluorescent sensors or imaging agents. The biological activity of these complexes remains to be explored, which provides direction for future work as zinc, being a bio essential element, would give chemotherapeutic agents with lesser toxicity.

6. Conclusion

In conclusion, the ethylenediamine, diethylenetriamine and dipicolylamine ligands are effective carrier ligands to synthesize sulfonamides due to their outstanding binding ability. The primary and secondary sulfonamide nitrogens deprotonate when coordinating with metal centers unlike the amine groups which coordinate via the lone pairs on nitrogen atoms. The bulky aromatic sulfonamide moieties incorporate interesting biological properties to the ligand while increasing the fluorescence and lipophilicity of the ligand system. Lipophilicity of a drug aids for the improved uptake of the compound by target cells while fluorescent properties of the molecule are used to synthesize imaging agents in diagnostics and theranostics. These properties along with the biological features brought about by the metal centers paly a synergistic role in complex synthesis giving unique biological properties to the complexes which make them potential candidates to be used in chemotherapeutic or diagnostic applications such as the copper sulfonamido complexes (Figure 9) which show strong interactions with DNA and the [$Re(CO)_3$(N(SO_2)(1-nap)dien)] complex which exhibits selective cytotoxicity. Thus, this

**Correspondence: theshi@sjp.ac.lk*

field offers a prospective path for future research to synthesize compounds of biological importance by utilizing the unique properties of different R groups.

References

Abhayawardhana, P. L., Marzilli, P. A., Fronczek, F. R. & Marzilli, L. G. 2014. Complexes possessing rare "tertiary" sulfonamide nitrogen-to-metal bonds of normal length: fac-[Re(CO)3(N(SO2R)dien)]PF6 complexes with hydrophilic sulfonamide ligands. Inorganic Chemistry, 53**,** 1144-1155.

Ali, H. & Van Lier, J. E. 1999. Metal complexes as photo-and radiosensitizers. Chemical Reviews, 99**,** 2379-2450.

Bodoki, A., Hangan, A., Oprean, L., Alzuet, G., Castiñeiras, A. & Borrás, J. 2009. Oxidative DNA cleavage by copper ternary complexes of 1, 10-phenanthroline and ethylenediamine-sulfonamide derivatives. Polyhedron, 28**,** 2537-2544.

Budzisz, E. 2019. Role of metal ions complexes and their ligands in medicine, pharmacy and cosmetology. Current Medicinal Chemistry, 26**,** 578-579.

Carlone, M., Fanizzi, F. P., Intini, F. P., Margiotta, N., Marzilli, L. G. & Natile, G. J. I. C. 2000. Influence of carrier ligand NH hydrogen bonding to the O6 and phosphate group of guanine nucleotides in platinum complexes with a single guanine ligand. Inorganic Chemistry, 39**,** 634-641.

Carlone, M., Marzilli, L. G. & Natile, G. J. I. C. 2004. Platinum complexes with NH groups on the carrier ligand and with only one guanine or hypoxanthine derivative. Informative models for assessing relative nucleobase and nucleotide hydrogen-bond interactions with amine ligands in solution. Inorganic Chemistry, 43**,** 584-592.

Chibale, K., Haupt, H., Kendrick, H., Yardley, V., Saravanamuthu, A., Fairlamb, A. H. & Croft, S. L. 2001. Antiprotozoal and cytotoxicity evaluation of sulfonamide and urea analogues of quinacrine. Bioorganic medicinal chemistry letters, 11**,** 2655-2657.

Chohan, Z. H. 2008. Metal-based sulfonamides: Their preparation, characterization and in-vitro antibacterial, antifungal & cytotoxic properties. X-ray structure of 4-[(2-hydroxybenzylidene) amino] benzenesulfonamide. Journal of Enzyme Inhibition and Medicinal Chemistry Research, 23**,** 120-130.

Christoforou, A. M. 2007. Exploring the binding of amine and sulfonamide ligands in Rhenium(I) Tricarbonyl and Platinum(II) complexes. Louisiana State University and Agricultural & Mechanical College.

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.

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.

Darshani, T., Fronczek, F. R., Priyadarshani, V. V., Samarakoon, S. R., Perera, I. C. & Perera, T. 2020a. Synthesis and characterization of novel naphthalene-derivatized tridentate ligands and their net neutral rhenium tricarbonyl complexes and cytotoxic effects on non-small cell lung cancer cells of interest. Polyhedron, 187**,** 114652-114652.

Darshani, T., Weldeghiorghis, T. K., Fronczek, F. R. & Perera, T. 2020b. The first structurally characterized sulfonamide derivatized Zn(II)-dipicolylamine complexes with eight membered chelate rings. Synthetic and structural studies. Journal of Molecular Structure, 1216**,** 128310-128310.

Deems, J. C., Reibenspies, J. H., Lee, H.-S. & Hancock, R. D. 2020. Strategies for a fluorescent sensor with receptor and fluorophore designed for the recognition of heavy metal ions. Inorganica Chimica Acta, 499**,** 119181.

Diltz, S., Aguirre, G., Ortega, F. & Walsh, P. 1997. Synthesis of chiral heteroaromatic tetradentate sulfonamide based ligands. Tetrahedron: Asymmetry, 8**,** 3559-3562.

Ezabadi, I. R., Camoutsis, C., Zoumpoulakis, P., Geronikaki, A., Soković, M., Glamočilija, J. & Ćirić, A. 2008. Sulfonamide-1, 2, 4-triazole derivatives as antifungal and antibacterial agents: Synthesis, biological evaluation, lipophilicity, and conformational studies. Bioorganic Medicinal Chemistry, 16**,** 1150-1161.

Feng, T., Chua, H. J. & Zhao, Y. 2017. Reduction-Responsive Carbon Dots for Real-Time Ratiometric Monitoring of Anticancer Prodrug Activation in Living Cells. ACS Biomater Sci Eng, 3**,** 1535-1541.

Gaynor, D. & Griffith, D. M. 2012. The prevalence of metal-based drugs as therapeutic or diagnostic agents: beyond platinum. Dalton Transactions, 41**,** 13239-13257.

Gielen, M. & Tiekink, E. R. 2005. Metallotherapeutic drugs and metal-based diagnostic agents: the use of metals in medicine, John Wiley & Sons.

Guo, X.-Q., Castellano, F. N., Li, L., Szmacinski, H., Lakowicz, J. R. & Sipior, J. 1997. A long-lived, highly luminescent Re(I) metal–ligand complex as a biomolecular probe. Analytical biochemistry, 254**,** 179-186.

He, H., Lipowska, M., Xu, X., Taylor, A. T. & Marzilli, L. G. 2007. Rhenium analogues of promising renal imaging agents with a $[99mTc(CO)3]^{+}$ core bound to cysteine-derived dipeptides, including lanthionine. Inorganic chemistry, 46**,** 3385-3394.

Johnstone, T. C., Park, G. Y. & Lippard, S. J. 2014. Understanding and improving platinum anticancer drugs–phenanthriplatin. Anticancer research, 34**,** 471-476.

Kennedy, J. F. & Thorley, M. 1999. Pharmaceutical Substances, A. Kleeman, J. Engel, B. Kutscher & D. Reichert George Thieme Verlag, Stuttgart/New York, 1999, 2286 pp., ISBN 3-13-558403-8/0-86577-817-5.[0pt][Electronic Version. ISBN 3-13-115133-1/0-86577-818-3]. Bioseparation, 8**,** 336-336.

Knopf, K. M., Murphy, B. L., Macmillan, S. N., Baskin, J. M., Barr, M. P., Boros, E. & Wilson, J. J. 2017. In vitro anticancer activity and in vivo biodistribution of rhenium (I) tricarbonyl aqua complexes. Journal of the American Chemical Society, 139**,** 14302-14314.

Levin, J., Chen, J., Du, M., Nelson, F., Killar, L., Skala, S., Sung, A., Jin, G., Cowling, R. & Barone, D. 2002. Anthranilate sulfonamide hydroxamate TACE inhibitors. Part 2: SAR of the acetylenic P1′ group. Bioorganic medicinal chemistry letters, 12**,** 1199-1202.

Liguori, P. F., Valentini, A., Palma, M., Bellusci, A., Bernardini, S., Ghedini, M., Panno, M. L., Pettinari, C., Marchetti, F., Crispini, A. & Pucci, D. 2010. Non-classical anticancer agents: Synthesis and biological evaluation of zinc(II) heteroleptic complexes. Dalton Transactions, 39**,** 4205-4212.

Lippert, B. J. V. H. C. A., Zürich 1999. Chemistry and biochemistry of a leading anticancer drug.

Louie, A. Y., Meade, T. J. & Lippard, S. 1999. Metal complexes as enzyme inhibitors. Chemical reviews, 99**,** 2711-2734.

Ma, T., Fuld, A. D., Rigas, J. R., Hagey, A. E., Gordon, G. B., Dmitrovsky, E. & Dragnev, K. H. 2012. A phase I trial and in vitro studies combining ABT-751 with carboplatin in previously treated non-small cell lung cancer patients. Chemotherapy, 58**,** 321-329.

**Correspondence: theshi@sjp.ac.lk*

Monroe, J. D., Hruska, H. L., Ruggles, H. K., Williams, K. M. & Smith, M. E. 2018. Anti-cancer characteristics and ototoxicity of platinum(II) amine complexes with only one leaving ligand. PLoS One, 13**,** e0192505.

Ndinguri, M. W., Fronczek, F. R., Marzilli, P. A., Crowe, W. E., Hammer, R. P. & Marzilli, L. G. 2010. Exploring water-soluble Pt(II) complexes of diethylenetriamine derivatives functionalized at the central nitrogen. Synthesis, characterization, and reaction with 5′-GMP. Inorganica Chimica Acta, 363**,** 1796-1804.

Obaleye, J. A., Tella, A. C. & Bamigboye, M. O. 2012. Metal complexes as prospective antibacterial agents. A Search for Antibacterial Agents. IntechOpen.

Ogden, R. C. & Flexner, C. W. 2001. Protease inhibitors in AIDS therapy.

Otter, C. A., Couchman, S. M., Jeffery, J. C., Mann, K. L., Psillakis, E. & Ward, M. D. 1998. Complexes of a new bidentate chelating pyridyl/sulfonamide ligand with copper(II), cobalt(II) and palladium(II): crystal structures and spectroscopic properties. Inorganica chimica acta, 278**,** 178-184.

Perera, T., Abhayawardhana, P., Marzilli, P. A., Fronczek, F. R. & Marzilli, L. G. 2013. 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**,** 2412-2421.

Ranasinghe, K., Marzilli, P. A., Pakhomova, S. & Marzilli, L. G. 2018. Linear bidentate ligands (L) with two terminal pyridyl N-donor groups forming Pt(II)LCl_2 complexes with rare eight-membered chelate rings. Inorganic Chemistry, 57**,** 12756-12768.

Rosenberg, B., Van Camp, L. & Krigas, T. J. N. 1965. Inhibition of cell division in Escherichia coli by electrolysis products from a platinum electrode. Nature, 205**,** 698-699.

Roush, W. R., Gwaltney, S. L., Cheng, J., Scheidt, K. A., Mckerrow, J. H. & Hansell, E. 1998. Vinyl sulfonate esters and vinyl sulfonamides: potent, irreversible inhibitors of cysteine proteases. Journal of the American Chemical Society, 120**,** 10994-10995.

Sakurai, H., Kojima, Y., Yoshikawa, Y., Kawabe, K. & Yasui, H. 2002. Antidiabetic vanadium(IV) and zinc(II) complexes. Coordination Chemistry Reviews, 226**,** 187-198.

Sánchez-Piso, J., García-Vázquez, J. A., Romero, J., Durán, M. L., Sousa-Pedrares, A., Labisbal, E. & Nascimento, O. R. 2002. Electrochemical synthesis and crystal structures of nickel(II), copper(II), zinc(II) and cadmium(II) complexes with N,N′-bis[(4-methylphenyl)sulfonyl]ethylenediamine. Inorganica Chimica Acta, 328**,** 111-122.

Schibli, R., La Bella, R., Alberto, R., Garcia-Garayoa, E., Ortner, K., Abram, U. & Schubiger, P. 2000. Influence of the denticity of ligand systems on the in vitro and in vivo behavior of 99mTc(I)tricarbonyl complexes: a hint for the future functionalization of biomolecules. Bioconjugate chemistry, 11**,** 345-351.

Simpson, P. V., Casari, I., Paternoster, S., Skelton, B. W., Falasca, M. & Massi, M. 2017. Defining the anti-cancer activity of tricarbonyl rhenium complexes: induction of G2/M cell cycle arrest and blockade of Aurora-A kinase phosphorylation. Chemistry–A European Journal, 23**,** 6518-6521.

Sorenson, J. 1992. Use of essential metalloelement complexes or chelates in biological studies. Free radical biology medicine, 13**,** 593-594.

Stephenson, K. A., Banerjee, S. R., Besanger, T., Sogbein, O. O., Levadala, M. K., Mcfarlane, N., Lemon, J. A., Boreham, D. R., Maresca, K. P. & Brennan, J. D. 2004. Bridging the gap between in vitro and in vivo imaging: isostructural Re and 99mTc complexes for correlating fluorescence and radioimaging studies. Journal of the American Chemical Society, 126**,** 8598-8599.

Stokes, S. S., Albert, R., Buurman, E. T., Andrews, B., Shapiro, A. B., Green, O. M., Mckenzie, A. R. & Otterbein, L. R. 2012. Inhibitors of the acetyltransferase domain of N-acetylglucosamine-1-phosphate-uridylyltransferase/glucosamine-1-phosphate-acetyltransferase (GlmU). Part 2: optimization

of physical properties leading to antibacterial aryl sulfonamides. Bioorganic medicinal chemistry letters, 22**,** 7019-7023.

Taylor, J. B. & Hansch, C. 1990. Comprehensive medicinal chemistry: the rational design, mechanistic study & therapeutic application of chemical compounds. 5. Biopharmaceutics, Pergamon Press.

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**,** 17658-17668.

Topală, T., Bodoki, A. E., Hangan, A., Gheorghe-Cetean, S. & Oprean, L. 2019. Revisiting therapeutic sulfonamides in the attempt to improve the antimicrobial properties through metal-ion coordination. FARMACIA, 67**,** 749-758.

Vullo, D., De Luca, V., Scozzafava, A., Carginale, V., Rossi, M., Supuran, C. T. & Capasso, C. 2013. The extremo-α-carbonic anhydrase from the thermophilic bacterium Sulfurihydrogenibium azorense is highly inhibited by sulfonamides. Bioorganic medicinal chemistry, 21**,** 4521-4525.

Wilson, C. O., Gisvold, O., Block, J. H. & Beale, J. M. 2004. Wilson and Gisvold's textbook of organic medicinal and pharmaceutical chemistry/edited by John H. Block, John M. Beale Jr. Philadelphia: Lippincott Williams & Wilkins.

Zhang, C. X. & Lippard, S. J. 2003. New metal complexes as potential therapeutics. Current opinion in chemical biology, 7**,** 481-489.

Zhang, P. & Sadler, P. J. J. E. J. I. C. 2017. Redox-active metal complexes for anticancer therapy. European Journal of Inorganic Chemistry, 12, 1541-1548.

Zhao, J., Wang, D., Yang, W.-L., Niu, J. & Wu, W. 2021. Unconventional Synthetic Process of Fasudil Hydrochloride: Costly Homopiperazine Was Avoided. Organic Process Research Development.

**Correspondence: theshi@sjp.ac.lk*