MJFAS MALAYSIAN JOURNAL OF FUNDAMENTAL AND APPLIED SCIENCES
PRINT ISSN: 2289-5981 | ONLINE ISSN: 2289-599X

RESEARCH ARTICLE

Tetradentate phenolic Schiff base ligands derived from aromatic diamine and their nickel (II) complexes: Synthesis, characterization, and *in vitro* anticancer screening

Shahrul Nizam Ahmad [a*], Hadariah Bahron [a], Amalina Mohd Tajuddin [b], Kalavathy Ramasamy [c]

[a] *Department of Chemistry, Faculty of Applied Sciences, Universiti Teknologi MARA, 40450, Shah Alam, Selangor, Malaysia*
[b] *Atta-ur-Rahman Institute for Natural Product Discovery, Level 9, Building FF3, UiTM Selangor, Kampus Puncak Alam, 42300, Bandar Puncak Alam, Selangor, Malaysia*
[c] *Collaborative Drug Discovery Research (CDDR) Group, Faculty of Pharmacy, UiTM Puncak Alam Campus, 43600, Bandar Puncak Alam, Selangor, Malaysia*

* *Corresponding author: shahruln@uitm.edu.my*

Article history
Received 21 Mac 2019
Revised 14 April 2019
Accepted 25 June 2019
Published Online 25 August 2019

Abstract

Two tetradentate phenolic Schiff base ligands namely 2,2'-((1*E*,1'*E*)-(1,2-phenylenebis(azanylylidene))bis(methanylylidene))diphenol, **L1H**, 2,2'-((1*E*,1'*E*)-(1,2-phenylenebis(azanylylidene))bis-(methanylylidene))bis(4-fluorophenol), **L1F** and their new nickel(II) complexes were successfully synthesized, characterized and evaluated for their *in vitro* anticancer activities against human colon cancer cell lines, HCT116. The compounds were characterized using FT-IR, ^{1}H and ^{13}C NMR, UV-Visible, elemental analysis and melting point. The anticancer results revealed that the parent ligands were more active than their corresponding complexes with **L1F** being the most potent anticancer compound with IC_{50} of 2.8 μg/ml.

***Keywords*:** Schiff bases, nickel (II), anticancer, HCT116

INTRODUCTION

Schiff bases have become a centre of attention of researchers due to their cost-effectiveness and easy availability of starting materials. Their electronic profiles can be fine-tuned through the incorporation of electron donating and/or withdrawing substituents in the structure, bringing about changes in the aspect of chemical, physical, and spectroscopic properties (Cozzi *et al*., 2004). The presence of donor atoms bearing lone pair(s) of electrons makes Schiff bases the ligands of choice for coordination with an array of metal centres. The Lewis acid-base interaction is a well-documented mechanism explaining the coordination of Schiff bases to metal centres where electron rich moiety of the imine nitrogen donates electrons to the metal centre, forming dative covalent bond(s) (Gupta & Sutar, 2008). The presence of oxygen and nitrogen donor atoms in phenolic Schiff bases is a great advantage where the former could be a hard donor, stabilizing higher oxidation states of the metal while the latter, on the other hand, acts as a soft donor, stabilizing the lower oxidation state of the metal *(*Drozdzak *et al.*, 2005; Guerriero *et al*., 1995; Vigato & Tamburini, 2004).

Metals especially transition metals are known for their potential as anticancer drugs. This is owing to their unique coordination numbers and geometries, available multiple redox states, facile adjustments of the thermodynamics, and kinetics of ligand substitution (van Rijt & Sadler, 2009). The discovery of cisplatin about 50 years ago have attracted many inorganic chemists to synthesize analogous platinum complexes such as oxaliplatin and carboplatin (Jung & Lippard, 2007). Despite their efficacy in killing cancer cells, platinum-based anticancer drugs have been reported to cause severe side effects on the cancer sufferers (Jung & Lippard, 2007) and costly.

Hence, the search for alternative drugs has become more eminent in these recent years. This includes the exploration of other metal complexes such as palladium and nickel - metals that are in the same group as platinum in the periodic table (Abu-Surrah *et al*., 2010). Coordinated with Schiff bases, metal complexes have been reported to possess good to excellent bioactivities against cancer, bacteria, and fungi (Joseyphus *et al.*, 2016). The high chemical resemblance of nickel complexes with platinum, the former being more earth-abundant and economically attractive, has spurred investigation on anticancer properties of nickel complexes. Hence, this paper reports the anticancer effects of two tetradentate phenolic Schiff base ligands and their respective nickel (II) complexes against HCT116 colon cancer cell lines.

EXPERIMENTAL

General Synthesis of Schiff Base Ligands

A hot solution of *ortho*-phenylenediamine (1 mmol) in absolute ethanol (10 ml) was added to a stirred solution of salicylaldehyde derivatives (2 mmol) in absolute ethanol (5 ml). After being refluxed for 4 h, the solution was cooled to room temperature. The yellow solid obtained was filtered off, washed with cold ethanol, and air-dried.

L1H

Yield: 56.0%. M.p.: 168-170 °C. Anal. Calc. (%) for $C_{20}H_{16}N_2O_2$ (Mr = 316.36 gmol^{-1}): C, 75.93; H, 5.10; N, 8.86. Found: C, 73.85; H, 4.87; N, 8.54. IR (KBr pellet, cm^{-1}): 1612 (C=N), 3222 (O-H); ^{1}H NMR ($CDCl_3$) δ; 6.95-7.40 (6H, m, ArH), 13.09 (1H, s, OH), 8.65 (1H, s, HC=N)

L1F

Yield: 79.3%. M.p.: 193-195 °C. Anal. Calc. (%) for $C_{22}H_{14}F_2N_2O_2$ (Mr = 352.34 $gmol^{-1}$): C, 68.18; H, 4.01; N, 7.95. Found: C, 67.79; H, 3.93; N, 8.03. IR (KBr pellet, cm^{-1}): 1618 (C=N), 3236 (O-H); ^1H NMR ($CDCl_3$) δ; 7.04-7.40 (5H, m, ArH), 12.82 (1H, s, OH), 8.61 (1H, s, HC=N)

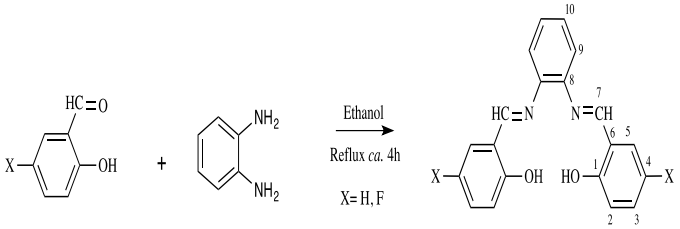

Fig. 1 Synthesis of Schiff base ligands.

General Synthesis of Nickel(II) Complexes

The nickel (II) acetate tetrahydrate (1 mmol) was dissolved in 10 mL of ethanol in a round bottom flask. Ligand (1 mmol) was dissolved separately in 10 mL of ethanol. The ligand solution was added dropwise into the flask containing the metal solution. The mixture was refluxed for 6 h. Then, the solid was filtered off, washed with a small amount of cold ethanol, and dried in air.

NiL1H

Yield: 74.7%. M.p.: >300 °C. Anal. Calc. (%) for $C_{20}H_{14}N_2O_2Ni$ (Mr $gmol^{-1}$= 373.04): C, 64.40; H, 3.78; N, 7.51. Found: C, 63.93; H, 3.76; N, 6.95. IR (KBr pellet, cm^{-1}): 1607 (C=N); ^1H NMR ($CDCl_3$) δ; 6.64-7.71 (6H, m, ArH); 8.61 (1H, s, HC=N)

NiL1F

Yield: 93.8%. M.p.: >300 °C. Anal. Calc. (%) for $C_{20}H_{12}F_2N_2O_2Ni$ (Mr $gmol^{-1}$= 409.02): C, 58.73; H, 2.96; N, 6.85. Found: C, 58.89; H, 2.76; N, 6.88. IR (KBr pellet, cm^{-1}): 1602 (C=N); ^1H NMR ($CDCl_3$) δ; 6.90-8.09 (5H, m, ArH); 8.90 (1H, s, HC=N)

.

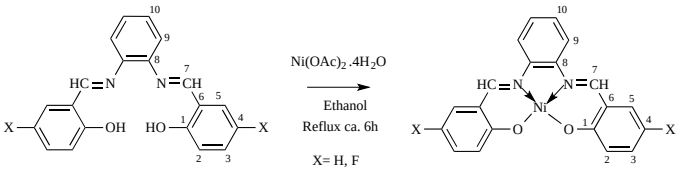

Fig. 2 Synthesis of nickel (II) Schiff base complexes.

Determination of Anticancer Activity

Human colorectal carcinoma (HCT116) were seeded at 2,500 cells/well in a 96-well plate and allowed to attach overnight. The cells were then exposed to the respective compounds at concentrations ranging between 0.001–100 μg/ml for 72 h before being subjected to Sulforhodamine B (SRB) assay (Rohilla *et al*., 2014).

RESULTS AND DISCUSSION

Physicochemical Properties

The micro-elemental data of the compounds are reported in Table 1. The percentages of C, H, and N were in concordance with the proposed structure. The melting points of the complexes were found to be higher than those of their parent ligands likely because of the increased molecular weights due to the addition of nickel (II) with strong dative covalent and ionic bonds between ligands and metal ions. Melting points were reported in temperature range, from the point at which the compound started to melt until it was completely molten.

Table 1 Physicochemical Properties of L1H, L1F and nickel (II) complexes.

Compounds	Colour	Percent Yield (%)	Chemical Formula	Melting Point (°C)	Elemental Analysis % Calculated (Found)		
					C	H	N
L1H	Yellow	56.0	$C_{20}H_{16}N2O_2$	168-170	75.93(**73.85**)	5.10(**4.87**)	8.86(**8.54**)
NiL1H	Orange	74.7	$C2_0H_{14}N_2O_2Ni$	>300	64.40(**63.93**)	3.78(**3.76**)	7.51 (**6.95**)
L1F	Orange	79.3	$C_{22}H_{14}F_2N_2O_2$	193-195	68.18(**67.79**)	4.01(**3.93**)	7.95 (**8.03**)
NiL1F	Red	93.8	$C_{20}H_{12}F_2N_2O_2Ni$	>300	58.73(**58.89**)	2.96(**2.76**)	6.85 (**6.88**)

Spectroscopic Investigation

FT-IR

The ν(C=N) peaks of all ligands appeared in the range of 1612–1618 cm^{-1}. These peaks shifted by about 10 cm^{-1} to lower frequencies of 1602–1607 cm^{-1} in Ni (II) complexes indicating that the C=N experience a lowering in bond strength upon complexation. The shifting of C=N nickel(II) complexes was a good indicator that coordination between metal centre with phenolic oxygen and imine nitrogen has been achieved (Nair *et al.,* 2016). Furthermore, the appearance of new peaks assignable to M-N and M-O signals in the range of 474–494 and 521–526 cm^{-1} is another useful evidence that the complexation between ligands and metal centres of Ni(II) has been successfully achieved between metal and ligand through azomethine nitrogen and phenolic oxygen (Nakamoto, 1986).

The vibration of hydroxyl group, ν(OH), for both ligands was found as a weak peak at 3222–3236 cm^{-1}. The weak and broad peak of OH indicated the occurrence of intermolecular hydrogen bonding of –OH with azomethine nitrogen HC=N (OH···N=C) (Aranha *et al.*, 2006). These peaks were not seen in all nickel(II) complexes signalling that the complexation was established between phenolic oxygen and metal centres through deprotonation of hydroxyl group *(*Natarajan Raman *et al.*, 2004).

Table 2 The main FTIR spectral data of L1H, L1F and their Ni(II) complexes.

Compounds	Assignments, cm^{-1}							
	OH	C=N	C-N	C-O (phenol)	M-N	M-O	=C-H oop bend	C-H sp^2 stretch
L1H	3222(*w*)	1612(*s*)	1192(*m*)	1045(*w*)	-	-	787(*s*), 830(*w*)	3056(*w*)
NiL1H	-	1607(*s*)	1192(*m*)	1045(*w*)	526(*w*)	494(*w*)	750(*s*), 843(*w*)	3014(*w*)
L1F	3236(*w*)	1618(*s*)	1190(*m*)	1046(*w*)	-	-	779(*m*), 824(*m*)	3064(*w*)
NiL1F	-	1602(s)	1150(*m*)	1047(*w*)	521(*w*)	474(*w*)	762(*m*), 859(*m*)	3060(*w*)

Note: *s*: strong; *m*: medium *w*: weak

^{1}H NMR

The phenolic OH peak appeared as a singlet at 12.82–13.09 ppm in the free ligands. Its protons were deshielded downfield due to the formation of hydrogen bonding (Aranha *et al*., 2006). The absence of OH peak in all spectra of nickel complexes supported the IR evidence that the coordination to metal centres was established through deprotonation of the hydroxyl groups (Raman *et al*., 2001). As listed in Table 3, azomethine proton, HC=N signal appears as singlet at 8.61 and 8.65 ppm for L1H and L1F, correspondingly. The signal was seen at 8.65 and 8.90 ppm for NiL1H and NiL1F, respectively. This echoes the shifting of azomethine peak in FTIR spectra which suggested the involvement of azomethine nitrogen in the coordination to metal centres (Maity *et al*., 2010).

The chemical shifts of aromatic hydrogen appear as multiplets in the range of 6.95–7.40 ppm for free ligands and 6.64–8.09 ppm for the complexes. This is in agreement with the chemical shifts reported previously (Bahron, Ahmad, & Tajuddin, 2017). These protons experienced the shielding effect of diamagnetic anisotropy caused by circulating π-electrons in the aromatic rings. The values of coupling constants as shown in Table 3 suggested the presence of *ortho*- and *meta*-hydrogens. The numbers of hydrogens obtained from the integration were in conformance with the proposed chemical structures.

Table 3 ^{1}H NMR chemical shifts δ (ppm) of of Schiff base ligands and their Ni (II) complexes.

Compounds	Assignments, d							
	C^{1}-OH	HC^{7}=N	C^{2}-H (Ar)	C^{9}-H (Ar)	C^{4}-H (Ar)	C^{10}-H (Ar)	C^{3}-H (Ar)	C^{5}-H (Ar)
L1H	13.09 (*s*, 1H)	8.65 (*s*, 1H)	6.95 (*t*, 1H, J=7.5 Hz)	7.08 (*d*, 1H, J=8.3 Hz)	7.25 (*dd*, 1H, 5.8, 3.5 Hz)	7.37 (*dd*, 1H, 6.5, 3.1 Hz)	7.40 (*d*, 1H, 7.6 Hz)	7.40 (*d*, 1H, 7.6 Hz)
NiL1H	-	8.22 (*s*, 1H)	6.64 (*td*, 1H, 7.2, 0.8 Hz)	7.17 (*d*, 1H, J=8.7 Hz)	7.22 (*dd*, 1H, 6.2, 3.2 Hz)	7.30 (*d*, 1H, 7.2 Hz)	7.30 (*d*, 1H, 7.2 Hz)	7.71 (*dd*, 1H, 6.2, 3.3 Hz)
L1F	12.82 (*s*, 1H)	8.61 (*s*, 1H)	7.04 (*dd*, 1H, 8.8, 4.5 Hz)	7.13 (*m*, 1H)	-	7.28 (*m*, 1H)	7.13 (*m*, 1H)	7.40 (*dd*, 1H, 5.9, 3.4 Hz)
NiL1F	-	8.90 (*s*, 1H)	6.90 (*dd*, 1H, 9.4, 4.6 Hz)	7.18 (*m*, 1H)	-	7.35 (*m*, 1H)	7.35 (*m*, 1H)	8.09 (*dd*, 1H, 6.3, 3.4 Hz)

^{13}C NMR

Peaks for azomethine carbon, HC=N was found at 163.74 and 162.65 ppm in L1H and L1F, respectively, and appeared in lower field regions of NiL1H at 167.57 ppm. The shifting verified that coordination of metal centres to the ligands was successfully established (Shanker, Reddy, & Rohini, 2009). Complexation can also be intimated by the shifting of aromatic carbons from 117.56–142.57 ppm in free ligands to the region of 114.86–142.80 ppm in complexes. The displacement of C-OH peak by about 6–9 ppm in complexes was also another evidence of the metal-phenolic oxygen coordination (Senol, Hayvali, Dal, & Hokelek, 2011). Due to solubility limitations, the NMR spectrum of NiL1F could not be obtained.

Table 4 UV-Visible spectral data of L1H, L1F and their Ni (II) complexes.

Compounds	Band Assignment, λmax, nm (ε, L mol^{-1} cm^{-1})			
	π-π* (benzene)	π-π* (C=N)	n-π* (C=N)	LMCT
L1H	210 (8842), 230 (7219)	270 (6350)	331 (4908)	-
NiL1H	233 (3655), 259 (17291)	308 (6504)	376 (9543)	478 (3022)
L1F	206 (8119), 231 (9692)	268 (6930)	343 (5687)	-
NiL1F	234 (6037), 257 (6701)	289 (3096)	379 (4344)	488 (1436)

UV-Visible

Two weak to medium peaks of π–π*(C=C) were observed in the range of 206–210 nm and 230–231 nm for ligands. The position of the bands was in agreement with previously reported values (Aranha et al., 2006; Temel & Otludil, 2001). The weak to medium absorption bands of π-π*(C=N) were observed at 268–270 nm for ligands, in concordance with the values reported by Khanmohammadi, Salehifard, and Abnosi (2009). The medium to strong peaks of n-π* (C=N) were observed at higher wavelengths, in the vicinity of 331–343 nm for ligands. This band indicated that there was a transition of an electron from a lone pair on nitrogen to the π* of imine group (Bosnich, 1968).

Two absorption bands of π–π*(C=C), experienced a red shift (bathochromic) relative to their parent ligands, discovered at 233–234 nm and 257–259 nm for nickel (II) complexes. The peak of π–π*(C=N) also experienced a bathochromic effect, shifting to a longer wavelength where the bands were seen at 289–308 nm. These observations suggested that complexation had occurred between the Schiff base ligands with metal ions (Guangbin, 1999). The absorption bands of n–π*(C=N) were observed to experience a bathochromic shift to 376–379 nm, occurring as a consequence of the lone electron pair donation from azomethine nitrogen to the metal (N→M) (Ghose & Lasisi, 1986).

New peaks were found at 478–488 nm for nickel (II) complexes attributable to ligand to metal charge transfer (LMCT). These bands indicated that an interaction between imine nitrogen and metal centre was established forming a dative covalent bond where the electrons moved from the ligand to the metal (Aranha *et al*., 2006).

Anticancer activity

The anticancer activity of L1H, L1F, and their Ni (II) complexes were tested against colon cancer (HCT116) cell lines using SRB assay. Table 5 lists the IC_{50} against HCT116. In this work, IC_{50} refers to the concentration required to inhibit 50% of HCT116. Each IC_{50} was determined from mean dose-response curve of three independent experiments. 5-FU, a standard anticancer drug, serves as positive control. It was discernible that uncoordinated ligands have higher anticancer properties than their corresponding nickel (II) complexes, indicating that the interaction with the DNA of the cancer cells was not predominantly metal driven. This was also the case observed for the Schiff base compounds and their complexes studied by Tajuddin et al. (2016).

L1F was found to be the most potent compound against HCT116 with IC_{50} of 2.8 μg/ml. The potency against colon cancer cells was seen to increase with the presence of electron withdrawing fluoro substituent, F, as similarly observed by Sharma et al. (2012). However, all the compounds were relatively less active than the standard anticancer drug, 5-fluorouracil (5-FU).

Table 5 IC_{50} of ligands and their Ni (II) complexes against human colon cell lines HCT116.

Compounds	IC_{50} (μg/ml)
L1H	65
L1F	2.8
NiL1H	>100
NiL1F	>100
Standard, 5-FU	0.74

CONCLUSION

Two tetradentate phenolic Schiff base ligands, **L1H** and **L1F** and their respective new nickel (II) complexes have been successfully synthesized and characterized via physicochemical and spectral techniques. It emerges from the findings that the parent ligands were more active as anticancer agents than their nickel (II) complexes, amongst which **L1F**, containing fluoro substituent, appeared as the most potent anticancer compound.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the help of Universiti Teknologi MARA for the research funding (PERDANA/5/3 BESTARI (046/2018)) and research facilities. The scholarship from Ministry of Education through SLAB/SLAI scheme is greatly appreciated.

REFERENCES

Abu-Surrah, A. S., Abu Safieh, K. A., Ahmad, I. M., Abdalla, M. Y., Ayoub, M. T., Qaroush, A. K., Abu-Mahtheieh, A. M. (2010). New palladium(II) complexes bearing pyrazole-based Schiff base ligands: Synthesis, characterization and cytotoxicity. *European Journal of Medicinal Chemistry*, *45*(2), 471–475.

Aranha, P. E., Santos, M. P., Romera, S., Dockal, E. R. (2006). Synthesis, characterization, and spectroscopic studies of tetradentate Schiff base chromium (III) complexes. *Polyhedron*, *26*(7), 1373–1382.

Bahron, H., Ahmad, S. N., Tajuddin, A. M. (2017). Substituent effect on catalytic activity of palladium(II) Schiff base complexes for Sonogashira reaction. *Pertanika Journal of Science and Technology*, *25*, 115–124.

Bosnich, B. (1968). An interpretation of the circular dichroism and electronic spectra of salicylaldimine complexes of square-coplanar diamagnetic nickel(II). *Journal of the American Chemical Society*, *90*(3), 627–632.

Cozzi, P. G., Ciamician, C. G., Selmi, V. (2004). Metal – Salen Schiff base complexes in catalysis : practical aspects. *Chemical Society Reviews*, *33*, 410–421.

Drozdzak, R., Allaert, B., Ledoux, N., Dragutan, I., Dragutan, V., Verpoort, F. (2005). Ruthenium complexes bearing bidentate Schiff base ligands as efficient catalysts for organic and polymer syntheses. *Coordination Chemistry Reviews*, *249*(24), 3055–3074.

Ghose, B. N., Lasisi, K. M. (1986). Schiff base complexes of Titanium: Reaction of titanium(IV) tetrachloride with dibasic tetradentate Schiff bases. *Synthesis and Reactivity in Inorganic and Metal-Organic Chemistry*, *16*(8), 1121–1133.

Guangbin, W. (1999). Studies on Cu(II), Zn(II), Ni(II) and Co(II) complexes derived from two dipeptide Schiff bases. *Spectroscopic Letters*, *32*(4), 679–688.

Guerriero, P., Tarnburini, S., Vigato, P. A. (1995). From mononuclear to polynuclear macrocyclic or macroacyclic complexes. *Coordination Chemistry Reviews*, *139*(C), 17–243.

Gupta, K. C., Sutar, A. K. (2008). Catalytic activities of Schiff base transition metal complexes. *Coordination Chemistry Reviews*, *252*, 1420–1450.

Joseyphus, R. S., Hassan, I.-, Naikoo, G. A. (2016). Synthesis, spectral characterization, grain size effect, antimicrobial, DNA cleavage and anticancer activities of cobalt(II), nickel(II), copper(II) and zinc(II) complexes of Schiff Base. *Asian Journal of Chemistry*, *28*(7), 1571–1574.

Jung, Y., Lippard, S. J. (2007). Direct cellular responses to platinum-induced DNA damage. *Chemical Reviews*, *107*(5), 1387–1407.

Khanmohammadi, H., Salehifard, M., Abnosi, M. H. (2009). Synthesis, characterization, biological and thermal studies of Cu(II) complexes of salen and tetrahedrosalen ligands. *Journal of the Iranian Chemical Society*, *6*(2), 300–309.

Maity, D., Drew, M. G. ., Godsell, J. F., Roy, S., Mukhopadhyay, G. (2010). Synthesis and characterization of Cu(II) complexes of tetradentate and tridentate symmetrical Schiff base ligands ... *Transition Metal Chemistry*, *35*, 197–204.

Nair, M. S., Arish, D., Johnson, J. (2016). Synthesis, characterization and biological studies on some metal complexes with Schiff base ligand containing pyrazolone moiety. *Journal of Saudi Chemical Society*, *20*, S591–S598.

Nakamoto, K. (1986). *Infrared and Raman spectra of inorganic and coordination compounds* (6th ed.). New Jersey: Wiley.

Raman, N., Kulandaisamy, A., Thangaraja, C., Manisankar, P., Viswanathan, S., Vedhi, C. (2004). Synthesis, structural characterisation and electrochemical and antibacterial studies of Schiff base copper complexes. *Transition Metal Chemistry*, *29*(2), 129–135.

Raman, N., Pitchaikani Raja, Y., Kulandaisamy, A. (2001). Synthesis and characterisation of Cu(II), Ni(II), Mn(II), Zn(II) and VO(II) Schiff base complexes derived from o-phenylenediamine and acetoacetanilide. *Chemical Science*, *113*(3), 183–189.

Rohilla, P., Deep, A., Kamra, M., Narasimhan, B., Ramasamy, K., Mani, V., … Lim, S. M. (2014). Synthesis, antimicrobial and anticancer evaluation of N′-(substituted benzylidene)-2-(benzo[d]oxazol-3(2H) -yl) acetohydrazide derivatives. *Drug Research*, *13*, 1–5.

Senol, C., Hayvali, Z., Dal, H., Hokelek, T. (2011). Syntheses, characterizations and structures of NO donor Schiff base ligands and nickel(II) and copper(II) complexes. *Journal of Molecular Structure*, *997*, 53–59.

Shanker, K., Reddy, P. M., Rohini, R. (2009). Encapsulation of Pd(II) by N4 and N_2O_2 macrocyclic ligands : their use in catalysis and biology. *Journal of Coordination Chemistry*, *62*(18), 3040–3049.

Sharma, S. K., Kumar, P., Narasimhan, B., Ramasamy, K., Mani, V., Mishra, R. K., Abdul Majeed, A. B. (2012). Synthesis, antimicrobial, anticancer evaluation and QSAR studies of thiazolidin-4-one derivatives. *European Journal of Medicinal Chemistry*, *48*, 16–25.

Tajuddin, A. M., Anouar, E. H., Ramasamy, K., Yamin, B. M., Alharthi, A. I., Bahron, H. (2016). DFT analysis and bioactivity of 2-((E)-(4-methoxybenzylimino)methyl)phenol and its Ni(II) and Pd(II) complexes. *Arabian Journal of Chemistry*.

Temel, H., Otludil, B. (2001). Synthesis , spectral and biological studies of Mn(II), Ni(II), Cu(II), and Zn(II) complexes with a tetradentate Schiff base ligand. Complexation studies and the determination of stability constants (K_e). *Synthesis and Reactivity in Inorganic and Metal-Organic Chemistry*, *31*(8), 1323–1337.

van Rijt, S. H., Sadler, P. J. (2009). Current applications and future potential for bioinorganic chemistry in the development of anticancer drugs. *Drug Discovery Today*, *14*(23–24), 1089–1097.

Vigato, P. A., Tamburini, S. (2004). The challenge of cyclic and acyclic schiff bases and related derivatives. *Coordination Chemistry Reviews*, *248*(2004), 1717–2128.