Advances in Bioresearch
Adv. Biores., Vol 11 (5) September 2020: 104-108

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.11.5.104108

Advances in Bioresearch

ORIGINAL ARTICLE

Synthesis, Synergistic Effect and Scavenging Activity of Schiff Base Ligands

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ABSTRACT

The ligands HL^1/HL^4 were synthesized by Schiff base condensation of o-hydroxyacetophenone/thiophene-2-carboxylic acid with phenyl hydrazine in 1:1 mole ratio and the ligands HL^2, HL^3 were synthesized using o-hydroxyacetophenone and corresponding diamine (N, N-bis(3-aminopropyl)methylamine/N, N-bis(3-aminopropyl)-1,2-ethylenedi ammine) in 2 : 1 mole ratio. All the ligands were characterized by electronic, IR and ^1H NMR spectral studies. IR and ^1H NMR spectral studies confirmed the formation of azomethine (HC=N-) group. The scavenging activity for the ligands were carried out by DPPH method. The ligands HL^1 and HL^4 had higher than other ligands.

Keywords: *Schiff base, thiophene-2-carboxoxlic acid, phenyl hydrazine, antioxidant.*

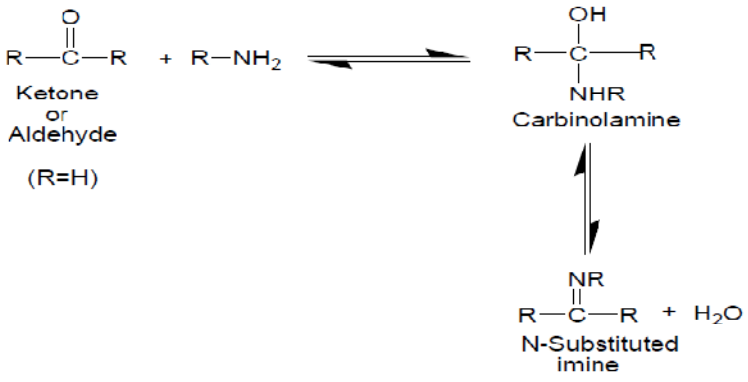
Received 11.03.2020 Revised 11.06.2020 Accepted 05.08.2020

How to cite this article:

N.Radhika , A.M. Uduman Mohideen. Synthesis, Synergistic Effect and Scavenging Activity of Schiff Base Ligands. Adv. Biores., Vol 11 (5) September 2020: 97-103

INTRODCUTION

Synthesis of novel ligand system with desired property has increased tremendously in recent years. Schiff bases ligands having oxygen, nitrogen and sulphur donor atoms and their metal complexes possess interesting properties [1-4] as catalysts and enzymatic agents in various biological systems. Several model systems using Schiff base ligands [5-8] have been reported and their metal complexes attracts much attention not only of its biological relevance but also due its own interesting coordination chemistry such as geometry, flexible redox property, and oxidation state. The Schiff-base complexes serve as an important stereochemical models in coordination chemistry due to their preparative accessibility and structural variety [13]. Schiff bases are versatile ligands formed by condensation of aldehydes (or) ketones with primary amines which was first reported by Hugo Schiff in 1864 [9, 10] and hence the name Schiff base. These ligands coordinate to metal ions via azomethine nitrogen (HC=N-). The azomethine or imine groups (Figure 1) are present in various natural, naturally derived and non-natural compounds. The imine group present in such compounds has been shown to be critical to their biological activities [15-17].



The new technologies of medicinal chemistry, is creating an exciting scenario for the development of a novel generation of highly active drugs with minimized side effects, which could add significantly to the current clinical research and practice. Zishen *et al*. [11] have reported that Schiff base complexes derived from 4-hydroxy salicylaldehyde and amines have strong anticancer activity against *Ehrlich ascites carcinoma*. Schiff bases of ketones and their derivatives, are active as anticancer and antioxidative agents [12–14]. Ajibade *et al*. have synthesised Schiff base ligand using ethylenediamine and 2', 4'-dihydroxyacetophenone and the antioxidant studies showed that the metal complexes had higher activity than the free ligand.

Antioxidants must be used in day today life on account of their many health benefits and are widely used in the food industry. It is well known that reactive oxygen species (ROS) such as superoxide anion, hydroxyl radical, and hydrogen peroxide are formed during biochemical processes in body system. These species causes oxidative damages on lipids, proteins, nucleic acids, etc. and generates various chronic diseases, such as coronary heart disease, atherosclerosis, cancer, and ageing. Hence, to prevent the free radical damage in the body, it is important to administer drugs that may be rich in antioxidants.

The Schiff base ligands containing thiazole and phenyl hydrazine group have attracted significant attention of the researchers because of their interesting physicochemical properties and prominent biological activities [14-16]. These compounds are of much interest because of their presence in many natural and synthetic products with a broad range of biological activities, such as anticancer, antiviral, antimicrobial and antioxidant activities. Thus, the available literature exhilarated us to prepare Schiff base ligands containing phenyl hydrazine and thiophene moiety. The synthesised Schiff base ligands were characterized by various spectral techniques. The antioxidant activity of Schiff base ligands have been studied.

MATERIAL AND METHODS

Materials

Chemicals phenyl hydrazine, o-hydroxyaectophenone, N, N-bis(3-aminopropyl)1,2-ethylenediammine, N, N-bis(3-aminopropyl)methylamine and DPPH were purchased from Merck. Solvents ethanol, methanol and DMSO were purchased from NICE chemicals and used as such.

Physical Measurements:

Infrared Spectra:

IR spectra of the ligands were recorded on IR 408 Shimadzu spectrometer by using potassium bromide pellet. The IR spectra was recorded in the spectral region of 4000 – 600 cm^{-1}.

UV Spectra:

The UV spectra of the ligands were taken in Hitachi 320 double beam spectrophotometer using HPLC ethanol as solvent.

^{1}H NMR:

^{1}H NMR spectra were recorded on Varian Mercury VX – 300 NMR spectrometer. NMR spectra were run at 300 MHz using $CDCl_3$ as solvent.

DPPH Radical Scavenging Assay:

The 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity was determined following the method of Mensor et al. [82] using DMSO with DPPH as the control. It is a rapid technique for screening the radical scavenging activity of specific compounds. The free radical scavenging effects of all the compounds and ligand with DPPH radical were evaluated with various concentrations (100, 200, 300, 400, and 500 μg/mL) of the test compound in 1 mL DMF and were added to 1.0 mL of 0.4 mM methanol solution of DPPH and were stirred thoroughly. After 30 min incubation period at room temperature, the scavenging ability determines the antiradical power of an antioxidant by measuring the decrease in the absorbance of DPPH at 517 nm. Resulting from a colour change, the absorbance decreased when the DPPH is scavenged by an antioxidant, through donation of hydrogen to form a stable DPPH molecule. All tests samples were performed with three replicates to obtain mean ± S.D. The percent of inhibition (%) of free radical production from DPPH was calculated by using the following equation:

DPPH scavenging ability (%) = Abs(control) – Abs(sample) / Abs(control) × 100

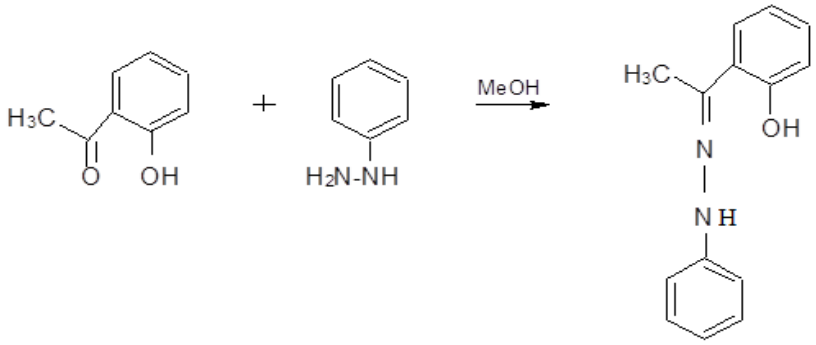
EXPERIMENTAL METHOD:

i) Synthesis of Ligand L^1:

To o-hydroxyacetophenone (1.36 g, 1 mole) in methanol (20 ml) was added phenyl hydrazine (1.08 g, 1 mole) in methanol (20 ml) and refluxed for 2 hours. Then the solvent was evaporated to get pale yellow crystals. This was filtered, washed with cold water and methanol. The crystals were further recrystallized using ethanol. (**Scheme -1**). IR (KBr) (cm^{-1}) : ν (N-H) 3348, ν(C=N) 1605,

ν(Ar) 1590. ^{1}H NMR ($CDCl_3$) (ppm) : δ 8.32 (s, CH=N), 7.04 – 6.15 (m, Ar - H), 2.52 (s, -CH_3), 2.18 (s, N –H). UV (EtOH) (nm) : 340, 290, 240, 210.

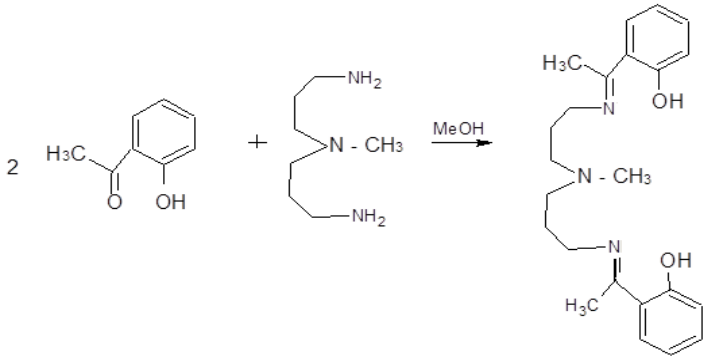
Scheme -1 Synthesis of ligand L^1:



ii) Synthesis of Ligand HL^2:

To o-hydroxyacetophenone (0.9 g, 2 mole) in methanol (20 ml) was added N, N-bis(3-aminopropyl)methylamine (0.45 g, 1 mole) in methanol (20 ml) and refluxed for 2 hours. Then the solvent was evaporated to get orange yellowish coloured crystals. This was filtered, washed with cold water and methanol. The crystals were further recrystallized using ethanol. (**Scheme -2**). IR (KBr) (cm^{-1}): ν (N-H) 3380, ν(C=N) 1604, ν(Ar) 1570. ^{1}H NMR ($CDCl_3$) (ppm): δ 8.3 (s, CH=N), δ 7.75 - 6.55 (m, Ar - H), δ 3.15 (s, -NCH_3), δ 2.3 (s, -CH_3), δ 2.15 (q, -CH_2-). UV (nm) (EtOH) : 390, 320, 220.

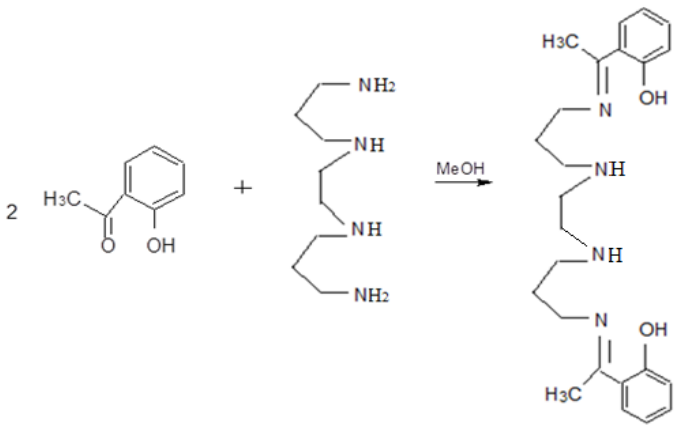
Scheme -2 Synthesis of ligand HL^2:



iii) Synthesis of Ligand HL^3:

To o-hydroxyacetophenone, (0. 8 g, 2 mole) in methanol (20 ml) was added N, N-bis(3-aminopropyl)1,2-ethylenediammine (0.60 g, 1 mole) in methanol (20 ml) and refluxed for 2 hours. Then the solvent was evaporated to get yellow coloured viscous solid. This was separated, washed with cold water and methanol. (**Scheme -3**). IR (KBr) (cm^{-1}) : ν (N-H) 3368, ν(C=N) 1610, ν (Ar) 1580, ν(C-OH) 1420. ^{1}H NMR($CDCl_3$) (ppm): δ 8.3 (s, CH=N), δ 7.85 - 6.75 (m, Ar-H), δ 2.3 (s, -CH_3), δ 2.15 (q, -CH_2-). UV (EtOH) (nm): 390, 320, 275, 250, 220.

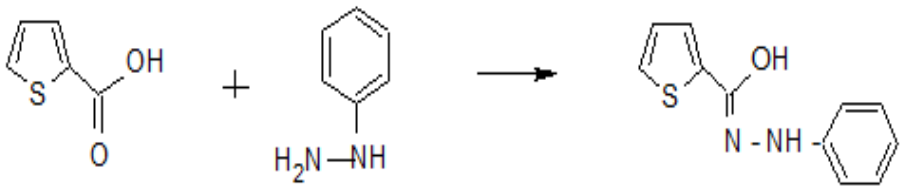
Scheme -3 Synthesis of ligand HL^3:



iv) Synthesis of Ligand L^4:

To thiophene-2-carboxylic acid (1.28 g, 1 mole) in methanol (20 ml) was added phenyl hydrazine (1.08 g, 1 mole) in methanol (20 ml) and refluxed for 2 hours. Then the solvent was evaporated to get yellow crystals. This was filtered, washed with cold water and methanol. The crystals were further recrystallized using ethanol. (**Scheme – 4**). IR (KBr) (cm^{-1}): ν (N-H) 3328, ν(C=N) 1610, ν (Ar) 1580, ν(C-OH) 1420, ν(C-S-C) 625. ^{1}H NMR ($CDCl_3$) (ppm): δ 10.23 (s, OH), δ 8.21 (s, CH=N), δ 7.75 – 6.22 (m, Ar - H), δ 2.25 (s, N –H). UV (EtOH) (nm) : 320, 290, 260, 225.

Scheme -4 Synthesis of Ligand L^4:



RESULTS AND DISCUSSION

The ligand HL^1/HL^4 was synthesized by Schiff base condensation of o-hydroxyacetophenone/thiophene-2-carboxylic acid with phenyl hydrazine in 1:1 mole ratio as shown in the **Scheme -1 and 4**. Ligands HL^2 and HL^3 were synthesized using o-hydroxyacetophenone and N, N-bis(3-aminopropyl)methylamine/N, N-bis(3-aminopropyl) 1,2-ethylenediammine in 2 : 1 mole ratio as shown in the **Scheme -2** and **3**.

Spectral Analysis:

The synthesized ligands were characterized by IR, ^{1}H-NMR and UV spectral analysis.

The IR spectra of all the ligands HL^1 – HL^4 exhibits an intense band around 1600 cm^{-1} assigned to ν(C=N) confirming the formation of azomethine group. Thiophene ν(C-S-C) band is observed at 625 cm^{-1}. A broad band at 3338-3328 cm^{-1} is assigned to stretching vibrations of –NH of phenyl hydrazine. ^{1}H-NMR spectra shows a peak around 8.2 ppm for all the ligands confirming the formation of HC=N group. The UV spectra of the ligands were observed at lower wavelength range 210 - 400 nm. The peak in the range 240 - 260 nm is due to n- π* transition assigned to C=N Schiff base and a peak observed in the range 320 – 340 nm is due to π -π* transition.

Antioxidant Studies:

The antioxidant studies of the ligands were carried out using DPPH at 516 nm using DMSO as solvent. The ligands showed a remarkable decrease in absorbance indicating the activity of Schiff base ligands and a change of colour from deep violet to yellow colour.

DPPH Radical Scavenging Assay:

1,1-Diphenyl-2-picrylhydrazyl (DPPH) is a stable organic radical compound and its oxidative assay is used extensively in the quantification of radical scavengers capacity or hydrogen donors ability of samples. The antioxidant activities of Schiff base ligands HL^1 – HL^4 together with the standard were assessed on the basis of free radical scavenging effect of the stable DPPH free radical activity [***]. The examined changes in the free radical scavenging ability of the test samples on the basis of absorbance.

The DPPH scavenging activity of Schiff base ligands HL^1 and HL^4 has significantly higher activity. But ligand HL^4 has very higher activity than ligand HL^1, indicating that ligand HL^4 has stronger free radical scavenger activity than HL^1. This may be due to the fact that the ligand HL^4 contains thiophene (sulphur) as well as acyl hydroxyl moiety [***]. The scavenging activity of Schiff base ligands HL^2 and HL^3 are moderate. But ligand HL^2 has higher activity than ligand HL^3. Generally the presence of azomethine group in a ligand shows antioxidant activity. On comparing HL^3 and HL^4 it can be that HL^4 has longer chain length than HL^3. The lower activity is due that as chain length increases the flexibility of the ligand also increases.

Synergistic effect of the ligands:

The synergistic effect and antioxidant activities of Schiff base ligands HL^1, HL^2 and HL^3 were determined [***]. The examined changes in the free radical scavenging ability of the test samples on the basis of absorbance are presented in **Figur**e . The ligands showed a remarkable decrease in absorbance indicating the activity of Schiff base ligands. The individual and combinational antioxidant activity of ligands are shown in **Table -1**.

Table -1

Individual Ligand Activity (%)				Synergistic Effect (%)			
HL^1	HL^2	HL^3	HL^4	HL^1, HL^2	HL^1, HL^3	HL^2, HL^3	HL^1, HL^2, HL^3
68.4	41.2	27.0	84.6	58.9	61.0	45.9	65.2

The antioxidant activity of ligand HL^1 has higher activity (68.4 %) than ligands HL^2 (41.2 %) and HL^3 (27.0 %) respectively. This may be due that as reported in literature [***] compounds with phenylhydrazine group and shorter chain length have higher antioxidant activity than compounds with longer chain length. In ligands HL^2 and HL^3, the presence of longer chain length and absence of phenyl hydrazine group lowers the antioxidant activity. It can also be seen from the combinational effect of HL^2, HL^3 (45.9 %). Since [HL^2, HL^3] have longer chain length and more flexible geometry compared to [HL^1, HL^2] and [HL^1, HL^3] they have lower activity.

The combination of the ligands [HL^1, HL^2] and [HL^1, HL^3] shows that [HL^1, HL^3] (61 %) has slightly higher activity than [HL^1, HL^2] (58.9 %). This may due, in [HL^1, HL^3] there are large number of N-H substituent. On combining all the ligands HL^1, HL^2, HL^3 the antioxidant activity becomes higher. This may be due to that this combination contain phenylhydrazine, larger number of – OH and – NH substituents. The oxidizing potentials of the samples are associated by breaking the free radical chain via hydrogen atom donation [***]. Therefore, the results obtained from antioxidant study show that the combination of ligands [HL^1, HL^2], [HL^1, HL^3] and [HL^1, HL^2, HL^3] have synergistic effect and can be used in the treatment of diseases that arise due to oxidative stress such as DNA damage and cancer.

CONCLUSION

The Schiff base ligands HL^1 – HL^4 were synthesized by Schiff base condensation and characterized by IR, ^1H NMR and UV spectral analysis. The observed results showed the formation of azomethine group (i.e Schiff base condensation product). The antioxidant activity of the ligands were studied. On comparing all the ligands HL^4 showed higher scavenging activity, this may be due to presence of both thiophene and phenyl hydrazine moiety. Hence ligand HL^4 can be used in the treatment of pathological diseases arising from oxidative stress under severe conditions and other ligands for mild to moderate conditions. The ligands also showed synergistic effect. Combination of all the ligands HL^1, HL^2, HL^3 the antioxidant activity becomes higher due to the presence of phenylhydrazine, larger number of – OH and– NH substituents.

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