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Applied Chemistry

Elixir Appl. Chem. 96 (2016) 41490-41492

ISSN: 2229-712X

Synthesis & Biological activities of 2,4,5-Trimethoxybenzaldehydethiosemicarbazone

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ARTICLE INFO

Article history:
Received: 31 May 2016;
Received in revised form:
1 July 2016;
Accepted: 5 July 2016;

Keywords
2,4,5-Trimethoxybenzaldehyde,
Thiosemicarbazide,
IR,
Anti Bacterial,
Antifungal,
Anti Oxidant Activity.

ABSTRACT
The Synthesis and biological activity of 2,4,5-trimethoxybenzaldehyde thiosemicarbazone have been reported. Elemental analysis and spectral characterization has been carried out. The data agree quite well with the proposed structures. The group sensitive fundamentals are compared with those of similar molecules already reported in the literature. Ligand was screened for antimicrobial activities by the disc diffusion technique using DMSO as solvent. These Schiff base has been studied for their anti-bacterial, anti-fungal, and anti oxidant activity. The antifungal activity of the said ligand has been screened against *Aspergillus flavus*, and *Asperjillus niger* as were as antibacterial activity tested against *Vibrio harveyi , VibrioVulnificus, Escherichia Coli, & Bacillus pumilus.* The anti oxidant activity was checked for *catalase assay.*

1. Introduction

Schiff bases are directly prepared as monodentate electron donors, with easily-tunable electronic and steric effects. A variety of possible Schiff base metal complexes, with wide choice of ligand, and coordination environments, has prompted us to undertake research in this area (Majumder *et.al*., 2006). Schiff bases have often been used as chelating ligands in the field of coordination chemistry and their metal complexes are of great interest for many years in India. Thiosemicarbazones are well conventional as a vital class of sulphur-donor Schiff base ligands, that are mainly useful for transition metal ions. This is appropriate to the significant biological activities observed for these ligands, which have been shown to be connected to their metal complexing capacity. The Schiff bases of thiosemicarbazone play an important role, in both medical and pharmaceutical fields. Some of the earlier findings in India points out that Schiff bases are very much important in medicinal and pharmaceutical fields. Presently, the areas in which thiosemicarbazones are receiving more attention, can be broadly classified according to their antioxidant, antibacterial, antifungal activities (Beraldo *et.al*., 2004). In recent years, new interesting applications have been found in the field of medicine, and the metal complexes with Schiff base ligands of alternative structure have attracted the attention of researchers (Irena Kostova *et. al.,* 2013). Thiosemicarbazides have occupied an important place in drug industry. Use of these compounds in organic synthesis has become a classical strategy for the synthesis of several heterocycles. Their reactions with compounds containing C=O and C=N groups is an important method for the synthesis of biologically active compounds, viz triazoles and thiazoles (Shailey Singhal *et. al*., 2013). In the recent years, thiosemicarbazones have gained significant attention because of their proposed use in the treatment of leishmaniasis, trypanosomiasis and malaria. These compounds were found to be potential inhibitors of some bacterial species (Patel, 2011).

2. Experimental details

2.1. Preparation of Schiff bases

2,4,5-trimethoxy benzaldehyde (0.01 mole) in hot ethanol (20 ml) was added to a 250ml RB flask containing (0.01 mole) of thiosemicarbazide in hot ethanol (20ml). The mixture was refluxed for 4hour, at 80 ^{o}C, then allowed to cool overnight at room temperature. The isolated light yellow colored precipitate was filtered, washed with cold EtOH and dried under vacuum. Yield (72%). Mp (260^{o}C).

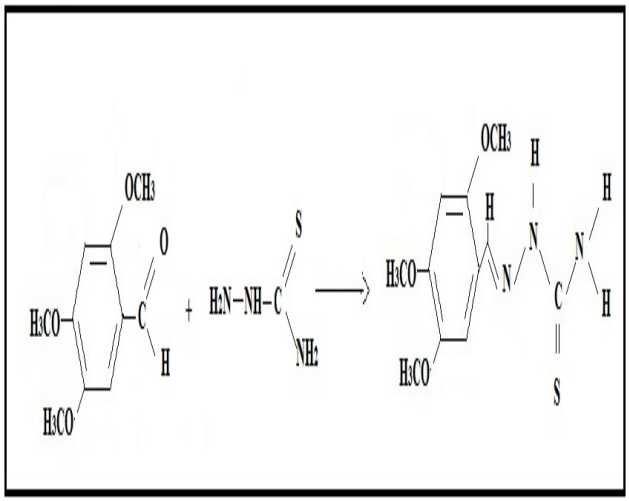

Figure 1

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Table 1

Molecular Formula	Molecular weight	Melting point ^{o}C	Colour
$C_{11}H_{15}N_3O_3S$	269.35	260	yellow

2.2. IR Spectrum

IR spectra were recorded (KBR) on a Shimadzu 8400S FTIR Spectrophotometer. It can be used to identify a compound and to investigate the composition of a sample. Infrared spectroscopy works because chemical bonds have specific frequencies at which they vibrate corresponding to energy levels. The resonant frequencies or vibrational frequencies are determined by the shape of the molecular potential energy surfaces, the masses of the atoms and, eventually by the associated vibronic coupling. In order for a vibrational mode in a molecule to be IR active, it must be associated with changes in the permanent dipole (Leji Latheef, 2007).

2.3. Anti Microbial activity

Antibacterial activity was screened using agar well diffusion method (Khurram Shoaib *et. al*., 2013). Bacterial activity was prepared using DMSO (Ilknur Babahan *et. al*., 2013). The diameters of the inhibition zones were measured in millimeters. The compound was evaluated for their in-vitro antibacterial activity against *Vibrio harveyi, Vibrio Vulnificus, Bacillus Pumilus* & *E.Coli*. The plates were incubated at 37^{o}C for 24 hrs. After incubation period the culture was diluted. In this method, Petri plates were prepared with 20 ml of sterile Agar.

Antifungal activity was determined using a modified Kirby Bauer disc diffusion method. Briefly, 100 µl of the test fungi was spread on to the potato-dextrose agar plate. The different test solvent extracts were loaded to the sterilized sterile 6 mm discs, allowed to dry and then the impregnated discs placed on the surface of medium. Plates were incubated at 37ºC at room temperature for 3–4 days. The diameters of the inhibition zones were measured in mm. Standard antibiotic fluconozole served as positive control

2.4. Anti oxidant activity

The newly synthesized compounds were screened for activity by *Catalase* method

2.4.1. *Catalase assay*

To 0.5 ml of enzyme extract added the reaction mixture containing 1ml of 0.01 M phosphate buffer (pH 7.0), 0.5 ml of 0.2 M H_2O_2, 0.4 ml H_2O and incubated for different time period. The reaction was terminated by the addition of 2 ml of acid reagent (dichromate/acetic acid mixture) which was prepared by mixing 5% potassium dichromate with glacial acetic acid (1:3). To the control, the enzyme was added after the addition of acid reagent. All the tubes were heated for 10 minutes and the absorbance was read at 610 nm.

3. Result and Discussion

3.1. IR Spectrum

IR Spectra of ligands (Figure: 2.) show bands around 3456.44cm^{-1} and 3329.14 cm^{-1} , which may be assigned to ν(N-H) of the amide and imide group respectively (Table 2). Vasantha kumar and suma have realized the absence of co-ordination through the amide and imide group nitrogen (Vasanthakumar *et.al.*, 2009). In the ligand the ν(C=S) mode is seen strongly absorbed at 1683.86cm^{-1}. The azomethine nitrogen of the free ligand, due to ν(C=N) show a strong absorption at 1577.19cm^{-1}. Co-ordination through nitrogen atom of (C=N) of azomethine group and ketonic sulphur of C=S, as enolic group were found as has been reported by S.K.Thampy and Prem Mohan Mishra *et.al.*, 2013.

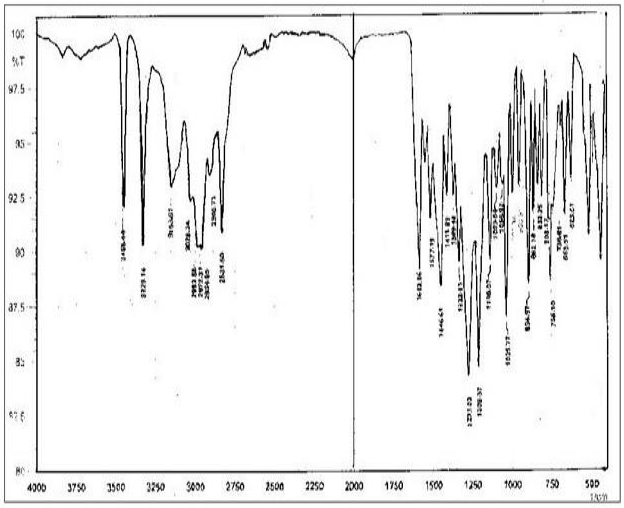

Figure 2

3.2. Anti bacterial Activity

2,4,5-trimethoxybenzaldehydethiosemicarbazone was tested against *E.Coli* in 21mm, *V.harveyi* in 13mm, *V.vulnificus* 12mm, *B.Pumilus* in 15mm. The compound showed better activity against E.Coli compared to other bacterial species. In activity against the tested organisms, the compound show an increasing range as *E.Coli* > *B.Pumilus* > *V.harveyi* > *V.vulnificus,* (21mm > 15mm > 13mm > 12mm) given in Table (3). The mode of action of the compounds may involve formation of a hydrogen bond through azomethine group (C=N) with the active centre of cell constituents resulting in interferences with the normal process (Muayed Ahmed Redayan, 2012). The variety of antimicrobial activity and types of bacteria affected may be due to differences in the ability to bind the cell wall, which is based on the structure of the prepared compound (Siddappa et.al., 2015, Omar *et. al*., 2013). Upon comparison of the biological activity of the Schiff bases with the standard (methanol), it is seen that the biological activity of the Schiff bases against the Gram–positive and Gram-negative bacteria are better than that in methanol. The compound exhibit varying degrees of inhibitory effect on the development of the tested bacterial species.

3.3. Anti fungal Activity

The experiment on antifungal activity shows that the compound inhibit the growth of fungi. It showed a significant effect on two fungi (*Aspergillus flavus & Aspergillus niger*) selected for the present study. In azomethine derivatives the C=N linkage is essential for biological activity. Similar observations were reported by Yadav & Co-worker (Yadav *et.al*., 1999). The replacement of hydrogen atom by methoxy group in carbonyl compounds, enhance fungitoxicity to some extent, but methoxy group has analogous effect. In activity against the test organisums the compound show an increasing range, *Aspergillus niger* > *Aspergillus flavus (24mm* > *21mm)* given in Table (4). Upon Comparison of the antifungal activity of the Schiff base with the standard (flucanazole), it was found that the Schiff base was better than that of standard positive control flucanazole.

Table 2

Compound	$C_{11}H_{15}N_3O_3S$
v(C=N)	1577.19
v(N-H)	3329.14
v(C=S)	1683.86

Table 3

Ligand	Gram-negative			Gram-positive
	Vibrio harveyi	*Vibrio Vulnificus*	*Escherichia Coli*	*Bacillus pumilus*
$C_{11}H_{15}N_3O_3S$	13mm	12mm	21mm	15mm

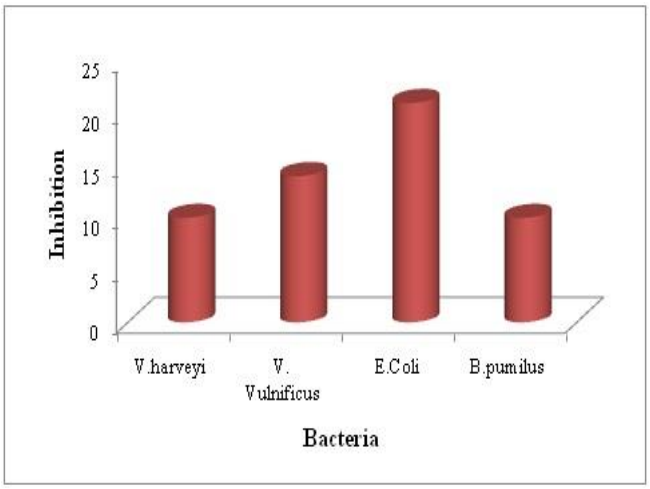

Figure 3

Table 4

Ligand	*Aspergillus niger*	*Aspergillus flavus*
$C_{11}H_{15}N_3O_3S$	14mm	13mm

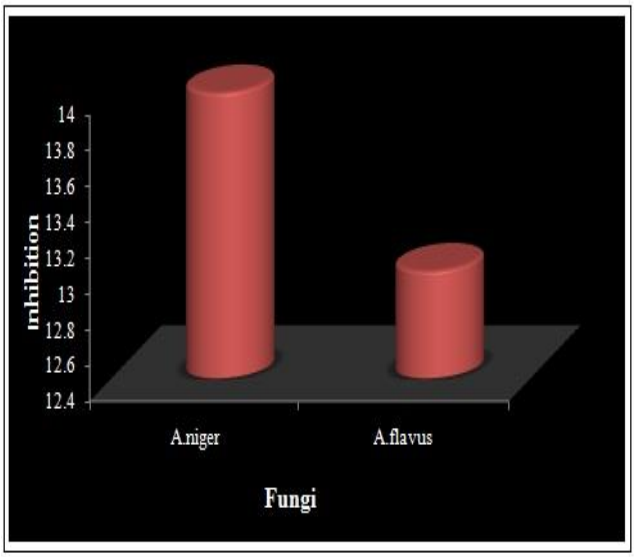

Figure 4

3.4. Anti Oxidant activity

Schiff bases form major sources of antioxidants. The relation between free radicals, antioxidants and functioning of various organs and organ systems is highly complex. Significant finding have come to light in the last few years (Firuzi *et. al.*, 2011). 2,4,5-trimethoxybenzaldehyde thiosemicarbazone was tested for its antioxidant activity using catalase assay . The compound exhibited different optical density (OD) values at different time intervals (Catalase assay 30 Sec, 60 Sec, 90 Sec) as given in (Table :5). The compound was screened for catalyst activity given in (Fig: 5).

Table 5

CATALASE ASSAY						
OD VALUE				RESULT % OF INHIBITION		
30 Sec	60 Sec	90 Sec	Control	30 Sec	60 Sec	90 Sec
0.618	0.804	0.719	0.951	35	15.3	17

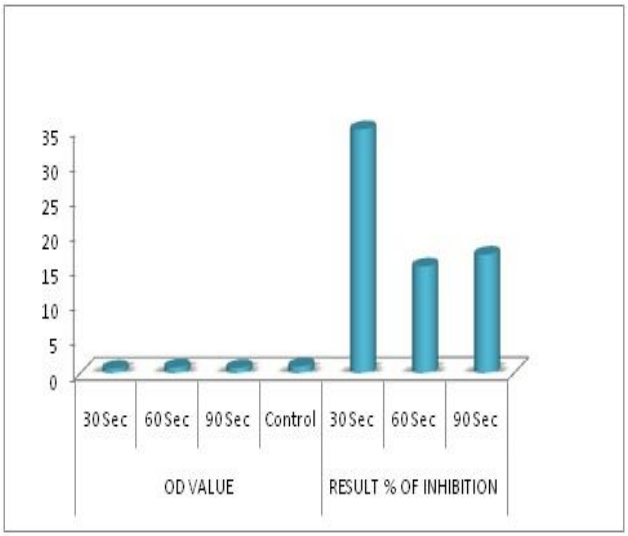

Figure 5

Conclusion

The compound 2,4,5-trimethoxybenzaldehyde thiosemicarbazone was found to exhibit good antibacterial, antifungal & antioxidant properties. Thus, is a good candidate for use in further clinical trials.

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