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In vitro evaluation of Antibacterial, Antioxidant and Anticancer activities of a new carbazole based Schiff base

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1. Introduction:

Schiff bases are highly noteworthy in the treatment of cancer due to their non- toxic, anticoagulant property and have a potential therapeutic function in renal cell carcinoma. Cancer is a dreadful disease affecting human in developed and developing nations. Half of all men and 33% of all ladies are diagnosed to have cancer [20]. It is realized that one-fourth of adults' mortality is because of malignancy [21]. Treatment of patients with breast and colon malignancies depends on the standard protocol whereby local excision is the underlying treatment took after by chemotherapy.

Diverse medications are generally used to treat colon and breast cancers. These are 5-fluorouracil (5-FU), Tamoxifen and Bevacizumab. However, these chemotherapeutic drugs are often ineffectual and sometimes cancer cells may exhibit or develop resistance to the administered drug [22]. Hence, the studies are going on to develop novel agents to overcome the resistance and side effects of the drugs. Polydentate N, O donors schiff bases derived from carbazole and salicyaldehyde have been widely studied in solid state. They have been studied for a variety of applications including biological, clinical and analytical applications [23-25]. This paper describes the results obtained from the *in vitro* antibacterial, antioxidant and anticancer screening of the synthesized CS Schiff base.

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2. Materials & Methods

2.1 Schiff base approach towards biological activities

Anti-bacterial activity

Bacterial infections, which pose a serious threat to human health, have become a global concern [77]. Therefore there is an urgent demand for novel antibacterial agents to counter the rise in resistance among bacteria [78].

Free radical scavenging ability of the extracts was tested by DPPH radical scavenging assay as described by Blois [23] and Desmarchelier et al. [24]. The hydrogen atom donating ability of the extractives was determined by the decolorization of methanol solution of 2,2-diphenyl-1-picrylhydrazyl (DPPH). DPPH produces violet/ purple color in methanol solution and fades to shades of yellow color in the presence of antioxidants. A solution of 0.1 mM DPPH in methanol was prepared, and 2.4 mL of this solution was mixed with 1.6 mL of extract in methanol at different concentrations (12.5–150 µg/mL). The reaction mixture was vortexed thoroughly and left in the dark at RT for 30 min. The absorbance of the mixture was measured spectrophotometrically at 517 nm. BHT was used as reference. Percentage DPPH radical scavenging activity was calculated by the following equation:

$$\% \text{ DPPH radical scavenging activity} = (A0 - A1)/A0 \times 100$$

where A0 is the absorbance of the control, and A1 is the absorbance of the extractives/standard. Then % of inhibition was plotted against concentration, and from the graph IC50 was calculated. The experiment was repeated three times at each concentration.

MTT cell viability assay

Viability assay for the cell lines was done using 3-(4,5dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cells were seeded into 96-well culture plates at a density of 1×104 cells/well and allowed to attach. After 24 hours, cells were treated with different concentrations of compound C1, ranging from 100 µg/mL to 1.25 µg/mL, and incubated at 37°C in 5% CO2 for 24, 48, and 72 hours. Afterward, 20 µL of MTT was added to each well, and the plates were further incubated in the same conditions for 2 hours. After incubation, the solution in each well was removed, and 100 µL DMSO was added into the wells to solubilize the produced formazan. The last row of wells were used as negative controls, to which only culture medium was added. The cytotoxic effect of cisplatin was examined against MCF-7 cells as positive control. Each concentration of the compound was tested in triplicate. A microplate reader was used to measure absorbance at 570 nm with a reference wavelength of 630 nm. Cell viability was stated as percentage of the value for control after 48 hours' exposure to compound C1. The concentration of compound with 50% cell growth inhibition was expressed as the half maximal inhibitory concentration (IC50) value.

Antibacterial Activity

The synthesized Schiff base ligand was evaluated for its bactericidal potential against eight bacterial strains which included four gram positive i.e. *Bacillus cereus, Mycobacterium*

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tuberculosis, *Staphylococcus aureus* and *Streptococcus pneumonia* and four gram negative strains i.e. *Escherichia coli*, *Enterobacter sp.*, *Klebsiella pneumonia* and *Pseudomonas aurogenosa.*

The antimicrobial activity of ligand is compared with standard drug ampicillin. A close survey of the results indicates that the ligand [CS] exhibited varied range of minimum inhibition depending upon the substituent on the ring structure. The ligand has shown moderate to good biological activity against the bacterial strains. Higher concentration have shown excellent activity against both gram (+) and gram (-) microbial strains. The effect of Schiff base ligand CS against the gram positive and gram negative strains are shown in figure-1. The ligand CS shows moderate activity on *Mycobacterium tuberculosis* (8 mm) and *P.aurogenosa* (6.5 mm). The Schiff base ligand shows good activity against *Staphylococcus aureus* (8.5 mm), *Bacillus cereus* (9 mm), and *Streptococcus pneumonia* (10 mm).

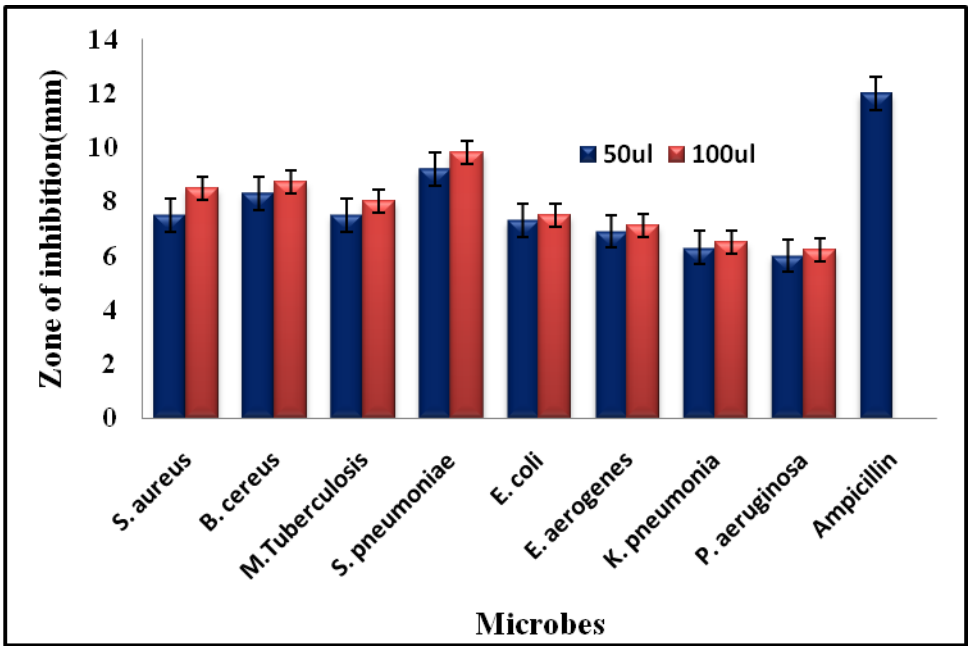

Figure-1: Bactericidal activity of CS against gram (+) and gram (-) strains

Compound CS was screened at two different concentrations as 50 and 100 µl have excellent action against *Streptococcus pneumonia* at zone of inhibition value of 10 mm. The compound showed a moderate inhibition within the considered range of concentrations against *M. tuerculosis* being inactive. Furthermore, the compound exhibited an inhibition against *E. coli* with maximum zone of inhibition. The difference in the efficiency of different organisms depends either on the impermeability of the cells of the microbes or differences in ribosomes of microbial cells.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11.Iss 12, 2022

Maximum inhibition of microbial growth was observed possibly due to the presence of an outer protective layer called lipopolysaccharide. The outer layer provides additional fortification to the cell membrane and limiting the concentration of test compound streaming through the bacterial cell wall [29]. Notably, the normal cell process may be affected by the formation of hydrogen bond through the azomethine nitrogen atom with the active centres of cell constituents leading to interference with the cell wall synthesis [30].

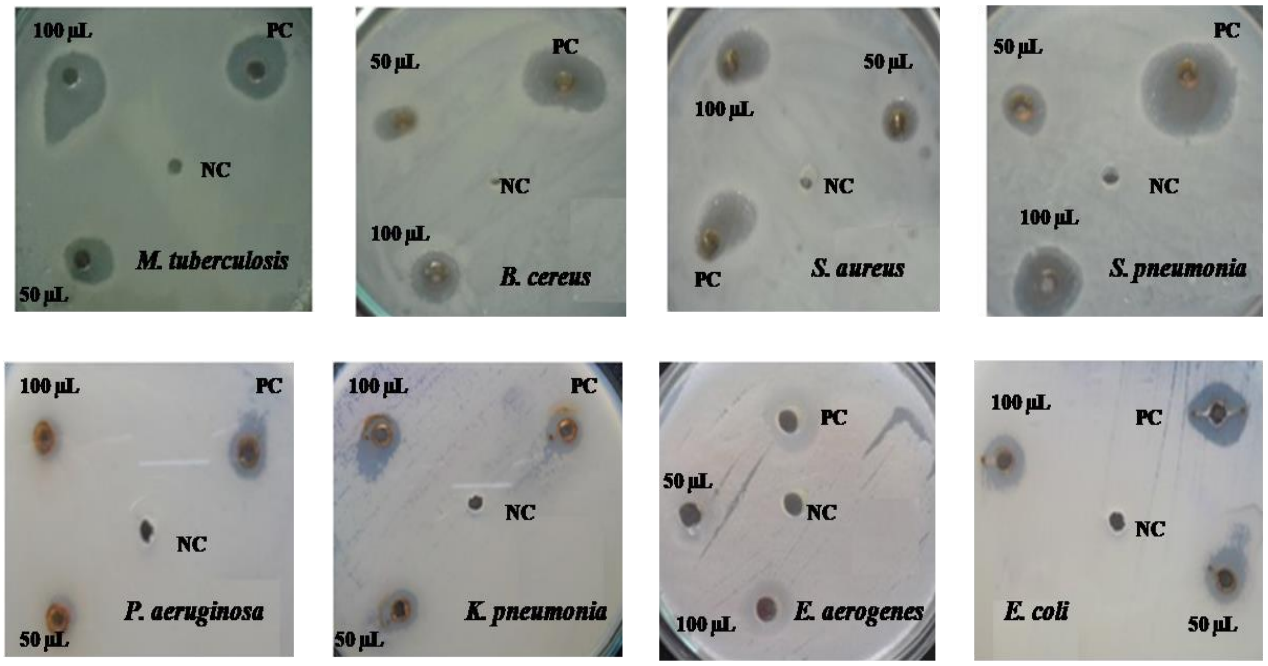

Figure-2: Antibacterial activity of CS against gram (+) and gram (-) strains

Antioxidant Assay

DPPH Radical Scavenging Assay

Different antioxidant techniques and modifications have been put forward to evaluate antioxidants reactivity and functionality in foods and biological systems as a means of checkmating variety of pathological activities such as cellular injury and ageing process; these damaging occurrences are caused by free radicals. Hence, one free radical was used for *in vitro* antioxidants activities of the test samples in this study, namely,1,1-diphenyl-2-picrylhydrazyl (DPPH). The activity of antioxidants on DPPH radical is believed to be centred on their ability to donate hydrogen. DPPH has been a stable free radical, with the ability to accept hydrogen radical or anelectron and then become a stable molecule.

The reduction in the DPPH radical capability is calculated by the decrease in its absorbance at 517 nm prompted by antioxidants. The percentage scavenging of DPPH free radical for each concentration of test compounds were calculated with reference to

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Research paper UGC CARE Listed (Group -I) Journal Volume 11.Iss 12, 2022

absorbance of negative control using the formula given below and the IC_{50} values, representing the concentration of sample compound where 50 % of free radicals were scavenged, were also calculated for analysis of scavenging activity.

The DPPH antioxidant assay is based on the ability of DPPH, a stable free radical, to decolorize in the presence of antioxidants. When DPPH accepts an electron donated by an antioxidant compound, the DPPH is decolorized, which can be quantitatively measured from the changes in absorbance. DPPH-free radical scavenging capacity of CS was evaluated at various concentrations to determine the IC_{50} value. Results of different concentrations of CS including 0, 50, 100, 150, 200, 250, 300 and 350 µg/ml was tabulated in Table-1. The IC_{50} value of CS was 74.04 µg /ml and found to be good antioxidant potential when compared with the standard Vitamin C. The IC_{50} value of ascorbic acid was 9 µg /ml. However, it could be inferred from the results that increasing the concentration of the CS was reducing the level of the free radical in the reaction mixture.

Table-1: IC50 values of different concentrations of CS

Concentration	IC_{50} value of CS
0	0
50	53.1
100	69.8
150	69.2
200	74.04
250	72.66
300	75.43
350	68.85

Free radicals are very unstable molecules with an unpaired electron that react quickly with other compounds to capture surrounding electron to gain stability and thus initiates a chain reaction which cascades and lastly results in loss of cellular function. Averagely, 10,000–20,000 free radicals attack body cell each day, on them oxygen free radicals, an intermediate of dioxygen reduction resulting in damage deoxyribosyl backbone of DNA, accelerate oxidation of polyunsaturated fatty acids, amino acids, co-factors. Free radicals are the main culprits for precipitation of diseases like cancer, Alzheimer's disease, cardiac abnormalities, neurotic disease, neurological complications, miscellaneous metabolic syndromes, etc. Antioxidants and agents with potential to reduce free radicals scavenge these radicals and cease the chain reaction, thereby, preventing further damage.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11.Iss 12, 2022

In the present study the capability of newly synthesized CS acts as a free radical scavenger was assessed spectrophotometrically at 517 nm absorbance on a UV/Visible light spectrophotometer by DPPH (2,2-diphenyl-1-picrylhydrazyl) assay. The IC_{50} value of CS was 69.8 µg /ml and found to be good antioxidant potential when compared with the standard Vitamin C. The IC_{50} value of ascorbic acid was 9 µg /ml.

6.4 Antiproliferative Studies

6.4.1 Anticancer Activity

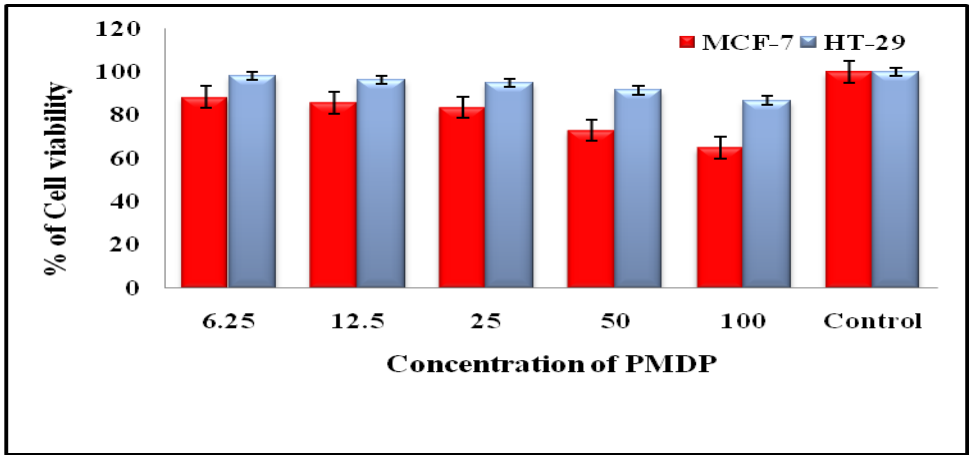
An intensive look for new compounds with anticancer activity originates from the growing abilities of cell line to develop resistance to the drugs in use. The ligand (CS) was subjected to cell lines at different concentrations towards breast cancer cell line (MCF-7) and human colorectal adenocarcinoma (HT-29). The test samples showed significant inhibition against the tested cell lines.

6.4.2 MTT Assay

Cytotoxcity was determined by means of a colorimetric microculture MTT assay, which measures mitochondrial dehydrogenase activity as an indication of cell viability. Cytotoxicity activity of CS was carried out against MCF-7 cell line at different concentrations to determine the IC_{50} (50% growth inhibition) by MTT assay.

6.4.3 Anticancer activity of PMDP

Results of different concentrations of PMDP including 6.25, 12.5, 25, 50 and 100 µg/ml are shown in graph. In MCF-7 cells incubated with PMDP at 6.25, 12.5, and 25 µg/ml, the amount of formazan was similar to control cells, while in other cells it was distinctly lower, the quantity of formazan produced varied between different concentration of CS treated cells, was shown in Fig. The formation of formazan crystals decreases when the concentration of CS increases in MCF-7 cells. MTT assay of CS showed significant effect on MCF-7 cell line in a concentration range between 50 µg/ml to 100 µg/ml compared with control. CS exerts high cytotoxicity in 100 µg/ml concentration against MCF-7 cell line with 35.1 percent of cell growth inhibition. The IC_{50} values of CS on MCF-7 was 39.18 µg /ml.



Graph Anticancer activity of CS at different concentrations

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Similarly, the cytotoxicity activity of CS was analysed in HT-29 cell line at various concentrations to determine the IC_{50} value by MTT assay. Different concentrations of CS (including 6.25, 12.5, 25, 50 and 100 µg/ml) was predicted in figure. In cells incubated with CS at 6.25, 12.5 µg/ml the amount of formazan was similar to control cells, while in other cells it was distinctly lower, the quantity of formazan produced varied between different concentration of CS treated cells, as shown in Fig. The formation of formazan crystals decreases when the concentration of CS increases in HT-29 cells. The inhibitory concentration of CS against HT-29 cell line was found at 100 µg/ml. CS showed only 13.20 percent of cell growth inhibition compare to control in HT-29 cells. The IC_{50} values of CS on HT-29 cell line was found to be 38.05 µg /ml.

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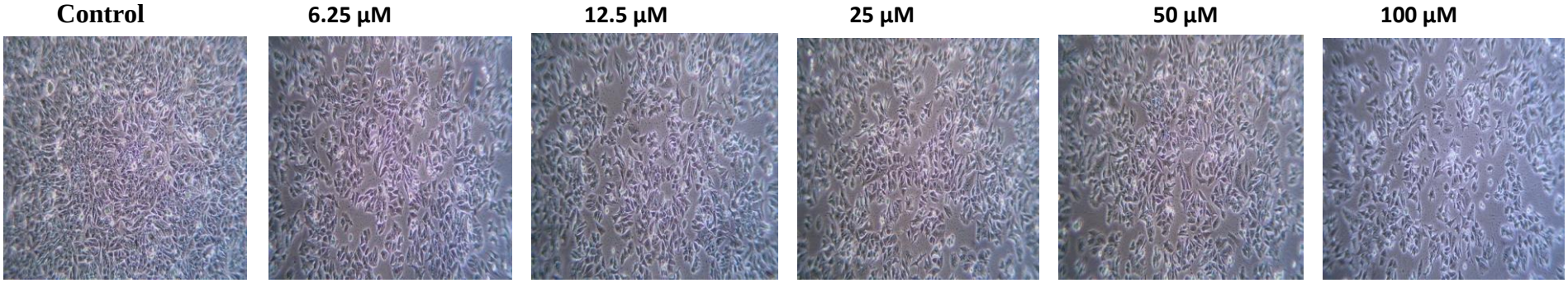

Figure. CS treated MCF-7 cell line at different concentrations

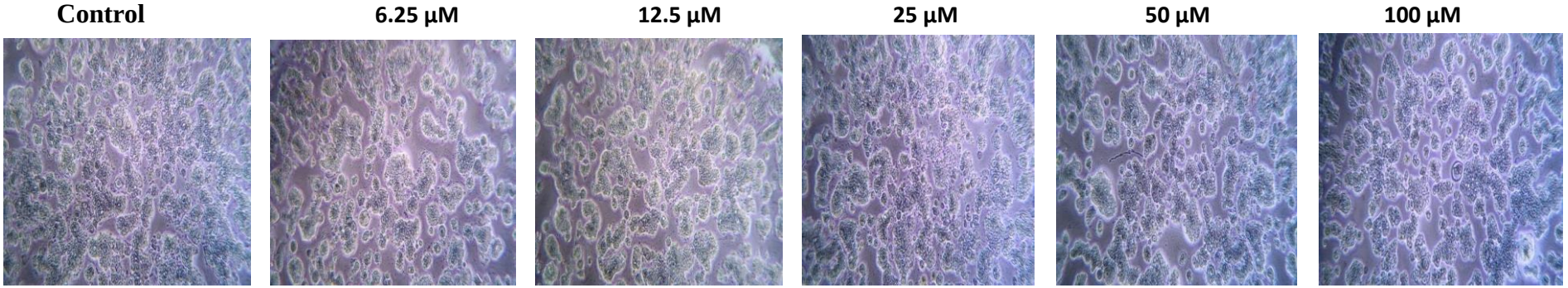

Figure. CS treated with HT-29 cell line at different concentrations

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11.Iss 12, 2022

Here in this study, we report that the CS has significant anticancer activity on both MC-7 and HT-26 cancer cell line. This CS exerts cytotoxicity against MCF-7 cell line at the concentration of 100 µg/ml with 35.1 percent of cell growth inhibition and the IC_{50} value was found to be 39.18 µg /ml by MTT assay.

The cytotoxicity of CS on HT-29 cells showed 13.2 percent of cell growth inhibition at the concentration of 100 µg/ml compared with control. IC_{50} value of CS on HT - 29 cell line was 38.86 µg /ml. The maximum cytotoxic effect of CS was observed at 100 µg/ml in MCF-7 cell line compare to HT-29 cell line.

Conclusion

Schiff base ligand CS showed strong *invitro* antioxidant, antibacterial and anticancer activity. CS ligand exhibited good antioxidant potential when compared with the standard Vitamin C and the IC_{50} value was found to be 48.23 µg /ml.

In the present study we tested the anticancer activity of CS on MCF-7 and HT-29 cancer cell lines. CS has significant cytotoxicity effect on MCF-7 cell line at the concentration of 100 µg/ml with 23.86 percent of cell growth inhibition and the IC_{50} value. In conclusion, the results of biological assays indicate that the synthesized compound may prove to be useful candidates for the preparation of a wide variety of pharmaceutically active agents after further investigations.

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