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Review Article

APPLICATION OF SCHIFF BASES AS THERAPEUTIC AGENT-A REVIEW

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ABSTRACT

Schiff base and its metal complexes have received a great attention because of their biological activities, including antitumour, anti-bacterial, anti-inflammatory, anti-tuberculosis, antihypertension activities. This paper reviews application of Schiff base and their metal complexes in biological system.

Keywords: Schiff base metal complexes, Antitumour, Anti-inflammatory.

INTRODUCTION

Schiff base ligands readily coordinate with a range of metal ions yielding stable complexes which exhibit interesting physical, chemical, biological and catalytical properties. [1]Recently there has been considerable interest in chemistry of the metal complexes of Schiff bases containing O, N and S donor. [2]

Research has shown significant progress in utilization of metal complexes as drugs to treat several human diseases like carcinomas, lymphomas, infection control, anti-inflammatory, diabetes and neurological disorders[3].

Antitumour activity in 1960 an inorganic complex cis –platin was discovered, today more than 50 years, it is still one of the world's best selling anticancer drugs. Schiff base metal complexes formed with other metals like copper, gold, gallium, germanium, tin, Ruthenium, iridium have shown significant antitumor activity in animals[3]

Recent progress in the field of cell biology provide new targets for anticancer agent which act by the formation of DNA adducts with cancer cell and results in the inhibition of DNA replication[4]

Shahriar Ghammamy et.al synthesized complexes such as [Fe(pythsal Br)]Cl_2 with the NSNO-donor tetradentate Schiff base ligands. Pythsal HX [(5-X-N-(2 Pyridylethyl sufanylethyl) salicylidenemine] (X=I, Br) 0btained from the inserted condensation of (1-2-pyridyl)-3-thia-5-aminopentane with the respective derivative salicyldehyde in a 1:1 molar ratio is reported. The anti-tumor properties of these two iron (III) Complexes have been studied. [5]

Mascharak et al. studied the structure and properties of a number of Iron (III) complexes with some amidate ligands because such complexes can be taken as a model for the metal coordination spheres of the antitumor drugs Bleomycin. [5]

Cancer or malignant neoplasm is a class of diseases in which a group of cells display uncontrolled growth, invasion and even sometimes metastasis [6, 7]. It continues as a serious public health problem throughout the world as the most feared diagnosis. It is the second leading cause of human death after cardiovascular diseases in developing as well as in developed countries [8]. Currently, the treatment for cancer primarily includes surgery and chemotherapy, but the curative effects of the existing chemotherapeutic drugs are not good enough and they have plentiful side effects. The development of more effective drugs for treating patients with cancer has been a main attempt over the past 50 years. In recent years, various 1, 2, 4-triazole derivatives have been found to be associated with anticancer [9, 10, 11]properties. AK-2123 (Sanazol), a nitrotriazole hypoxic cell sensitizer has supposedly improved results in head and neck cancers, uterine cervical cancers and other solid tumors when added to radical radiotherapy [12]. Non-steroidal aromatase inhibitors obtained from triazole derivatives are used in the treatment of breast cancer [13]. Current literature shows 1, 2-pyrazole derivatives to possess various biological activities [14, 15]. It is also observed that incorporation of aryl substituents and halogen atoms into the heterocyclic ring systems enhances the biological activities considerably[16]. Several Schiff bases were reported to possess potential anticancer properties [17].

Kuzmin et al 2000 studied the anticancer activity relationship in a series of macrocyclic Schiff bases of 2, 6-bis(formylaryloxymethyl) pyridines by the topological approach. Correlation equations describing the relationship between the anticancer activity and structural parameters of the molecules studied and descriptors characterizing their structure were obtained on the basis of *in vitro* screening data. The influence of structure of the investigated substances as reflected by the parameters studied on the anticancer activity, was established.[18]

Chaviara et.al., 2005, synthezied A new series of complexes of the type [Cu(dien)(2a-2tzn)Y(2)] and [Cu(dienXX)(2a-2tzn)Y(2)] and their structure established by IR and electronic spectra; magnetic susceptibility; and molar conductivity. The second bromine atom exists as a discrete anion and is responsible for the cationic nature of the complex. The present investigation indicates that these compounds have an anti tumor activities.[19]

Kuz'min et.al., 2005, investigated anticancer activity of macro cyclic Schiff bases by means of 4D-QSAR based on simplex representation of molecular structure. All the investigated molecules, the 3D structural models were first created and the set of conformers was used. These conformer was represented as a system of different simplexes. Increasing and decreasing number of molecular fragments indicated the anticancer activity according to their length which might be useful for the designing and direct synthesis of novel anti cancer agents[20].

Dihydrofolate reductase (DHFR) is the important target for anticancer drugs belonging to the class of antimetabolites as the enzyme plays important role in the de novo purine synthesis. Nerkar et.al., 2011, report the *in silico* screening to obtain best fit molecules as DHFR inhibitors, synthesis of some 'best fit' quinazolinone from 2-phenyl-3-(substituted-benzilidine-amino) quinazolinones (Quinazolinone Shiff's bases) QSB1-5 and pyridine-4-carbohydrazide Shiff's bases (ISB1-5) derivatives and their *in vitro* anticancer assay. Synthesis of the molecules was performed using microwave assisted synthesis. The structures of these molecules were elucidated by IR and 1H-NMR. These compounds were then subjected for *in vitro* anticancer evaluation against five human cancer cell-lines for anticancer cyto-toxicity assay. Methotrexate (MTX) was used as standard for this evaluation to give a comparable inhibition of the cell proliferation by DHFR inhibition. Placlitaxel, adriamycin and 5-fluoro-uracil were also used as standard to give a comparable activity of these compounds with other mechanism of anticancer activity. ISB3 (4-(*N*, *N*-dimethyl-amino)-phenyl) Schiff's base derivative of pyridine carbohydrazide showed equipotent activity with the standards used in *in vitro* anticancer assay as per the NCI (National Cancer Institute) guidelines.[21]

Gupta et.al 2011 synthesised the ligands N-benzyl-2-(diethylamino)acetamide, (HL^1) and 2-(diethylamino)-N-phenylethylacetamide(HL^2), have been used to synthesize copper(II) complexes, $[Cu(HL^1)_2](ClO_4)_2$ (1)] and $[Cu(HL^2)_2](ClO_4)_2$ (2)], using ligand respectively.Screening results for anti-proliferative studies against the U87 and HeLa cancerous cells indicate promising activity. The complexes enhanced growth inhibition and cell death in a concentration and time dependent manner for both U87 and HeLa cell lines. Of the two compounds, complex (2) exhibits better activity against both HeLa and U87 cells. Further, both complexes are specifically potent against U87 after 72 h of treatment. Micronucleus and apoptosis frequencies are 3 - 4 times higher in treated cells when compared with untreated control. Despite potent in vitro activity, both complexes exhibit diminished cytotoxicity against the normal human HEK cells at all effective concentrations.[22]

A series of 5- or 7-substituted 3-{4-(5-mercapto-1, 3, 4-oxadiazol-2-yl)phenylimino}-indolin-2-one derivatives were synthesized by treating 5-(4-aminophenyl)-1, 3, 4-oxadiazole-2-thiol with different is a tin derivatives by gudipati et.al. All the synthesized derivatives were screened for anticancer activity against HeLa cancer cell lines using MTT assay. All the synthetic compounds produced a dose dependant inhibition of growth of the cells. The IC_{50} values of all the synthetic test compounds were found between 10.64 and 33.62 μM. The potency (IC_{50} values) of anticancer activity of compounds VIb–d was comparable with that of known anticancer agent, Cisplatin. Among the synthesized 2-indolinones, compounds VIb–d with halogen atom (electron withdrawing groups) at C5 position showed the most potent activity. These results indicate that C5 substituted derivatives may be useful leads for anticancer drug development in the future.[23]

CONCLUSION

Recent advances in inorganic Chemistry have made possible formation of number of Schiff base metal complexes with organic ligand of interest, which can be used as therapeutic agent. Development of transition metal complexes as drugs is not an easy task; considerable effort is required to get a compound of interest. Beside all these limitations and side effects Schiff base metal complexes are still the most widely used chemotherapeutic agents and make a large contribution to medicinal therapeutics in a way that is, unimaginable in few years back.

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