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Schiff Base Metal Organic Frameworks for Biological Applications - A Review

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Abstract

Schiff bases are the organic compounds which are prepared by condensation method with aldehyde and amine derivatives. These have wide range of applications in chemistry due to their binding property with metal ions. Schiff base alone and Schiff base metal complexes have vital applications in inorganic, organic, medicinal and material sciences. Binding properties of Schiff bases can form the network with metal ions which leads to Metal Organic Frameworks (MOF's). This review covers the detailed recent progress of Schiff base-based metal organic frameworks for various biological applications like, antibacterial, antifungal, anticancer, anti-inflammatory, DNA binding, DNA interaction and drug delivery studies.

Keywords: Biological Activities, Metal Organic Frameworks, Schiff Base.

1.0 Introduction

The metal complexes of Schiff base are of paramount interest in coordination chemistry. It is due to their preparation techniques, structural ranges, and numerous applications they seem to exhibit a good choice in research and development. Their applicability can be felt in a huge variety of organic transformations. Numerous publications on metal complexes of Schiff bases have evinced an exponentially high interest among various researchers who are working under this area, in their diversified applications. The Schiff base metal complexes have proven their mettle in a host of applications ranging from the medical field, separation, catalysis, bioinorganic chemistry, material science, and encapsulation processes to the process of compound formation with baffling properties and interesting structures.

In the area of coordination chemistry, Schiff base ligands are regarded as esteemed ligands. Almost all metallic ions may be complexed with Schiff base ligands, which are simple to synthesize and can connect to other metal ions *via* azomethine nitrogen[1]. Because of

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their accessible nature, straightforward synthesis, and favourable electronic characteristics, Schiff base ligands have lately come under the global limelight. There has also been a great surge in interest in exploring Schiff base chemistry owing to its wide array of important functions such as inorganic synthesis, metal refining, electroplating, metallurgy, and photography[2]. Besides, these ligands are considered as a dynamic potential tool in various analytical and biomedical industries. In the modern world of advanced technology, an amalgamation of Schiff base and Metal-Organic Frameworks (MOFs) has become a promising area of research and development with a special focus on medical science. With an objective for extending the life span and providing a promising platform in health sciences, the biological activity of numerous azomethines was said to possess diuretic, anticancer, and antimicrobial (antibacterial, antifungal) properties. Hence, in supramolecular chemistry, catalysis, biological applications, and in the synthesis of molecules with exceptional structures and characteristics, the significance of Schiff base complexes has been extensively acknowledged and discussed[3].

In biological systems, the metal ion binding site that couples with different biomolecules, such as proteins and various amino acids- for anti-germ action, is provided by the azomethine nitrogen in the Schiff bases. Inside the human body, Schiff bases accelerate several metabolic processes in the form of enzymes that have antimicrobial activity. Researchers have enhanced the bio reactivity of Schiff bases and related Schiff base metal complexes. Basis the transition metal ions found in the Schiff bases, they illustrate antibacterial, antifungal, antiviral, anticancer, and antiulcer properties. Although metal ions have proven to be effective and exhibit potent antibacterial activity, they can occasionally be very harmful to human cells or tissues. So as an alternative measure to overcome the tissue toxicity caused by these metal ions, metal-organic frameworks came into play.

Metal-Organic Frameworks (MOFs) (are also termed as Porous Coordination Polymers (PCPs) and nanocomposite-based MOFs systems have shown strong long-term antibacterial activity[4-6]. The MOFs are a group of low-density, three-dimensional (3D) crystalline solids that are held together with the assistance of coordination bonds in between metal ions and organic or inorganic ligands. They have proven to be excellent candidates for a large assortment of potential applications, including gas adsorption and separation, drug delivery, catalytic reactions, and other tasks, due to their diverse and customizable framework and porous structures, high surface area, large framework flexibility/dynamism, along with other characteristics.

Among several kinds of known MOFs, iron-based MOFs like MIL-100(Fe) are often used as a wide range of metal sources and linkers. With efficient thermal and chemical stability, unsaturated metal centres with redox characteristics, and less hazardous in nature they are the best choice for many industrial applications[7,8]. This makes Fe-based MOFs, a comparatively appealing MOFs material. In addition, several Fe-based MOF composites are extensively used in controlling the distribution of antibacterial, antiviral, and anti-parasitic properties, pathogen-mimetic, anticancer, and many drug delivery components[9-11]. This review article summarizes various pharmacological properties, potential applications, and synthetic strategies toward MOF-dependent Schiff base chemistry. In this review exploring the anticancer, Antifungal.

2.0 MOF as a Key Player in Pharmacology

2.1 Anticancer Activity

Malignant neoplasms, sometimes known as cancer, are a set of disorders in which a population of cells undergoes uncontrolled development, invasion, and frequent metastasis. They continue to pose a severe threat to public health. Cancer biology is an emerging trend in scientific research but in spite of many advances like, surgery and chemotherapy the cure is not sure[12,13]. In chemotherapy, treatment with platinum-based complexes like cis-platin has been found ineffective against cancer. Subsequently, scientists are creating complexes that do not include platinum. Recently, it was shown that Schiff base derivatives had effective anticancer effects.

As per the research conducted by Dongfang *et al.,* and Hajrezaie *et al*., ternary complexes of rare earth elements along with co-ligands L-phenylalanine, salicylaldehyde, and *o*-phenanthroline effectively fight the K562 tumour cell. By using the MTT test, the *in vitro* anti-cancer effects of platinum (II) complexes of decreased amino acid linked Schiff bases were assessed against the HL-60, BGC-823, KB, and Bel-7402 cell lines[14,15]. To inhibit the proliferation of HT-29 colon cancer cells, a Schiff base complex called $Cu(BrHAP)_2$ has been tested, and the results pinpointed being a contender. Many compounds like, PHP [*N*-(1-phenyl-2-hydroxy-2-phenyl ethylidine)-2'-hydroxy phenyl imine], PDH [*N*-(1-phenyl-2-hydroxy-2-phenyl ethylidine)-2',4'-dinitrophenyl hydrazine], and HHP [*N*-(2-hydroxybenzylidine)-2'-hydroxy phenyl imine] are examples of Schiff bases that were used to restore depleted haematological parameters[16]. Dinuclear copper(II) and cobalt(II) complexes of Schiff bases were studied for their anticancer qualities, apoptosis-inducing abilities, and catecholase mimicking properties[17]. To investigate their anticancer properties, 2-[(*E*)-(2-hydroxy-3-methoxyphenyl)methylidene]amino-2-methylpropanoic acid complexes of di- and triorganotin(IV) were used. 4-Aminosalicylic acid and 2-acetylferrocene were combined to form ferrocenyl Schiff base of Co(II), Cu(II), and Zn(II) complexes of the compound were produced. These complexes were then tested for anticancer properties against the breast cancer (MCF-7) cell line[18]. The human hepatoma (HepG2) cell line was used in testing the cytotoxic and apoptotic effects of transition metal complexes Schiff base of a multidentate ligand containing guanidine. These outcomes are suggestive of the complexes' anticancer activities. With the use of Schiff base 1-[(2-aminophenylimino) methyl] naphthalen-2-ol and its Cu(II), Ni(II), Co(II), and Zn(II) complexes, the anticancer activity for colon carcinoma HCT-116 cell lines was evaluated[19]. Compared to the Schiff base, the Fe(III) complex showed more anticancer efficacy against MCF-7 breast cancer cells. The cytotoxicity of the cancer cell lines MCF-7 and HeLa revealed that the 5-(diethylamino)-2-[(2,6-diethylphenylimino) methyl] phenol is a potent anticancer agent. The work conducted by John *et al.*, revealed that Co/Ni/Cu/Zn(II) complexes of 6-methyl-2-aminopyridine and furfural-derived Schiff base furfural-MAP showed potential anticancer action against the human ovarian cancer L929 cells[20]. It has been claimed that the copper complex of the Schiff base, which is made from acetylacetone and salicylaldehyde as well as *o*-phenylenediamine, has antimicrobial and anticancer properties[21]. The antitumor activity of the heteronuclear Mn(II)-copper(II) complex of Schiff base against prostate cancer, as studies indicate, was found to be increased *in vitro* and *in vivo* by poloxamer P85[22]. Higher anticancer activity was demonstrated by mono- or binuclear Fe(III), Co(II), Cu(II), Ni(II), and Zn(II) complexes of various Schiff bases against MCF-7 breast cancer cells, sometimes along with ovarian cancer, human prostate, and colon cancer.

2.2 Antifungal Activity

Human infectious diseases like those caused by pathogenic, harmful fungal species, contribute to morbidity/mortality in a major way and pose an extensive menace to the global public health system, annually[23,24]. The possibility of combining multiple uses within the framework makes such polymeric materials an optimum system for the creation of many periodic arrangements-along with multi-functional molecular subunits. These well-defined properties of MOFs have led to their use in wide areas of application[25,26].

Fungi are eukaryotic organisms that include moulds and yeasts. Among the various extensively studied fungal pathogens, *Candida* spp., *Aspergillus* spp., and *Fusarium* spp. cause infections that are detrimental and widespread. *Candida albicans* is a dimorphic fungus that forms both yeast and filamentous cells. It is a commercially important fungus since it typically contaminates food leading to food-borne disease and food spoilage, thereby causing huge losses to the global food industry. In certain clinical situations, *C. albicans* may become virulent because it can disseminate through the bloodstream to areas that are remote from the site of primary infection[27]. In addition to it, another causative agent of food spoilage is the *Aspergillus* species. *Aspergillus oryzae* and *A. niger* are generally found intermediate-moisture food products, in bakery products, dairy products like cheeses, and preserved plant produce. *C. albicans, A. niger* and *A. oryzae* when treated with Cu-BTC, a strong biocidal agent used in this case proved to be a life saver of the food industry. In addition to the above said fungal species, another ubiquitous fungus - *Fusarium oxysporum*, generally found as one of the soil microflorae, causes contamination in agricultural products. It was chosen as another important representative fungus because it has a huge repercussion on the environment. It can be grown on organic matter present in soils and the rhizosphere around plants, further giving rise to saprophytic plant pathogens[28].

Although the above-cited materials have proved to be of superior antimicrobial activity, the use of the same sometimes is greatly retarded due to the fact they exhibit high cellular toxicity in human cells and tissues.

The anti-inflammatory and antioxidant activities were also seen to be equally effective, strengthening the fact that synthesized Schiff bases are biologically powerful in action, having high potential pyrazolone moiety.

The in-depth applications of Schiff base breakthroughs that involve element and chemical element donor ligand pushes the scientific community to synthesize and characterize new pyrine- basis the Schiff bases and their auriferous complexes[29]. The coordination polymers, normally seen as Metal-Organic Frameworks (MOFs), are currently inviting excessive levels of deep study and research in the field of chemical sciences[30]. MOFs are generally created *via* condensation reactions of carbonyl compounds along with amines, forming Schiff bases as the end product. Chemically speaking, these bases are imines[31].

The aim is to develop a novel, effective antimicrobial drug that has a broader and extended action time, that are low in toxicity levels, thereby rendering safer treatments to subjects. Under ideal conditions, the Fe(III)-MOF shows exceptional antifungal activity against *Aspergillus* spp., *Fusarium* spp., and *Candida albicans*. The Fe(III)-MOF demonstrates potentially great antifungal activity towards lab-cultured yeast strains like *Candida* spp. and *A. Niger* with prominent inhibition zones forming on the agar media. The Fe(III)-MOF shows high activity in contrast to common, conventional drugs.

The chief advantage of such a group of materials as antimicrobial agents are - MOFs are chemically stable agents and they operate as metal ions reservoir which releases ions continually in an extended period, thanks to their synergistic action[32].

The encouraging results of the antimicrobial study disclosed that it could be one of the most promising and favourably affordable antimicrobial agents for the future that may be used against drug-resistant pathogens. In short, it stands as a simple, yet outstanding answer for one of the pressing environmental and public health issues.

2.3 Antibacterial Activity

The metal-organic frameworks are promising antimicrobial agents, more specifically antibacterial agents. The construction of ligands is one of the primary and essential steps in coordination chemistry. Schiff bases are formed as bidentate or multidentate in behaviour from a variety of aldehydes and amines, and their arrangement with various transition metal ions to form novel complexes[33-37]. Schiff bases that are derived from salicylaldehyde and *o*-vanillin are widely used as bidentate or multi-dentate ligands. This can be pointed to the presence of an ortho-position hydroxyl group beside the azomethine group, which forms upon the fusion of the aldehyde and amine groups. The Schiff bases and their metal complexes are employed in a myriad of applications; a few being enumerated here - namely, solar cells, catalytic reactions, antibacterial, antifungal, antiviral, antitumor and biosensing processes[38-42].

A German chemist, Hugo Schiff, is credited with first reporting of the Schiff bases in the year 1864; hence the name is given as, Schiff bases. These are concurrently also called as imines or azomethines[43]. Schiff base complexes based on salicylaldehyde have a strong bactericidal effect on many bacterial species[44]. *N*-(Salicylidene)-2-hydroxyaniline is a salicylaldehyde-based Schiff base derivative that is known as a powerful antibacterial agent - especially against *Mycobacterium tuberculosis*[45]. Lately, a reported scientific work proved that Fe(III) and Zn(II) monodentate containing Schiff base metal complexes showed antibacterial properties[46]. A Schiff base ligand composed of *o*-vanillin and 4-aminoazobenzene combined with transition metal complexes of Ni(II), Zn(II), Co(II), Mn(II), Cu(II), and Zr(IV) were chemically synthesized under microwave-assisted irradiation as a greener approach in contrast to the stereotypical methods in use. Schiff bases were chosen due to the fact; their compounds have strong association abilities with DNA, thereby rendering them as potential antibacterial agents[47].

It has been observed that the chelation process brings down the metal atom polarity; primarily due to the positive charge present on the metal, which is partially shared with oxygen and nitrogen atoms present on the free Schiff base ligand. The whole complex ring undergoes electron delocalization, which in turn enhances the lipophilic character of the metal chelate and furthers its permeation through the phospholipid layers of the microbial membranes.

In a few instances, the modest properties of some metal complexes has been recorded. This low inhibition may be accounted to the low levels of lipophilicity, which curtails the ability of the metal complex to penetrate the lipid membrane[48]. Additionally, the existence of metal ions in complexes with azomethine derivatives demonstrated more effectiveness in membrane destabilization rather than the free ligand. This leads to the disruption of the structural integrity of the cell and eradication of the microorganism[49]. The Fe(III)-MOF revealed excellent antimicrobial efficiency against both Gram-positive/negative bacterial species, under favourable laboratory conditions. Complexes of Co(II), Zn(II), and Ni(II) with that of the OV-Azo group showed a medium to highest inhibition zone diameter and thus proved to be bactericidal against *Staphylococcus aureus* and *Bacillus subtilis* (Gram-positive bacteria). The antimicrobial efficacy of the ligand with its metal complexes employed against the bacterial strains demonstrated that Schiff base ligand is biologically not active. Tweedy's chelation theory is directly responsible for metal complexes that become more active upon chelation. Laboratory findings indicated complexes of Ni(II), Co(II), and Zn(II) of OV-Azo achieved a moderate to high inhibition zone diameter. This is directly proportional to the antagonistic activity of Schiff bases against bacteria.

Thus, the importance of Schiff base metal complexes has been widely recognized in the area of bioinorganic chemistry and biomedical applications. The astounding results considerably open the gates for the use of laboratory-prepared materials as an efficacious antibacterial agent.

2.4 Anti-Inflammatory

Anti-inflammatory activity using metal organic frame works has not been studied much. Khaled AbouAitah group has studied and developed nano formulated for two types of MOF's one is zirconium based (Zr-MOF) and another one is titanium based (Ti-MOF). Both MOFs and nano formulations were evaluated *in vivo* for anti-inflammatory and antioxidant effects. The nano formulations had enhanced anti-inflammatory and antioxidant effects than any of their elements singly, and those with Ru or Pip alone showed stronger effects than those with both agents. Results of assays using a paw edema model, leukocyte migration, and plasma antioxidant capacity were in agreement. Our preliminary findings indicate that nano formulations with these agents exert better anti-inflammatory and antioxidant effects than the agents in their free form[50].

2.5 DNA Interactions

The physical properties of multifunctional homo/pseudoheterometallic Metal-Organic Frameworks (MOFs) have been exploited in recent years, not only for basic intensive research but also for their compelling potential applications in newer, cutting-edge technologies[51-56]. Of late, different scientific groups have reported the synthesis of various bimetallic complexes with bifunctional-magnet material properties in a multitude of scientific literature[57-60].

The functionality and transition of Schiff base ligands and lanthanide complexes in the analytical, industrial, and biological fields make further research in this area highly lucrative and beneficial. A unique class of organic moieties (precursors)-Pyrazolones-(nitrogen-heterocyclic compounds) are used in the preparation of Schiff bases. A number of naturally occurring Schiff base ligands that are formed from heterocyclic compounds, are widely spread in nature and are indispensable to many biological systems[61]. A popular antipyretic agent, 4-amino antipyrine (4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one), is one of the important classes of pyrazolone derivatives. Among other pyrazolone derivatives, 4-aminoantipyine forms a varieties of Schiff bases when reacted with aldehydes or ketones, and is, therefore, regarded as superior reagent in biological, pharmacological, clinical, as well as analytical applications[62]. There are three means of coordination that take place in the 4-amino antipyrine. They are enumerated as: (i) as unidentate with bonding through the carbonyl oxygen, (ii) as the unidentate mode through the amino nitrogen, and (iii) as the bidentate mode through chelation, by using both of the oxygen and nitrogen donors. Condensation in aqueous or alcoholic solutions yields the majority of Schiff bases of 4-amino antipyrine derivatives in high yield[63]. It is also possible to obtain both neutral and protonated forms of the ligands based on the form of the ligand precursor.

The 4-amino antipyrine-derived heterocyclics are of prime importance as it is found abundantly in nature and have a wide array of pharmacological activities; Salicylidene-4-amino antipyrine is one of them. Its derivatives are known for their biological properties. It is because the presence of the azomethine group which is accelerated in coordination with several transition metals and lanthanides. The Schiff bases and metal complexes of 4-amino antipyrine and its derivatives are used in a variety of applications such as in the catalytic[64,65], biological, clinical, pharmacological[65], and analytical areas[67]. Salicylidene-4-aminoantipyrine metal complexes and their derivatives have been researched in recent years, owing to its effective DNA-binding properties. The interplay between DNA and transition metal complexes has become pertinent in medicinal and biological fields- in particular, in the fabrication of new, efficacious, and less deadly metallodrugs for chemotherapy.

The development of metal complexes of salicylaldehyde-4-aminoantipyrine derivatives can be a probable means of achieving success as promising drugs or biological probes. Its deep research in other areas of scientific interest such as catalysis, chemo sensing, and material science, makes its study relevant and research-worthy. With an increase in the exploration of the synthesized Schiff bases, it would be interesting to see how its interaction with the DNA of resistant bacteria to common drugs, unfolds. In almost all peer-reviewed studies, the anti-biological activities of the Schiff base-metal complexes were higher than those of freely occurring Schiff bases strengthening the fact that the Schiff base metal complexes (or MOFs) are definitely the potential drugs of the future.

2.6 Drug Delivery System (DDS)

There are several drug carrier molecules used in medical therapy to cure many diseases mainly cancer. Currently, some biodegradable polymers, liposomes, and organic macromolecules are among the first-choice cargo carriers in drug delivery. But these molecules possess many disadvantages and side effects such as poor stable configuration, more body rejection, and at times failure to show sufficient drug loading capacity[68,69]. To have a better option more diverse, flexible, porous, biocompatible material with good adsorption covering a large surface area came into existence. These modern-day composite materials, MOFs are being widely used as drug delivery cargo molecules in medical and health sciences. Many successful drug loading systems by integrating MOFs and nanotechnology are achieving significant results, predominantly in cancer therapy. The research work conducted by Danping Ling and co-workers[70] summarizes the uploading of 2 anti-cancer drugs in Hela cell lines DOX and 5-FU successfully by using MOFs on the surface of nanoparticles. The system developed by MOFs showed the least toxicity and excellent biocompatibility.

MOF-based, Drug Delivery System (DDS) has picked up momentum in recent years not only for its fast and efficient drug loading and release kinetic reaction but also for reducing the potential side effects caused by the drugs. There are various levels of MOF based drug delivery system which show an increase of complexity from a Normal MOF to Multi-stimuli response Drug delivery system[71].

2.6.1 Normal MOF-based DDS

This method is based on the encapsulation of the desired drug into MOF pores to the target cell through simple diffusion. Researchers found the successful release of the anti-cancer drug Oridonin[72] by using MIL-53 (Fe), MOF encapsulated with tyrosinase enzyme as a pro-drug Paracetamol activator, causing notable tumour regression[73].

2.6.2 Stimuli-responsive MOF-based DDS

MOF-dependent stimuli responsive method is based on getting activated by a specific stimulus with respect to physiological conditions and setting the cascade of reactions by releasing the encapsulated carrier molecule with the drug to the target cell. There are 2 modes of stimuli based on their source. If the cell stimulus is present internally (endogenous), the activation begins by triggering the release of encapsulated drug through MOF. When the process begins there is a difference in concentration gradient between a normal cell and a cancerous cell related to internal stimulus such as differences in pH, ions, and redox potential. On the other hand, exogenous stimuli-responsive drug delivery depends on the factors controlling outside the body. These include radiations, temperature, light, intensity, magnetic field, etc. In this system, the release of a particular drug can be controlled as per our choice (Figure 1). The method was commonly used for treating cancer cells *in vitro* with many successful MOF-based drugs coated with NPs such as AUNPs, FeNPs[74,75] and PEG- NH_2 coated designed gold nanorods with porphyrinic MOF and injected the drug Camptothecin (CPT)[76,77].

The major advantage of exogenous DDS is that it is not dependent on any physiological internal factors but at the same time activation of drug release and degree of penetration is a remarkable challenge.

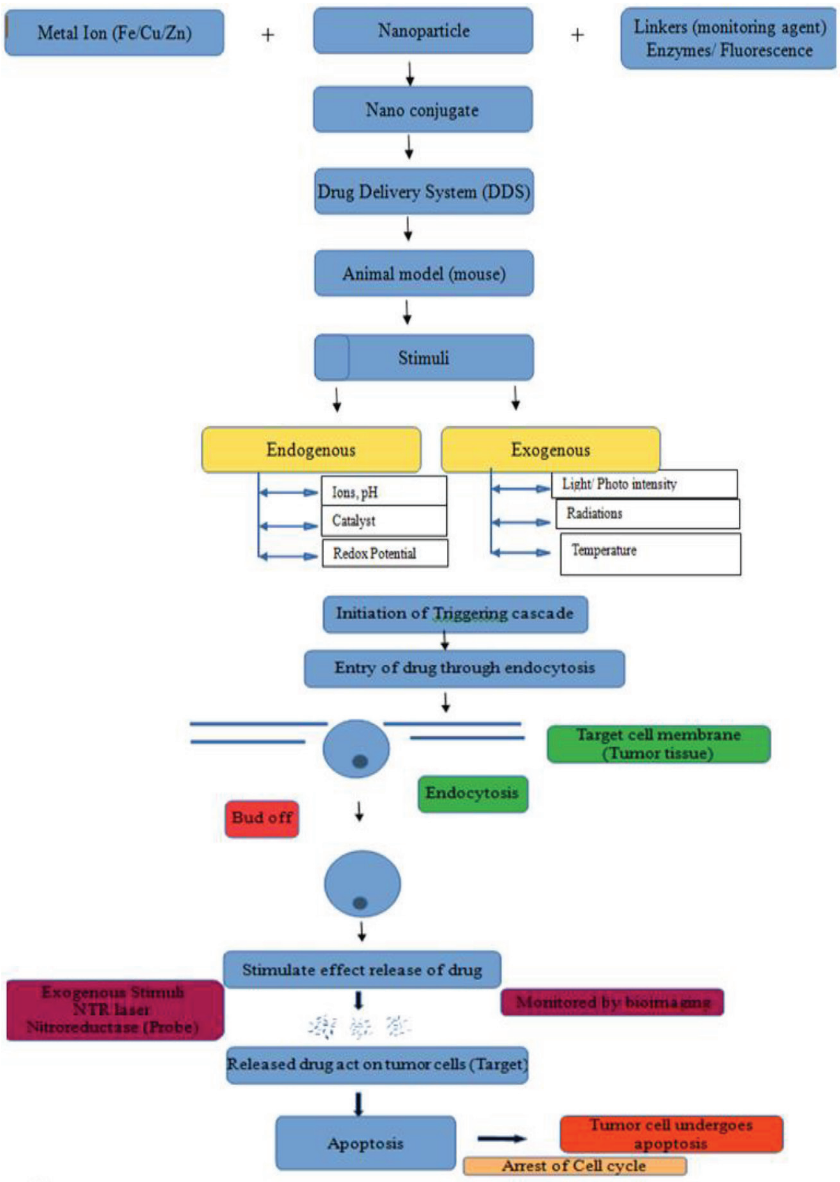

Figure 1. Diagrammatic representation of triggering cascade of stimuli dependent MOF-Drug Delivery System (DDS).

3.0 Conclusion

Metal-Organic Frameworks (MOFs) are one of the modern porous hybrid organic-inorganic materials widely used in biomedical fields. This very MOF layout has witnessed tremendous growth due to their fascinating structures and potential attributes forming Schiff bases as the end product. Schiff's bases are one of the cutting-edge and novel non-transitional metallic complexes that are attributable to its own appropriate properties, utility, and employment in each of the theoretical and sensible domain. Furthermore, it can help to curb the advancement of emerging pathogens and decrease death rates significantly. The basic principle of MOF reveals the mode of action of trapping the biomolecules and adsorbing them during the synthetic process. Hence, exploring MOF-dependent Schiff base, as a potential tool for various therapeutic, pathological, and drug delivery systems will be a promising approach in the medical realm. Future studies will definitely be needed in order to research further the efficacy of the Schiff bases as potent, formidable drugs for various co-morbid conditions.

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