# Biocompatibility and Toxicity Perspective for the Development of Nanomaterials for Cancer Detection and Treatment


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## 1 Introduction

When common critical diseases are evaluated throughout the world, cancer is at the beginning of these diseases. Cancer is a type of disease that reduces the quality of life of patients, requires painful and long treatment, uses many drugs and side effects of these drugs, and sometimes even causes death [1]. Early diagnosis and correct treatment are very important in cancer cases [2]. Since it is such a common type of disease, new studies on this subject are brought to the literature every day. Moreover, the diagnosis and treatment of cancer, as well as the biocompatibility and toxicity of the compounds used in the treatment, are included in these studies.

Chemotherapy is the most widely used method in the treatment of cancer cases [3]. However, as it is known, some anticancer drugs used in chemotherapy can not only destroy cancer cells but also damage normal cells [4]. Patients also experience various adverse side effects such as poor specificity and limited accumulation of such drugs, myelosuppression (depression of the immune system), organ damage, alopecia (hair loss), and gastrointestinal distress. For this reason, there are many studies that are predicted to be used in the treatment of cancer diseases every day. Many different areas stand out among these studies. There are many organic-based,

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inorganic-based, DNA-based, RNA-based, polymer-based nanomaterials and anticancer studies in the literature.

In this study, the biocompatibility and toxicity of anticancer studies involving organic- and inorganic-based nanomaterials will be determined, and the effects of organic- and inorganic-based nanomaterial-containing structures on anticancer studies will be revealed.

## *1.1 Nanotechnology*

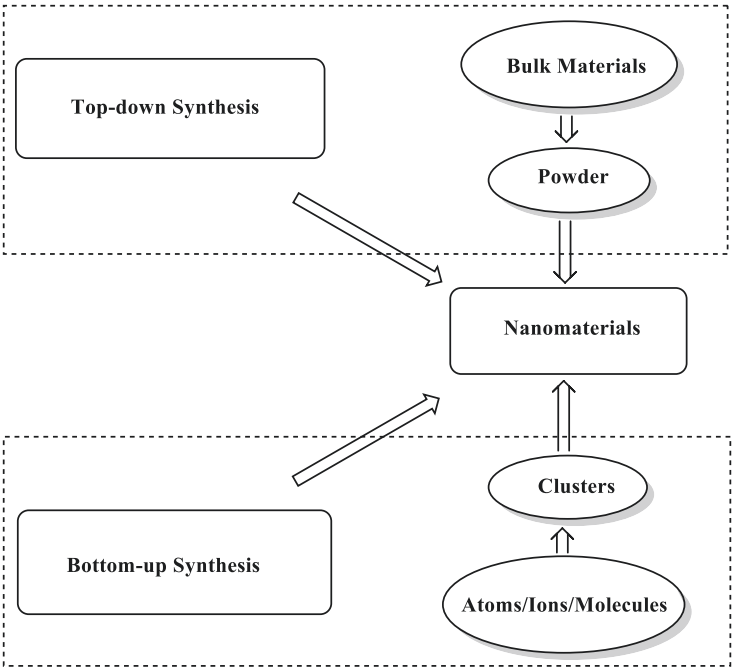
Nanotechnology is a phrase that has been around for a long time. Although nanotechnology has existed from the beginning of time, the discovery of nanotechnology is commonly credited to Dr. Richard Phillips Feynman, an American physicist and Nobel Laureate [5]. Taniguchi is credited as being the first to adopt the term "nanotechnology" in 1974. In his book *Engines of Creation*, Eric Drexler popularized the term "nanotechnology" in 1986 [6].

The most generally cited definition of nanotechnology comes from the US government's National Nanotechnology Initiative (NNI). Nanotechnology is defined as "research and technology development at the atomic, molecular, and macromolecular levels in the length scale of approximately 1–100 nanometer range, to provide a fundamental understanding of phenomena and materials at the nanoscale, and to create and use structures, devices, and systems that have novel properties and functions because of their small and/or intermediate size," according to the National Nanotechnology Initiative [6].

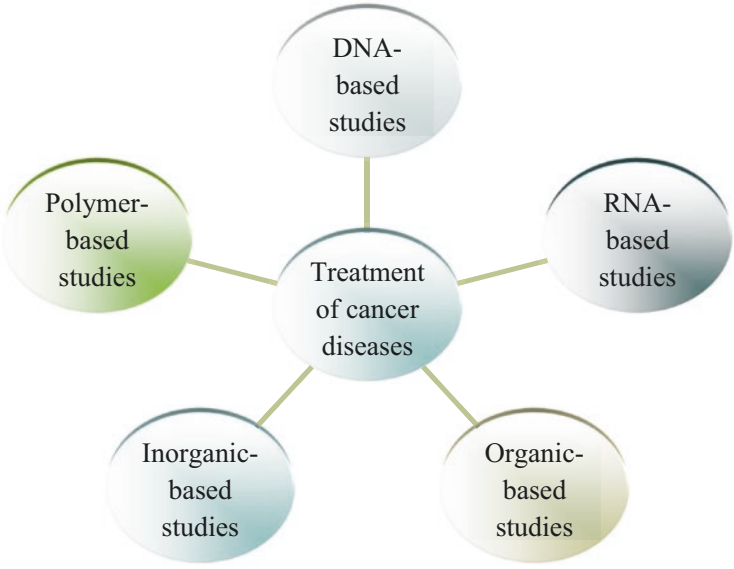
The development of useful materials and structures in the nanoscale range of 0.1–100 nanometers by different physical or chemical processes is known as nanotechnology or molecular engineering [7]. The word "nano" comes from the Greek word *nanos*, which means "dwarf." A nanometer is one billionth of a meter ($10^{-9}$) [5]. To put it another way, it's atomic and molecular engineering. It's an interdisciplinary field that encompasses chemistry, colloidal science, biology, and applied physics among others.

The methods of obtaining nanoscale materials can be evaluated in two ways. These are top-down, and bottom-up approaches as given in Scheme 1.

There are many nanoscale studies in the literature. The usage areas of nanomaterials are increasing daily. Especially in medicine and medicinal chemistry branches, interest in this field has intensified as the remarkable effects of nanoscale materials have been observed. Nanoscale anticancer studies can be classified as organic-based, inorganic-based, DNA-based, RNA-based, polymer-based nanomaterials as shown in Scheme 2.




**Scheme 1** Top-down and bottom-up approaches for nanomaterials' synthesis




**Scheme 2** Different-based studies for the treatment of cancer diseases

## *1.2 Nanomaterials in Treatment of Cancer Diseases*

### 1.2.1 Organic-Based Nanomaterial Studies

Organic nanomaterials are used in anticancer applications [8]. Because of its intriguing pharmacological features and therapeutic potential, the stream of heterocycles has sparked a lot of curiosity. Its relevance as a building block for critical intermediates in the synthesis of numerous natural products with a wide spectrum of pharmacological and biological actions, such as anticancer medicines and antitumor chemicals, has increased [9].

### 1.2.2 Inorganic-Based Nanomaterial Studies

Several commonly used inorganic nanomaterials have been employed as nanomedicine to deliver medicinal and/or in vivo imaging ingredients selectively for cancer therapy and diagnostic purposes [10, 11]. Carbon nanostructures (e.g., graphene, nanotubes, nanodiamonds), metallic NPs (e.g., titanium, silver, iron, gold), and inorganic NPs such as mesoporous silica NPs are all examples of inorganic nanomaterials [10–12]. In cellular models of breast cancer, studies have revealed that GO-doxorubicin has stronger anticancer activity [13].

### 1.2.3 DNA-Based Nanomaterial Studies

DNAzymes are single-stranded DNA molecules that catalyze a variety of processes, including RNA or DNA cleavage and ligation [14–16]. DNAzymes have been widely exploited as effective signal transducers for enhanced biosensing due to their unique cofactor-dependent and sequence-specific catalytic properties [17–20] and even as potent gene silencing therapeutic agents [21–23]. The medicinal RNA-hydrolytic DNAzyme has recently been identified as a potent anticancer medication capable of blocking several tumorigenic pathways by effective intracellular biocatalytic cleavage of oncogene substrates [24–29]. In comparison with ribozymes, siRNA, and antisense oligonucleotides, DNAzyme has a high biostability and does not hijack the endogenous RNA-induced silencing complex [28, 29].

DNA nanoparticles outperform other nanomaterials in terms of properties. DNA molecules serve as both construction materials (self-assembly) and medicinal agents (gene therapy), allowing for the integration of complex structures and functions. Because of its programmability, DNA is an excellent building block for nanostructures of diverse dimensions and shapes. The nanostructures created can be employed as carriers to deliver a range of medications efficiently [30]. Further, the addition of functional DNA sequences [31–33] (G-quadruplex, ribozyme, aptamer, i-motif sequence, and among others) endows DNA nanostructures with functions such as stimulus responsiveness, targeting, and life activity regulation, promoting DNA nanostructures' great potential in the cure of major diseases (Table 1) [34–37].

**Table 1** List of nanomedicines for cancer therapy approved by the FDA [34–37]

| Tradename | Material | Drug | Company | Indicatiın | Year(s) Approved |
|---|---|---|---|---|---|
| Doxi ® | Liposome-PEG | Doxorubicin | Janssen | MBC, metastatic ovarian cancer | 1995 |
| Eligard ® | PLGA | Leuprolide acetate | Tolmar | Prostate cancer | 2002 |
| Abraxane ® | Albumin | Paclitaxel | Celgene | Metastatic breast cancer | 2005 |
| Genexol PM ® | mPEG-PLA | Paclitaxel | Samyang corporation | Metastatic breast cancer | 2007 |
| Onivyde ® | Liposome | Irinotecan | Merrimack | Pancreatic cancer | 2015 |

### 1.2.4 RNA-Based Nanomaterial Studies

RNA interference (RNAi) might be used to treat cancer [38, 39]. MicroRNA (miRNA) is a noncoding short RNA with a length of 20–24 base pairs that may efficaciously control gene expression in the intracellular area and is one of the critical constituents for the induction of RNAi [40]. Closely positioned mature miRNA interacts to supplementary target messenger RNA in the cytoplasm (mRNA). By limiting ribosome binding and mRNA translation, the condition may impede gene expression. Furthermore, the development of a microribonucleoprotein complex (miRISC) including abscisate beta-glucosyltransferase (AOG) and glycine-tryptophan proteins causes RNAi to degrade mRNA (thus downregulating the oncogene and suppressing cancer). Short interference RNA (siRNA) is a noncoding small RNA that can be used in RNA interference-mediated cancer treatment [41].

### 1.2.5 Polymer-Based Nanomaterial Studies

Polymersomes, hydrogels, nanofibers, micelles, NPs, nanogels, and dendrimers are examples of polymeric nanomaterials [8, 11, 42]. PVP has recently been effectively introduced as a substitute for the PEG moiety, combining the benefits of PVP with the micellar morphology [43–45]. PVP was coupled to hydrophobic polymer blocks such as poly(D, L-lactide) [43], poly(-caprolactone) [44], and poly(vinylacetate) [45] in these investigations, and the resultant NPs had minimal toxicity and improved the efficacy of numerous anticancer medicines.

## *1.3 Benefits of Nanomaterials in the Therapy of Cancer Diseases*

With the use of nanotechnology in the diagnosis, therapy, and management of cancer, the fight against the disease has begun to be addressed in a much larger dimension. NPs, by active or passive targeting, increase the intracellular concentration of

medicines to cancerous tissue while showing as little toxicity as possible to healthful tissue. Prepared NPs can be designed to be sent to the target region. Drug release can be provided and regulated with temperature-sensitive or pH-sensitive nanoparticles. Prepared NPs can be designed to be sent to the target region. Drug release can be provided and regulated with temperature-sensitive or pH-sensitive nanoparticles. Such that, in the drug distribution of pH-sensitive nanoparticles, drugs can be administered in an acidic TME, or the drug is released in the target region by temperature-sensitive nanoparticles sent by the temperature given by sources such as ultrasound waves and magnetic fields. Moreover, by adjusting the physicochemical features of the NPs such as dimension, form, molecular mass, and surface chemistry, nanoparticles can be sent to the targeted region [46].

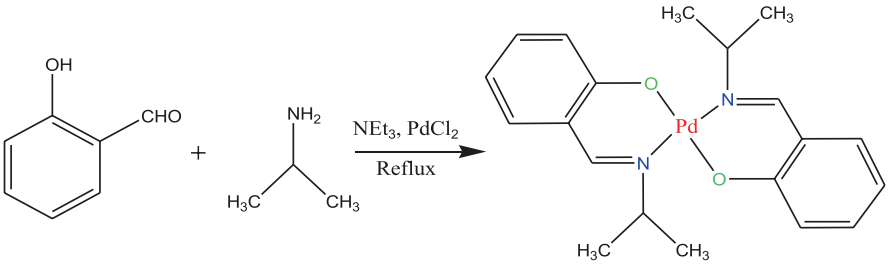
## *1.4 Current Research*

In this section, examples from recent nanoscale anticancer studies in the literature will be given. Moreover, inferences will be made by making evaluations on the biocompatibility and toxicity of these studies.

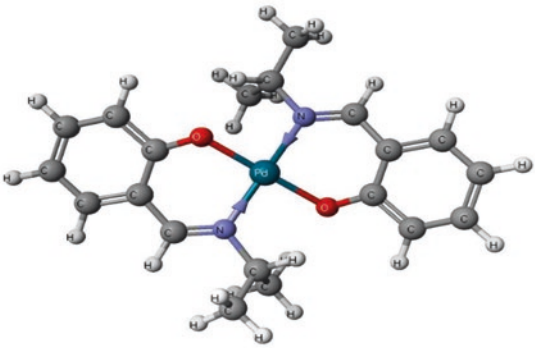
In 2018, Dehkhodaei used a sonochemical approach to synthesize a novel Schiff base Pd (II) complex in bulk and nanoscales. In the study, Schiff base derived from isopropylamine and 2-hydroxybenzaldehyde and its Pd (II) complex (**N1**) were synthesized (Scheme 3). Afterward, it was stirred in an ultrasonic bath at 180 W for 30 min and then centrifuged at 5000 rpm for 15 min to obtain a nanoscale Pd (II) Schiff base complex. The MTT assay was then utilized to define the fraction of HeLa carcinoma cells that were viable. The findings confirmed that shrinking the size has a significant impact on cancer cell annihilation. In addition, nanoscale complexes attained $IC_{50}$ at a concentration of 10 μM. Using a mix of experimental and computational approaches, the binding capacity of the nano- and bulk-scale Pd(II) Schiff base complex with calf thymus DNA and human serum albumin was examined. The predicted binding constants for the complex at both the bulk and nanoscales revealed that the nanoscale complex binds to DNA more strongly than the bulk-scale complex. This finding is consistent with the results of the MTT experiment. The ONIOM findings revealed that the compound's structural characteristics altered in tandem with its binding to DNA and HSA, demonstrating a strong interplay between the compound and the current biomolecules [47].

In 2017, Dehkhodaei obtained Schiff base from the reaction of 3-amino-prop-1-ene with 2-hydroxybenzaldehyde. Then, by immersing the ultrasonic probe in the reaction medium and giving high-intensity ultrasonic waves, the Schiff base ligand was metalized in nanosize with Ni $(OAc)_2$ (**N2**) (Scheme 4). The anticancer activity of the chemical is modified by its size, according to the MTT assay. The binding constants for the DNA complex and the HSA complex were calculated to be about $10^4\ M^{-1}$ [48].

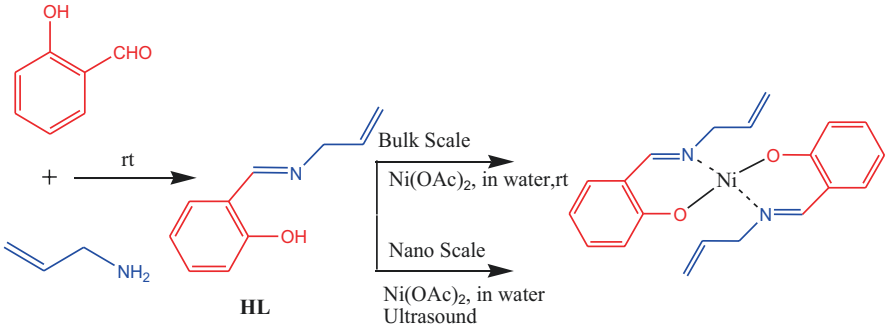
In 2016, Abdel-Rahman synthesized and characterized the Schiff base ligand derived from 3-methoxysalicylaldehyde and 2-amino-3-hydroxypyridine and its



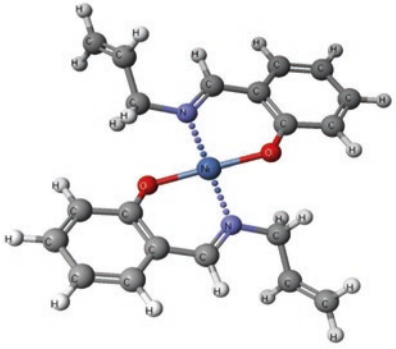

**N1**



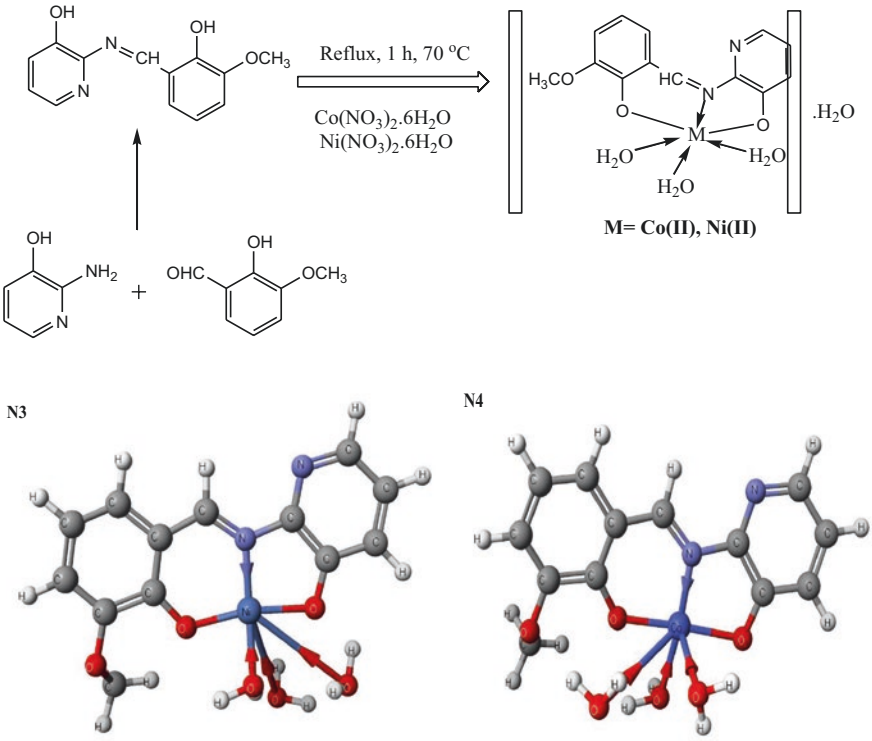
**Scheme 3** Synthetic paths for preparation of $PdL_2$ and optimized structure of $PdL_2$ (**N1**) [47]




**N2**



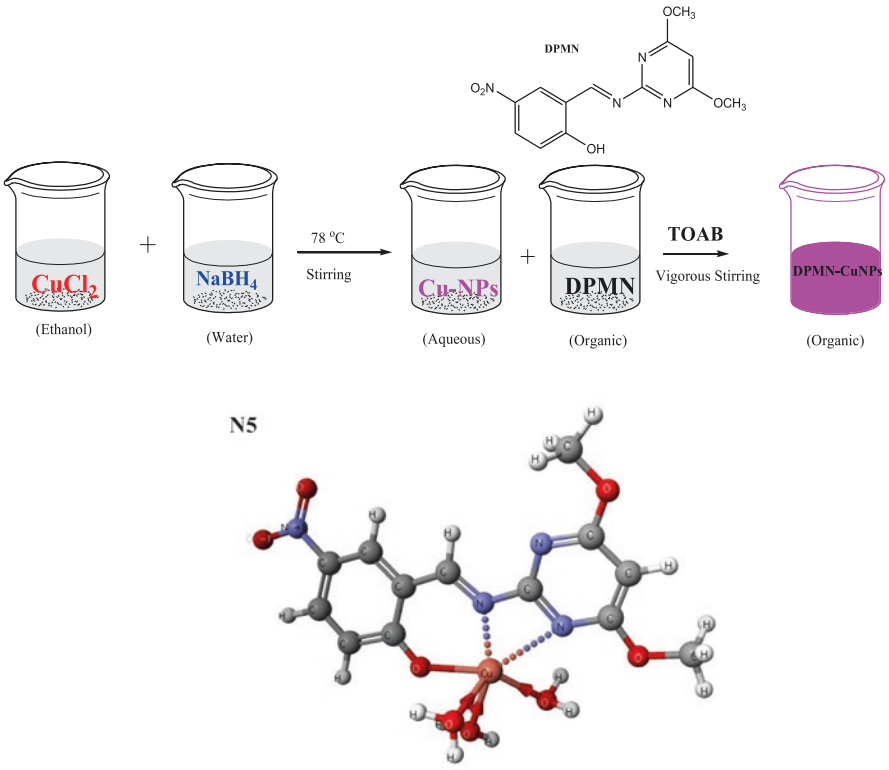
**Scheme 4** Synthetic paths for the preparation of $NiL_2$ in its bulk and nanoscale forms and optimized structure of $NiL_2$ (**N2**) [48]




**Scheme 5** Synthetic paths for the preparation of Ni(II) (**N3**), Co(II) (**N4**) complexes and optimized structure of Ni(II) and Co(II) complexes [49]

nanoscale Ni(II) (**N3**) and Co(II) (**N4**) complexes (Scheme 5). The nanoscale of the complexes was achieved by the sonochemistry method. Afterward, metal oxide nanoparticles were prepared by calcination of the related complex at 500 °C. When controlled with the clinically utilized vinblastine standard, the cytotoxicity of the Schiff base complexes on human breast carcinoma cells (MCF-7 cell line) and colon cancer cells (HCT-116 cell line) exhibited substantial cytotoxicity against carcinoma cell proliferation [49].

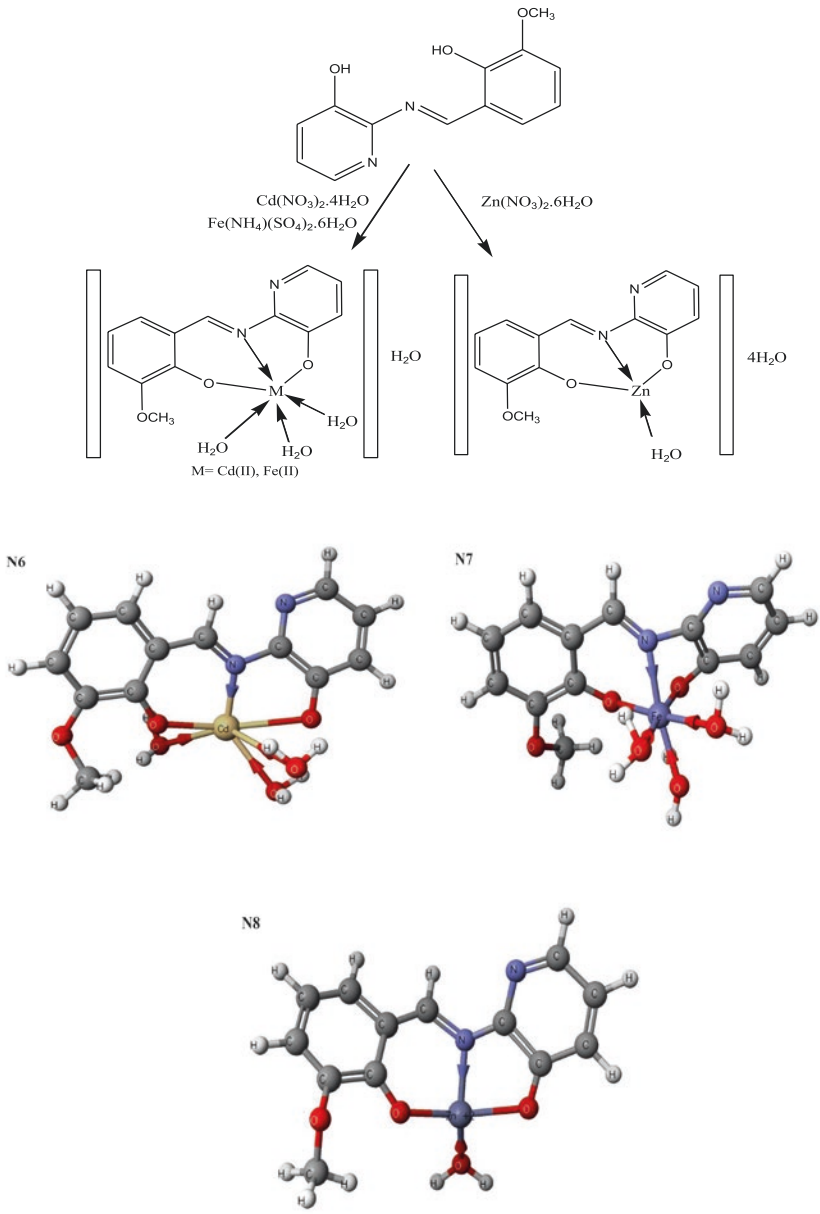
In 2022, Adwin Jose synthesized and characterized Schiff base ligand (DPMN) from the reaction of 2-amino-4,6-dimethoxypyrimidine and 2-hydroxy-5-nitrobenzaldehyde. Air stable copper nanoparticles (DPMN-CuNPs) (**N5**) were synthesized by the modified Brust-Schiffrin method using Schiff base and $CuCl_2$ (Scheme 6). In the study, antioxidant, antibacterial, and anticancer studies were conducted. When the anticancer results of the prepared DPMN-CuNPs were evaluated, it was stated that they had important anticancer activity toward distinct cancer cells and at the same time showed the least toxic effect against normal cells. Moreover, this material (DPMN-CuNPs) has been reported to have catalytic activity in nitrophenol reduction, methylene blue degradation, and methyl orange reduction [50].



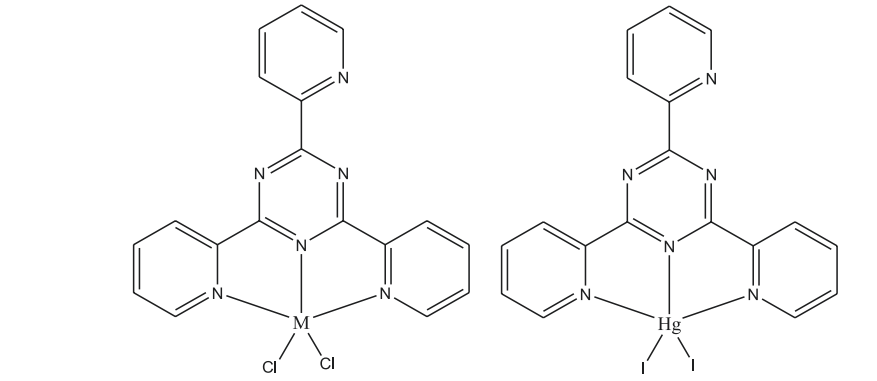

**Scheme 6** Synthetic paths for the suggested structure of DPMN-CuNPs (**N5**) in its nanoscale forms and optimized structure of DPMN-CuNPs [50]

In 2016, Abdel-Rahman synthesized and characterized Schiff base ligand and its Cd(II) (**N6**), Fe(II) (**N7**), and Zn(II) (**N8**) complexes derived from 3-methoxysalicylaldehyde and 2-amino-3-hydroxypyridine (Scheme 7). The synthesized complexes prepared metal oxide nanoparticles by thermal decomposition. Antimicrobial and anticancer studies of the complexes have been carried out. Furthermore, when checked with the clinically utilized vinblastine standard, the cytotoxic activity of the produced Schiff base complexes on human hepatic cellular carcinoma cells (HepG-2) and colon cancer cells (HCT-116 cell line) demonstrated substantial cytotoxicity impact against carcinoma cell proliferation [51].

Yaghabi synthesized and characterized both bulk and nano forms of Zn(II) (**N9**), Cd(II) (**N10**), and Hg(II) (**N11**) complexes derived from 2,4,6-tri(2-pyridyl)-1,3,5-triazine (tptz) in 2019 (Fig. 1). The MTT technique was used to assess the cytotoxic activity of the complexes in bulk and nano forms against the MCF-7 cell line in vitro. The $IC_{50}$ values vary from 2.2 ± 0.1 to 28.6 ± 0.6 μM. These findings showed that the produced complexes might be used as anticancer drugs in both nano and bulk forms [52].




**Scheme 7** Suggested structures of ligand and its Cd(II) (**N6**), Fe(II) (**N7**), Zn(II) (**N8**) metal complexes [51]




M=Zn(II), Cd(II)

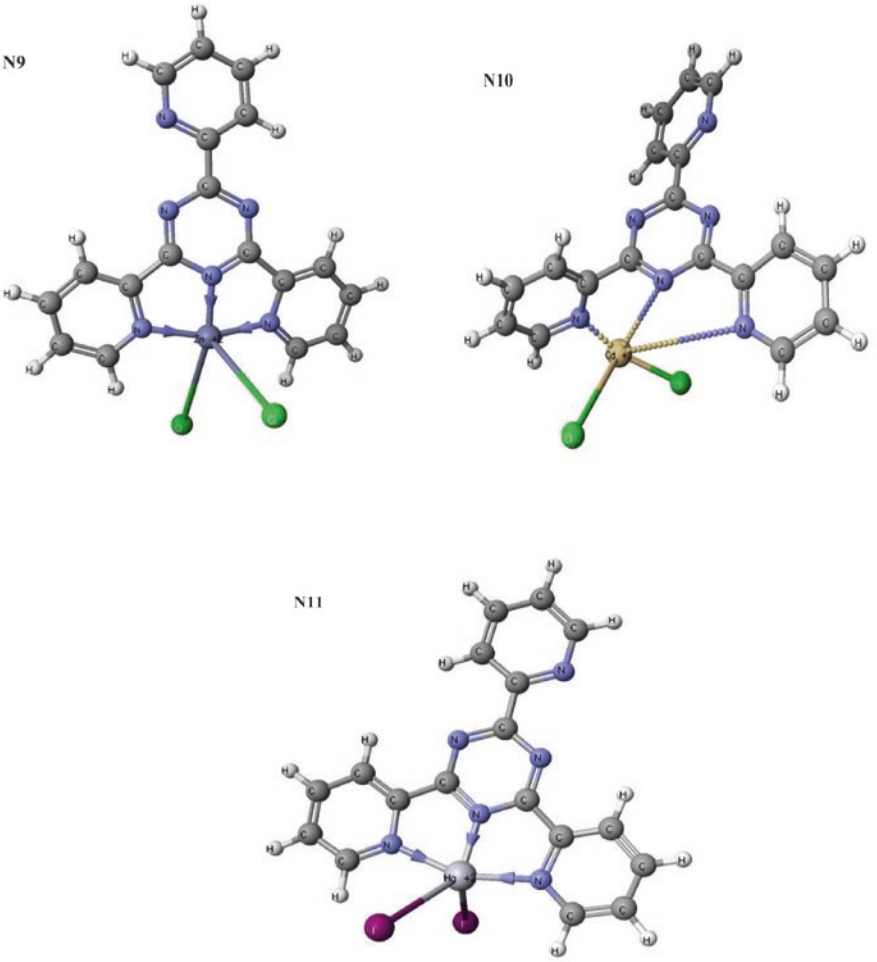
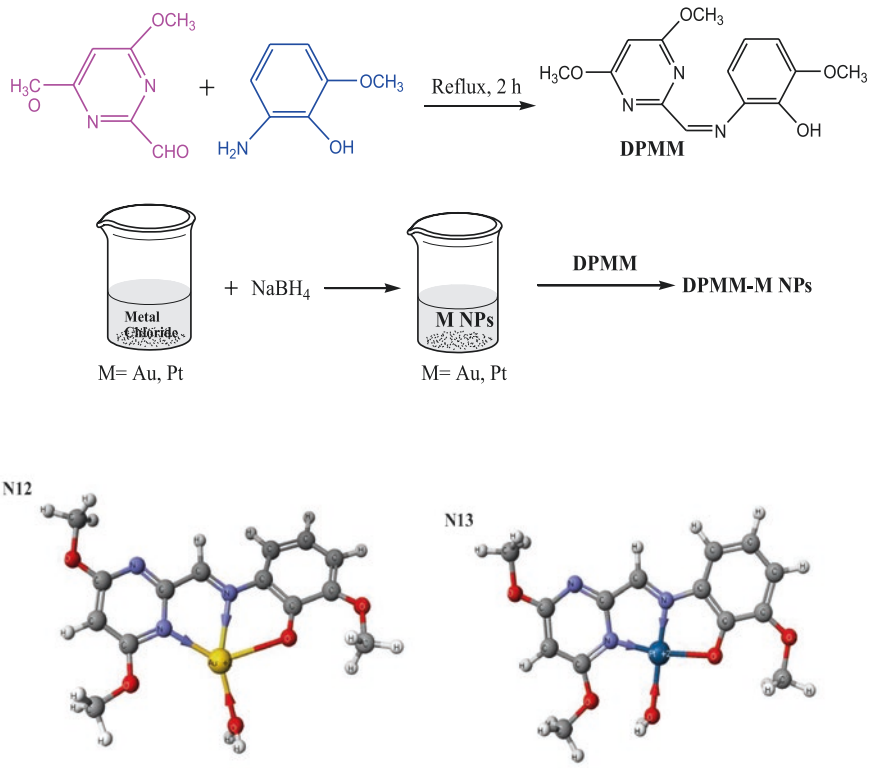



**Fig. 1** Suggested and optimized structures of Zn (II) (**N9**), Cd(II) (**N10**), and Hg(II) (**N11**) metal complexes [52]




**Scheme 8** Synthetic routes for the preparation of DPMM. Generation of DPMM capped Au (**N12**) and Pt NPs (**N13**) and optimized structures of metal complexes [53]

In 2017, Sankarganesh reported [They prepared pyrimidine-based Schiff base ligand 2-(4,6-dimethoxypyrimidine-2-yl)methyleneenamino)-6-methoxyphenol (DPMM) and gold (Au) (**N12**) and platinum (Pt) (**N13**) nanoparticles prepared by the modified Brust-Schiffrin method], given in Scheme 8. In addition to the anticancer study, antioxidant and antimicrobial studies were conducted. Furthermore, the MTT assay was used to test the anticancer activity of DPMM, DPMM-Au NPs, and DPMM-Pt NPs in vitro against cancer (MCF-7, HeLa, and HEp2) and normal (NHDF) cell lines. In comparison with the conventional medication cisplatin, these findings show that DPMM-Au NPs and DPMM-Pt NPs have high cytotoxic action against cancer cell lines and have the least damaging effect on normal cell lines [53].

In 2022, El-ghamry synthesized the tridentate hydrazone ligand and its Co (II), Ni(II), and Cu(II) complexes (Figs. 2 and 3). Moreover, it has been reported to synthesize and characterize hydrazone ligand and 8-hydroxyquinoline (8-HQ) and mixed ligand Co(II), Ni(II), and Cu(II) complexes. Besides these, the nano Cu (II) complex was also prepared. The antitumor activity investigation demonstrated that the ligand HL inhibited HepG-2 cell growth, with activity increasing with complexation, the Cu (II) complex 1 displayed the maximum cytotoxic activity [54].

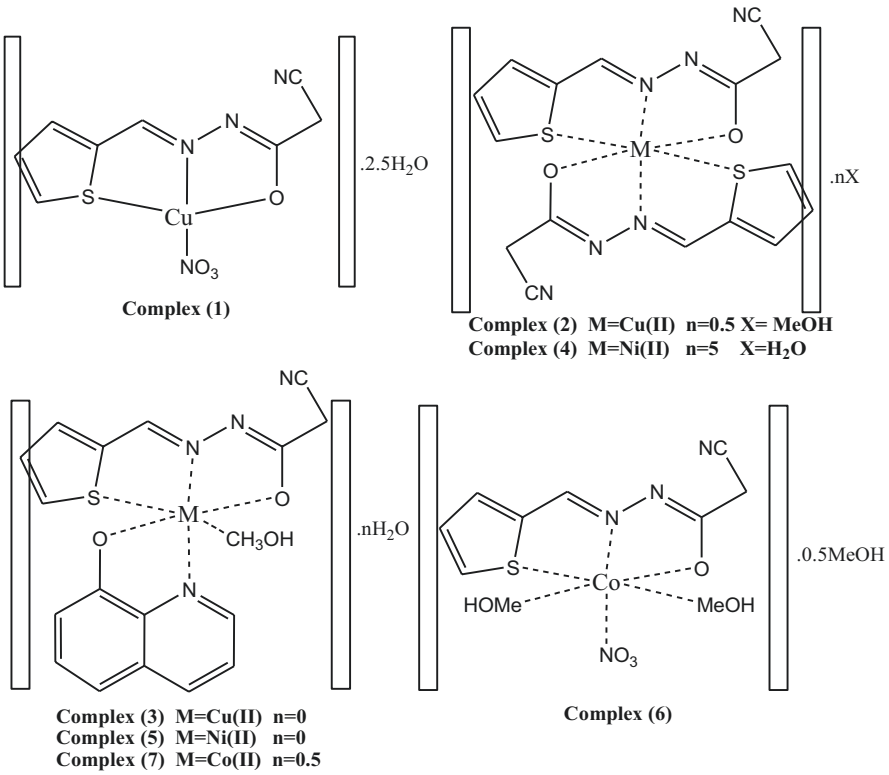



**Fig. 2** Suggested structures of 1 (**N14**), 2 (**N15**), 3 (**N16**), 4 (**N17**), 5 (**N18**), 6 (**N19**), 7 (**N20**) metal complexes [54]

## *1.5 The Related Nanomaterials Under Perspective of In Silico Methods*

In recent times, nanomaterials have progressively found applications in different areas such as technology, industry, and medicine. Their small particle size and their chemical and physical features are useful for diverse biomedical activities. Due to their physical resemblance with proteins, nanomaterials can improve medical imaging, diagnostics, and therapy.

In recent years, the development of in silico techniques such as combinatorial chemistry and high-throughput screening, absorption, and dispersal remarkably enhanced the number of compounds for which early information on absorption, distribution, metabolism, and excretion (ADME) and toxicity (T) were required, which in turn drove development. The absorption, distribution, metabolism, excretion, and toxicity (ADMET) features of chemicals act as vital roles at each step of drug exploration and advancement. So, it is essential to find effective molecules with better ADMET features.

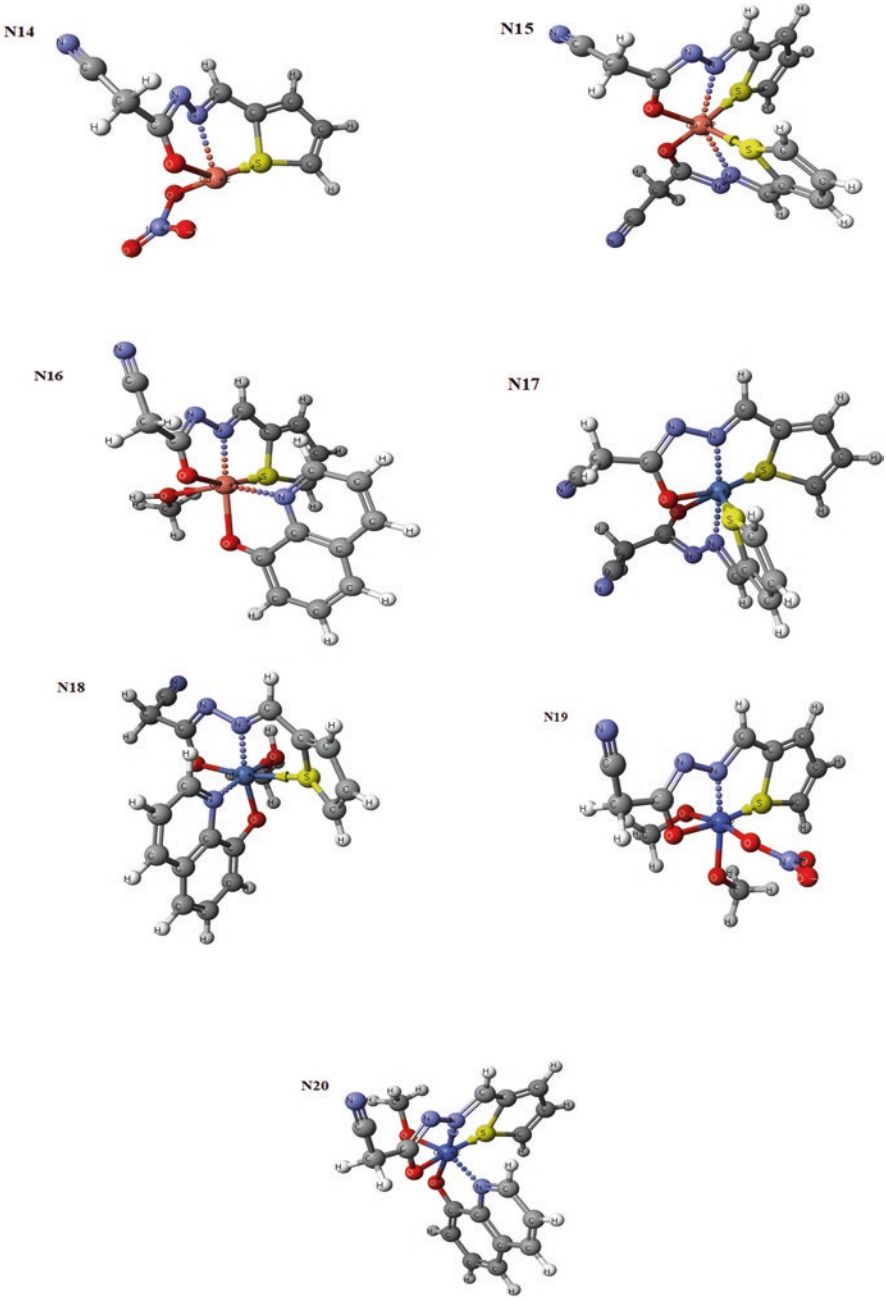



**Fig. 3** Suggested optimized structures of 1 (**N14**), 2 (**N15**), 3 (**N16**), 4 (**N17**), 5 (**N18**), 6 (**N19**), 7 (**N20**) metal complexes [54]

The structure of the selected inorganic nanomaterials (**N1–N20**) was drawn (Table 2) and optimized accurately in MO-G using PM6 parameters in a vacuum using SCIGRESS [55]. *Drug-like properties* including solubility, permeability, metabolic stability, and transporter impacts are of critical importance. These factors affect oral bioavailability, metabolism, clearance, toxicity, as well as in vitro pharmacology. The drug-likeness prediction is performed to define pharmacokinetic properties of the selected nanomaterials. It includes studies (Lipinski et al. [56] and Veber et al. [57]) performed using Discovery Studio (DS) 3.5 [58] for the nanomaterials. The *in silico absorption*, *distribution*, *metabolism*, *excretion*, *and toxicity* (ADMET) properties that are very significant in the medicine process for the selection of a probable agent were generated with the help of the sub-protocol of DS 3.5. Afterward, *molecular docking* was conducted using AutoDock 4.2 [59] program to learn more about the interaction mechanisms of the current nanomaterial-DNA. A 3D structure model Protein Data Bank (PDB) code, 1BNA of DNA as the target, was obtained from PDB [60]. The nucleotides in the crystal structure did not mutate. Crystal structure resolution was <2.0 Å. The conformational views occurred for each nanomaterial docking with DNA based on the Lamarckian genetic algorithm. The best modes for the nanomaterials (**N1–N20**) with the lowest binding free energy complex in the biomolecules as targets were investigated for docking results including the docking energy, interplay types, and RMSD values.

### 1.5.1 Computational Results

ADMET analysis is a significant technique to control whether in vivo agents can reach the acceptable ranges. These rules are molecular weight no more than 500, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, and LogP (the log value of octanol-water partition coefficient) no more than 5, according to the "Rule of Five" [56, 57]. The other second rule by Veber et al. suggests no more than 10 rotatable bonds, polar surface area no more than 140 $A^2$, or no more than 12 hydrogen bond donors and acceptors. These ranges are employed to filter drug-like compounds in DS 3.5 [58]. All the nanomaterials except **N5**, **N6**, and **N7** revealed zero violations of Lipinski and Veber rules as given in Table 3. In addition, aqueous solubility, human intestinal absorption (HIA), blood-brain barrier penetration (BBB), Cytochrome P450 (CYP450) 2D6 inhibition, hepatotoxicity, and plasma protein binding were used and analyzed as ADME descriptors for the nanomaterials, (**N1–N20** in Table 4).

The ADME results of nanomaterial compounds, which are thought to exhibit potential drug candidates, except for **N5**, **N14**, and **N19** compounds, are given in Table 4. If attention is paid, all of them show hepatotoxic properties. Toxicity estimation analysis was also performed to determine whether the respective nanomaterials were toxic. Expected results are listed in Table 5. Nearly all compounds were found to exhibit acceptable toxicity for drug development in the treatment of cancer diseases.

**Table 2** The simplified molecular-input line-entry system (SMILES) of the 20 nanomaterial compounds (**N1–N20**)

| Compound | SMILES |
|---|---|
| **N1** | CC(C)[N+]1=Cc2ccccc2O[Pd]13Oc4ccccc4C=[N+]3C(C)C |
| **N2** | C=CC[N+]1=Cc2ccccc2O[Ni]13Oc4ccccc4C=[N+]3CC=C |
| **N3** | COc1cccc2C=[N+]3c4ncccc4O[Ni]3(Oc12)([OH2])([OH2])[OH2] |
| **N4** | COc1cccc2C=[N+]3c4ncccc4O[Co]3(Oc12)([OH2])([OH2])[OH2] |
| **N5** | O.O.O.COc1cc(OC)nc(\N=C\c2cc(ccc2O[Cu])[N+](=O)[O−])n1 |
| **N6** | O.O.O.[Cd].COc1cccc(\C=N\c2ncccc2O)c1O |
| **N7** | O.O.O.[Fe].COc1cccc(\C=N\c2ncccc2O)c1O |
| **N8** | O.[Zn+2].COc1cccc(\C=N\c2ncccc2O)c1O |
| **N9** | [Cl−][Zn+2][Cl−].c1ccc(nc1)c2nc(nc(n2)c3ccccn3)c4ccccn4 |
| **N10** | Cl[Cd]Cl.c1ccc(nc1)c2nc(nc(n2)c3ccccn3)c4ccccn4 |
| **N11** | [I−][Hg+2][I−].c1ccc(nc1)c2nc(nc(n2)c3ccccn3)c4ccccn4 |
| **N12** | O.[Au].COc1cc(OC)nc(\C=N\c2cccc(OC)c2O)n1 |
| **N13** | O.[Pt].COc1cc(OC)nc(\C=N\c2cccc(OC)c2O)n1 |
| **N14** | [O−][N+](=O)O[Cu+2]12OC(=N[N+]1=CC3=CC=[CH2]S23)CC#N |
| **N15** | N#CCC1=N[N+]2=CC3=CC=CS3[Cu+2]245(OC(=N[N+]4=CC6=CC=CS56)CC#N)O1 |
| **N16** | CO[Cu+2]123(OC(=N[N+]1=CC4=CC=CS24)CC#N)Oc5cccc6ccc[n+]3c56 |
| **N17** | N#CCC1=N[N]2=CC3=CC=CS3[N+2]245(OC(=N[N]4=CC6=CC=CS56)CC#N)O1 |
| **N18** | CO[N+2]123(OC(=N[N]1=CC4=CC=CS24)CC#N)Oc5cccc6C=CC=[N]3c56 |
| **N19** | CO[Co+2]12(OC)(O[N+](=O)[O−])OC(=N[N+]1=CC3=CC=CS23)CC#N |
| **N20** | CO[Co+2]123(OC(=N[N+]1=CC4=CC=CS24)CC#N)Oc5cccc6ccc[n+]3c56 |

We executed molecular docking studies regardless of the results of drug-likeness and ADMET analyses in the previous parts. A total of 20 compounds were selected for the analysis on affinity, which is shown by the docking binding energy (a low docking binding energy indicates a high binding affinity) (Table 6). Three-dimensional (3D) representation of the binding pose, interactions, H bond donor and acceptor surface of the five compounds (**N3, N10, N11, N9, and N2**) with the highest binding energies in the **N1–N20** compounds towards DNA complex are presented in (Fig. 4).

The binding energies of 20 nanomaterials, which react with DNA targets in molecular docking calculations, are between −9.35 and −5.30 kcal/mol. Compound **N3** (Ni(II)L) is the structure that exhibits the best binding and interplay with DNA, with a binding energy value of −9.35 kcal/mol. When we examine the interaction types of compound 3, it makes hydrogen bonds with the B, DT20; A, DA6; A, DT7; and A, DT8 nucleotides of DNA; electrostatic interactions with A, DT8, and B, DC21; and also hydrophobic interaction with B: DT19 (Fig. 4). Then, **N10**, **N7**, **N11**, **N5**, **N9**, and **N2** are followed by their binding energy values in Table 5. The molecule with the lowest binding tendency with DNA is the nanomaterial structure formed by **N19** which is Co (II) metal, with an organic molecule.

**Table 3** Drug-likeness properties of the 20 nanomaterial compounds based on the Lipinski and Veber rules

| Name | MW (≤500 g/mol) | AlogP (≤5) | MPSA (≤140 $A^2$) | NRB(≤10) | HA_Lipinski (≤10) | HD_Lipinski (≤5) | HA_Veber (≤12) | HD_Veber (≤12) |
|---|---|---|---|---|---|---|---|---|
| **N1** | 432.853 | 4.707 | 33.26 | 2 | 4 | 2 | 2 | 2 |
| **N2** | 381.094 | 4.488 | 33.26 | 4 | 4 | 2 | 2 | 2 |
| **N3** | 355.977 | 1.836 | 116.68 | 1 | 8 | 7 | 7 | 4 |
| **N4** | 356.217 | 1.836 | 116.68 | 1 | 8 | 7 | 7 | 4 |
| **N5** | 420.842 | 2.368 | 206.15 | 6 | 12 | 6 | 11 | 3 |
| **N6** | 410.703 | 1.693 | 169.44 | 3 | 8 | 8 | 8 | 5 |
| **N7** | 354.137 | 1.693 | 169.44 | 3 | 8 | 8 | 8 | 5 |
| **N8** | 327.67 | 2.107 | 123.05 | 3 | 6 | 4 | 6 | 3 |
| **N9** | 450.659 | −2.916 | 163.07 | 3 | 6 | 0 | 6 | 0 |
| **N10** | 495.645 | 3.61 | 77.34 | 3 | 6 | 0 | 6 | 0 |
| **N11** | 768.743 | −3.792 | 212.67 | 3 | 6 | 0 | 6 | 0 |
| **N12** | 504.268 | 2.329 | 117.56 | 5 | 8 | 3 | 8 | 2 |
| **N13** | 502.38 | 2.329 | 117.56 | 5 | 8 | 3 | 8 | 2 |
| **N14** | 322.808 | 1.839 | 115.51 | 3 | 8 | 3 | 6 | 4 |
| **N15** | 452.013 | 0.89 | 113.96 | 2 | 8 | 2 | 6 | 4 |
| **N16** | 433.972 | 2.281 | 82.84 | 2 | 7 | 2 | 5 | 3 |
| **N17** | 403.482 | 0.478 | 113.96 | 2 | 9 | 3 | 6 | 5 |
| **N18** | 385.44 | 1.87 | 82.84 | 2 | 8 | 3 | 5 | 4 |
| **N19** | 379.255 | 1.507 | 129.7 | 5 | 10 | 3 | 8 | 4 |
| **N20** | 429.359 | 2.281 | 83.03 | 2 | 7 | 2 | 5 | 3 |

*MW* molecular weight, *ALogP* octanol/water partition coefficient, a measure for lipophilicity, *MPSA* molecular polar surface area, *nRB* number of rotatable bonds, *Num_H_Acceptors_Lipinski* number of hydrogen bond acceptors, *Num_H_Donors_Lipinski* number of hydrogen bond donors, *Num_H_Acceptors* number of hydrogen bond acceptors based on Veber, *Num_H_Donors* number of hydrogen bond donors based on Veber

Overall, as a result of all computational applications on the 20 compounds discussed, **N3**, **N10**, **N11**, **N9**, and **N2** nanomaterial structures should be considered as potential agents in cancer treatment and diagnostic studies.

## 2 Conclusion

Cancer is one of the diseases which is a major problem for all countries of the world today. The prediction of the International Agency for Research on Cancer (IARC) affiliated to the World Health Organization (WHO) for 2030 is that cancer will rank first among the causes of death. Various disadvantages of traditional methods used in cancer diagnosis and treatment reduce the effectiveness of these methods. However, although there have been many attempts to combine new technologies

**Table 4** ADMET analysis of the 20 nanomaterial compounds

| Comp. | PSA_2D (<140 Å$^2$) | AlogP98 (<5) | HIA | Solubility | BBB | CYP2D6 | Hepa-totoxic | PPB |
|---|---|---|---|---|---|---|---|---|
| **N1** | 17.86 | 4.645 | 0 | 1 | 0 | I | T | True |
| **N2** | 17.86 | 4.426 | 0 | 2 | 0 | I | T | True |
| **N3** | 38.051 | 1.804 | 0 | 2 | 2 | NI | T | False |
| **N4** | 38.051 | 1.804 | 0 | 2 | 2 | NI | T | False |
| **N5** | 103.458 | 2.989 | 0 | 3 | 4 (undefined) | NI | T | False |
| **N6** | 73.145 | 2.314 | 0 | 3 | 3 | NI | T | False |
| **N7** | 73.145 | 2.314 | 0 | 3 | 3 | NI | T | False |
| **N8** | 73.145 | 2.314 | 0 | 3 | 3 | NI | T | True |
| **N9** | 67.566 | 2.639 | 0 | 2 | 2 | NI | T | False |
| **N10** | 67.566 | 2.639 | 0 | 2 | 2 | NI | T | True |
| **N11** | 67.566 | 2.639 | 0 | 2 | 2 | NI | T | False |
| **N12** | 81.451 | 2.536 | 0 | 3 | 3 | NI | T | True |
| **N13** | 81.451 | 2.536 | 0 | 3 | 3 | NI | T | True |
| **N14** | 93.438 | −1.458 | 1 | 4 | 4 (undefined) | NI | T | False |
| **N15** | 86.376 | 1.396 | 0 | 3 | 3 | NI | T | False |
| **N16** | 66.397 | 2.543 | 0 | 2 | 2 | NI | T | True |
| **N17** | 86.376 | −0.152 | 0 | 3 | 3 | NI | T | False |
| **N18** | 66.397 | 0.996 | 0 | 2 | 3 | NI | T | True |
| **N19** | 111.299 | −2.159 | 3 | 4 | 4 (undefined) | NI | T | False |
| **N20** | 66.397 | 2.543 | 0 | 2 | 2 | NI | T | True |

*PSA_2D* 2D polar surface area, *AlogP98* the logarithm of the partition coefficient between n-octanol and water, *HIA* human intestinal absorption, *BBB* blood-brain barrier, *CYP2D6* cytochrome P450 2D6 binding, *NI* non-inhibitor; for CYP2D6, non-inhibitor, *NT* nontoxic for hepatotoxic, *PPB* plasma protein binding; more than 90% for PPB value is true, chemicals strongly bound. Less than 90% for PPB value is false, chemicals weakly bound

with traditional approaches to fight cancer, nanotechnology has shown wide applications in both treatment and diagnosis [61].

Nanotechnology has also been widely used in the remedy of several carcinomas lately. Because nanomaterials provide the opportunity to diagnose tumors at an early stage, in other words, nanostructures can enter a single tumor cell and increase the limits of imaging techniques. Chemotherapy drugs used in cancer treatment directly target tumors and have limited effects on healthy tissues, and the side effects of chemotherapy drugs are eliminated. Thus, the necessary doses are delivered to the cancerous tissues, shortening the recovery period and increasing the success of the treatment. In summary, nanomaterials have contributed to the improvement of cancer diagnosis and therapy with their improved pharmacokinetics and pharmacodynamics features.

Many nanomaterials, especially inorganic and organic nanomaterials, can be used as a potential nanocarrier for the early detection of cancer and loading of chemotherapeutic drugs. Particularly relevant nanomaterials, due to their small size and surface modifications, can remain in the circulation for a long time and be effective

**Table 5** Toxicity prediction of the 20 nanomaterial compounds

| Comp. | Mouse female NTP prediction | Mouse male NTP prediction | Rat female NTP prediction | Rat male NTP prediction | Ames prediction | Skin irritancy | Ocular irritancy | Aerobic biodegradability prediction |
|---|---|---|---|---|---|---|---|---|
| **N1** | Carcinogen | Carcinogen | Carcinogen | Carcinogen | Non-mutagen | None | None | Non-degradable |
| **N2** | Carcinogen | Non-carcinogen | Non-carcinogen | Carcinogen | Non-mutagen | None | None | Non-degradable |
| **N3** | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-mutagen | None | Mild | Non-degradable |
| **N4** | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-mutagen | None | Mild | Non-degradable |
| **N5** | Non-carcinogen | Non-carcinogen | Carcinogen | Carcinogen | Mutagen | Mild | Mild | Non-degradable |
| **N6** | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-carcinogen | Mutagen | None | Moderate | Non-degradable |
| **N7** | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-carcinogen | Mutagen | None | Moderate | Non-degradable |
| **N8** | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-carcinogen | Mutagen | None | Moderate | Non-degradable |
| **N9** | Non-carcinogen | Carcinogen | Non-carcinogen | Non-carcinogen | Non-mutagen | None | Mild | Non-degradable |
| **N10** | Non-carcinogen | Carcinogen | Non-carcinogen | Non-carcinogen | Non-mutagen | None | Severe | Non-degradable |
| **N11** | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-carcinogen | Mutagen | None | Mild | Non-degradable |
| **N12** | Non-carcinogen | Non-carcinogen | Carcinogen | Carcinogen | Mutagen | None | Moderate | Non-degradable |
| **N13** | Non-carcinogen | Non-carcinogen | Carcinogen | Carcinogen | Mutagen | None | Moderate | Non-degradable |
| **N14** | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-mutagen | Mild | Moderate | Non-degradable |
| **N15** | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-mutagen | Mild | Moderate | Non-degradable |
| **N16** | Carcinogen | Carcinogen | Non-carcinogen | Carcinogen | Non-mutagen | Mild | None | Non-degradable |
| **N17** | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-mutagen | Mild | Moderate | Non-degradable |
| **N18** | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-mutagen | Mild | None | Non-degradable |
| **N19** | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-carcinogen | Non-mutagen | Mild | Moderate | Non-degradable |
| **N20** | Carcinogen | Carcinogen | Non-carcinogen | Carcinogen | Non-mutagen | Mild | None | Non-degradable |

*NTP* National Toxicology Program, *comp* compound

**Table 6** Binding energy values of the compounds **N1–N20** against DNA

| Compound | Free energy of binding (kcal/mol) |
|---|---|
| **N1** | −7.99 |
| **N2** | *−8.48* |
| **N3** | *−9.35* |
| **N4** | −7.91 |
| **N5** | −8.74 |
| **N6** | −7.12 |
| **N7** | −9.07 |
| **N8** | −8.12 |
| **N9** | *−8.55* |
| **N10** | *−9.22* |
| **N11** | *−8.94* |
| **N12** | −6.51 |
| **N13** | −6.50 |
| **N14** | −7.33 |
| **N15** | −7.05 |
| **N16** | −8.34 |
| **N17** | −7.59 |
| **N18** | −7.19 |
| **N19** | −5.30 |
| **N20** | −6.80 |

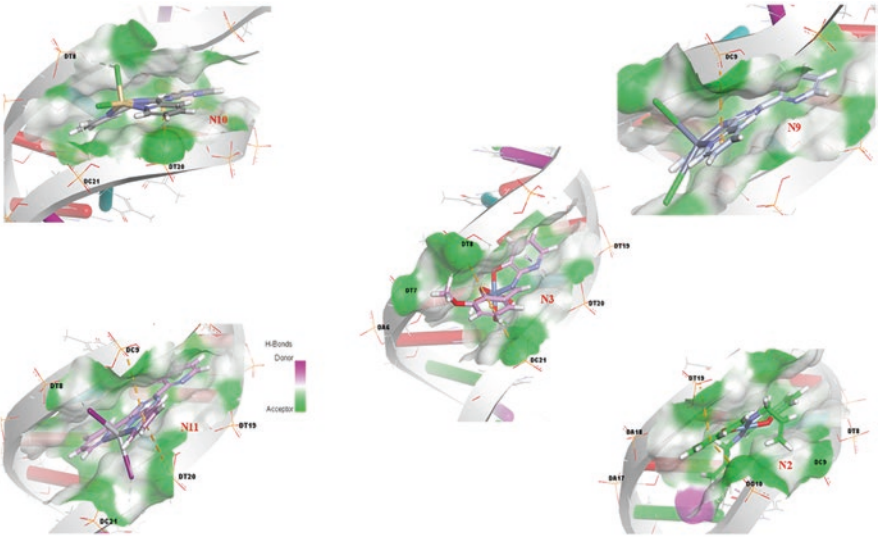



**Fig. 4** 3 D orientations of the compounds **N3, N10, N11, N9 and N2** against DNA based on the calculated binding energy values of the compounds **N1–N20**

by targeting primarily tumor sites. Among metallic nanomaterials, especially Ni, Cd, Fe, Hg, Cu, Zn, Pd, Co, Au, and Pt, nanomaterials are widely used in drug delivery systems. Despite their extremely advantageous properties, nanomaterials to be used on living organisms must have various properties such as being physiologically compatible (biocompatible), degradable in a physiological environment, and the ability to be excreted through the kidneys or bile. However, the studies reveal that some nanomaterials cause irreversible damage to cells in various ways depending on their composition and size [62–65].

Given the limitations associated with nanotechnology, further studies are needed to develop medicine releases, maximizing their effectiveness while keeping damages to a minimum. By improving the interplay between the physicochemical features of the nanomaterials used, safer and more effective derivatives can be provided for diagnosis and therapy in cancer management. In many studies, the toxicity of nanomaterials is attributed to their physicochemical features, namely, their small size and surface area. Therefore, unlike traditional toxicology, the safety/toxicity evaluation of a particular nanomaterial is based not only based on its chemical content but also on its size, surface structure, form, etc. [65–67]. For these reasons, nanomaterials in this chapter were investigated using in silico methods, which are more economical in terms of labor, time, and cost, to investigate the biocompatibility and toxic effects of nanomaterials very carefully.

As a result of in silico methods including drug-likeness, ADME, toxicological analyzes, and molecular docking processes between twenty nanomaterials (**N1–N20**) with DNA, it has been suggested that **N3**, **N10**, **N11**, **N9**, and **N2** compounds may be potential candidates for cancer diagnosis and therapy. This study will also form the basis of studies on new inorganic and organic nanomaterials.

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