

Review

Schiff Bases: Interesting Scaffolds with Promising Antitumoral Properties

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Abstract: Schiff bases, named after Hugo Schiff, are highly reactive organic compounds broadly used as pigments and dyes, catalysts, intermediates in organic synthesis, and polymer stabilizers. Lots of Schiff bases are described in the literature for various biological activities, including antimalarial, antibacterial, antifungal, anti-inflammatory, and antiviral. Schiff bases are also known for their ability to form complexes with several metals. Very often, complexes of Schiff bases with metals and Schiff bases alone have demonstrated interesting antitumor activity. Given the innumerable vastness of data regarding antitumor activity of all these compounds, we focused our attention on mono- and bis-Schiff bases alone as antitumor agents. We will highlight the most significant examples of compounds belonging to this class reported in the literature.

Keywords: Schiff bases; antitumor agents; apoptosis; antiproliferative activity; imines



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1. Introduction

Since their discovery by the German chemist Hugo Schiff [1], Schiff bases (imines), scaffolds with high chemical reactivity, and their metal complexes have been very well known for catalysis in various synthetic processes and for their biological properties. In therapy, Schiff bases and their metal complexes have been reported to manifest a wide range of biological activities [2,3] such as antimicrobial [4], ureases inhibitory [5], anti-inflammatory [6,7], anti-ulcerogenic [8], antioxidant [9–11], pesticidal, cytotoxic, and anticancer [12] including DNA damage [13–15]. Schiff bases have been also successfully used in scientific studies [16] as highly efficient and selective sensing materials for optical, electrochemical [17,18], and membrane sensors [19]. Zinc-Schiff bases have been proposed as carrier vehicles for the delivery of zinc to prostate cells. Indeed, the use of the membrane-penetrating peptide Novicidin connected to zinc-Schiff base has been studied as a therapeutic approach for prostate cancer [20]. Schiff base ligands, as some other organic small molecules [21], have received great attention from researchers thanks to their easy preparation and ability to form complexes with almost all metals, due to the electron-donating nitrogen in their base structure [22–24]. Several metal complexes, in which the metal is coordinated to various ligands, are able not only to stabilize the metal but also to modify its chemical and pharmaceutical properties and are receiving attention in medicinal chemistry [25–30]. The general structure of a Schiff base is shown in Figure 1, R^1 , R^2 and R^3 being an alkyl or aryl moiety.

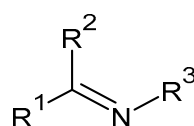


Figure 1. General structure of a Schiff base.

Schiff bases are particularly interesting in the field of antitumor agents [31–34] as many other small organic molecules (for instance, diarylureas [35], indoles [36,37], carbazoles [38], phthalimides [39], and so on [40,41]). The most salient and recent data on Schiff bases will be, herein, reviewed.

For instance, in a recent study, the introduction of Schiff bases in the *N*-phenylcarbazole/triphenylamine modified half-sandwiched iridium(III) compounds determined an enhancement of antitumor activity of about 13 times that of the clinical cisplatin [42]. This review focused on studies of the last decades on mono- and bis-Schiff bases as antiproliferative agents, paying attention particularly on Schiff bases showing high activity (concentration which kills or inhibits cell viability by 50% (IC₅₀) in the range of micromolar to nanomolar).

2. Schiff Bases as Antiproliferative Agents

2.1. Mono-Schiff Bases

Vicini et al. (2003) [43] studied a series of Schiff bases and tested their antiproliferative activity against a panel of human cell lines derived from hematological and solid tumors. The most interesting compounds were 1–3 (Table 1). All of them inhibited the growth of leukemia cell lines, with IC₅₀ values ranging between 1.5 and 7 μM against human CD4⁺ lymphocytes (MT-4), human CD4⁺ acute T-lymphoblastic leukemia (CCRF-CEM), human splenic B-lymphoblastoid cells (WIL-2NS), and human acute B-lymphoblastic leukemia (CCRF-SB). The 2-Amino-6-mercaptopurine was used as reference drug (IC₅₀ between 0.1 and 0.5 μM). Particularly, compound 3 was also active against solid tumor-derived cell lines' skin melanoma and breast adenocarcinoma cells (IC₅₀ = 6 and 10 nM) against human skin melanoma SK-MEL-28 and human breast adenocarcinoma MCF-7 cell lines, respectively. The values for 2-amino-6-mercaptopurine were 5 and 4 μM, respectively. Zhou et al. (2007) [44] studied several imines bearing thiazole and triazole moieties and evaluated their antiproliferative activities against leukemia, stomach, and larynx cancer cell lines. The 2,4-dinitro substituted Schiff base 4 displayed high activity against HL-60, BGC-823 and Hep-2 cell lines, showing percentage inhibition of 91.97, 98.49, and 91.16%, respectively. Abdel-Hafez et al. (2009) [45] studied several Schiff bases as derivatives of xanthotoxin and evaluated their antitumor activities against cervical carcinoma (HeLa) and breast carcinoma (MCF 7) cell lines. The Schiff base 5 was inactive against MCF-7 cell line but was the most interesting against HeLa, showing an IC₅₀ value of 7.2 μM and a percent viability of 70% (xanthotoxin, 7.6 μM and 62%, respectively). Kraicheva et al. (2009) [46] studied three Schiff bases and evaluated their antiproliferative activity, using the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltriazolium bromide (MTT) assay, against four human leukemic cell lines, viz., LAMA-84 (peripheral chronic myeloid leukemia cells), K-562 (non-adherent chronic myelogenous leukemia cells of the erythroleukemia type), HL-60 (acute promyelocytic leukemia cells) and its multi-drug-resistant sub-line HL-60/Dox (multi-drug resistant acute myeloblastic leukemia cell line), characterized by the overexpression of MRP-1 protein (ABC-C1). Compound 6 showed antiproliferative activity (IC₅₀ = 39.9 μM, 29.9 μM, and 68.6 μM against LAMA-84, K-562, and HL-60/Dox, respectively), while compound 7 was less active (IC₅₀ = 251.9 μM, 212.9 μM, and 226.1 μM against LAMA-84, K-562, and HL-60/Dox, respectively). Both the investigated compounds were identified as capable of evoking the distinctly marked lower cytotoxic effects (with the IC₅₀ values over 400 μM) against the sensitive leukemic cell line HL-60 in a preliminary antitumor screening.

Nawaz et al. (2009) [47] studied Schiff bases with ferrocene addition and evaluated their antitumor, antioxidant, and DNA-protecting activities. Antitumor activity was eval-

uated by Potato disc tumor induction assay using *Agrobacterium tumefaciens* (At-10) to induce tumors on potato discs, that is, a prescreen assay and its results were in accordance with other commonly used in vitro antitumor assays. All the tested compounds inhibited tumor production for treatment of 1000, 100, and 10 $\mu\text{g}/\text{mL}$ concentration at $p < 0.05$ (vincristine, used as positive control, showed 100% tumor inhibition at all concentrations tested). The inhibition was observed in a dose-dependent manner with the highest inhibition at 1000 $\mu\text{g}/\text{mL}$ concentration. Moreover, the highest tumor growth inhibition of 71% was observed with ferrocene containing Schiff base **8**, followed by **9** with 58% inhibition at 1000 $\mu\text{g}/\text{mL}$. IC_{50} values were 20 and 563 $\mu\text{g}/\text{mL}$ versus 0.003 $\mu\text{g}/\text{mL}$ of vincristine. Zaheer et al. (2010) [48] studied several Schiff bases and tested their cytotoxic activity by the brine shrimp lethality assay. Medium lethal concentration (LD_{50}) values for compounds **10** and **11** were 292.95 and 18.22 ppm, respectively.

Cheng et al. (2010) [49] studied eight Schiff bases and evaluated their antiproliferative effects on human hepatoma HepG2 cells by sulforhodamine B assay. Compounds **12** and **13** were comparable to positive control, etoposide, showing IC_{50} values of 5.6 and 6.8 μM , respectively, versus 4.1 μM of etoposide. Jesmin et al. (2010) [50] studied two Schiff bases, PHP [*N*-(1-phenyl-2-hydroxy-2-phenylethylidene)-2-hydroxyphenylimine, **14**] and HHP [*N*-(2-hydroxybenzylidene)-2-hydroxyphenylimine, **15**] as anticancer agents acting on Ehrlich ascites carcinoma (EAC) cells in Swiss albino mice. All compounds were more active than standard anticancer drug, bleomycin, in improving the life span, lowering tumor weight, and inhibiting the tumor cell growth of EAC cell-bearing mice. The toxicity of the tested compounds was evaluated by measuring LD_{50} values that were of 16 and 15.5 mg/kg for **14** and **15**, respectively. The maximum percentage cell growth inhibition of 93% was observed with **15** with dose loading of 2 mg/kg. Etaiw et al. (2011) [51] studied a Schiff base derived from 2-aminobenzothiazole and 2-thiophenecarboxaldehyde (**16**) for its antiproliferative activity against five human cancer cell lines (cervical carcinoma, HeLa; breast carcinoma, MCF-7; liver carcinoma, HepG2; colon carcinoma, HCT-116; and larynx carcinoma, HEP2). Compound **16** showed activity against HeLa cancer cells ($\text{IC}_{50} = 0.186 \mu\text{M}$). Moreover, its complexes with Cu(II), Fe(III), and Ni(II) showed a higher activity. Hranjec et al. (2011) [52] prepared series of 14 imines and studied the suppression of proliferation of different human cancer cell lines (HeLa (cervical carcinoma), SW620 (colorectal adenocarcinoma, metastatic), MiaPaCa-2 (pancreatic carcinoma), MCF-7 (breast epithelial adenocarcinoma, metastatic)) and their cytotoxic activity on normal human fibroblasts (WI38 normal diploid human fibroblasts) using the MTT assay. Compounds **17** and **18** exerted a strong non-specific antiproliferative effect on all cell lines tested and a concentration-dependent effect on HeLa and MCF-7 cell lines at micromolar concentrations ($\text{IC}_{50} = 4.73$ and 3.24 μM on HeLa and 9.23 and 15.27 μM on MCF-7). However, they were also highly cytotoxic on human fibroblasts. Shaker et al. (2011) [53] synthesized surfactants containing Schiff bases with hydrocarbon chains of different lengths (from C12 to C18). In vitro anticancer cytotoxic activity of these compounds was investigated using EAC as a model system of mice cell tumor at different concentrations (25, 50, and 100%) against liver carcinoma (HepG2), breast carcinoma (MCF-7), and colon carcinoma (HCT-116) cell lines. Compound **19**, bearing a C14 hydrocarbon chain, caused the death of 95% of EAC cell at the highest concentration. The IC_{50} values for compound **19** at different concentrations ranged from 1 to 10 mg/mL. It showed high activity in in vitro system on the tumor cell lines investigated and the highest cytotoxic effect on HepG2, HCT-116, and MCF-7, respectively, and SBC12 surfactant-affected tumor tissue at very low concentrations at values lower than their critical micelle concentration (cmc) values.

Kraicheva et al. (2012) [54] synthesized two anthracene-containing Schiff bases, 9-anthrylidene-*p*-toluidine (**20**) and 9-anthrylidene-furfurylamine (**21**), and tested their anticancer activities in vitro on a panel of human epithelial cancer cell lines (cell lines from ductal carcinoma of the breast with low and high metastatic potential, MCF-7 and MDA-MB-231, respectively; colostrum-derived myoepithelial cells, expressing polyoma virus large T-antigen, HBL-100 line; bladder carcinoma, 647-V; hepatocellular carcinoma, HepG2;

colon carcinoma, HT-29; cervical carcinoma, HeLa). Compounds **20** and **21** showed high cytotoxic activity toward colon carcinoma HT-29 cell line ($IC_{50} = 0.08$ and 0.20 mg/mL versus 0.58 mg/mL of doxorubicin). The authors also performed their safety testing, both *in vitro* (Neutral Red Uptake Assay, 3T3 NRU test) and *in vivo* on ICR mice for genotoxicity and antiproliferative activity. Both compounds were shown not to induce clearly expressed dose-effect clastogenic activities, in contrast to the alkylating agent Mitomycin C. Bae et al. (2012) [55] synthesized new Schiff bases and evaluated their anti-melanogenesis activity, in murine B16F10 melanoma cells, through the inhibition of tyrosinase. Compound **12** exhibited the most potent and non-competitive inhibition on mushroom tyrosinase, even better than the kojic acid used as positive reference (IC_{50} value of 17.22 μ M versus 51.11 μ M of the kojic acid). This compound decreased the melanin production stimulated by the alpha-melanocyte-stimulating hormone and inhibited murine tyrosinase activity in a dose-dependent manner. Sondhi et al. (2012) [56] synthesized several mono-Schiff bases and bis-Schiff bases and studied their anticancer activities against five human cancer cell lines (lung, NCI H-522; ovary, PA1; breast T47D; colon, HCT-15; liver, HepG2) by MTT assay. The percentage growth (PG) inhibition of cancer cell lines was determined at a concentration of 1×10^{-5} M. The most active mono-Schiff base against lung cancer cells (49% versus 59% of actinomycin-D) was compound **22**. The other active bis-Schiff bases are reported in the next paragraph. Klimczak et al. (2013) [57] studied several small molecules bearing an imine moiety and studied their activity against four esophageal cancer cell lines. Compound **23** was the most active of the series, showing IC_{50} values of 50.12 , 158.49 , and 111.2 μ M against KYSE 150, KYSE 30 and KYSE 270.

Hafez et al. (2013) [58] studied several Schiff bases as antiproliferative agents against various cell lines by using the MTT assay. The most interesting compounds, more active than standard drugs, were **24–26**. In particular, **24** was active on ovarian carcinoma (SK OV-3) cell line ($IC_{50} = 0.44$ μ M versus 4.16 μ M of doxorubicin), whereas compound **25** showed good activity on leukemia (U937) ($IC_{50} = 0.09$ nM versus 4.45 of doxorubicin), neuroblastoma (GOTO and NB-1) ($IC_{50} = 0.45$ nM and 0.64 nM, respectively, versus $IC_{50} = 4.73$ nM and $IC_{50} = 5.15$ nM, respectively, of doxorubicin), and fibrosarcoma (HT1080) cell lines ($IC_{50} = 0.54$ nM versus 1.16 nM of tamoxifen). Finally, compound **26** was active on cervical carcinoma (KB) ($IC_{50} = 0.54$ μ M versus 4.46 μ M of fluorouracil), CNS (SF-268) ($IC_{50} = 0.30$ nM versus 7.68 nM of cytarabine), leukemia (K-562) ($IC_{50} = 0.43$ nM versus 6.66 of doxorubicin), liver (HepG2) ($IC_{50} = 0.09$ nM versus 1.31 nM of tamoxifen), and non-small cell lung (NCI H460) cancer cell lines ($IC_{50} = 6.60$ nM versus 2.13 nM of gencitabine hydrochloride). Hassan et al. (2015) [59] synthesized several imines and evaluated their cytotoxicity against four human cancer cell lines (colon HCT-116, lung A549, breast MCF-7, and liver HepG2) according to Sulforhodamine-B stain (SRB) assay. Compound **27** was the only compound to show slight activity against liver HepG2 ($IC_{50} = 6.20$ μ g/mL) and breast MCF-7 ($IC_{50} = 7$ μ g/mL) cells in comparison with the standard drug, doxorubicin ($IC_{50} = 4.20$ and 4.70 μ g/mL, respectively).

Zhao et al. (2013) [60] studied a series of Schiff bases and evaluated the *in vitro* antiproliferative activities against human breast cancer cell MCF-7 and mouse lymphocyte leukemia cell L1210 by the WST-8 ([2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfohenyl)-2H-tetrazolium monosodium salt]) assay as a substitute for the most classic MTT assay. The lead compound 2-phenyl-4-carboxyl-1,3-selenazole (PCS) was taken as a comparison. Compounds **28–30** were the most potent compounds against MCF-7 ($IC_{50} = 4.02$, 7.55 and 8.51 μ M, respectively, versus 16.56 μ M of PCS). Compound **31** was the most active against L1210 ($IC_{50} = 38.73$ μ M versus 60.11 μ M of PCS). Noureen et al. (2013) [61] reported a study on Schiff bases and evaluation of their antioxidant, antitumor, and anti-inflammatory potentials. The antitumor activity was assessed by the potato disc anti-tumor assay. Compounds **32** and **33** were the most active, showing IC_{50} values of 0.15 and 8.03 μ g/mL, respectively, versus 0.003 μ g/mL of vincristine, used as reference drug.

Zhang et al. (2014) [62] synthesized a series of Schiff bases and evaluated the *in vitro* antitumor activity against three human tumor cell lines (human liver SMMC-7721, hu-

man breast MCF-7, and human lung A549) using the WST-8 assay and 5-Fluorouracil (5-FU) as a positive control. Compound **34** was the most active against SMMC-7721 cells ($IC_{50} = 2.84 \mu\text{M}$ versus 5-FU, $IC_{50} = 5.62 \mu\text{M}$), whereas compounds **35** and **36** showed significant antiproliferative activity against MCF-7 cells ($IC_{50} = 4.56$ and $4.25 \mu\text{M}$, respectively, versus $14.26 \mu\text{M}$ of 5-FU). Finally, the most interesting compounds against A549 cells were **37** and **36** ($IC_{50} = 4.11$ and $4.13 \mu\text{M}$, respectively, versus $8.13 \mu\text{M}$ of 5-FU). Gupta et al. (2015) [63] synthesized 13 Schiff bases and studied their potential as Hsp 90ATPase inhibitors by malachite green assay and antiproliferative activity against PC3 prostate cancer cell lines by MTT assay. Compound **38** showed a high effect toward PC3 cells with an IC_{50} of $4.83 \mu\text{M}$ (versus $2.45 \mu\text{M}$ of geldanamycin), followed by compounds **39** and **40** ($IC_{50} = 7.43 \mu\text{M}$ and $7.15 \mu\text{M}$, respectively), which were the other promising anticancer molecules among the newly synthesized compounds. In malachite green assay for Hsp90 ATPase suppression, none of the molecules demonstrated IC_{50} values in nanomolar range. Only compounds **41** and **42** showed the maximum inhibitory potential, with an IC_{50} value of $0.02 \mu\text{M}$. In conclusion, the authors identified the compound **38**, showing sub micro-molar target affinity and good cellular potency, as the lead molecule for pre-clinical evaluation in animals and development of Hsp90 inhibitors as anticancer agents. Abd-Elzaher et al. (2016) [64] synthesized and studied a Schiff base ligand (**43**) and its complexes with metal ions. Compound **43** was tested for its anticancer activity against different human tumor cell lines (liver HepG2, breast MCF-7, and colorectal HCT116) and doxorubicin was used as a reference drug. It showed $IC_{50} = 9.22$, 10.00 , and $9.50 \mu\text{M}$ against the three cell lines, respectively (IC_{50} values for doxorubicin were 4.20 , 4.40 , and $5.25 \mu\text{M}$, respectively).

Sabbah et al. (2018) [65] described the design, synthesis, and biological evaluation of new phenylimino-1,2-diphenylethanol derivatives in human colon carcinoma (HCT-116), breast adenocarcinoma (MCF-7), and breast carcinoma (T47D) cell lines. Among the tested compounds, the authors evidenced a selectivity toward the adopted cells lines, indicating that the highest inhibitory activity toward the MCF-7 and T47D cells was obtained under the imine **44** treatment (IC_{50} values of 0.024 and 0.034 M , respectively). Moreover, they suggested that this different selectivity could depend on the difference forms of the phosphatidylinositol 3-kinases (PI3Ks) present in the adopted cell models. This hypothesis was proven by the means of *in silico* and *in vitro* studies, indicating that the phosphoinositide 3-kinase α (PI3K α) is one of the targets of the compound **44**, which influences the fundamental PI3K/Akt signaling pathway [66] leading, ultimately, to cancer cell apoptosis. At the same time, compound **44** reduces the expression of the Vascular Endothelial Growth factor (VEGF) in MCF-7 cells, suggesting a role in inhibiting the angiogenesis process. However, no evidence about the effects on normal cell lines has been reported. Hassan et al. (2018) [67] described a series of Schiff bases and evaluated their antiproliferative activities against HepG2 (liver) and MCF-7 (breast) cell lines using the MTT assay. The majority of prepared Schiff bases displayed better antitumor activity than doxorubicin. Compounds **45** and **46** were the most interesting of the series. Compound **45** was the most active against HepG2 cell line compared to doxorubicin ($IC_{50} = 66.3 \mu\text{M}$ versus $80.9 \mu\text{M}$), while compound **46** showed high activity against MCF-7 ($IC_{50} = 60.8 \mu\text{M}$ versus $65.6 \mu\text{M}$ of doxorubicin). They were also demonstrated to induce apoptosis in HepG2 and MCF-7, increasing the caspase-3 levels. Hassanin et al. (2018) [68] reported a series of Schiff bases bearing a pyranoquinolinone moiety. They were evaluated for topoisomerase II β (TOP2B) inhibitory activity [69,70] and cytotoxicity against breast cancer cell line (MCF-7). The compounds **47–49** displayed a significant TOP2B cytotoxicity compared to the reference doxorubicin ($IC_{50} = 0.042$, 0.83 , and $0.6 \mu\text{M}$ versus $IC_{50} = 1.17 \mu\text{M}$ of doxorubicin).

Several Schiff bases derived from 2-aminobenzothiazole were reported by Saipriya et al. (2018) [71], who performed *in vitro* MTT assay on HeLa cell lines to validate the cytotoxic activity against cervical cancer cells. Compound **50** showed high activity with an IC_{50} value of $2.517 \mu\text{g/mL}$ (cisplatin: $IC_{50} = 17.2 \mu\text{g/mL}$). Uddin et al. (2019) [72] studied a series of Schiff bases and evaluated their cytotoxicity against cancer cell lines (HeLa and

MCF-7) and a normal cell line (BHK-21) by means of the MTT assay. Compounds **51** and **53** showed a slight cytotoxic activity against HeLa ($IC_{50} = 56.7$ and $20.8 \mu\text{M}$, respectively, versus $5.13 \mu\text{M}$ of carboplatin) and BHK-21 cells ($IC_{50} = 32.2$ and $60.2 \mu\text{M}$, respectively). The mechanism of action for the active compound L5 was deepened, studying the pro-apoptotic mechanism by fluorescence microscopy, cell cycle analysis, caspase-9 and -3 activity, reactive oxygen species (ROS) production, and DNA binding. Compound **52** exhibited disintegrated cell membranes and condensed cellular protein, probably due to the lipids' and proteins' oxidation, suggesting that it could be a potent drug against cancer. Several Schiff bases of tetrahydrocurcumin have been recently reported by Mahal et al. (2019) [73] as potential anticancer agents. The in vitro anticancer activity was evaluated against three human cancer cell lines: human epithelial lung carcinoma (A549) and cervical cancer (HeLa) and human breast adenocarcinoma (MCF-7) cells. Most compounds exhibited moderate to good anticancer activity against all three tested cell lines and were significantly more active than tetrahydrocurcumin. The most interesting was compound **53** ($IC_{50} = 11.9, 12.7, 4.8 \mu\text{M}$, against the three cell lines considered, respectively). Erturk et al. (2020) [74] synthesized and studied two Schiff bases (**54** and **55**) for different biological activities, among them the antitumor one, against MCF-7 human breast cancer cell line. The IC_{50} values were 6.70, 2.20, and $<0.1 \text{ mM}$ for **54**; 1.00, 0.30, and 0.14 mM for **55** for 24, 48, and 72 h, respectively. The higher activity of compound containing 10-chloroanthracene **55** than that containing 8-hydroxyquinoline **54** was in agreement with theoretical calculations obtained by various spectroscopic analyses and single-crystal X-ray diffraction and Hirshfeld surface analysis and fingerprint plots of the two compounds. Suyambulingam et al. (2020) [75] synthesized two Schiff bases (**56** and **57**) and evaluated their antiproliferative activity against MCF-7 cells, obtaining IC_{50} values of $80.19 \mu\text{M}$ for compound **56** and $44.12 \mu\text{M}$ for compound **57** (doxorubicin: $IC_{50} = 2.05 \mu\text{M}$). Molecular docking studies were also carried out against six different active sites [76,77]. Mishra et al. (2020) [78] studied several Schiff bases containing a benzothiazole nucleus and studied the DNA binding interaction with pBR322 plasmid DNA by means of electrophoretic mobility shift assay [79]. The anticancer study was performed using the MTT assay. Imine **58** showed 85.82% inhibition of MCF-7 cancer cell lines at a concentration of $200 \mu\text{g/mL}$. It was less toxic to normal cells at the concentration required to produce the anticancer effect ($IC_{50} = 973 \mu\text{g/mL}$).

Table 1. Mono-Schiff bases.

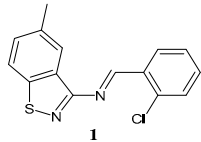
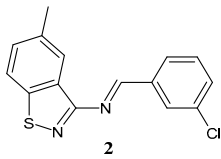
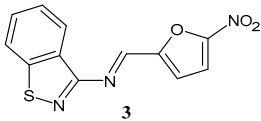
 <p style="text-align: center;">1</p>	$IC_{50} = 1.5\text{--}7 \mu\text{M}$ (MT-4, CCRF-CEM, WIL-2NS, CCRF-SB).	Vicini et al., 2003 [43]
 <p style="text-align: center;">2</p>	$IC_{50} = 1.5\text{--}7 \mu\text{M}$ (MT-4, CCRF-CEM, WIL-2NS, CCRF-SB).	Vicini et al., 2003 [43]
 <p style="text-align: center;">3</p>	$IC_{50} = 1.5\text{--}7 \mu\text{M}$ (MT-4, CCRF-CEM, WIL-2NS, CCRF-SB). $IC_{50} = 6 \mu\text{M}$ (SK-MEL-28). $IC_{50} = 10 \mu\text{M}$ (MCF-7).	Vicini et al., 2003 [43]

Table 1. Cont.

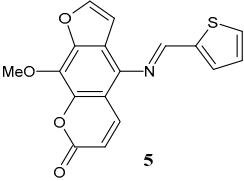
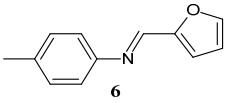
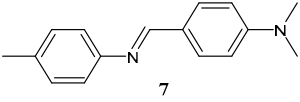
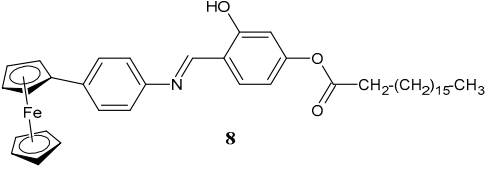
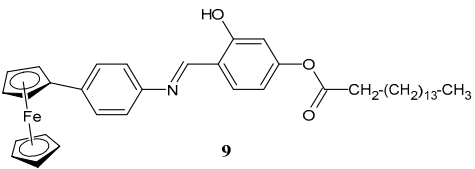
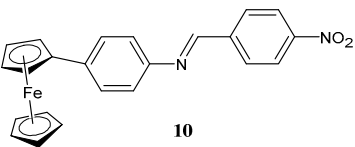
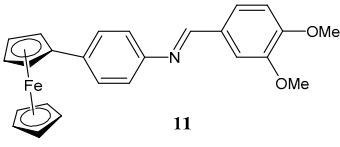
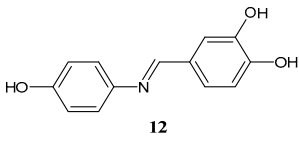
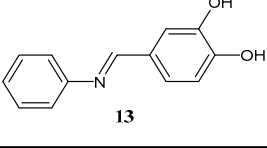
 <p>5</p>	$IC_{50} = 7.2 \mu\text{M}$ (HeLa).	Abdel-Hafez et al., 2009 [45]
 <p>6</p>	$IC_{50} = 39.9 \mu\text{M}$ (LAMA-84), $29.9 \mu\text{M}$ (K-562), $68.6 \mu\text{M}$ (HL-60/Dox). $IC_{50} > 400 \mu\text{M}$ (HL-60).	Kraicheva et al., 2009 [46]
 <p>7</p>	$IC_{50} = 251.9 \mu\text{M}$ (LAMA-84), $212.9 \mu\text{M}$ (K-562), $226.1 \mu\text{M}$ (HL-60/Dox). $IC_{50} > 400 \mu\text{M}$ (HL-60).	Kraicheva et al., 2009 [46]
 <p>8</p>	Tumor growth inhibition = 71%; $IC_{50} = 20 \mu\text{g/mL}$ (Potato disc tumor induction assay using <i>A. tumefaciens</i> (At-10)).	Nawaz et al., 2009 [47]
 <p>9</p>	Tumor growth inhibition = 58%; $IC_{50} = 563 \mu\text{g/mL}$ (Potato disc tumor induction assay using <i>A. tumefaciens</i> (At-10)).	Nawaz et al., 2009 [47]
 <p>10</p>	$LD_{50} = 292.95 \text{ ppm}$ (brine shrimp lethality assay).	Zaheer et al., 2010 [48]
 <p>11</p>	$LD_{50} = 18.22 \text{ ppm}$ (brine shrimp lethality assay).	Zaheer et al., 2010 [48]
 <p>12</p>	$IC_{50} = 5.6 \mu\text{M}$ (HepG2). $IC_{50} = 17.22 \mu\text{M}$ (murine B16F10 melanoma cells).	Cheng et al., 2010 [49] Bae et al., 2012 [55]
 <p>13</p>	$IC_{50} = 6.8 \mu\text{M}$ (HepG2).	Cheng et al., 2010 [49]

Table 1. Cont.

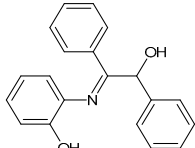
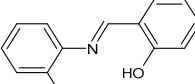
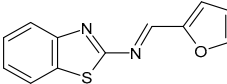
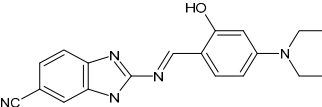
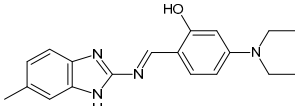
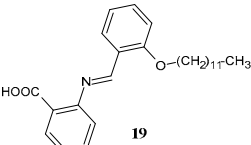
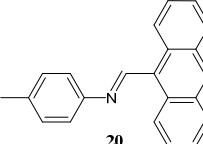
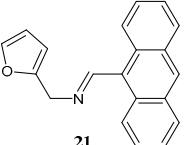
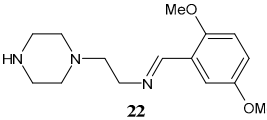
 <p>14 (PHP)</p>	LD ₅₀ = 16 mg/kg.	Jesmin et al., 2010 [50]
 <p>15 (HHIP)</p>	LD ₅₀ = 15.5 mg/kg; maximum percentage cell growth inhibition = 93% (EAC).	Jesmin et al., 2010 [50]
 <p>16</p>	IC ₅₀ = 0.186 μM (HeLa).	Etaiw et al., 2011 [51]
 <p>17</p>	IC ₅₀ = 4.73 (HeLa), 9.23 (MCF-7, metastatic).	Hranjec et al., 2011 [52]
 <p>18</p>	IC ₅₀ = 3.24 μM (HeLa), 15.27 μM (MCF-7, metastatic).	Hranjec et al., 2011 [52]
 <p>19</p>	IC ₅₀ = 1–10 mg/mL (HepG2, HCT-116 and MCF-7).	Shaker et al., 2011 [53]
 <p>20</p>	IC ₅₀ = 0.08 mg/mL (HT-29 cell line).	Kraicheva et al., 2012 [54]
 <p>21</p>	IC ₅₀ = 0.20 mg/mL (HT-29 cell line).	Kraicheva et al., 2012 [54]
 <p>22</p>	PG inhibition = 49% (at 1 × 10 ⁻⁵ M against NCI H-522).	Sondhi et al., 2012 [56]

Table 1. Cont.

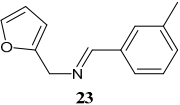
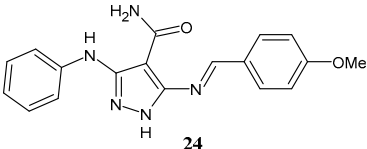
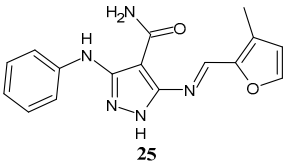
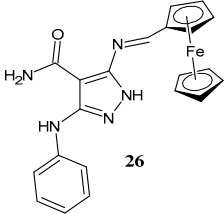
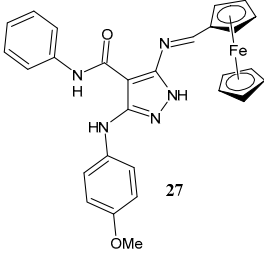
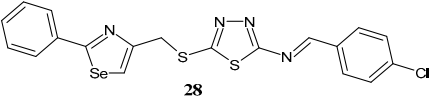
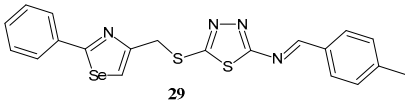
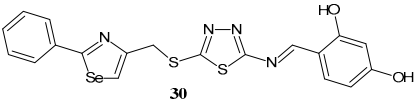
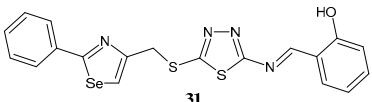
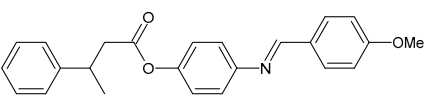
 <p>23</p>	$IC_{50} = 50.12 \mu\text{M}$ (KYSE 150), $158.49 \mu\text{M}$ (KYSE30), $111.2 \mu\text{M}$ (KYSE 270).	Klimczak et al., 2013 [57]
 <p>24</p>	$IC_{50} = 0.44 \mu\text{M}$ (SK OV-3).	Hafez et al., 2013 [58]
 <p>25</p>	$IC_{50} = 0.09 \text{ nM}$ (U937), $IC_{50} = 0.45 \text{ nM}$ (GOTO), $IC_{50} = 0.64 \text{ nM}$ (NB-1), $IC_{50} = 0.54 \text{ nM}$ (HT1080).	Hafez et al., 2013 [58]
 <p>26</p>	$IC_{50} = 0.54 \mu\text{M}$ (KB), $IC_{50} = 0.30 \text{ nM}$ (CNS, SF-268), $IC_{50} = 0.43 \text{ nM}$ (K-562), $IC_{50} = 0.09 \text{ nM}$ (HepG2), $IC_{50} = 6.60 \text{ nM}$ (NCI H460).	Hafez et al., 2013 [58]
 <p>27</p>	$IC_{50} = 6.20 \mu\text{g/mL}$ (HepG2), $IC_{50} = 7 \mu\text{g/mL}$ (MCF-7).	Hassan et al., 2015 [59]
 <p>28</p>	$IC_{50} = 4.02 \mu\text{M}$ (MCF-7).	Zhao et al., 2013 [60]
 <p>29</p>	$IC_{50} = 7.55 \mu\text{M}$ (MCF-7).	Zhao et al., 2013 [60]
 <p>30</p>	$IC_{50} = 8.51 \mu\text{M}$ (MCF-7).	Zhao et al., 2013 [60]
 <p>31</p>	$IC_{50} = 38.73 \mu\text{M}$ (L1210).	Zhao et al., 2013 [60]
 <p>32</p>	$IC_{50} = 0.15 \mu\text{g/mL}$ (potato disc).	Noureen et al., 2013 [61]

Table 1. Cont.

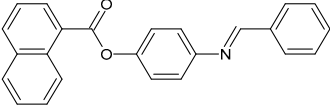
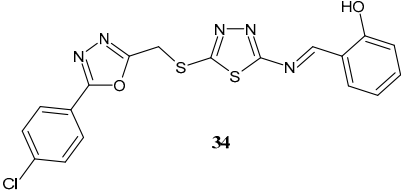
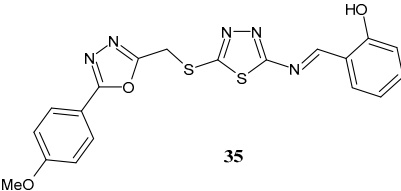
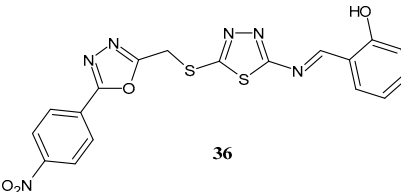
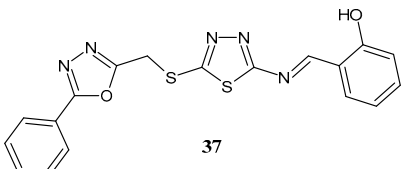
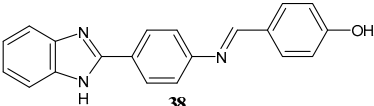
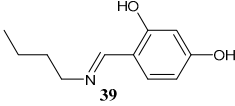
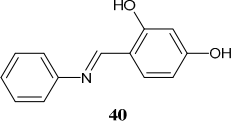
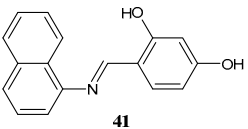
 33	IC ₅₀ = 8.03 µg/mL (potato disc).	Noureen et al., 2013 [61]
 34	IC ₅₀ = 2.84 µM (SMMC-7721).	Zhang et al., 2014 [62]
 35	IC ₅₀ = 4.56 µM (MCF-7).	Zhang et al., 2014 [62]
 36	IC ₅₀ = 4.25 µM (MCF-7), IC ₅₀ = 4.13 µM (A549).	Zhang et al., 2014 [62]
 37	IC ₅₀ = 4.11 µM (A549).	Zhang et al., 2014 [62]
 38	IC ₅₀ = 4.83 µM (PC3).	Gupta et al., 2015 [63]
 39	IC ₅₀ = 7.43 µM (PC3).	Gupta et al., 2015 [63]
 40	IC ₅₀ = 7.15 µM (PC3).	Gupta et al., 2015 [63]
 41	IC ₅₀ value of 0.02 µM (Hsp90 ATPase suppression).	Gupta et al., 2015 [63]

Table 1. Cont.

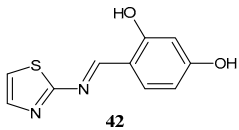
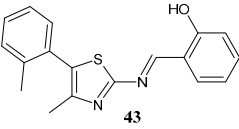
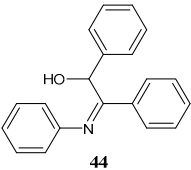
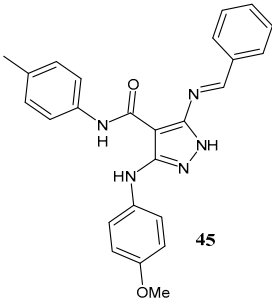
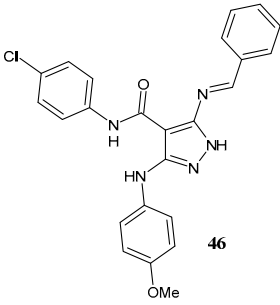
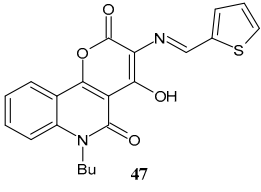
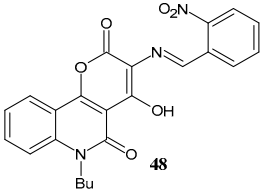
 <p>42</p>	$IC_{50} = 0.02 \mu\text{M}$ (Hsp90 ATPase suppression).	Gupta et al., 2015 [63]
 <p>43</p>	$IC_{50} = 9.22$ (HepG2), $IC_{50} = 10.00 \mu\text{M}$ (MCF-7), $IC_{50} = 9.50 \mu\text{M}$ (HCT116).	Abd-Elzaher et al., 2016 [64]
 <p>44</p>	$IC_{50} = 0.024 \text{ M}$ (MCF-7), $IC_{50} = 0.034 \text{ M}$ (T47D).	Sabbah et al., 2018 [65]
 <p>45</p>	$IC_{50} = 66.3 \mu\text{M}$ (HepG2).	Hassan et al., 2018 [67]
 <p>46</p>	$IC_{50} = 60.8 \mu\text{M}$ (MCF-7).	Hassan et al., 2018 [67]
 <p>47</p>	$IC_{50} = 0.042 \mu\text{M}$ (MCF-7).	Hassanin et al., 2018 [68]
 <p>48</p>	$IC_{50} = 0.83 \mu\text{M}$ (MCF-7).	Hassanin et al., 2018 [68]

Table 1. Cont.

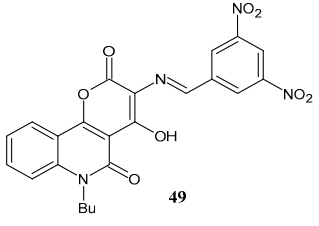
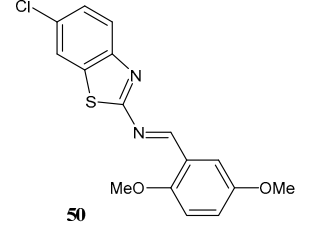
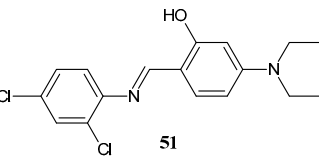
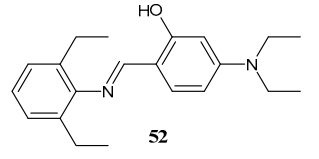
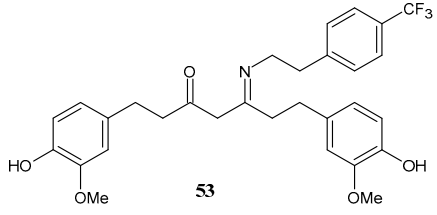
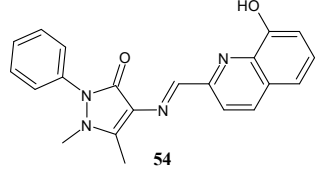
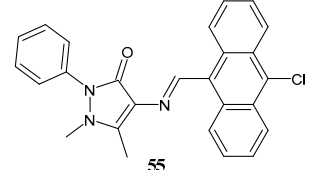
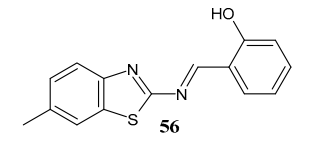
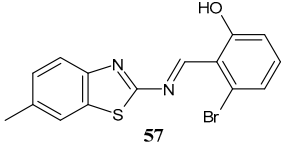
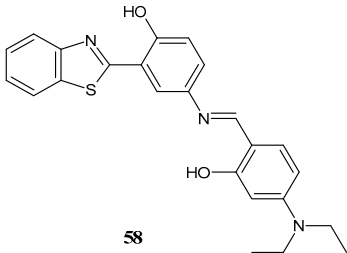
 <p>49</p>	IC ₅₀ = 0.6 μM (MCF-7).	Hassanin et al., 2018 [68]
 <p>50</p>	IC ₅₀ = 2.517 μg/mL (HeLa).	Saipriya et al., 2018 [71]
 <p>51</p>	IC ₅₀ = 56.7 μM (HeLa), IC ₅₀ = 32.2 μM (BHK-21).	Uddin et al., 2019 [72]
 <p>52</p>	IC ₅₀ = 20.8 μM (HeLa), IC ₅₀ = 60.2 μM (BHK-21).	Uddin et al., 2019 [72]
 <p>53</p>	IC ₅₀ = 11.9 μM (A549), IC ₅₀ = 12.7 μM (HeLa), IC ₅₀ = 4.8 μM (MCF-7).	Mahal et al., 2019 [73]
 <p>54</p>	IC ₅₀ = 6.70, 2.20, and < 0.1 mM (for 24, 48 and 72 h against MCF-7).	Erturk et al., 2020 [74]
 <p>55</p>	IC ₅₀ = 1.00, 0.30 and 0.14 mM (for 24, 48 and 72 h against MCF-7).	Erturk et al., 2020 [74]
 <p>56</p>	IC ₅₀ = 80.19 μM (MCF-7).	Suyambulingam et al., 2020 [75]

Table 1. Cont.

 <p>57</p>	IC ₅₀ = 44.12 μM (MCF-7).	Suyambulingam et al., 2020 [75]
 <p>58</p>	Percentage inhibition = 85.82% (at 200 μg/mL against MCF-7).	Mishra et al., 2020 [78]

2.2. Bis-Schiff Bases

Desai et al. (2001) [80] reported a study on 10 Schiff bases and evaluated their antiproliferative activity by measuring their effect on the (PG) of 57 different cancer cell lines, including lung, colon, central nervous system (CNS), ovarian, renal, prostate, melanoma, leukemia, and breast cancer. Compounds 59–62 (Table 2) showed activity against different cell lines. Particularly, compounds 59 and 60 were effective on leukemia (SR and MOLT-4) and colon (COLO-205), compound 62 on leukemia (SR and MOLT-4), CNS (SF-539) and melanoma (SK-MEL-28 and UACC-257). Against some of the abovementioned cell lines, other compounds have also been reported to be active, particularly, compound 61 on CNS, melanoma, and breast and compound 59 on leukemia, colon, and breast. Compound 60 was the most effective of imines analogues on leukemia. Padhye et al. (2009) [81] studied several Schiff bases and copper complexes as proteasome inhibitors and apoptosis inducers in human colon cancer HCT-116 cells, in comparison to curcumin. Among the synthesized compounds, the authors demonstrated that the fluorine-substituted curcumin analogs were superior to the curcumin against HCT-116 and BxPC-3 pancreatic cancer cells, probably because of the higher metabolic stability allowed by the fluoro substituents. Compound 63 showed approximately 80%, 60%, and 60% proteasome inhibition at 10, 20, and 30 μM (curcumin: 27%, 47%, and 64% at 10, 20, and 30 μM, respectively). In the study by Sondhi et al. (2012) [56], described in the paragraph below, the activity of mono-Schiff bases and bis-Schiff bases was evaluated. Compound 64 showed activity against ovary (PA1) cancer cells (62% versus 93% of actinomycin-D) and 65 against both breast (T47D) and ovary (PA1) (41% and 53%, respectively, versus 21% and 93% of actinomycin-D, respectively) cancer cells.

Shokrollahi et al. (2020) [82] recently studied four tetrahydrobenzothiazole-based Schiff bases and tested their cytotoxic activity against the human breast cancer (MCF-7) and hepatocellular liver carcinoma (HepG2) cell lines by MTT assay. The compounds showed cytotoxic activity against both cell lines in a concentration-dependent manner. Compound 66 was the most active against MCF-7 (IC₅₀ = 7.75 and 34.52 μM, at 24 and 48 h, respectively) and HepG2 (IC₅₀ = 3.01 and 1.29 μM, at 24 and 48 h, respectively). Morsy et al. (2021) [83] recently reported some selected bis-Schiff bases studied for their in vitro antiproliferative activity toward three human carcinoma HepG2 (liver), MCF-7 (breast), and RPE-1 (normal retina pigmented epithelium) cell lines using MTT assay. The results showed that compound 67 was found to be the active candidate against HepG2 (IC₅₀ = 84.2 μM versus 25.3 μM of doxorubicin) and MCF-7 cells (IC₅₀ = 99.4 μM versus 20.9 μM of doxorubicin), while compound 68 was found to be the most active of the series against RPE-1 cells (IC₅₀ = 127.7 μM versus 19.1 μM of doxorubicin).

Table 2. Bis-Schiff bases.

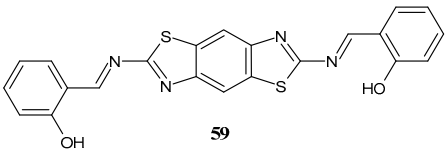
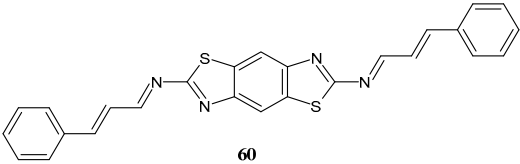
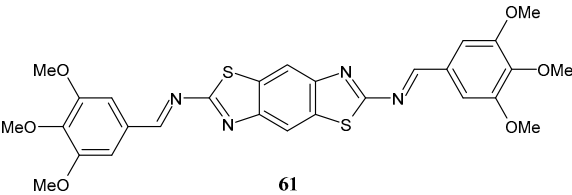
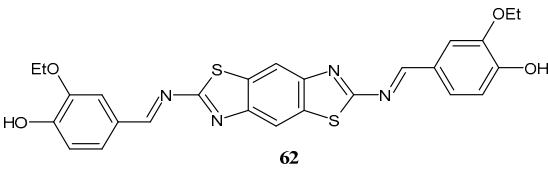
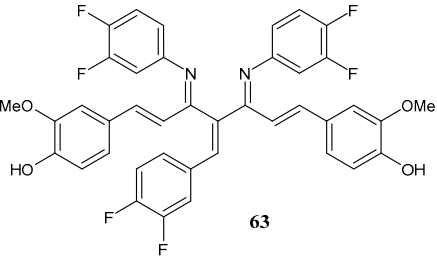
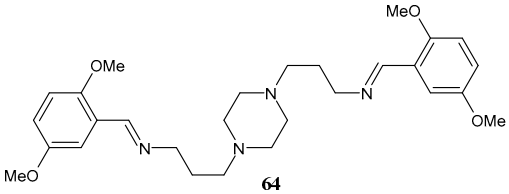
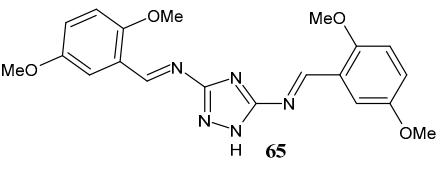
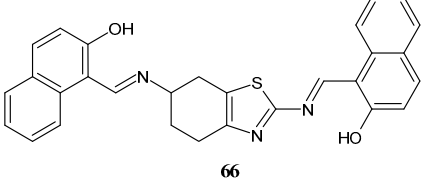
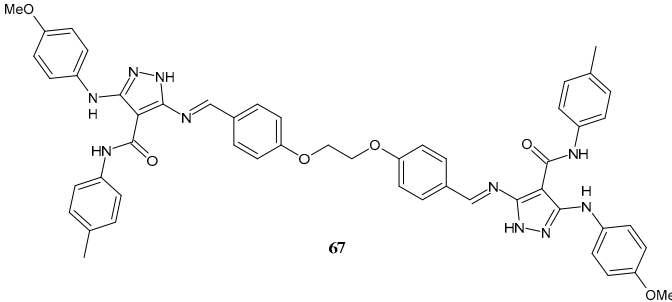
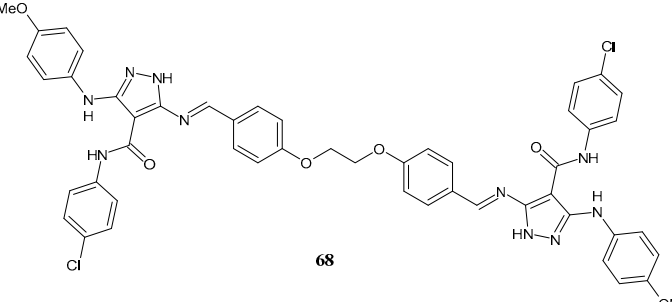
 <p style="text-align: center;">59</p>	effective on leukemia (SR and MOLT-4), colon (COLO-205) and breast. IC ₅₀ values not reported.	Desai et al., 2001 [80]
 <p style="text-align: center;">60</p>	effective on leukemia (SR and MOLT-4), colon (COLO-205) and leukemia. IC ₅₀ values not reported.	Desai et al., 2001 [80]
 <p style="text-align: center;">61</p>	effective on CNS (SF-539), melanoma (SK-MEL-28 and UACC-257) and breast. IC ₅₀ values not reported.	Desai et al., 2001 [80]
 <p style="text-align: center;">62</p>	effective on leukemia (SR and MOLT-4), CNS (SF-539), melanoma (SK-MEL-28 and UACC-257). IC ₅₀ values not reported.	Desai et al., 2001 [80]
 <p style="text-align: center;">63</p>	proteasome inhibition: about 80%, 60% and 60% at 10, 20 and 30 μM.	Padhye et al., 2009 [81]
 <p style="text-align: center;">64</p>	PG inhibition: 62% (ovary, PA1).	Sondhi et al., 2012 [56]
 <p style="text-align: center;">65</p>	PG inhibition: 41% (T47D) and 53% (PA1).	Sondhi et al., 2012 [56]
 <p style="text-align: center;">66</p>	IC ₅₀ = 7.75 and 34.52 μM, at 24 and 48 h, against MCF-7), IC ₅₀ = 3.01 and 1.29 μM, at 24 and 48 h, against HepG2).	Shrollaki et al., 2020 [82]

Table 2. Cont.

 <p style="text-align: center;">67</p>	$IC_{50} = 84.2 \mu\text{M}$ (HepG2), $IC_{50} = 99.4 \mu\text{M}$ (MCF-7).	Morsy et al., 2021 [83]
 <p style="text-align: center;">68</p>	$IC_{50} = 127.7 \mu\text{M}$ (RPE-1).	Morsy et al., 2021 [83]

3. Summary

Schiff bases have long attracted researchers due to their chemical reactivity and to the broad range of pharmacological activities that they exert as such or complexed with metals, including antibacterial, antifungal, anti-inflammatory, antioxidant, and anticancer. They are also employed as versatile tools in several applications such as fluorescent turn-on/turn-off sensors for the determination of diverse analytes. Their easy preparation and capability of forming complexes with almost all metals make them interesting compounds in medicinal chemistry. Recently, several organic compounds bearing Schiff base structure or their complexes with metals were used as effective drugs against cancer. Metal complexes' actions are multiple, depending on the broad range of coordination numbers, geometries, and kinetic properties and, after the worldwide use of cisplatin, different papers reported the importance of Schiff bases' anticancer actions in metal complexes. The reviewed paper indicated that the use of these compounds offered better anticancer properties with respect to the reference molecules, viz., cisplatin, doxorubicin, and vincristine, for instance, both in *in vitro* and *in vivo*. It is worthy to note that these compounds displayed the anticancer effects against a very broad variety of tumor cell models, solid or liquid, without hampering, in the most cases, the growth of the normal cells used as control. Furthermore, Schiff bases may target different intracellular regulator enzymes, together with the already known interactions with nuclear DNA, producing cancer cells' death by apoptosis. Finally, different evidence about their ability to modulate the intracellular redox equilibrium, strongly associated with tumor prevention, onset, and progression, have been revealed, confirming the multiple actions exerted by these molecules. In this review, studies regarding mono- and bis-Schiff bases with potent antitumor activity on several cell lines were reviewed. In the future, the study of structure–activity relationships of Schiff bases against cancer cells may help in synthesizing new and effective antitumor agents derived by modification of the already studied imines.

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Abbreviations

647-V	bladder carcinoma cell lines
A549	lung cancer cell lines
B16F10	murine melanoma cells
BGC-823	stomach cancer cell lines
BHK-21	normal cell line
CCRF-CEM	human CD4 ⁺ acute T-lymphoblastic leukemia cells
CCRF-SB	human acute B-lymphoblastic leukemia cells
SF-268	central nervous system (CNS) cancer cell lines
SF-539	colon cell lines
COLO-205	colon cell lines
EAC	Ehrlich Ascites Carcinoma
5-FU	5-Fluorouracil
GOTO	neuroblastoma cancer cell lines
HBL-100	colostrum derived myoepithelial cells, expressing polyoma virus large T-antigen line
HCT-15	colon cancer cells
HCT-116	human colon cancer cells lines
HeLa	cervical carcinoma cell lines
Hep-2	larynx cancer cell lines
HepG2	human hepatoma cell lines
HHP	N-(2-hydroxy benzylidene)-2-hydroxyl phenyl imine
HL-60	leukemia cell lines
HL-60/Dox	multi-drug resistant acute myeloblastic leukemia cell line
HT1080	fibrosarcoma cell lines
IC ₅₀	concentration which kills or inhibits cell viability by 50%
K-562	non-adherent chronic myelogenous leukemia cells of the erythroleukemia type
KB	cervical carcinoma cell lines
KYSE 30	esophageal cancer cell lines
KYSE 150	esophageal cancer cell lines
KYSE 270	esophageal cancer cell lines
L1210	mouse lymphocyte leukemia cells
LAMA-84	peripheral chronic myeloid leukemia cells
LD ₅₀	medium lethal concentration
MCF-7	human breast adenocarcinoma cell lines (low metastatic potential)
MDA-MB-231	human breast adenocarcinoma cell lines (high metastatic potential)
MiaPaCa-2	pancreatic carcinoma
MOLT-4	leukemia cell lines
MT-4	human CD4 ⁺ lymphocytes
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltriazolium bromide
NB-1	neuroblastoma cancer cell lines
NCI H460	non-small cell lung cancer cell lines
NCI H-522	lung cancer cell lines
NRU	Neutral Red Uptake
PA1	ovary cancer cell lines
PC3	prostate cancer cell lines
PCS	2-phenyl-4-carboxyl-1,3-selenazole
PG	percentage growth
PHP	N-(1-phenyl, 2-hydroxy-2-phenyl ethylidene)-2-hydroxyl phenyl imine
ROS	reactive oxygen species
RPE-1	normal retina pigmented epithelium
SK-MEL-28	melanoma cell lines
SK OV-3	ovarian carcinoma
SMMC-7721	human liver cancer cell lines
SRB	Sulforhodamine-B stain
SW620	colorectal adenocarcinoma, metastatic

T47D	breast cancer cell lines
U937	leukemia cell lines
UACC-257	melanoma cell lines
WIL-2NS	human splenic B-lymphoblastoid cells
WST-8	2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfofenyl)-2H-tetrazolium monosodium salt

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