Copper Complexes as Topoisomerases Inhibitors

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Organometallics, such as copper compounds, are cancer chemotherapeutics used alone or in combination with other drugs. A group of copper complexes exerts an effective inhibitory action on topoisomerases, which participate in the regulation of DNA topology. Copper complexes of topoisomerase inhibitors work by different molecular mechanisms that have repercussions on the cell cycle checkpoints and death effectors.

copper-complexes topoisomerase inhibitor cancer therapy

1. Introduction

Chemotherapy is a systemic treatment proposed to patients suffering from cancer. It is often a complementary approach to surgery or radiotherapy. The discovery of platinum's inhibitory effect on tumor cell growth in the 1960s [1] was a milestone for anticancer drug application in medicine [2]. Platinum (II) sets at the center of the squared planar structure of cisplatin and is coordinated with two chlorides and two ammonia molecules in a cis configuration. Cisplatin and its derivative drugs (carboplatin of second generation and oxaliplatin of third generation) are used worldwide in clinical applications and several other platinum analogs (lobaplatin, nedaplatin, and heptaplatin) are approved in several countries (Figure 1) [3][4]. However, serious side effects including toxicities on the kidney, heart, ear, and liver, decrease in immunity, hemorrhage, and gastrointestinal disorders limit the use of platinum derivatives [5][6][7]. The appearance of drug resistances, issuing from acquired or intrinsic multiple genetic and epigenetic changes, has also limited the clinical use of platinum-derived drugs [8]. Platinum-based treatment efficiency is challenged by cross-resistance and multiple changes including a decreased accumulation of the drug, a reduction in DNA–drug adducts, a modification in cell survival gene expression, an alteration of DNA damage repair mechanisms, modifications of transporters, protein trafficking, and altered cell metabolism [9][10][11][12][13][14].

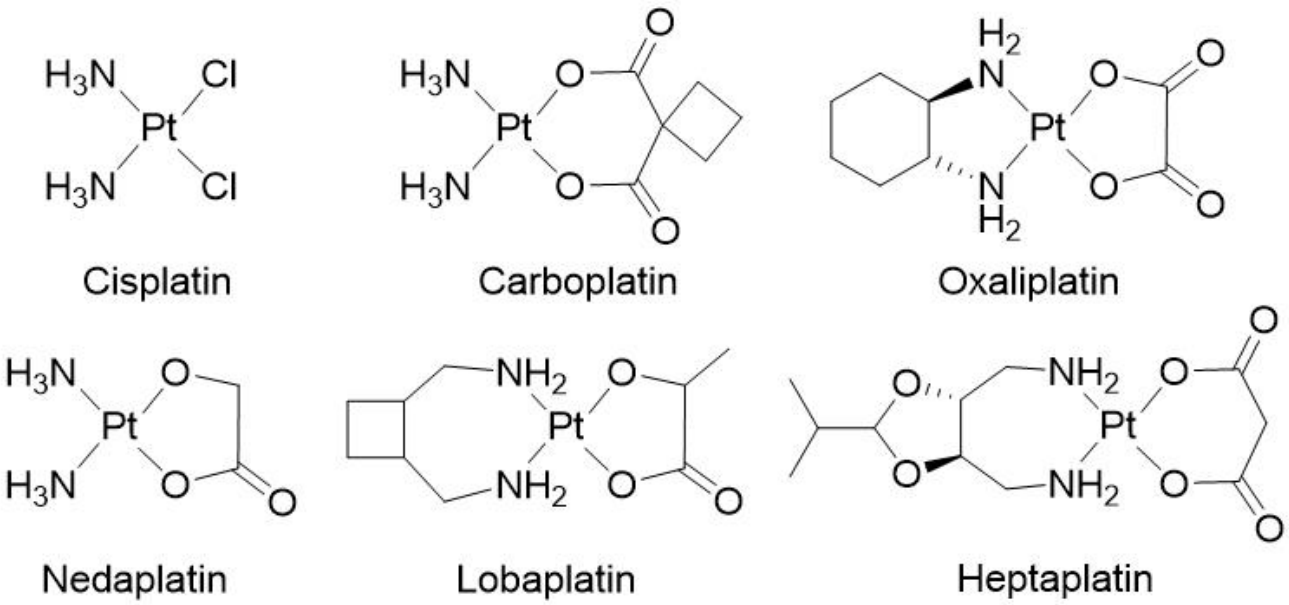


Figure 1. Platinum (II) complexes.

To circumvent drug resistance, a possible approach consists of designing and developing new therapeutic metal-based anticancer drugs [15][16][17][18][19][20][21]. Several transition metals from the d-block of the periodic table (groups 3 to 12) and particularly essential trace metals [15][22][23], such as copper [24][25][26][27][28][29], are useful for the implementation of metal-based complexes in anticancer therapies. Copper plays central roles in various cellular processes being an essential micronutrient and an important cofactor for several metalloenzymes involved in mitochondrial metabolism (cytochrome c oxidase), or cellular radical detoxification against reactive oxygen species (ROS) (superoxide dismutase) [30]. Copper is essential for angiogenesis, proliferation, and migration of endothelial cells [31][32][33]. Elevated copper favors tumor growth and metastasis. It is detected in several brain [34], breast [35], colon, prostate [36], and lung [37] tumors and serves as an indicator of the course of the disease [38]. The differences in tumor cells' responses to copper compared to normal cells laid the foundation of copper complexes' (CuC) evolution as anticancer agents. Numerous developed CuC contain different sets of N, S, or O ligands and demonstrate high cytotoxicity and efficient antitumor activity [25]. Different mechanisms are involved in copper drugs' anticancer effect. They act as chelators, and interact with and sequester endogenous copper, reducing its availability for tumor growth and angiogenesis [39]. On the contrary, ionophores trigger intracellular copper accumulation, cytotoxicity, and activate apoptosis inhibitor factor (XIAP) [24][40][41][42][43][44][45][46]. Other CuC are proteasome inhibitors [47][48]. Several CuC are actually on clinical trials: a number of copper/disulfiram-based drug combinations for therapy and as diagnostic tools (metastatic breast cancer and germ cell tumor), several casiopeínas compounds and elesclomol (leukemia), and thiosemicarbazone-based copper complexes labeled with a radioactive isotope for positron emission tomography imaging of hypoxia (in head and neck cancers) [49].

The cisplatin DNA-targeting principle of action also conditioned the development of anticancer copper-based drugs [4][23][50]. Antitumor activities of copper-based drugs are based on the interactive properties of both copper and the ligand. Copper toxicity results from its redox capacities (Cu(I) and Cu(II) redox states' interconversion in oxidation–reduction cycles), the property to displace other ions from the enzyme binding sites, a high DNA binding affinity,

and the ability to promote DNA breaks [28][51]. In most cases, copper modifies the backbone of the complexed ligand and grants better DNA affinity, specificity, and stability [52]. Copper derivatives can interact with DNA without the formation of covalent adducts. The noncovalent interactions with DNA include binding along with the major or the minor DNA grooves, intercalation, or electrostatic binding. Some copper-based drugs generate reactive oxygen species (ROS) that overwhelm cellular antioxidant defenses to produce oxidative damages in the cytoplasm, mitochondria, and DNA [53]. An important class of CuC, actually on focus for chemotherapy, inhibits topoisomerases (Top) 1 and 2, resulting in severe DNA damages, cell cycle arrest, and death [40][54][55][56][57]. Chemotherapeutics that target Top as poisons convert a transient DNA-enzyme complex into lethal DNA breaks [58][59][60][61][62]. However, topoisomerase inhibitors' activity and their multifaceted binding modes to DNA, the effects, and the modulations they produce on the control of cancer cell division necessitate better understanding to optimize their efficiency.

2. Copper Complexes as Topoisomerases Inhibitors

DNA topoisomerases have been molecular targets for anticancer agents since their discovery in 1971 [63]. Topoisomerases regulate DNA winding and play essential functions in DNA replication and transcription [59][64]. Topoisomerase 1 (Top1) creates transient single-DNA nicks, while topoisomerases 2 (Top2α and Top2β) produce transient double-stranded DNA breaks. Both nuclear Top1 and Top2 are important targets for cancer chemotherapy, and Top inhibitors are used in therapeutic protocols [65][66][67]. Top inhibitors are classified into two groups: poisons and catalytic inhibitors. Top poisons (or interfacial poisons) stabilize the reversible cleavage complex formed between Top and DNA and form a ternary complex. Top2 catalytic inhibitors can prevent DNA strands cleavage through inhibition of the ATPase activity (novobiocin, merbarone), by impeding ATP hydrolysis to block Top dissociation from the DNA (ICRF-193), or by DNA intercalation at the Top fixation site (aclarubicinet) see [68]. In all cases, inhibitors convert the indispensable nuclear Top enzyme into a killing tool.

Top inhibitors' activity increases upon complexation with copper ion. Top1, Top2, or Top1/2 inhibitors synthesized in the form of copper complexes (CuC) are mostly mononuclear Cu(II) complexes associated with a variety of ligands (Table 1). Different strategies are currently proposed to design and develop Top inhibitory agents based on ligands' properties [69]. If both Top1 and Top2 inhibitors CuC primarily target DNA by a direct interaction through intercalation or cleavage, their antiproliferative activity is reinforced by ROS production and other molecular targets (Table 1) [25][52].

Table 1. Copper complexes inhibitors of topoisomerases: targeted top isoforms, cancer cell lines responses, and molecular mechanisms are summarized. * Tests were realized in vitro with human Top1 or Top2α/β unless specified. IC50: half-maximal inhibitory concentration. EC50: half-maximal effective concentration. GI50: half-average of growth inhibition.

Ligand Class of Cu-C	Compound Number	Targeted Top(s)	Inhibition of DNA	Inhibition Mecanism	Cancer Cell Lines	IC50 (μM)	Cell Cycle	Cell Death	Other Specificity	Reference Number

			Relaxation Total (μM) (minimal (μM))				Arrest	Type		
Oxindolimine	**1**	Top1	50 (25)	Fixation in the DNA Top1 binding site	Neuroblastoma SH-SY5Y		G2/M arrest	Apoptosis	ROS induction	[70][71][72][73]
					Promonocytic U937					
Hydrazone with triphenylphosphonium	**2**	Top1	40	DNA Binding	Lung A549	4.2 ± 0.8				[74]
				Enzyme complex formation	Prostatic PC-3	3.2 ± 0.2				
Plumbagin	**3**	Top1	1.56	DNA intercalation	Breast MCF-7	3.2 ± 1.1				[75]
					Colon HCT116	5.9 ± 1.4				
					Hepatoma BEL7404	12.9 ± 3.6				
					Hepatoma HepG2	9.0 ± 0.7				
					Kidney 786-O	2.5 ± 0.9				
					Lung NCI-H460	2.0 ± 1.2				

				Nasopharyngeal cancer CNE2	11.8 ± 5.9		
Phenanthroline with amino acids	4	Top1	50 (10)	DNA intercalation	Nasopharyngeal cancer HK1	2.2 - 5.2	Apoptosis	[76]
Pyrophosphate	5	Top1	500	DNA interaction	Ovarian A2780/AD	0.64 ± 0.12		[77]
Heterobimetallic Cu(II)-Sn2(IV) phenanthroline	6	Top1	20	DNA intercalation	Breast Zr-75–1			[78]
				cleavage	Cervix SiHa			
					Colon HCT15, SW620	< 10 (GI50)		
					Kidney 786-O, A498			
					Lung Hop-62, A569			
					Pancreatic MIA PaCa-2			
					Neuroblastoma SH-SY5Y	2 – 8	Apoptosis	[79]
Analogs								[80]

		Top1	25	DNA binding	Hepatoma HuH7	25	ROS	[81][82]
Tridentate chiral Schiff base	**7, 8**		(15)	major groove	Hepatoma HepG2	6.2 ± 10	Cytokine TGFb	
							mRNA upregulation	
		Top1	(E. coli)*	DNA binding	Prostatic PC-3	7.3 ± 0.2	antimetastasis	[83]
				DNA cleavage	Breast MCF7	51.1 ± 1.6		[84]
					Colon HT29	16.6 ± 0.6		
Salicylidene	**9**				Hepatoma HepG2	2.3 ± 0.1		
					Lung A549	16.8 ± 1.0		
					Ovary A2780	14.6 ± 0.2		
					Prostatic LNCaP	25.4 ± 0.8		
Chalcone-derived	**10**	Top1	3	DNA binding	Breast MCF-7	0.16 ± 0.06		[85]

Thiosemicarbazone			(0.75)	DNA cleavage Religation inhibition	Leukemia THP-1	0.20 ± 0.06			
Pyridyl-substituted tetrazolopyrimidie	**11**	Top1	(Molecular docking) *	DNA binding groove mode	Cervix HeLa Colon HCT-15 Lung A549	0.565 ± 0.01 0.358 0.733	Apoptosis	CDK receptor binding	[86]
Tetrazolopyrimidine Diimine		Top1	102 ± 1.1	DNA binding groove mode	Cervical HeLa Colon HCT-15 Lung A549	0.620 ± 0.0013 0.540 ± 0.00015 0.120 ± 0.002	Apoptosis	vEGF receptor binding	[87]
Piperazine	**12**	Top1	12.5 (5)	DNA binding minor groove				SOD mimic	[88]
Elesclomol	**13**	Top1	50	Poison	Erythroleukemic K562	0.0075	Apoptosis	Copper chelator	[89]

							Necrosis	Not a substrat for	
							Oxidative stress	ABC transporters	
Cu(SBCM)2	**14**	Top1	*(Molecular docking)	DNA intercalation DNA binding	Breast MCF7 Breast MDA-MB-231	27 18.7 ±3.1	G2/M arrest	Apoptosis No ROS	p53 increase [90] [91]
TSC and TSC CuC									[92][93][94] [95][96][97]
Pyridine-TSC	**15**	Top2α	50 (10)	ATP hydrolysis inhibition	Breast MDA-MB-231 Breast MCF7	1.01 0.0558			[98] [99]
		Top2β	(5)	ATP hydrolysis inhibition					[100]
Piperazine-TSC	**16**	Top2α	0.9 ± 0.7	Potentially catalytic	Breast MCF7 Breast SK-BR-3	4.7 ± 0.3 1.3 ± 0.3			[101][102] [99]

Thiazole-TSC	**17**	Top2α	4		Breast MDA-MB-231	1.41 (EC50)	[103]
			(2)		Breast MCF7	0.13 (EC50)	
		Top2α	25	ATP hydrolysis inhibition	Breast		[104][105]
	17–18		(10)	+ Poison	HCC 70, HCC 1395,	1 to 20	
					HCC 1500, and HCC 1806		
					Colon	0.83 to 41.2	
					Caco-2, HCT-116 and HT-29		
L- and D-Proline-TSC	**19**	Top2α	300		Ovarian carcinoma CH1	113 ± 16	[106]
Quinoline-TSC	**20**	Top2α	0.48	Potentially catalytic	Lymphoma U937	0.48-16.2	[107]

Naphthoquinone-TSC	**21**	Top2α	1 mM		Breast MCF7	3.98 ± 1.01		No apoptosis	[108]
		Top2α	100	Poison	Breast MDA-MB-231	1.45 ± 0.07	G2/M arrest	Apoptosis	DNA synthesis	[109]
Bis-TSC	**22**		(5)		Colon HCT116	1.23 ± 0.27			inhibition	
					Keratinocyte HaCaT	0.65 ± 0.07			No ROS	
					Colon HCT116	Delayed mice xenograft				
Carbohydrazone	**23**	Top2α	250	DNA binding	Breast MCF7	9.916		Apoptosis		[110]
			(25)	major groove	Breast MDA-MB-231	7.557				
					Breast HCC 1937	3.278				
					Breast MX1	4.534				
					Breast MDA-MB-436	5.249				
					Breast MX-1	Reducted mice				

					xenograft (83%)			
		Top2α	25	DNA binding	Breast MCF7	18.6 (GI 50)		[111]
			(15)	major groove	Breast Zr-75-1	25.2 (GI 50)		
					Colon HT29	>80 (GI 50)		
Chromone	**24**				Cervix SiHa	34.6 (GI 50)		
					Kidney A498	73.3 (GI 50)		
					Lung A549	31.7 (GI 50)		
					Ovary A2780	17.4 (GI 50)		
Quinolinone Shiff Base	**25**	Top2α	9	No intercalation	Hepatic HepG2	17.9 ± 3.8	DNA synthesis	[112]
							inhibition	
							Slight substrate	

								for ABC transporter	
Bis-pyrazolyl Carboxylate	**26**	Dual Top1/Top2	(Molecular docking) *	ATP entry (potentially) DNA religation inhibition (potentially)	Hepatic HepG2	3.3 ± 0.02	Apoptosis	DNA replication ROS	[113]

2.1. CuC Top1 Inhibitors

All the structures of CuC Top1 inhibitors are reported in Figure 2 and the main characteristics in Table 1. Oxindolimine-Cu(II) Top1 inhibitors such as **1** are planar copper compounds [70] that do not permit enzyme-DNA complex formation [71][72][73]. Besides, they produce ROS [70]. Cu(II) derivative complexes of the hydrazone ligand with triphenylphosphonium moiety **2** can bind DNA and the Top enzyme [74] Plumbagin-Cu(II) **3** selectively intercalates into DNA [75]. The latter compound [75] and the phenanthroline-Cu(II) complexes modulated by amino acids **4** [76] can induce cancer cell apoptosis via mitochondrial signaling. Copper pyrophosphate-bridged binuclear complex **5** interacts with DNA, and based on the redox chemistry of copper, induces significant oxidative stress in cancer cell lines [77].

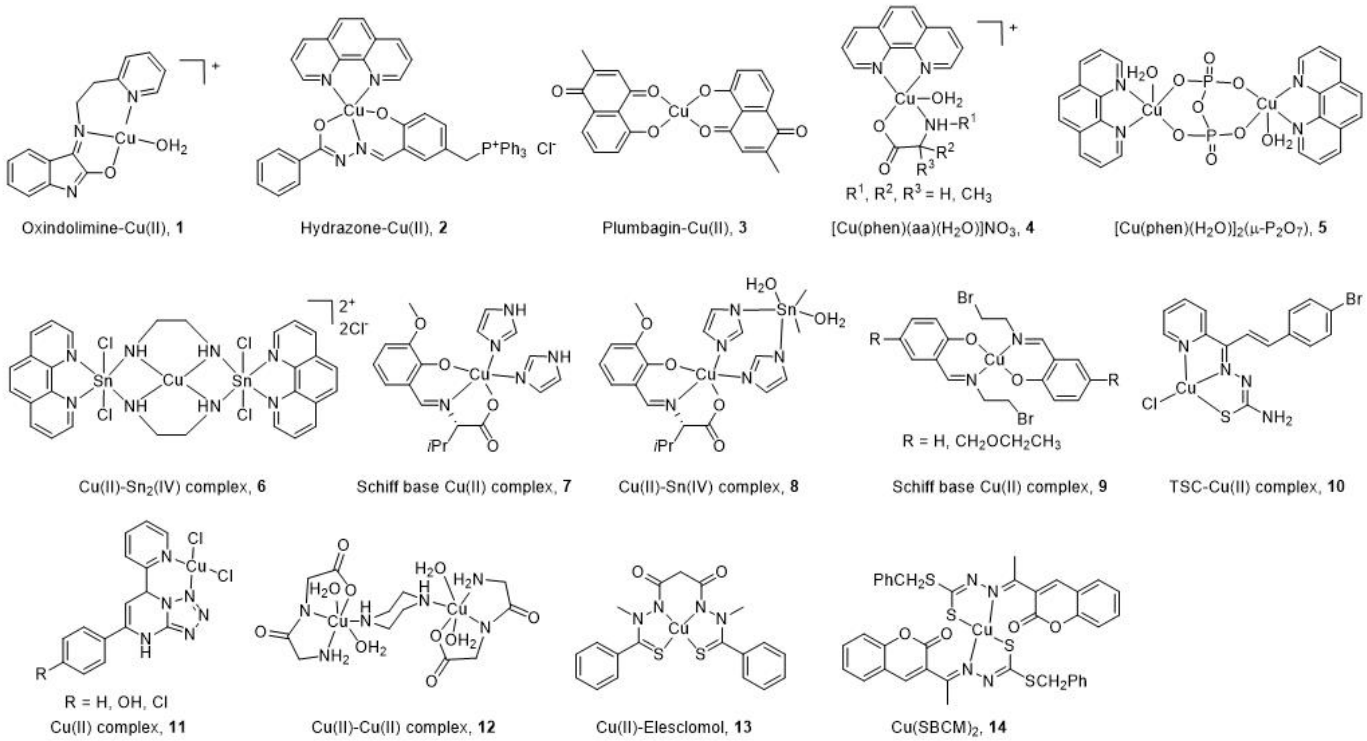


Figure 2. Structure of Cu(II) complexes as Top1 inhibitors.

In the heterobimetallic Cu(II)-Sn_2(IV) (copper/tin) complex **6**, the planar phenanthroline heterocyclic ring approaches the Top−DNA complex Cu(II)-Sn_2(IV) toward the DNA cleavage site and forms a stable complex with Top1 [78][79]. Other Cu(II)-Sn_2(IV) analogs induce apoptosis [80]. Chiral monometallic or heterobimetallic complexes **7** and **8** with tridentate chiral Schiff base–ONO-ligand are DNA groove binders and produce ROS [81][82].

Salicylidene-Cu(II) derivative **9** of 2-[2-bromoethyliminomethyl] phenol [83][84] is a bifunctional drug that inhibits both cancer cell growth and metastasis.

Chalcone-derived thiosemicarbazone (TSC) Cu(II) complex **10** prevents the DNA cleavage step of the Top1 catalytic cycle and DNA relegation [85].

Tetrazolo[1,5-*a*]pyrimidine-based Cu(II) complexes **11** have a square planar geometry, and despite their high capability to inhibit Top1, interact with CDK for **11** [86] and VEGF receptors for an analog of **11** [87]. Binuclear Cu(II) dipeptide piperazine-bridged complex **12** recognizes specific sequences in the DNA, oxidatively cleaves DNA, and displays superoxide dismutase (SOD) activity [88].

Derived from elesclomol (in clinical trials: phase 3 against melanoma and randomized phases 2 and 3 for the treatment of a variety of other cancers), the elesclomol-Cu(II) complex **13** inhibits Top1 and induces apoptosis in cancer cells [89].

As recently studied, Cu(II)$(SBCM)_2$ **14** derived from *S*-benzyldithiocarbazate and 3-acetylcoumarin intercalates into DNA, induces ROS production, and has an antiproliferative activity in breast cancer lines [90][91].

2.2. CuC Top2α Inhibitors

Due to its cell cycle phase dependence and its high expression in proliferating cells, the Top2α isoform is primarily targeted by copper complexes (CuC), whereas Top2β remains unchanged during the course of the cell cycle [66]. Another reason to limit the clinical application of Top2β inhibitors is the strong unwanted side effects produced (secondary leukemia, myelodysplastic syndrome (MDS), and cardiac toxicity [92][93]).

The main characteristics and structures of CuC Top2 inhibitors are reported in Figure 3 and Table 1. Several α-(*N*)-heterocyclic thiosemicarbazone (TSC) CuC [94][95] present a greater inhibitory effect on Top2α than corresponding TSC ligands alone [96][97] due to a square planar structure around the Cu(II) ion. A specific subset of pyridine-TSC CuC **15** inhibits Top2α [98] acting as ATP hydrolysis inhibitors in a non-competitive mode [94][99][100]. Another pyridine-TSC CuC inhibits Top2β [100]. Molecular modeling supports the binding of the complexes near but outside the ATP binding pocket in communication with the DNA cleavage/ligation site of Top2. Piperazine-TSCs based CuC **16** inhibit Top2α [101][102] by a strong interaction with the ATP-binding pocket residues [99] without ROS production [102]. Thiazole-TSC CuC **17** and **18** are Top2α catalytic inhibitors [103][104] or poisons [105]. The highly water-soluble proline-TSC CuC series **19** inhibit Top2α and cell proliferation [106]. Quinoline-TSC CuC **20** interact with the DNA

phosphate group preventing relegation**.** The presence of two methyl groups on the terminal nitrogen is responsible for high activity and confers a cationic nature responsible for easier passive access into the cell [107].

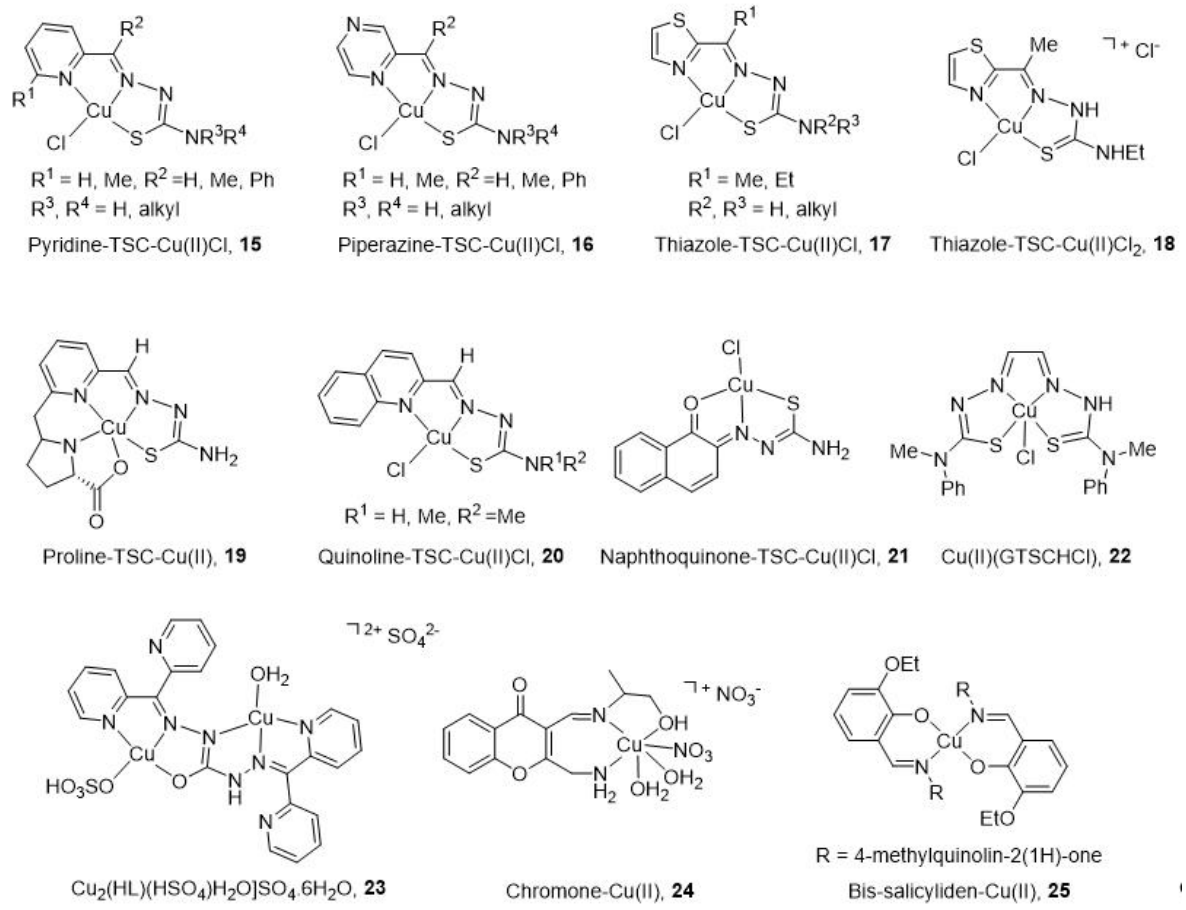
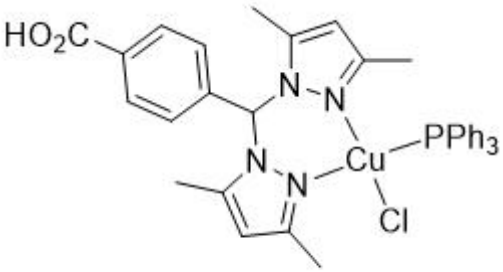


Figure 3. Structure of Cu(II) complexes as Top2 inhibitors.

Non-heterocycle naphthoquinone-TSC CuC **21** [108] and bis-TSC CuC **22** [109] are Top2α inhibitors acting as poisons [109]; they induce apoptosis in various human cancer cell lines and delay colorectal growth of carcinoma xenografts in mice [109]. Carbohydrazone CuC **23** [110] is a Top2α inhibitor that binds DNA, induces apoptosis, and reduces mice xenograft (83% after a treatment of 2 mg/kg). Chiral chromone Cu(II)/Zn(II) **24** [111] revealed catalytic inhibition of Top2α with DNA binding in the major groove. Quinolinone CuC **25** [112] inhibit Top2α and DNA synthesis without DNA intercalation and are only minimized PGP (P-glycoprotein efflux transporter) substrates.

2.3. CuC Dual Top1/Top2α Inhibitors

Heteroleptic Cu(I) complexes of the bis-pyrazolyl carboxylate ligand with auxiliary phosphine **26** (Figure 4) may inhibit Top1 by blocking the relegation step and inhibit Top2α by preventing ATP hydrolysis, as proposed by molecular docking analysis. They also perturb DNA replication, generate ROS, and induce apoptosis [113].



bis-pyrazolyl-Cu(I) complex, **26** .

Figure 4. Structure of Cu(I) complex as a Top1/2α dual inhibitor.

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