Chapter 13
Current State of Platinum Complexes for the Treatment of Advanced and Drug-Resistant Breast Cancers

Bernhard Biersack and Rainer Schobert

Abstract Breast cancer represents the major cause of death in female cancer patients. New efficient treatments are desperately needed, particularly especially for patients suffering from advanced stages and metastases, or those who are no longer responding to the clinically established drugs such as cisplatin or carboplatin. New promising therapy regimens and platinum complexes have emerged over the last few years that displayed efficacy in advanced platinum- and/or drug-resistant breast tumors and metastases. This chapter provides an overview of the latest developments in the field of platinum-based drugs against advanced and resistant breast cancers since 2013.

Keywords Platinum complexes · Anticancer agents · Breast cancer · Metastasis · Multidrug resistance (MDR) · Triple-negative breast cancer (TNBC)

13.1 Introduction

Rosenberg and coworkers discovered the anticancer activity of the platinum(II) complex cisplatin in 1969, and after its approval by the FDA about 10 years later cisplatin became a salient drug in the therapy of solid tumors (Fig. 13.1) [1]. DNA is the main cellular target of cisplatin which binds to it via metal coordination to the *N*-7 atom of purine bases such as guanine in exchange for its chlorido ligands. The resulting intra- and interstrand links lead to morphological changes of the platinated DNA eventually evoking apoptosis of the affected cells [2, 3]. Platinum therapy, however, comes at a price. Toxicity, severe side-effects and intrinsic or acquired platinum resistance confine the clinical applicability of platinum complexes [3–6]. This is true also for the second and third generation drugs carboplatin and oxaliplatin that are clinically approved in the USA and the EU (Fig. 13.1) [2–4]. Fortunately, the renaissance of interest in the medicinal chemistry of platinum opens a way out

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A. Ahmad (ed.), *Breast Cancer Metastasis and Drug Resistance*,
Advances in Experimental Medicine and Biology 1152,
https://doi.org/10.1007/978-3-030-20301-6_13

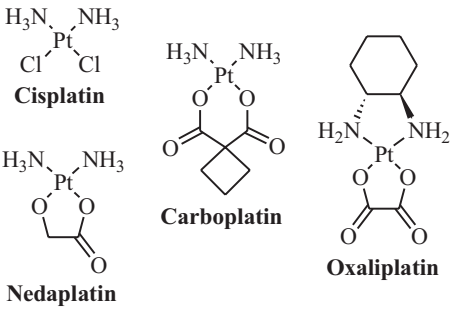

Fig. 13.1 Platinum complexes in advanced stages of investigation as breast cancer therapeutics

of this predicament. A plethora of new promising platinum complexes was disclosed that harness novel structural motifs, oxidation states, and conjugates with other drugs to overcome the eminent drawbacks of cisplatin, carboplatin and oxaliplatin [7–10]. Typical such examples are *trans*-Pt complexes, Pt(IV) complexes, heteronuclear complexes, and *N*-heterocyclic carbene complexes.

Breast cancer still represents the major cause of death among all female cancer patients (more than 40,000 deaths per year alone in the USA), although a reduction of the mortality rates by 36% was observed since 1989 [11, 12]. Surgery and chemotherapy as well as hormone therapy for estrogen receptor positive breast cancer represent the main treatment options for breast cancer patients. Platinum complexes such as cisplatin and its less toxic congener carboplatin appear to be promising agents against particularly aggressive triple-negative breast cancers (TNBC) [13]. The efficacy of cisplatin and carboplatin treatment against breast cancer cells seems to be regulated epigenetically and tightly correlated with certain miRNA expression profiles including tumor suppressor miRNAs and oncogenic miRNAs (oncomirs) [14, 15]. Several new platinum complexes were disclosed that proved particularly active against aggressive, metastatic and/or drug-resistant breast cancers [8, 16]. In the following, an overview is presented of platinum–based anticancer agents for the targeted treatment of drug-resistant breast cancer and breast cancer metastases, published over the last 4 years, with a focus on those breast cancers that are associated with a poor prognosis.

13.2 Platinum Complexes in Advanced Stages of Investigation for the Treatment of Aggressive and Resistant Breast Cancers

Clinically approved platinum complexes such as cisplatin and carboplatin already represent valuable options for the treatment of advanced breast cancer diseases either alone or in combination with other drugs [17]. About 15–20% of all patients are diagnosed with triple-negative breast cancer (TNBC) which lacks expression of estrogen receptor (ER) and progesterone receptor (PR) and doesn't overexpress

human epidermal growth factor receptor 2 (HER2) [18]. TNBC is often associated with the development of brain and lung metastases and, thus, with a reduced overall survival rate and poor prognosis [18]. Platinum complexes have gained importance concerning the therapy of TNBC because of their DNA-damaging properties [13]. In a recent phase II trial, several patients suffering from metastatic TNBC responded well to platinum-based therapy (either cisplatin or carboplatin). In particular, patients with either germline BRCA1/2 mutations or with otherwise induced homologous recombination (HR) deficiency associated with ineffective DNA damage repair exhibited therapy response (Table 13.1) [19]. Indeed, HR deficiency on the basis of loss of heterozygosity (LOH), telomeric allelic imbalance (TAI) and large-scale state transition (LST) was discovered as a prognostic factor for BRCA1/2-mutated and sporadic TNBC response to treatment with platinum drugs [20]. In line with this finding, it was shown that the HR-repair inhibitor triapine augmented cisplatin activity in BRCA wild-type cancer cells [21]. A recent phase III trial of cisplatin in combination with gemcitabine for the treatment of metastatic TNBC revealed very promising results (median PFS/progression free survival = 7.73 months) when compared with paclitaxel plus gemcitabine (median PFS = 6.57 months), and cisplatin plus gemcitabine was suggested as the preferred first-line chemotherapy for this tumor disease in the future (Table 13.1) [22]. Another study revealed a median PFS of 4 months in patients with heavily pre-treated metastatic breast cancer who received cisplatin plus ifosfamide as salvage treatment

Table 13.1 Recent clinical studies of promising platinum complexes at advanced stages of breast cancer

Drugs	Study	Conclusion
Cisplatin or carboplatin	Phase 2, metastatic TNBC patients: RR = 25.6% (54.5% in BRCA1/2-mutant patients), CR = 3.5%, PR = 22.1%, SD = 4.7%	Germline BCRA1/1 mutation and HR-deficiency as prognostic factors for platinum response
Cisplatin plus ifosfamide	Retrospective analysis of 20 metastatic breast cancer patients: median PFS = 4 months, OS = 8.5 months	More effective than platinum monotherapy, caution: grade 3/4 toxicities
Cisplatin plus gemcitabine	Phase 3, metastatic TNBC patients: median PFS = 7.73 months	Recommended as preferred first-line therapy of TNBC
Carboplatin plus everolimus	Phase 2, metastatic TNBC patients: CBR = 36% (1 CR, 6 PRs, 7 SDs), median PFS = 3 months, OS = 16 months	Efficacious and well tolerated therapy with enduring responses
Nedaplatin plus taxanes, gemcitabine or navelbine	Analysis of 171 advanced breast cancer patients: RR = 48.2%, TTF = 13.87 months, OS = 31.53 months	Well-tolerated and suitable cisplatin surrogate with higher activity than cisplatin
Oxaliplatin plus vinorelbine	Phase 2, metastatic TNBC patients: CBR = 50.0%, RR = 31.6%, median PFS = 4.3 months, OS = 12.6 months, CR = 2.6%, PR = 28.9%, SD = 26.3%	Effective with good safety, strongly recommended for phase 3 trials

CBR clinical benefit rate, *CR* complete response, *PFS* progression free survival, *PR* partial response, *OS* overall survival, *RR* response rate, *SD* stable disease, *TTF* time to treatment failure

(Table 13.1) [23]. The combination of cisplatin with the bisphosphonate zoledronic acid (a clinically approved drug for the treatment of cancer-mediated bone diseases) exhibited synergistic effects in TNBC cells (MDA-MB-231) which was associated with suppressed Mcl-1 expression and inhibition of mTOR signalling [24].

The less toxic cisplatin congener carboplatin was investigated in combination with the mTOR inhibitor everolimus in 25 metastatic TNBC patients in a phase 2 trial (Table 13.1) [25]. Carboplatin treatment was well tolerated by the patients and one complete response, six partial responses, and seven stable diseases were observed while eight patients showed progressing disease [25]. In a study with TNBC intracranial models, the combination of carboplatin with the PARP inhibitor ABT888 showed improved survival in the BRCA-mutant intracranial TNBC models and might be a suitable therapy option for BRCA-mutant TNBC patients with brain metastases in future clinical trials [26].

The second generation platinum complex nedaplatin is a close analog of carboplatin and its activity against advanced breast cancer was evaluated and compared with cisplatin [27]. Indeed, nedaplatin-based chemotherapy (in combination with paclitaxel or docetaxel, and gemcitabine or navelbine) showed distinctly longer time-to-treatment failure (TTF) = 13.87 months and overall survival (OS) times = 31.53 months in advanced breast cancer patients when compared with cisplatin-based chemotherapy (TTF = 8.7 months, OS = 24.87 months) (Table 13.1) [27].

Oxaliplatin with the characteristic *trans*-(1*R*,2*R*)-DACH (diaminocyclohexane) ligand is approved for the therapy of colorectal cancer because it lacks cross-resistance to cisplatin and carboplatin. Thus, the effects of oxaliplatin against TNBC were evaluated in a phase 2 trial as well [28]. The biweekly administered combination of oxaliplatin and vinorelbine against pre-treated second- or third-line metastatic TNBC revealed a median PFS of 4.3 months, an OS of 12.6 months and it was characterized by a good safety profile that warrants a phase 3 study of this therapy regimen (Table 13.1) [28].

13.3 New Platinum Complexes for the Treatment of Advanced and Resistant Breast Cancers

As a suitable model for TNBC, the MDA-MB-231 breast carcinoma cell line was frequently employed in order to study the effects of new platinum complexes at the pre-clinical stage [16]. The *cis*-diphenyl pyridineamine platinum(II) complex **1** inhibited MDA-MB-231 TNBC cell growth at much lower doses (IC_{50} = 1.0 μM) than cisplatin (IC_{50} = 10 μM) (Fig. 13.2) [29]. In addition to its DNA-binding and apoptosis induction, complex **1** also suppressed the migration of MDA-MB-231 cells and, thus, has potential as an anti-metastatic agent [29]. The *trans*-2-phenylindole platinum complex **2a** and the *cis*-derivative **2b** revealed distinct growth inhibition of MDA-MB-231 cells (IC_{50} = 4.3–4.4 μM) (Fig. 13.2) [30]. While **2a** caused changes in the tertiary structure of treated plasmid DNA, **2b**

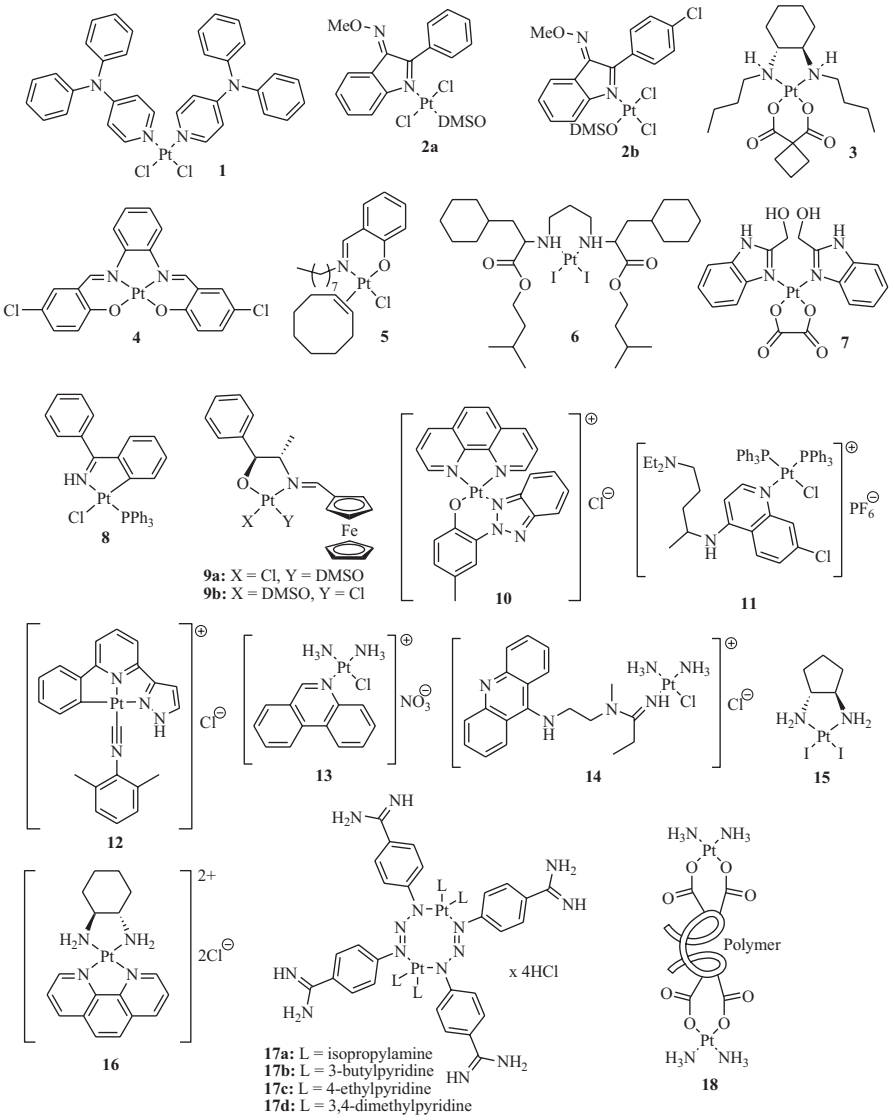

Fig. 13.2 Platinum(II) complexes with activity against the TNBC model MDA-MB-231

exerted no effects on plasmid DNA [30]. The di-*n*-butyl-DACH platinum(II) complex **3** proved more strongly growth inhibitory (IC_{50} = 13.79 μM) against MDA-MB-231 cells than oxaliplatin (IC_{50} = 26.82 μM) and cisplatin (IC_{50} = 18.27 μM) [31]. In addition, complex **3** bound more slowly to DNA when compared with cisplatin due to sterical hindrance by the dibutyl-DACH ligand which suggests a mode of action different from cisplatin (Fig. 13.2) [31]. The Schiff base platinum(II) complex **4** was tested against MDA-MB-231 cells and showed an

IC_{50} value of 6.6 μM (Fig. 13.2) [32]. Complex **4** induced cell cycle arrest (G1-phase) and apoptosis while DNA interaction proceeded via intercalation [32]. Another Schiff base (*N*-octyl-salicylimine)(*cis*-cyclooctene)platinum(II) complex **5** was found to be a strong inducer of apoptosis in MDA-MB-231 cells (Fig. 13.2) [33]. The diiodido complex **6** inhibited MDA-MB-231 cell growth (IC_{50} = 6.6 μM) much more strongly than cisplatin (IC_{50} = 21.9 μM) due to its increased accumulation in cancer cells and to an increased DNA binding (Fig. 13.2) [34]. The 2-hydroxybenzimidazole oxalatoplatinum(II) complex **7** showed growth inhibition in MDA-MB-231 cells similar to cisplatin and greater than carboplatin (Fig. 13.2) [35]. Complex **7** changed the tertiary structure of plasmid DNA like cisplatin and efficiently protected plasmid DNA from digestion by a restriction enzyme [35]. The cycloplatinated benzophenone imine **8** also inhibited MDA-MB-231 tumor cell growth (IC_{50} = 5.0 μM), it showed antioxidant activity, and it bound to plasmid DNA leading to changes in its tertiary structure (Fig. 13.2) [36]. The ferrocene-platinum(II) complexes **9a** and **9b** strongly inhibited growth of MDA-MB-231 cells (IC_{50} = 1.4 μM) (Fig. 13.2) [37]. While **9a** initiated distinct changes in the tertiary structure of plasmid DNA, complex **9b** showed no such effects at all, which disproves DNA binding being a major aspect of the mode of action of these novel anticancer platinum complexes [37]. The 1,10-phenanthroline 2-(2′-hydroxy-5′-methylphenyl)-benzotriazole platinum complex **10** also showed significant growth inhibitory activity against MDA-MB-231 TNBC cells (IC_{50} = 5.2 μM) (Fig. 13.2) [38]. The triphenylphosphino chloroquine complex **11** was antiproliferative in MDA-MB-231 cells at similar concentrations (IC_{50} = 5.5 μM) (Fig. 13.2) [39]. Complex **11** bound to DNA and bovine serum albumin (BSA). When reacted with guanosine complex **11** underwent a Pt coordination to guanosine via the N7 atom [39]. The luminescent platinum(II) complex **12** featuring a pincer ligand led to a distinct growth inhibition of MDA-MB-231 cells growth inhibition (IC_{50} = 1.6 μM) when compared with cisplatin (IC_{50} = 25 μM) and it accumulated in the cancer cell lysosomes leading to an increased lysosomal membrane permeability and eventually to cell death (Fig. 13.2) [40]. The cationic platinum(II) complex phenanthriplatin (**13**) was of similar antiproliferative activity in MDA-MB-231 cells (IC_{50} = 3.1 μM) (Fig. 13.2) [41]. Its conjugation to tobacco mosaic virus (TMV) as a nano-carrier system gave a conjugate **13**-TMV with even higher activity (IC_{50} = 2.2 μM). It also led to a distinct tumor growth reduction in MDA-MB-231 tumor xenograft models at doses of 1.0 mg/kg (weekly i.v. injection) with the **13**-TMV nanoparticles accumulating in the tumor tissue [41]. The acridine-platinum(II) complex conjugate **14** inhibited MDA-MB-231 cell growth completely at doses between 5 and 10 μg/mL after 72 h (Fig. 13.2) [42]. Increased accumulation of **14** in MDA-MB-231 cells was achieved by coating of multi-walled carbon nanotubes with **14** (**14-**MWCNT) which also induced S-phase arrest and non-apoptotic cell death in MDA-MB-231 breast cancer cells [42]. The *trans*-1,2-diaminocyclopentane platinum(II) complex **15** and its conjugate with a fructose-based glyco-methacrylate-copolymer carrier (**15-**FMA) revealed potent activity against MDA-MB-231 cells (IC_{50} = 5.1 μM for **15**, IC_{50} = 4.8 μM for **15**-FMA) and the conjugate was readily

taken up by breast cancer cells probably via the GLUT-5 receptor (Fig. 13.2) [43]. Reaction of *trans*-(1*S*,2*S*)-diaminocyclohexane-dichloridoplatinum(II) with 1,10-phenanthroline gave the bis-cationic complex **16** which was very active against MDA-MB-231 cells (IC_{50} = 0.64 μM) (Fig. 13.2) [44]. Intercalation of the cationic complex **16** into montmorillonite clay as a drug vehicle only slightly reduced the activity against MDA-MB-231 cells (IC_{50} = 0.9 μM) [44].

The dinuclear berenil-platinum(II) complex **17a** with isopropylamino ligands showed distinct tumor cell growth inhibition (IC_{50} = 18 μM) of MDA-MB-231 cells in contrast to cisplatin (IC_{50} = 96 μM) (Fig. 13.2) [45]. Complex **17a** increased ROS levels in MDA-MB-231 cells and decreased the cellular concentrations of antioxidants such as GSH and vitamin E [45]. The analogous berenil-complex **17b** with 3-butylpyridine ligands disclosed improved growth inhibitory activity in MDA-MB-231 cells (IC_{50} = 11 μM) when compared with complex **17a** [46]. Complex **17b** induced apoptosis in MDA-MB-231 cells in a caspase-dependent way via mitochondrial damage [46]. The new dinuclear berenil 4-ethylpyridine platinum(II) complex **17c** also exhibited stronger growth inhibition of MDA-MB-231 cells (IC_{50} = 18 μM) when compared with cisplatin (IC_{50} = 92 μM) [47]. Complex **17c** showed a more pronounced apoptosis induction in MDA-MB-231 cells (38%, 10 μM **17c**) than cisplatin (11%, 10 μM cisplatin), and the activity of **17c** was augmented by combination with anti-MUC1 antibodies (58% apoptotic cells, 10 μM **17c** and 10 μg/mL anti-MUC1) which was associated with increased levels of caspases-8, −9, and −3, and of the pro-apoptotic Bax protein [48]. More recently, another potent dinuclear berenil-platinum(II) complex **17d** with 3,4-dimethylpyridine ligands was disclosed (IC_{50} = 12 μM, MDA-MB-231 cells) which induced apoptosis both by mitochondrial damage and by the external pathway [49]. A micelles-forming carboxy-functionalized polymer was reacted with cisplatin in order to obtain the diammineplatinum(II) functionalized multinuclear polymer **18** for improved drug delivery (Fig. 13.2) [50]. Though the growth inhibitory activity of **18** (IC_{50} ca. 10 μg/mL after 48 h) was reduced in MDA-MB-231 cells when compared with cisplatin, increased platinum release was observed from the polymer micelles **18** at lower pH values (pH 5) [50].

Platinum(IV) complexes are usually more inert than platinum(II) complexes and they need to get activated by reduction to cytotoxic platinum(II) species in the hypoxic tumor environment. A prominent example is the orally applicable Pt(IV) complex satraplatin (Fig. 13.3) that had entered advanced clinical trials [51]. However, a phase 2 trial of satraplatin for the treatment of metastatic breast cancer patients dating from 2009 revealed only limited activity of satraplatin as a single agent (2 PRs, 18 SDs, from a total number of 31 metastatic breast cancer patients) [52]. A more focussed clinical study with patients suffering from advanced breast cancer characterized by HR repair deficiency would probably lead to better results for satraplatin treatment as it was the case for cisplatin and carboplatin [19, 20]. Due to the octahedral structure of Pt(IV) complexes, two more ligands can be introduced which may be applied for the fine-tuning of the biological and pharmacological properties. Inorganic chemists already took advantage of this option in designing new potent anticancer active Pt(IV) complexes [53].

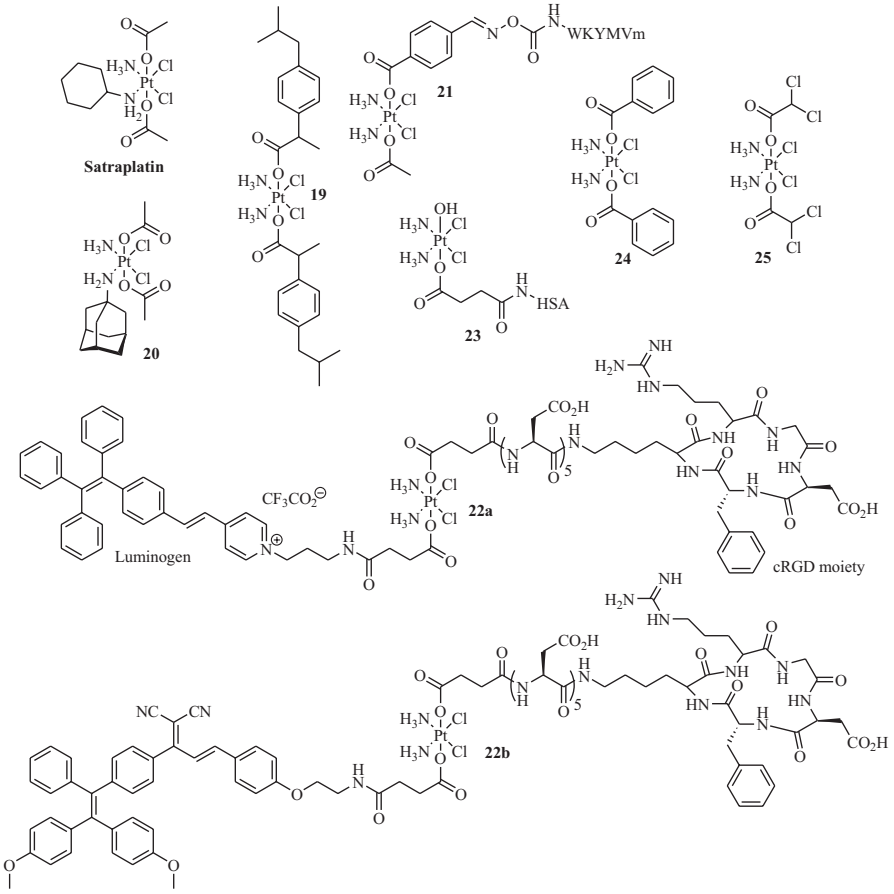

Fig. 13.3 Platinum(IV) complexes with activity against TNBC cells

The lipophilic ibuprofen platinum(IV) complex **19** revealed excellent growth inhibitory activity in MDA-MB-231 cells (IC_{50} = 0.05 μM) and was much more active than the platinum(II) complex cisplatin (IC_{50} = 20 μM) as a consequence of a much higher accumulation in the cancer cells (Fig. 13.3) [54]. LA-12 (**20**), a close adamantylamine analog of satraplatin, was also distinctly inhibiting the growth of MDA-MB-231 cells (IC_{50} = 2.4 μM) (Fig. 13.3) [55]. Interestingly, its formulation as a tumor-targeted folate-cyclodextrin conjugate augmented its activity against MDA-MB-231 cells significantly (IC_{50} = 0.7 μM) [55]. Since the FPR1/2 formyl peptide receptor is overexpressed in immune cells as well as in metastases, the Pt(IV) complex **21** was conjugated to a FPR1/2-targeting peptide (WKYMVm) in order to achieve synergy effects [56]. While **21** exhibited growth inhibitory activity against MDA-MB-231 cells in the range of cisplatin, **21** led to an enhanced secretion of TNF-α and IFN-γ in peripheral blood mononuclear cells (PBMC) when compared to cisplatin [56]. The fact that PBMCs activated by **21** efficiently inhibited

MDA-MB-231 cell growth renders this complex a promising potential immunomodulating drug candidate [56]. Another Pt(IV) complex **22**, comprising an aggregation-induced emission luminogen and the integrin-targeting moiety cRGD (cyclic arginine-glycine-aspartate), was used for the study of bio-reduction of the Pt(IV) moiety [57]. The $\alpha_v\beta_3$ integrin-expressing MDA-MB-231 cells responded much better to **22a** (IC_{50} = 30.2 μM) than MCF-7 breast cancer cells with only low integrin expression (no response up to 50 μM) [57]. Following this, a similar cRGD-Pt(IV) complex **22b** linked to a photosensitizer with AIE characteristics was prepared, and irradiation with light strongly enhanced the growth inhibitory activity of **22b** in MDA-MB-231 cells (IC_{50} = 4.2 μM) when compared with its efficacy in the dark (IC_{50} = 37.1 μM) and with that of cisplatin (IC_{50} = 33.4 μM) [58]. Human serum albumin (HSA) was linked to Pt(IV) via a succinate to give complex **23** which served as starting material for the preparation of calcium phosphate(CaP)-**23** nanoparticles that release the platinum drug under acidic and hypoxic conditions [59]. Indeed, CaP-**23** exhibited better activity against MDA-MB-231 cells (IC_{50} = 1.36 μM) than cisplatin (IC_{50} = 2.66 μM) [59]. Another potent Pt(IV) complex is the bis-benzoyl complex **24** which was highly active against MDA-MB-231 cells (IC_{50} = 0.59 μM) [60]. Incorporation of **24** into silk fibroin nanoparticles (SNF) even augmented the activity of **24** slightly (IC_{50} = 0.39 μM) and increased its tumor selectivity [60]. MDA-MB-468 is another TNBC cell line that was applied to study the anticancer effects of mitaplatin **25** [61]. Complex **25** (1 mg/kg) inhibited the in vivo growth of MDA-MB-468 mouse xenograft tumors distinctly (tumor volume ca. 200 mm^3 for **25** vs. ca. 900 mm^3 for the control mice after 24 days) [61]. Encapsulation of **25** into polymer nanoparticles led to a similar tumor growth inhibition and to a prolonged drug circulation in the blood system of the treated mice while the accumulation in the kidneys was reduced [61].

ER-positive T47D breast carcinoma cells are less responsive to cisplatin than ER-positive MCF-7 breast carcinoma cells due to an enhanced glutathione-*S*-transferase (GST)-mediated drug resistance [62, 63]. However, the triazolopyrimidine diacetatoplatinum(II) complex **26** (Fig. 13.4) showed excellent and tumor selective activity against T47D breast cancer cells (IC_{50} = 0.26 μM) and it exceeded the activity both of cisplatin (IC_{50} = 14.4 μM) and of oxaliplatin (IC_{50} = 18.3 μM) by far [64]. A similar malonatoplatinum(II) complex **27** exhibited distinct growth inhibition of T47D cells (IC_{50} = 3.4 μM) while non-malignant cells were affected less (IC_{50} = 55.8 μM) [65]. A new platinum(II) conjugate **28** bearing a steroidal 7-azaindole ligand also showed increased activity against T47D cells (IC_{50} = 13 μM) when compared with cisplatin (IC_{50} = 33 μM) (Fig. 13.4) [66]. Complex **28** was also accumulated to a greater extend in the T47D cancer cells than cisplatin, and it displaced the intercalator ethidium bromide from plasmid DNA and inhibited cathepsin B [66]. The analogous tri-(*p*-trifluoromethylphenyl)-phosphinoplatinum(II) complex **29** inhibited the growth of T47D cells much more strongly (IC_{50} = 1.84 μM) than cisplatin (IC_{50} = 30 μM) [67]. Complex **29** arrested the cancer cell cycle in the G0/G1 phase and it inhibited cathepsin B (IC_{50} = 8.1 μM) [67]. The *trans*-dichloridoplatinum(II) complex **30** featuring a ferrocene-based ligand was also a

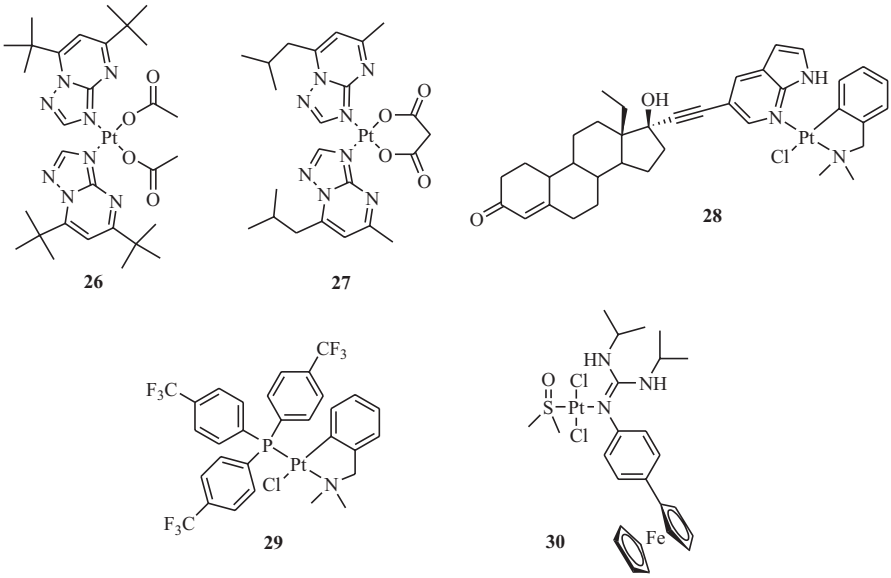

Fig. 13.4 Platinum complexes with improved activity against cisplatin-resistant T47D breast cancer cells

stronger inhibitor of the growth of T47D cells (IC_{50} = 2.4 μM) than cisplatin (IC_{50} = 15 μM) [68].

HER2 epidermal growth factor receptors are overexpressed in many aggressive tumors including breast cancer. Trastuzumab is a clinically approved monoclonal antibody that targets HER2, and a trastuzumab-platinum(IV) conjugate **31** was prepared as a tumor-targeted drug (Fig. 13.5) [69]. Complex **31** bound to HER2 and was much more active against HER2-positive SK-BR-3 breast carcinoma cells when compared with HER2-negative cell lines and it inhibited the growth of SK-BR-3 cells (IC_{50} = 21.3 μM) as effectively as cisplatin (IC_{50} = 20.7 μM) [69]. A platinum(II) conjugate **32** (Fig. 13.5) of the HER2-targeting antibody herceptin showed similar results (IC_{50} = 19.7 μM in SK-BR-3 cells) and an activity better than that of oxaliplatin (IC_{50} = 31.0 μM) [70]. In addition, a HER2-targeting affibody (= small peptidic antibody mimics) was conjugated to cisplatin-loaded liposomes, and the resulting affisome showed increased cytotoxicity and cellular accumulation in SK-BR-3 cells and it exhibited distinct tumor growth inhibition of HER2-positive TUBO breast cancer xenograft models [71].

Another study disclosed that epithelial breast cancer cells were 16-times more sensitive to complex **33** (IC_{50} = 5.3 μM) than to cisplatin (IC_{50} = 94.7 μM) (Fig. 13.5) [72]. Complex **33** reduced the expression of the anti-apoptotic Bcl-2 protein and augmented pro-apoptotic Bax expression leading to the efficient induction of apoptosis by **33** in cisplatin-resistant epithelial breast cancer cells [72].

ER-positive MCF-7 breast cancer cells under hypoxic conditions showed reduced sensitivity to cisplatin. The tetrachloridoplatinum(IV) complex **34** (Fig. 13.5)

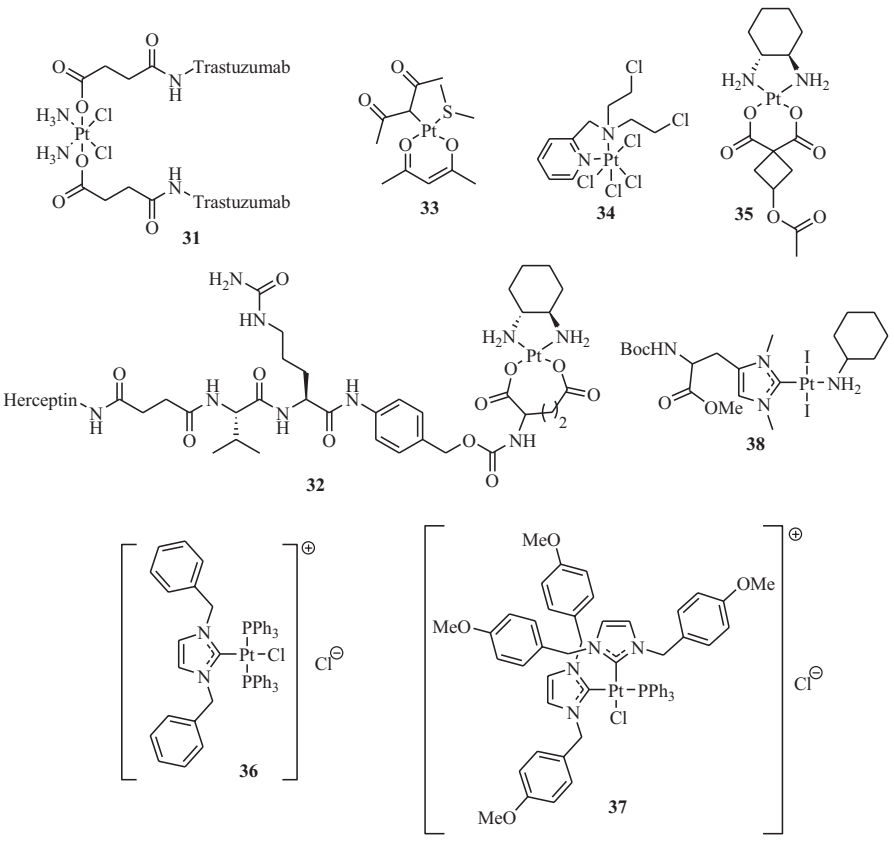

Fig. 13.5 Platinum complexes with distinct activity against various advanced or resistant breast cancers

containing the alkylating nitrogen mustard motif exhibited higher activity against MCF-7 cells both under normoxic (IC_{50} = 11.4 μM) and hypoxic conditions (IC_{50} = 8.6 μM) than cisplatin (IC_{50} = 14.1 μM under normoxic, 18.7 μM under hypoxic conditions) [73]. In addition, **34** was more efficacious in MCF-7 cells supplemented with the cisplatin-resistance factor glutathione (GSH) (IC_{50} = 12.9 μM under normoxic, 11.2 μM under hypoxic conditions) when compared with cisplatin (IC_{50} = 27.8 μM under normoxic, 29.0 μM under hypoxic conditions). **34** also showed an increased accumulation in MCF-7 cells (more than twice as high than that for cisplatin) [73]. In addition, **34** induced apoptosis and reduced the motility of MCF-7 cells [73]. The new water-soluble oxaliplatin/carboplatin analogue **35** showed growth inhibitory activity (IC_{50} = 15.0 μM) comparable with oxaliplatin (IC_{50} = 10.4 μM) and much better than carboplatin (IC_{50} = 154 μM) in multidrug-resistant MCF-7/ADR breast cancer cells (Fig. 13.5) [74]. The in vivo anticancer

activity of **35** was evaluated in KM mice bearing Sarcoma 180. Complex **35** led to a greater inhibition of the tumor growth (53.2% inhibition) than oxaliplatin (32.5% inhibition) [74].

In addition, various *N*-heterocyclic carbene platinum complexes were recently investigated for their effect on multidrug-resistant MCF-7/Topo breast cancer cells which overexpress the BCRP transporter [75–77]. Complex **36** (Fig. 13.5) showed excellent and selective growth inhibition (IC_{50} = 0.15 μM) in MCF-7/Topo cells when compared with cisplatin (IC_{50} = 10.6 μM) [75]. Although **36** did not bind covalently to DNA, this complex induced DNA aggregation in addition to cell cycle arrest in the G1 phase. It also led to the disruption of blood vessels [75]. Similar DNA aggregation effects were observed for biscarbene complex **37** (Fig. 13.5), which also showed strong MCF-7/Topo cell growth inhibition (IC_{50} = 0.52 μM) [76]. Another *trans*-diiodidoplatinum(II) NHC complex **38** featuring a histidine-derived NHC-ligand also strongly inhibited the growth of MCF-7/Topo cells (IC_{50} = 1.6 μM) (Fig. 13.5) [77]. Complex **38** induced morphological changes in plasmid DNA and caused vascular disruption [77]. Its in vivo activity was evaluated in mice with cisplatin-resistant A2780cis ovarian tumors. Complex **38** (30 mg/kg, i.p.) was roughly as effective a tumor growth inhibitor as cisplatin (6 mg/kg, i.p.), yet showed a superior toxicity profile with treated mice regaining their normal weight far more quickly [77]. Hence, complex **38** is likely applicable in much higher doses than cisplatin to the effect of a significantly better tumor mass reduction.

In order to reduce the systemic toxicity of platinum complexes, a tumor-selective Pt(IV) complex conjugate **39** comprising a short self-assembling peptide sequence was prepared (Fig. 13.6) [78]. Alkaline-phosphatase (AP)-catalyzed cleavage of the phosphate group of **39** led to self-assembly and bioreduction to active platinum species in the tumor (high levels of AP are found in the environment of many tumors). Increased tumor cell accumulation as well as reduced liver and kidney toxicity were observed for 4T1-breast carcinoma xenograft models treated with **39** while the in vivo 4T1 tumor growth was inhibited by **39** similarly to cisplatin [78].

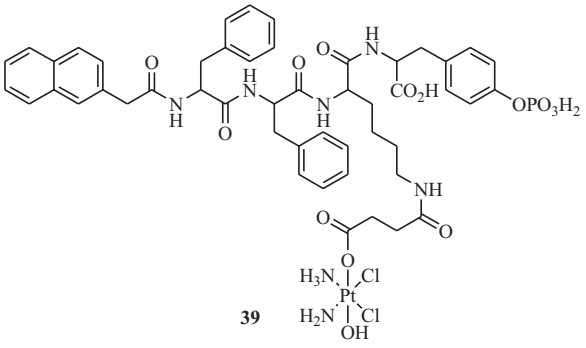

Fig. 13.6 Self-assembling Pt(IV) complex prodrug **39** for 4T1-breast cancer targeting

13.4 Conclusions

The platinum complex cisplatin has been and still is a mainstay in the therapy of solid tumors. However, meanwhile more platinum complexes have passed clinical trials and quite a few of them were found active against drug-resistant and advanced breast cancers. HR-repair deficient triple-negative breast cancers appeared to be especially sensitive to platinum drugs. Their chemical tuning in terms of structure, redox chemistry, and synergistic effects of ligands and co-conjugates has led to a plethora of new complexes with enhanced activity against and selectivity for drug-resistant and/or aggressive/metastatic breast cancers. In addition, novel delivery systems for the targeted therapy of breast cancers with platinum complexes have overcome the notorious drawbacks of the first- and second-generation platinum complexes. Taken together, there are distinct glimpses of hope that new therapies with platinum complexes will prevent or overcome drug resistance, improve prognosis and survival, reduce side-effects, and increase the quality of life of breast cancer patients in a not too distant future.

Acknowledgments Own work referenced in this chapter was supported by grants from the Deutsche Forschungsgemeinschaft (Scho 402/8 and Scho 402/12).

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