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Communication

Tricarbonylrhenium(I) complexes with heterodentate ligands based on functionalized amides: Synthesis, structural features, and cytotoxic activity

Diana V. Aleksanyan [a, *], Svetlana G. Churusova [a], Ekaterina Yu. Rybalkina [b], Oleg I. Artyushin [a], Alexander S. Peregudov [a], Yulia V. Nelyubina [a, c], Zinaida S. Klemenkova [a], Olga V. Bykhovskaya [a], Vladimir A. Kozlov [a]

[a] Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, Moscow, 119991, Russia
[b] Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation, Kashirskoe Shosse 23, Moscow, 115478, Russia
[c] Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, Leninskii pr. 31, Moscow, 119991, Russia

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ABSTRACT

The reactions of 2-diphenylphosphorylaniline with 2-methylsulfanylbenzoyl chloride or 2-diphenylphosphinobenzoic acid in the presence of a coupling agent afforded new potentially tridentate ligands with different donor sets. Upon interaction with $Re(CO)_5Br$, the compounds obtained formed either bidentately bound molecular or pincer-type tricarbonylrhenium(I) complexes depending on the reaction conditions. The resulting complexes were fully characterized in solution and in the solid state by multinuclear NMR and IR spectroscopy and, in most cases, by single-crystal X-ray diffraction. The preliminary evaluation of cytotoxicity of the complexes obtained against human colon (HCT116), breast (MCF7), and prostate (PC3) cancer cell lines revealed the high activity of κ^3-*S,N,O*-pincer-type complex with ancillary *S*-donor group. The latter demonstrated considerable effect also on transformed breast cell line HBL100 and its doxorubicin-resistant subline HBL100/Dox.

1. Introduction

Rhenium compounds bearing ^{186}Re and ^{188}Re radionuclides have already been recognized as efficient radiopharmaceuticals in nuclear medicine and found a special niche in cancer treatment [1]. Owing to the unique photophysical properties, cold organometallic rhenium complexes are traditionally designed and used as luminescent probes for cell imaging, emissive phosphors in organic light-emitting diodes, and photosensitizers in photocatalysis [2]. Despite the remarkable cytotoxic activities of a range of rhenium complexes with bidentate heterocyclic, organophosphorus and organoselenium, labile alkoxide and hydroxide ligands (Fig. 1), their potential as antitumor agents is still essentially underestimated [3]. At the same time, in pursuit of new anticancer agents, many research groups focus their attention on different transition metal complexes, including platinum, ruthenium, zinc, palladium, and gold derivatives [4]. Organometallic and metal-organic compounds are of particular interest for the development of potential drugs owing to the possibility to finely tune their properties by variation of the metal nature and its oxidation state as well as the number and type of coordinated ligands.

Functionalized carboxamides with the central secondary amide units and ancillary donor groups both in the amine and acid parts can serve as versatile ligands for different transition metals, including Re(I) ions [5]. Depending on the reaction conditions, they usually adopt either neutral bidentate or monoanionic tridentate pincer-type coordination mode, the latter resulting from smooth cyclometalation *via* activation of the amide N–H bond. It is noteworthy that there are only a few examples of cytotoxic cationic rhenium(I) complexes with multidentate ligands [6], whereas the anticancer activity of cyclometallated derivatives has not been studied at all. At the same time, the application of multidentate ligands can ensure higher stability of the potential drugs in biological environment. Furthermore, recently it was found that cyclopalladated complexes of different functionalized amides can exhibit high cytotoxic activity against several cancer cell lines [7].

* Corresponding author.
E-mail address: aleksanyan.diana@ineos.ac.ru (D.V. Aleksanyan).

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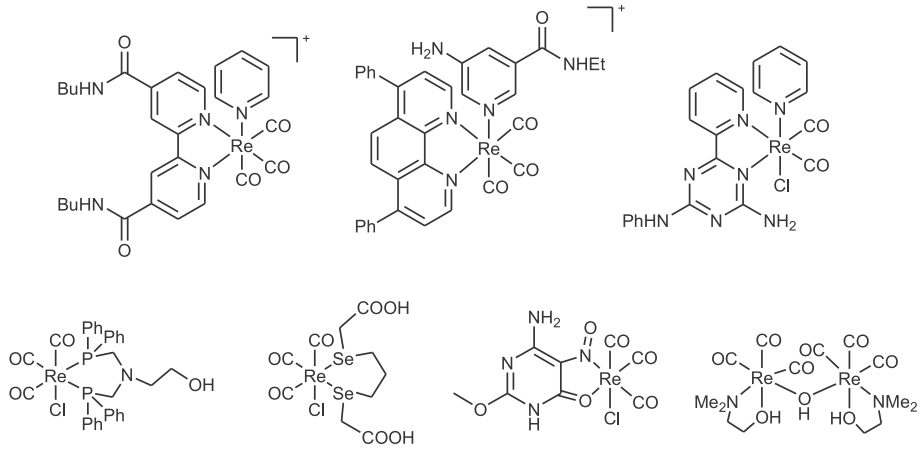


Fig. 1. Examples of cytotoxic rhenium(I) complexes (for recent reviews, see Ref. [3]).

Therefore, it seemed interesting to obtain Re(I) complexes based on multidentate carboxamide ligands and evaluate the effect of their structures on cytotoxic properties.

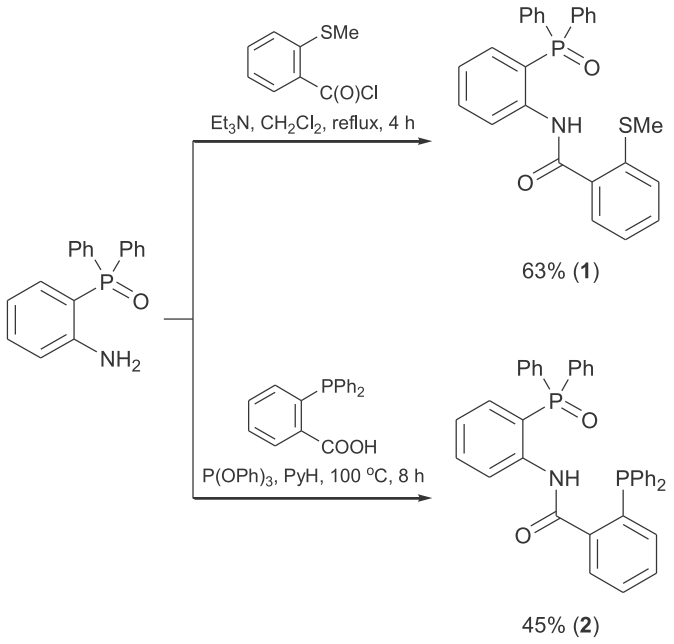
Herein, we report on the synthesis of new functionalized amide ligands based on 2-diphenylphosphorylaniline and 2-methylsulfanyl- or 2-diphenylphosphinobenzoic acid and their complexing features toward Re(I) ions. The cytotoxic effects of the resulting tricarbonylrhenium(I) complexes are discussed.

2. Results and discussion

The target amide bearing ancillary *S*-donor group was readily obtained by the reaction of the key aniline, 2-diphenylphosphorylaniline, with 2-methylsulfanylbenzoic acid chloride under mild conditions (compound **1**, Scheme 1). Its counterpart with diphenylphosphino donor group in the acid part was obtained upon interaction of the mentioned aniline and the corresponding acid in the presence of a coupling agent (compound **2**, Scheme 1). It should be emphasized that the key phosphorylated aniline has been already used for the successful synthesis of several series of multidentate ligands affording transition metal complexes with unusual structures and high catalytic activities [5a,8].

The ligands obtained are thermally stable crystalline solids, soluble in common organic solvents. Their structures were confirmed by the multinuclear NMR and IR spectroscopic data. The ^{31}P NMR spectrum of ligand **1** shows a sole singlet signal at 37.16 ppm, whereas the phosphorus resonances of its P(III)-analog are observed at $\delta_P = -7.39$ and 37.18 ppm, in the regions typical for tertiary phosphines and phosphine oxides, respectively. The ^{1}H NMR spectra show, along with the aromatic proton signals, the expected downfield broad singlets of NH protons ($\delta_H = 11.66$ (**1**), 11.56 (**2**) ppm). Despite the presence of a large amount of benzene rings, the ^{13}C NMR spectra of these compounds can be readily assigned (see Experimental section). Finally, the IR spectra of the solid samples display the characteristic stretching (ν(C=O): *ca.* 1675 cm^{-1}, ν(N–H): 3250–3296 cm^{-1}) and bending (1513–1531 cm^{-1}) vibrations associated with the secondary amide unit. The absorption bands of P=O bonds are observed at 1160–1171 cm^{-1}. The identities of heterodentate ligands **1**, **2** were also supported by the elemental analyses.

The complexing features of the functionalized amides derived toward Re(I) ions were studied in reactions with $Re(CO)_5Br$ both in the presence and in the absence of a base. It was found that the

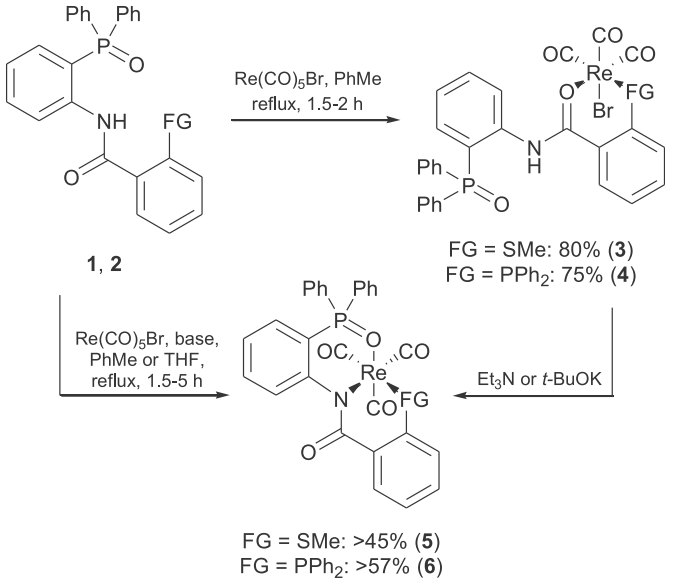


Scheme 1. Synthesis of functionalized carboxamide ligands **1**, **2**.

interaction of **1** and **2** with the mentioned rhenium(I) precursor upon refluxing in toluene without addition of a base affords κ^2-*X*,*O*-complexes **3** and **4**, respectively (Scheme 2). The bidentate coordination of ligands **1** and **2** in these molecular complexes is realized through the oxygen atom of the carbonyl moiety and ancillary *S*- or *P*-donor group of the acid component. The reactions performed in the presence of a base resulted in the metalation of the central secondary amide unit with concomitant coordination of both Ph_2P=O and MeS- or Ph_2P-donor groups, affording κ^3-*X*,*N*,*O*-pincer complexes **5** and **6** (Scheme 2). The same cyclometallated products were also obtained in good yields upon treatment of compounds **3** and **4** with a base, which confirms the intermediate role of the latter in the formation of pincer-type complexes. Interestingly, the related heterodentate ligand derived from 2-diphenylphosphorylaniline and phosphorylacetic acid afforded a stable ten-membered metallocycle as an intermediate compound in the synthesis of a κ^3-*O*,*N*,*O*-pincer complex [5a]. In this unusual

derivative, the neutral ligand appeared to be coordinated *via* the oxygen atoms of both of the pendant phosphoryl arms, whereas the central amide unit remained intact. Presumably, the predominant formation of six-membered metallocycles in the case of ligands **1** and **2** is connected with the more rigid ligand framework compared to the above-mentioned phosphorylacetic acid amide. It should also be noted that sulfide-based complex **5** can be obtained using Et_3N as a base, while the synthesis of its counterpart with diphenylphosphino group requires the application of a stronger base, for example, *t*-BuOK. The reaction of ligand **2** with $Re(CO)_5Br$ in the presence of Et_3N in air led to a mixture of bi- and tridentately bound complexes **4** and **6** with bis(phosphine oxide) **7**, which resulted from partial oxidation of the starting phosphine. The products were separated by column chromatography. The identity of the bis(phosphine oxide) derivative was confirmed by comparison with an authentic sample obtained by the oxidation of ligand **2** with H_2O_2. In turn, the reaction with *t*-BuOK can be carried out without taking precautions to exclude air.

The structures of all the complexes obtained were confirmed by the multinuclear NMR and IR spectroscopic data. Thus, the ^{31}P NMR spectra of bromide complexes **3** and **4** show singlet signals associated with the $Ph_2P(O)$-group in the region typical for free tertiary triarylphosphine oxides ($\delta_P = 38.98$ and 38.78 ppm, respectively). The absence of coordination by the phosphoryl pendant arm in these complexes is further supported by the P═O bond stretching vibrations in the IR spectra, which are observed at 1152–1175 cm^{-1} (compare with ν(P═O) of ligands **1**, **2**: 1160–1171 cm^{-1}). In turn, the phosphorus resonance of the Ph_3P-group in the ^{31}P NMR spectrum of complex **4** appeared to be strongly deshielded due to complexation ($\delta_P = 14.52$ ppm, $\Delta\delta_P = 21.91$ ppm). The coordination of the methylsulfanyl group in its counterpart **3** is indirectly evidenced by the shifts of the signals of SMe hydrogen and carbon nuclei ($\Delta\delta_H = 0.33$ ppm, $\Delta\delta_C = 1.36$ ppm). The presence of downfield NH proton signals in the ^1H NMR spectra of both intermediate complexes **3** and **4** ($\delta_H = 13.12$ (**3**), 12.97 (**4**) ppm), the characteristic stretching and bending vibrations of the non-metallated C(O)NH moiety (at 1537–1555 and 3166 cm^{-1}) along with the low-frequency displacement of C═O bond stretching vibrations ($\Delta\nu$(C═O) up 75 cm^{-1}) in their IR spectra confirm the coordination of the central amide unit by the oxygen atom. In contrast, the NMR and IR spectra of pincer complexes **5** and **6** are indicative of metalation of the amide group *via* activation of the N–H bond. This is reflected in the absence of the mentioned NH proton signals in their ^1H NMR spectra and the absence of characteristic absorption bands of the secondary amide group in the IR spectra (for example, ν(N–H)). Furthermore, the C═O bond stretching vibrations appeared to be displaced down to 1593 cm^{-1} ($\Delta\nu$(C═O): 77–82 cm^{-1}). Unlike their molecular predecessors, coordination of the P═O groups in complexes **5** and **6** afforded significant low-frequency displacement of the corresponding absorption bands: ν(P═O) 1124–1129 cm^{-1}, $\Delta\nu$(P═O) up to 47 cm^{-1}. Strong downfield shifts of all the phosphorus signals in the ^{31}P NMR spectra of compounds **5** and **6** compared to those of the free ligands confirm the complexation by the phosphorus-containing ancillary donor groups. The ^{31}P NMR spectrum of bis(phosphorus) derivative **6** revealed a spin–spin coupling between two phosphorus atoms through the metal center ($^3J_{PP} = 4.0$ Hz). Interestingly, the ^{31}P and ^1H NMR spectra of complex **5** in $CDCl_3$ at room temperature showed broadened and poorly resolved signals. Heating of the solution to 50 °C afforded a sharp singlet with $\delta_P = 48.32$ ppm (Fig. S1 in Supplementary Data (SD)). In contrast, cooling to −15 °C resulted in two phosphorus resonances with close chemical shifts, which correspond to two different isomeric species with relative contents of 54% ($\delta_P = 48.07$ ppm) and 46% ($\delta_P = 49.43$ ppm). Earlier, the formation of two isomeric forms in solution was observed for a palladium(II) pincer complex based on the related thiophosphoryl-functionalized ligand [9]. As well as in the case of the mentioned Pd(II) complex, two isomers of complex **5** are likely to result from complicated inversion of the sulfur-containing metallocycle and, therefore, differ in the mutual disposition of two fused six-membered metal-containing rings.



Scheme 2. Complexation of ligands **1**, **2** with Re(I) ions.

The structures of complexes **3**, **5**, and **6** were also elucidated by single-crystal X-ray diffraction (Figs. 2–4). The results obtained confirm the bidentate coordination mode of neutral ligand **1** in complex **3** and tridentate pincer-type coordination of deprotonated ligands **1** and **2** in complexes **5** and **6**, respectively. Table 1 lists the selected bond lengths and angles for the complexes explored. In all cases, $Re(CO)_3$ moiety adopted facial configuration and the metal center displayed a slightly distorted octahedral geometry. Thus, three carbonyls in each compound appeared to be nonequivalent due to the heterodentate nature of the coordinated ligands, with the largest Re–C bond observed for the carbonyl ligand *trans* to the phosphine group (1.965 Å) and the shortest Re–C bonds observed for the carbonyl ligand *trans* to the phosphoryl group in both pincer derivatives (1.887–1.890 Å). The lengths of Re–O, Re–N, Re–P, Re–S, and Re–Br bonds were within the expected ranges (Table 1). Of note are the changes in the geometric parameters of the central amide unit and phosphoryl pendant arm on passing from molecular complex **3** to parent pincer product **5**: elongation of the C–N and P═O bonds along with shortening of the C═O bond. In crystal, the molecules of complex **3** are arranged into centrosymmetric dimers owing to the NH…O hydrogen bonds between the non-metallated amide unit and phosphoryl group.

The cytotoxic properties of the complexes obtained were tested against several cancer cell lines, including human colon (HCT116), breast (MCF7), and prostate (PC3) cancer. The results are presented in Table 2 as the concentrations required for 50% inhibition of cell growth. While tricarbonylrhenium(I) bromide complex **3** bearing ancillary *S*-donor group appeared to be almost inactive even at the relatively high concentration (80 μM, entry 1), its counterpart with diphenylphosphino moiety displayed the high level of cytotoxic effect on all the cancer cell lineages explored (entry 2). A further increase in the antiproliferative activity was observed on passing to κ^3-*S,N,O*-pincer derivative **5**, for which the values of IC_{50} fell into the low micromolar range (10.0–12.5 μM, entry 3) and were even

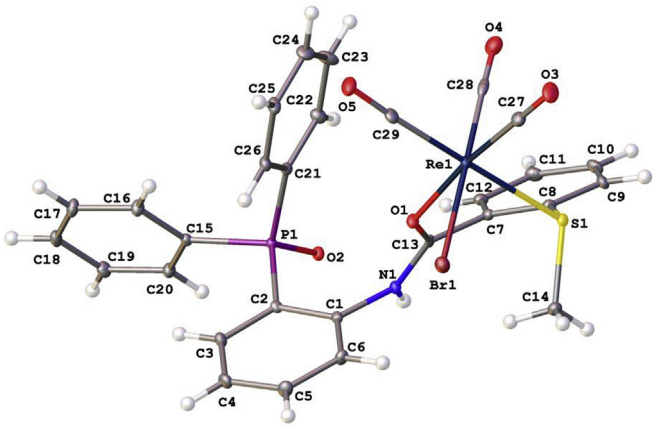


Fig. 2. General view of complex **3.** Solvate toluene molecules are omitted for clarity. Hereinafter, the non-hydrogen atoms are shown as thermal ellipsoids at 50% probability level.

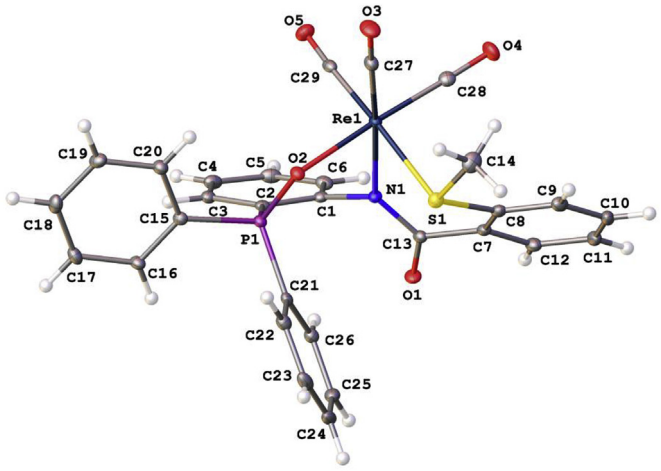


Fig. 3. General view of complex **5**.

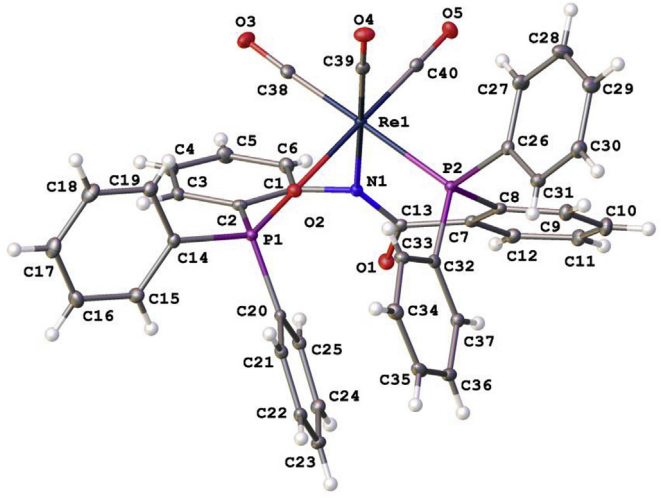


Fig. 4. General view of complex **6**. Solvate chloroform molecules are omitted for clarity.

somewhat lower than for a clinically used drug—cisplatin (entry 4). Unfortunately, we failed to measure the cytotoxicity of its P(III)-counterpart **6** due to its low solubility in DMSO. Furthermore, additional tests on healthy human embryonic kidney cells (HEK293) did not reveal the selectivity in action of the compounds under consideration. However, the cytotoxicity assays with pincer complex **5** on transformed breast cells HBL100 and doxorubicin-resistant subline HBL100/Dox showed almost the same levels of efficiency (*cf.* IC_{50} 13.5 and 15.5 μM, Fig. S2 in SD), whereas the corresponding values of IC_{50} for doxorubicin composed 0.40 (HBL100) and 53.0 (HBL100/Dox) μM, respectively. This opens prospects for the development of potential therapeutic agents that would be able to overcome drug resistance based on the related Re(I) complexes. Of particular interest are further modification of the functionalized carboxamide ligand framework and detailed investigations on the effect of structures of tricarbonylrhenium(I) complexes on their cytotoxic activity.

3. Conclusions

To summarize the results presented, new carboxamide ligands based on *ortho*-phosphorylated aniline and *ortho*-functionalized benzoic acids were found to form tricarbonylrhenium(I) complexes with either bidentate neutral or tridentate monoanionic pincer-type coordination. Preliminary investigations on the cytotoxic activity of the resulting complexes against several human cancer cell lines revealed high efficiency of κ^3-*S,N,O*-pincer complex, rendering further search for potential anticancer agents among related Re(I) pincer complexes very promising.

4. Experimental

4.1. General remarks

If not mentioned otherwise, all manipulations were carried out without taking precautions to exclude air and moisture. Dichloromethane was distilled from P_2O_5. Tetrahydrofuran was distilled over sodium benzophenone ketyl. Pyridine was distilled over CaH_2. 2-(Diphenylphosphoryl)aniline was synthesized by the oxidation of 2-diphenylphosphinoaniline [10] according to the published procedure [5a]. 2-(Methylsulfanyl)benzoyl chloride was obtained from thiosalicylic acid *via* sequential treatment with MeI [11] and $SOCl_2$ [12]. 2-Diphenylphosphinobenzoic acid was obtained starting from 2-chlorobenzoic acid and triphenylphosphine [13]. All other chemicals and solvents were used as purchased.

The NMR spectra were recorded on Bruker Avance 300, Avance 400, and Avance 500 spectrometers, and the chemical shifts (δ) were referenced internally by the residual solvent signals relative to tetramethylsilane (^1H, ^{13}C) or externally to H_3PO_4 (^{31}P). In most cases, $^{13}C\{^1H\}$ NMR spectra were registered using the *J*MODECHO mode; the signals for the *C* nuclei bearing odd and even numbers of protons have opposite polarities. The NMR spectra of the ligands and complexes were assigned based on the data obtained previously for the related compounds [5a,7b,9].

The IR spectra were recorded on a Nicolet Magna-IR750 FT spectrometer (resolution 2 cm^{-1}, 128 scans). The assignment of absorption bands in the IR spectra was made according to Ref. [14]. Column chromatography was carried out using Macherey-Nagel silica gel 60 (MN Kieselgel 60, 70–230 mesh). Melting points were determined with an MPA 120 EZ-Melt automated melting point apparatus (Stanford Research Systems).

Table 1
Selected bond lengths (Å) and angles (°) for compounds **3**, **5**, and **6**.

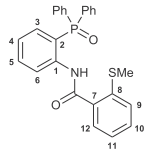
3			
Re(1)–C(27)	1.903(3)	N(1)–C(13)	1.332(3)
Re(1)–C(28)	1.955(3)	C(27)–Re(1)–C(28)	87.89(11)
Re(1)–C(29)	1.926(3)	C(28)–Re(1)–C(29)	89.24(11)
Re(1)–Br(1)	2.6185(3)	C(29)–Re(1)–C(27)	87.35(10)
Re(1)–S(1)	2.4905(6)	O(1)–Re(1)–Br(1)	81.64(5)
Re(1)–O(1)	2.1801(16)	Br(1)–Re(1)–S(1)	89.808(15)
S(1)–C(8)	1.788(2)	S(1)–Re(1)–O(1)	82.36(5)
S(1)–C(14)	1.809(3)	C(27)–Re(1)–O(1)	173.70(9)
P(1)–O(2)	1.4969(17)	C(28)–Re(1)–Br(1)	177.95(7)
O(1)–C(13)	1.252(3)	C(29)–Re(1)–S(1)	178.65(8)
5			
Re(1)–C(27)	1.914(3)	N(1)–C(13)	1.360(3)
Re(1)–C(28)	1.890(3)	C(27)–Re(1)–C(28)	87.12 (12)
Re(1)–C(29)	1.924(3)	C(28)–Re(1)–C(29)	86.29(12)
Re(1)–O(2)	2.1904(19)	C(29)–Re(1)–C(27)	90.72(12)
Re(1)–S(1)	2.4749(8)	S(1)–Re(1)–N(1)	79.57(6)
Re(1)–N(1)	2.181(2)	N(1)–Re(1)–O(2)	82.50(8)
S(1)–C(8)	1.789(3)	S(1)–Re(1)–O(2)	81.98(5)
S(1)–C(14)	1.806(3)	C(27)–Re(1)–N(1)	172.37(11)
P(1)–O(2)	1.526(2)	C(28)–Re(1)–O(2)	174.57(10)
O(1)–C(13)	1.233(3)	C(29)–Re(1)–S(1)	173.25(8)
6			
Re(1)–C(38)	1.965(3)	C(38)–Re(1)–C(39)	88.70(12)
Re(1)–C(39)	1.915(3)	C(39)–Re(1)–C(40)	89.99(12)
Re(1)–C(40)	1.887(3)	C(40)–Re(1)–C(38)	88.73(12)
Re(1)–P(2)	2.4331(7)	P(2)–Re(1)–N(1)	84.14(6)
Re(1)–O(2)	2.1992(19)	N(1)–Re(1)–O(2)	82.53(8)
Re(1)–N(1)	2.192(2)	O(2)–Re(1)–P(2)	89.59(5)
P(1)–O(2)	1.519(2)	C(38)–Re(1)–P(2)	177.48(9)
O(1)–C(13)	1.244(3)	C(39)–Re(1)–N(1)	175.21(10)
N(1)–C(13)	1.351(4)	C(40)–Re(1)–O(2)	176.75(10)

Table 2
Cytotoxic activity of the rhenium(I) complexes obtained (IC_{50}, μM).

Entry	Compound	Cancer cell lines			Healthy cell line
		HCT116	MCF7	PC3	HEK293
1	**3**	62.0 ± 18.0	>80	>80	>80
2	**4**	16.0 ± 2.0	26.0 ± 4.0	32.0 ± 2.0	18.0 ± 4.0
3	**5**	10.0 ± 2.0	12.5 ± 3.5	10.0 ± 2.0	5.5 ± 1.5
4	cisplatin	18.0 ± 2.0	25.0 ± 4.0	16.0 ± 3.0	12.5 ± 1.5

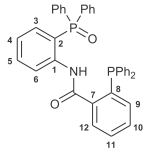
4.2. Syntheses

4.2.1. N-[2-(diphenylphosphoryl)phenyl]-2-(methylsulfanyl) benzamide, 1



2-(Methylsulfanyl)benzoyl chloride (0.42 g, 2.25 mmol) was added to a solution of 2-diphenylphosphorylaniline (0.66 g, 2.25 mmol) and Et_3N (0.23 g, 2.27 mmol) in 15 mL of CH_2Cl_2. The stirred reaction mixture was refluxed for 4 h. After cooling to room temperature, the resulting mixture was sequentially washed with water, aqueous solution of $NaHCO_3$, and again with water. The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated to dryness. The resulting residue was recrystallized from EtOAc–hexane (2:1) to give 0.63 g of ligand **1** as a white crystalline solid. Yield: 63%. Mp: 138–140°C. $^{31}P\{^1H\}$ NMR (161.98 MHz, $CDCl_3$): δ 37.16 ppm. ^1H NMR (400.13 MHz, $CDCl_3$): δ 2.42 (s, 3H, Me), 7.02–7.10 (m, 2H, H_{Ar}), 7.20 (dt, 1H, H_{Ar}, $^3J_{HH} = 7.5$ Hz, $^4J_{HH} = 1.1$ Hz), 7.30 (d, 1H, H_{Ar}, $^3J_{HH} = 8.0$ Hz), 7.40 (dt, 1H, H_{Ar}, $^3J_{HH} = 7.7$ Hz, $^4J_{HH} = 1.4$ Hz), 7.47–7.52 (m, 4H, H_{Ar}), 7.57–7.70 (m, 8H, H_{Ar}), 8.85 (dd, 1H, H(C6), $^3J_{HH} = 8.3$ Hz, $^4J_{HP} = 4.6$ Hz), 11.66 (br. s, 1H, NH) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$); δ 16.24 (s, Me), 117.37 (d, C2, $^1J_{CP} = 100.5$ Hz), 122.21 (d, C6, $^3J_{CP} = 7.4$ Hz), 122.85 (d, C4, $^3J_{CP} = 12.7$ Hz), 124.47 (s, C11), 125.86 (s, C9), 127.73 (s, C12), 128.74 (d, *m*-C in $P(O)Ph_2$, $^3J_{CP} = 12.4$ Hz), 130.99 (s, C10), 131.51 (d, *ipso*-C in $P(O)Ph_2$, $^1J_{CP} = 108.9$ Hz), 132.10 (d, *o*-C in $P(O)Ph_2$, $^2J_{CP} = 10.2$ Hz), 132.50 (d, *p*-C in $P(O)Ph_2$, $^4J_{CP} = 2.7$ Hz), 132.76 (d, C3, $^2J_{CP} = 10.8$ Hz), 133.47 (d, C5, $^4J_{CP} = 1.9$ Hz), 133.56 (s, C7), 140.22 (s, C8), 144.48 (d, C1, $^2J_{CP} = 3.0$ Hz), 166.61 (s, C=O) ppm. IR (KBr, ν/cm^{-1}): 489(w), 523(m), 550(s), 598(w), 655(w), 696(m), 733(m), 739(m), 752(m), 897(w), 997(w), 1057(w), 1120(m), 1134(w), 1164(m) and 1171(m) (both νP=O), 1246(w), 1305(s), 1437(s), 1513(br, m) and 1529(m) (C(O)NH), 1575(m), 1676(s) (νC=O), 3057(w), 3296(w) (νNH). Anal. Calcd for: $C_{26}H_{22}NO_2PS$: 70.41; H, 5.00; N, 3.16. Anal. Found: C, 70.21; H, 4.91; N, 3.07%.

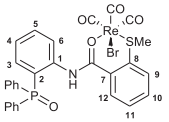
4.2.2. 2-(Diphenylphosphino)-N-[2-(diphenylphosphoryl)phenyl] benzamide, 2



A stirred solution of 2-diphenylphosphorylaniline (1.91 g, 6.51 mmol) and 2-diphenylphosphinobenzoic acid (1.99 g, 6.50 mmol) in 10 mL of pyridine was heated to 100 °C under an argon atmosphere. Triphenyl phosphite (2.02 g, 6.51 mmol) was

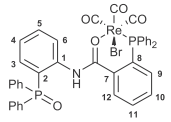
added at this temperature, and heating was continued for 8 h. After cooling to room temperature, pyridine was removed under vacuum. A solution of the resulting residue in chloroform was sequentially washed with water (3 × 30 mL), aqueous solution of $NaHCO_3$ (4 × 30 mL), and again with water (3 × 30 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue obtained was purified by column chromatography on silica gel (eluent: EtOAc–hexane (1:3)) to give 1.70 g of ligand **2** as a light-yellow crystalline solid. Yield: 45%. Mp: 91–92°C. $^{31}P\{^1H\}$ NMR (161.98 MHz, $CDCl_3$): δ −7.39 (PPh_2), 37.18 ($P(O)Ph_2$) ppm. ^1H NMR (400.13 MHz, $CDCl_3$): δ 6.94–7.03 (m, 3H, H_{Ar}), 7.26–7.33 (m, 11H, H_{Ar}), 7.38 (dt, 1H, H_{Ar}, $^3J_{HH} = 7.6$ Hz, $^4J_{HH} = 1.0$ Hz), 7.43–7.51 (m, 5H, H_{Ar}), 7.55–7.65 (m, 6H, H_{Ar}), 7.76 (dd, 1H, H(C12), $^3J_{HH} = 7.4$ Hz, $^4J_{HP} = 3.6$ Hz), 8.50 (dd, 1H, H(C6), $^3J_{HH} = 8.4$ Hz, $^4J_{HP} = 4.4$ Hz), 11.56 (br. s, 1H, NH) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 117.23 (d, C2, $^1J_{CP} = 101.0$ Hz), 122.41 (d, C6, $^3J_{CP} = 7.2$ Hz), 122.63 (d, C4, $^3J_{CP} = 12.7$ Hz), 126.95 (d, C9, $^2J_{CP} = 3.8$ Hz), 128.11 (s, *o*-C in PPh), 128.18 (s, *o*-C in PPh and *p*-C in PPh_2), 128.60 (d, *m*-C in $P(O)Ph_2$, $^3J_{CP} = 12.4$ Hz), 128.62 and 130.35 (both s, C10 and C11), 131.41 (d, *ipso*-C in $P(O)Ph_2$, $^1J_{CP} = 104.5$ Hz), 131.98 (d, *o*-C in $P(O)Ph_2$, $^2J_{CP} = 10.3$ Hz), 132.34 (d, *p*-C in $P(O)Ph_2$, $^4J_{CP} = 2.8$ Hz), 132.43 (d, C3, $^2J_{CP} = 11.0$ Hz), 133.22 (d, C5, $^4J_{CP} = 2.4$ Hz), 133.62 and 133.82 (both s, *m*-C in PPh_2), 134.60 (s, C12), 138.38 (d, C7, $^2J_{CP} = 12.0$ Hz), 138.55 (d, *ipso*-C in PPh_2, $^1J_{CP} = 23.0$ Hz), 140.04 (d, C8, $^1J_{CP} = 21.7$ Hz), 144.18 (d, C1, $^2J_{CP} = 3.1$ Hz), 166.63 (s, C=O) ppm. IR (KBr, ν/cm^{-1}): 503(w), 520(m), 551(s), 593(w), 695(s), 712(w), 727(m), 745(s), 897(w), 936(w), 998(w), 1027(w), 1070(w), 1096(w), 1119(m), 1137(w), 1160(sh, m) and 1167(m) (both νP=O), 1185(w), 1251(w), 1308(s), 1436(s), 1481(w), 1531(br, m) (C(O)NH), 1581(s), 1605(m), 1675(m) (νC=O), 3053(m), 3250(br, w) (νNH). Anal. Cacld for $C_{37}H_{29}NO_2P_2$: C, 76.41; H, 5.03; N, 2.41. Found: C, 76.44; H, 4.91; N, 2.31%.

4.2.3. Complex [κ^2-S,O-(LH)Re(I)(CO)$_3$Br], 3



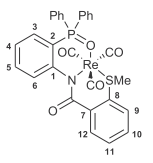
A stirred mixture of ligand **1** (73 mg, 0.165 mmol) and $Re(CO)_5Br$ (67 mg, 0.165 mmol) in toluene (9 mL) was refluxed for 2 h. The resulting precipitate was collected by filtration, washed with diethyl ether, and dried under vacuum to give 105 mg of complex **3** as a light-yellow crystalline solid. Yield: 80%. Mp: >250°C (dec.). $^{31}P\{^1H\}$ NMR (161.98 MHz, $CDCl_3$): δ 38.98 ppm. ^1H NMR (400.13 MHz, $CDCl_3$): δ 2.75 (s, 3H, Me), 7.17–7.22 (m, 1H, H_{Ar}), 7.27–7.32 (m, 1H, H_{Ar}), 7.53–7.81 (m, 14H, H_{Ar}), 8.04–8.07 (m, 1H, H_{Ar}), 8.87 (br. s, 1H, H_{Ar}), 13.12 (br. s, 1H, NH) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$–$(CD_3)_2SO$ (1:1)): δ 14.88 (s, Me), 116.27 (d, C2, $^1J_{CP} = 100.1$ Hz), 120.62 (d, C6, $^3J_{CP} = 7.3$ Hz), 122.00 (d, C4, $^3J_{CP} = 12.5$ Hz), 123.30 (s, C11), 124.72 (s, C9), 126.34 (s, C12), 127.72 (d, *m*-C in $P(O)Ph_2$, $^3J_{CP} = 12.5$ Hz), 130.01 (s, C10), 130.11 (d, *ipso*-C in $P(O)Ph_2$, $^1J_{CP} = 105.6$ Hz), 130.77 (d, *o*-C in $P(O)Ph_2$, $^2J_{CP} = 10.3$ Hz), 131.57 (s, *p*-C in $P(O)Ph_2$), 131.77 (d, C3, $^2J_{CP} = 10.6$ Hz), 132.25 (s, C5), 132.50 (s, C7), 138.70 (s, C8), 143.04 (d, C1, $^2J_{CP} = 2.9$ Hz), 165.16 (s, C=O) ppm (the signals of carbonyl ligand were not observed). IR (KBr, ν/cm^{-1}): 500(w), 524(m), 556(s), 597(vw), 620(vw), 649(w), 694(m), 708(m), 726(m), 752(m), 765(m), 787(w), 922(w), 974(vw), 998(vw), 1072(w), 1100(w), 1122(m), 1136(m), 1159(m) and 1175(m) (both νP=O), 1228(vw), 1312(w), 1336(m), 1437(s), 1445(s), 1481(w), 1537/1542(br, s) (C(O)NH), 1562(m), 1577(s), 1611(s) (νC=O), 1902(vs) (νCO), 1933(vs) (νCO), 2034(vs) (νCO), 2927(vw), 3058(w), 3166(w) (νNH). Anal. Calcd for $C_{29}H_{22}BrNO_5PReS$: C, 43.89; H, 2.79; Br, 10.07; N, 1.76. Found: C, 43.97; H, 2.84; Br, 10.09; N, 1.74%.

4.2.4. Complex [κ^2-P,O-(LH)Re(I)(CO)$_3$Br], 4



A stirred mixture of ligand **2** (87 mg, 0.150 mmol) and $Re(CO)_5Br$ (61 mg, 0.150 mmol) in toluene (10 mL) was refluxed for 1.5 h. The solvent was removed under vacuum. The resulting residue was purified by column chromatography on silica gel (eluent: $CHCl_3$) to give 104 mg of complex **4** as a light-yellow crystalline solid. Yield: 75%. Mp: >269°C (dec.). $^{31}P\{^1H\}$ NMR (161.98 MHz, $CDCl_3$): δ 14.52 (PPh_2), 38.78 ($P(O)Ph_2$) ppm. ^1H NMR (400.13 MHz, $CDCl_3$): δ 6.86–6.90 (m, 1H, H_{Ar}), 7.07 (dd, 1H, H(C3), $^3J_{HP} = 13.9$ Hz, $^3J_{HH} = 7.7$ Hz), 7.15–7.18 (m, 1H, H_{Ar}), 7.21–7.31 (m, 8H, H_{Ar}), 7.36–7.71 (m, 15H, H_{Ar}), 8.13 (dd, 1H, H(C12), $^3J_{HH} = 7.6$ Hz, $^4J_{HP} = 4.5$ Hz), 8.21 (dd, 1H, H(C6), $^3J_{HH} = 8.2$ Hz, $^4J_{HP} = 4.4$ Hz), 12.97 (br. s, 1H, NH) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 118.14 (d, C2, $^1J_{CP} = 98.6$ Hz), 122.80 (d, C6, $^3J_{CP} = 7.3$ Hz), 124.99 (d, C4, $^3J_{CP} = 12.6$ Hz), 127.89 (d, *ipso*-C in PPh, $^1J_{CP} = 45.4$ Hz), 128.75 (d, *o*-C in PPh, $^2J_{CP} = 10.2$ Hz), 128.77 (d, *o*-C in PPh, $^2J_{CP} = 10.4$ Hz), 128.87 (d, *m*-C in P(O)Ph, $^3J_{CP} = 12.6$ Hz), 129.01 (d, *m*-C in P(O)Ph, $^3J_{CP} = 12.7$ Hz), 129.48 (d, C9, $^2J_{CP} = 6.6$ Hz), 130.53 (d, *ipso*-C in P(O)Ph, $^1J_{CP} = 106.4$ Hz), 130.60 (d, *ipso*-C in PPh, $^1J_{CP} = 47.8$ Hz), 130.69 (d, *p*-C in P(O)Ph, $^4J_{CP} = 2.2$ Hz), 130.76 (d, *ipso*-C in P(O)Ph, $^1J_{CP} = 106.2$ Hz), 131.06 (d, C8, $^1J_{CP} = 36.7$ Hz), 131.37 (d, *p*-C in P(O)Ph, $^4J_{CP} = 2.3$ Hz), 131.60 (d, C11, $^4J_{CP} = 1.7$ Hz), 131.91 (d, *o*-C in P(O)Ph, $^2J_{CP} = 10.5$ Hz), 131.95 (d, *o*-C in P(O)Ph, $^2J_{CP} = 10.4$ Hz), 132.21 (d, C10, $^3J_{CP} = 6.5$ Hz), 132.84 (d, *p*-C in PPh, $^4J_{CP} = 2.8$ Hz), 132.93 (d, C3, $^2J_{CP} = 10.4$ Hz), 133.02 (d, *p*-C in PPh, $^4J_{CP} = 2.8$ Hz), 133.29 (d, *m*-C in PPh, $^3J_{CP} = 11.4$ Hz), 133.87 (d, C5, $^4J_{CP} = 2.7$ Hz), 133.89 (d, C12, $^3J_{CP} = 2.1$ Hz), 135.19 (d, *m*-C in PPh, $^3J_{CP} = 11.7$ Hz), 135.23 (d, C7, $^2J_{CP} = 9.6$ Hz), 142.24 (d, C1, $^2J_{CP} = 2.7$ Hz), 168.06 (d, C=O, $^3J_{CP} = 3.9$ Hz), 190.31 (d, CO, $^2J_{CP} = 7.1$ Hz), 190.98 (d, CO, $^2J_{CP} = 75.4$ Hz), 195.18 (d, CO, $^2J_{CP} = 7.0$ Hz) ppm. IR (KBr, ν/cm^{-1}): 514(m), 527(m), 544(m), 557(m), 598(w), 677(w), 694(m), 709(m), 737(m), 747(m), 913(w), 999(w), 1072(w), 1097(m), 1121(m), 1152(m) and 1160(m) (both νP=O), 1168(w), 1187(w), 1280(w), 1312(w), 1348(m), 1437(s), 1443(s), 1482(w), 1547(s) and 1555(sh, m) (both C(O)NH), 1575(s), 1600(s) (νC=O), 1894(vs) (νCO), 1919(vs) (νCO), 2023(vs) (νCO), 3056 (w) (νNH not observed). Anal. Cacld for $C_{40}H_{29}BrNO_5P_2Re$: C, 51.56; H, 3.14; Br, 8.58; N, 1.50. Found: C, 51.44; H, 3.08; Br, 9.09; N, 1.48%.

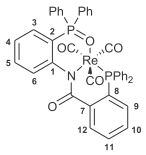
4.2.5. Complex [κ^3-S,N,O-(L)Re(I)(CO)$_3$], 5



A stirred mixture of ligand **1** (74 mg, 0.167 mmol), $Re(CO)_5Br$ (68 mg, 0.167 mmol), and Et_3N (25 μL, 0.179 mmol) in toluene (10 mL) was refluxed for 5 h. The reaction mixture was purified by

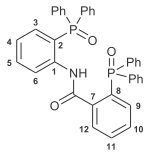
column chromatography on silica gel (gradient elution with EtOAc–hexane (from 30: 1 to 1:1)) to give 53 mg of complex **5** as a light-yellow crystalline solid. Yield: 45%. Mp: >305°C (dec.). $^{31}P\{^1H\}$ NMR (161.98 MHz, $CDCl_3$, 258 K): δ 48.07 (54%), 49.43 (46%) ppm. $^{31}P\{^1H\}$ NMR (161.98 MHz, $CDCl_3$, 323 K): δ 48.32 ppm. ^1H NMR (400.13 MHz, $CDCl_3$, 323 K): δ 2.49 (br. s, 3H, Me), 6.84 (dd, 1H, H(C3), $^3J_{HP} = 14.4$ Hz, $^3J_{HH} = 7.8$ Hz), 7.06–7.09 (m, 1H, H_{Ar}), 7.19–7.28 (m, 3H, H_{Ar}), 7.33 (t, 1H, H_{Ar}, $^3J_{HH} = 7.6$ Hz), 7.41–7.74 (m, 11H, H_{Ar}), 8.18 (d, 1H, H_{Ar}, $^3J_{HH} = 7.8$ Hz) ppm. IR (KBr, ν/cm^{-1}): 448(w), 480(w), 504(w), 519(m), 551(m), 566(s), 626(w), 653(w), 697(m), 723(m), 731(m), 751(m), 764(m), 789(w), 836(w), 943(w), 959(w), 998(w), 1028(w), 1058(m), 1087(m), 1124(br, s) (νP=O), 1146(w), 1164(w), 1215(w), 1265(w), 1335(br, s), 1425(sh, m), 1438(s), 1462(m), 1558(m), 1581(m), 1599(s) (νC=O), 1878(vs) (νCO), 1918(vs) (νCO), 2022(vs) (νCO), 2928(vw), 3062(vw). Anal. Calcd for $C_{29}H_{21}NO_5PReS$: C, 48.87; H, 2.97; N, 1.97. Found: C, 48.97; H, 3.07; N, 1.90%.

4.2.6. Complex [κ^3-P,N,O-(L)Re(I)(CO)$_3$], 6



A stirred mixture of ligand **2** (87 mg, 0.150 mmol), $Re(CO)_5Br$ (61 mg, 0.150 mmol), and *t*-BuOK (17 mg, 0.151 mmol) in THF (10 mL) was refluxed for 1.5 h. The solvent was removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel (eluent: $CHCl_3$) to give 72 mg of a light-yellow crystalline solid. Yield: 57%. Mp: >280°C (dec.). $^{31}P\{^1H\}$ NMR (161.98 MHz, $CDCl_3$): δ 16.79 (d, PPh_2, $^3J_{PP} = 4.0$ Hz), 46.87 (d, $P(O)Ph_2$, $^3J_{PP} = 4.0$ Hz) ppm. ^1H NMR (400.13 MHz, $CDCl_3$): δ 6.58–6.63 (m, 1H, H_{Ar}), 6.73 (dd, 1H, H(C3), $^3J_{HP} = 13.9$ Hz, $^3J_{HH} = 7.6$ Hz), 6.92–7.08 (m, 10H, H_{Ar}), 7.19–7.25 (m, 2H, H_{Ar}), 7.32–7.46 (m, 5H, H_{Ar}), 7.50–7.58 (m, 7H, H_{Ar}), 7.63–7.67 (m, 1H, H_{Ar}), 8.46 (dd, 1H, H(C6), $^3J_{HH} = 7.5$ Hz, $^4J_{HP} = 4.3$ Hz) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 122.56 (d, C2, $^1J_{CP} = 101.9$ Hz), 123.30 (d, C4, $^3J_{CP} = 13.3$ Hz), 127.29 (d, *ipso*-C in PPh, $^1J_{CP} = 54.2$ Hz), 127.52 (d, C8, $^1J_{CP} = 43.1$ Hz), 127.91 (d, C6, $^3J_{CP} = 8.2$ Hz), 128.02 (d, *o*-C in PPh, $^2J_{CP} = 10.1$ Hz), 128.21 (d, *m*-C in P(O)Ph, $^3J_{CP} = 13.3$ Hz), 128.59 (d, C9, $^2J_{CP} = 6.1$ Hz), 128.61 (d, *o*-C in PPh, $^2J_{CP} = 10.3$ Hz), 128.70 (d, *m*-C in PPh, $^3J_{CP} = 12.4$ Hz), 128.95 (d, *ipso*-C in P(O)Ph $^1J_{CP} = 109.7$ Hz), 130.17 (d, *p*-C in P(O)Ph, $^4J_{CP} = 2.3$ Hz), 130.66 (d, *p*-C in P(O)Ph, $^4J_{CP} = 2.2$ Hz), 131.00 (d, C11 or C12, $J_{CP} = 2.1$ Hz), 131.56 (d, C12 or C11, $J_{CP} = 2.5$ Hz), 131.75 (d, C3, $^2J_{CP} = 9.1$ Hz), 131.83 (s, C5), 132.52 (d, *ipso*-C in PPh, $^1J_{CP} = 51.5$ Hz), 132.71–133.22 (presumably, overlapping signals of *ipso*-C in P(O)Ph, *o*-C in $P(O)Ph_2$, C10, C7 and *p*-C in PPh_2), 133.77 (d, *m*-C in PPh, $^3J_{CP} = 10.8$ Hz), 134.09 (d, *m*-C in PPh, $^3J_{CP} = 11.2$ Hz), 145.05 (d, C1, $^2J_{CP} = 15.5$ Hz), 170.97 (d, C=O, $^3J_{CP} = 5.6$ Hz), 190.67 (d, CO, $^2J_{CP} = 73.0$ Hz), 194.84 (d, CO, $^2J_{CP} = 7.2$ Hz), 196.02 (d, CO, $^2J_{CP} = 8.7$ Hz) ppm. IR (KBr, ν/cm^{-1}): 514(m), 528(m), 553(s), 565(s), 629(w), 647(w), 692(s), 707(m), 721(w), 732(m), 743(m), 748(m), 759(m), 833(w), 943(w), 957(w), 999(w), 1027(w), 1061(m), 1089(m), 1129(s) (νP=O), 1145(w), 1163(w), 1188(w), 1209(w), 1263(w), 1334(s), 1435(s), 1462(w), 1483(w), 1547(m), 1574(m), 1593(m) (νC=O), 1891(vs) (νCO), 1895(vs) (νCO), 1911(vs) (νCO), 2018(vs) (νCO), 3061(w). Anal. Calcd for $C_{40}H_{28}NO_5P_2Re$: C, 56.47; H, 3.32; N, 1.65. Found: C, 56.58; H, 3.56; N, 1.49%.

4.2.7. 2-(Diphenylphosphoryl)-N-[2-(diphenylphosphoryl)phenyl] benzamide, 7



A solution of 30% aq. H_2O_2 (0.50 g) in 5 mL of water was added slowly to a stirred solution of compound **2** (143 mg, 0.246 mmol) in chloroform (10 mL). The reaction mixture was refluxed for 3 h and, after cooling to room temperature, washed with water (3 × 10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated to dryness. The resulting residue was recrystallized from EtOAc to give 138 mg of phosphine oxide **7** as a white crystalline solid. Yield: 94%. Mp: 217–220°C. $^{31}P\{^1H\}$ NMR (121.49 MHz, $CDCl_3$): δ 31.39, 36.42 ppm. ^1H NMR (300.13 MHz, $CDCl_3$): δ 6.91–7.02 (m, 2H, H_{Ar}), 7.30–7.43 (m, 6H, H_{Ar}), 7.48–7.66 (m, 14H, H_{Ar}), 7.73–7.79 (m, 5H, H_{Ar}), 8.00 (dd, 1H, H_{Ar}, $^3J_{HP} = 13.2$ Hz, $^3J_{HH} = 7.0$ Hz), 11.22 (br. s, 1H, NH) ppm. IR (KBr, ν/cm^{-1}): 515(w), 524(w), 545(s), 552(s), 599(vw), 647(vw), 695(m), 710(m), 721(m), 732(m), 757(m), 799(vw), 897(vw), 998(vw), 1027(vw), 1072(w), 1099(m), 1120(s), 1132(m), 1166(br, m) and 1183(m) (both νP=O), 1257(w), 1275(w), 1313(m), 1438(s), 1484(w), 1535(br, w) (C(O)NH), 1579(m), 1604(w), 1687(m) (νC=O), 1714(w), 3057(w), 3176(br, w) and 3241(br, w) (both νNH). Anal. Calcd for $C_{37}H_{29}NO_3P_2$: C, 74.37; H, 4.89; N, 2.34. Found: C, 74.46; H, 4.92; N, 2.34%.

4.3. X-ray diffraction

Single crystals of complexes **5** and **6** were obtained by recrystallization from $CHCl_3$–Et_2O. Single crystals of complex **3** were formed during crystallization from the toluene reaction mixture. X-ray diffraction experiments were carried out with a Bruker APEX2 DUO CCD diffractometer for **3** and a Bruker APEX2 CCD diffractometer for **5** and **6**, using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å, ω-scans) at 120 K. Using Olex2 [15], the structures were solved with the ShelXT [16] structure solution program *via* Intrinsic Phasing and refined with the olex2.refine [17] refinement package using Gauss–Newton minimization. Positions of hydrogen atoms were calculated, and they were refined in isotropic approximation in riding model. Crystal data and structure refinement parameters for **3**, **5** and **6** are given in Table 3. CCDC 1906196, 1906197, and 1906198 contain the supplementary crystallographic information for complexes **3**, **5**, and **6**, respectively.

4.4. Cytotoxicity studies

The cytotoxic activities of tricarbonylrhenium(I) complexes **3**, **4** and **5** were studied against human colon cancer cell line HCT116, human breast cancer cell line MCF7, human prostate cancer cell line PC3, and normal human embryonic kidney cells HEK293 as well as transformed breast cell line HBL100 and its doxorubicin-resistant subline HBL100/Dox. RPMI-1640 and DMEM media were obtained from Gibco. Fetal bovine serum (FBS) was purchased from HyClone. Cells were cultured in RPMI-1640 (in the case of PC3 and HBL100) or DMEM (in the other cases) media supplemented with 10% FBS and 50 μg/mL gentamicin in a humidified incubator with 5% CO_2 atmosphere. The effect of the compounds on cell viability was evaluated by the standard MTT assay (ICN Biomedicals, Germany). Cells were seeded in triplicate at a cell density of 5 × 10^3/well in 96-

Table 3
Crystal data and structure refinement parameters for complexes **3**, **5**, and **6**.

	3	**5**	**6**
Empirical formula	$C_{79}H_{67}Br_2N_2O_{10}P_2Re_2S_2$	$C_{20}H_{20}NO_5PSRe$	$C_{81}H_{57}Cl_3N_2O_{10}P_4Re_2$
Formula weight	1862.72	712.74	1821.03
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	P21/c	P-1	C2/c
Z	2	2	4
a, Å	23.8626(8)	10.3984(6)	31.6704(12)
b, Å	12.1311(4)	11.1516(6)	12.3103(5)
c, Å	25.1476(9)	11.9836(7)	23.8948(16)
α, °	90	91.4250(10)	90
β, °	150.1532(10)	103.3920(10)	129.3440(10)
γ, °	90	104.9690(10)	90
V, Å^3	3623.0(2)	1300.63(13)	7204.5(6)
D_{calc} (g cm^{-1})	1.707	1.820	1.679
Linear absorption, μ (cm^{-1})	46.04	48.55	36.20
F(000)	1831	695	3590
$2\theta_{max}$, °	58	58	54
Reflections measured	47752	17441	62874
Independent reflections	9647	6909	7874
Observed reflections [$I > 2\sigma(I)$]	8391	6226	6972
Parameters	454	344	469
R1	0.0236	0.0244	0.0217
wR2	0.0536	0.0501	0.0578
GOF	1.033	1.045	1.082
$\Delta\rho_{max}/\Delta\rho_{min}$ (e Å^{-3})	1.35/−0.98	1.30/−1.40	3.35/−0.68

well plates in 100 μL complete medium and preincubated for 24 h. The tested compounds were initially dissolved in DMSO. Then the compounds at various concentrations were added to the media. The well plates were incubated for 48 h followed by addition of MTT solution (Sigma) (20 μL, 5 mg/mL). The cells were incubated at 37 °C for further 3 h; then the culture medium was removed, and formazan crystals were dissolved in DMSO (70 μL). The absorbance of the resulting solutions was measured on a multi-well plate reader (Multiskan FC, Thermo scientific) at 540 nm to determine the percentage of surviving cells. The reported values of IC_{50} are the averages of three independent experiments (Table 2). Cisplatin and doxorubicin from commercial sources were used as references.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jorganchem.2019.04.020.

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