The [(Cp)M(CO)$_3$] (M = Re, ^{99m}Tc) Building Block for Imaging Agents and Bioinorganic Probes: Perspectives and Limitations

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Starting from asymmetric *Thiele*'s acid derivatives, two different imaging probes [^{99m}Tc(CO)$_3$(CpR)] (R = potential targeting vector) are generated simultaneously in one-pot and from one substrate. This extends the previously introduced labeling strategy of metal-mediated *retro-Diels–Alder* reaction with HCp-R dimers. We demonstrate that chemically active functionalities such as hydroxamic acids are not following this labeling strategy. Adopting the principle of replacing phenyl rings by [Re(CO)$_3$(Cp)] entities, potent histone deacetylase (HDAC)-inhibiting Re analogs of suberoylanlilide hydroxamic acid (SAHA; *N*-hydroxy-*N*′-phenyloctanediamide) were synthesized and characterized. Cytotoxic evaluation on different tumor cell lines revealed low IC_{50} values [μM] for these compounds, comparable to their purely organic congeners.

Introduction. – Organometallic complexes with bioactive ligands are nowadays essential for both, the noninvasive visualization of biological features and the therapeutic treatment of diseases. While several transition metals across the periodic table are frequently used for therapy, ^{99m}Tc is the most prominent nuclide in nuclear medicine [1–4]. Clinically applied imaging agents frequently consist of a [^{99m}Tc^{V}O]$^{3+}$ or [^{99m}Tc^{V}O$_2$]$^{+}$ core, thermodynamically stabilized by tetradentate ligands with mixed N-, S-, and O-donors [1]. Examples are diethylenetriaminepentaacetic acid (DTPA), mercaptoacetyl-glycine-glycine-glycine (MAG3), or oxime-bridged hexamethylpropylenamine oxime (HMPAO). Currently extensively investigated ^{99m}Tc fragments are the *fac*-{^{99m}Tc^{I}(CO)$_3$}$^{+}$, {^{99m}Tc^{V}N(PNP)}$^{2+}$, {^{99m}Tc^{III}(NS$_3$)}, or *fac*-{^{99m}Tc^{VII}O$_3$}$^{+}$ cores [5–7]. In contrast to the aforementioned perfusion agents, molecules labeled with these fragments follow the concept of targeted imaging with the bifunctional chelator approach. Such complexes are often generated from a robust core fraction with a few coordination sites occupied by weakly bound substitution-labile ligands. These ligands correspond, for example, to the H_2O molecules in [^{99m}Tc(H$_2$O)$_3$(CO)$_3$]$^{+}$ [8][9] or to the halides in [^{99m}TcN(PNP)Cl$_2$][5] respectively. [^{99m}Tc(NS$_3$)L]-Containing targeting molecules are formed in a 4+1 approach from [^{99m}Tc(edta)]$^{-}$ in one pot together with the NS$_3$ chelator and an additional bifunctional ligand L [10–14]. The *fac*-{^{99m}TcO$_3$}$^{+}$ core can be used as a derivatized [^{99m}TcO$_3$(TACN)]$^{+}$ moiety, where the biologically active functionality is either introduced with the 1,4,7-triazacyclononane (TACN) or, *via* 3+2 cycloaddition, to two O-atoms [15][16].

Tridentate σ- or π-donors, coupled to a targeting vector are popular ligand systems for *fac*-$\{^{99m}Tc^{I}(CO)_3\}^+$ [3][17–19]. Cyclopentadiene (Cp) is for imaging a conceptually and structurally uncommon ligand. It does not contain any heteroatoms, rendering the molecule hydrophobic and, therefore, in fact unsuitable for aqueous syntheses. Moreover, Cp and many derivatives are unstable as a monomer and undergo *Diels–Alder* polymerization. However, *Jaouen* and co-workers developed a variety of highly potent selective estrogen receptor inhibitors by replacing a phenyl (Ph) ring in *Tamoxifen* by $[Re(CO)_3(Cp\text{-}R)]$. Bioorganometallic complexes containing this moiety exhibit potential as therapeutic agents. The resulting molecules retain a relatively high binding affinity for the estrogen receptor [20–26].

We developed a synthetic route to $[^{99m}Tc(CO)_3(Cp\text{-}R)]$ which allowed a fully aqueous preparation of a variety of complexes bearing a bioactive vector R at the Cp ligand [27][28]. The metal-mediated *retro-Diels–Alder* reaction of the $(HCp\text{-}R)_2$ dimer with $[^{99m}Tc(H_2O)_3(CO)_3]^+$ or directly with $[^{99m}TcO_4]^-$ permitted to transfer the principle of replacing Ph rings in bioactive substances to ^{99m}Tc-labeled compounds, as demonstrated with melanin-targeting agents or with high-affinity carbonic anhydrase inhibitors [29][30].

Since Re and Tc belong to the same triade, it is possible to use identical compounds for combined therapy and imaging in a theragnostics sense [30–32]. While Re-based compounds can be used for therapy, the homologous compounds with ^{99m}Tc can serve as imaging agents for single-photon emission computed tomography (SPECT) [1][4][33].

Histone deacetylases (HDACs) catalyze the removal of Ac groups of ε-lysine tails on histone proteins, causing condensed chromatin and, therefore, transcriptional silencing. Hence, cancer cells escape apoptosis. As HDAC inhibitors can counter cancer progression, they contribute to apoptosis and the formation of growth-arrest proteins [34][35]. Since HDACs are highly overexpressed in cancer tissues, they are targets for both, cancer diagnosis and therapy. Suberoylanilide hydroxamic acid (SAHA; *N*-hydroxy-*N*′-phenyloctanediamide) is a clinically approved HDAC inhibitor (HDACi). It is administered for the treatment of a number of hematological and solid tumors [36]. While different organometallic SAHA analogs containing ferrocene or cisplatin, respectively, have been investigated for therapeutic application [37–39], such bioinorganic SAHA analogs for radiopharmaceutical application are still unknown.

In this communication, we report the extensions but also the limitations of the metal-mediated *retro-Diels–Alder* reaction of $(HCp\text{-}R)_2$: the adaption of the aforementioned synthetic pathway to asymmetric *Thiele*'s acid derivatives allows the generation of two different bioactive imaging probes in one pot and from one substrate. Furthermore, we demonstrate with the example of new organometallic analogs of SAHA that the principle of replacing Ph rings by $[Re(Cp)(CO)_3]$ is consistent to a large extent. However, chemically active functionalities like unprotected hydroxamic acids can oxidize $[^{99m}Tc(H_2O)_3(CO)_3]^+$ to form $[^{99m}TcO_4]^-$ and are, therefore, unsuitable for this labeling route.

Results and Discussion. – *The Rhenium Complexes. Meggers et al.* showed with protein kinase inhibitors that organometallic complexes, as compared to organic compounds, can have the property of enhanced three-dimensional population of

chemically relevant biological space [40–42]. Such molecules can achieve better selectivity for specific targets. We recently demonstrated with organometallic carbonic anhydrase inhibitors (CAi) that compounds containing $[Re(CO)_3(Cp)]$ truly follow this concept [30]. $[Re(CO)_3(Cp)]$ Complexes containing a bioactive targeting vector are, therefore, very important pharmaceutical building blocks. Moreover, $[Re(CO)_3(Cp)]$ can be introduced into bioactive substances by replacing Ph rings. Combining these two concepts, organometallic SAHA analogs **1**–**3** were synthesized (*Scheme 1*). To tune interactions with the binding pocket, the investigated compounds differ in the position of the amide linker adjacent to Cp and in the length of the aliphatic spacer between the amide group and the hydroxamic acid portion.

$[Re(CO)_3(Cp\text{-}COOH)]$ (**23**) was activated with pentafluorophenyl trifluoroacetate and coupled to the appropriate amine to form complexes **14** and **15**. $[M(CO)_3(Cp\text{-}NHCO(CH_2)_6COOMe)]$ (**16a/b**, M = Re/Mn) was synthesized by activating suberic acid monomethyl ester with $ClCOO^iBn$ and coupling with $[M(Cp\text{-}NH_2)(CO)_3]$. The obtained ester **16a** was hydrolyzed with aqueous LiOH. The Mn complex **16b** was synthesized exclusively for crystallographic purposes and was not exploited further. Crystals were grown by dissolving **16b** in a minimum of CH_2Cl_2 and slow addition of hexane as a precipitant (*Fig. 1*). Crystallographic details are given in the *Exper. Part*. Activation of the terminal carboxylic acids with ClCOOEt and treatment with NH_2OH gave the final products **1**–**3** (*Scheme 1*). All compounds were purified by silica-gel chromatography and analyzed by NMR, ESI-MS, and IR.

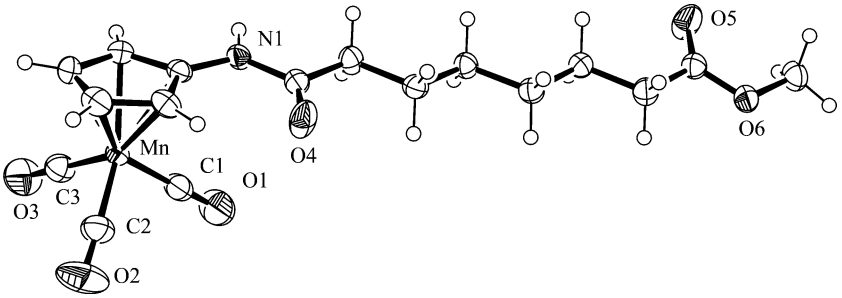
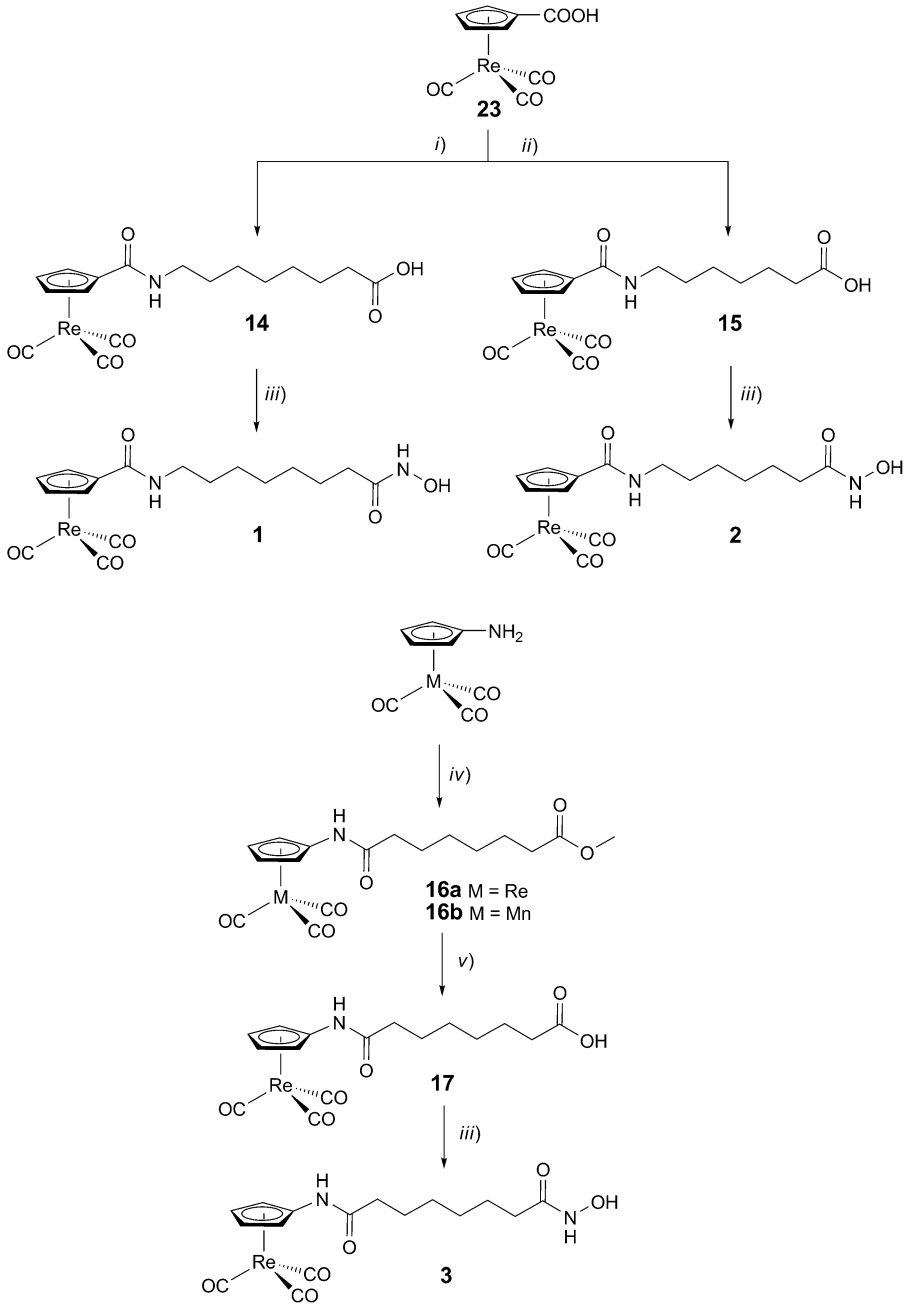


Fig. 1. *ORTEP Representation* (50% probability) *of [Mn(CO)$_3$(Cp-NHCO(CH$_2$)$_6$COOMe)]* (**16b**)

The ^{1}H-NMR spectrum of **1** in MeOD shows the two aromatic Cp signals as *pseudo-triplets* at 6.15 and at 5.56 ppm, respectively. The amide H-atom exhibits a *triplet* at 8.19 ppm. The CH_2 signals were detected as *multiplet*s between 3.26 and 1.35 ppm. Characteristic strong ν_{CO} bonds of the *fac*-$[Re(CO)_3]$ were observed in the IR spectrum at 2020 and at 1905 cm^{-1} (KBr). ESI-MS (MeOH) indicated two adducts: *m*/*z* 559.1 ($[M+Na]^+$) and 537.2 ($[M+H]^+$).

The ^{1}H-NMR in (D_6)DMSO for **2** showed broad *singlet*s for OH and NH of the hydroxamic acid at 10.32 and at 8.63, respectively. The amide H-atom signal was observed at 8.20 as a *triplet*. The Cp signals appeared as *pseudo-triplet*s at 6.27 and at 5.70 ppm, respectively. The methylene *multiplet*s appeared between 3.13 and 1.25 ppm. The IR ν_{CO} bands of the *fac*-$[Re(CO)_3]$ were observed at 2020 and at 1907 cm^{-1} (KBr). ESI-MS (MeOH) exhibited a peak at 545.1, corresponding to the $[M+Na]^+$ adduct (*m*/*z*).

Scheme 1

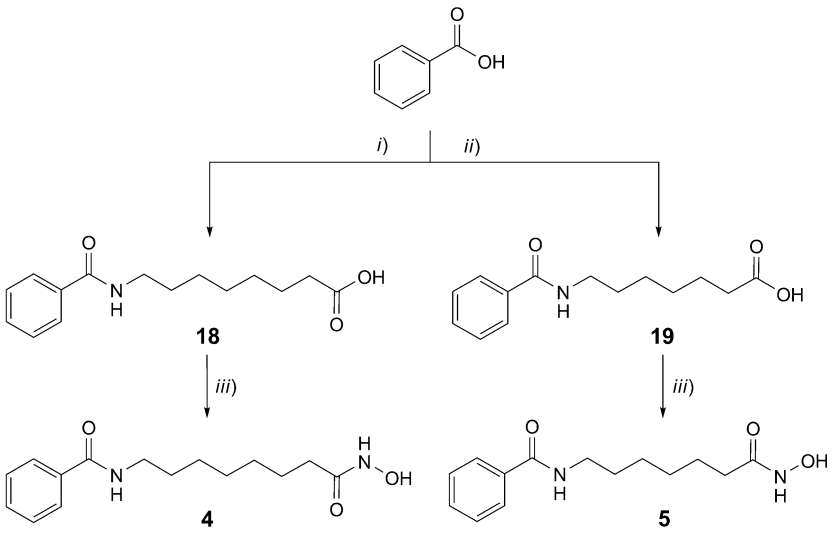


i) Pentafluorophenyl trifluoroacetate, 8-aminocaprylic acid, DMF; 88%. *ii*) Pentafluorophenyl trifluoroacetate, 7-aminoheptanoic acid, DMF, 86%. *iii*) Ethyl chloroformate (ClCOOEt), NH_2OH, THF; 80–86%. *iv*) Suberic acid monomethyl ester activated with isobutyl chloroformate, THF; 98%. *v*) LiOH, H_2O, MeOH, THF; 98%

^{1}H-NMR for **3** in (D_6)DMSO displayed broad *singlest* at 10.30 and 8.63 ppm for OH and NH of the hydroxamic acid, respectively. At 8.63 ppm, the *singlet* for the amide H-atom was observed, and the Cp *pseudo-triplet*s were found at 5.78 and at 5.48 ppm. *Multiplet*s between 2.14 to 1.22 ppm indicated presence of the CH_2 groups. Characteristic IR ν_{CO} bands were observed at 2019 and at 1913 cm^{-1} (KBr). A peak at *m*/*z* 545.1 indicated the $[M+Na]^+$ adduct in the ESI-MS (MeOH). ^{1}H-NMR Cp Signals are due to couplings within a high-order *AA′BB′* spin system and, therefore, assigned as *multiplet*s in the *Exper. Part*.

The Organic SAHA Analogs. To support the concept of replacing Ph rings by [$Re(CO)_3$(Cp)] under retention of bioactivity holds also true for organometallic HDAC inhibitors, the organic congeners of compounds **1** and **2**, **4**, and **5** were synthesized. Compound **3** corresponds to native SAHA. Syntheses were performed analogously to those of the organometallic inhibitors (*Scheme 2*). The compounds were purified by silica-gel chromatography and characterized by NMR, ESI-MS, and elemental analysis.

Scheme 2



i) Pentafluorophenyl trifluoroacetate, 8-aminocaprylic acid, DMF; 90%. *ii*) Pentafluorophenyl trifluoroacetate, 7-aminoheptanoic acid, DMF; 89%. *iii*) ClCOOEt, NH_2OH, THF; 90–92%.

Biological Studies. To analyze the antitumor activity of organometallic HDAC inhibitors **1**–**3**, their cytotoxicities towards five carcinoma cell lines were evaluated. For a direct comparison, the corresponding organic congeners SAHA, **4** and **5** were treated the same way. The cancer cell lines were exposed to increasing concentrations of the different compounds for 72 h, and the cellular viability was determined by MTT (= 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide) assay. The viability of cells in the presence of the tested compounds was compared to that observed in control cultures, and the inhibition of growth [%] was calculated. The dose–response curves demonstrate the antiproliferative effects of all compounds, exemplified in *Fig. 2*

for human cervical carcinoma HeLa and vulva epidermal carcinoma A431 cells. The IC_{50} (*i.e.*, the concentration producing 50% inhibition of growth) values (in μM) determined for five cells lines are compiled in the *Table*.

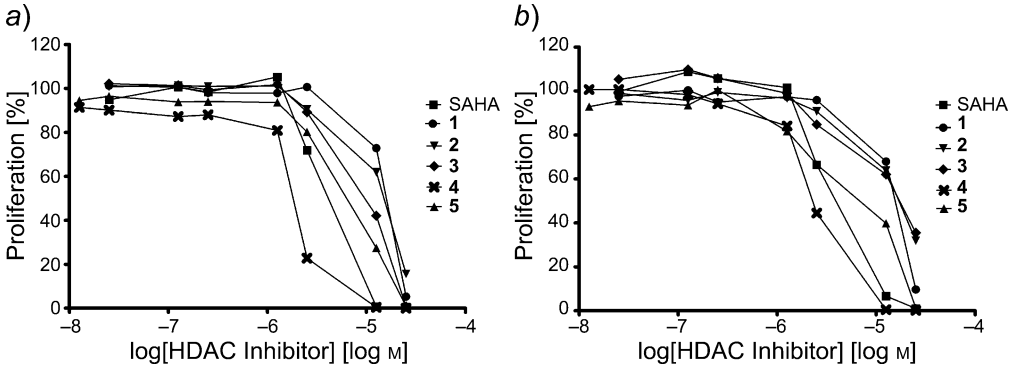


Fig. 2. *Cytotoxicity on human cervical carcinoma HeLa cells* (*a*) *and vulva epidermal carcinoma A431 cells* (*b*)

Table. *Cytotoxicity Profile* (IC_{50} [μM]) *of Compounds* **1**–**5** *and of the Reference HDAC Inhibitor SAHA for 72 h* (37°, 5% CO_2) *Continuous Treatment of Five Different Tumor Cell Lines*[a])

Compound	MCF-7	A431	HeLa	A375	B16F1	Mean ± SD
1	9.47	13.7	14.4	14.7	9.82	12.4 ± 2.6
2	15.2	17.1	13.3	23.3	12.6	16.3 ± 4.3
3	11.4	17.3	8.34	12.5	15.2	12.9 ± 3.4
4	1.71	2.51	1.65	2.63	3.10	2.32 ± 0.62
5	7.19	5.22	5.83	4.85	8.88	6.39 ± 1.65
SAHA	3.74	4.44	4.45	4.58	3.67	4.18 ± 0.43

[a]) MCF-7, Human breast carcinoma; A431, human vulva epidermal carcinoma; HeLa, human cervical carcinoma; A375, human melanoma; B16F1, murine melanoma.

The analysis of the data presented in the *Table* allows us to understand how the position of the amide linker and the length of the alkyl chain, attached to the [$Re(CO)_3$(Cp)] framework, may affect the antitumoral capacity of organometallic HDCA inhibitors. Moreover, it allows the possibility of finding evidence whether the replacement of Ph rings by [$Re(CO)_3$(Cp)] is tolerated in the investigated examples.

The *Table* reveals that, after a drug-administration period of 72 h, SAHA displayed a broad cytotoxicity across cell lines from different tumor entities with a mean IC_{50} value of 4.2 ± 0.4 μM. This value, obtained from the MTT assay, is in agreement with the antiproliferative activity of SAHA previously reported by using the Alamar Blue cell viability assay (IC_{50} 3.3 μM, a mean value for several tumor cell lines) [43].

Among the new compounds reported here, the organic SAHA analog **4** showed the lowest IC_{50} values for all cell lines used. This indicates a superior potency for HDCA inhibition *in vitro*, even higher than the one described for the native SAHA. In fact, the mean IC_{50} value for compound **4** (2.32 ± 0.62 μM; **4** contains a longer aliphatic chain and inverted amide linker as compared to SAHA) was about two or three times lower than

that obtained for SAHA or compound **5**, respectively (4.2 ± 0.4 and 6.39 ± 1.65 μM, resp.), both containing the shorter hexyl alkyl chain. These results suggest that cytotoxicity of HDAC inhibitors of the class of benzamide derivatives may depend on the length of the CH_2 chain attached to the benzamide framework.

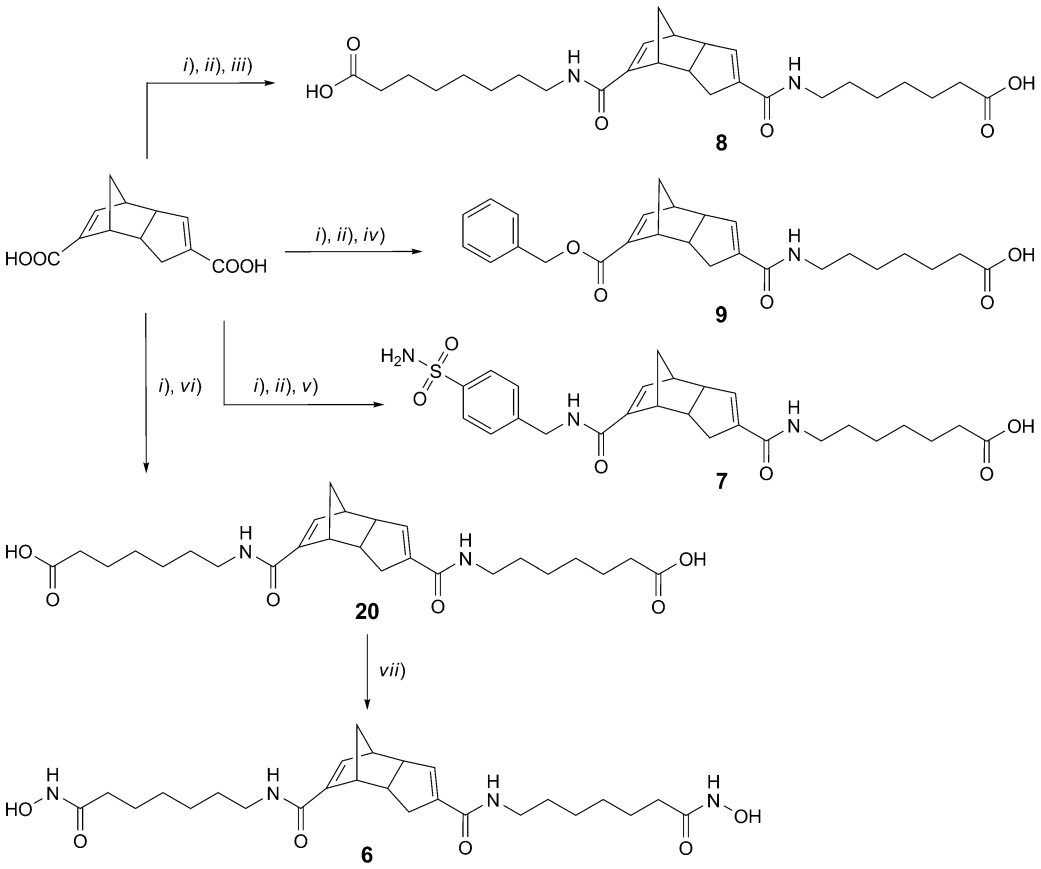
The organometallic HDACis, **1**, **2**, and **3**, are less active in each case as compared to the corresponding organic congeners SAHA, **4**, and **5**. The mean IC_{50} value for **1** was 12.4 μM, compared to 2.3 μM for **4**. Complex **2** and the corresponding congener **5** displayed IC_{50} values of 16.3 and 6.4 μM, respectively, and while SAHA presented a value of 4.2 μM, complex **3** displayed a higher IC_{50} value of 12.9 μM. This slight decrease of antiproliferative capacity of the Re complexes indicates that the bulkier [Re(-$CO)_3$(Cp)] moiety is disfavored over a simple planar Ph ring and might be the cause of reduced ability of cellular penetration. Nevertheless, the Re complexes still retain a high cytotoxic activity, comparable to their organic congeners. No significant effect on cytotoxicity was observed by altering the position of the amide linker at the Cp. Similar mean values of IC_{50} were obtained for **2** and **3** (16.3 ± 4.3 *vs.* 12.9 ± 3.4 μM). All biological experiments were performed by using MeOH as co-solvent (to a final concentration of $\leq 0.1\%$). Although this solvent is known to be toxic to cells, here, due to its low concentration, the cell viability in the control experiments was higher than 90%.

The Ligands. [^{99m}Tc$(CO)_3$(Cp-R)] complexes are accessible *via* metal-mediated *retro-Diels–Alder* reaction from amide coupled *Thiele*'s acid derivatives and [$^{99m}TcO_4]^-$ in H_2O [28]. So far, $(HCp\text{-}R)_2$ dimers contained two identical substituents R which led to the generation of one imaging agent [^{99m}Tc$(CO)_3$(Cp-R)]. Demonstrating the versatile possibilities of [M$(CO)_3$(Cp)]-type complexes in medicinal inorganic chemistry and extending the labeling strategy of metal-mediated *retro-Diels–Alder* reaction, we synthesized the asymmetric derivatives of *Thiele*'s acid, **7**–**9** (*cf. Scheme 3*). If none of the Cp fragments in $(HCp\text{-}R)_2$ dimers is favored for the formation of [^{99m}Tc$(CO)_3$(Cp-R)], this would allow for the synthesis of two different imaging agents with one single substrate. According to the theragnostic concept, the potent Re-HDACis **1**–**3** could be applied in combination with the corresponding ^{99m}Tc-labelled compounds; macroscopic amounts of Re for therapy and microscopic amounts of the ^{99m}Tc analogs for diagnosis. We synthesized **6**, a dimeric species of the ligand of compound **2** evaluated *in vitro* for its cytotoxicity.

Compounds **6**–**9** were prepared from one single isomer of *Thiele*'s acid (*Scheme 3*). Products were obtained after activation of both carboxylic acids with pentafluorophenyl trifluoroacetate and coupling to the appropriate amines. Depending on the amount of amine used and the presence of a base, mono- or disubstituted products were obtained. Singly substituted derivatives were mainly observed as their pentafluorophenyl esters at the bridged side of the $(HCp)_2$ dimer which could be isolated. Subsequent addition of the second substituent along with Et_3N led to the final products **7**–**9**.

Two equiv. of 7-aminoheptanoic acid together with an excess of Et_3N led to the formation of the doubly substituted compound **20**. Activation of the terminal carboxy groups with *O*-(7-aza-1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) and treatment with *O*-[(*tert*-butyl)dimethylsilyl]hydroxylamine gave product **6**.

Scheme 3

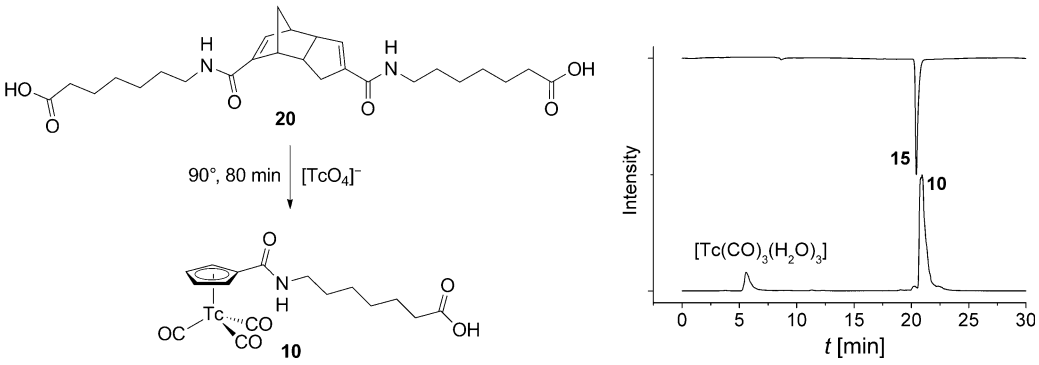


i) Pentafluorophenyl trifluoroacetate. *ii*) 7-Aminoheptanoic acid, DMF; 34%. *iii*) 8-Aminocaprylic acid, Et_3N, DMF; 32%. *iv*) BnOH, Et_3N, DMF; 9%. *v*) 4-(Aminomethyl)benzensulfonamide, Et_3N, DMF; 80%. *vi*) 7-Aminoheptanoic acid, Et_3N, DMF; 54%. *vii*) 2-(7-Aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), *O*-[(*tert*-butyl)dimethylsilyl]hydroxylamine, H_2O, DMF; 70%.

The ^{99m}Tc Complexes. Labeling of bioactive functionalized ligands with the *fac*-$\{^{99m}Tc^{I}(CO)_3\}^+$ core was significantly simplified with the introduction of the *Isolink*® *Kit* enabling the fast formation of the $[^{99m}Tc(H_2O)_3(CO)_3]^+$ precursor [8][9]. $[^{99m}Tc(CO)_3(Cp\text{-}R)]$-type complexes are accessible from aqueous solutions [27][28]. The metal-mediated *retro-Diels–Alder* reaction of the $(HCp\text{-}R)_2$ with $[^{99m}Tc(H_2O)_3(CO)_3]^+$ or with $[^{99m}TcO_4]^-$ allowed transfer of the principle of replacing Ph rings in bioinorganic substances to ^{99m}Tc-labelled compounds. Introducing suitable biologically active residues R, this labeling approach can be regarded as an applicable easy-to-use protocol for routine use in nuclear medicine [29][30][44].

To complement the Re-HDACis **1**–**3** with the corresponding ^{99m}Tc-labelled compounds, attempts were made to label **6** with $[^{99m}Tc(H_2O)_3(CO)_3]^+$. However, heating 1 μM solution of **6** with $[^{99m}Tc(H_2O)_3(CO)_3]^+$ at 90° resulted only in the quantitative formation of $[^{99m}TcO_4]^-$. Obviously, hydroxamic acids are oxidants towards $[^{99m}Tc(H_2O)_3(CO)_3]^+$. Thus, the desired compound was not obtained. On the other hand, the labeling of **20** with $[^{99m}TcO_4]^-$ afforded after 80 min at 90° the expected product **10** in 87% yield and high radiochemical purity (*Scheme 4*). The nature of the obtained ^{99m}Tc compound was confirmed by co-injection with the corresponding Re complex **15**.

Scheme 4. Bottom-Up Trace: *γ-Trace of the One-Pot Labeling of* **20** *with* $[^{99m}TcO_4]^-$ *and* Isolink Kit. Top-Down Trace: *UV Trace of Re Compound* **15**.

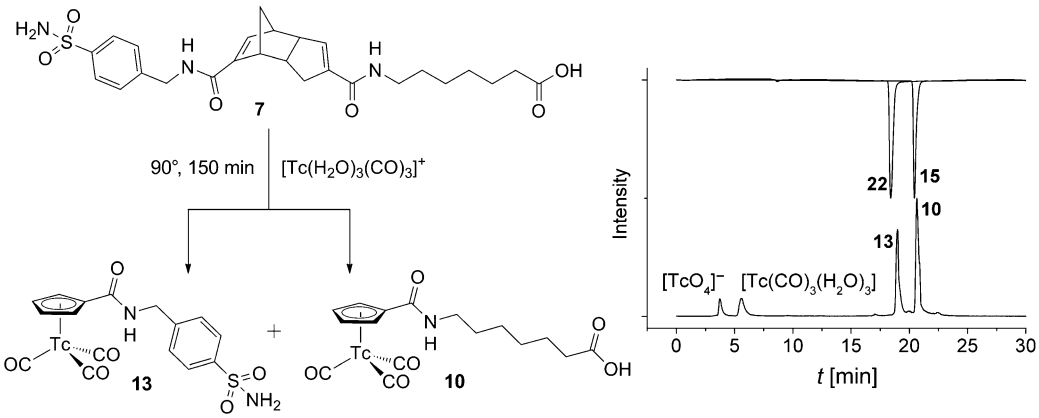


In extension to the labeling strategy of symmetrical $(HCp\text{-}R)_2$, the asymmetric derivatives of *Thiele*'s acid, **7**–**9**, were treated accordingly. Compounds **7**, **8**, and **9** all exhibited two main peaks in the HPLC trace when reacted with $[^{99m}Tc(H_2O)_3(CO)_3]^+$. Ligands again were present in μM concentrations, and reactions were performed at 90° in aqueous saline. Beside the two main products **10** and **13**, the labeling of **7** furnished a small portion (7%) of $[^{99m}TcO_4]^-$ (*Scheme 5*). The product ratio of 45:55 for **13**/**10** indicated no clear preference of complex formation concerning localization of the derivatives at the unbridged or at the bridged side of the (HCp) dimer. Co-injection of the Re congeners $[Re(CO)_3(Cp\text{-}CONHCH_2C_6H_4SO_2NH_2)]$ (**22**) [30] and **15**, respectively, clearly confirmed the nature of the products.

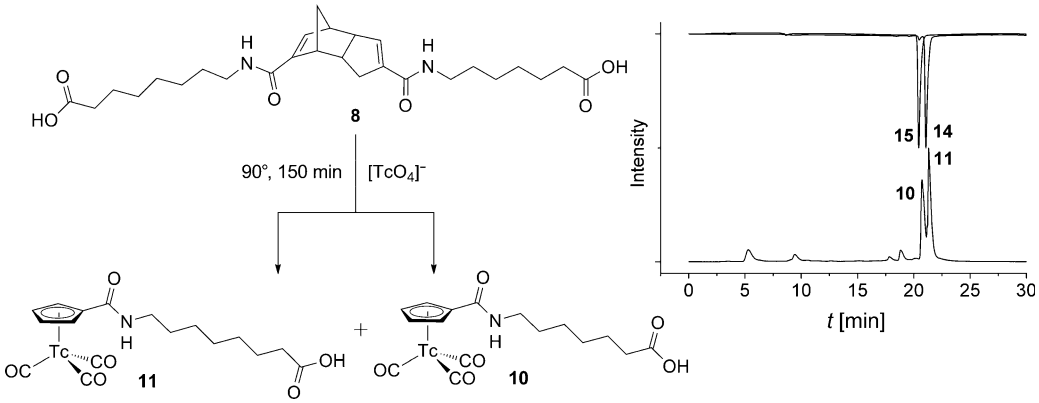
A very similar result was obtained with **8**, having two different aliphatic chain lengths but the same conjugation to Cp (*Scheme 6*). Two products, **10**/**11**, in a similar ratio of 45:55 were formed as before, confirming the lack of preference for one of the regions in the *Thiele*'s acid dimers.

Compound **9** contains an amide-bound substituent on one side and an ester group on the other. Even though the labeling of **9**, similar to **7** and **8**, gave two products, the benzyl ester $[^{99m}Tc(CO)_3(Cp\text{-}COOCH_2C_6H_5)]$ was not obtained but hydrolyzed during the process. Product **12** was identified as the free acid $[^{99m}Tc(CO)_3(CpCOOH)]$, the ^{99m}Tc-form of $[Re(CO)_3(Cp\text{-}COOH)]$ (**23**) [45]. The second peak again corresponded to **10**, the ^{99m}Tc analog **15**. The product ratio was nearly 50:50 (*Scheme 7*).

Scheme 5. Bottom-Up Trace: *γ-Trace of the Two-Step Labeling of* **7** *with* $[^{99m}Tc(H_2O)_3(CO)_3]^+$. Top-Down Trace: *UV Trace of Re Compounds* **22** *and* **15**.



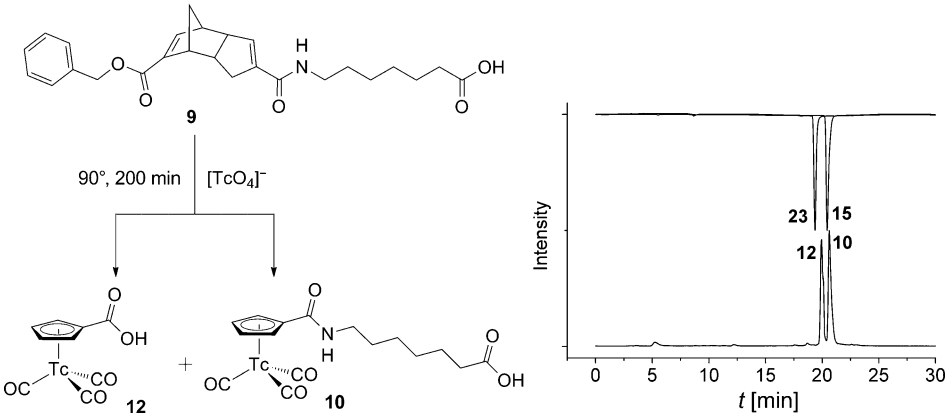
Scheme 6. Bottom-Up Trace: *γ-Trace of the One-Pot Labeling of* **8** *with* $[^{99m}TcO_4]^-$. Top-Down Trace: *UV Trace of Re Compounds* **15** *and* **14**.



Conclusions. – A series of new organometallic HDAC inhibitors as well as their organic congeners were synthesized and characterized. Cytotoxic evaluation revealed low μM IC_{50} values for these compounds against different tumor cell lines. These values are in the same range as for SAHA and establish the concept of replacing Ph rings by $[Re(CO)_3(CpR)]$ for organometallic HDAC inhibitors. Slight alterations in the aliphatic spacer as compared to the hexyl chain in SAHA do not affect activity of HDACis. Increasing the number by one CH_2 group even showed increased cytotoxic capacity. No significant effect was observed by altering the position of the amide linker at the Cp ring.

Using asymmetrically derivatized *Thiele*'s acid, two different imaging agents, $[^{99m}Tc(CO)_3(Cp\text{-}R)]$ (R = potential targeting vector), were generated in one pot and from one substrate. Introducing appropriate vectors, combined imaging of two targets from one substrate is now possible.

Scheme 7. Bottom-Up Trace: *γ-Trace of the One-Pot Labeling of* **9** *with* $[^{99m}TcO_4]^-$. Top-Down Trace: *UV Trace of Re Compounds* **23** *and* **15**.



Ester linkers are generally hydrolyzed during labeling under the applied conditions. Furthermore, oxidation of $[^{99m}Tc(H_2O)_3(CO)_3]^+$ to $[^{99m}TcO_4]^-$ prior to complex formation occurred, when hydroxamic acids were used. Chemically labile functionalities are, therefore, limitations to this labeling strategy. $[^{99m}Tc(CO)_3(CpR)]$ Complexes, where R is a HDAC-targeting vector with hydroxamic acid, were not accessible *via* metal-mediated *retro-Diels–Alder* reaction.

Experimental Part

General. Reactions were carried out in dried glassware under N_2. Solvents were dried using standard techniques and stored over molecular sieves. $[Re(CO)_3(Cp\text{-}COOH)]$ [45] (**23**), $[Re(CO)_3(Cp\text{-}NH_2)]$ [46], and $[Re(CO)_3(Cp\text{-}CONHCH_2C_6H_4SO_2NH_2)]$ [30] (**22**) were prepared according to literature procedures. RP-HPLC was performed on a *Merck Hitachi LaChrom L7200* tunable UV detector and a radiodetector, separated by a *Teflon* tube, which causes a *ca.* 0.4–0.7-min delay compared to UV/VIS detection. UV/VIS Detection was performed at 250 nm. Anal. columns (*Macherey-Nagel Nucleosil 100-5 C18*) were eluted with a flow rate of 0.5 ml min^{-1} using 0.1% TFA in H_2O (solvent *A*) and MeOH (solvent *B*) as eluents with a variable gradient (0–3 min, 100% *A*; 3–3.1 min, 0–25% *B*; 3.1–9 min, 25% *B*; 9–9.1 min, 25–34% *B*; 9.1–20 min, 34%–100% *B*; 20–25 min, 100% *B*; 25–25.1 min 100% *B* to 100% *A*; 25.1–30 min 100% *A*). IR Spectra were recorded as KBr pellets on a *Perkin-Elmer BX II* IR spectrometer; in cm^{-1}. ^1H- and ^{13}C-NMR spectra were recorded on a *Bruker Advance 400 MHz* or *500 MHz* spectrometer; δ in ppm, *J* in Hz. Mass spectra were recorded on a *Bruker Esquire HCT* (ESI) instrument; in *m*/*z*. The detection of radioactive ^{99m}Tc complexes was performed with a *Berthold LB 507* radiodetector equipped with a NaI(Tl) scintillation detector.

For biological studies, *Dulbecco*'s Modified Eagle Medium (DMEM) with *GlutaMax-I*, fetal bovine serum (FBS), penicillin/streptomycin antibiotic soln., phosphate-buffered saline (PBS), and trypsin were purchased from *Gibco Invitrogen Co.* (*Alfagene*, Portugal). MeOH, DMSO, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT), and Trypan Blue were bought from *SigmaChemical Co.* (*Sigma*, Portugal). Suberoylanilide hydroxamic acid (SAHA) was purchased from *Cayman Corporation*. For the determination of the IC_{50} values, absorbance at 570 nm was measured using a microplate spectrophotometer (*PowerWave Xs*, *Bio-Tek Instruments*, Winooski, VT, USA).

Crystallographic data was collected at 183(2) K with MoK_α radiation ($\lambda = 0.7107$ Å) that was graphite-monochromated on an *Oxford Diffraction CCD Xcalibur* system with a *Ruby* detector. Suitable

crystals were covered with oil (*Infineum V8512*, formerly known as *Paratone N*), mounted on top of a *CryoLoop*™ (*Hampton Research)* and immediately transferred to the diffractometer. The program suite CrysAlis^{Pro} was used for data collection, multi-scan absorption correction, and data reduction [47]. The structure was solved with direct methods using SIR97 [48] and were refined by full-matrix least-squares methods on F^2 with SHELXL-97 [49]. The H-atoms were placed on calculated positions. CCDC No. 868628 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif.

Tricarbonyl(8-{[(η^5-cyclopentadienyl)carbonyl]amino}-N-*hydroxyoctanamide)rhenium* (**1**). To a soln. of **14** (318 mg, 0.61 mmol) in 5 ml of dry THF, Et_3N (123 µl, 0.88 mmol) and ClCOOEt (78 µl, 1.0 mmol) were added. After stirring the mixture for 1 h at r.t., a soln. of $NH_2OH \cdot HCl$ (141 mg, 2.03 mmol) and MeONa (30% in MeOH, 381 µl, 2.03 mmol) in 2 ml of MeOH was added, and the mixture was stirred at r.t. for 18 h. Solvents were evaporated at reduced pressure, and the residue was redissolved in THF, filtered, and evaporated to dryness. Silica-gel chromatography with a gradient from CH_2Cl_2/AcOH 100:5 to CH_2Cl_2/MeOH 100:5 afforded **1** (80%). Calc. for M_r ($C_{16}H_{13}N_2O_6ReS$) 535.5. IR: 2020, 1905, 1633, 1548, 1367, 1303, 1036. ^{1}H-NMR (500 MHz, MeOD): 8.19 (*t*, $J = 5.6$, 2 N*H*CH_2); 6.15 (*m*, 2 H, Cp); 5.56 (*m*, 2 H, Cp); 3.26 (*m*, CH_2); 2.08 (*m*, CH_2); 1.60 (*m*, 2 CH_2); 1.35 (*m*, 3 CH_2). ^{13}C-NMR (125 MHz, MeOD): 194.3 (CO); 173.2 (CONHOH); 164.9 (CONH); 96.2 (Cp1); 87.9 (Cp2); 86.6 (Cp3); 40.7, 33.9, 30.5, 30.2, 30.1, 27.9, 26.8 (CH_2). ESI-MS (MeOH): 559.1 ($[M+Na]^+$), 537.2 ($[M+H]^+$).

Tricarbonyl(7-{[(η^5-cyclopentadienyl)carbonyl]amino}-N-*hydroxyheptanamide)rhenium* (**2**). Compound **2** was prepared as described for **1** using **15**. Silica-gel chromatography with a gradient from CH_2Cl_2/AcOH 100:5 to CH_2Cl_2/MeOH 100:5 afforded **2** (83%). Calc. for M_r ($C_{16}H_{19}N_2O_6Re$) 521.5. IR: 2020, 1907, 1633, 1549, 1368, 1303, 1036. ^{1}H-NMR (400 MHz, (D_6)DMSO): 10.32 (*s*, OH); 8.63 (*s*, N*H*OH); 8.20 (*t*, $J = 5.6$, 2 N*H*CH_2); 6.27 (*m*, 2 H, Cp); 5.70 (*m*, 2 H, Cp); 3.13 (*m*, CH_2); 1.92 (*m*, CH_2); 1.45 (*m*, 2 CH_2); 1.25 (*m*, 2 CH_2). ^{13}C-NMR (125 MHz, (D_6)DMSO): 194.2 (CO); 169.1 (CONHOH); 161.2 (CONH); 96.1 (Cp1); 87.3 (Cp2); 86.2 (Cp3); 38.7, 32.3, 29.0, 28.4, 26.1, 25.1 (CH_2). ESI-MS (MeOH): 545.1 ($[M+Na]^+$).

*Tricarbonyl[*N^1*-(η^5-cyclopentadienyl)-*N^8*-hydroxyoctanediamide]rhenium* (**3**). Compound **3** was prepared as described for **1** using **17**. Silica-gel chromatography with a gradient from CH_2Cl_2/AcOH 100:5 to CH_2Cl_2/MeOH 100:5 afforded **3** (86%). Calc. for M_r ($C_{16}H_{19}N_2O_6Re$) 521.5. IR: 2019, 1913, 1640, 1558, 1487, 1385. ^{1}H-NMR (400 MHz, (D_6)DMSO): 10.30 (*s*, OH); 10.02 (*s*, NH); 8.63 (*s*, *NH*OH); 5.78 (*m*, 2 H, Cp); 5.48 (*m*, 2 H, Cp); 2.14 (*m*, CH_2); 1.92 (*m*, CH_2); 1.47 (*m*, 2 CH_2); 1.22 (*m*, 2 CH_2). ^{13}C-NMR (125 MHz, (D_6)DMSO): 195.5 (CO); 171.3 (NHCO); 169.0 (CONHOH); 118.7 (Cp1); 81.4 (Cp2); 72.5 (Cp3); 35.7, 32.2, 28.3, 28.2, 25.0, 24.8 (CH_2). ESI-MS (MeOH): 545.1 ($[M+Na]^+$). Anal. calc.: C 39.02, H 4.09, N 2.84; found: C 38.91, H 3.95, N 2.76.

N-*[8-(Hydroxyamino)-8-oxooctyl]benzamide* (**4**). Compound **4** was prepared as described for **1** using **18**. Silica gel chromatography with a gradient from CH_2Cl_2/AcOH 100:5 to CH_2Cl_2/MeOH 100:5 afforded **4** (90%). Calc. for M_r ($C_{15}H_{22}N_2O_3$) 278.4. ^{1}H-NMR (400 MHz, (D_6)DMSO): 10.33 (*s*, OH); 8.62 (*s*, *NH*OH); 8.41 (*t*, $J = 5.5$, NH); 7.81 (*m*, 2 arom. H); 7.46 (*m*, 3 arom. H); 3.24 (*m*, CH_2); 1.93 (*m*, CH_2); 1.50 (*m*, 2 CH_2); 1.15 (*m*, 3 CH_2). ^{13}C-NMR (125 MHz, MeOD): 173.2 (CONHOH); 170.4 (CONH); 136.0 (Ar1); 132.7 (Ar2); 129.7 (Ar3); 128.4 (Ar4); 48.0, 41.1, 33.9, 30.6, 30.2, 28.0, 26.8 (CH_2). ESI-MS (MeOH): 279.1 ($[M+H]^+$), 301.1 ($[M+Na]^+$), 277.1 ($[M-H]^-$). Anal. calc.: C 64.73, H 7.97, N 10.06; found: C 64.32, H 7.88, N 9.91.

N-*[7-(Hydroxyamino)-7-oxoheptyl]benzamide* (**5**). Compound **5** was prepared as described for **1** using **19**. Silica-gel chromatography with a gradient from CH_2Cl_2/AcOH 100:5 to CH_2Cl_2/MeOH 100:5 afforded **5** (92%). Calc. for M_r ($C_{14}H_{20}N_2O_3$) 264.3. ^{1}H-NMR (400 MHz, (D_6)DMSO): 10.33 (*s*, OH); 8.64 (*s*, *NH*OH); 8.42 (*t*, $J = 5.5$, NH); 7.83 (*m*, 2 arom. H); 7.46 (*m*, 3 arom. H); 3.24 (*m*, CH_2); 1.93 (*m*, CH_2); 1.50 (*m*, 2 CH_2); 1.15 (*m*, 2 CH_2). ESI-MS (MeOH): 265.2 ($[M+H]^+$), 263.2 ($[M-H]^-$). Anal. calc. for **5** + 0.5 H_2O: C 61.52, H 7.74, N 10.25; found: C 61.14, H 7.67, N 9.89.

*3a,4,7,7a-Tetrahydro-*N^2*,*N^6*-bis[7-(hydroxyamino)-7-oxoheptyl]-4,7-methano-1*H*-indene-2,6-dicarboxamide* (**6**). Compound **20** (50 mg, 0.11 mmol) was dissolved in 1 ml of DMF and *N*-methylmorpholine (3 equiv., 35.1 µl, 0.32 mmol) and *O*-(7-aza-1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexa-

fluorophosphate (NATU; 3 equiv., 121.1 mg, 0.32 mmol) was added. The soln. was stirred for 30 min at r.t. *O*-[(*tert*-Butyl)dimethylsilyl]hydroxylamine (3 equiv., 47 mg, 0.32 mmol) dissolved in 1 ml of DMF was added, and the mixture was stirred for 5 h at r.t. The solvent was evaporated *in vacuo*. The residue was suspended in dist. H_2O and extracted three times with 20 ml of AcOEt. The aq. phase was evaporated, and the residue was purified by silica-gel chromatography with CH_2Cl_2/MeOH/AcOH 10:1:0.1 (70%). Calc. for M_r ($C_{26}H_{40}N_4O_6$) 504.6. ^{1}H-NMR (400 MHz, MeOD): 7.86 (*t*, *J* = 5.7, NH); 7.59 (*t*, *J* = 5.6, NH); 6.68 (*m*, CH); 6.33 (*m*, CH); 3.53 (*m*, CH); 3.38 (*m*, CH); 3.21 (*m*, 5 H, CH_2 superimposed with CH); 3.02 (*m*, CH); 2.49 (*m*, CH); 2.12 (*dt*, *J* = 7.4, 4 CH); 2.06 (*m*, CH); 1.65 (*m*, 5 H, CH_2 superimposed with CH); 1.51 (*m*, 5 H, CH_2 superimposed with CH); 1.36 (*m*, 4 CH_2). ESI-MS (MeOH): 527.3 ($[M+Na]^+$).

*7-[({6-[({[4-(Aminosulfonyl)phenyl]methyl}amino)carbonyl]-3a,4,7,7a-tetrahydro-4,7-methano-1*H*-inden-2-yl}carbonyl)amino]heptanoic acid* (**7**). 4-(Aminomethyl)benzensulfonamide hydrochloride (1.2 equiv., 92.4 mg, 0.42 mmol) was dissolved in 1 ml of DMF. Et_3N (5 equiv., 235.6 µl, 1.7 mmol) and **21** (174.6 mg, 0.34 mmol) were added. The reaction progress was monitored by HPLC. When the starting compound was consumed, the solvent was evaporated *in vacuo*, and the residue was purified by silica-gel chromatography with CH_2Cl_2/MeOH/AcOH 100:5:5 (80%). Calc. for M_r ($C_{26}H_{33}N_3O_6S$) 515.6. ^{1}H-NMR (400 MHz, MeOD): 7.86 (*m*, 2 arom. H); 7.61 (*t*, *J* = 5.9, NH); 7.41 (*m*, 2 arom. H); 6.77 (*m*, CH); 6.35 (*m*, CH); 3.56 (*m*, CH); 4.52 (*m*, CH_2) 3.41 (*m*, CH); 3.22 (*m*, 3 H, CH_2 superimposed with CH); 3.03 (*m*, CH); 2.51 (*m*, CH); 2.27 (*t*, *J* = 7.4, CH_2); 2.11 (*m*, CH); 1.69 (*m*, CH); 1.56 (*m*, 5 H, CH_2 superimposed with CH); 1.35 (*m*, 2 CH_2). ESI-MS (MeOH): 514.1 ($[M-H]^-$), 538.2 ($[M+Na]^+$).

*8-{[(2-{[(6-Carboxyhexyl)amino]carbonyl}-3a,4,7,7a-tetrahydro-4,7-methano-1*H*-inden-6-yl)carbonyl]amino}octanoic acid* (**8**). Compound **8** was synthesized as described for **7** using 8-aminocaprylic acid. The crude product was purified by flash chromatography (FC) on silica gel (with gradient from CH_2Cl_2 to CH_2Cl_2/MeOH/AcOH 20:1:1) to give pure **8** (32%). Calc. for M_r ($C_{27}H_{40}N_2O_6$) 488.3. ^{1}H-NMR (500 MHz, MeOD): 7.83 (*t*, *J* = 5.7, NH); 7.54 (*t*, *J* = 5.7, NH); 6.66 (*m*, CH); 6.33 (*m*, CH); 3.52 (*m*, CH); 3.37 (*m*, CH); 3.17 (*m*, 2 CH_2); 3.13 (*m*, CH); 3.01 (*m*, CH); 2.48 (*m*, CH); 2.30 (*dt*, *J* = 7.3, 2 CH_2); 2.06 (*m*, CH); 1.65 (*m*, 5 H, CH_2 superimposed with CH); 1.51 (*m*, 5 H, CH_2 superimposed with CH); 1.35 (*m*, 5 CH_2). ESI-MS (MeOH): 527.3 ($[M+K]^+$), 511.3 ($[M+Na]^+$), 489.3 ($[M+H]^+$).

*6-Benzyl 2-{[(6-Carboxyhexyl)amino]carbonyl}-3a,4,7,7a-tetrahydro-4,7-methano-1*H*-indene-6-carboxylate* (**9**). To a soln. of **21** (934.5 mg, 1.82 mmol) in 3 ml of DMF, BnOH (4 equiv., 754 µl, 7.28 mmol) and Et_3N (4 equiv., 1.01 ml, 7.28 mmol) were added, and the mixture was stirred at r.t. under N_2. Reaction control by NMR still showed incomplete coupling after 7 d. Hence, more BnOH (4 equiv., 754 µl, 7.28 mmol) and Et_3N (2 equiv., 500 µl, 3.64 mmol) were added, and the mixture was stirred during additional 24 h at 50°. The solvent was evaporated at reduced pressure. The residue was suspended in 4 ml of sat. $NaHCO_3$ soln. diluted 20-fold with H_2O and extracted with 100 ml of AcOEt. The aq. phase was then acidified with 1M HCl to pH 1, and extracted three times with 100 ml of AcOEt. The combined org. phases were dried (Na_2SO_4), and the solvent was removed *in vacuo* to yield 700 mg of crude product. The crude product was purified by FC on silica gel (with gradient from CH_2Cl_2 to CH_2Cl_2/MeOH 9:1) to give pure **9** (70 mg, 9%). Calc. for M_r ($C_{26}H_{31}NO_5$) 473.2. ^{1}H-NMR (500 MHz, MeOD): 7.64 (*t*, *J* = 5.5, NH) 7.35 (*m*, 5 arom. H); 6.95 (*m*, CH); 6.32 (*m*, CH); 3.55 (*m*, CH); 3.36 (*m*, CH); 3.20 (*m*, 3 H, CH_2 superimposed with CH); 3.01 (*m*, CH); 2.49 (*m*, CH); 2.28 (t, *J* = 7.4, CH_2); 2.02 (*m*, CH); 1.67 (*m*, CH); 1.60 (*m*, CH); 1.48 (*m*, 2 CH_2); 1.33 (*m*, 2 CH_2). ESI-MS (MeOH): 460.1 ($[M+Na]^+$), 438.1 ($[M+H]^+$), 436.1 ($[M-H]^-$).

Tricarbonyl(7-{[(η^5-cyclopentadienyl)carbonyl]amino}heptanoic Acid)-99m-technetium (**10**). A vial was charged with [H_3BCOOH] (4 mg), $Na_2[C_4H_4O_6]\cdot 2\,H_2O$ (7 mg), $Na_2B_4O_7\cdot 10\,H_2O$ (7 mg), and **20** (5 mg). The vial was sealed and flushed with N_2 for 5 min. Freshly eluted $Na[^{99m}TcO_4]$ (1 ml) was injected, and the mixture was heated at 85–90°. After cooling to r.t. and filtering, the products were analyzed by HPLC. After 80 min, 87% conversion of $[^{99m}TcO_4]^-$ was observed. Co-injection of the corresponding Re complex confirmed the nature of the product.

Tricarbonyl(7-{[(η^5-cyclopentadienyl)carbonyl]amino}heptanoic Acid)-99m-technetium (**10**) *and Tricarbonyl(8-{[(η^5-cyclopentadienyl)carbonyl]amino}octanoic Acid)-99m-technetium* (**11**). A vial was charged with [H_3BCOOH] (4 mg), $Na_2[C_4H_4O_6]\cdot 2\,H_2O$ (7 mg), $Na_2B_4O_7\cdot 10\,H_2O$ (7 mg), and **8** (8 mg). The vial was sealed and flushed with N_2 for 5 min. Freshly eluted $Na[^{99m}TcO_4]$ (1 ml) was injected, and

the mixture was heated at 85–90°. After cooling to r.t. and filtering, the products were analyzed by HPLC. After 150 min, 80% conversion of $[^{99m}TcO_4]^-$ was observed. The radio **10**/**11** was 45:55. The nature of the products was confirmed by co-injection of the corresponding Re complex.

Tricarbonyl(7-{[(η⁵-cyclopentadienyl)carbonyl]amino}heptanoic Acid)-99m-technetium (**10**) *and Tricarbonyl[(η⁵-cyclopentadienyl)carboxylic Acid]-99m-technetium* (**12**). A vial was charged with [H_3BCOOH] (4 mg), $Na_2[C_4H_4O_6]\cdot 2\,H_2O$ (7 mg), $Na_2B_4O_7\cdot 10\,H_2O$ (7 mg), and **9** (3–4 mg). The vial was sealed and flushed with N_2 for 5 min. Freshly eluted $Na[^{99m}TcO_4]$ (1 ml) was injected, and the mixture was heated at 85–90°. After cooling to r.t. and filtering, the products were analyzed by HPLC. After 200 min, 98% conversion of $[^{99m}TcO_4]^-$ was observed. The radio **12**/**10** was nearly 50:50. The nature of the products was confirmed by co-injection of the corresponding Re complex.

Tricarbonyl(7-{[(η⁵-cyclopentadienyl)carbonyl]amino}heptanoic Acid)-99m-technetium (**10**) *and Tricarbonyl(*N*-{[4-(aminosulfonyl)phenyl]methyl}(η⁵-cyclopentadienyl)carboxamide)-99m-technetium* (**13**). To a commercially available *Isolink-Kit*, freshly eluted $Na[^{99m}TcO_4]$ (1 ml) was injected, and the mixture was heated at 85–90°. The full conversion of $[^{99m}TcO_4]^-$ to $[^{99m}Tc(H_2O)_3(CO)_3]^+$ was confirmed by HPLC after 30 min. A new vial was charged with **7** (3–5 mg), sealed, and flushed with N_2 for 5 min. A $[^{99m}Tc(H_2O)_3(CO)_3]^+$ soln. (1 ml) was injected into the vial, and the mixture was heated at 85–90°. After cooling to r.t. and filtering, the products were analyzed by HPLC. After 150 min, 81% conversion of $[^{99m}Tc(H_2O)_3(CO)_3]^+$ to the products was observed; 7% of $[^{99m}TcO_4]^-$ was formed as a side product. The radio **13**/**10** was 45:55. The nature of the products was confirmed by co-injection of the corresponding Re complexes.

Tricarbonyl(8-{[(η⁵-cyclopentadienyl)carbonyl]amino}octanoic Acid)rhenium (**14**). [(Cp–COOH)-$Re(CO)_3$] was activated with pentafluorophenyl trifluoroacetate according to the procedure described in [28]. PFP-Activated acid (360.4 mg, 0.53 mmol) was dissolved in 5 ml of DMF and cooled to 0°. A soln. of 8-aminocaprylic acid (100 mg, 0.63 mmol) and $NaHCO_3$ (53 mg, 0.63 mmol) in 5 ml of H_2O was slowly added. A thick cream-colored precipitate formed instantly. The mixture was allowed to reach r.t. and was stirred for 18 h, whereupon the precipitate was consumed. Removal of the solvent under reduced pressure and silica-gel chromatography with CH_2Cl_2/MeOH/AcOH 100:1:1 afforded **14** (88%). Calc. for M_r ($C_{16}H_{13}N_2O_6ReS$) 547.6. IR: 2022, 1907, 1706, 1621, 1551. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.16 (*t*, *J* = 5.7, NH); 6.26 (*m*, 2 H, Cp); 5.70 (*m*, 2 H, Cp); 3.13 (*m*, CH_2); 2.17 (*m*, CH_2); 1.45 (*m*, 2 CH_2); 1.25 (*m*, 3 CH_2). ^{13}C-NMR (125 MHz, (D_6)DMSO): 194.2 (CO); 174.5 (COOH); 161.2 (NHCO); 96.0 (Cp1); 87.2 (Cp2); 86.2 (Cp3); 38.7, 33.7, 29.0, 28.6, 28.5, 26.2, 24.5 (CH_2). ESI-MS (MeOH): 519.8 ([*M* − H]$^-$). Anal. calc.: C 39.07, H 4.24, N 2.68; found: C 38.19, H 3.97, N 2.86.

Tricarbonyl(7-{[(η⁵-cyclopentadienyl)carbonyl]amino}heptanoic Acid)rhenium (**15**). Compound **15** was prepared as described for **14** using 7-aminoheptanoic acid. Silica-gel chromatography with CH_2Cl_2/MeOH/AcOH 100:1:1 afforded **15** (86%). Calc. for M_r ($C_{16}H_{18}NO_6Re$) 506.5. IR: 2022, 1909, 1705, 1623, 1551. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.17 (*t*, *J* = 5.7, NH); 6.26 (*m*, 2 H, Cp); 5.70 (*m*, 2 H, Cp); 3.13 (*m*, CH_2); 2.18 (*m*, CH_2); 1.30 (*m*, 2 CH_2); 1.26 (*m*, 2 CH_2). ^{13}C-NMR (125 MHz, (D_6)DMSO): 194.2 (*C*O); 174.5 (COOH); 161.2 (CONH); 96.0 (Cp1); 87.2 (Cp2); 86.2 (Cp3); 38.6, 33.6, 28.9, 28.3, 26.1, 24.5 (CH_2). ESI-MS (MeOH): 508.0 ([*M*+H]$^+$), 530.0 ([*M*+Na]$^+$), 505.7 ([*M* − H]$^-$). Anal. calc.: C 37.94, H 3.58, N 2.77; found: C 37.74, H 3.61, N 2.60.

Tricarbonyl{methyl 8-[(η⁵-Cyclopentadienyl)amino]-8-oxooctanoate}rhenium (**16a**) *and Tricarbonyl{methyl 8-[(η⁵-Cyclopentadienyl)amino]-8-oxooctanoate}manganese* (**16b**). Suberic acid monomethyl ester (309 µl, 1.72 mmol) was dissolved in 10 ml of dry THF. Addition of *N*-methylmorpholine (190 µl, 1.72 mmol) and $ClCOO^iBu$ of (225.5 µl, 1.72 mmol) resulted in formation of a colorless precipitate. After stirring the suspension for 10 min, [$M(CO)_3$(Cp-NH_2)] (**16a**: M = Re, **16b**: M = Mn) [46] (0.86 mmol) was added, and the mixture was stirred for further 17 h at r.t. The solvent was removed at reduced pressure. H_2O (30 ml) was added, and the residue was extracted three times with 50 ml of AcOEt. The combined org. fractions were dried (Na_2SO_4) and evaporated under reduced pressure. Silica-gel chromatography with hexane/AcOEt 2:1 afforded **16a**/**16b** in quant. yield.

Data of **16a**. Calc. for M_r ($C_{17}H_{20}NO_6Re$) 520.6. IR: 2024, 1910, 1719, 1703, 1541, 1487, 1235, 1163. ^{1}H-NMR (400 MHz, (D_6)DMSO): 10.02 (*s*, NH); 5.78 (*m*, 2 H, Cp); 5.48 (*m*, 2 H, Cp); 3.57 (*s*, CH_3); 2.27 (*m*, CH_2); 2.14 (*m*, CH_2); 1.25 (*m*, 2 CH_2); 1.23 (*m*, 2 CH_2). ^{13}C-NMR (125 MHz, (D_6)DMSO): 195.5 (CO); 173.3 (*C*OOMe); 171.3 (NHCO); 118.7 (Cp1); 81.4 (Cp2); 72.5 (Cp3); 51.2 (COO*Me*); 35.6, 33.2,

28.1, 28.0, 24.7, 24.2 (CH_2). ESI-MS (MeOH): 544.0 ($[M+Na]^+$). Anal. calc.: C 39.02, H 4.09, N 2.84; found: C 38.91, H 3.95, N 2.76.

Data of **16b**. ESI-MS (MeOH): 412.0 ($[M+Na]^+$). Crystals of **16b** were grown from CH_2Cl_2/hexane. Crystallographic parameters: empirical formula, $C_{17}H_20\,MnNO_6$; M_r, 398.28 g/mol; crystal system, monoclinic; space group, *P*21/*c*; unit cell parameters: $a=12.2182(4)$, $b=19.1058(7)$, $c=7.5939(3)$ Å, $\alpha=90$, $\beta=90.240(3)$, $\gamma=90°$; *V*, 1772.69(11) Å^3; density (calc.), 1.459 Mg/m^3; absorption coefficient, 0.777 mm^{-1}; $Z=4$; crystal size, $0.35\times0.23\times0.17$ mm^3; crystal description, colorless block; reflections collected, 12863; independent reflections (R(int)), 5402 (0.0334); reflections observed ($I>2\sigma(I)$), 4080; number of parameters, 228; completeness to Θ, 99.7% to 30.51°; goodness-of-fit on F^2, 1.066; final *R* indices ($I>2\sigma(I)$), $R_1=0.0460$ and $wR_2=0.1119$; *R* indices (all data), $R_1=0.0650$ and $wR_2=0.1217$; diff. peak and hole, 0.400 and −0.914 e/Å^3. Relevant bond lengths [Å] and angles [°]: Mn(1)–C(1) 1.784(3), Mn(1)–C(2) 1.784(3), Mn(1)–C(3) 1.776(3), Mn(1)–C(4) 2.194(2), Mn(1)–C(5) 2.146(2), Mn(1)–C(6) 2.102(3), Mn(1)–C(7) 2.105(3), Mn(1)–C(8) 2.133(3), C(1)–O(1) 1.147(4), C(2)–O(2) 1.138(4), C(3)–O(3) 1.143(4), C(4)–N(1) 1.400(3), C(9)–O(4) 1.212(3), C(16)–O(5) 1.192(3), C(16)–O(6) 1.325(3), C(3)–Mn(1)–C(2) 93.72(15), C(3)–Mn(1)–C(1) 92.19(15), C(2)–Mn(1)–C(1) 90.54(14), O(4)–C(9)–N(1) 121.7(3), O(4)–C(9)–C(10) 123.6(3), O(5)–C(16)–O(6) 122.9(3), O(5)–C(16)–C(15) 124.8(3), C(16)–O(6)–C(17) 116.0(2).

Tricarbonyl{8-[(η^5-Cyclopentadienyl)amino]-8-oxooctanoic Acid}rhenium (**17**). Compound **16a** (342 mg, 0.66 mmol) was dissolved in a mixture of 2 ml of THF and 4 ml of MeOH. LiOH (138 mg, 3.28 mmol) in 2 ml of H_2O was added, and the mixture was stirred at r.t. for 2 h. Solvents were evaporated at reduced pressure to *ca.* 2 ml, and the mixture was acidified with HCl (conc.) to pH 1. Extraction of the aq. layer with AcOEt afforded **17** (310 mg, 92%). Calc. for M_r ($C_{16}H_{18}NO_6Re$) 506.5. ^{1}H-NMR (400 MHz, (D_6)DMSO): 10.02 (*s*, NH); 5.78 (*m*, 2 H, Cp); 5.48 (*m*, 2 H, Cp); 2.17 (*m*, 2 CH_2); 1.47 (*m*, 2 CH_2); 1.24 (*m*, 2 CH_2). ESI-MS (MeOH): 530.0 ($[M+Na]^+$), 506.0 ($[M-H]^-$).

8-(Benzoylamino)octanoic Acid (**18**). Benzoic acid (250 mg, 2.05 mmol) was dissolved in 5 ml of dry DMF. Pyridine (180.6 µl, 2.24 mmol) and pentafluorophenyl trifluoracetate (386.8 µl, 2.24 mmol) were added, and the soln. was stirred for 3 h at r.t. DMF was evaporated at reduced pressure. AcOEt was added, and the residue was extracted three times with 0.1M HCl and three times with 5% $NaHCO_3$. The org. fraction was washed with fresh H_2O, dried (Na_2SO_4), and evaporated to dryness. The activated acid (151.3 mg, 0.53 mmol) was dissolved in 5 ml of DMF and cooled to 0°. A soln. of 8-aminocaprylic acid (100 mg, 0.63 mmol) and $NaHCO_3$ (53 mg, 0.63 mmol) in 1 ml of H_2O was slowly added. A thick cream-colored precipitate formed instantly. The mixture was allowed to reach r.t. and was stirred for 18 h. Silica-gel chromatography with AcOEt/hexane 1:1 afforded **18** (90%). Calc. for M_r ($C_{15}H_{21}NO_3$) 263.3. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.41 (*t*, $J=5.4$, NH); 7.81 (*m*, 2 arom. H); 7.46 (*m*, 3 arom. H); 3.24 (*m*, CH_2); 2.19 (*m*, CH_2); 1.50 (*m*, 2 CH_2); 1.29 (*m*, 3 CH_2). ^{13}C-NMR (125 MHz, MeOD): 177.9 (COOH); 170.4 (CONH); 136.0 (Ar1); 132.7 (Ar2); 129.7 (Ar3); 128.4 (Ar4); 41.1, 35.1, 30.6, 30.3, 30.2, 28.1, 26.2 (CH_2). ESI-MS (MeOH): 286.1 ($[M+Na]^+$), 264.0 ($[M+H]^+$), 262.0 ($[M-H]^-$). Anal. calc.: C 68.42, H 8.04, N 5.32; found: C 67.99, H 7.76, N 5.26.

7-(Benzoylamino)heptanoic Acid (**19**). Compound **19** was prepared as described for **18** using 7-aminoheptanoic acid. Silica-gel chromatography with AcOEt/hexane 1:1 afforded **19** (89%). Calc. for M_r ($C_{15}H_{19}NO_3$) 249.3. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.41 (*t*, $J=5.3$, NH); 7.81 (*m*, 2 arom. H); 7.46 (*m*, 3 arom. H); 3.24 (*m*, CH_2); 2.19 (*m*, CH_2); 1.50 (*m*, 2 CH_2); 1.30 (*m*, 2 CH_2). ^{13}C-NMR (125 MHz, MeOD): 177.9 (COOH); 170.5 (CONH); 136.1 (Ar1); 132.7 (Ar2); 129.7 (Ar3); 128.4 (Ar4); 41.1, 35.1, 30.5, 30.1, 27.9, 26.2 (CH_2). ESI-MS (MeOH): 250.0 ($[M+H]^+$), 272.0 ($[M+Na]^+$), 247.9 ($[M-H]^-$). Anal. calc.: C 67.45, H 7.68, N 5.62; found: C 67.25, H 7.48, N 5.46.

*7,7′-[(3a,4,7,7a-Tetrahydro-4,7-methano-1*H*-indene-2,6-diyl)bis(carbonylimino)]bisheptanoic acid* (**20**). *Thiele*'s acid was activated with pentafluorophenyl trifluoroacetate as described in [28]. 7-Aminoheptanoic acid (2.2 equiv., 115.7 mg, 0.80 mmol) was dissolved in 1 ml of DMF, and Et_3N (4.4 equiv., 220.8 µl, 1.59 mmol) was added. The activated acid (200 mg, 0.36 mmol) was added in one portion, and the mixture was stirred for 20 h at r.t. The solvent was evaporated in *vacuo*, and the residue was purified by silica-gel chromatography with CH_2Cl_2/MeOH/AcOH 100:0.5:0.1 to give **20** (54%). Calc. for M_r ($C_{26}H_{38}N_2O_6$) 474.6. ^{1}H-NMR (400 MHz, MeOD): 7.81 (*t*, $J=5.7$, NH); 7.52 (*t*, $J=5.7$, NH); 6.63 (*m*, CH); 6.30 (*m*, CH); 3.48 (*m*, CH); 3.34 (*m*, CH); 3.18 (*m*, 2 CH_2); 3.10 (*m*, CH); 2.97 (*m*, CH);

2.45 (*m*, CH); 2.27 (*dt*, $J = 7.3$,2 CH_2); 2.00 (*m*, CH); 1.60 (*m*, 5 H, CH_2 superimposed with CH); 1.47 (*m*, 5 H, CH_2). ESI-MS (MeOH): 497.2 ($[M+Na]^+$), 475.3 ($[M+H]^+$).

*6-(2,3,4,5,6-Pentafluorophenyl) 2-[[(6-Carboxyhexyl)amino]carbonyl]-3a,4,7,7a-tetrahydro-4,7-methano-1*H*-indene-6-carboxylic acid* (**21**). *Thiele*'s acid was activated with pentafluorophenyl trifluoroacetate as described in [28]. 7-Aminoheptanoic acid (1.2 equiv., 60.3 mg, 0.42 mmol) was dissolved in 1 ml of DMF. The activated acid (191 mg, 0.34 mmol) was added in one portion, and the mixture was stirred for 20 h at r.t. The solvent was evaporated *in vacuo*, and the residue was purified by silica-gel chromatography (CH_2Cl_2/MeOH/AcOH 100 : 1 : 1) to afford **21** (34%). Calc. for M_r ($C_{25}H_{24}F_5NO_5$) 513.5. ^{1}H-NMR (400 MHz, MeOD): 7.67 (*t*, $J = 5.5$, NH); 7.35 (*m*, CH); 6.38 (*m*, CH); 3.67 (*m*, CH); 3.47 (*m*, CH); 3.22 (*m*, 3 H, CH_2 superimposed with CH); 3.11 (*m*, CH); 2.58 (*m*, CH); 2.29 (*t*, $J = 7.4$, CH_2); 2.08 (*m*, CH); 1.81 (*m*, CH); 1.57 (*m*, 5 H, CH_2 superimposed with CH); 1.35 (*m*, 2 CH_2). ESI-MS (MeOH): 536.1 ($[M+Na]^+$).

Tumor Cell Lines. The human breast carcinoma MCF-7, prostate carcinoma PC3, cervical carcinoma HeLa, vulva epidermal carcinoma A43, and melanoma A375 cell lines as well as the murine melanoma B16F1cell line used in this study were grown in *Dulbecco*'s Modified Eagle Medium (DMEM) containing *GlutaMax-I* supplemented with 10% heat-inactivated foetal bovine serum (FBS) and 1% penicillin/streptomycin antibiotic soln. (all from *Gibco*, *Alfagene*, Lisbon). Cells were cultured in a humidified atmosphere of 95% air and 5% CO_2 at 37° (*Heraeus*, Germany), with the medium changed every other day. The cells were adherent in monolayers and, when confluent, were harvested from the cell culture flasks with trypsin EDTA (*Gibco*, *Alfagene*, Lisbon) and seeded farther apart.

Cytotoxic Activity. The antiproliferative activity on tumor cells was evaluated using a colorimetric method based on MTT (= 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide), which is reduced in viable cells to yield purple formazan crystals. The optimal plating density of each cell line, which ensures exponential growth throughout all of the exper. period, was first optimized. MCF-7 (15×10^3 cells), HeLa (9×10^3 cells), A431 (7.5×10^3 cells), A375 (7×10^3 cells), PC3 (6×10^3 cells), and B16F1 (6×10^3 cells) cells were plated in 96-well sterile plates in 150 µl of culture medium per well and incubated for 24 h at 37°/5% CO_2 for seeding. Then, the cells were incubated with various concentrations of the compounds **1**–**5** for 72 h at 37°/5% CO_2, dissolved in MeOH and diluted in the culture medium (final concentration in MeOH 0.025% and 0.1%, resp.). The effect of the vehicle solvent (MeOH) on the growth of these cell lines was evaluated in all experiments by exposing untreated control cells to both concentrations of MeOH used (0.025% and 0.1%).

At the end of the incubation period, the compounds were removed and cells were washed with 200 µl of PBS. Cell viability was then determined by incubating cells with 200 µl of MTT soln. (0.5 mg ml^{-1} in PBS). After 3 h at 37°/5% CO_2, the soln. was removed and the purple formazan crystals formed inside the cells were dissolved in 200 µl of DMSO by thorough shaking. For each test compound and for each cell line, a dose–response curve was obtained. The cytotoxic effects of ligands and Re complexes were quantified by calculating the compound concentration inhibiting tumor cell growth by 50% (IC_{50}), based on non-linear regression analysis of dose–response data (GraphPad Prisma 5 software). For comparison, suberoylanilide hydroxamic acid (SAHA) was evaluated under the same experimental conditions. All compounds were tested in at least two independent studies with eight replicates for each concentration.

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