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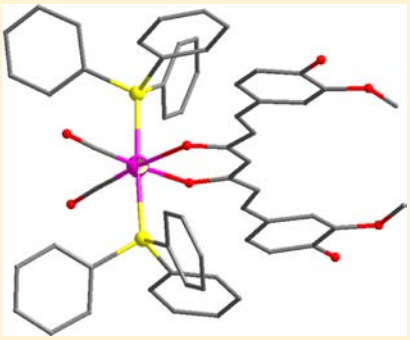
Synthesis and Characterization of *fac*-[M(CO)$_3$(P)(OO)] and *cis-trans*-[M(CO)$_2$(P)$_2$(OO)] Complexes (M = Re, ^{99m}Tc) with Acetylacetone and Curcumin as OO Donor Bidentate Ligands

Charalampos Triantis,[†] Theodoros Tsotakos,[†] Charalampos Tsoukalas,[†] Marina Sagnou,[‡] Catherine Raptopoulou,[§] Aris Terzis,[§] Vassilis Psycharis,[§] Maria Pelecanou,[‡] Ioannis Pirmettis,[†] and Minas Papadopoulos*[,†]

[†]Institute of Nuclear and Radiological Sciences and Technology, Energy and Safety, [‡]Institute of Biosciences & Applications, and [§]Institute of Advanced Materials, Physicochemical Processes, Nanotechnology and Microsystems, Department of Materials Science, National Centre for Scientific Research "Demokritos", 15310 Athens, Greece

Supporting Information

ABSTRACT: The synthesis and characterization of neutral mixed ligand complexes *fac*-[M(CO)$_3$(P)(OO)] and *cis-trans*-[M(CO)$_2$(P)$_2$(OO)] (M = Re, ^{99m}Tc), with deprotonated acetylacetone or curcumin as the OO donor bidentate ligands and a phosphine (triphenylphosphine or methyldiphenylphosphine) as the monodentate P ligand, is described. The complexes were synthesized through the corresponding *fac*-[M(CO)$_3$(H$_2$O)(OO)] (M = Re, ^{99m}Tc) intermediate aqua complex. In the presence of phosphine, replacement of the H$_2$O molecule of the intermediate complex at room temperature generates the neutral tricarbonyl monophosphine *fac*-[Re(CO)$_3$(P)(OO)] complex, while under reflux conditions further replacement of the trans to the phosphine carbonyl generates the new stable dicarbonyl bisphosphine complex *cis-trans*-[Re(CO)$_2$(P)$_2$(OO)]. The Re complexes were fully characterized by elemental analysis, spectroscopic methods, and X-ray crystallography showing a distorted octahedral geometry around Re. Both the monophosphine and the bisphosphine complexes of curcumin show selective binding to β-amyloid plaques of Alzheimer's disease. At the ^{99m}Tc tracer level, the same type of complexes, *fac*-[^{99m}Tc(CO)$_3$(P)(OO)] and *cis-trans*-[^{99m}Tc(CO)$_2$(P)$_2$(OO)], are formed introducing new donor combinations for ^{99m}Tc(I). Overall, β-diketonate and phosphine constitute a versatile ligand combination for Re(I) and ^{99m}Tc(I), and the successful employment of the multipotent curcumin as β-diketone provides a solid example of the pharmacological potential of this system.



INTRODUCTION

In recent years Tc and Re radiopharmaceutical chemistry with the tricarbonyl precursor *fac*-[M(CO)$_3$(H$_2$O)$_3$]$^+$ (M = ^{99m}Tc, Re) introduced in 1998[1] has been continuously expanding with the development of suitably derivatized novel ligand systems which efficiently displace the coordinated water molecules to produce complexes with high in vivo stability, favorable pharmacokinetic properties, and target tissue specificity.[2] The ligands are usually tridentate bearing combinations of various donor atom groups including amines, imines, thioethers, thiols, carboxylates, and so on, and give stable hexacoordinated complexes.[3] However, completion of the coordination sphere of the *fac*-[M(CO)$_3$]$^+$ core is also achieved by combining a bidentate and a monodentate ligand to produce "2 + 1" mixed ligand complexes.[4] The versatile "2 + 1" system is suitable for fine-tuning of the properties of the complexes and has so far generated a number of very interesting multifunctional complexes.[5]

Acetylacetone (acacH) is a well-established and widely used OO donor bidentate ligand that coordinates to Re(I) and Tc(I) through the acetylacetonate anion (acac)[6,7] and can be synthetically modified to incorporate a targeting biomolecule both at the center and at the edge carbons.[8] Recently, the synthesis of new "2 + 1"acetylacetonato *fac*-[M(CO)$_3$X(OO)] (M = Re, ^{99m}Tc) complexes with X being pyridine, methylimidazole, and ethylamine was reported through the intermediate *fac*-[Re(CO)$_3$(H$_2$O)(OO)] aqua complex.[9] Our group subsequently employed the β-diketones acetylacetone and the natural α,β-unsaturated β-diketone curcumin (curH) as OO donor bidentate ligands to generate, through the intermediate formation of the corresponding *fac*-[M(CO)$_3$(H$_2$O)(OO)], new "2 + 1" *fac*-[M(CO)$_3$X(OO)] complexes with the monodentate X being imidazole, or isocyanide.[10] In view of the wide spectrum of pharmacological properties of curcumin,[11] that include selective binding to amyloid plaques of Alzheimer's disease, the investigation of its coordination chemistry with Tc(I) and Re(I) is an appealing prospect that may lead to diagnostic or therapeutic applications.

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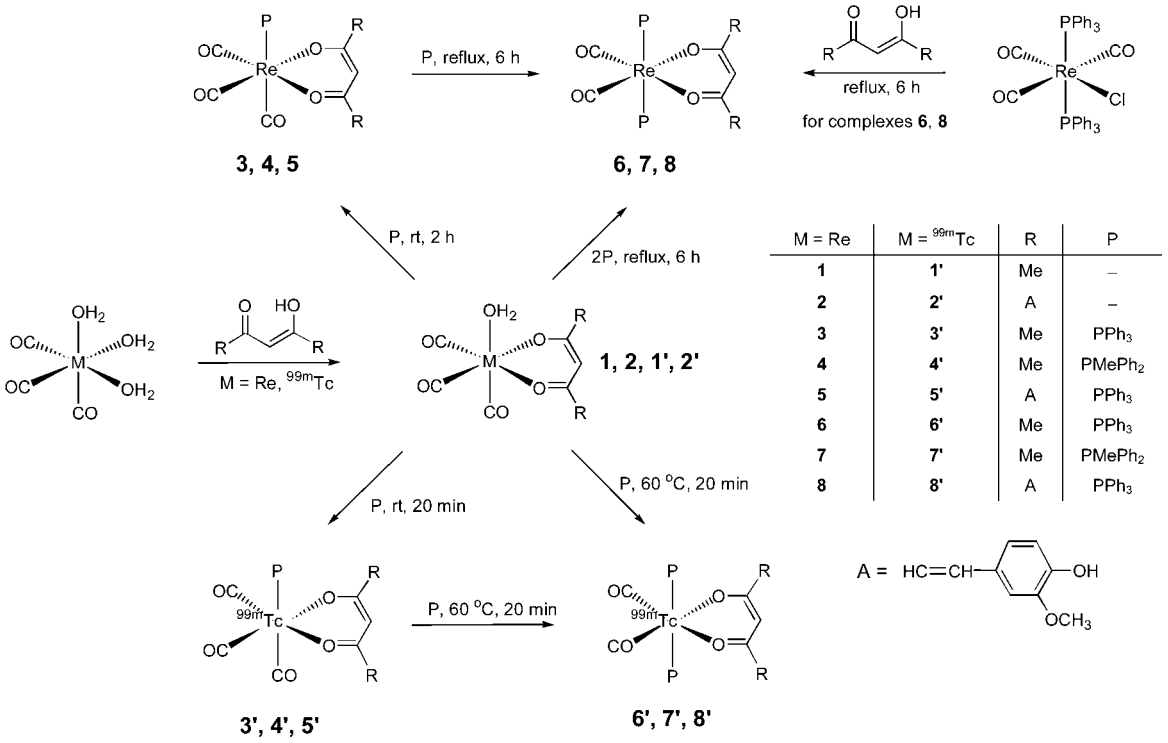
Scheme 1



In this work, phosphine (PPh_3 or $PMePh_2$) is employed as the monodentate ligand to react with the tricarbonyl aqua *fac*-$[M(CO)_3(H_2O)(OO)]$ complex of acetylacetone or curcumin. Phosphine is a strong, amenable to derivatization, monodentate ligand often used in technetium and rhenium chemistry.[12] Two types of mixed ligand complexes were isolated and fully characterized, the tricarbonyl monophosphine *fac*-$[Re(CO)_3(P)(OO)]$ **3**–**5** and the dicarbonyl bisphosphine *cis-trans*-$[Re(CO)_2(P)_2(OO)]$ **6**–**8** (Scheme 1). The corresponding *fac*-$[^{99m}Tc(CO)_3(P)(OO)]$ and *cis-trans*-$[^{99m}Tc(CO)_2(P)_2(OO)]$ complexes **3′**–**8′** were also prepared (Scheme 1) introducing a new type of "2 + 1" [OO][P] as well as "2 + 1+1" [OO][P][P] donor atom set combination at the ^{99m}Tc level.

EXPERIMENTAL SECTION

Warning! *^{99m}Tc is a gamma emitter (140 KeV, $T_{1/2}$: 6.03 h) and requires special radioprotective measures during handling.*

Synthesis. All reagents and organic solvents used in this study were purchased from Aldrich and used without further purification. Solvents for high-performance liquid chromatography (HPLC) were HPLC-grade. They were filtered through membrane filter (0.22 μm, Millipore, Milford, MA) and degassed by a helium flux before and during use. Curcumin (95% total curcuminoid content) was purchased from Alfa Aesar.

IR spectra were recorded on a Nicolet 6700 FT-IR from Thermo Scientific in the region 4000–500 cm^{-1}. NMR spectra were obtained in DMSO-d_6 at 25 °C on a Bruker Avance 500 MHz DRX spectrometer. The ^1H (500.13 MHz) and ^{13}C (125.77 MHz) chemical shifts are referenced to internal TMS while the ^{31}P (202.46 MHz) chemical shifts are reported relative to 85% H_3PO_4 as external reference. Elemental analysis for H and C was conducted on a Perkin–Elmer 2400 automatic elemental analyzer. HPLC analysis was performed on a Waters 600 chromatography system coupled to both a Waters 2487 Dual λ absorbance detector and a Gabi gamma detector from Raytest. Separations were achieved on a C-18 RP column (250 × 4 mm, 10 μm) eluted with a binary gradient system at a 1 mL/min flow rate. Mobile phase A was methanol containing 0.1% trifluoroacetic acid, while mobile phase B was water containing 0.1% trifluoroacetic acid. The elution gradient was for 0–1 min 90% B (10% A), followed by a linear gradient to 90% A (10% B) in 9 min; this composition was held for 15 min. After a column wash with 95% A for 5 min, the column was re-equilibrated by applying the initial conditions for 15 min prior to the next injection.

The intermediate complexes *fac*-$[Re(CO)_3(H_2O)(acac)]$ **1**, *fac*-$[Re(CO)_3(H_2O)(cur)]$ **2**, *fac*-$[^{99m}Tc(CO)_3(H_2O)(acac)]$ **1′**, and *fac*-$[^{99m}Tc(CO)_3(H_2O)(cur)]$ **2′**, as well as the *mer-trans*-$[Re(CO)_3(PPh_3)_2Cl]$ precursor were prepared according to published procedures.[10,13] The synthesis of complexes **3**, **4**, and **6** has been reported in the literature through different methods.[6f-h]

Rhenium Complexes. *Synthesis of fac-$[Re(CO)_3(PPh_3)(acac)]$ **3** and fac-$[Re(CO)_3(PMePh_2)(acac)]$ **4**.* To a stirred solution of **1** (39 mg, 0.1 mmol) in 8 mL of methanol, the corresponding phosphine (0.1 mmol) in 4 mL of methanol was added. The solution was stirred at room temperature (RT) for 2 h, and the reaction progress was monitored by HPLC. The solvent was subsequently removed under reduced pressure, and the remaining solid was washed with cold methanol and ether. The product was dried at high vacuum to give complex *fac*-$[Re(CO)_3(PPh_3)(acac)]$ **3** or *fac*-$[Re(CO)_3(PMePh_2)(acac)]$ **4** as white solids in excellent yield. Crystals suitable for X-ray analysis were obtained by slow evaporation from dichloromethane/methanol.

*fac-$[Re(CO)_3(PPh_3)(acac)]$ **3**.* Yield: 94%. HPLC: t_R = 17.3 min. IR (cm^{-1}): 2014, 1914, 1886, 1578, 1560,1512, 742, 690. ^1H NMR (ppm, DMSO-d_6) 7.37 (6H, *ortho* PPh_3), 7.53 (9H, *meta, para* PPh_3), 5.07 (s, 1H, acacCH), 1.63 (s, 6H, $acacCH_3$). ^{13}C NMR (ppm, DMSO-d_6) 196.59 ($^1J_{CP}$ 7.7 Hz), 193.60, 192.96 (C≡O), 188.57 (acacCO), 133.50 (*ortho*, PPh_3, $^2J_{CP}$ 10.7 Hz), 130.91 (*para*, PPh_3), 128.88 (*meta*, PPh_3, $^3J_{CP}$ 9.1 Hz), 129.73 (*ipso* PPh_3, $^1J_{CP}$ 44.1 Hz), 101.90 (acacCH), 27.06 ($acacCH_3$). ^{31}P (ppm, DMSO-d_6) 19.6. Anal. Calc. for $C_{26}H_{22}O_5PRe$: C: 49.44%, H: 3.51%. Found: C: 49.25%, H: 3.44%.

*fac-$[Re(CO)_3(PMePh_2)(acac)]$ **4**.* Yield: 95%. HPLC: t_R = 16.7 min, IR (cm^{-1}): 2016, 1914, 1866, 1580, 1518, 740, 690 . ^1H NMR (ppm, DMSO-d_6) 7.50 (m, 10H, PPh_2), 5.24 (s, 1H, acacCH), 1.98 (d, 3H, PCH_3, $^2J_{HP}$ 7.3 Hz), 1.69 (s, 6H, $acacCH_3$). ^{13}C NMR (ppm, DMSO-d_6) 196.59 ($^1J_{CP}$ 6.7 Hz), 194.38, 193.74 (C≡O), 188.26 (acacCO),

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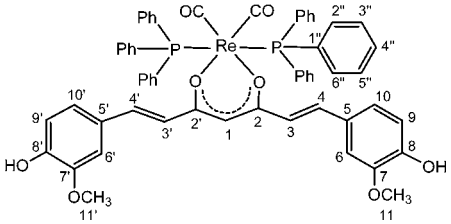
Table 1. ^{1}H, ^{13}C, and ^{31}P Chemical Shifts for the *fac*-[Re(cur)(PPh_3)$(CO)_3$] 5 and the *fac*-[Re(cur)$(PPh_3)_2(CO)_2$] 8 Complexes at 25 °C in DMSO-d_6[a]



	5	8		5	8
H-1	5.47	4.80	C-1	105.42	105.15
H-3, H-3′	6.44	5.93 $^{3}J_{trans}$ = 15.6 Hz	C-2, C-2′	179.46	176.69
H-4, H-4′	7.21	6.95 $^{3}J_{trans}$ = 15.6 Hz	C-3, C-3′	124.93	125.31
H-6, H-6′	7.24	7.10 Hz	C-4, C-4′	139.52	137.17
H-9, H-9′	6.81	6.79 J_{ortho} = 7.8 Hz	C-5, C-5′	127.32	127.36
H-10, H-10′	7.10	7.01 J_{ortho} = 7.8 Hz	C-6, C-6′	111.26	110.69
H-11, H-11′	3.84	3.83	C-7, C-7′	148.39	147.88
OH	9.52 (broad)	9.38 (broad)	C-8, C-8′	149.00	148.09
P-phenyl	7.44 (*ortho*), 7.41 (*meta, para*)	7.46 (*ortho*), 7.31 (*meta, para*)	C-9, C-9′	116.19	115.71
			C-10, C-10′	122.76	121.47
			C-11, C-11′	56.09	55.62
			C-1″	130.00 $^{1}J_{CP}$ = 43.2 Hz	133.28 triplet $^{1}J_{CP}$ = 21.1 Hz
			C-2″, 6″	133.58 $^{2}J_{CP}$= 10.8 Hz	133.63
			C-3″, 5″	128.77 $^{3}J_{CP}$= 9.6 Hz	128.02
			C-4″	130.66	129.45
			C≡O	197.21 194.38 193.74	203.21
^{31}P	19.5	25.0			

[a]The numbering of the atoms is shown in the structure.

131.94 (*ortho* PPh_2, $^{2}J_{CP}$ 10.6 Hz), 131.89 (*ipso* PPh_2, $^{1}J_{CP}$ 42.9 Hz), 130.47 (*para* PPh_2), 128.68 (*meta* PPh_2, $^{3}J_{CP}$ = 9.6 Hz), 102.03 (acacCH), 26.96 ($acacCH_3$), 11.16 (PCH_3 $^{1}J_{CP}$ = 28.8 Hz). ^{31}P (ppm, DMSO-d_6) 6.3. Anal. Calc. for $C_{21}H_{20}O_5PRe$: C: 44.28%, H: 3.54%. Found: C: 44.45%, H: 3.59%.

Synthesis of fac-[Re(CO)$_3$(PPh$_3$)(cur)] ***5***. The complex was prepared using equimolar quantities from the corresponding aqua complex *fac*-[Re$(CO)_3(H_2O)$(cur)] **2** (66 mg, 0.1 mmol) and PPh_3 (26 mg, 0.1 mmol) following the procedure described above. The complex was isolated as red crystals. Yield: 87%. HPLC: t_R = 17.5 min. IR (cm^{-1}): 2010, 1885, 1621, 1589, 1503, 741, 694. ^{1}H and ^{13}C NMR data are given in Table 1. Anal. Calc. for $C_{42}H_{34}O_9PRe$: C: 56.06%, H: 3.81%. Found: C: 55.76%, H: 3.64%.

Synthesis of cis-trans-[Re(CO)$_2$(PPh$_3$)$_2$(acac)] ***6***. *Method A: from fac-[Re(CO)$_3$(H$_2$O)(acac)]* ***1***. To a stirred solution of **1** (39 mg, 0.1 mmol) in 8 mL of methanol, triphenylphosphine (52 mg, 0.2 mmol) in 6 mL of methanol was added. The solution was stirred under reflux for 6 h, and the reaction progress was monitored by HPLC. Subsequently, the solvent was removed under reduced pressure, and the residue was recrystallized from dichloromethane/methanol to give complex **6** as white crystals in high yield. Crystals suitable for X-ray analysis were obtained by slow evaporation from dichloromethane/methanol. Yield: 78%. HPLC: t_R = 18.4 min. IR (cm^{-1}): 1910, 1826, 1576, 1559, 1509, 741, 690. ^{1}H NMR (ppm, DMSO-d_6) 7.50 (m, 30H, PPh_3), 4.57 (s, 1H, acacCH), 1.07 (s, 6H, $acacCH_3$). ^{13}C NMR (ppm, DMSO-d_6) 203.16 (C≡O), 185.40 (acacCO), 133.57 (*ortho* PPh_3), 133.09 (*ipso* PPh_3 $^{1}J_{CP}$ = 22.1 Hz), 129.82 (*para* PPh_3), 128.19 (*meta* PPh_3), 101.43 (acacCH), 26.68 ($acacCH_3$). ^{31}P (ppm, DMSO-d_6) 27.6. Anal. Calc. for $C_{43}H_{37}O_4P_2Re$: C: 59.64%, H: 4.31%. Found: C: 59.38%, H: 4.23%.

Method B: from fac-[Re(CO)$_3$(PPh$_3$)(acac)] ***3***. To a stirred solution of **3** (63 mg, 0.1 mmol) in 10 mL of hot methanol, a solution of triphenylphosphine (26 mg, 0.1 mmol) in 4 mL of methanol was added. The solution was stirred under reflux for 6 h. HPLC analysis of the reaction mixture demonstrated the formation of the desired complex (peak at 18.4 min). White crystals were isolated in 90% yield by a procedure similar to that described in Method A.

Method C: from mer-trans-[Re(CO)$_3$(PPh$_3$)$_2$Cl]. To a solution of *mer-trans*-[Re$(CO)_3(PPh_3)_2$Cl] (166 mg, 0.2 mmol) in 10 mL of toluene a mixture of acetylacetone (30 mg, 0.3 mmol) and triethylamine (30 mg, 0.3 mmol) in 5 mL of methanol was added dropwise under stirring. The solution was refluxed for 6 h and HPLC analysis of the reaction mixture demonstrated the formation of **6** (peak at 18.4 min). The solution was cooled to room temperature and then washed with water. White crystals were isolated in 85% yield by a procedure similar to that described in Method A.

Synthesis of cis-trans-[Re(CO)$_2$(PMePh$_2$)$_2$(acac)] ***7***. Complex 7 was synthesized as described above for **6**. Yield 80% and 90% for Methods A and B, respectively. Crystals suitable for X-ray analysis were obtained by slow evaporation from dichloromethane/methanol. HPLC: t_R =

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Table 2. Crystallographic Data for Complexes 3, 4, 6−8

	3	4	6	7	8·2($C_6H_5CH_3$)·CH_3OH·C_2H_5OH
formula	$C_{26}H_{22}O_5PRe$	$C_{21}H_{20}O_5PRe$	$C_{43}H_{37}O_4P_2Re$	$C_{33}H_{33}O_4P_2Re$	$C_{76}H_{75}O_{10}P_2Re$
Fw	631.61	569.54	865.87	741.73	1395.49
crystal system	orthorhombic	triclinic	monoclinic	monoclinic	monoclinic
space group	$Pc2_1n$	$P\bar{1}$	$C2/c$	$C2/c$	$I2/a$
a (Å)	8.8359(1)	8.1563(2)	15.5790(2)	21.7703(4)	26.7881(4)
b (Å)	14.7292(2)	8.7719(2)	9.4479(1)	9.1874(1)	9.1486(1)
c (Å)	18.2243(3)	14.6828(3)	25.0922(5)	16.2740(3)	30.0583(6)
α (deg)	90	81.171(1)	90	90	90
β (deg)	90	85.348(1)	101.587(1)	104.730(1)	112.127(1)
γ (deg)	90	85.773(1)	90	90	90
V (Å^3)	2371.82(6)	1032.62(3)	3618.02(9)	3148.03(9)	6823.96(19)
Z	4	2	4	4	4
T (°C)	−113	−113	−113	25	−113
radiation	Cu Kα	Cu Kα	Cu Kα	Cu Kα	Cu Kα
ρ_{calcd} (g cm^{-3})	1.769	1.832	1.590	1.565	1.358
μ (mm^{-1})	10.954	12.493	7.746	8.788	4.389
data completeness (%)	98.2	92.8	97.2	96.1	96.7
reflections with $I > 2\sigma(I)$	3793	3156	2861	2520	5468
R_1[a]	0.0264	0.0398	0.0449	0.0224	0.0373
wR_2[a]	0.0639	0.0902	0.1042	0.0560	0.1026

[a] $R_1 = \sum(|F_o| - |F_c|)/\sum(|F_o|)$ and $wR_2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$, $w = 1/[\sigma^2(F_o^2) + (\alpha P)^2 + bP]$ and $P = [\max(F_o^2,0) + 2F_c^2]/3$.

17.8 min. IR (cm^{-1}): 1901, 1816, 1580, 1562, 1514, 738, 689. ^{1}H NMR (ppm, DMSO-d$_6$) 7.50 (8H *ortho* PPh_2), 7.41 (*meta*, *para* 12H, PPh_2), 4.90 (s, 1H, acacCH), 1.93 (6H, PCH_3), 1.28 (s, 6H, $acacCH_3$). ^{13}C NMR (ppm, DMSO-d$_6$) 203.45 (C≡O), 186.13 (acacCO), 135.30 (*ipso* PPh_2, $^1J_{CP}$ 21.1 Hz), 132.06 (*ortho* PPh_2), 129.59 (*para* PPh_2), 128.23 (*meta* PPh_2), 101.66 (acacCH), 26.86 ($acacCH_3$), 13.86 (PCH_3 $J_{CP\ virtual}$ 15.4 Hz). ^{31}P (ppm, DMSO-d$_6$) 12.8. Anal. Calc. for $C_{33}H_{33}O_4P_2Re$: C: 53.43%, H: 4.48%. Found: C: 53.58%, H: 4.56%.

Synthesis of cis-trans-[Re(CO)$_2$(PPh$_3$)$_2$(cur)] ***8***. The compound was synthesized as described above for **6**. Yield 75%, 90%, and 78% for Methods A, B, and C, respectively. Slow evaporation of a toluene/ethanol/methanol solution afforded red crystals suitable for X-ray analysis. HPLC: t_R = 18.0 min. IR (cm^{-1}): 1896, 1814, 1625, 1599, 1505, 741, 691. ^{1}H and ^{13}C NMR data are given in Table 1. Anal. Calc. for $C_{59}H_{49}O_8P_2Re$: C: 62.48%, H: 4.35%. Found: C: 62.19%, H: 4.12%.

Tc-99m Complexes. *fac-[^{99m}Tc(CO)$_3$(PPh$_3$)(acac)]* ***3′***, *fac-[^{99m}Tc(CO)$_3$(PMePh$_2$)(acac)]* ***4′***, *cis-trans-[^{99m}Tc(CO)$_2$(PPh$_3$)$_2$(acac)]* ***6′***, *and cis-trans-[^{99m}Tc(CO)$_2$(PMePh$_2$)$_2$(acac)]* ***7′***. To a solution of the *fac*-[^{99m}Tc(CO)$_3$(H$_2$O)(acac)] complex **1′** (450 μL, 1−10 mCi) a solution of triphenylphosphine or methyldiphenylphosphine in methanol (50 μL,10^{-3} M) was added. The mixture was left at room temperature for 20 min, and samples were analyzed by HPLC. In each case, the formation of a new radioactive peak was observed in about 15% yield with retention time 17.7 or 17.1 min, respectively, corresponding to **3′** or **4′**. The remaining 85% was the starting complex **1′**. Heating the reaction mixture at 60 °C for 20 min resulted in quantitative formation of a single complex (yield >97%) with HPLC retention time 18.9 or 18.3 min, respectively, corresponding to **6′** or **7′**.

fac-[^{99m}Tc(CO)$_3$(PPh$_3$)(cur)] ***5′*** *and cis-trans-[^{99m}Tc(CO)$_2$(PPh$_3$)$_2$(cur)]* ***8′***. Complex **5′** was prepared using the intermediate aqua complex *fac*-[^{99m}Tc(CO)$_3$(H$_2$O)(cur)] **2′** and triphenylphosphine, as described above for **3′** and **4′**. HPLC analysis of the reaction mixture demonstrated the formation of a new radioactive peak (yield 80%) with retention time 17.9 min corresponding to **5′**. The remaining 20% was the starting complex **2′**. Heating the reaction mixture at 60 °C for 20 min resulted in quantitative formation of a single complex (yield >97%) with HPLC retention time 18.3 min corresponding to **8′**.

The identity of all ^{99m}Tc complexes was established by comparative HPLC studies using the well characterized analogous rhenium complexes as references. During the analysis of the ^{99m}Tc complexes the radioactivity recovery of the HPLC column after the injections was monitored and found to be quantitative.

Stability Studies of the ^{99m}Tc Complexes. Aliquots of 100 μL of the ^{99m}Tc complexes **6′**−**8′** were added to 900 μL of a 10^{-3} M histidine or cysteine solution in saline. The mixtures were incubated at 37 °C and were analyzed by HPLC after 24 h.

β-Amyloid Plaque Staining. Five micrometer thick serial sections of fixed and paraffin-embedded neuropathologically diagnosed AD brain were deparaffinized with 2 × 5 min washes in xylene; 2 × 3 min washes in 100% ethanol; 5 min wash in 80% ethanol/H$_2$O; 5 min wash in 60% ethanol/H$_2$O; running tap water for 10 min, and then incubated in PBS (1.3 M NaCl, 27 mM KCl, 81 mM Na_2HPO_4, 14.7 mM KH_2PO_4, pH 7) for 15 min. The tissue preparations were first wetted with dimethylsulfoxide (DMSO) and then treated with 200 μM solutions of curcumin and curcuminato complexes **5** and **8** in DMSO for 45 min. The sections were finally washed with 40% ethanol for 1 min, followed by rinsing with water for 30 s. Fluorescent observation was performed with a Zeiss Axioplan2 microscope equipped with FITC filter set (excitation at 495 nm).

X-ray Crystallography. Colorless crystals of **3** (0.03 × 0.10 × 0.80 mm), **4** (0.04 × 0.23 × 0.44 mm), **6** (0.05 × 0.29 × 0.33 mm), and a red crystal (0.12 × 0.27 × 0.56 mm) of **8**·2($C_6H_5CH_3$)·CH_3OH·C_2H_5OH were taken directly from the mother liquor and immediately cooled to −113 °C. A colorless crystal of **7** (0.11 × 0.29 × 0.41 mm) was mounted in air. Diffraction measurements were made on a Rigaku R-AXIS SPIDER Image Plate diffractometer using graphite monochromated Cu Kα (λ = 1.54178 Å) radiation. Data collection (ω-scans) and processing (cell refinement, data reduction and Empirical absorption correction) were performed using the CrystalClear program package.[14] The structures were solved by direct methods using SHELXS-97[15] and refined by full-matrix least-squares techniques on F^2 using SHELXL-97.[16] Important crystallographic and refinement data are listed in Table 2. Further crystallographic details for **3**: $2\theta_{max}$ = 130°; reflections collected/unique/used, 14845/3900 [R_{int} = 0.0569]/3900; 300 parameters refined; $[\Delta\rho]_{max}/[\Delta\rho]_{min}$ = 0.959/−1.043 e/Å^3; $[\Delta/\sigma]_{max}$ = 0.001; *R*1/w*R*2 (for all data) = 0.0271/0.0646. All hydrogen atoms were introduced at calculated positions as riding on bonded atoms, all non-H atoms were refined anisotropically. Further crystallographic details for **4**: $2\theta_{max}$ = 130°; reflections collected/unique/used, 13328/3267 [R_{int} = 0.1062]/3267; 297 parameters refined; $[\Delta\rho]_{max}/[\Delta\rho]_{min}$ = 1.570/−1.567 e/Å^3; $[\Delta/\sigma]_{max}$ = 0.001;

$R1$/w$R2$ (for all data) = 0.0408/0.0910. Hydrogen atoms were either located by difference maps and were refined isotropically or were introduced at calculated positions as riding on bonded atoms; all non-H atoms were refined anisotropically. Further crystallographic details for **6**: $2\theta_{max}$ = 130°; reflections collected/unique/used, 12034/2994 [R_{int} = 0.1379]/2994; 281 parameters refined; $[\Delta\rho]_{max}/[\Delta\rho]_{min}$ = 2.121/−1.424 e/Å^3; $[\Delta/\sigma]_{max}$ = 0.002; $R1$/w$R2$ (for all data) = 0.0489/0.1052. Hydrogen atoms were either located by difference maps and were refined isotropically or were introduced at calculated positions as riding on bonded atoms; all non-H atoms were refined anisotropically. Further crystallographic details for **7**: $2\theta_{max}$ = 130°; reflections collected/unique/used, 20253/2570 [R_{int} = 0.0417]/2570; 227 parameters refined; $[\Delta\rho]_{max}/[\Delta\rho]_{min}$ = 0.856/−1.057 e/Å^3; $[\Delta/\sigma]_{max}$ = 0.004; $R1$/w$R2$ (for all data) = 0.0229/0.0565. Hydrogen atoms were either located by difference maps and were refined isotropically or were introduced at calculated positions as riding on bonded atoms; all non-H atoms were refined anisotropically. Further crystallographic details for **8**·2($C_6H_5CH_3$)·CH_3OH·C_2H_5OH: $2\theta_{max}$ = 130°; reflections collected/unique/used, 24043/5619 [R_{int} = 0.0439]/5619; 467 parameters refined; $[\Delta\rho]_{max}/[\Delta\rho]_{min}$ = 1.427/−0.636 e/Å^3; $[\Delta/\sigma]_{max}$ = 0.000; $R1$/w$R2$ (for all data) = 0.0382/0.1032. Hydrogen atoms in **3**, **4**, **6**−**8** were either located by difference maps and were refined isotropically, or were introduced at calculated positions as riding on bonded atoms. All non hydrogen atoms in **3**, **4**, **6**−**8** were refined anisotropically, except of the solvate molecules in **8** which were refined isotropically and their H-atoms were not included in the refinement. Plots of all structures were drawn using the Diamond 3.1 program package.[17]

CCDC deposition numbers: 942285 for **3**, 942286 for **4**, 942287 for **6**, 942288 for **7** and 942289 for **8**.

RESULTS AND DISCUSSION

Synthesis. Acetylacetone and curcumin react with the *fac*-$[Re(CO)_3Br_3]^{2-}$ precursor through the β-diketonato moiety (OO) and generate, under mild synthetic conditions, the aqua complexes *fac*-$[Re(CO)_3(H_2O)(acac)]$ **1**, and *fac*-$[Re(CO)_3(H_2O)(cur)]$ **2**, respectively.[10] The aqua ligand in both complexes is labile and can be easily replaced at room temperature by a monodentate phosphine ligand (P) to generate the corresponding tricarbonyl monophosphine *fac*-$[Re(CO)_3(P)(OO)]$ complexes **3**, **4**, and **5** (Scheme 1). Excess of phosphine leads under reflux in methanol to the formation of the new dicarbonyl bisphosphine *cis-trans*-$[Re(CO)_2(P)_2(OO)]$ complexes **6**, **7** and **8**. Apparently, in the tricarbonyl complexes **3**, **4**, and **5** the phosphine ligand which has a large trans effect labilizes the trans carbonyl[18] which is quantitatively replaced by a second phosphine ligand. The bisphosphine complexes **6** and **8** were also prepared using the *mer-trans*-$[Re(CO)_3(PPh_3)_2Cl]$ precursor. In this case, the incoming OO donor bidentate ligand displaces the Cl and one of the CO ligands. In the *mer*-$[Re(CO)_3]^+$ configuration, labilization of the CO is attributed to the presence of a *trans*-CO ligand.[18] In all cases, HPLC analysis of the reaction mixture showed the existence of a single product peak. The acetylacetonato complexes **3**, **4**, **6**, and **7** were collected as whitish crystals, while the curcuminato complexes **5** and **8** as red crystals. It should be noted that complexes **3**, **4**, and **6** have been previously reported in the literature synthesized through alternative starting materials or methods (e.g, $[Re(CO)_3acac]_2\cdot 2H_2O$,[6f] $[Re(CO)_3acac]_2$dme (dme: dimethoxyethane),[6g] $Re H_2(PPh_3)_3(acac)$.[6h]

All complexes were isolated in high yield and characterized by elemental analysis, spectroscopic methods, and, with the exception of complex **5**, X-ray crystallography. All complexes are soluble in dichloromethane, chloroform, benzene, and toluene, slightly soluble in methanol and ethanol, and insoluble in water. The bisphosphine complexes are stable in solution for months as shown by HPLC and NMR. In solutions of the monophosphine complexes however, a gradual release of the coordinated phosphine ligand is noted over time, more intense in solvents with coordinating potential like DMSO.

The IR spectra of the complexes **3**, **4**, and **5** show the typical pattern for the *fac*-$[Re(CO)_3]^+$ moiety with bands in the range 2016−1866 cm^{-1}.[19] The IR spectra of complexes **6**, **7**, and **8** demonstrate two strong bands in the range 1910−1814 cm^{-1} typical for a dicarbonyl species with cis geometry.[18] The carbonyl stretching frequencies are significantly lower in the bisphosphine (**6**, **7**, and **8**) complexes relative to the monophosphine (**3**, **4**, and **5**) reflecting the higher "net" electron donor ability of phosphine ligands relative to CO which increases the electron density on the metal and results in weakening of the C≡O bond through increased metal-CO backbonding.[20] The presence of two strong bands at approximately 740 and 690 cm^{-1} attributed to out-of-plane bending vibrations of the monosubstituted phenyl ring provide evidence for the presence of phosphine ligands. The broad peak at 1605 cm^{-1} of the enolic CO of acac is decreased in intensity and shifted to lower energy appearing at aprox. 1580 and 1515 cm^{-1}, a shift observed in previous studies of analogous complexes.[6] Accordingly, the peaks in the range 1627−1507 cm^{-1} of free curcumin, attributed in the literature[21] to the CO of the enolic form of curcumin and to C═C aromatic and β-diketonate stretch, are also slightly shifted to lower energies in the curcuminato complexes **5** and **8**.

NMR Studies. NMR spectra of all complexes were obtained in DMSO-d_6 at 25 °C, and the NMR data are consistent with the proposed structures and existing literature data on complex **4**.[6h] The ^{1}H and ^{13}C peaks for the curcuminato complexes **5** and **8** are presented in Table 1, while the HMBC spectrum of complex **8** is shown in Supporting Information, Figure S1. All complexes prepared possess a plane of symmetry passing through C-1 of the OO donor bidentate ligand, the P atom(s) of phosphine ligand(s), and the metal Re(I) core and therefore only "half" of the bidentate OO ligand is present in the ^{1}H and ^{13}C spectra. Upon coordination, characteristic shifts of the acetylacetone (complexes **3**, **4**, and **6**, **7**) and curcumin (complexes **5** and **8**) moieties are noted relative to their noncoordinated state[6] (see Supporting Information). These shifts are in the same direction as those observed in similar "2 + 1" acetylacetonato and curcuminato complexes with isonitrile or imidazole as monodentate ligands.[10]

The ^{31}P NMR spectra of the complexes exhibited a single peak confirming the absence of isomers and, in the case of bisphosphine complexes, the symmetric trans arrangement of the phosphine ligands. A significant downfield shift (26−33 ppm for the monophosphine **3**−**5** complexes and 33−40 ppm for the bisphosphine **6**−**8** complexes) with respect to the resonance of the free ligands (−6.0 ppm for triphenylphosphine and −27.0 ppm for methyldiphenylphospine in DMSO-d_6, our data) is observed in agreement with the formation of a phosphorus−metal bond.[12a] The ^{31}P shifts of the $PMePh_2$ complexes are shielded by approximately 12 ppm compared with those of the corresponding PPh_3 complexes reflecting the higher electron-donating ability of the Me compared to the Ph substituent.[22] Steady chemical shift differences are noted between the monophosphine and the bisphosphine complexes, with the bisphosphine appearing deshielded by 6−8 ppm compared to the corresponding monophosphine.

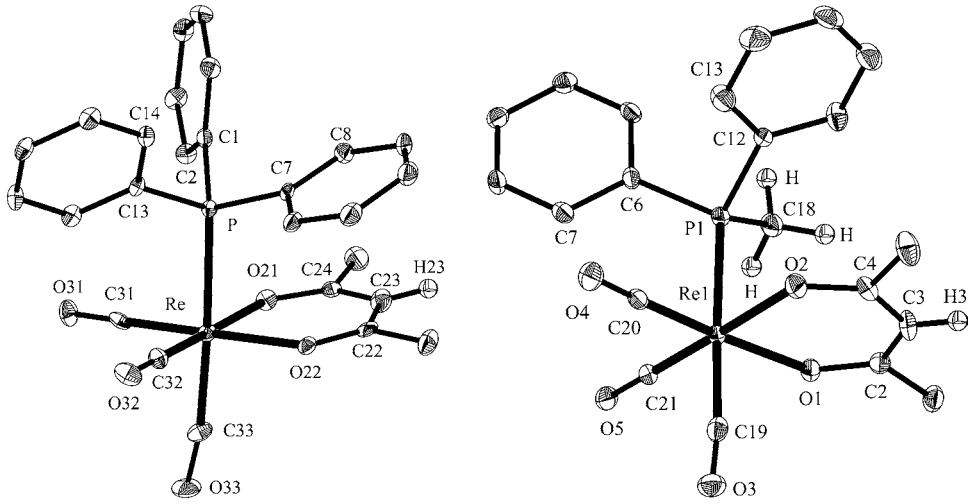

Figure 1. Partially labeled plot of the molecular structures of **3** (left) and **4** (right) with the atomic labeling (thermal ellipsoids are shown with 40% probability). Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg): for **3**: Re−C(31) = 1.910(5), Re−C(32) = 1.900(5), Re−C(33) = 1.962(5), Re−O(21) = 2.142(3), Re−O(22) = 2.132(3), Re−P = 2.498(1), C(31)−Re−O(22) = 1771.1(2), C(32)−Re−O(21) = 176.6(2), C(33)−Re−P = 175.2(1); for **4**: Re−C(19) = 1.958(7), Re−C(20) = 1.888(6), Re−C(21) = 1.894(7), Re−O(1) = 2.131(4), Re−O(2) = 2.118(4), Re−P(1) = 2.464(2), C(21)−Re−O(2) = 176.6(2), C(20)−Re−O(1) = 176.4(2), C(19)−Re−P(1) = 177.9(2).

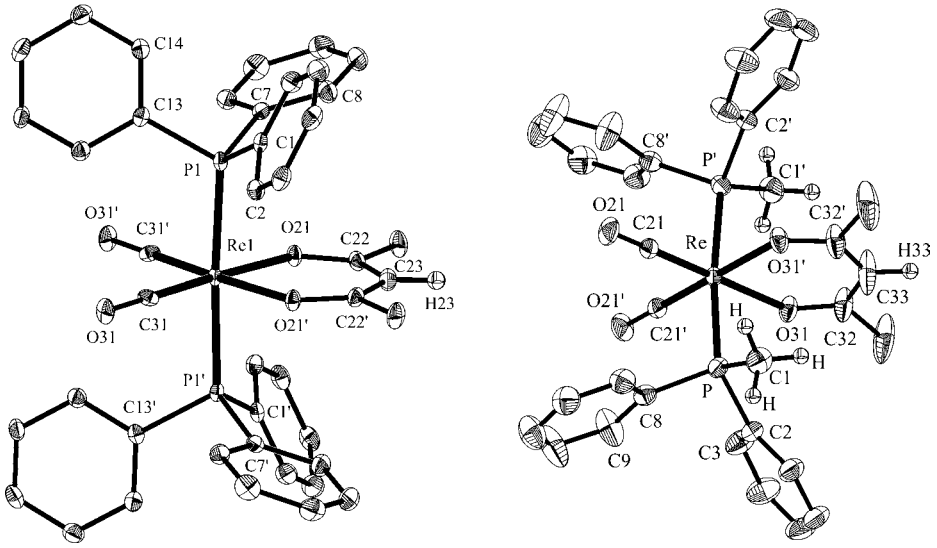

Figure 2. Partially labeled plot of the molecular structures of **6** (left) and **7** (right) with the atomic labeling (thermal ellipsoids are shown with 40% probability). Hydrogen atoms have been omitted for clarity. Primed atoms are generated by symmetry: (′) = $-x, y, 1.5-z$ in both structures. Selected bond lengths (Å) and angles (deg): for **6**: Re−C(31) = 1.877(5), Re−O(21) = 2.132(3), Re−P(1) = 2.414(2), C(31)−Re−O(21) = 177.0(2), P(1)−Re−P(1′) = 176.5(1); for **7**: Re−C(21) = 1.878(3), Re−O(31) = 2.132(2), Re−P = 2.408(1), C(21)−Re−O(31) = 178.4(1), P−Re−P′ = 173.9(1).

In the monophosphine complex **4**, the protons of the methyl P-CH_3 group appear as a doublet because of coupling to phosphorus with a $^2J_{HP}$ equal to 7.3 Hz (Supporting Information, Figure S1). The corresponding P-CH_3 carbon appears also as a doublet with a $^1J_{CP}$ equal to 28.8 Hz, significantly increased compared with that of free methyldiphenylphosphine (13.4 Hz, our data). The increase in the $^1J_{CP}$ coupling constant, which is also present for the P−C_{ipso} carbon is in accordance to literature reports[12a,20] and provides evidence for coordination. In the bisphosphine complex **7**, the doublet is not present but instead both proton (Supporting Information, Figure S1) and carbon resonances of the methyl group appear as distorted triplets. This is due to virtual coupling and is typical for trans phosphines, in which, because of the trans arrangement, the P−P coupling becomes large and affects the appearance of the methyl substituent.[23] The *ipso* carbon of the phenyl group of phosphine ligands (Supporting Information, Figure S2) is similarly affected in all complexes appearing as a clear doublet with a $^1J_{CP}$ ranging from 42.9−44.1 Hz in the monophosphine complexes **3**, **4**, and **5**, and as a triplet with a virtual coupling constant of 21.1−22.1 Hz. in the bisphosphine complexes **6**, **7**, and **8**.

Description of the Structures. Partially labeled plots of the molecular structures of **3**, **4**, **6**, **7**, and **8** are given in Figures 1−3, respectively; selected bond distances and angles are given in the figure captions. The coordination geometry about rhenium in **3** and **4** is distorted octahedral and consists of the *fac*-$[Re(CO)_3]^+$ moiety, one chelate bidentate acetylacetonate ligand (acac), and a monodentate phosphine ligand (PPh_3 and $PMePh_2$ in **3** and **4** respectively). The apical positions of the

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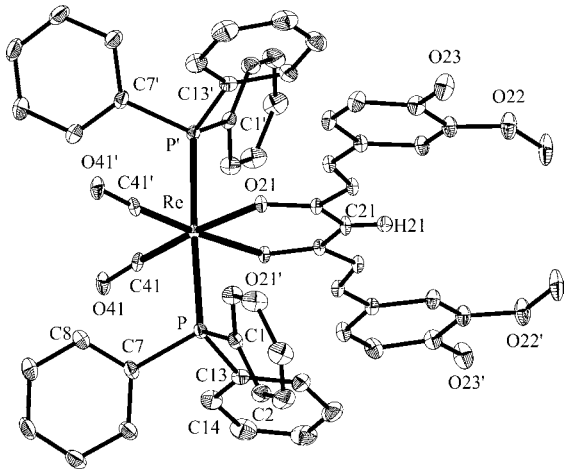

Figure 3. Partially labeled plot of the molecular structure of **8** with the atomic labeling (thermal ellipsoids are shown with 40% probability). Hydrogen atoms have been omitted for clarity. Primed atoms are generated by symmetry: (′) = −0.5-*x*, *y*, −2−*z*. Selected bond lengths (Å) and angles (deg): Re−C(41) = 1.867(4), Re−O(21) = 2.123(3), Re−P = 2.427(1), C(41)−Re−O(21) = 175.8(1), P−Re−P′ = 176.8(1).

octahedron are occupied by the monodentate phosphine ligand and one of the carbonyl groups. Rhenium almost lies on the equatorial plane in **3** and **4** (displacement 0.013 and 0.032 Å, respectively). The six-membered ring defined by the metal ion and the chelate bidendate acac in **3** and **4** is planar. The Re−CO bond distances in the apical positions (1.962(5) and 1.958(7) Å in **3** and **4**, respectively) are longer than those in the equatorial plane (∼1.90 Å) because of the trans influence of the phosphine ligands as expected.

The coordination geometry about rhenium in **6** and **7** is distorted octahedral and consists of two cis carbonyl groups, two trans monodentate phophine ligands (PPh_3 and $PMePh_2$ in **6** and **7** respectively), and one chelate bidentate acac ligand. In both compounds, the metal ion and the −CH− carbon of the acac ligand are situated on a 2-fold axis of symmetry; thus only half of the atoms are crystallographically independent. Similarly the coordination geometry about rhenium in **8** is distorted octahedral and consists of two cis carbonyl groups, two trans monodentate PPh_3, and two oxygen atoms of the chelate curcumin. Complex **8** sits on a 2-fold axis of symmetry passing through the metal ion and carbon C21 of curcumin. In all three compounds, the apical positions of the octahedron are occupied by the two symmetry related monodentate phosphine ligands; rhenium lies on the equatorial plane. The six-membered rings defined by the metal ion and the chelate bidendate molecule (acetylacetone in **6**/**7** and curcumin in **8**) are planar.

The Re−P bond distances in **3**, **4**, and **6**−**8** are in the range 2.408(1)−2.498(1) Å, and the Re−O bond lengths in the very narrow range 2.118(4)−2.142(3) Å. The Re−CO bond lengths in the equatorial plane in **3**, **4**, and **6**−**8** are also in the very narrow range 1.867(4)−1.910(5) Å. All bond distances in the coordination sphere fall in the ranges observed in analogous complexes.[18,24] The angles around the metal within the tetragonal plane of the octahedron range from 84.5(1) to 93.1(1)° in **3**, from 85.9(2) to 92.3(2)° in **4**, from 84.0(2) to 93.1(2)° in **6**, from 84.6(1) to 94.2(1)° in **7**, and from 84.6(1) to 92.8(1)° in **8**, whereas those involving the apical atoms range from 85.8(2) to 93.9(2)° in **3**, from 87.2(1) to 92.0(2)° in **4**, from 87.5(1) to 93.5(2)° in **6**, from 87.5(1) to 93.0(1)° in **7**, and from 86.3(1) to 96.0(1)° in **8**.

Technetium-99m Chemistry. The technetium-99m complexes were prepared by addition of the appropriate phosphine to the intermediate radioactive aqua complex *fac*-[^{99m}Tc-$(CO)_3(H_2O)$(acac)] **1**′ or *fac*-[^{99m}Tc$(CO)_3(H_2O)$(cur)] **2**′. Their structures have been established by HPLC comparative studies by applying parallel radiometric and photometric detection using the authentic well characterized rhenium complexes as reference.

Specifically, addition of triphenylphosphine to the intermediate aqua complex *fac*-[^{99m}Tc$(CO)_3(H_2O)$(acac)] **1**′ and incubation at RT for 20 min gave a new compound in low yield (15%), as shown by HPLC. The similarity of its retention time (17.7 min) to that of the analogous Re complex **3** (17.3 min) is indicative of the generation of the tricarbonyl compound **3**′ (Supporting Information, Figure S4A). By increasing the incubation temperature to 40 °C the yield was improved to 40%, but a second compound (yield 25%) eluting at 18.9 min was formed. Co-injection experiments using the rhenium complex **6** (t_R = 18.4 min) as reference showed that the second peak can be attributed to the dicarbonyl complex **6**′. By incubating the reaction mixture at 60 °C for 20 min the dicarbonyl complex **6**′ was obtained as a single product (Supporting Information, Figure S4C). When $PMePh_2$ was used, similar results were obtained for complexes **4**′ and **7**′ (Supporting Information, Figure S5). For both phosphines, it was not possible to obtain the tricarbonyl complexes **3**′ and **4**′ as the only reaction products quantitatively.

In the case of curcumin, addition of PPh_3 to the intermediate aqua complex *fac*-[^{99m}Tc$(CO)_3(H_2O)$(cur)] **2**′ and incubation at RT for 20 min resulted in the formation of complex **5**′ in 80% yield, while the remaining 20% was the aqua complex *fac*-[^{99m}Tc$(CO)_3(H_2O)$(cur)] **2**′, as indicated by HPLC (Supporting Information, Figure S6). By incubating the reaction mixture at 60 °C for 20 min the dicarbonyl complex **8**′ was quantitatively formed (Figure 4), while in intermediate conditions mixtures of **5**′ and **8**′ were obtained.

Stability studies showed that the dicarbonyl complexes **6**′−**8**′ are stable in their reaction mixture for 24 h. Furthermore, no transchelation or decomposition is observed when the complexes are challenged with excess histidine or cysteine for 24 h as shown by HPLC analysis (Supporting Information, Figures S7−S9).

***β*-Amyloid Plaque Staining.** Our previous studies have shown that rhenium "2 + 1" tricarbonyl curcuminato complexes bind selectively to amyloid plaques.[10b] Thus, as a first step in the biological evaluation of the synthesized curcuminato complexes **5** and **8**, the binding affinity for *β*-amyloid plaques of Alzheimer's disease (AD) was examined following standard staining procedures.[10b,25] Figure 5 shows the results of the in vitro staining of human post-mortem AD fixed brain sections with complexes **5** and **8** as they appear under the fluorescence microscope. The results of staining with plain curcumin are also presented as a positive control. Both complexes bind selectively to the plaques, allowing clear visualization of both diffused and dense core ones. Even though quantitative comparison of binding affinities between the curcuminato complexes and curcumin is not possible because of differences in fluorescence intensity, it is clear that complexes **5** and **8** stain amyloid plaques in a similar to curcumin mode.

These results indicate that rhenium tricarbonyl and dicarbonyl curcuminato complexes retain affinity for *β*-amyloid

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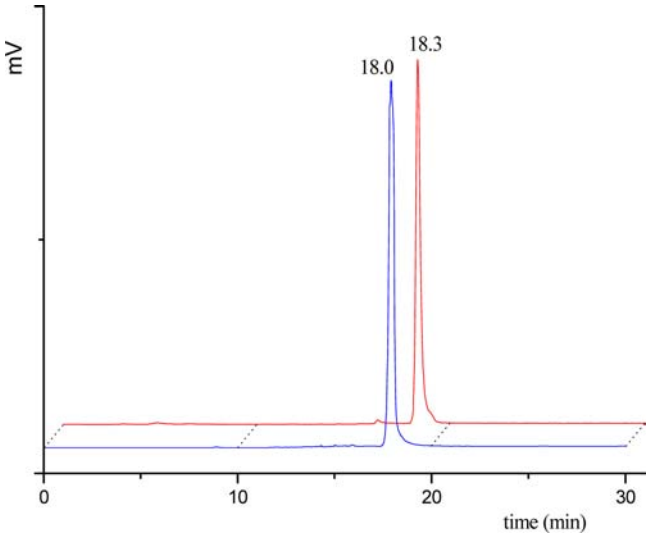

Figure 4. Representative comparative reverse-phase HPLC chromatograms: (i) radiometric detection of complex **8′** (red) ; (ii) UV detection at 254 nm of complex **8** (blue). Column: C-18 (250 × 4 mm, 10 μm). Gradient: A(0.1%TFA in methanol), B(0.1%TFA in water): 0−1 min, 10% A, 1−10 min, linear to 90%A; 10−25 min, 90% A; 25−30 min, 95%A. Flow 1 mL/min.

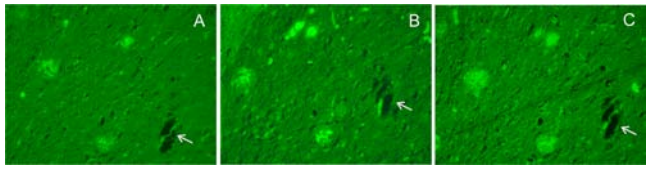

Figure 5. Fluorescence microscopy images (FITC filter, magnification ×20) of almost adjacent closely located sections from Alzheimer's disease brain stained with (A) complex **5**, (B) complex **8**, and (C) curcumin. The arrows indicate cross sections of a blood vessel running through the tissue that serve as the anatomical mark for positioning the plaques on the slice.

plaques in the presence of a variety of monodentate ligands in their coordination sphere and may serve as a scaffold for the development of a ^{99m}Tc-radiodiagnostic for Alzheimer's disease.

In conclusion, reaction of the *fac*-[Re(CO)$_3$(H$_2$O)(OO)] aqua complexes of acetylacetone or curcumin with phosphine ligands (P) proceeds quickly at room temperature to generate "2 + 1" neutral tricarbonyl monophosphine *fac*-[Re(CO)$_3$(P)(OO)] complexes as sole products. Under reflux conditions the trans-labilizing effect of the P donor leads to replacement of the trans to the phosphine ligand carbonyl by a second phosphine to generate the new stable dicarbonyl bisphosphine complexes *cis-trans*-[Re(CO)$_2$(P)$_2$(OO)]. The dicarbonyl complexes become the sole products of the reaction when phosphine is present in at least 2-fold excess compared to the intermediate aqua complex *fac*-[Re(CO)$_3$(H$_2$O)(OO)].

At the ^{99m}Tc tracer level, the same type of complexes, *fac*-[^{99m}Tc(CO)$_3$(P)(OO)] and *cis-trans*-[^{99m}Tc(CO)$_2$(P)$_2$(OO)], are formed introducing new donor atom combinations for ^{99m}Tc(I). The monophosphine complex is quickly converted to the stable bisphosphine, a process that is further accelerated by heating the aqueous reaction mixture to 60 °C.

Both the bidentate OO and the monodentate P ligands are versatile and amenable to structural variations and/or derivatizations. As a result, the biological properties of their Re(I) and ^{99m}Tc(I) complexes may be fine-tuned rendering them convenient chemical platforms for the development of target specific therapeutic and diagnostic radiopharmaceuticals. Especially the curcuminato complexes are of particular interest in view of the rich pharmacology and the wide range of therapeutic activities of curcumin, and will be biologically evaluated in appropriate model systems. Furthermore, their detailed characterization, including the unique for Re X-ray crystallographic structure of **8**, constitutes a notable contribution to the chemical literature of curcumin.

■ ASSOCIATED CONTENT

Supporting Information

HMBC spectrum of curcuminato complex **8**; ^{1}H NMR spectra of complexes **4** and **7**; ^{13}C NMR spectra of curcuminato complexes **5** and **8**; tables with selected bond distances and angles for **3**, **4**, and **6**−**8**; HPLC chromatograms of rhenium and technetium-99m complexes and stability studies of the technetium-99m complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mspap@rrp.demokritos.gr. Phone: + 30210 6503909. Fax: + 30210 6503829.

Notes

The authors declare no competing financial interest.

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