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Chemically Triggered Assembly of Chiral Triangular Metallomacrocycles**

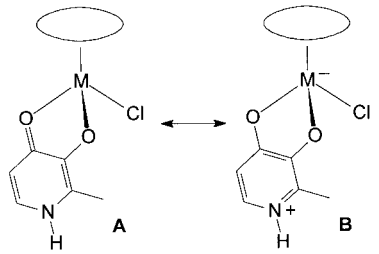
Tassilo Habereder, Marcus Warchhold, Heinrich Nöth, and Kay Severin*

Dedicated to Professor Theodore Severin on the occasion of his 70th birthday

Self-assembly processes that are based on interactions between transition metals and ligands are among the most elegant methods for the construction of large macrocyclic compounds. In recent years a variety of amazingly complex structures have been built in this way.[1] The focus of interest has been on two-dimensional polygons such as squares and rectangles, but three-dimensional polyhedra[2] and possible applications are now beginning to be explored.[1, 3] In comparison with rectangular assemblies there have been relatively few reports on triangular metallomacrocycles.[4–6] This is especially true for complexes with rigid heterocyclic ligands, a class of compounds that was very successfully employed for the construction of other polynuclear assemblies. A possible explanation, as suggested by Stang et al.,[1b] is the fact that the required 60° turning angle is quite uncommon in transition metal chemistry.[7]

Herein we describe the synthesis and crystal structure of two chiral, triangular macrocycles in which half-sandwich complexes of iridium(III) and ruthenium(II) occupy the corner positions. The heterocyclic bridging ligand is the dianion of 3-hydroxy-2-methyl-4(1*H*)-pyridone. This ligand[8] as well as *N*-substituted derivatives[9] are easily synthesized from commercially available 3-hydroxy-2-methyl-4-pyrone (maltol). These ligands have received considerable attention since they are good chelators of various metal ions, especially iron(III).[10] Recently, we reported the first examples of organometallic complexes with *N*-alkyl and *N*-aryl pyridones.[11] During the course of the work we realized that the nonsubstituted 3-hydroxy-2-methyl-4(1*H*)-pyridone should be an ideal candidate for the synthesis of well defined oligonuclear transition metal assemblies. The starting point of our investigations was the chiral pentamethylcyclopentadienyl (Cp*) iridium(III) complex **1**. This compound was obtained as a racemic mixture from $[\{Cp^*IrCl_2\}_2]$ and 3-hydroxy-2-methyl-4(1*H*)-pyridone in the presence of one equivalent of base.

In accordance with previous studies on transition metal pyridone complexes it was assumed that the mesomeric form B (Figure 1) contributes significantly to the electronic structure of **1**.[11, 12] We therefore anticipated that the proton bound



1 ML_n = Cp*Ir
3 ML_n = (η^6-cymene)Ru

Figure 1. Mesomeric forms that contribute to the electronic structure of **1** and **3**.

at the nitrogen atom should be acidic. Simultaneously the chloride ligand was expected to be labile. Combining these two characteristics should allow a base-induced oligomerization of **1**. In fact, if **1** was stirred with one equivalent of NaOMe (or NEt_3) in methanol the yellow complex **2** was obtained in quantitative yield (Scheme 1).[13] Alternatively, **2** can be prepared directly from $[\{Cp^*IrCl_2\}_2]$, the pyridone ligand, and NaOMe (molar ratio 1:2:4).

The ^{1}H NMR spectrum of **2** was indicative of a highly symmetrical structure: only one signal was observed for the Cp* protons and only one set of signals was detected for the pyridone protons. It is known that the symmetry of supramolecular assemblies based on metal – ligand interactions is strongly biased by the geometric requirements of the ligand as well as the transition metal.[1a,b] The geometry of half-sandwich complexes can be described as pseudo-octahedral with angles between the three "piano-stool legs" approaching 90° (for example, Cl-Ir-(μ-Cl) = 88.49° in $[\{Cp^*IrCl_2\}_2]$[14]). Since the heterocyclic ligand is nearly planar our initial guess

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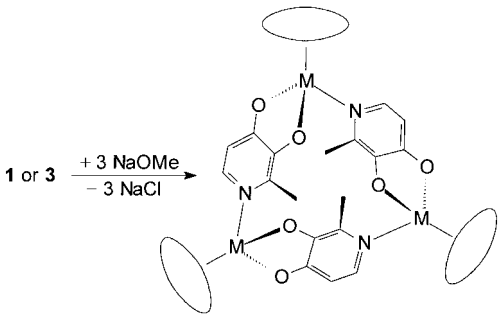

Scheme 1. Base-induced formation of chiral triangular metallomacrocycles.

for the molecular structure of **2** was a square geometry with four iridium atoms in the corner.[15] The mass spectrum of **2**, however, showed no peak with the expected mass but showed a peak at *m*/*z* 1352, which is indicative of a trinuclear complex.[16] This conclusion was confirmed by the result of a single-crystal X-ray structure analysis.[17] The structure of one enantiomer of the cyclic trimer in the crystal is shown in Figure 2. As expected, the bridging pyridone ligand acts as an

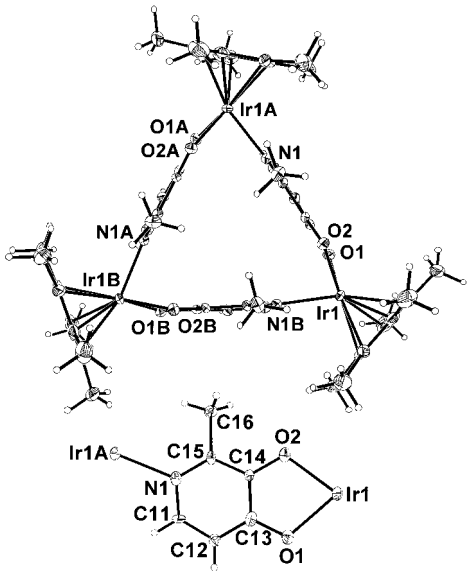

Figure 2. Structure of **2** in the crystal (top) and side view of the bridging pyridone ligand (bottom); selected bond lengths [Å] and angles [°]: Ir(1)-O(1) 2.118(7), Ir(1)-O(2) 2.085(7), Ir(1)-N(1) 2.141(8), O(1)-C(13) 1.319(11), O(2)-C(14) 1.328(10), C(13)-C(14) 1.437(14), C(14)-C(15) 1.380(12), N(1)-C(15) 1.340(12), N(1)-C(11) 1.335(12), C(11)-C(12) 1.374(13), C(12)-C(13) 1.389(13); O(1)-Ir(1)-N(1) 82.4(3), O(2)-Ir(1)-N(1) 85.0(3), O(2)-Ir(1)-O(1) 79.6(3).

O,O′-chelate and simultaneously coordinates through the nitrogen atom in position 4 to another iridium atom. The C–O bond length as well as the bond lengths within the six-membered ring are in agreement with an aromatic structure as depicted in Scheme 1. The iridium atoms are 7.24 Å apart from each other. Contrary to other "molecular triangles", which show a concave[6] or distorted[4a,b] geometry, the bridging ligands in **2** (as well as the Cp* ring) are almost orthogonal to the plane defined by the metal atoms forming a trigonal prism. This geometry requires that the O,O′-chelate is coordinated in a slightly bent fashion. Thus, a torsion angle of C(13)-C(14)-O(2)-Ir(1) = 16.2° is observed, as opposed to other pyridone complexes that show a linear arrangement.[11, 12]

We were especially interested in the diastereoselectivity of the self-assembly process since three stereogenic centers were produced simultaneously. Both the NMR data and the result of the X-ray structure analysis indicated that only one diastereoisomer was formed (as a racemate) in which all metal centers had the same configuration. Nevertheless it would have been possible that in solution epimerization was fast on the NMR time scale and consequently the other diastereoisomer was not detected. To exclude this possibility we tried to incorporate the structurally related {(η^6-cymene)Ru^{II}} fragment into the macrocycle. The *i*Pr-methyl groups of the cymene ligand provide an excellent spectroscopic probe for the configurational stability of the adjacent metal center in {(η^6-cymene)Ru^{II}} complexes: if epimerization is slow on the NMR time scale they appear as two separate doublets, otherwise only one doublet should be observed.

When the reactions were carried out using [{(η^6-cymene)-$RuCl_2$}$_2$] instead of [{Cp*$IrCl_2$}$_2$] the new ruthenium complexes **3** and **4** were obtained. Again, only the signals of one isomer was observed in the ^{1}H NMR spectrum of the trimeric compound **4**. Furthermore, epimerization was shown to be slow even in polar organic solvents at elevated temperatures (CD_3OD, 50° C). We therefore conclude that the assembly process is completely diastereoselective.[18] The monomeric complex **3**, on the other hand, was unstable towards epimerization (on the ^{1}H NMR time scale) even in less polar solvents such as CD_2Cl_2. The remarkable configurational stability of the chiral metal centers in **4** can be explained by the rigidity of the cyclic complex.

Single crystals of **4** suitable for X-ray structure analysis were obtained by the slow diffusion of pentane into a solution of **4** in tetrahydrofuran.[17] The structure is very similar to that of **2** though **4** shows no C_3 symmetry in the crystal (Figure 3). Again, the pyridone ligand is coordinated to the ruthenium

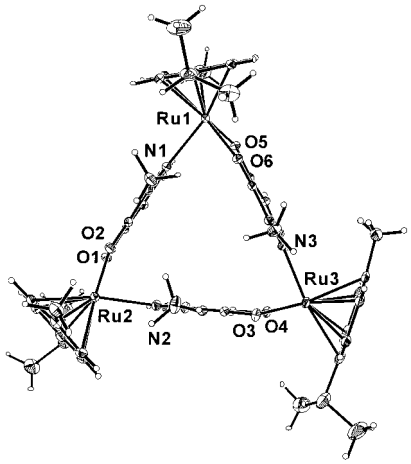

Figure 3. Structure of **4** in the crystal; selected bond lengths [Å] and angles [°]: Ru(1)-O(5) 2.066(2), Ru(1)-O(6) 2.063(3), Ru(1)-N(1) 2.169(3), O(5)-C(45) 1.322(4), O(6)-C(46) 1.345(4); O(6)-Ru(1)-N(1) 83.29(11), O(5)-Ru(1)-N(1) 83.11(11), O(6)-Ru(1)-O(5) 80.07(10).

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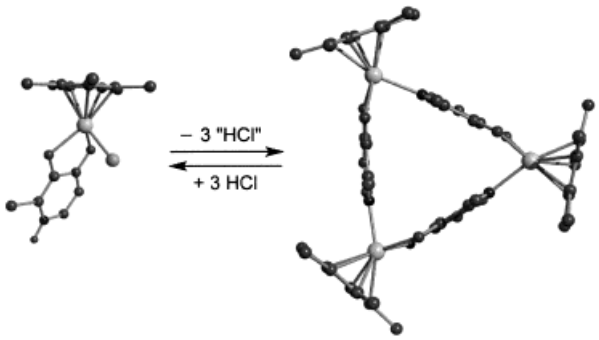
atoms through both oxygen atoms (in a bent fashion: C(34)-C(33)-O(1)-Ru(2) = 14.2°) and the nitrogen atom. All bond lengths and angles lie within the expected range. The distance between the ruthenium atoms (7.24 Å) is exactly the same as for the iridium atoms in **2**.

There are very few reports on the controlled disassembly of polynuclear macrocyclic complexes such as molecular "squares" or cages.[19] Chemical or physical means that trigger the assembly–disassembly process are nevertheless highly desirable because of the possible applications in host–guest chemistry. The organometallic macrocycles **2** and **4** can be transformed quantitatively into their constituent monomeric complexes by adding three equivalents of HCl (0.6 M in ethyl acetate). Thus, macrocyclization can be induced *and* reversed by addition of appropriate amounts of base or acid, respectively (Scheme 2).



Scheme 2. The assembly–disassembly process can be triggered by addition of acid or base, respectively.

We have shown that triangular organometallic macrocycles can be obtained with the dianion of 3-hydroxy-2-methyl-4(1*H*)-pyridone as the bridging ligand. The assembly process, which proceeds in virtually quantitative yields, is absolutely diastereoselective and can be reversed chemically. The strategy for the construction of such "molecular triangles" appears to be rather general since different half-sandwich complexes can be incorporated. Utilization of other fragments such as {Cp*Rh^{III}} or {Cp*$Ru^{II/III}$} therefore seems possible. Because of the shape of these macrocycles they are potential hosts for small organic and inorganic molecules.

Experimental Section

1: A 2.3 M solution of NaOMe in methanol (0.2 mmol) was added to a suspension of 3-hydroxy-2-methyl-4(1*H*)-pyridone (25 mg, 0.2 mmol) in methanol (10 mL). [{Cp*$IrCl_2$}$_2$] (80 mg, 0.1 mmol) was added to the resulting clear solution and the mixture was stirred for 2 h. After removal of the solvent in vacuo the product was extracted with a mixture of dichloromethane/diethyl ether (30 mL, 2/1). Subsequent addition of hexane (20 mL) and evaporation of the solvent under reduced pressure gave a yellow powder which was dried in vacuo. Yield: 84%; IR (KBr): ν = 3236 cm^{-1} (m, NH), 3130 (m, NH), 1588 (m), 1523 (s), 1493 (s); ^{1}H NMR (270 MHz, CD_2Cl_2): δ = 1.61 (s, 15H; Cp*), 2.09 (s, 3H; CH_3), 6.23 (d, ^3J = 5.8 Hz, 1H; CH, pyridone), 7.00 (d, ^3J = 5.7 Hz, 1H; CH, pyridone); ^{13}C NMR (68 MHz, CD_2Cl_2): δ = 8.80 (CH_3, Cp*), 13.41 (CH_3, pyridone), 81.77 ($C(CH_3)_5$), 109.35, 128.29, 131.36, 160.99, 177.17 (pyridone); M_{calcd} = 487.02, MS (FAB): (*m*/*z*): 452.1 $[M-Cl]^+$; elemental analysis calcd for $C_{16}H_{21}IrNO_2$: C 39.46, H 4.35, N 2.88; found: C 40.05, H 4.76, N 2.94.

2: A 2.3 M solution of NaOMe in methanol (0.8 mmol) was added to a suspension of 3-hydroxy-2-methyl-4(1*H*)-pyridone (50 mg, 0.4 mmol) in methanol (10 mL). [{Cp*$IrCl_2$}$_2$] (159 mg, 0.2 mmol) was added to the resulting clear solution and the mixture was stirred for 1.5 h. After removal of the solvent in vacuo the product was extracted with dichloromethane (100 mL). A yellow powder was obtained after evaporation of the solvent under reduced pressure and drying in vacuo. Yield: 78%; IR (KBr): ν = 1578 cm^{-1} (s), 1540 (m), 1483 (s), 1450 (m); ^{1}H NMR (400 MHz, CD_2Cl_2 + 10% CD_3OD): δ = 1.53 (s, 15H; Cp*), 2.43 (s, 3H; CH_3), 5.88 (d, ^3J = 6.1 Hz, 1H; CH, pyridone), 6.90 (d, ^3J = 6.3 Hz, 1H; CH, pyridone); ^{13}C NMR (101 MHz, CD_2Cl_2 + 10% CD_3OD): δ = 10.43 (CH_3, Cp*), 19.95 (CH_3, pyridone), 83.87 ($C(CH_3)_5$), 111.43, 142.51, 144.86, 161.32, 170.73 (pyridone); M_{calcd} = 1351.68, MS (FAB): (*m*/*z*): 1352.1 $[M]^+$; elemental analysis calcd for $C_{48}H_{63}IrN_3O_6 \cdot CH_2Cl_2$: C 40.97, H 4.35, N 2.92; found: C 40.81, H 4.26, N 2.59.

3: The synthesis was performed analogous to **1** using [{(η^6-cymene)-$RuCl_2$}$_2$]. Orange powder, yield: 81%; IR (KBr): ν = 3230 cm^{-1} (m, NH), 3123 (m), 1587 (m), 1523 (s), 1492 (s); ^{1}H NMR (270 MHz, CD_2Cl_2): δ = 1.23 (d, ^3J = 6.7 Hz, 6H; $CH(CH_3)_2$), 1.99 (br s, 3H; CH_3), 2.18 (s, 3H; CH_3), 2.78 (sept, ^3J = 7.0 Hz; 1H; $CH(CH_3)_2$), 5.14 (d, ^3J = 5.9 Hz, 2H; CH, cymene), 5.38 (d, ^3J = 6.0 Hz, 1H; CH, cymene), 6.13 (br s, 1H; CH, pyridone), 6.82 (br s, 1H; CH, pyridone); ^{13}C NMR (68 MHz, CD_2Cl_2): δ = 13.39, 18.23, 22.05 (CH_3), 31.09 ($CH(CH_3)_2$), 77.74, 79.68 (CH, cymene), 95.38, 98.56 (C, cymene), 108.78, 128.11, 130.61, 159.07, 175.83 (pyridone); M_{calcd} = 394.86, MS (FAB): (*m*/*z*): 360.0 $[M-Cl]^+$; elemental analysis calcd for $C_{16}H_{20}NO_2Ru$: C 48.67, H 5.11, N 3.55; found: C 48.52, H 5.91, N 3.40.

4: The synthesis was performed analogous to **3** using [{(η^6-cymene)-$RuCl_2$}$_2$]. Orange powder, yield: 82%; IR (KBr): ν = 1576 cm^{-1} (s), 1539 (m), 1482 (s), 1445 (m); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.20 (d, ^3J = 7.3 Hz, 3H; $CH(CH_3)_2$), 1.27 (d, ^3J = 7.3 Hz, 3H; $CH(CH_3)_2$), 1.98 (s, 3H; CH_3), 2.34 (s, 3H; CH_3), 2.68 (s, ^3J = 7.2 Hz, 1H; $CH(CH_3)_2$), 4.96 (d, ^3J = 5.7 Hz, 1H; CH, cymene), 4.98 (d, ^3J = 5.8 Hz, 1H; CH, cymene), 5.15 (d, ^3J = 5.8 Hz, 1H; CH, cymene), 5.31 (d, ^3J = 5.8 Hz, 1H; CH, cymene), 5.60 (d, ^3J = 6.3 Hz, 1H; CH, pyridone), 6.78 (d, ^3J = 6.0 Hz, 1H; CH, pyridone); ^{13}C NMR (68 MHz, CD_2Cl_2): δ = 17.55, 22.10, 22.28, 22.41 (CH_3), 31.08 ($CH(CH_3)_2$), 78.92, 79.38, 79.65, 80.18 (CH, cymene), 94.58, 99.52 (C, cymene), 107.67, 139.85, 141.96, 157.60, 167.93 (pyridone); M_{calcd} = 1075.20, MS (FAB): (*m*/*z*): 1074.9 $[M]^+$; elemental analysis calcd for $C_{48}H_{57}N_3O_6Ru_3 \cdot THF$: C 54.44, H 5.71, N 3.66; found: C 53.91, H 5.64, N 3.51.

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[15] Square and cubic assemblies with {Cp*Rh} corners were recently described by Rauchfuss et al.: a) K. K. Klausmeyer, S. R. Wilson, T. B. Rauchfuss, *J. Am. Chem. Soc.* **1999**, *121*, 2705 – 2711; b) K. K. Klausmeyer, T. B. Rauchfuss, S. R. Wilson, *Angew. Chem.* **1998**, *110*, 1808 – 1810; *Angew. Chem. Int. Ed.* **1998**, *37*, 1694 – 1696.

[16] Trinuclear {Cp*M^{III}} complexes (M = Rh, Ir) with bridging amino carboxylates[5] or nucleobases[3b, 6] were reported by Beck, Fish, and Carmona. Some of these "bioorganometallic" compounds can act as a host for aromatic amino acids[6] or show interesting catalytic behavior.[5]

[17] Crystal structure analysis: General: Siemens CCD area detector, $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, semiempirical absorption correction with SADABS. The structure was solved with direct methods (SHELXS-97, Sheldrick, 1990). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-127378 (**2**) and CCDC-127377 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Crystal structure analysis of $\mathbf{2}\cdot 0.5\,CHCl_3$: crystal size $0.02 \times 0.01 \times 0.01$ mm. The crystal was mounted in perfluoropolyether oil, $T = 173$ K, yellow prism, hexagonal, space group $R\bar{3}$, $a = b = 19.6202(6)$, $c = 21.9013(9)$ Å, $V = 7301.4(4)$ Å^3, $Z = 6$, $\rho_{calcd} = 1.926$ Mg m^{-3}, $\mu = 8.313$ mm^{-1}. Data collection: 2θ from 3.04 to 59.02, $-25 \leq h \leq 25$, $-24 \leq k \leq 24$, $-28 \leq l \leq 24$, 14799 reflections collected, 3515 independent reflections, 2590 observed reflections ($F > 4\sigma(F)$), max./min. transmission 0.9215/0.8514, $R_1 = 0.0471$, $wR_2 = 0.1038$ ($F > 4\sigma(F)$), GOF(F^2) = 1.047, residual electron density 5.080/-2.994 e Å^{-3}, the weighting scheme is $w^{-1} = \sigma^2 F_o^2 + (0.0477P)^2 + 221.7031P$ with $P = (F_o^2 + 2F_c^2)/3$. A riding model was employed for the hydrogen atoms. There is a high electron density near the Ir atom (0.78 Å, 5.08 e Å^{-3}). The solvent molecule is only partially occupied (GOF = 0.1666). Crystal structure analysis of $\mathbf{4}\cdot THF$: crystal size $0.20 \times 0.10 \times 0.10$ mm. The crystal was mounted in perfluoropolyether oil, $T = 183$ K, red prism, monoclinic, space group $C2/c$, $a = 35.694(2)$, $b = 14.6090(7)$, $c = 22.456(1)$ Å, $\beta = 123.527(1)^\circ$, $V = 9761.3(8)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.550$ Mg m^{-3}, $\mu = 0.970$ mm^{-1}. Data collection: 2θ from 3.10 to 58.60, $-44 \leq h \leq 44$, $-18 \leq k \leq 18$, $-27 \leq l \leq 28$, 28663 reflections collected, 9848 independent reflections, 6759 observed reflections ($F > 4\sigma(F)$), max./min. transmission 0.9092/0.8296, $R_1 = 0.0356$, $wR_2 = 0.0797$ ($F > 4\sigma(F)$), GOF(F^2) = 0.943, residual electron density 1.013/-0.786 e Å^{-3}, weighting scheme $w^{-1} = \sigma^2 F_o^2 + (0.0488\ P)^2 + 0.0000P$ with $P = (F_o^2 + 2F_c^2)/3$. For the hydrogen atoms a riding model was employed. The disordered solvent molecule was refined isotropically and no hydrogens were added.

[18] Chiral, tetranuclear metallomacrocycles were described by Stang et al.: a) C. Müller, J. A. Whiteford, P. J. Stang, *J. Am. Chem. Soc.* **1998**, *120*, 9827 – 9837; b) P. Stang, B. Olenyuk, *Angew. Chem*. **1996**, *108*, 798 – 802; *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 732 – 736.

[19] The formation of trinuclear rhodium complexes with bridging 9-methylhypoxanthine ligands from monomeric or dinuclear complexes was shown to be pH dependent.[6b]

Inhibition of Angiogenesis In Vivo by *ets-1* Antisense Oligonucleotides—Inhibition of Ets-1 Transcription Factor Expression by the Antibiotic Fumagillin**

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Dedicated to Professor Konrad Sandhoff on the occasion of his 60th birthday

The formation of new blood capillaries from preexisting ones (angiogenesis or neovascularization; Scheme 1) is a fundamental aspect of many physiological and pathological processes[1] such as reproduction, embryonic development, wound healing, chronic inflammation, and malignant growth. Folkman's view of the early 1970s[2] that an appropriate blood supply is necessary for tumor growth has been confirmed meanwhile. Furthermore, subsequent investigations have shown that not only tumor growth but also tumor metastasis is dependent on angiogenesis.[3] For these reasons anti-angiogenesis became an attractive strategy for the treatment of neoplastic diseases.[4–7] Angiogenesis inhibitors are likewise useful for the treatment of other frequent angiogenesis-dependent diseases such as diabetic retinopathy[8] and rheumatoid arthritis.[9]

The mechanisms of angiogenesis have been intensively investigated during the last years, and several endogenous regulators have been identified.[10] Vascular endothelial

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