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Sterically Congested Adamantylnaphthalene Quinone Methides

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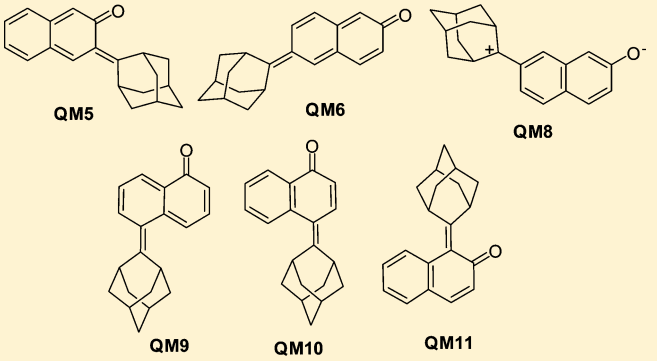
Supporting Information

ABSTRACT: Five new (2-adamantyl)naphthol derivatives (**5**−**9**, quinone methide precursors, **QMP**) were synthesized and their photochemical reactivity was investigated by preparative photolyses, fluorescence spectroscopy, and laser flash photolysis (LFP). Excitation of **QMP 5** to S_1 leads to efficient excited state intramolecular proton transfer (ESIPT) coupled with dehydration, giving quinone methide **QM5** which was characterized by LFP (in CH_3CN-H_2O, λ_{max} = 370 nm, τ = 0.19 ms). On irradiation of **QMP 5** in CH_3OH-H_2O (4:1), the quantum yield of methanolysis is Φ = 0.70. Excitation of naphthols **QMP 6**−**8** to S_1 in CH_3CN leads to photoionization and formation of naphthoxyl radicals. In a protic solvent, **QMP 6**−**8** undergo solvent-assisted PT giving **QM6** or zwitterion **QM8** that react with nucleophiles delivering adducts, but with a significantly lower quantum efficiency. **QMP 9** in a protic solvent undergoes two competitive processes, photosolvolysis via **QM9** and solvent-assisted PT to carbon atom of the naphthalene giving zwitterion. **QM9** has been characterized by LFP (in CH_3CN-H_2O, λ_{max} > 600 nm, τ = 0.9 ms). In addition to photogenerated QMs, two stable naphthalene QMs, **QM10** and **QM11** were synthesized thermally and characterized by X-ray crystallography. **QM10** and **QM11** do not react with H_2O but undergo acid-catalyzed fragmentation or rearrangement. Antiproliferative activity of **5**−**9** was investigated on three human cancer cell lines. Exposure of MCF-7 cells treated with **5** to 300 nm irradiation leads to an enhanced antiproliferative effect, in accordance with the activity being due to the formation of **QM5**.



INTRODUCTION

In past two decades, quinone methides (QM) have become a subject of significant scientific interest. They are important intermediates in many chemical and biological processes.[1] Their electrophilic nature makes them potent reagents with nucleophiles. It has been demonstrated that QMs alkylate amino acids and proteins[2] and in that way induce enzyme inhibition.[3] QMs inhibit tyrosine hydroxylases,[4] β-lactamase,[5] β-glucosidases,[6] phosphatase,[7] or ribonuclease-A.[8] Furthermore, QMs react with nucleosides[9] and induce alkylation of DNA.[10] It is now well-established that QMs cross-link DNA,[11] which renders them as potential anticancer therapeutics.[12] Some antineoplastic agents such as mitomycin,[13] daunomycin, and similar anthracyclines,[14] as well as CC 1065 and the synthetic cyclopropylpyrroloindole analogues,[15] base their antiproliferative action on the metabolic formation of QMs that alkylate DNA. Furthermore, Freccero et al. recently reported on antiproliferative activity of some BINOL−QM derivatives.[16] However, for the ultimate application of simple QM derivatives in anticancer therapy it is of pivotal importance to understand their reactivity with nucleophiles, particularly with nucleosides. Furthermore, several libraries of new QM derivatives should be prepared whose reactivity with nucleophiles and antiproliferation activity would be investigated and structure−activity relationship established.

QMs can be formed under mild conditions in photochemical reactions of suitably substituted phenols, such as photodehydroxylation of hydroxybenzylphenols,[17] photoelimination of acetic acid[18] or amines.[19] We became interested in the photochemical formation of sterically congested QMs with potential biological applicability.[20] The steric congestion with a bulky adamantyl substituent at the methylene position stabilize the QM structure, making it longer-lived and more selective in reactions with nucleophiles.[20] In continuation of this line of research, the 2-hydroxyadamantyl moiety was introduced into 2-, 3-, and 4-phenylphenols, and formation and reactivity of QMs was studied by LFP.[21] In addition, we performed an investigation of antiproliferative activity on three human cancer cell lines and found that alkyl substitution (e.g., with adamantane) at the methylene position leads to an enhancement of the antiproliferative activity of 3- and 4-phenylphenols upon 300 nm irradiation, in accordance with the enhancement being due to the formation of QMs.

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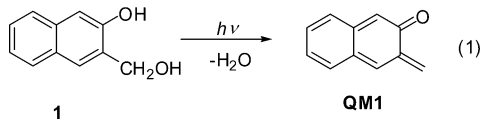
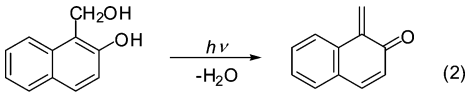
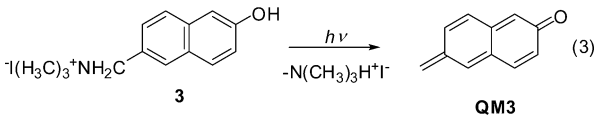
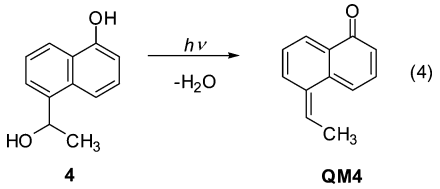
The logical extension of the study is photochemical formation of naphthalene QM derivatives and investigation of their antiproliferative action. To date, four isomeric naphthalene QMs have been reported. Arumugam and Popik have reported photochemical generation of naphthalene **QM1** and **QM2** by irradiation of 3-hydroxymethyl-2-naphthol (**1**) or 1-hydroxymethyl-2-naphthol (**2**), respectively (eqs 1 and 2).[22]





QMs react with nucleophiles to give addition products[22] or with electron-rich dienophiles to give chromanes.[23] Freccero and co-workers have reported on photochemical generation of naphthalene **QM3** from the ammonium salt **3** (eq 3),[24] whereas Wan and co-workers have reported on photodehydration of **4** giving **QM4** (eq 4).[25]

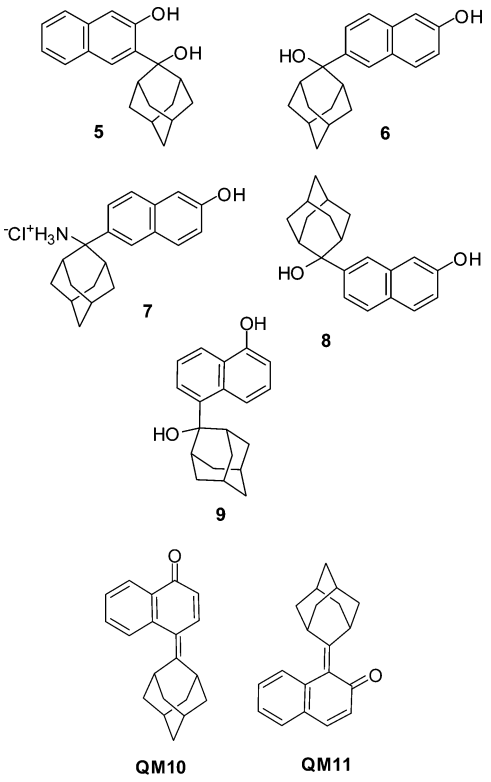




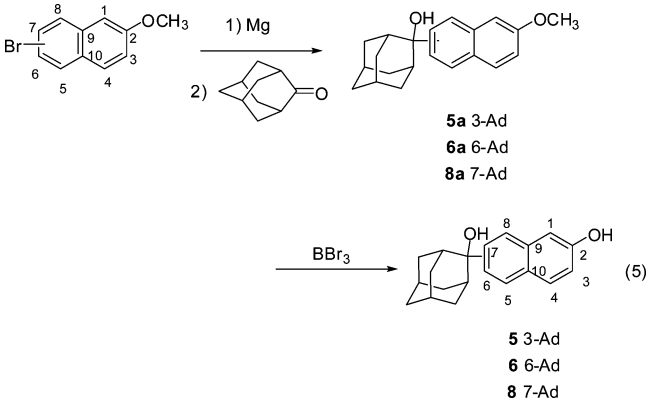
Prompted by the discovery of lead compounds with enhanced antiproliferative activity on irradiation in the biphenyl series[21] and by reports[22−25] on photochemical generation of naphthalene QMs, we investigated chemistry and photochemistry of (2-hydroxyadamantyl)naphthalenes. The investigation was conducted on a series of five adamantylnaphthols **5**−**9** that are expected to undergo excited-state intramolecular proton transfer (ESIPT) or solvent-assisted proton transfer (PT) coupled with a dehydration (or deamination in case of **7**) to deliver naphthalene QMs. Indeed, on irradiation in nucleophilic solvents **5**−**9** undergo photosolvolysis. The mechanism of the photochemical reaction was studied by preparative irradiations, fluorescence spectroscopy and laser flash photolysis (LFP). In addition, we attempted to synthesize naphthalene derivatives **10** and **11**, but instead we obtained stable QM derivatives **QM10** and **QM11** that were fully characterized and their reactivity investigated. Antiproliferatve activity was investigated for derivatives **5**−**9** on three human cancer cell lines, with and without irradiation.

RESULTS AND DISCUSSION

Synthesis. Compounds **5**, **6** and **8** were obtained by the standard synthetic protocol from the corresponding bromomethoxynaphthalenes, similar to the synthesis of adamantylphenol[20] and (adamantylphenyl)phenol derivatives,[21] that were



coupled in a Grignard reaction with 2-adamantanone, and the methoxy group was removed by use of BBr_3 (eq 5). However,



in an attempt to prepare **9**−**11** from the corresponding methoxy compounds **9a**−**11a**, the adamantyl moiety was cleaved off by BBr_3 giving α-naphthol or β-naphthol as main product. The cleavage of the adamantane also took place by use of sodium thiolate.[26] Therefore, a synthetic approach with the use of benzyl protection of the phenol was undertaken. Benzyl ethers **12** were prepared from the corresponding bromonaphthols (Scheme 1) and coupled in a Grignard reaction with 2-adamantanone. The subsequent hydrogenolysis (H_2, 60 Psi, Pd/C) gave cleanly in high yields phenols **5**, **8**, and **9**. On the other hand, hydrogenation of **10b** surprisingly gave **QM10** (83%, Scheme 2). **QM11** was also obtained as a stable product in a ground-state reaction (48%) by treatment of 1-bromo-2-hydroxynaphthalene with 2.5 equiv of BuLi and 2-adamantanone (Scheme 3). The ammonium derivative **7** was prepared from **6** (overall yield 17%) in a reaction with sodium azide giving **13** that was reduced to the corresponding amine and transformed to the HCl salt **7** (eq 6).

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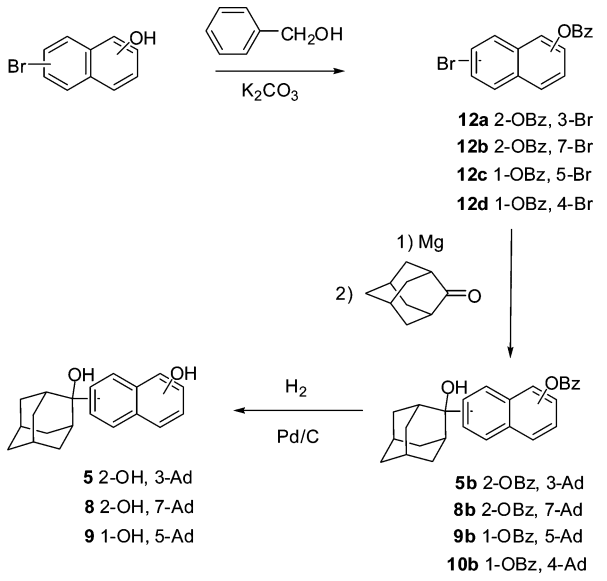
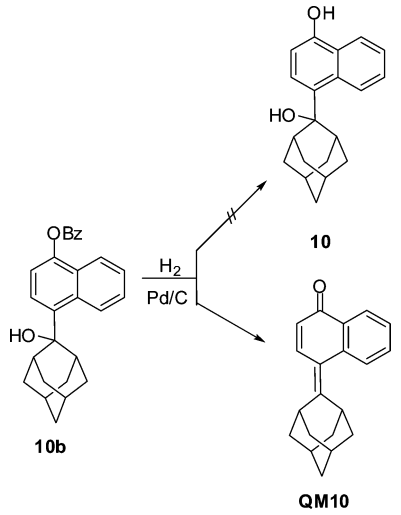
Scheme 1

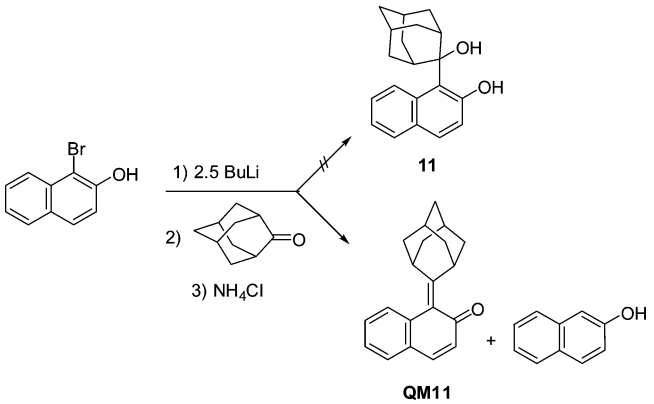


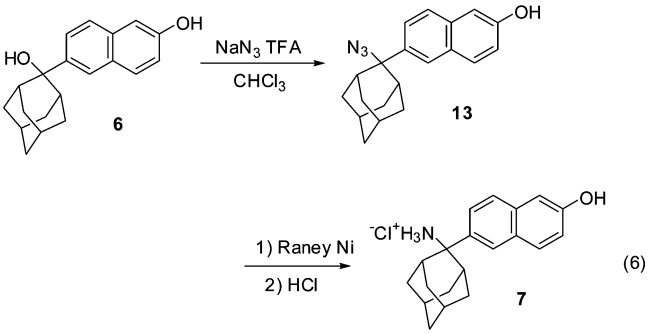
Scheme 2



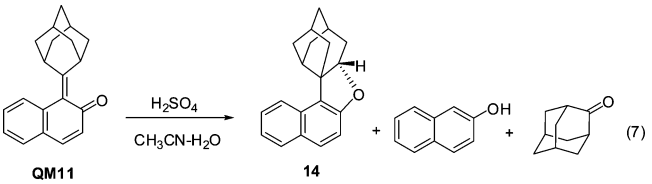
QM10 and **QM11** were unusually stable molecules, which enabled us to characterize them by spectroscopic methods as well as X-ray crystallography (Figure S61, Supporting Information). In addition, we investigated their reactivity with

Scheme 3



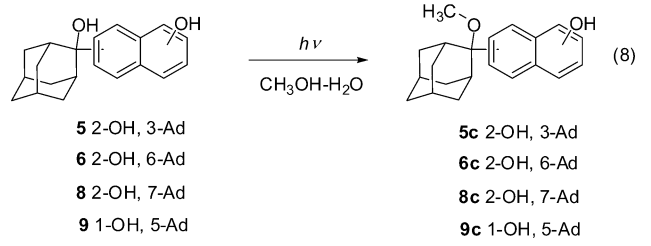


nucleophiles. Interestingly, stirring of the CH_3CN-H_2O (1:1) solution of **QM11** for several days did not result in H_2O addition. However, in acidic media, in the presence of conc. H_2SO_4, besides cleavage delivering α-naphthol, QM underwent a rearrangement of the adamantane skeleton giving proto-adamantane derivative **14** (20%, eq 7, for the crystal structure



see the Supporting Information). Under less acidic conditions, e.g., in the presence of HOAc, **QM11** is stable. Similarly, **QM10** did not react in H_2O under neutral conditions, whereas in the presence of concd H_2SO_4 it was cleaved (several days; conversion 40%) to furnish α-naphthol and adamantanone.

Photochemistry. After preliminary irradiations in UV−vis cuvettes (see the Supporting Information), photolyses of **5**−**9** were performed in CH_3OH which is a nucleophilic solvent that is expected to react with QMs and give photomethanolysis products (formal substitution of the benzyl alcohol or the NH_3Cl by OCH_3). Typically, 10−100 mg of the compound was dissolved in 100 mL of CH_3OH or CH_3OH-H_2O and irradiated (254 or 300 nm, 1 min−1 h). Progress of the photoreaction was monitored by HPLC (see the Supporting Information). Addition of H_2O significantly increased the efficiency of methanolysis, except for **5** wherein the efficiency did not depend on the H_2O content. The observed increase is in line with the mechanism of the photomethanolysis involving a proton transfer to solvent, which is more efficient in the aqueous solvent than in neat CH_3OH because of a faster transfer of proton to the clusters of H_2O than CH_3OH.[27] Photomethanolyses were clean and gave rise to the methanolysis products **5c**−**9c** in medium to high yields (eq 8) that were separated from the unreacted starting material by



preparative TLC. However, on attempts of purifying methyl ethers **6c** and **8c** on silica gel, elimination of CH_3OH took place giving the starting materials. For the purpose of character-

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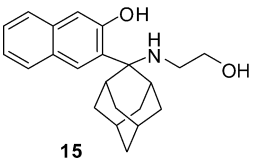
ization, **6c** and **8c** were obtained from **6** and **8**, respectively, by acidic (H_2SO_4) thermal methanolysis. Irradiation of **5** was also performed in CH_3CN in the presence of ethanolamine as a nucleophile. It gave adduct **15** in 59% yield.



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Photomethanolysis can in principle take place via cations and QMs.[21] If the reaction takes place via cationic intermediates, the efficiency for the methanolysis of naphthols **5**–**9** and the corresponding methoxy derivatives **5a**–**9a** should be similar. To probe for the cationic pathway of photomethanolysis we performed irradiations of **5**, **6**, **5a**, and **6a** in CH_3OH (20 mg, Rayonet, 16 lamps 300 nm, 30 min). Whereas irradiation of **5** and **6** gave the methanolysis products **5c** (quantitatively) and **6c** (23%), the methoxy derivatives **5a** and **6a** under the same conditions remained unchanged. The finding strongly indicates that the free naphthol OH is essential in the photomethanolysis mechanism. Consequently, if the cationic mechanism takes place its quantum efficiency is probably very low.

The importance of the free phenolic OH in the photomethanolysis suggests PT step and QM intermediates. Therefore, the efficiency of the methanolysis should principally depend on the pH of the solution. We have reported for 3-phenylphenols that increased pH above the pK_a of the phenol OH decreased efficiency of the methanolysis,[21c] whereas some 4-phenylphenols undergo acid-catalyzed photomethanolysis.[21b] To probe for the effect of pH on the efficiency of photomethanolysis in the naphthol series, we performed irradiations of CH_3OH–H_2O (2:1) solutions at different pH. The pH of the aqueous part of the solvent was varied in the range 2–10, and the conversion of the reaction was followed by HPLC (see the Supporting Information). Increase of the acidity below pH 2 gave rise to acid-catalyzed thermal methanolysis. Therefore, the effect of acidity below pH 2 on the photochemical reaction was not studied. Whereas the change of the pH (in the range 2–10) had no effect on the efficiency of the photomethanolysis of **5**, we observed acid catalysis for **6** and **8** (see the Supporting Information). The finding suggests that the benzylic OH becomes more basic in the S_1 state.

Quantum yields for the photomethanolysis were determined by use of a primary actinometer, photolysis of valerophenone in aqueous solvent giving acetophenone ($\Phi = 0.65$).[28] The values are compiled in Table 1. The measured value for **9** contains a large uncertainty due to a high sensitivity of the reaction on methanol supplier. The quantum yield for the photomethanolysis of **5** and **9** is significantly higher than for **6**–**8**.

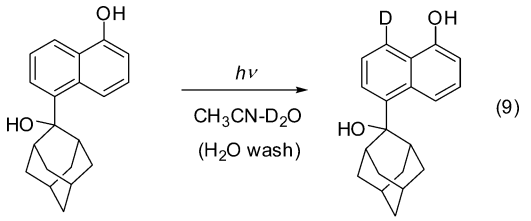
Table 1. Quantum Yields for the Photomethanolysis Reaction[a]

QMP	Φ (CH_3OH)[a]
5	0.70 ± 0.05
6	~1×10^{-4}
7	$(2 \pm 1) \times 10^{-3}$
8	0.010 ± 0.005
9	0.3 ± 0.2

[a]Irradiations performed in CH_3OH–H_2O (4:1). Qunatum yields were determined by use of valerophenone actinometer ($\Phi = 0.65$).[28]

The finding is in line with the reported photochemical stability of the parent 6-hydroxymethyl-2-naphthol by Freccero.[24] The ammonium derivative **7** exhibits higher efficiency in the photosolvolysis than the benzyl alcohol **6**. However, Φ for **7** is lower than for **8** for which formation of a Kekulé-QM derivative is not possible. Comparing the quantum yield of photomethanolysis of **5**, and the parent compound reported by Popik et al ($\Phi = 0.17 \pm 0.02$)[22] indicates that incorporation of the adamantane increased quantum yield of the photosolvolysis about 3 times, similar to the observation in the simple phenol series.[20] However, measured Φ for **9** is about 3 times lower than for the parent compound **3** ($\Phi = 0.84 \pm 0.04$).[25] The finding suggests that increase of the sterical hindrance at the position 1 of the naphthalene decreased efficiency of the photodehydration.

It has been demonstrated by D-exchange experiments that 1-naphthol derivatives undergo solvent-assisted proton transfer from the phenolic OH to the carbon atoms at the positions 5 and 8 of the naphthalene ring giving QM intermediates.[25,29] Therefore, photosolvolysis and solvent-assisted PT should principally be competitive reactions for **9**. To probe for the solvent-assisted PT in **9** we performed irradiations in CH_3CN–D_2O. After the irradiations and H_2O workup, the mixture was analyzed by NMR and MS to determine the position and the extent of the deuteration, respectively. Irradiation (Luzchem, 8 lamps) gave rise to 40% D-exchange at the position 8 of the naphthalene ring (according to NMR), wheras MS idnicated presnece of 37% monodeuterated and 7% of dideuterated species. Competition between the D-exchange and photosolvolysis was investigated by irradiation in CH_3OD. After the irradiation NMR indicated presence of 10% of **9c**, whereas ~5% of molecules **9** and **9c** contained D at the position 8 of the naphthalene ring. The finding indicates that photosolvolysis is about two times more efficient than the D-exchange ($\Phi \sim 0.15$), which is in line with the reported value for 1-naphthol ($\Phi \sim 0.11$).[25]



9 **9-D** (9)

Fluorescence. It is generally accepted that PT reactions of naphthols take place from the singlet excited state due to increased acidity of naphthol in S_1.[27,29] Therefore, we investigated fluorescence properties of **5**–**9** to get more information about their singlet excited state properties and reactivity. Fluorescence quantum yields were measured in CH_3CN and CH_3CN–H_2O (1:4) by use of two standards, fluorene in CH_3OH reference ($\Phi = 0.68$) and quinine sulfate in 0.05 M aqueous H_2SO_4 ($\Phi = 0.53$).[30] Singlet excited state lifetimes were measured by time-correlated single photon timing (SPT) method. The results are compiled in Table 2. In CH_3CN, fluorescence spectra of **5**–**9** are characterized by the presence of a band with a maximum at ~350 nm. Spectra of **5**–**8** are narrower (half intensity band with ~3000 cm^{-1}) than the spectrum of **9** (half intensity band with ~4500 cm^{-1}). The finding is in accordance with the typical fluorescence properties

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Table 2. Photophysical Parameters of Naphthols 5−9

QMP	Φ (CH_3CN)[a]	Φ (CH_3CN−H_2O)[a]	τ (CH_3CN)/ns[b]	τ (CH_3CN−H_2O)/ns[b]
5	0.23 ± 0.03	0.18 ± 0.01	3.30 ± 0.05 (40%)	3.0 ± 0.5 naphthol
			6.5 ± 0.1 (60%)	6.1 ± 0.5 naphtholate
6	0.30 ± 0.05	0.22 ± 0.03	8.14 ± 0.01	6.4 ± 0.5 naphthol
				9.7 ± 0.3 naphtholate
7	0.30 ± 0.01	0.3 ± 0.1	3.2 ± 0.1 (4%)	12.3 ± 0.3 naphthol
			10.6 ± 0.1 (96%)	4.7 ± 0.1 naphtholate
8	0.30 ± 0.05	0.22 ± 0.02	7.78 ± 0.01	6.3 ± 0.1 naphthol
				7.8 ± 0.3 naphtholate
9	0.33 ± 0.01	0.10 ± 0.01	4.46 ± 0.01	0.2 and 0.5 naphthol
				5.7 ± 0.2 naphtholate

[a]Quantum yields of fluorescence measured by use of fluorene in CH_3OH (Φ = 0.68) or quinine sulfate in 0.05 M aqueous H_2SO_4 (Φ = 0.53) as a reference.[30] [b]Fluorescence lifetimes measured by time-correlated single photon timing method.

of 2- and 1-naphthols, respectively. The emissive state in 2-naphthols can be characterized according to the Pratt nomenclature[31] as ^1L_b, whereas in 1-naphthols ^1L_a and ^1L_b states are overlapping.[32] Interestingly, decay of fluorescence in CH_3CN could be fitted to single exponential function for 2-naphthols **6** and **8**, as well as for 1-naphthol **9**. On the other hand, for **5** and **7** fluorescence decay in CH_3CN was best fitted to two-exponential function.

Addition of H_2O to the CH_3CN solution of phenols or naphthols opens a possibility for the deactivation from S_1 by PT to solvent, with concomitant quenching of fluorescence.[27,33] Therefore, we performed fluorescence titration of the CH_3CN solutions of **5−9** with H_2O to probe for the PT deactivation pathways. Interestingly, on addition of H_2O to the CH_3CN solution of **5−8** fluorescence increases, and only for **9** we observed quenching (see the Supporting Information.). However, increase of fluorescence in H_2O-titration experiments has already been reported for some adamantylphenols and adamantyl derivatives of phenylphenols.[20,21] The presumable explanation was different solvation of the molecules by CH_3CN and H_2O due to the presence of very lipophilic adamantyl group. Although for **5−8** we have not observed quenching of fluorescence by addition of H_2O, at high concentration of H_2O PT takes place. It is demonstrated by lower quantum yields of fluorescence at high H_2O content than in neat CH_3CN (Table 2) and additional bands in the fluorescence spectra at longer wavelengths not seen in CH_3CN. The bands are assigned to the fluorescence of naphtholates formed by an adiabatic PT to the solvent (Figure 2). For **5**, **6**, and **8** in CH_3CN−H_2O (1:4) the naphtholate emission appears in the spectrum as a shoulder at ∼450 nm (see Figure 1 and Figures S11, S15 and S22, Supporting Information), whereas for **7** and **9** a strong new band can be seen at 475 and 500 nm, respectively. In particular, in the fluorescence spectrum of **9** taken in CH_3CN−H_2O (1:4) fluorescence of naphthol can be seen only as a shoulder at 375 nm, whereas fluorescence from the naphtholate dominates the spectrum. The findings are in line with the acidity of the investigated derivatives in S_1, being much higher for 1-naphthols (pK_a = 0.4),[29] than 2-naphthols (pK_a ∼2.8,[34] for 3-hydroxymethyl-2-naphthol pK_a = 0.77[22]). Furthermore, **7** bearing the ammonium moiety with a positive charge should clearly be more acidic in the ground and excited state compared to the alcohol **6** (positive charge stabilizes the naphthoxide formed by PT). In addition to the steady-state fluorescence spectra, PT to the aqueous solvent for **5−9** is indicated by SPT measurements. In aqueous media, an additional longer-lived decay component with a negative pre-exponential factor can be seen, contributing more at longer wavelengths. The rising component was assigned to the naphtholate formed in the adiabatic PT to the solvent (Table 2).

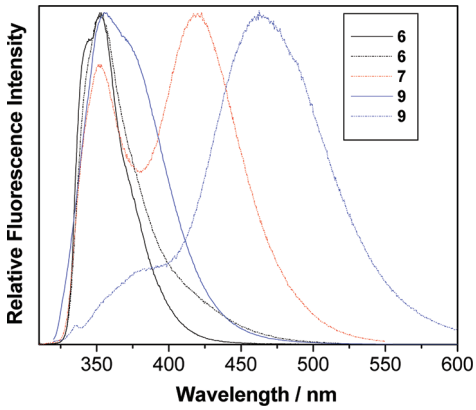

Figure 1. Normalized fluorescence spectra of naphthols **6**, **7**, and **9** in CH_3CN (solid line) and CH_3CN−H_2O (1:4) (dashed line).

Acid−base properties in the S_1 for **5−9** were investigated by titrations with acid and base. Addition of base (NaOH) to the CH_3CN−H_2O (1:4) solution of **5−9** significantly changed the appearance of the spectra. The bands associated to the emission of naphthol gradually disappeared, and only longer wavelength bands at 400−600 nm from the naphtholate emission could be seen. The finding corroborates the assignation of the long-wavelength emission (only seen in the aqueous solvent) to naphtholates. On the contrary, titration with acid ($HClO_4$) in the pH range 2.5−3.0 resulted in the quenching of fluorescence without the change of the spectra. The relative ratio of the emission from the naphthol and the naphtholate remained the same (only small differences were observed in the normalized spectra of **7**). The finding indicates that the most basic site of the molecules in S_1 is not the naphtholate anion, but rather benzylic alcohol or the carbon atoms of the naphthalene. The Stern−Volmer plots ($Φ/Φ_0$ vs H^+ concentration) showed a linear relationship, indicating a dynamic quenching with quenching constants in the range k_q = (1−6) × 10^9 dm^3 mol^{-1} s^{-1} for **6−8** and somewhat higher values for **5** [k_q = (1−3) × 10^{10} dm^3 mol^{-1} s^{-1}] and **9** (k_q = ∼3 × 10^{10} dm^3 mol^{-1} s^{-1}). The values of the quenching constants are in line with the quantum efficiencies for the photomethanolysis (Table 1).

Laser Flash Photolysis (LFP). LFP was performed to characterize QMs and other long-lived transient species in the photochemical reactions of **5−9**. The measurements were performed in N_2- and O_2-purged CH_3CN and CH_3CN−H_2O

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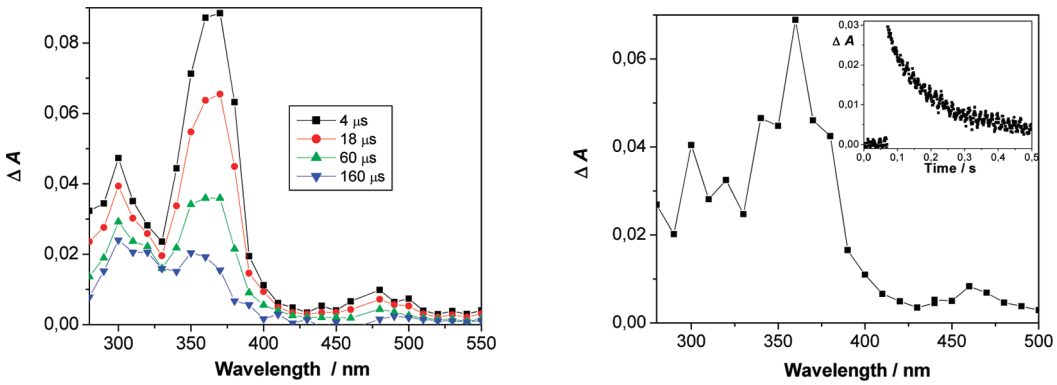

Figure 2. Transient absorption spectra of **5** in O_2-purged $CH_3CN–H_2O$ (left), and O_2-purged CH_3CN solution (right) taken at 350 ns after the laser pulse (inset: decay at 350 nm).

(1:1) solutions. In principle, the difference in the transient spectra measured in CH_3CN and $CH_3CN–H_2O$ could correspond to the species formed in pathways involving PT. In N_2-purged CH_3CN and CH_3CN-H_2O solutions of all derivatives we observed a transient absorbing with a maximum at 430–450 nm decaying with the rate constant $k = (1–3) \times 10^5$ s^{-1} ($\tau = 3–7$ μs). The transient is quenched by O_2 (in O_2-purged solution, $k = (1–2) \times 10^7$ s^{-1}, $\tau = 20–60$ ns). Based on the quenching by O_2 and similarity with the published spectra of naphthol triplets,[35] we assign the observed transient to the triplet–triplet absorption.

In the transient spectra of **5** obtained in O_2-purged CH_3CN solution, a strong transient absorption was observed with a maximum at 360 nm, decaying with $k = 6.7$ s^{-1} ($\tau = 0.15$ s) (Figure 2). The transient was not affected by O_2 but experienced a small bathochromic shift and a significant quenching on addition of H_2O. In O_2-purged $CH_3CN–H_2O$ (1:1), the maximum of the transient is observed at 370 nm, decaying with a rate $k = 5.0 \times 10^3$ s^{-1} ($\tau = 0.19$ ms). On the basis of the above findings, the transient was assigned to **QM5**. Further evidence which undoubtedly allowed for the assignation of the transient were the quenching constants (Table 3) with nucleophiles (CH_3OH, ethanolamine, NaN_3)

Table 3. Bimolecular Quenching Rate Constants for QM5

	k_q (dm^3 mol^{-1} s^{-1})
CH_3OH[a]	$(8.0 \pm 0.6) \times 10^3$
ethanolamine[a]	$(1.08 \pm 0.05) \times 10^5$
ethanolamine[b]	$(1.1 \pm 0.2) \times 10^5$
NaN_3[b]	$(3.7 \pm 0.5) \times 10^6$
ethyl vinyl ether[a]	85 ± 10

[a]Measurement performed in CH_3CN. [b]Measurement performed in $CH_3CN–H_2O$ (1:1).

and ethyl vinyl ether, which are in agreement with the published constants for QMs.[11c,22] However, Popik et al. reported that photolysis of **1** gave rise to a benzoxete absorbing at 370 nm which decayed ($\tau = 12–13$ μs), giving **QM1** ($\tau = 4–8$ ms, $A_{max} = 330$ nm).[22] We have not detected any intermediate in the QM formation; the transient was formed within the laser pulse, indicating that the corresponding benzoxete was not formed or that it has a shorter lifetime than 20 ns.

The transient spectra obtained by LFP of naphthols **6–8** were more complex than those of **5**. Besides the signal of the triplet (vide supra), a broad transient absorption was observed at 500–700 nm that was not affected by O_2 and decayed faster in aqueous solution. According to the comparison with the published spectra of naphthol radical cations,[36] the transients were tentatively assigned to the presence of radical cation **16** and solvated electron. In aqueous solvent, the phenoxyl radical cations decay by deprotonation[37] to give phenoxyl radicals.[38] Therefore, more persistent transient absorption with a maximum at 350 and 500 nm, decaying with $k = (1.6–2.5) \times 10^4$ s^{-1} ($\tau = 40–60$ μs) was assigned to radical **17**. The supporting evidence for the assignation is as follows: the decay is not affected by solvent polarity or O_2, and the maximum of the absorption is at the same wavelengths as in the published spectra of the naphthoxyl and phenoxyl radicals.[35–38] The decay of **17** matches the rise of the most persistent transient absorption at 330 nm ($\tau = 1–2$ s). Freccero et al. reported formation of **QM3** characterized by the transient absorption at 310–330 nm ($\tau > 1$ ms), which is formed by a decay of the transient absorbing at 370 nm ($\tau \approx 20$ μs). In analogy, we could tentatively assign the observed transient formed by decay of **17** in the LFP experiments of **6** and **7** to **QM6**. However, we observed the same transient absorption in the LFP experiment of **8** for which a Kekulé QM structure is not possible. Therefore, with the present data, a firm assignment of the long-lived transient absorption with the maximum at 330 nm is not possible.

Since we did not detect presence of QMs formed from **6–8** in $CH_3CN–H_2O$ (1:1), we carried out LFP experiment in the acidic media. We observed that acid (pH range 2–3) catalyzes photomethanolysis of **6** and **8** (vide supra), probably due to the protonation of the benzyl alcohol which is more basic in S_1. Hence, it was anticipated that LFP experiments carried out in $CH_3CN–H_2O$ (1:1) solution at pH 2 should give rise to the transients that are associated to cations or QMs formed via cationic intermediates. Furthermore, LFP experiments were performed in 2,2,2-trifluoroethanol (TFE) which is acidic, but less nucleophilic than H_2O, wherein QMs[20,21,39] and cations[40] generally have longer lifetimes. However, in the transient absorption spectra of **6** and **7** in $CH_3CN–H_2O$ (1:1) at pH 2 we detected similar transients as in the neutral $CH_3CN–H_2O$ that were assigned to the naphthoxyl radical. In the transient absorption spectra of **6** and **8** recorded in O_2-purged TFE, naphthoxyl radicals were also detected, decaying slower ($k = 6.5 \times 10^3$ s^{-1}, $\tau = 150$ μs) than the analogous transient species observed in $CH_3CN–H_2O$. However, in O_2-purged TFE solution of **8** we detected the presence of a transient absorbing

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at 350−450 nm, decaying with the rate $k = (7-8) \times 10^6$ s^{-1} (τ = 125−140 ns). According to the comparison with the spectra of naphthylmethyl cations,[40] the transient was assigned to the zwitterionic **QM8**. In addition, the transient was quenched by ethanolamine. However, because of the overlap with the signal of the triplet, a precise quenching rate constant could not be estimated.

Transient absorption spectra of **9** were different from the spectra of **5**−**8**. Addition of H_2O to the CH_3CN solution induced significant change of the spectrum with appearance of rather a strong absorption band at >600 nm, decaying in O_2-purged solution with a biexponential law ($k = 6.0 \times 10^4$ s^{-1}, τ = 17 μs and $k = 1.1 \times 10^3$ s^{-1}, τ = 0.9 ms). The long wavelength absorption band was not affected by O_2 or N_2O, indicating that it does not correspond to triplets, radicals, or solvated electrons. In TFE solution, the LFP gave rise to the same appearance of the transition spectra (Figure 3), however, decaying slower,

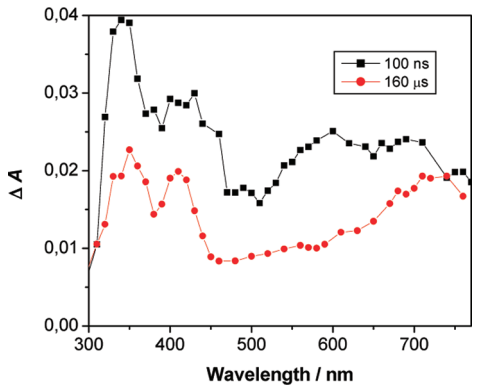


Figure 3. Transient absorption spectra of **9** in O_2-purged TFE.

with $k = 9.0 \times 10^4$ s^{-1}, τ = 11 μs, and k = 40 s^{-1}, τ = 25 ms. Furthermore, the transients could be quenched by ethanolamine and sodium azide (Table 4). Consequently, we assigned the short-lived transient (τ = 11 μs) to the zwitterion **Zw9** and long-lived (τ = 25 ms) to **QM9**.

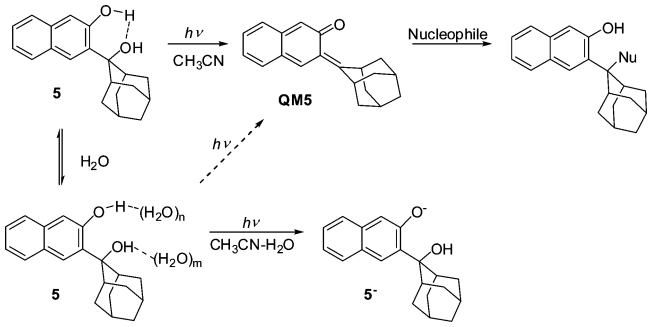
Table 4. Bimolecular Quenching Rate Constants (k_q (dm^3 mol^{-1} s^{-1})) for QM9 and Zw9

	QM9	ZW9
ethanolamine[a]	$(2.6 \pm 0.5) \times 10^3$	$\sim 1 \times 10^9$
NaN_3[b]	$(1.1 \pm 0.1) \times 10^7$	

[a]Measurement performed in TFE. [b]Measurement performed in CH_3CN−H_2O (1:1).

Reaction Mechanisms. Excitation of 2,3-substituted naphthalene derivative **5** to S_1 leads to an efficient ESIPT wherein the phenolic OH is transferred to the alcohol group along the intramolecular H-bond trajectory. The ESIPT is coupled with dehydration, delivering **QM5** (Scheme 4). Because of the efficient ESIPT, the quantum yield of fluorescence for **5** is lower than for the other investigated derivatives. Formation of **QM5** and subsequent reactions with nucleophiles probably do not require presence of a protic solvent. That is demonstrated by LFP measurements performed in neat CH_3CN, wherein the transient assigned to **QM5** was detected. Furthermore, quantum efficiency of the photomethanolysis does not depend on the addition of H_2O or pH of the solution (in the range 2−10), in agreement with the

Scheme 4



operation of an intrinsic ESIPT delivering **QM5** that reacts with methanol (or other nucleophiles) giving adducts. Estimated quenching constants for the reaction of **QM5** with nucleophiles by LFP are higher than reported by Popik for the parent naphthol system[22] but in line with those reported by Freccero[11d] for QMs derived from BINOLs. On addition of H_2O to the CH_3CN solution, the intramolecular H-bond between the phenol OH and the alcohol is partly perturbed, the ESIPT quantum yields are lowered, and the fluorescence is enhanced. In H_2O, in addition to ESIPT, a PT to solvent takes place delivering naphtholate, as demonstrated by fluorescence measurements. Furthermore, a H_2O-mediated PT may also ultimately deliver **QM5** that reacts with nucleophiles or H_2O.

Excitation of derivatives **6**−**8** to the S_1 cannot give rise to ESIPT due to a larger distance between the phenolic OH and the alcohol group R (Scheme 5) or absence of the basic site in **7**. Therefore, the fluorescence quantum yield of the CH_3CN solution of **6**−**8** is higher than the one of **5**. Population of the S_1 state in CH_3CN does not lead to the formation of QMs. Instead, a photoionization takes place delivering radical-cations **16** and solvated electron, as suggested by the LFP measurements. Photoionization and formation of naphthoxyl radicals may account to the formation of high-weight material and spectral changes observed on photolyses in CH_3CN and CH_3CN−H_2O in UV−vis cuvettes. Naphthoxyl radical cations are very acidic,[36−38] so **16** decays in the presence of proton-accepting solvent by PT giving naphthoxyl radicals **17** that were detected by LFP. In case of **6**, radical **17** may undergo homolytic cleavage of the OH· to give **QM6**. Homolytic cleavage of radicals is a well-documented reaction, for example, in the Norrish type-I[41] or photo-Kolbe reactions.[42] Furthermore, formation of QMs in the electron-transfer reactions has already been reported by Freccero et al.[43] This pathway may account to minor formation of **6c** on irradiation of **6** in CH_3OH (Φ for methanolysis is only 1×10^{-4}). The reason for such a low overall quantum yield is probably back-electron transfer after photoionization giving starting material **6**−**8**. In aqueous solvent, PT to H_2O clusters takes place giving naphtholates.[27,33] Incorporation of the ammonium salt in the molecule results in stronger acidity of the phenolic OH in **7** (compared to **6**) which is demonstrated in fluorescence spectra, by stronger contribution of the naphtholate emission, and higher quantum yield of the photomethanolysis reaction. Deprotonation of the phenolic OH in S_1 coupled with the elimination of H_2O or ammonia from **6** and **7**, respectively, delivers **QM6**. Similarly, solvent-assisted PT and dehydration gives rise to zwitterionic **QM8** from **8**. Due to low quantum yield of formation, **QM6** was not detected by LFP, but **QM8**

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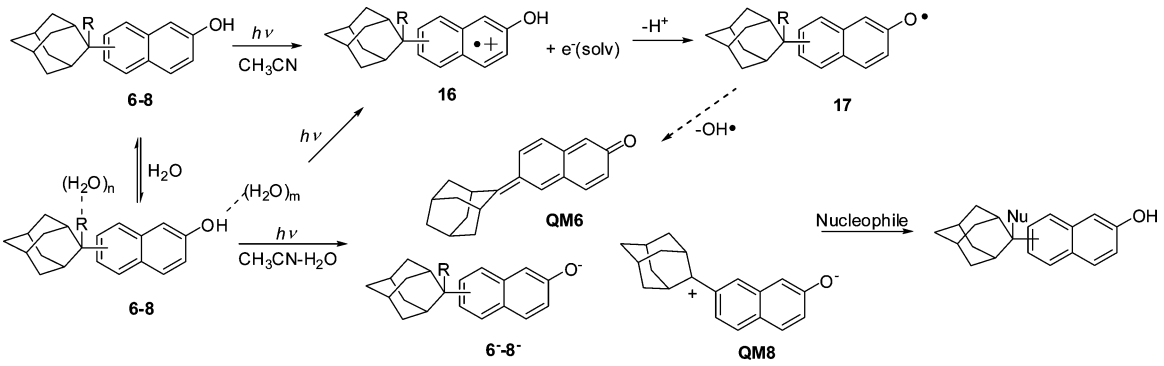
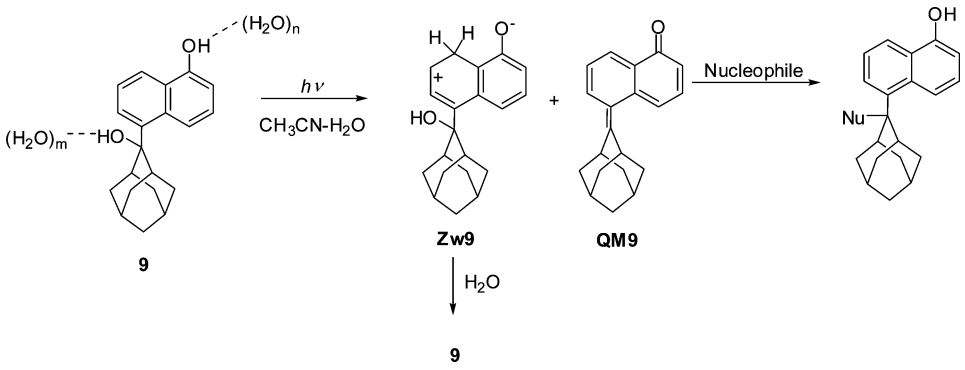
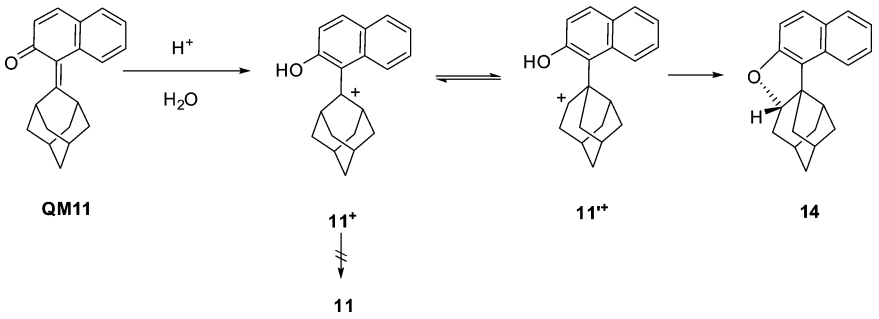
Scheme 5



Scheme 6



Scheme 7



was detected in the TFE solution. Reaction of **QM6** and **QM8** with nucleophiles gives adducts or photosolvolysis products.

Photoexcitation of **9** to S_1 in aprotic solvent cannot give rise to ESIPT, similar to **6**–**8**. Therefore, for the formation of **QM9** (Scheme 6), addition of a protic solvent is required to mediate the deprotonation of the naphthol OH and protonation of the benzyl alcohol which is coupled with a dehydration. Since 1-naphthols are more acidic than the corresponding 2-naphthol derivatives, less protic solvent is required for the formal solvent-assisted PT and formation of **QM9**. Hence, already a small addition of H_2O (up to 5%) significantly propels the photosolvolysis reaction in CH_3OH, and pH (in the range 2–10) has no effect on the quantum efficiency. **QM9** has been detected by LFP in $CH_3CN–H_2O$ and its kinetics with ethanolamine and NaN_3 determined. Interestingly, **QM9** reacts ~3 times faster with NaN_3 than **QM5**, but the quenching rate constant with ethanolamine is about 100 times smaller. The estimated quenching constants are in line with those previously reported for sterically congested QMs.[21] Obviously, structure of the QMs influences largely their reactivity with nucleophiles. In addition to photosolvolysis, **9** undergoes solvent-assisted PT wherein carbon atom of the naphthalene is the basic site. This PT process gives zwitterion **Zw9** that does not react with nucleophiles but undergoes tautomerization to the starting material. LFP in TFE gave rise to a short-lived transient (τ = 11 μs) that was tentatively assigned to **Zw9**. On irradiation in $CH_3CN–D_2O$ formation of **Zw9** leads to deuteration of the position 8 of the naphthalene ring. Competition of photosolvolysis and solvent-assisted PT leading to deuteration of carbon atoms has already been reported.[21a,25]

Attempts to synthesize naphthol derivatives **10** and **11** gave the corresponding **QM10** and **QM11**, suggesting that QMs are characterized by similar stability as naphthols. According to B3LYP/6-311G, the energy gain in the hydration reaction of **QM10** and **QM11** is only 13.84, and 30.71 kJ/mol, respectively, whereas hydration of **QM5** is highly exergonic (ΔE = −138.60 kJmol^{-1}). Therefore, **QM10** and **QM11** do not react with H_2O even under acidic conditions. However, in the presence of concd H_2SO_4 under very acidic conditions, they undergo cleavage to naphthol and adamantanone. In addition,

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Table 5. IC_{50} Values (in μM)[a]

	cell lines					
	HCT116		MCF-7		H 460	
compd	not irradiated	irradiated[b]	not irradiated	irradiated[b]	not irradiated	irradiated[b]
5	≥100	≥100	≥100	5 ± 1	≥100	≥100
6	17 ± 3	16 ± 2	19 ± 3	16 ± 3	19 ± 1	18 ± 2
7	11 ± 0.1	12 ± 1	12 ± 2	11 ± 1	10 ± 1	6 ± 5
8	39 ± 1	34 ± 1	23 ± 6	18 ± 2	45 ± 10	29 ± 12
9	36 ± 25	45 ± 35	39 ± 16	24 ± 4	25 ± 1	20 ± 8
QM10	2.0 ± 0.1		1.0 ± 0.4		2.0 ± 0.2	
QM11	2.0 ± 0.1		3.0 ± 0.1		2.0 ± 0.1	
Trioxsalen[c]	19 ± 2	0.2 ± 0.02	34 ± 6	0.24 ± 0.1	≥100	0.1 ± 0.1

[a]IC_{50}; the concentration that causes 50% growth inhibition. [b]Irradiated 3 × 1 min at 300 nm with six lamps. In the calculation of IC_{50}, the treated and irradiated cells were compared with only irradiated control cells so that 25% inhibition of growth caused by 300 nm light does not influence the reported result. [c]Trioxsalen IUPAC name: 2,5,9-trimethyl-7*H*-furo[3,2-*g*]chromen-7-one

protonation of the carbonyl moiety of **QM11** gives carbocation that undergoes rearrangement to less sterically hindered protoadamantyl cation **11'**$^+$ that reacts with phenol in the intramolecular reaction giving **14** (Scheme 7). Rearrangement of the adamantyl cation to the protoadamantyl skeleton has been intensively studied,[44] as well as reactions of protonated QMs.[18,45] However, to the best of our knowledge the lack of reactivity of protonated QMs with H_2O has not yet been reported. The unusual stability of **QM10** and **QM11**, compared to the previously studied QMs may be rationalized by loss of aromaticity in only one benzene ring of the naphthalene moiety, high-resonance stabilization of the carbocations obtained by protonation, and steric effect of the adamantane hindering the attack of nucleophiles to QMs or the carbocations.

Antiproliferative Investigation. To investigate the antiproliferative effect of QMs we performed testing of compounds on three human cancer cell lines HCT 116 (colon), MCF-7 (breast), and H 460 (lung). The testing was performed on **5**–**9** in the presence and absence of 300 nm irradiation, as well as on **QM10** and **QM11** without the irradiation. In addition, we performed a control experiment wherein the cells were only irradiated at 300 nm, but without the treatment with compounds, as well as a positive control experiment wherein the cells were treated with trioxsalen that is known to exhibit antiproliferative activity on photoactivation (see the Supporting Information).[16,24] After 72 h of incubation the cell growth rate was evaluated by performing the MTT assay[46] which detects dehydrogenase activity in viable cells. Compounds **6**–**9** as well as **QM10** and **QM11** showed an antiproliferative effect to all cell lines in the micromolar concentration range without exposure to light (Table 5). QMs exhibited activity in approximately 10 times lower concentration than **6**–**9**. The antiproliferative effect of **6**–**9** was very similar and cannot be correlated with the molecular structure, lipophylicity, or solubility in H_2O. On the contrary, naphthol **5** exhibited very low activity on the cells that were kept in dark. Irradiations of cells (3 × 1 min at 300 nm with six lamps) resulted in significant enhancement of the activity, reaching almost the one of the trioxsalen, but only on the MCF-7 cell line. Enhancement of the antiproliferative action with compound **5** can be correlated with the highest efficiency of the QM formation in the investigated series (see Table 1). Although we cannot give an explanation for the observed selectivity on the MCF-7 cell line, the selective antiproliferative action of the photogenerated QMs has already been reported by us[21] and Freccero.[16,24] The observed enhancement of the activity of **5** on exposure to light, and selective action to only one cancer cell line classifies it as a potential lead for further investigations.

CONCLUSION

New (2-adamantyl)naphthol derivatives **5**–**9** were synthesized and their ESIPT, and solvent-assisted PT reactivity was investigated. All derivatives undergo photosolvolysis via QM intermediates. **QM5** formed from **5** in the S_1 via ESIPT and dehydration was characterized by LFP and its rate constants with nucleophiles determined. Incorporation of the adamantyl moiety results in different reactivity pattern compared to the nonsusbtituted structure. Naphthols **6**–**8** in S_1 undergo photoionization and formation of naphthoxyl radicals. Photosolvolysis via **QM6** and zwitterion **QM8** takes place in a protic solvent but with significantly lower overall quantum efficiency. Naphthol **9** in S_1 in a protic solvent undergoes photosolvolysis via **QM9** and solvent-assisted PT to carbon atom of the naphthalene giving zwitterion **Zw9**. **QM9** has been characterized by LFP. Determined quenching rate constants for **QM9** with nucleophiles reveal very different reactivity patterns. In addition to photogenerated QMs, two stable naphthalene QM derivatives **QM10** and **QM11** were synthesized and fully characterized. **QM10** and **QM11** do not react with H_2O but undergo acid-catalyzed fragmentation or rearrangement. The results indicate importance of preparing new QM derivatives and studying their reactivity to fully understand their chemistry before the ultimate use in biology and medicine. Antiproliferative activity of **5**–**9** was investigated on three human cancer cell lines HCT 116 (colon), MCF-7 (breast), and H 460 (lung). Exposure of cells treated with **5** to 300 nm irradiation leads to enhanced antiproliferative effect on MCF-7 cell line, classifying **5** (or **QM5**) as a potential lead for further antiproliferative studies.

EXPERIMENTAL SECTION

General Procedure for the Preparation of Compounds 12a and 12b. A solution of bromonaphthol (1110 mg, 5.0 mmol) and benzyl bromide (0.9 mL, 7.5 mmol) in DMF (15 mL) was treated with K_2CO_3 (1380 mg, 10.0 mmol), and the resulting mixture was heated at 60 °C for 2 h. After cooling and filtration, the mixture was evaporated. The residue was dissolved in ethyl acetate (50 mL), and the organic solution was washed with 1 M HCl (3 × 25 mL) and brine (2 × 20 mL), dried over unhydrous $MgSO_4$, filtered, and evaporated. The

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residue was chromatographed on silica gel using dichloromethane/hexane (1:1) as eluent to afford the pure compounds.

2-Benzyloxy-3-bromonaphthalene (12a). Compound **12a** was prepared in 78% yield according to the general procedure from 2-bromo-3-hydroxynaphthalene (1 g, 4.5 mmol) and benzyl bromide (0.8 mL, 6.7 mmol): mp 83−84 °C; IR (KBr) ν/cm^{-1} 3029 (vw), 1587 (m), 1379 (s), 1247 (s), 1020 (s), 727(s); ^{1}H NMR ($CDCl_3$, 300 MHz) δ/ppm 8.06 (s, 1H), 7.63−769 (m, 2H), 7.49−7.54 (m, 2H), 7.29−7.45 (m, 5H), 7.18 (s, 1H), 5.23 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ/ppm 152.6 (s), 136.4 (s), 133.4 (s), 132.3 (d), 129.5 (s), 128.6 (d), 127.9 (d), 126.9 (d), 126.7 (d), 126.6 (d), 124.6 (d), 113.9 (s), 108.3 (d), 70.7 (t).

2-Benzyloxy-7-bromonaphthalene (12b). Compound **12b** was prepared in 86% yield from 2-bromo-7-hydroxynaphthalene (556 mg, 2.5 mmol) and benzyl bromide (0.36 mL, 3.0 mmol) as described in the general procedure: mp 117−119 °C; IR (KBr) ν/cm^{-1} 3050 (wv), 1624 (s), 1500 (s), 1170 (s), 1003 (m), 845 (s), 735 (s); ^{1}H NMR ($CDCl_3$, 300 MHz) δ/ppm 7.87 (d, 1H, J = 1.7 Hz), 7.71 (d, 1H, J = 8.9 Hz), 7.62 (d, 1H, J = 8.7 Hz), 7.32−7.50 (m, 6H), 7.22 (dd, 1H, J = 2.3 Hz, J = 8.9 Hz), 7.10 (d, 1H, J=2.4 Hz), 5.16 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ/ppm 157.5 (s), 136.6 (s), 135.8 (s), 129.4 (d), 129.3 (d), 128.8 (d) 128.7 (d), 128.1 (d), 127.5 (d), 127.4 (s), 127.0 (d), 120.6 (s), 119.5 (d), 106.4 (d), 70.1 (t).

General Procedure for the Grignard Reaction. The reaction was carried out under N_2 inert atmosphere in a two-neck, round-bottom flask (100 mL) equipped with a condenser and a dropping funnel. Magnesium (10 mmol) which was freshly activated prior to the reaction was placed in the flask and suspended in THF (10 mL). In the dropping funnel was placed a THF solution (20 mL) of bromonaphthol (10 mmol). A few drops of the solution were added to the suspension in the flask, and the reaction was initiated by adding a crystal of iodine and heating. The remaining solution in the funnel was added over 30 min at rt. After the addition was completed, reaction mixture was refluxed until all magnesium reacted (1−1.5 h). The solution of the Grignard reagent was cooled to rt, and a THF solution (20 mL) of 2-adamantanone (10 mmol) was added dropvise during 1 h. After addition was completed, the reaction mixture was refluxed for 4 h and stirred at rt overnight. The next day, to the reaction mixture was added a saturated solution of ammonium chloride (100 mL), the layers were separated, and the aqueous layer was additionally acidified with 1 M HCl until all solid dissolved. The acidified aqueous layer was extracted with diethyl ether (3 × 30 mL), and the organic extracts were combined and dried over anhydrous $MgSO_4$. After filtration and removal of the solvent, the crude product was obtained that was additionally purified by chromatography on silica gel using CH_2Cl_2 as eluent.

2-(2-Hydroxy-2-adamantyl)-3-methoxynaphthalene (5a). The Grignard reagent was prepared from 2-bromo-3-methoxynaphthalene (970 mg, 4.1 mmol) and magnesium (119 mg, 4.9 mmol) and reacted with 2-adamantanone (736 mg, 4.9 mmol) to afford 1.5 g of the crude product that was purified on a column of silica gel using CH_2Cl_2 as eluent to give the product (1.10 g, 87%) in the form of colorless crystals: mp 208−210 °C; IR (KBr) ν/cm^{-1} 3554 (s), 2902 (s), 2842 (m), 1630 (m), 1448 (m), 1217 (m), 1176 (m), 1001 (m), 742 (m); ^{1}H NMR ($CDCl_3$, 300 MHz) δ/ppm 7.86 (s, 1H), 7.76 (d, 1H, J = 8.0 Hz), 7.69 (d, 1H, J = 8.0 Hz), 7.42 (dt, 1H, J = 1.2 Hz, J = 8.0 Hz), 7.34 (dt, 1H, J = 1.2 Hz, J = 8.0 Hz), 7.17 (s, 1H), 3.97 (s, 3H, OCH_3), 3.56 (s, 1H, OH), 2.78 (br s, 2H), 2.55 (br s, 2H), 1.60−2.08 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ/ppm 156.4 (s), 134.2 (s), 133.0 (s), 128.3 (s), 127.9 (d), 127.6 (d), 126.2 (d), 125.8 (d), 123.8 (d), 106.4 (d), 76.7 (s), 55.0 (q), 37.9 (t), 35.5 (d, 2C), 35.3 (t, 2C), 33.1 (t, 2C), 27.3 (d), 26.9 (d); HRMS (MALDI) calcd for $C_{21}H_{24}O_2$ (+H$^+$ − H_2O) 291.1743, found 291.1742.

2-Benzyloxy-3-(2-hydroxy-2-adamantyl)naphthalene (5b). The Grignard reagent was prepared from 2-benzyloxy-3-bromonaphthalene (**12a**, 640 mg, 2.0 mmol) and magnesium (60 mg, 2.5 mmol) and reacted with 2-adamantanone (300 mg, 2.0 mmol) to afford 696 mg of the crude product that was purified on a column of silica gel using CH_2Cl_2 /hexane 7:3 and 9:1 as eluent to give the product (550 mg, 72%) in the form of colorless crystals: mp 182−183 °C; IR (KBr) ν/cm^{-1} 3537 (s), 2900 (s). 2854 (m), 1454 (m), 1215 (s), 1176 (s), 979 (m), 760 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.89 (s, 1H), 7.76 (d, 1H, J = 8.2 Hz), 7.67 (d, 1H, J = 8.0 Hz), 7.38−744 (m, 5H), 7.31−7.36 (m, 2H), 7.25 (s, 1H), 5.24 (s, 2H), 3.64 (s, 1H), 2.83 (br s, 2H), 2.48−2.56 (m, 2H), 1.77−1.98 (m, 6H), 1.73 (br s, 2H), 1.60−1.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 155.5 (s), 136.3 (s), 134.5 (s), 133.1 (s), 128.8 (d), 128.6 (s), 128.2 (d), 128.0 (d), 127.9 (d), 127.3 (d), 126.4 (d), 126.0 (d), 124.1 (d), 107.7 (d), 76.9 (s), 70.3 (t), 38.1 (t, 2C), 35.7 (d, 2C), 35.5 (t), 33.1 (t, 2C), 27.5 (d), 27.0 (d); HRMS (MALDI) calcd for $C_{27}H_{28}O_2$ (+Na$^+$) 407.1981, found 407.1988.

2-(2-Hydroxy-2-adamantyl)-6-methoxynaphthalene (6a). The Grignard reagent was prepared from 2-bromo-6-methoxynaphthalene (2.40 g, 10 mmol) and magnesium (264 mg, 11 mmol) and reacted with 2-adamantanone (1.5 g, 10 mmol) to afford 3.2 g of the crude product that was purified on a column of silica gel using CH_2Cl_2 as eluent to give the product (2.50 g, 81%) in the form of colorless crystals: mp 162−163 °C; IR (KBr) ν/cm^{-1} 3562 (s), 2931 (s), 2903 (s), 2852 (m), 1606 (m), 1479 (m), 1194 (m), 852 (m); ^{1}H NMR ($CDCl_3$, 300 MHz) δ/ppm 7.86 (d, 1H, J = 1.1 Hz), 7.68−7.76 (m, 2H), 7.63 (dd, 1H, J = 1.8 Hz, J = 8.8 Hz), 7.09−7.16 (m, 2H), 3.90 (s, 3H, OCH_3), 2.66 (br s, 2H), 2.47 (br s, 1H), 2.43 (br s, 1H), 1.92 (br s, 1H), 1.68−1.80 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ/ppm 157.7 (s), 140.4 (s), 136.6 (s), 129.6 (d), 128.8 (s), 127.2 (d), 124.2 (d), 124.1 (d), 118.6 (d), 105.3 (d), 75.6 (s), 55.2 (q), 37.6 (t), 35.7 (d, 2C), 34.9 (t, 2C), 32.9 (t, 2C), 27.4 (d), 26.9 (d); HRMS (MALDI) calcd for $C_{21}H_{24}O_2$ (+H$^+$ − H_2O) 291.1743, found 291.1731.

2-(2-Hydroxy-2-adamantyl)-7-methoxynaphthalene (8a). The Grignard reagent was prepared from 2-bromo-7-methoxynaphthalene (1.00 g, 4.2 mmol) and magnesium (130 mg, 5.4 mmol) and reacted with 2-adamantanone (740 mg, 4.9 mmol) to afford 1.4 g of the crude product that was purified on a column of silica gel using CH_2Cl_2 as eluent to give the product (1.15 g, 88%) in the form of colorless crystals: mp 135−136 °C; IR (KBr) ν/cm^{-1} 3522 (s), 2904 (s), 2845 (m), 1632 (m), 1464 (m), 1211 (m), 829 (m); ^{1}H NMR ($CDCl_3$, 300 MHz) δ/ppm 7.86 (s, 1H), 7.77 (d, 1H, J = 8.6 Hz), 7.70 (d, 1H, J = 9.6 Hz), 7.53 (dd, 1H, J = 1.6 Hz, J = 8.6 Hz), 7.10−7.15 (m, 2H), 3.91 (s, 3H, OCH_3), 2.68 (br s, 2H), 2.53 (br s, 1H), 2.48 (br s, 1H), 1.92 (br s, 1H), 1.70−1.80 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ/ppm 157.6 (s), 143.2 (s), 134.5 (s), 128.7 (d), 128.1 (d), 128.0 (s), 123.3 (d), 121.3 (d), 118.7 (d), 106.1 (d), 75.7 (s), 55.2 (q), 37.6 (t), 35.7 (d, 2C), 34.9 (t, 2C), 32.9 (t, 2C), 27.3 (d), 26.9 (d); HRMS (MALDI) calcd for $C_{21}H_{24}O_2$ (+H$^+$ − H_2O) 291.1743, found 291.1744.

2-Benzyloxy-7-(2-hydroxy-2-adamantyl)naphthalene (8b). The Grignard reagent was prepared from 2-benzyloxy-7-bromonaphthalene (**12b**, 1.44 g, 4.6 mmol) and magnesium (140 mg, 5.8 mmol) and reacted with 2-adamantanone (690 mg, 4.6 mmol) to afford 1.66 g of the crude product that was purified on a column of silica gel using CH_2Cl_2 as eluent to give the product (1.32 g, 75%) in the form of colorless crystals: mp 195−197 °C; IR (KBr) ν/cm^{-1} 3554 (m), 3440 (m), 2902 (s), 1629 (s), 1217 (s), 835 (s); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.83 (d, 1H, J = 1.9 Hz), 7.77 (d, 1H, J = 8.7 Hz), 7.71 (d, 1H, J = 9.6 Hz), 7.53 (dd, 1H, J = 8.7 Hz, J = 1.9 Hz), 7.46−7.49 (m, 2H), 7.37−7.41 (m, 2H), 7.31−7.35 (m, 1H), 7.20−7.23 (m, 2H), 5.17 (s, 2H), 2.67 (s, 2H), 2.46 (s, 1H), 2.45 (s, 1H), 1.92 (s,1H), 1.70−1.80 (m, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 156.9 (s), 143.3 (s), 136.9 (s), 134.6 (s), 128.9 (d), 128.6 (d), 128.3 (s), 128.2 (d), 128.0 (d), 127.5 (d), 123.5 (d), 121.5 (d), 119.2 (d), 107.7 (d), 75.8 (s), 70.1 (t), 37.7 (t), 35.8 (d, 2C), 35.0 (t, 2C), 33.0 (t, 2C), 27.5 (d), 27.0 (d); HRMS (MALDI) calcd for $C_{27}H_{28}O_2$ (+Na$^+$) 407.1981, found 407.1982.

1-Benzyloxy-5-(2-hydroxy-2-adamantyl)naphthalene (9b). The Grignard reagent was prepared from 1-benzyloxy-5-bromonaphthalene[47] (**12c**, 468 mg, 1.5 mmol) and magnesium (50 mg, 2 mmol) and reacted with 2-adamantanone (225 mg, 1.5 mmol) to afford 530 mg of the crude product that was purified on a column of silica gel using hexane/diethyl ether (9:1) as eluent to give the product (321 mg 56%) in the form of colorless crystals: mp 155−157 °C; IR (KBr) ν/

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cm^{-1} 3545 (m), 2893 (s), 2849 (m), 1256 (m), 1227 (m), 793 (s); ^1H NMR ($CDCl_3$, 600 MHz), δ/ppm 8.40 (d, 1H, J = 8.91 Hz), 8.35 (d, 1H, J = 8.27 Hz), 7.68 (dd, 1H, J = 7.32 Hz, J = 0.79 Hz), 7.49−7.54(m, 2H), 7.28−7.44 (m, 5H), 6.85 (d, 1H, J = 7.47 Hz), 5.22 (s, 2H), 2.62 (br s, 1H), 2.64 (br s, 1H), 1.89−1.97 (m, 2H, with a discernible singlet at 1.90), 1.65−1.80 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 155.0 (s), 140.2 (s), 137.4 (s), 132.8 (s), 128.7 (d), 128.0 (d), 127.8 (s), 127.5 (d), 125.9 (d), 124.6 (d), 123.8 (d), 122.4 (d), 120.7 (d), 104.7 (d), 78.2 (s), 70.3 (t), 38.0 (t), 27.8 (d), 27.1 (d); HRMS (MALDI) calcd for $C_{27}H_{28}O_2$ ($-e^-$) 384.2095, found 384.2096.

1-Benzyloxy-4-(2-hydroxy-2-adamantyl)naphthalene (10b). The Grignard reagent was prepared from 1-benzyloxy-4-bromonaphthalene[48] (**12d**, 850 mg, 2.7 mmol) and magnesium (100 mg, 4.2 mmol) and reacted with 2-adamantanone (408 mg, 2.7 mmol) to afford 1.0 g of the crude product that was purified on a column of silica gel using CH_2Cl_2/hexane 3:1 as eluent to give the product (609 mg, 58%) in the form of colorless crystals: mp 152−153 °C; IR (KBr) ν/cm^{-1} 3570 (s), 3444 (s), 2906 (s), 2854 (w), 1596 (w), 1363 (w), 1088 (w), 764 (m); ^1H NMR ($CDCl_3$, 600 MHz) δ/ppm 8.78−8.81 (m, 1H), 8.39−8.48 (m, 1H), 7.52−7.57 (m, 3H, with a discernible doublet at 7.55, J = 8.3 Hz), 7.41−7.49 (m, 4H), 7.35−7.38 (m, 1H), 6.79 (d, 1H, J = 8.3 Hz), 5.26 (s, 2H), 2.67 (br s, 1H), 2.65 (br s, 1H), 1.95 (br s, 1H), 1.85 (s, 1H), 1.70−1.82 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 153.9 (s), 137.0 (s), 132.8 (s), 132.6 (s), 128.5 (d), 127.8 (d), 127.5 (d), 127.3 (s), 127.2 (d), 125.2 (d), 125.1 (d), 124.4 (d), 122.6 (d), 103.1 (d), 77.8 (s), 69.9 (t), 37.9 (t), 27.7 (d), 26.9 (d); HRMS (MALDI) calcd for $C_{27}H_{28}O_2$ ($+Na^+$) 407.1981, found 407.1977.

1-(2-Adamantylidene)naphthalen-2(1*H*)-one (QM11). The reaction was carried out in a three-neck flask (100 mL) equipped with a N_2 inlet and a septum. The flask was charged with dry THF (30 mL) and *n*-BuLi (4 mL, 2.5 M solution in hexane). The mixture was cooled to 0 °C. To the cooled solution of BuLi, by use of a syringe, was added a solution of 1-bromo-2-hydroxynaphthalene (1.0 g, 4.5 mmol) in THF (10 mL). After being stirred for 5−10 min at 0 °C, the reaction mixture was cooled to −78 °C, and solution of 2-adamantanone (0.67 g, 4.5 mmol) in THF (10 mL) was added dropvise. After being stirred at −78 °C for 1 h, the reaction mixture was allowed to reach rt overnight. The next day, saturated aqueous solution of NH_4Cl (50 mL) was added, and extractions with diethyl ether (3 × 50 mL) were carried out. The extracts were dried over anhydrous $MgSO_4$. After filtration and evaporation of the solvent 1.5 g of the crude product was obtained that was purified on a column of silica gel using CH_2Cl_2 to afford 600 mg (48%) of the pure product in the form of yellow crystals: mp 158−160 °C; IR (KBr) ν/cm^{-1} 2908 (s), 2847 (m), 1639 (s), 1556 (m), 837 (m); ^1H NMR (DMSO-d_6, 600 MHz) δ/ppm 7.48−7.52 (m, 2H), 7.30−7.37 (m, 3H), 6.22 (d, 1H, J = 9.8 Hz), 4.10 (br s, 1H), 3.43 (br s, 1H), 1.94−2.02 (m, 6H), 1.84−1.90 (m, 4H), 1.77 (d, 2H, J = 12.2 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ/ppm 192.2 (s), 165.4 (s), 141.2 (d), 133.9 (s), 130.4 (s), 125.6 (d), 128.2 (d), 128.0 (d), 127.8 (d), 127.6 (s), 127.0 (d), 39.7 (t), 39.3 (t), 36.0 (t), 34.5 (d), 31.4 (d), 26.9 (d, 2C); HRMS (MALDI) calcd for $C_{20}H_{20}O$ ($+H^+$) 277.1587, found 277.1595.

General Procedure for the Removal of the Methyl Groups from Naphthols with BBr_3. The reaction was carried out under N_2 atmosphere in a three-neck, round-bottom flask (250 mL) equipped with a septum and a syringe. In the flask was placed methoxynaphthalene derivative (10 mmol) dissolved in dry CH_2Cl_2 (100 mL) and the solution cooled to 0 °C by ice bath. To the cold solution, by use of a syringe, was added dropwise a solution of BBr_3 in CH_2Cl_2 (1 M, 30 mL) during 1 h. After the addition was completed, the stirring was continued 1 h at 0 °C and at rt overnight. The next day, to the reaction mixture was added cold water (100 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL) and ethyl acetate (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, solid was removed by filtration, and solvent was removed on a rotary evaporator. The obtained crude product was purified on a column filled with silica gel by use of CH_2Cl_2 and CH_2Cl_2−EtOAc (4:1) as eluent.

2-(2-Hydroxy-2-adamantyl)-3-hydroxynaphthalene (5). From 2-(2-hydroxy-2-adamantyl)-3-methoxynaphthalene (**5a**, 650 mg, 2.1 mmol) and solution of BBr_3 (1 M, 8 mL), the reaction gave 630 mg of the crude product that was purified by column filled with silica gel by use of CH_2Cl_2 and CH_2Cl_2−EtOAc to afford 400 mg (64%) of the pure product in a form of colorless crystals: mp 226−228 °C; IR (KBr) ν/cm^{-1} 3485 (s), 3105 (s), 2902 (s), 2854 (m), 1633 (m), 1225 (s), 995 (s), 746 (s); ^1H NMR (DMSO-d_6, 600 MHz) δ/ppm 9.69 (s, 1H, OH), 7.85 (s, 1H), 7.80 (d, 1H, J = 8.1 Hz), 7.63 (d, 1H, J = 8.1 Hz), 7.36 (t, 1H, J = 8.1 Hz), 7.25 (t, 1H, J = 8.1 Hz), 7.16 (s, 1H), 5.07 (s, 1H, OH), 2.76 (br s, 2H), 2.50 (br s, 1H, covered by DMSO), 2.47 (br s, 1H), 1.80−1.85 (m, 3H), 1.72−1.80 (m, 3H), 1.67 (br s, 2H), 1.57 (d, 2H, J = 11.6 Hz); ^{13}C NMR (DMSO-d_6, 150 MHz) δ/ppm 154.7 (s), 133.8 (s), 133.1 (s), 127.9 (d), 127.4 (s), 126.8 (d), 125.9 (d), 125.0 (d), 122.7 (d), 110.5 (d), 75.9 (s), 37.6 (t), 35.0 (t, 2C), 34.8 (d, 2C), 32.7 (t, 2C), 26.8 (d), 26.4 (d); HRMS (MALDI) calcd for $C_{20}H_{22}O_2$ ($+H^+ - H_2O$) 277.1587, found 277.1600.

2-(2-Hydroxy-2-adamantyl)-6-hydroxynaphthalene (6). From 2-(2-hydroxy-2-adamantyl)-6-methoxynaphthalene (**6a**, 1.50 g, 4.8 mmol) and a solution of BBr_3 (1 M, 15 mL), the reaction gave 1.5 g of the crude product that was purified by crystallization from ethyl acetate to afford 880 mg (62%) of the pure product in a form of colorless crystals: mp 196−198 °C; IR (KBr) ν/cm^{-1} 3456 (m), 3238 (m), 2902 (s), 2854 (m), 1604 (m), 1217 (m), 997 (m), 871 (m); ^1H NMR (DMSO-d_6, 300 MHz) δ/ppm 9.63 (s, 1H, OH), 7.80 (br s, 1H), 7.74 (d, 1H, J = 8.6 Hz), 7.63 (d, 1H, J = 8.8 Hz), 7.53 (dd, 1H, J = 1.2 Hz, J = 8.8 Hz), 7.01−7.08 (m, 2H), 4.57 (s, 1H, OH), 2.57 (br s, 2H), 2.44 (br s, 1H), 2.40 (br s, 1H), 1.82 (br s, 1H), 1.45−1.65 (m, 9H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ/ppm 155.1 (s), 140.3 (s), 133.3 (s), 129.6 (d), 127.6 (s), 125.8 (d), 124.7 (d), 124.0 (d), 118.3 (d), 108.2 (d), 73.6 (s), 37.5 (t), 34.9 (d, 2C), 34.5 (t, 2C), 32.6 (t, 2C), 27.0 (d), 26.6 (d); HRMS (MALDI) calcd for $C_{20}H_{22}O_2$ ($+H^+ - H_2O$) 277.1587, found 277.1599.

2-(2-Hydroxy-2-adamantyl)-7-hydroxynaphthalene (8). From 2-(2-hydroxy-2-adamantyl)-7-methoxynaphthalene (**8a**, 650 mg, 2.1 mmol) and solution of BBr_3 (1 M, 8 mL), the reaction gave 660 mg of the crude product that was purified by crystallization from ethyl acetate to afford 390 mg (63%) of the pure product in a form of colorless crystals: mp 250−252 °C; IR (KBr) ν/cm^{-1} 3515 (s), 3240 (s), 2914 (s) 1629 (m), 1211 (s), 1003 (m); ^1H NMR (DMSO-d_6, 300 MHz) δ/ppm 7.66−7.74 (m, 3H), 7.40 (d, 1H, J = 8.8 Hz), 7.11 (d, 1H, J = 2.2 Hz), 7.03 (dd, 1H, J = 2.2 Hz, J = 8.7 Hz), 2.58 (br s, 2H), 2.44 (br s, 1H), 2.40 (br s, 1H), 1.82 (br s, 1H), 1.56−1.72 (m, 9H), OH signals were not seen; ^{13}C NMR (DMSO-d_6, 75 MHz) δ/ppm 155.2 (s), 143.8 (s), 134.6 (s), 128.6 (d), 127.3 (d), 126.5 (s), 122.5 (d), 121.2 (d), 118.2 (d), 109.1 (d), 73.7 (s), 37.5 (t), 34.9 (d, 2C), 34.4 (t, 2C), 32.6 (t, 2C), 27.0 (d), 26.6 (d); HRMS (MALDI) calculated for $C_{20}H_{22}O_2$ ($+H^+ - H_2O$) 277.1587, found 277.1582.

General Procedure for the Removal of the Benzyl Group. The benzyl derivative (1 mmol) was dissolved in a mixture of THF (10 mL) and methanol (0.5 mL) and placed in a vessel for hydrogenation. Palladium catalyst (5% Pd/C, 40 mg) and pyridine (20 μL) were added. The reaction mixture was hydrogenated in a Paar apparatus under pressure of 49 psi (3 atm) for 4−48 h, and followed by TLC, until all benzyl derivative was transformed to naphthol. The reaction mixture was filtered to remove the catalyst, and the solvent was removed on a rotary evaporator. The crude product was purified on a column filled with silica gel by use of CH_2Cl_2 or hexane/diethyl ether mixture (3:2) as eluent.

Hydrogenation of 2-Benzyloxy-3-(2-hydroxy-2-adamantyl)-naphthalene (5b). 2-Benzyloxy-3-(2-hydroxy-2-adamantyl)-naphthalene (**5b**, 270 mg, 0.70 mmol) was dissolved in a mixture of THF, CH_3OH, and pyridine (10 mL, 0.5 mL, and 20 μL, respectively) and hydrogenated during 34 h to furnish 200 mg (97%) of the pure product **5**.

Hydrogenation of 2-Benzyloxy-7-(2-hydroxy-2-adamantyl)-naphthalene (8b). 2-Benzyloxy-7-(2-hydroxy-2-adamantyl)-naphthalene (**8b**, 342 mg, 0.9 mmol) was dissolved in a mixture of THF, CH_3OH, and pyridine (10 mL, 0.5 mL, and 20 μL, respectively)

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and hydrogenated during 48 h to furnish 256 mg (97%) of the crude product. Obtained crude product was purified on a column filled with silica gel by use of CH_2Cl_2 with THF (0→10%) as eluent giving 160 mg (60%) of the pure product **8**.

Hydrogenation of 1-Benzyloxy-5-(2-hydroxy-2-adamantyl)-naphthalene (9b). 1-Benzyloxy-5-(2-hydroxy-2-adamantyl)-naphthalene (**9b**, 176 mg, 0.46 mmol) was dissolved in a mixture of THF, CH_3OH, and pyridine (10 mL, 0.5 mL, and 20 μL, respectively) and hydrogenated during 4 h to furnish 140 mg of the crude product that was purified on a column of silica gel by use of hexane/ether 3:2 to afford pure product **9** (111 mg, 82%): mp 218−220 °C; IR (KBr) ν/cm^{-1} 3518 (m), 3230 (s), 2914 (s), 1599 (m), 1279 (s), 783 (s);^{1}H NMR (CD_3OD, 600 MHz) δ/ppm 8.26 (d, 1H, J = 8.8 Hz), 8.17 (d, 1H, J = 8.5 Hz), 7.65 (d, 1H, J = 7.4 Hz), 7.32 (dd, 1H, J = 8.2, J = 7.5 Hz), 7.16 (dd, 1H, J = 8.8, J = 7.5 Hz), 6.75 (d, 1H, J = 7.5 Hz), 2.70 (s, 1H), 2.69 (s, 1H), 1.87 (br s,1H), 1.62−1.81 (m, 6H); ^{13}C NMR (CD_3OD, 150 MHz) δ/ppm 154.7 (s), 141.4 (s), 134.4 (s), 128.3 (s), 126.7 (d), 125.3 (d), 123.8 (d), 122.9 (d), 120.6 (d), 108.0 (d), 78.7 (s), 39.2 (t), 29.3 (d), 28.6 (d); HRMS (MALDI) calcd for $C_{20}H_{22}O_2$ (+Na$^+$) 317.1512, found 317.1512.

Hydrogenation of 1-Benzyloxy-4-(2-hydroxy-2-adamantyl)-naphthalene (10b). 1-Benzyloxy-4-(2-hydroxy-2-adamantyl)-naphthalene (**10b**, 520 mg, 1.35 mmol) was dissolved in THF (50 mL) and hydrogenated during 48 h at 48 psi. The obtained crude product was purified on a column filled with silica gel by use of THF (0→10%) in CH_2Cl_2 as eluent. Pure compound was identified as **QM10** (311 mg 83%).

4-(2-Adamantylidene)naphthalene-1(4*H*)-one (QM10): yellow crystals; mp 152−153 °C; IR (KBr) ν/cm^{-1} 2918 (s), 2850 (m), 1630 (s), 1595 (s), 1540 (s), 1305 (m), 958 (w), 756 (m); ^{1}H NMR (DMSO-d_6, 600 MHz) δ/ppm 8.14 (d, 1H, J = 10.3 Hz), 8.04 (dd, 1H,J = 7.8 Hz, J = 1.4 Hz), 7.71 (d, 1H, J = 7.8 Hz), 7.64 (dt, 1H, J = 1.3 Hz, J = 8.0 Hz), 7.51 (dt, 1H, J = 0.9 Hz, J = 7.4 Hz), 6.3 (d, 1H, J = 10.3 Hz), 3.73 (s, 1H), 3.61 (s, 1H), 1.85 − 2.17 (m. 12H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ/ppm 183.9 (s), 168.3 (s), 139.4 (d), 135.6 (s), 132.0 (s), 130.6 (d), 127.6 (d), 127.2 (d) 125.7 (d), 123.8 (d), 123.0 (s), 39.7 (t, 2C), 39.5 (t, 2C), 37.2 (d), 35.9 (t), 35.3 (d), 27.7 (d, 2C); HRMS (MALDI) calcd for $C_{20}H_{20}O_2$ (+ H$^+$) 277.1587, founded 277.1583.

2-(2-Azido-2-adamantyl)-6-hydroxynaphthalene (13). A two-neck flask (50 mL) was charged with sodium azide (130 mg, 2.0 mmol) and $CHCl_3$ (6 mL). The obtained suspension was cooled in a salt−ice bath, and by use of a syringe, and TFA (375 μL, 5 mmol) was slowly added. After 10 min of stirring, a suspension of alcohol **6** (294 mg, 1.0 mmol) in $CHCl_3$ (5 mL) was added. The reaction mixture was stirred at −5 °C for 4 h and at rt overnight. To the reaction mixture was added aqueous ammonia (10 mL, 15%), and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (2 × 10 mL), The combined extracts were dried over anhydrous $MgSO_4$, the solution was filtered, and solvent was removed on a rotary evaporator to furnish crude azide that was purified on a column of silica gel by use 20% EtOAc in CH_2Cl_2 as as eluent to afford pure product (287 mg, 90%) in a form of pale yellow crystals: mp 134−135 °C; IR (KBr) ν/cm^{-1} 3446 (s), 2920 (m), 2089 (m), 1635 (w), 1238 (w); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 7.82 (d, 1H, J = 1.8 Hz), 7.76 (d, 1H, J = 8.9 Hz), 7.72 (d, 1H, J = 8.9 Hz), 7.54 (dd, 1H, J = 1.8 Hz, J = 8.9 Hz), 7.14 (d, 1H, J = 2.5 Hz), 7.11 (dd, 1H, J = 2.5 Hz, J = 8.9 Hz), 5.04 (s, 1H), 2.75 (s, 2H), 2.37 (s, 1H), 2.34 (s, 1H), 1.97 (br s, 1H), 1.72−1.86 (m, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 154.0 (s), 135.5 (s), 134.0 (s), 130.5 (d), 128.8 (s), 127.3 (d), 124.9 (d), 124.3 (d), 118.2 (d), 109.3 (d), 37.8 (t), 34.2 (t), 33.5 (t), 33.4 (d), 27.5 (d), 26.9 (d); HRMS (MALDI) calcd for $C_{20}H_{21}N_3O$ (+Na$^+$) 342.1577, found 342.1577.

2-(2-Amino-2-adamantyl)-6-hydroxynaphthalene Hydrochloride (7). A two-neck flask (100 mL) equipped with a condenser was charged with an absolute ethanol solution (10 mL) of azide **13** (287 mg, 0.9 mmol). To the solution was added a suspension of freshly activated Raney Ni (∼2.5 g). The suspension was heated at ∼70 °C overnight. The next day, the reaction mixture was filtered to remove the Raney Ni, and the ethanol solution was evaporated to afford 259 mg of the crude amine. The solid was washed with hexane and ethyl acetate and used in the next step without purification. The amine was dissolved in dry ethyl ether (50 mL) and purged with HCl during 30 min, whereupon a colorless precipitate formed. The precipitate was filtered through a sinter funnel, washed with ether and CH_2Cl_2, and dried in vacuum to afford pure product (56 mg, 19%): colorless crystals; mp 256−258 °C; IR (KBr) ν/cm^{-1} 3196 (m), 3036 (m), 2920 (s), 1605 (m), 1508 (m), 1198 (m); ^{1}H NMR (DMSO-d_6, 300 MHz) δ/ppm 9.92 (s, 1H), 8.12 (br s, 3H), 7.98 (br s, 1H), 7.75−7.85 (m, 2H), 7.56−7.62 (m, 1H), 7.11−7.16 (m, 2H), 2.86 (br s, 2H), 2.34 (br s, 1H), 2.29 (br s, 1H), 1.63−1.97 (m, 10H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ/ppm 156.1 (s), 134.1 (s), 132.6 (s), 129.9 (d), 127.3 (s), 126.4 (d), 126.3 (s), 124.0 (d), 119.0 (d), 108.2 (d), 61.2 (s), 37.2 (t), 33.3 (t, 2C), 31.8 (d, 2C), 31.0 (t, 2C), 26.3 (d), 25.8 (d); HRMS (MALDI) calcd for $C_{20}H_{24}ClNO$ (+H$^+$ − NH_4Cl) 277.1587, found 277.1579.

Reaction of QM in the Presence of Acid: General Procedure. A mixture of **QM11** or **QM10** (83 mg, 0.3 mmol), CH_3CN (8 mL), H_2O (2 mL), and H_2SO_4 (2 drops) was refluxed for 3 days. After being cooled to rt, the reaction mixture was poured into cold water, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$. The solution was filtered and the solvent was removed on a rotary evaporator to furnish a crude mixture of products that was chromatographed on silica gel using hexane/ether (3:2) as eluent.

QM10 furnished after column chromatography starting **QM10** (42 mg, 0.15 mmol), adamantan-2-one (22 mg, 0.15 mmol), and α-naphthol (21 mg, 0.15 mmol).

QM11 furnished after column chromatography protoadamantane derivative **14** (18 mg, 0.06 mmol), starting **QM11** (5 mg, 0.02 mmol), adamantan-2-one (25 mg, 0.17 mmol), and β-naphthol (26 mg, 0.18 mmol).

3-(*H*-*endo*)-2-Oxahexacyclo[9.8.0.1^{5,9}. 1^{7,10}.0^{3,10}.0^{12,17}]-unicosa-11,13,15,17,19-pentaene (14): colorless crystals; mp 118−119 °C; IR (KBr) ν/cm^{-1} 2939 (s), 1585 (m), 1454 (m), 1252 (s), 976 (s) 812 (s), 752 (m); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 8.02 (d, 1H, J = 8.1 Hz), 7.78 (d, 1H, J = 8.1 Hz), 7.61 (d, 1H, J = 8.6 Hz), 7.37−742 (m, 1H), 7.24−7.29 (m, 1H), 7.15 (d, 1H, J = 8.6 Hz), 4.85 (d, 1H, J = 9.5 Hz), 3.16−3.21 (m, 1H), 2.5 (br s, 1H), 2.27−2.35 (m, 2H), 2.17−2.23 (m, 1H), 2.07−2.12 (m, 1H), 1.97−2.04 (m, 2H), 1.83−1.89 (m, 1H), 1.64−1.69 (m, 2H), 1.49−1.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 157.8 (s), 130.3 (s), 130.2 (s), 129.3 (d), 128.6 (s), 128.3 (d), 126.0 (d), 122.5 (d), 121.6 (d), 112.7 (d), 89.6 (d), 53.3 (s), 43.9 (t), 43.07 (t), 43.05 (d), 37.9 (t), 36.5 (d), 35.3 (t), 34.0 (t), 26.7 (d); HRMS (MALDI) calcd for $C_{20}H_{20}O$ 276.1509, found 276.1519.

Photochemical Experiments: General Method. In a quartz vessel was placed a CH_3OH or CH_3OH−H_2O (3:1 or 4:1) solution (100 mL, c ∼10^{-3} M) of naphthalene derivatives **5**−**9** (20−100 mg) and the solution irradiated in a Rayonet reactor using 16 lamps (1 lamp −8 W, with the output at 254 or 300 nm) for 1 min to 1 h. Prior to, and during the irradiation, the solution was continuously purged with a stream of Ar and cooled by a coldfinger condenser. After irradiation, CH_3OH was removed on a rotary evaporator and the residue (if irradiated in CH_3OH−H_2O) extracted with EtOAc (3 × 75 mL). Extracts were dried over anhydrous $MgSO_4$, filtered and solvent was removed on a rotary evaporator. The residue was chromatographed on a TLC using CH_2Cl_2−EtOAc (30%) as eluens.

Irradiation of **5** (15 mg, 0.051 mmol) in CH_3OH (100 mL) for 15 min gave after evaporation of the methanol crude mixture that was pure enough for the characterization.

2-Hydroxy-3-(2-methoxy-2-adamantyl)naphthalene (5c): mp 148−150 °C; IR (KBr) ν/cm^{-1} 3305 (s), 2901 (s), 2854 (m), 1637 (m), 1504 (m), 1458 (m), 1290 (m), 1163 (m), 1041 (m), 872 (m), 742 (m); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 8.32 (s, 1H, OH), 7.80 (s, 1H), 7.73 (dd, 1H, J = 0.6 Hz, J = 8.0 Hz), 7.66 (dd, 1H, J = 0.6 Hz, J = 8.0 Hz), 7.39 (dt, 1H, J = 1.2 Hz, J = 8.0 Hz), 7.29 (dt, 1H, J = 1.2 Hz, J = 8.0 Hz), 7.24 (s, 1H, covered by $CDCl_3$), 3.04 (s, 3H, OCH_3), 2.73 (br s, 2H), 2.54 (br s, 1H), 2.51 (br s, 1H), 2.23 (dd, 1H, J = 2.0

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Hz, J = 12.0 Hz), 2.04 (ddd, 1H, J = 2.8 Hz, J = 2.9 Hz, J = 12.8 Hz), 1.90 (br s, 1H), 1.83 (br s, 1H), 1.70−1.74 (m, 2H), 1.69 (ddd, 1H, J = 2.6 Hz, J = 2.8 Hz, J = 12.8 Hz), 1.64 (ddd, 1H, J = 2.6 Hz, J = 2.8 Hz, J = 12.8 Hz), 1.59 (ddd, 1H, J = 2.6 Hz, J = 2.8 Hz, J = 12.8 Hz), 1.35 (d, 1H, J = 12.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ/ppm 154.1 (s), 134.1 (s), 129.4 (d), 128.8 (s), 127.7 (d), 127.6 (s), 126.3 (d), 125.8 (d), 123.2 (d), 111.9 (d), 83.8 (s), 48.7 (q), 37.6 (t), 36.2 (t), 35.3 (d), 34.2 (t), 33.1 (t), 32.5 (t), 30.7 (d), 27.1 (d), 26.7 (d); HRMS (MALDI) calcd for $C_{21}H_{24}O_2$ (+K^+) 347.1408, found 347.1394.

Irradiation of **6** (30 mg, 0.10 mmol) in CH_3OH (100 mL) for 1 h gave after evaporation of the methanol crude mixture that contained 15% of the product (according to NMR). Separation attempt on TLC using CH_2Cl_2−EtOAc (5%) afforded the starting material.

The pure product **6c** was obtained by stirring **6** (50 mg) in CH_3OH (50 mL) in the presence of H_2SO_4 (200 mg) overnight. After the conversion was completed, as indicated by HPLC analysis, to the solution $NaHCO_3$ was added (1.0 g), and stirring was continued over 1 h. The mixture was filtered and the solvent evaporated. The remaining solid was extracted by ethyl acetate to afford the pure product (35 mg, 65%).

2-Hydroxy-6-(2-methoxy-2-adamantyl)naphthalene (6c): mp 195−197 °C; IR (KBr) ν/cm^{-1} 3232 (m), 2930 (s), 2856 (m), 1639 (m), 1290 (m), 1047 (m), 893 (m); ^{1}H NMR (DMSO-d_6, 300 MHz) δ/ppm 7.82 (s, 1H), 7.78 (d, 1H, J = 8.5 Hz), 7.65 (d, 1H, J = 8.6 Hz), 7.47 (d, 1H, J = 8.6 Hz), 7.04−7.10 (m, 2H), 2.70 (br s, 2H), 2.68 (s, 3H, OCH_3), 2.28 (br s, 1H), 2.24 (br s, 1H), 1.85 (br s, 1H), 1.55−1.80 (m, 9H), OH signal was not observed; ^{13}C NMR (DMSO-d_6, 75 MHz) δ/ppm 155.7 (s), 134.4 (s), 133.7 (s), 129.7 (d), 127.0 (s), 126.5 (d), 125.9 (d), 125.1 (d), 118.6 (d), 108.2 (d), 79.3 (s), 47.5 (q), 37.2 (t), 34.2 (d, t, 4C), 32.4 (t, 2C), 27.1 (d), 26.3 (d); HRMS (MALDI) calcd for $C_{21}H_{24}O_2$ (+Na^+) 331.1668, found 331.1676.

Irradiation of **8** (40 mg, 0.10 mmol) in CH_3OH (100 mL) for 15 min gave after evaporation of the methanol crude mixture that contained 30% of the product (according to NMR). Attempt of separation on a TLC using CH_2Cl_2−EtOAc (5%) afforded the starting material.

The pure product **8c** was obtained by stirring **8** (50 mg) in CH_3OH (50 mL) in the presence of H_2SO_4 (200 mg) overnight. After the conversion was completed, as indicated by HPLC analysis, to the solution was added $NaHCO_3$ (1.0 g), and stirring was continued over 1 h. The mixture was filtered and the solvent evaporated. The remaining solid was extracted by ethyl acetate to afford the pure product (35 mg, 65%).

2-Hydroxy-7-(2-methoxy-2-adamantyl)naphthalene (8c): mp 118−120 °C; IR (KBr) ν/cm^{-1} 3417 (m), 2908 (s), 2852 (m), 1630 (m), 1448 (m), 1207 (m); ^{1}H NMR (DMSO-d_6, 300 MHz) δ/ppm 7.70 (d, 1H, J = 8.6 Hz), 7.67 (d, 1H, J = 8.6 Hz), 7.66 (br s, 1H), 7.29 (dd, 1H, J = 1.5 Hz, J = 8.6 Hz), 7.11 (d, 1H, J = 2.3 Hz), 7.06 (dd, 1H, J = 2.3 Hz, J = 8.6 Hz), 2.68 (s, 3H, OCH_3), 2.67 (br s, 2H), 2.27 (br s, 1H), 2.23 (br s, 1H), 1.84 (br s, 1H), 1.55−1.75 (m, 9H), OH signal was not observed; ^{13}C NMR (DMSO-d_6, 75 MHz) δ/ppm 156.8 (s), 137.8 (s), 134.3 (s), 128.4 (d), 127.4 (d), 126.3 (s), 124.8 (d), 121.1 (d), 119.3 (d), 109.2 (d), 79.4 (s), 47.6 (q), 37.2 (t), 34.2 (d, t, 4C), 32.4 (t, 2C), 27.1 (d), 26.3 (d); HRMS (MALDI) calcd for $C_{21}H_{24}O_2$ (+Na^+) 331.1668, found 331.1668.

Irradiation of **9** (40 mg, 0.14 mmol) in CH_3OH−H_2O (9:1, 100 mL) for 15 min gave after evaporation of the solvent crude mixture that was purified on a TLC using CH_2Cl_2 to afford 30 mg (72%) of the pure product.

1-Hydroxy-5-(2-methoxy-2-adamantyl)naphthalene (9c): 156−158 °C; IR (KBr) ν/cm^{-1} 3294 (m), 2916 (s), 2858 (m), 1595 (m), 1269 (m), 783 (m); ^{1}H NMR ($CDCl_3$, 600 MHz) δ/ppm 8.43 (dd, 1H, J = 0.6 Hz, J = 8.8 Hz), 8.18 (dt, 1H, J = 8.3 Hz, J = 1.0 Hz), 7.62 (d, 1H, J = 7.1 Hz), 7.40 (dd, 1H, J = 7.1 Hz, J = 8.3 Hz), 7.21 (dd, 1H, J = 7.3 Hz, J = 8.8 Hz), 6.76 (dd, 1H, J = 0.6 Hz, J = 7.3 Hz), 3.12 (br s, 1H), 2.89 (s, 3H, OCH_3), 2.92 (br s, 1H), 2.71 (d, 1H, J = 12.2 Hz), 2.64 (d, 1H, J = 12.2 Hz), 2.36−2.42 (m, 2H), 1.90−1.98 (m, 2H), 1.68−1.80 (m, 3H), 1.58 (dq, 1H, J = 12.1 Hz, J = 2.5 Hz), 1.47 (dq, 1H, J = 13.1 Hz, J = 3.0 Hz), 1.09 (dq, 1H, J = 13.1 Hz, J = 2.1 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm 151.6 (s), 136.8 (s), 133.1 (s), 128.5 (d), 126.0 (s), 124.3 (d), 123.1 (d), 121.5 (d), 120.3 (d), 107.8 (d), 82.8 (s), 48.3 (q), 37.9 (t), 37.2 (d), 36.0 (t), 34.0 (t), 33.6 (t), 32.9 (t), 31.4 (d), 27.8 (d), 27.0 (d); HRMS (MALDI) calcd for $C_{21}H_{24}O_2$ (+K^+) 347.1408, found 347.1399.

Irradiation in the Presence of Ethanolamine. Naphthol derivative **5** (50 mg, 0.17 mmol) was dissolved in CH_3CN−H_2O (3:1, 100 mL). To the solution was added ethanolamine (150 mg, 2.45 mmol). The solution was purged with Ar for 30 min and irradiated in a Rayonet reactor at 254 nm for 5 min. After the irradiation, H_2O (100 mL) was added, and the extractions with ethyl acetate (3 × 75 mL) were carried out. The extracts were dried over anhydrous $MgSO_4$, the solution was filtered, and the solvent was removed on a rotary evaporator. The residue was chromatographed on a TLC using CH_2Cl_2/ethyl acetate (20%) as eluent to afford pure product **15** (34 mg, 59%) in a form of yellowish crystals.

2-[2-(2-Hydroxyethylamino)-2-adamantyl]-3-hydroxynaphthalene (15): mp 134−135 °C; IR (KBr) ν/cm^{-1} 3381 (m), 2914 (s), 28587 (m), 1631 (m), 1454 (m), 738 (m); ^{1}H NMR (DMSO-d_6, 600 MHz) δ/ppm 11.60 (br s, 1H), 7.79 (d, 1H, J = 7.3 Hz), 7.78 (s, 1H), 7.61 (d, 1H, J = 8.0 Hz), 7.35 (ddd, 1H, J = 1.1 Hz, J = 7.3 Hz, J = 8.0 Hz), 7.23 (ddd, 1H, J = 1.1 Hz, J = 7.3 Hz, J = 8.0 Hz), 7.07 (s, 1H), 4.60 (br s, 1H), 3.34−3.40 (m, 2H), 2.76 (br s, 1H), 2.62 (br s, 1H), 2.50−2.54 (m, 2H), 2.37 (d, 1H, J = 13.0 Hz), 2.25 (d, 1H, J = 13.0 Hz), 1.85−1.95 (m, 3H), 1.76 (br s, 1H), 1.65−1.72 (m, 3H), 1.62 (dd, 1H, J = 13.0 Hz, J = 2.0 Hz), 1.57 (dd, 1H, J = 13.0 Hz, J = 3.0 Hz), 1.26 (d, 1H, J = 12.8 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ/ppm 155.6 (s), 133.3 (s), 131.1 (s), 128.9 (d), 127.8 (d), 127.0 (s), 125.8 (d), 125.1 (d), 122.4 (d), 110.5 (d), 62.4 (s), 60.4 (t), 42.8 (t), 37.9 (t), 34.9 (t), 34.1 (t), 33.7 (d), 31.9 (t), 31.8 (t), 30.1 (d), 27.0 (d), 26.2 (d); HRMS (MALDI) calculated for $C_{22}H_{27}NO_2$ (+Na^+) 360.1934, found 360.1933.

Irradiation in CH_3CN−D_2O. To a solution of **9** (5 mg, 0.017 mmol) in CH_3CN (12 mL) was added D_2O (3 mL). The solution was purged with Ar for 30 min and irradiated in a Luzchem reacator at 300 nm (8 lamps) for 20 min. After the irradiation, H_2O (30 mL) was added, and the extractions with EtOAc (3 × 25 mL) were carried out. The extracts were dried over anhydrous $MgSO_4$. After filtration and evaporation of the solvent, the crude mixture was analyzed by NMR and MS: MS (ESI) 37% D, 7% 2D.

Quantum Yields for the Photomethanolysis Reaction. Solutions of **5**−**9** in CH_3OH−H_2O (4:1) as well as a solution of valerophenone in CH_3CN−H_2O (1:1) were freshly prepared and their concentrations adjusted to have absorbances 0.4−0.8 at 254 nm. After adjustment of the concentration and measurement of the corresponding UV−vis spectra the solutions were filled in quartz cuvettes (15 mL), purged with a stream of N_2 (20 min each), and sealed with a septum. The cuvettes were irradiated at the same time in a Luzchem reactor equipped with a merry-go-round and two lamps with the output at 254 nm for 0.5, 1, 2, 5, 10, and 15 min. After each irradiation, the samples were taken from the cuvettes by use of a syringe and analyzed by HPLC. Quantum yields for the methanolysis were calculated using valerophenone actinometer (formation of acetophenone in aqueous media, Φ = 0.65 ± 0.03).[28]

Antiproliferative Investigation. Cells (HCT 116, MCF-7, and H 460) were cultured as monolayers and maintained in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 2 mM L-glutamine, 100 U/mL of penicillin, and 100 μg/mL of streptomycin in a humidified atmosphere with 5% CO_2 at 37 °C. The cells were inoculated in parallel on two 96-well microtiter plates on day 0, at 1.5 × 10^4 cells/mL (HCT 116 and H 460), and at 2 × 10^4 cells/mL (MCF-7). Test agents were added in 10-fold dilutions (10^{-8} to 10^{-4} M) on the next day and incubated for a further 72 h. Working dilutions were freshly prepared on the day of testing. One of the plates was left in the dark, while the other was irradiated in a Luzchem reactor (6 lamps 300 nm, 1 min) 4, 28, and 52 h after the addition of the compounds. After 72 h of incubation, the cell growth rate was evaluated by performing the MTT assay[46] which detects dehydrogenase activity in viable cells. The absorbance (A) was

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measured on a microplate reader at 570 nm. Each test was performed in quadruplicate in at least two individual experiments.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures, data obtained by fluorescence measurements, LFP, B3LYP calculations, ^{1}H and ^{13}C NMR spectra, and crystallographic data (collection and structure refinement data, details on crystal structures CCDC nos. 865242−865244). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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