Synthesis and Cytotoxic and Antiplatelet Activities of Dibenzofuran- and Carbazole-Substituted Oximes

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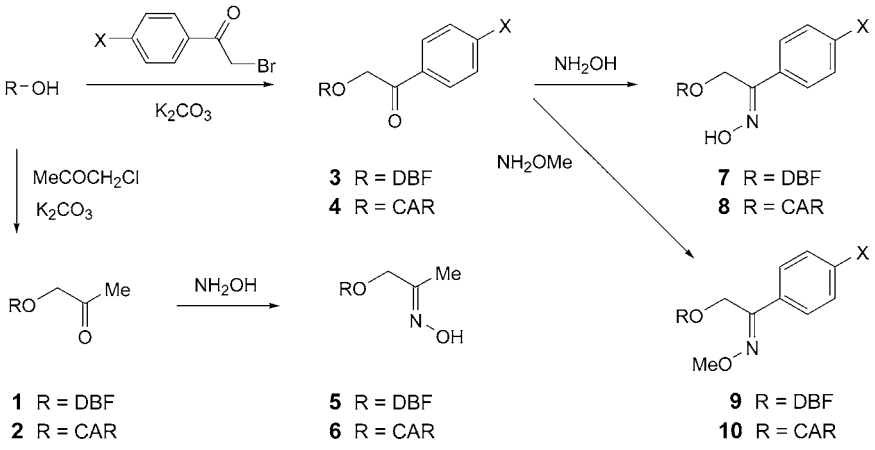
The dibenzofuran- and carbazole-substituted oximes or methyloximes **5**–**10** were prepared and evaluated for their cytotoxic and antiplatelet activities. These compounds were synthesized *via* alkylation of dibenzofuran-2-ol or 9*H*-carbazol-2-ol with α-halocarbonyl reagents, followed by reaction with NH_2OH or NH_2OMe (*Scheme*). A preliminary anticancer assay indicated that the oxime-type dibenzofuran derivatives **5** and **7a**–**d** are active, while the corresponding oxime ethers **9b** and **9c** are inactive at the same concentration. Therefore, a H-bond-donating group seems to be crucial for cytotoxicity. Among the compounds tested, 2-[(dibenzo[*b*,*d*]-furan-2-yl)oxy]-1-(4-methoxyphenyl)ethan-1-one *O*-methyloxime (**9c**) exhibited potent inhibitory activity against platelet aggregation induced by arachidonic acid, with an IC_{50} value of 14.87 μM, without being cytotoxic at a concentration of 100 μM.

1. Introduction. – Although DNA intercalators exhibit a wide range of biological activities, their anticancer properties have attracted the most attention [1–4]. Extensive SAR (structure/activity relationship) studies with DNA-intercalating chromophores have revealed a positive correlation between the strength of reversible DNA binding and cytotoxic potency [5–7]. Efforts to identify molecules with a greater affinity for DNA have resulted in the development of 'dimeric' intercalators, in which two intercalating ligands are bridged by a central linkage [8–15]. Recently, we have reported cytotoxic and antiplatelet evaluations of α-methylidene-γ-butyrolactones linked to potential DNA-intercalating carriers such as flavone, xanthone, carbazole (CAR), and dibenzofuran (DBF) [16]. Among them, the dibenzofuran derivatives were the most cytotoxic. The present report describes the preparation and cytotoxic evaluation of selected dibenzofuran- and carbazole-substituted oximes and oxime ethers. We expected the oximes (H-bond donors) and *O*-methyloximes (H-bond acceptors) to form H-bonds with DNA during the intercalation process of the carbazole and dibenzofuran moieties.

Certain dibenzofuran derivatives exhibit a great variety of biological effects, including inhibition of the clotting activity of thrombin [17] and inhibition of serotonin (5-hydroxytryptamine; 5HT)-induced bradycardia in rats [18]. Therefore, the anti-platelet activity of these dibenzofuran and carbazole derivatives has also been evaluated in the hope to identify potential drug candidates that selectively inhibit either platelet aggregation or growth of cancer cells.

2. Results and Discussion. 2.1. *Synthesis.* The preparation of compounds **1**–**10** is illustrated in the *Scheme.* Alkylation of dibenzo[*b*,*d*]furan-2-ol (DBF–OH) with chloroacetone under basic conditions gave the propan-2-one **1**, which was treated with NH_2OH to afford exclusively the (*E*)-configured oxime **5** in 59% overall yield. The configuration of the oxime moiety was determined by through-space nuclear-*Overhauser*-effect spectroscopy (NOESY), which revealed a coupling connectivity to the Me H-atoms. Accordingly, **7a**–**d** were obtained in fairly good overall yields from DBF–OH and different bromomethyl ketones, followed by treatment of **3a**–**d** with NH_2OH. Compounds **7a**–**d** were found to be mostly (*Z*)-configured, with only trace amounts of the (*E*)-isomers being present. The OCH_2 C-atom of the (*E*)-oxime was shifted downfield (δ_C 70.42 for (*E*)-**5**), while that of the (*Z*)-isomer was shifted upfield (δ_C 59.47 for (*Z*)-**7a**) [19][20].

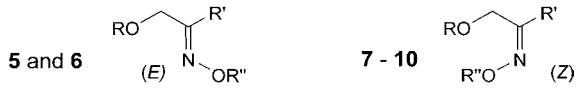
Scheme



Reaction of 2-[(dibenzofuran-2-yl)oxy]-1-(4-fluorophenyl)ethan-1-one (**3b**) and of its 4-MeO counterpart **3c** with NH_2OMe provided the (*Z*)-configured *O*-methyloximes **9b** and **9c**, respectively. The same synthetic procedure was applied for the synthesis of the carbazole derivatives of type **6**, **8**, and **10**.

2.2. *Cytotoxicity.* All compounds were evaluated *in vitro* against a three-cell-line panel, consisting of MCF7 (breast), NCI-H460 (lung), and SF-268 (CNS) [21]. The results are shown in *Table 1*. All DBF-substituted oximes (**5** and **7a**–**d)** were active, in contrast to the *O*-methyloxime counterparts **9b** and **9c**, which were inactive at the same concentration. Therefore, a H-bond-donating group seems to be crucial for cytotoxicity.

Table 1. *Primary Anticancer Assay of Dibenzofuran and Carbazole Derivatives.* DBF, dibenzo[*b*,*d*]furan-2-yl; CAR, 9*H*-carbazol-2-yl (see the *Scheme*).



Compound	Substituents			Growth [%][a])			GI_{50} [μM][b])[c])
	R	R′	R″	NCI-H460 (Lung)	MCF 7 (Breast)	SF-268 (CNS)	
5	DBF	Me	H	0	0	0	40.5
6	CAR	Me	H	99	130	107	n.d.[d])
7a	DBF	C_6H_5	H	0	0	0	16.4
7b	DBF	4-F-C_6H_4	H	1	0	0	21.9
7c	DBF	4-MeO-C_6H_4	H	0	0	0	19.6
7d	DBF	[1,1′-Biphenyl]-4-yl	H	0	−1	0	22.0
8a	CAR	C_6H_5	H	1	3	1	17.7
8b	CAR	4-F-C_6H_4	H	0	0	0	21.1
8c	CAR	4-MeO-C_6H_4	H	5	5	9	18.3
8d	CAR	[1,1′-Biphenyl]-4-yl	H	1	1	1	16.3
9b	DBF	4-F-C_6H_4	Me	59	79	101	n.d.
9c	DBF	4-MeO-C_6H_4	Me	108	108	107	n.d.
10b	CAR	4-F-C_6H_4	Me	17	76	80	48.7
10c	CAR	4-MeO-C_6H_4	Me	11	67	53	29.5

[a]) For details, see *Exper. Part.* [b]) Data obtained by the *in vitro* disease-oriented tumor-cell screen of *NCI* [22]. GI_{50} stands for 'drug concentration causing 50% cell-growth inhibition'. [c]) Mean values over all cell lines (see *Exper. Part*) tested. [d]) Not determined.

The active DBF compounds **5** and **7a**–**d** were evaluated in the full panel of 60 human-tumor-cell lines derived from nine types of cancer cells (leukemia, non-small-cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer; see *Exper. Part*). For each compound, dose-response curves for each cell line were determined for five different drug concentrations, and the concentrations causing 50% cell-growth inhibition (GI_{50}) relative to a control were calculated [22]. As can be seen from *Table 1*, a Me group is inferior to a Ph substituent ($GI_{50} = 40.5$ *vs.* 16.4 μM for **5** *vs.* **7a**). Comparable mean GI_{50} values for **7a**–**d** indicated that cytotoxicity was not affected by *para*-substituents on the Ph ring. A similar trend was observed for the carbazole (CAR) derivatives **6**, **8a**–**d**, **10b**, and **10c**. Here, **6** was inactive, and **10b** and **10c** exhibited weak cytotoxicities. Hence, **5** is more cytotoxic than **6**, which is in accordance with our previous finding that α-methylidene-γ-butyrolactone-containing dibenzofurans are more cytotoxic than their carbazole counterparts [16]. However, the oxime-type DBF (**7a**–**d**) and CAR (**8a**–**d**) derivatives exhibited similar cytotoxicities.

2.3. *Antiplatelet Activity.* The antiplatelet activities of compounds **5**–**10** were evaluated in washed rabbit platelets (*Table 2*). Platelet aggregation was induced by thrombin (Thr; 0.1 U/ml), arachidonic acid (AA; 200 μM), and collagen (Col; 10 μg/ml), and the final drug concentration was 100 μM. All compounds were found to be inactive against Thr-induced aggregation. With the exception of **7b** and **8b**, which strongly inhibit Col-induced aggregation, most compounds exhibited only weak or

marginal inhibitory activities. However, **6**, **7a**, **7b**, **8a**–**c**, **9b**, **9c**, and **10c** were strongly inhibiting the platelet aggregation induced by AA. Among them, **7b**, **9c**, and **10c** were the most-potent drugs with IC_{50} values of 14.43, 14.87, and 14.60 μM, respectively. This finding is promising, because **9c** was found to be noncytotoxic at a concentration of 100 μM.

Table 2. *Inhibition of Thrombin* (Thr), *Arachidonic Acid* (AA), *and Collagen* (Col) *Induced Platelet Aggregation by Dibenzofuran- and Carbazol-Substituted Oximes or Oxime Ethers.* Parameters: Thr, 0.1 U/ml; AA, 200 μM; Col, 10 μg/ml; mean values for aggregation (± S.E.M, $n = 3–5$) and inhibition (IC_{50}) are given. Aqueous DMSO mixtures (1.5, 5, 15, and 50% of DMSO) were used as the control group, and compounds were tested at 4, 10, 20, 50, and 100 μM concentration.

Compound (100 μM)	Aggregation [%]			IC_{50} [μM]	
	Thr	AA	Col	AA	Col
Control	91.38 ± 0.16	89.83 ± 0.67	91.4 ± 0.38	–	–
5	90.55 ± 0.62	91.54 ± 1.13	90.33 ± 1.11	–	–
6	87.5 ± 0.37	0[a])	54.93 ± 1.45[a])	34.77 ± 0.19	107.53 ± 3.4
7a	89.52 ± 1.23	0[a])	22.4 ± 1.84[a])	39.73 ± 6.98	65.12 ± 3.45
7b	86.95 ± 0.73[a])	0[a])	3.72 ± 3.04[a])	14.43 ± 2.33	35.19 ± 5.34
7c	89.01 ± 1.27	78.39 ± 2.29[a])	59.4 ± 13.1	–	–
7d	90.57 ± 0.92	83.76 ± 1.54[a])	91.25 ± 0.73	–	–
8a	86.93 ± 1.98	0[a])	15.2 ± 0.08[a])	27.9 ± 5.27	56.93 ± 1.18
8b	81.53 ± 2.8[b])	0[a])	0[a])	36.07 ± 1.32	54.63 ± 7.34
8c	87.57 ± 0.95	0[a])	19.17 ± 2.99[a])	34.6 ± 0.09	81.0 ± 1.25
8d	84.73 ± 0.38[c])	83.7 ± 1.24[a])	39.87 ± 2.88[a])	–	96.13 ± 3.58
9b	82.5 ± 1.08[a])	0[a])	29.5 ± 13.46[a])	34.53 ± 0.03	87.33 ± 16.93
9c	76.5 ± 0.24[a])	0[a])	83.0 ± 1.04[a])	14.87 ± 0.03	–
10b	81.77 ± 0.22[a])	79.97 ± 2.9[c])	46.63 ± 10.7[a])	–	–
10c	82.1 ± 3.65[a])	0[a])	41.67 ± 6.43 [a])	14.60 ± 0.12	69.0 ± 12.28

[a]) Significantly different from control value at $P < 0.001$. [b]) Significantly different from control value at $P < 0.05$. [c]) Significantly different from control value at $P < 0.01$.

3. Conclusions. – A number of dibenzofuran- and carbazole-substituted oximes and *O*-methyloximes have been synthesized and evaluated for their antiplatelet and cytotoxic activities. A preliminary anticancer assay indicated that the methyloximes were inactive (**9b** and **9c**) or less active (**10b** and **10c**) than their oxime counterparts (**7b**, **7c**, **8b**, and **8c**), which indicates that a H-bond-donating group upon DNA-intercalation of the dibenzofuran and carbazole moieties is more favorable than that of a H-bond-accepting group. Compound **9c** exhibited a potent inhibitory activity against platelet aggregation induced by arachidonic acid, with an IC_{50} value of 14.87 μM, without being cytotoxic at a concentration of 100 μM.

Experimental Part

General. TLC: precoated (0.2 mm) silica gel *60 F_{254}* plates (*EM Laboratories, Inc.*); detection by UV light (254 nm). M.p.: *Electrothermal IA9100* digital melting-point apparatus; uncorrected. ^{1}H-NMR spectra: *Varian Unity-400* or *Varian Gemini-200* spectrometer (400 and 200 MHz, resp.), chemical shifts δ in ppm rel. to $SiMe_4$ as internal standard (= 0 ppm), coupling constants J in Hz. Elemental analyses were carried out on a *Heraeus CHN-O-Rapid* elemental analyzer.

*1-[(Dibenzo[*b,d*]furan-2-yl)oxy]propan-2-one* (**1**). Dibenzo[*b*,*d*]furan-2-ol (1.84 g, 10 mmol), K_2CO_3 (1.38 g, 10 mmol), and anh. DMF (50 ml) were stirred at r.t. for 30 min. To this soln. was added chloroacetone[1]) (0.92 g, 10 mmol) in DMF (10 ml) in one portion. The resulting mixture was stirred at r.t. for 24 h (TLC monitoring) and then poured into ice-water (100 ml). The white solid thus obtained was collected and recrystallized from Et_2O to afford **1** (2.21 g, 92%). M.p. 80–81°. ^{1}H-NMR ($CDCl_3$): 2.33 (*s*, Me); 4.64 (*s*, OCH_2); 7.06 (*dd* $J = 8.8$, 2.8, H–C(3)); 7.38 (*d*, $J = 2.8$, H–C(1)); 7.48 (*d*, $J = 8.8$, H–C(4)); 7.31–7.91 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 26.62 (Me); 74.12 (CH_2O); 105.10, 111.78, 112.38, 115.47, 120.62, 122.56, 124.16, 124.90, 127.38, 151.41, 154.02, 156.99 (arom. C); 205.82 (C=O). Anal. calc. for $C_{15}H_{12}O_3$ (240.25): C 74.99, H 5.03; found: C 74.82, H 4.96.

*1-[(9*H*-Carbazol-2-yl)oxy]propan-2-one* (**2**). From 9*H*-carbazol-2-ol and chloroacetone, as described for **1**: 92% yield. M.p. 179–180°. ^{1}H-NMR (DMSO): 2.20 (*s*, Me); 4.87 (*s*, OCH_2); 6.79 (*dd*, $J = 8.8$, 2.4, H–C(3)); 6.92 (*d*, $J = 2.4$, H–C(1)); 7.97 (*d*, $J = 8.8$, H–C(4)); 7.09–8.00 (*m*, 4 arom. H); 11.10 (*s*, NH). ^{13}C-NMR (DMSO): 26.32 (Me); 72.64 (CH_2O); 95.53, 107.81, 110.64, 116.67, 118.58, 119.32, 120.93, 122.54, 124.28, 139.82, 140.88, 156.86 (arom. C); 204.64 (C=O). Anal. calc. for $C_{15}H_{13}NO_2$ (239.27): C 75.30, H 5.48, N 5.85; found: C 75.11, H 5.44, N 5.96.

*2-[(Dibenzo[*b,d*]furan-2-yl)oxy]-1-(4-fluorophenyl)ethan-1-one* (**3b**). From 2-bromo-1-(4-fluorophenyl)ethan-1-one, as described for **1**: 84% yield. M.p. 138–139°. ^{1}H-NMR ($CDCl_3$): 5.31 (*s*, OCH_2); 7.11 (*dd*, $J = 8.8$, 2.8, H–C(3)); 7.45 (*d*, $J = 2.8$, H–C(1)); 7.47 (*d*, $J = 8.8$, H–C(4)); 7.16–8.11 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 72.16 (CH_2O); 105.69, 111.77, 112.30, 115.76, 115.93, 116.15, 120.65, 122.52, 124.21, 124.88, 127.34, 131.01, 131.11, 151.49, 154.23, 156.99, 164.88, 167.42 (arom. C); 193.42 (C=O). Anal. calc. for $C_{20}H_{13}FO_3$ (320.31): C 74.99, H 4.09; found: C 74.84, H 4.15.

*2-[(Dibenzo[*b,d*]furan-2-yl)oxy]-1-(4-methoxyphenyl)ethan-1-one* (**3c**). From 2-bromo-1-(4-methoxyphenyl)ethan-1-one, as described for **1**: 93% yield. M.p. 143–144°. ^{1}H-NMR ($CDCl_3$): 3.88 (*s*, MeO); 5.31 (*s*, OCH_2); 7.12 (*dd*, $J = 8.8$, 2.4, H–C(3)); 7.45 (*d*, $J = 2.4$, H–C(1)); 7.46 (*d*, $J = 8.8$, H–C(4)); 6.97–8.05 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 55.50 (MeO); 71.98 (CH_2O); 105.65, 111.72, 112.20, 114.03, 115.83, 120.66, 122.46, 124.29, 124.81, 127.24, 127.73, 130.59, 151.40, 154.44, 156.97, 164.07 (arom. C); 193.24 (C=O). Anal. calc. for $C_{21}H_{16}O_4$ (332.35): C 75.89, H 4.85; found: C 75.91, H 4.83.

*1-([1,1′-Biphenyl]-4-yl)-2-[(dibenzo[*b,d*]furan-2-yl)oxy]ethan-1-one* (**3d**). From 1-([1,1′-biphenyl]-4-yl)-2-bromoethan-1-one, as described for **1**: 79% yield. M.p. 185–186°. ^{1}H-NMR ($CDCl_3$): 5.40 (*s*, OCH_2); 7.15 (*dd*, $J = 9.2$, 2.8, H–C(3)); 7.47 (*d*, $J = 2.8$, H–C(1)); 7.48 (*d*, $J = 9.2$, H–C(4)); 7.30–8.14 (*m*, 13 arom. H). ^{13}C-NMR ($CDCl_3$): 72.19 (CH_2O); 105.75, 111.75, 112.27, 115.87, 120.67, 122.50, 124.28, 124.87, 127.28, 127.33, 127.46, 128.42, 128.83, 128.93, 129.01, 133.35 139.69, 146.61, 154.39, 157.00 (arom. C); 194.34 (C=O). Anal. calc. for $C_{26}H_{18}O_3$ (378.42): C 82.52, H 4.79; found: C 82.22, H 4.86.

*2-[(9*H*-Carbazol-2-yl)oxy]-1-(4-fluorophenyl)ethan-1-one* (**4b**). From 9*H*-carbazol-2-ol and 2-bromo-1-(4-fluorophenyl)ethan-1-one, as described for **1**: 85% yield. M.p. 187–188°. ^{1}H-NMR (DMSO): 5.63 (*s*, OCH_2); 6.84 (*dd*, $J = 8.4$, 2.4, H–C(3)); 6.98 (*d*, $J = 2.4$, H–C(1)); 7.97 (*d*, $J = 8.4$, H–C(4)); 7.09–8.18 (*m*, 8 arom. H); 11.08 (*s*, NH). ^{13}C-NMR (DMSO): 70.54 (CH_2O); 95.70, 108.02, 110.61, 115.82, 116.04, 116.64, 118.56, 119.31, 120.85, 122.54, 124.25, 130.99, 131.08, 131.29, 139.79, 140.85, 157.00, 164.08, 166.60 (arom. C); 193.67 (C=O). Anal. calc. for $C_{20}H_{14}FNO_2$ (319.33): C 75.22, H 4.42, N 4.39; found: C 75.13, H 4.48, N 4.38.

*2-[(9*H*-Carbazol-2-yl)oxy]-1-(4-methoxyphenyl)ethan-1-one* (**4c**). From 9*H*-carbazol-2-ol and 2-bromo-1-(4-methoxyphenyl)ethan-1-one, as described for **1**: 91% yield. M.p. 162–163°. ^{1}H-NMR (DMSO): 3.86 (*s*, MeO); 5.56 (*s*, OCH_2); 6.83 (*dd*, $J = 8.8$, 2.4, H–C(3)); 6.96 (*d*, $J = 2.4$, H–C(1)); 7.97 (*d*, $J = 8.8$, H–C(4)); 7.08–8.08 (*m*, 8 arom. H); 11.08 (*s*, NH). ^{13}C-NMR (DMSO): 55.61 (MeO); 70.36 (CH_2O); 95.62, 108.08, 110.60, 114.09, 116.55, 118.55, 119.29, 120.84, 122.60, 124.22, 127.42, 130.32, 139.77, 140.88, 157.15, 163.58 (arom. C); 193.30 (C=O). Anal. calc. for $C_{21}H_{17}NO_3$ (331.36): C 76.12, H 5.17, N 4.23; found: C 76.12, H 5.26, N 4.25.

*1-([1,1′-Biphenyl]-4-yl)-2-[(9*H*-carbazol-2-yl)oxy]ethan-1-one* (**4d**). From 9*H*-carbazol-2-ol and 1-([1,1′-biphenyl]-4-yl)-2-bromoethan-1-one, as described for **1**: 93% yield. M.p. 223–224°. ^{1}H-NMR (DMSO): 5.68 (*s*, OCH_2); 6.87 (*dd*, $J = 8.8$, 2.4, H–C(3)); 7.01 (*d*, $J = 2.4$, H–C(1)); 7.99 (*d*, $J = 8.8$, H–C(4)); 7.10–8.18 (*m*, 13 arom. H); 11.10 (*s*, NH). ^{13}C-NMR (DMSO): 70.63 (CH_2O); 95.68, 108.06, 110.63, 116.61, 118.56, 119.32, 120.88, 122.57, 124.25, 127.04, 128.52, 128.70, 129.14, 133.30, 138.83, 139.79, 140.90, 145.15, 157.07 (arom. C); 194.55 (C=O). Anal. calc. for $C_{26}H_{19}NO_2$ (377.43): C 82.74, H 5.07, N 3.71; found: C 82.66, H 5.17, N 3.72.

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[1]) Systematic name: 1-chloropropan-2-one.

*(*E*)-1-[(Dibenzo[*b,d*]furan-2-yl)oxy]propan-2-one Oxime* (**5**). To a soln. of **1** (0.24 g, 1 mmol) in EtOH (20 ml) was added a soln. of $NH_2OH \cdot HCl$ (0.14 g, 2 mmol) in EtOH (2 ml). The mixture was heated at reflux for 24 h (TLC monitoring) and evaporated to a white solid, which was purified by flash chromatography (FC; silica gel; CH_2Cl_2/hexane 1:1) and recrystallization (Et_2O/hexane 1:1): 0.16 g (63%). M.p. 129–130°. ^{1}H-NMR (DMSO): 1.90 (*s*, Me); 4.66 (*s*, OCH_2); 7.15 (*dd*, *J* = 8.8, 2.6, H–C(3)); 7.61 (*d*, *J* = 8.8, H–C(4)); 7.78 (*d*, *J* = 2.6, H–C(1)); 7.34–8.12 (*m*, 4 arom. H); 10.96 (*s*, NOH). ^{13}C-NMR (DMSO): 11.52 (Me); 70.42 (CH_2O); 105.96, 111.62, 112.09, 116.03, 121.10, 122.76, 123.76, 124.11, 127.52, 150.25, 152.01, 154.47, 156.14 (arom. C and C=N). Anal. calc. for $C_{15}H_{13}NO_3$ (255.27): C 70.58, H 5.13, N 5.49; found: C 70.66, H 5.24, N 5.45.

*(*E*)-1-[(9*H*-Carbazol-2-yl)oxy]propan-2-one Oxime* (**6**). From **2**, as described for **5**: 67% yield. M.p. 229–230°. ^{1}H-NMR (DMSO): 1.89 (*s*, Me); 4.64 (*s*, OCH_2); 6.81 (*dd*, *J* = 8.8, 2.4, H–C(3)); 7.02 (*d*, *J* = 2.4, H–C(1)); 7.97 (*d*, *J* = 8.8, H–C(4)); 7.09–8.00 (*m*, 4 arom. H); 10.93, 11.13 (2*s*, NOH and NH). ^{13}C-NMR (DMSO): 11.49 (Me); 69.80 (CH_2O); 95.84, 108.20, 110.60, 116.59, 118.53, 119.29, 120.87, 122.54, 124.24, 139.79, 140.87, 152.26, 157.27 (arom. C and C=N). Anal. calc. for $C_{15}H_{14}N_2O_2$ (254.28): C 70.85, H 5.55, N 11.02; found: C 70.85, H 5.56, N 10.98.

*(Z)-2-[(Dibenzo[*b,d*]furan-2-yl)oxy]-1-phenylethan-1-one Oxime* (**7a**). From **3a**, as described for **5**: 69% yield. M.p. 139–140°. ^{1}H-NMR (DMSO): 5.37 (*s*, OCH_2); 7.09 (*dd*, *J* = 8.8, 2.0, H–C(3)); 7.59 (*d*, *J* = 8.8, H–C(4)); 7.80 (*d*, *J* = 2.0, H–C(1)); 7.39–8.10 (*m*, 9 arom. H); 11.96 (*s*, NOH). ^{13}C-NMR (DMSO): 59.47 (CH_2O); 105.41, 111.66, 112.13, 115.51, 121.07, 122.80, 123.75, 124.15, 126.36, 127.56, 128.29, 128.85, 134.39, 150.26, 152.82, 154.26, 156.15 (arom. C and C=N). Anal. calc. for $C_{20}H_{15}NO_3$ (317.34): C 75.70, H 4.76, N 4.41; found: C 75.59, H 4.82, N 4.42.

*(Z)-2-[(Dibenzo[*b,d*]furan-2-yl)oxy]-1-(4-fluorophenyl)ethan-1-one Oxime* (**7b**). From **3b**, as described for **5**: 83% yield. M.p. 160–161°. ^{1}H-NMR (DMSO): 5.37 (*s*, OCH_2); 7.08 (*dd*, *J* = 8.8, 2.4, H–C(3)); 7.59 (*d*, *J* = 8.8, H–C(4)); 7.79 (*d*, *J* = 2.4, H–C(1)); 7.21–8.10 (*m*, 8 arom. H); 11.98 (*s*, NOH). ^{13}C-NMR (DMSO): 59.50 (CH_2O); 105.44, 111.68, 112.16, 115.13, 115.35, 115.51, 121.08, 122.81, 123.75, 124.16, 127.59, 128.55, 128.62, 130.81, 130.84, 150.29, 152.08, 154.16, 156.16, 161.24, 163.69 (arom. C and C=N). Anal. calc. for $C_{20}H_{14}FNO_3$ (335.33): C 71.64, H 4.21, N 4.18; found: C 71.24, H 4.32, N 4.03.

*(Z)-2-[(Dibenzo[*b,d*]furan-2-yl)oxy]-1-(4-methoxyphenyl)ethan-1-one Oxime* (**7c**). From **3c**, as described for **5**: 63% yield. M.p. 133–134°. ^{1}H-NMR (DMSO): 3.77 (*s*, MeO); 5.33 (*s*, OCH_2); 7.09 (*dd*, *J* = 8.8, 2.4, H–C(3)); 7.59 (*d*, *J* = 8.8, H–C(4)); 7.80 (*d*, *J* = 2.4, H–C(1)); 6.95–8.10 (*m*, 8 arom. H); 11.73 (*s*, NOH). ^{13}C-NMR (DMSO): 55.10 (MeO); 59.39 (CH_2O); 105.35, 111.66, 112.13, 113.74, 115.51, 121.05, 122.80, 123.77, 124.15, 126.77, 127.56, 127.71, 150.23, 152.32, 154.28, 156.15, 159.80 (arom. C and C=N). Anal. calc. for $C_{21}H_{17}NO_4$ (347.36): C 72.61, H 4.93, N 4.03; found: C 72.60, H 4.98, N 3.92.

*(Z)-1-([1,1′-Biphenyl]-4-yl)-2-[(dibenzo[*b,d*]furan-2-yl)oxy]ethan-1-one Oxime* (**7d**). From **3d**, as described for **5**: 81% yield. M.p. 174–175°. ^{1}H-NMR (DMSO): 5.38 (*s*, OCH_2); 7.11 (*dd*, *J* = 8.8, 2.4, H–C(3)); 7.59 (*d*, *J* = 8.8, H–C(4)); 7.82 (*d*, *J* = 2.4, H–C(1)); 7.35–8.10 (*m*, 13 arom. H); 12.01 (*s*, NOH). ^{13}C-NMR (DMSO): 59.41 (CH_2O); 105.44, 111.69, 112.21, 115.57, 121.10, 122.84, 123.78, 124.21, 126.59, 126.92, 127.62, 127.68, 128.97, 133.45, 139.44, 140.49, 150.30, 152.50, 154.31, 156.18 (arom. C and C=N). Anal. calc. for $C_{26}H_{19}NO_3$ (393.43): C 79.37, H 4.87, N 3.56; found: C 79.40, H 4.93, N 3.53.

*(Z)-2-[(9*H*-Carbazol-2-yl)oxy]-1-phenylethan-1-one Oxime* (**8a**). From **4a**, as described for **5**: 60% yield. M.p. 187–188°. ^{1}H-NMR (DMSO): 5.35 (*s*, OCH_2); 6.74 (*dd*, *J* = 8.4, 2.4, H–C(3)); 7.04 (*d*, *J* = 2.4, H–C(1)); 7.93 (*d*, *J* = 8.4, H–C(4)); 7.08–7.98 (*m*, 9 arom. H); 11.16, 11.92 (2*s*, NOH and NH). ^{13}C-NMR (DMSO): 59.13 (CH_2O); 95.29, 107.85, 110.60, 116.59, 118.53, 119.28, 120.88, 122.52, 124.22, 126.44, 128.24, 128.80, 134.39, 139.77, 140.90, 153.20, 157.04 (arom. C and C=N). Anal. calc. for $C_{20}H_{16}N_2O_2$ (316.35): C 75.93, H 5.10, N 8.86; found: C 75.91, H 5.13, N 8.76.

*(Z)-2-[(9*H*-Carbazol-2-yl)oxy]-1-(4-fluorophenyl)ethan-1-one Oxime* (**8b**). From **4b**, as described for **5**: 67% yield. M.p. 189–190°. ^{1}H-NMR (DMSO): 5.35 (*s*, OCH_2); 6.73 (*dd*, *J* = 8.4, 2.0, H–C(3)); 7.03 (*d*, *J* = 2.0, H–C(1)); 7.93 (*d*, *J* = 8.4, H–C(4)); 7.09–7.98 (*m*, 8 arom. H); 11.15, 11.94 (2*s*, NOH and NH). ^{13}C-NMR (DMSO): 59.19 (CH_2O); 95.33, 107.84, 110.61, 115.07, 115.30, 116.65, 118.56, 119.29, 120.92, 122.52, 124.27, 128.61, 128.70, 130.81, 130.84, 139.79, 140.90, 152.47, 156.92, 161.23, 163.67 (arom. C and C=N). Anal. calc. for $C_{20}H_{15}FN_2O_2$ (334.34): C 71.85, H 4.52, N 8.38; found: C 71.87, H 4.56, N 8.31.

*(Z)-2-[(9*H*-Carbazol-2-yl)oxy]-1-(4-methoxyphenyl)ethan-1-one Oxime* (**8c**). From **4c**, as described for **5**: 72% yield. M.p. 174–175°. ^{1}H-NMR (DMSO): 3.76 (*s*, MeO); 5.32 (*s*, OCH_2); 6.74 (*dd*, *J* = 8.8, 2.0, H–C(3)); 7.03 (*d*, *J* = 2.0, H–C(1)); 7.93 (*d*, *J* = 8.8, H–C(4)); 6.92–7.98 (*m*, 8 arom. H); 11.15, 11.70 (2*s*, NOH and NH). ^{13}C-NMR (DMSO): 55.03 (MeO); 59.01 (CH_2O); 95.19, 107.78, 110.53, 113.61, 116.48, 118.47, 119.19, 120.80, 122.46, 124.14, 126.70, 127.71, 139.69, 140.83, 152.62, 156.99, 159.69 (arom. C and C=N). Anal. calc. for $C_{21}H_{18}N_2O_3$ (346.38): C 72.82, H 5.24, N 8.09; found: C 72.51, H 5.35, N 7.98.

*(Z)-1-([1,1'-Biphenyl]-4-yl)-2-[(9*H*-carbazol-2-yl)oxy]ethan-1-one Oxime* (**8d**). From **4d**, as described for **5**: 64% yield. M.p. 195–196°. ^{1}H-NMR (DMSO): 5.38 (*s*, OCH_2); 6.77 (*dd*, *J* = 8.8, 2.4, H–C(3)); 7.06 (*d*, *J* = 2.4, H–C(1)); 7.94 (*d*, *J* = 8.8, H–C(4)); 7.08–7.99 (*m*, 8 arom. H); 11.16, 11.97 (2*s*, NOH and NH). ^{13}C-NMR (DMSO): 59.07 (CH_2O); 95.27, 107.82, 110.55, 116.58, 118.49, 119.23, 120.85, 122.48, 124.18, 126.45, 126.53, 126.92, 127.61, 128.90, 133.42, 139.41, 139.76, 140.37, 140.87, 152.79, 157.03 (arom. C and C=N). Anal. calc. for $C_{26}H_{20}N_2O_2$ (392.45): C 79.57, H 5.14, N 7.14; found: C 79.57, H 5.20, N 7.12.

*(Z)-2-[(Dibenzo[*b,d*]furan-2-yl)oxy]-1-(4-fluorophenyl)ethan-1-one* O-*Methyloxime* (**9b**). To a soln. of **3b** (0.32 g, 1 mmol) in EtOH (20 ml) was added a soln. of $NH_2OMe \cdot HCl$ (0.17 g, 2 mmol) in EtOH (2 ml). The mixture was heated at reflux for 24 h (TLC monitoring) and evaporated to a crude oil, which was purified by FC (silica gel; CH_2Cl_2/hexane 1:1): 0.25 g (72%). M.p. 167–168°. ^{1}H-NMR (DMSO): 4.04 (*s*, MeO); 5.34 (*s*, OCH_2); 7.06 (*dd*, *J* = 8.8, 2.8, H–C(3)); 7.59 (*d*, *J* = 8.8, H–C(4)); 7.79 (*d*, *J* = 2.8, H–C(1)); 7.20–8.13 (*m*, 8 arom. H). ^{13}C-NMR (DMSO): 60.09 (CH_2O); 62.28 (MeO); 97.67, 105.45, 111.66, 112.21, 115.12, 115.55, 121.09, 122.85, 123.69, 124.16, 127.61, 128.97, 129.13, 129.67, 129.73, 150.35, 153.18, 154.01, 156.16, 160.31, 165.22 (arom. C and C=N). Anal. calc. for $C_{21}H_{16}FNO_3$ (349.36): C 72.20, H 4.62, N 4.01; found: 72.18, H 4.70, N 4.04.

*(Z)-2-[(Dibenzo[*b,d*]furan-2-yl)oxy]-1-(4-methoxyphenyl)ethan-1-one* O-*Methyloxime* (**9c**). From **3c**, as described for **9b**: 69% yield. M.p. 95–96°. ^{1}H-NMR (DMSO): 3.76 (*s*, MeO); 4.01 (*s*, MeON); 5.29 (*s*, OCH_2); 7.05 (*dd*, *J* = 9.2, 2.8, H–C(3)); 7.58 (*d*, *J* = 9.2, H–C(4)); 7.75 (*d*, *J* = 2.8, H–C(1)); 6.94–8.10 (*m*, 8 arom. H). ^{13}C-NMR (DMSO): 55.15 (MeO); 59.92 (CH_2O); 62.05 (MeON); 105.35, 111.67, 112.19, 113.80, 115.58, 121.07, 122.83, 123.73, 124.15, 125.59, 127.59, 128.14, 150.31, 153.37, 154.15, 156.16, 160.23 (arom. C and C=N). Anal. calc. for $C_{22}H_{19}NO_4$ (361.39): C 73.12, H 5.30, N 3.88; found: C 73.52, H 5.20, N 3.56.

*(Z)-2-[(9*H*-Carbazol-2-yl)oxy]-1-(4-fluorophenyl)ethan-1-one* O-*Methyloxime* (**10b**). From **4b**, as described for **9b**: 72% yield. M.p. 180–181°. ^{1}H-NMR (DMSO): 4.04 (*s*, MeO); 5.33 (*s*, OCH_2); 6.70 (*dd*, *J* = 8.6, 2.2, H–C(3)); 6.98 (*d*, *J* = 2.2, H–C(1)); 7.93 (*d*, *J* = 8.6, H–C(4)); 7.07–8.00 (*m*, 8 arom. H); 11.16 (*s*, NH). ^{13}C-NMR (DMSO): 59.96 (CH_2O); 62.63 (MeO); 95.57, 108.11, 110.91, 115.37, 115.81, 116.99, 118.86, 119.61, 121.24, 122.76, 124.60, 129.30, 129.47, 129.93, 129.99, 140.05, 141.10, 153.90, 157.00, 160.57, 165.48 (arom. C and C=N). Anal. calc. for $C_{21}H_{17}FN_2O_2$ (348.37): C 72.40, H 4.92, N 8.04; found: C 72.42, H 4.97, N 8.00.

*(Z)-2-[(9*H*-Carbazol-2-yl)oxy]-1-(4-methoxyphenyl)ethan-1-one* O-*Methyloxime* (**10c**). From **4c**, as described for **9b**: 67% yield. M.p. 154–155°. ^{1}H-NMR (DMSO): 3.76 (*s*, MeO); 4.02 (*s*, MeON); 5.29 (*s*, OCH_2); 6.71 (*dd*, *J* = 8.4, 2.0, H–C(3)); 7.00 (*d*, *J* = 2.0, H–C(1)); 7.93 (*d*, *J* = 8.4, H–C(4)); 6.93–7.98 (*m*, 8 arom. H); 11.17 (*s*, NH). ^{13}C-NMR (DMSO): 55.16 (MeO); 59.53 (CH_2O); 62.12 (MeON); 95.21, 107.87, 110.63, 113.77, 116.64, 118.58, 119.32, 120.95, 122.51, 124.28, 125.56, 128.21, 139.77, 140.87, 153.81, 156.89, 160.20 (arom. C and C=N). Anal. calc. for $C_{22}H_{20}N_2O_3$ (360.41): C 73.32, H 5.59, N 7.77; found: C 73.21, H 5.61, N 7.73.

Antiplatelet Evaluation. The following materials were used: collagen (type 1, bovine *Achilles* tendon; *Sigma Chemical Co.*) was homogenized in 25 mM AcOH and stored (1 mg/ml) at –70°. Arachidonic acid (AA), EDTA ('ethylenediamine tetraacetate'), and bovine serum albumin were purchased from *Sigma* and dissolved in $CHCl_3$. For the determination of cell growth rel. to a control, each cell line was inoculated and pre-incubated on a microtiter plate. Test agents (100 μM) were then added, and the culture was incubated for 48 h. End-point determinations were made with alamar blue [21]. Compounds that reduced the growth of any one of the cell lines to 32% or less (negative numbers in *Table 2* indicate cell kill) were passed on for evaluation in the full panel of 60 cell lines over a fivefold-logarithmic dose range. Theses cell lines were: *1*) leukemia (CCRF-CEM, HL-60 (TB), K-562, MOLT-4, PRMI-8226, and SR); *2*) non-small-cell lung cancer (A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, and NCI-H522); *3*) colon cancer (COLC 205, HCC-2998, HCT-116, HCT-15, HT29, KM12, and SW-620); *4*) CNS cancer (SF-268, SF-295, SF-539, SNB-19, SNB-75, and U251); *5*) melanoma (LOX IMVI, MALME-3M, M14, SK-MEL-2, SK-MEL-28, SK-MEL-5, and UACC-257); *6*) ovarian cancer (IGROV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, and SK-OV-3); *7*) renal cancer (786–0, A498, ACHN, CAKI-1, RXF 393, SN12C, TK-10, and UO-31); *8*) prostate cancer (PC-3 and DU-145); and *9*) breast cancer (MCF 7, MCF 7/ADR-RES, MDA-MB-231/ ATCC, HS 578T, MDA-MB-435, MDA-N and T-47D).

Platelet Aggregation. Blood was collected from the rabbit marginal ear vein, anticoagulated with EDTA (6 mM) and centrifuged for 10 min at 90 *g* at r.t. Platelet suspensions were prepared from the plasma according to the washing procedures described in [23]. Platelet numbers were determined with a *Coulter-ZM* counter and adjusted to 3×10^8 platelets/ml. The platelet pellets were suspended in *Tyrode*'s soln. of the following composition (mM): NaCl (136.8), KCl (2.8), $NaHCO_3$ (11.9), $MgCl_2$ (2.1), NaH_2PO_4 (0.33), $CaCl_2$ (1.0), and glucose (11.2), containing bovine serum albumin (0.35%). The platelet suspension was stirred at 1200 rpm, and aggregation was measured at 37° by the turbidimetric method, as described by *O'Brien* [24], using a *Payton Lumi* aggregometer (model *600B*). To eliminate solvent effects, the final conc. of DMSO was fixed at 0.5%.

Percentage of aggregation was calculated using the absorbance of a platelet suspension as 0% aggregation, and the absorbance of *Tyrode*'s soln. as 100% aggregation.

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