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N-Phosphorylated 3,5-bis(Arylidene)4-Piperidones: Synthesis, X-Ray Structure, and Evaluation of Antitumor Activity

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ABSTRACT: *In a search for cytotoxic fluorescent materials, a series of N-phosphorylated compounds* **2a–c** *were prepared by phosphorylation of 3,5-bis(4-N,N-dimethylbenzylidene)-4-piperidone* **1**. *According to X-ray investigations, molecule* **2a** *is E,E-isomer with axial position of the* $P(O)(OCH_2CF_3)_2$ *substituent. Fluorescence of compounds* **2a–c** *was found to be similar to fluorescence of nonphosphorylated compound* **1**. *The cytotoxicity of the compounds* **2a–c** *was estimated on several human tumor cell lines (H9, K562, and MCF7).* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:497–502, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20147

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INTRODUCTION

It is well recognized that organophosphorus compounds exhibit different types of bioactivity, and therefore form an important series of compounds in the search for new drugs. For instance, high-level anticancer activity has been found in a number of phosphorus compounds of quite different structural types, among them discovered in 1958 cyclophosphamide [1], which still remains in wide clinical use, *N*-phosphonoacetyl-L-aspartic acid (PALA), phosphonyl derivatives of choline and modified nucleotide derivatives, such as the unsymmetrical pyrophosphate. An excellent review on the design of new phosphorus-based chemotherapeutical agents has been published in 1992 by Engel [2]. We may also note the use of phosphorylated compounds as prodrugs to improve drug delivery to particular targets. Finally, solubility of drugs could be modified by attaching phosphorus groups; for example phosphorylation significantly increases poor solubility of steroidal drugs in water.

During last decade 3,5-bis(arylidene)-4-piperidones and 2,6-bis-benzylidenecyclohexanones have been studied as cytotoxic and anticancer agents [1–6]. It was reported that molecular modification

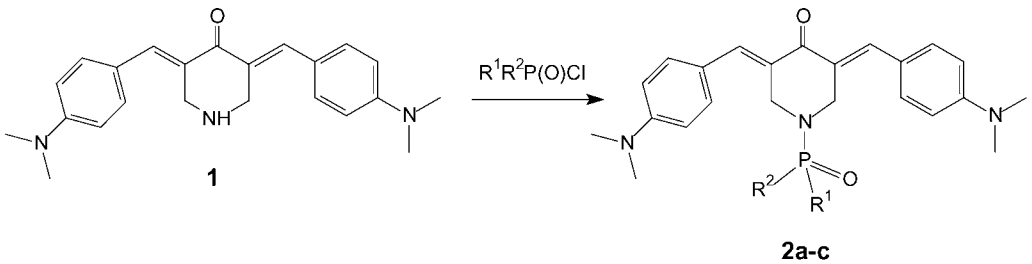
at the nitrogen atom, e.g. N-acylation, affects the capacity of transportation of this biologically active molecules via the cellular membrane and therefore resulted in the significantly higher level of anticancer activity. Another interesting feature of these compounds observed recently is fluorescent properties of some representatives of this group [7,8]. It is worth noting that natural fluorescence in the case of cytotoxic materials might be very helpful in tracking of their cellular pathway in chemotherapy. In an effort to obtain more efficient antitumor agents among the bis(arylidene)-4-piperidone derivatives, we suggested that combination of the phosphoryl moiety and cytotoxic skeleton may result in improved activity along with water solubility, stability, and fluorescent properties. In this paper, we report our starting results concerning the introduction of phosphorus groups to the nitrogen atom in the molecule of 3,5-bis(arylidene)-4-piperidones and evaluation of the anticancer activity of N-P compounds obtained.

RESULTS AND DISCUSSION

As a starting model substrate, we used 3,5-bis(4-*N*,*N*-dimethylbenzylidene)-4-piperidone **1** (Scheme 1). According to the published data, N-substituted derivatives of **1** do not have high cytotoxicity but possess noticeable fluorescence [7,8]. It was found that phosphorylation using the appropriate phosphoryl and phosphonyl chlorides (Scheme 1) in the presence of triethylamine as a base proceeds under the ambient conditions in ca. 50–55 yield according the ^{31}P NMR spectra. The rather low yields could be explained first by poor solubility in organic solvents of the starting NH-piperidone that results in proceeding of phosphorylation under heterogeneous conditions. Second, the starting piperidone **1** obtained according to [9] followed by prolonged drying in vacuum (2.5 h, 80°C) still contained about 3 wt% of water which was equivalent to ~23–25 mol% [10]. Therefore, the side reaction of the phosphorus acid chloride results in formation of the corresponding acid $R^1R^2P(O)OH$. The latter interacts with the former yielding the pyrophosphate species $R^1R^2P(O)OP(O)R^1R^2$ registered in ^{31}P NMR spectra. Fortunately, these compounds are easy to separate from the target-phosphorylated compounds **2**. Changing of the tertiary amine for the more basic one, for example DBU, gives the same results.

Phosphorylated piperidones appeared as sharp singlets in the ^{31}P NMR spectra in the regions typical for the corresponding surrounding at the phosphorus atom (ca. −8.2, −0.9 or ca. 31.2 ppm for **2a, 2b**, and **2c**, respectively). For compound **2a**, the trifluoromethyl group resonates at 2.65 ppm as a singlet in the ^{19}F NMR spectra. In the ^{1}H and ^{13}C NMR spectra of the compounds, the signals of the protons and skeletal carbon atoms can be found in the typical regions in agreement with the suggested structure. For example, ring methylene groups adjacent to the nitrogen atom are observed in the ^{13}C NMR spectra as a doublet at ca. 46 ppm with $^{2}J_{PC}$ coupling constants up to 5.5 Hz.

Single crystal X-ray analysis was carried out for representative piperidone **2a** bearing two 2,2,2-trifluoroethoxy substituents at the phosphorus atom. The results of X-ray analysis revealed the following information. The heterocyclic ring of **2a** has the sofa conformation (Fig. 1) with the N1 atom lying at 0.633(4) Å out of the C2–C3–C4–C5–C6 plane (planar within 0.016 Å). The substituent at the N1 atom adopts axial position similar to what was found in [9,11]. Both olefinic bonds have *E* configuration, which is in agreement with the results obtained earlier for similar compounds [12–15]. Taking into consideration the general similarity of the spectral data, we also assigned the structures of compounds **2b,c** to *E*,*E*-isomers. It can be noticed that steric hindrance is present in the dienone fragment of the molecule, i.e. some angles differ from the strain-free ones (Table 1). For example, repulsion between H atoms at C2 and those at C22 in phenyl ring causes the distortion of angles at C7 and C16 atoms (Table 1). The same repulsion rotates both phenyl rings about the



R^1=R^2=OCH_2CF_3 (**a**); OPh (**b**): R^1=Me, R^2=OPh (**c**)

SCHEME 1

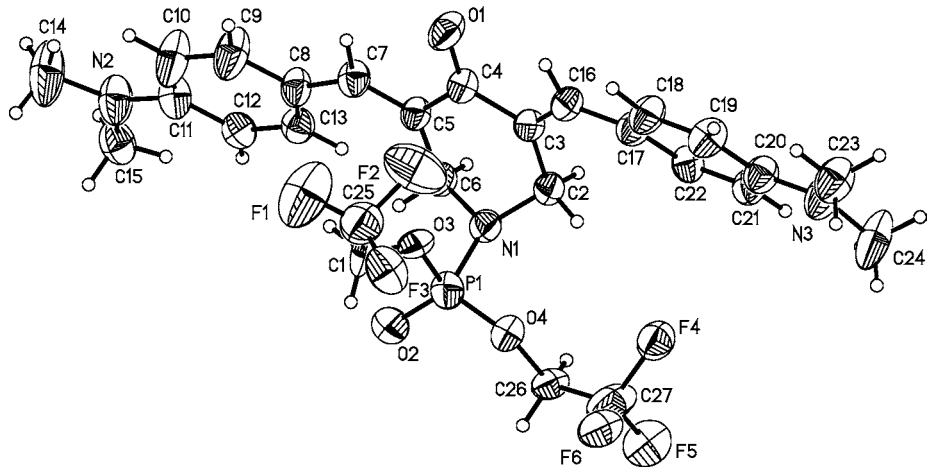


FIGURE 1 View of the molecule **2a** with atom-numbering scheme. Non-H atoms are shown with displacement ellipsoids drawn at the 50% probability level. For clarity, only one position of disordered $-OCH_2CF_3$ group is shown.

C–Ph bonds (Table 1). The dihedral angles between the flat fragment of central heterocycle that includes also C7, C16, and O1 and mean planes of phenyl rings are 19.9(2)° (C8–C13) and 29.7(2)° (C17–C22). Difference in rotation of two Ph rings is caused by closer position of one of them to trifluoroethyl fragment of the $-PO(OCH_2CF_3)_2$ group. This result is consistent with X-ray data obtained for similar compounds with bulky substituents at nitrogen atom in central heterocyclic ring [9,11]. The bond-length distribution in the conjugated part shows a small deviation of single and double bonds from standard values [16].

It was found previously [7,8] that bisarylidenpiperidones are fluorescent, for this reason absorption and emission spectra of compounds **1, 2a–2c** have been studied. The absorption spectra of compounds **1, 2a–2c** are shown in Fig. 2. It can be seen that each compound has two absorption peaks, one around 275 nm and the second one around 454 nm. To obtain fluorescent spectra, compounds were excited at $\lambda_{ex} = \max \lambda_{abs}$ (for each peak). The fluorescence emission was measured at the wavelength intervals of $\max \lambda_{abs} + 15$ nm to 700 nm for both absorption peaks. It was also found that higher intensity emission was observed when solutions were excited at maximum of a longer wavelength peak. Absorption and emission maxima of all compounds in chloroform are listed in Table 2. Figure 3 represents the example of emission spectrum of **2a**, which is typical for all compounds.

The cytotoxicity of the compounds **2a–c** was estimated on several human tumor cell lines (Table 3). Concentrations resulting in the 50% of cell death was achieved only for the compound **2c** in the case of MCF7 cells, since the solubility of the test compounds in water and saline was rather low and they precipitate from the solutions at the concentrations exceeding 50 μM (and 20 μM for **2b**). Taking into account that compounds may metabolize by hepatic enzymes, e.g. isoforms of cytochrome P-450,

TABLE 1 Selected Bond Lengths (Å) Bond and Torsion Angles (0°) for **2a**

O(1)–C(4)	1.234(4)	C(16)–C(3)–C(4)	117.7(3)	C(4)–C(5)–C(7)–C(8)	178.4(4)
N(2)–C(11)	1.382(5)	C(16)–C(3)–C(2)	124.2(3)	C(5)–C(7)–C(8)–C(9)	164.0(4)
N(3)–C(20)	1.376(5)	C(7)–C(5)–C(4)	116.3(3)	C(4)–C(3)–C(16)–C(17)	−177.9(3)
C(3)–C(16)	1.360(5)	C(7)–C(5)–C(6)	125.3(3)	C(3)–C(16)–C(17)–C(18)	−157.2(4)
C(5)–C(7)	1.339(5)	O(1)–C(4)–C(3)	120.5(3)		
C(3)–C(4)	1.485(5)	O(1)–C(4)–C(5)	120.6(3)		
C(4)–C(5)	1.495(5)	C(3)–C(4)–C(5)	118.9(3)		
C(7)–C(8)	1.452(5)	C(4)–C(3)–C(2)	118.0(3)		
C(16)–C(17)	1.446(5)	C(4)–C(5)–C(6)	118.4(3)		
		C(5)–C(7)–C(8)	133.1(3)		
		C(3)–C(16)–C(17)	131.3(3)		
		C(6)–N(1)–C(2)	112.4(3)		
		C(6)–N(1)–P(1)	118.1(2)		
		C(2)–N(1)–P(1)	121.3(2)		

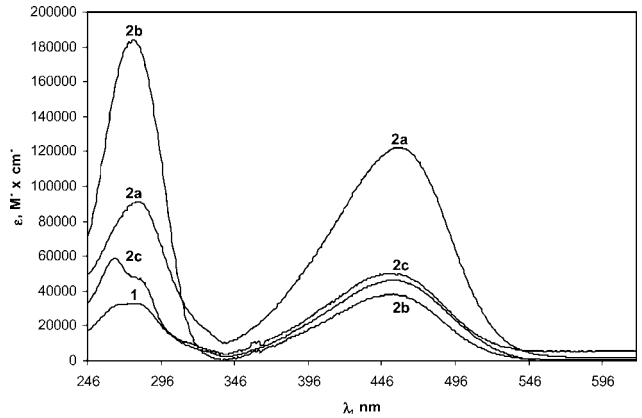


FIGURE 2 Spectra of molar absorptivity of compounds **1, 2a–2c** in chloroform.

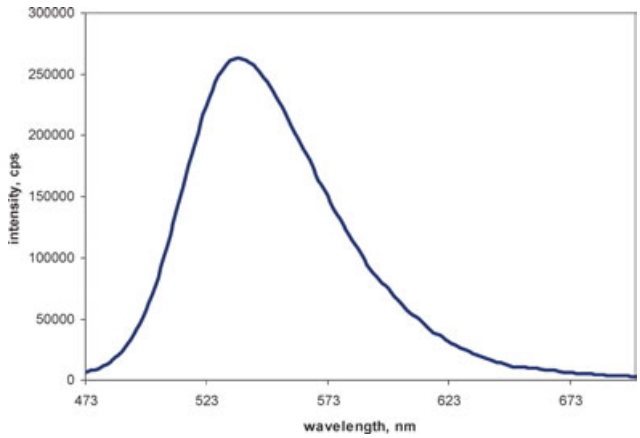


FIGURE 3 Fluorescence spectrum of **2a**. The solution of **2a** in chloroform ($2.182 \cdot 10^{-6}$ M) was exited at 458 nm, emission was acquired in wavelength interval of 473–700 nm. The spectrum presented is typical for all studied compounds.

yielding the products with toxic properties, we used the cell line McA RH 7777—cells of rat liver carcinoma with activated isoenzymes P-450 to check this suggestion. However, we also did not achieve the 50% death of such cells in this case. In fact, the IC_{50} values obtained are similar to N-acylated derivatives bearing dimethylamino groups in the aryl rings, which are known to demonstrate lower cytotoxicity that analogs with acceptor substituted aryl groups [3].

EXPERIMENTAL

General

The NMR (^{1}H, ^{13}C, and ^{31}P) spectra were recorded with a Bruker AMX-400 spectrometer using residual proton signals of deuterated solvent as an internal standard (^{1}H, ^{13}C) and 85% H_3PO_4 (^{31}P) as an external standard. The ^{13}C NMR spectra were registered using the JMODECHO mode; the signals for the C atom bearing odd and even numbers of protons have opposite polarities. IR spectra were recorded in KBr pellets on a Fourier spectrometer "Magna-IR750"(Nicolet), resolution 2 cm^{-1}, 128 scans. Melting points are uncorrected. The starting 3,5-bis(arylidene)4-piperidone **1** [9] was obtained by the known procedures as reported. The phosphoryl and phosphonyl chlorides were obtained by phosphorylation of the corresponding alcohols either by $POCl_3$ or by $CH_3P(O)Cl_2$ according the procedures reported by us earlier [17].

N-phosphorylated 3,5-bis(arylidene)4-piperidones (typical procedure). Triethylamine (0.14 g, 1.00 mmol) was added to a slurry of the piperidone **1** (0.36 g, 1.00 mmol) in 15 mL of THF, the equimolar amount of the corresponding phosphoryl or phosphonyl chloride was added dropwise. The mixture was stirred at room temperature overnight, the precipitate formed was filtered off, the filtrate was evaporated in vacuo, and the residue was recrystallized from benzene to afford the desired compound.

bis(2,2,2-Trifluoroethyl)(3E,5E)-3,5-bis[4-(dimethylamino)benzylidene]-4-oxopiperidin-1-ylphosphate **2a**. Yield 42%; mp 189–190°C. IR, KBr, ν (cm^{-1}): 1581 (C=O), 1524 (C=C), 1370, 1264, 1168 (P=O), 1072 (P–O–C), 987. ^{31}P NMR ($CDCl_3$) δ: −8.18. ^{19}F

TABLE 2 Absorption and Fluorescence Data for Compounds **1, 2a–2c**

	Max. Absorption λ (nm)	*Extinction Coefficient (L mol^{-1} cm^{-1})*	*Emission λ_{max} (nm)*
1	280	33,000	307.0
	453	46,000	538.0
2a	281	91,000	400.0/536.0
	458	122,000	536.0
2b	277	184,000	400.0/523.0
	454	38,000	529.0
2c	264	59,000	371.0/542.0
	452	50,000	536.0

TABLE 3 Cytotoxicity of Compounds Against Human Tumor Cells

	IC_{50} (mM)			
	H9	*K562*	*MCF7*	*McA RH7777*
2a	>50	>50	>50	>50
2b	>20	>20	na	>20
2c	>50	>50	8.5	>50

NMR ($CDCl_3$) δ: 2.65.^{1}H NMR ($CDCl_3$) δ: 3.03 (s, 12H, $N(CH_3)_2$), 4.12–4.30 (ABXY pattern, 4H, $^3J_{PH}$ = 12.0 Hz, $^3J_{FH}$ = 8.8 Hz, OCH_2) 4.51 (d, 4H, $^3J_{PH}$ = 8.4 Hz, CH_2N-P), 6.70 (d, 4H, $^3J_{HH}$ = 8.8 Hz, $-C_6H_4-$N), 7.32 (d, 4H, $^3J_{HH}$ = 8.8 Hz, $-C_6H_4-$N), 7.80 (s, 2H, CH=C^5). ^{13}C NMR ($CDCl_3$) δ 39.89 (s, NCH_3), 46.11 (d, $^2J_{PC}$ = 3.80 Hz, C^2,C^6), 111.61 (s, C^7), 62.72 (dq, $^2J_{FC}$ = 37.8 Hz, $^2J_{PC}$ = 4.2 Hz, OCH_2), 111.46 (s, C^7), 122.26 (dq, $^1J_{FC}$ = 278.1 Hz, $^3J_{PC}$ = 11.1 Hz, CF_3), 122.80 (s, C^8), 126.86 and 126.91 (2s, N-C in $-C_6H_4-N(CH_3)_2$), 129.53 and 132.57 (2s, C^9, C^{10}), 150.80 (s, C^3, C^5), 185.32 (s, C^4). Found: C 54.47; H 5.25; N 6.73. Calcd for $C_{28}H_{34}F_6N_3O_4P$: C 54.11, H 5.51; N 6.76.

Diphenyl (3E,5E)-3,5-bis[4-(dimethylamino)benzylidene]-4-oxopiperidin-1-ylphosphate **2b**. Yield 53 (%); mp 209–211°C. IR, KBr, ν (cm^{-1}): 1581 (C=O), 1524 (C=C), 1370, 1280, 1182, and 1169 (P=O), 1076 (P–O–C), 987, 927. ^{31}P NMR ($CDCl_3$) δ: −0.90. ^{1}H NMR ($CDCl_3$) δ: 3.04 (s, 12H, $N(CH_3)_2$), 4.60 (d, 4H, $^3J_{PH}$ = 8.4 Hz, CH_2N-P), 6.71 (d, 4H, $^3J_{HH}$ = 8.8 Hz, $-C_6H_4-$N), 7.11 (d, 4H, $^3J_{HH}$ = 8.8 Hz, $-C_6H_4-$N), 7.08–7.28 (m, 10H, C_6H_5O), 7.67 (s, 2H, CH=C^5). ^{13}C NMR ($CDCl_3$) δ: 39.99 (s, NCH_3), 46.40 (d, $^2J_{PC}$ = 4.0 Hz, C^2,C^6), 117.70 (s, C^7), 120.08 (d, $^3J_{PC}$ = 5.1 Hz, *m*-C in C_6H_5OP), 121.75 (s, C^8), 124.85 (s, *o*-C in C_6H_5OP), 127.51 and 127.56 (2s, N-C in $-C_6H_4-N(CH_3)_2$), 132.60 and 137.74 (2s, C^9, C^{10}), 137.19 (s, *p*-C in C_6H_5OP), 150.44 (d, $^2J_{PC}$ = 6.5 Hz, P–O–C in C_6H_5OP), 150.72 (s, C^3, C^5), 185.66 (s, C^4). Found: C 70.67; H 6.05; N 7.09; P 4.95. Calcd for $C_{35}H_{38}N_3O_4P$: C 70.81, H 6.11; N 7.08; P 5.22.

Phenyl (3E,5E)-3,5-bis[4-(dimethylamino)benzylidene]-4-oxopiperidin-1-yl(methyl)phosphonate **2c**. Yield 34 (%); mp 184–185°C. IR, KBr, ν (cm^{-1}): 1580 (C=O), 1522 (C=C), 1369, 1164 (P=O), 1068 (P–O–C), 987, 917. ^{31}P NMR ($CDCl_3$) δ: 31.19. ^{1}H NMR ($CDCl_3$) δ: 1.48 (d, 3H, CH_3P, $^2J_{PH}$ = 16.5 Hz), 3.03 (s, 12H, $N(CH_3)_2$), 4.60 (d, 4H, $^3J_{PH}$ = 8.4 Hz, CH_2N-P), 6.70 (d, 4H, $^3J_{HH}$ = 9.0 Hz, $-C_6H_4-$N), 7.32 (d, 4H, $^3J_{HH}$ = 9.0 Hz, $-C_6H_4-$N), 7.09–7.15 (m, 2H, C_6H_5O), 7.26–7.31 (m, 3H, C_6H_5O), 7.72 (s, 2H, CH=C^5). ^{13}C NMR ($CDCl_3$) δ: 12.33 (d, $^1J_{PC}$ = 214.0 Hz, PCH_3), 39.69 (s, NCH_3), 45.39 (d, $^2J_{PC}$ = 5.5 Hz, C^2, C^6), 111.46 (s, C^7), 120.06 (d, $^3J_{PC}$ = 7.5 Hz, *m*-C in C_6H_5OP), 122.40 (s, C^8), 124.29 (s, *o*-C in C_6H_5OP), 127.81 and 127.78 (2s, N-C in $-C_6H_4-N(CH_3)_2$), 129.36 and 132.40 (2s, C^9, C^{10}), 137.38 (s, *p*-C in C_6H_5OP), 150.21 (d, $^2J_{PC}$ = 8.8 Hz, P–O–C in C_6H_5OP), 150.51 (s, C^3, C^5), 185.77 (s, C^4). Found: C 69.66; H 6.69; N 8.19. Calcd for $C_{30}H_{34}N_3O_3P$: C 69.89, H 6.65; N 8.15.

X-ray Crystallography

Crystals of **2a** suitable for X-ray diffraction were grown by slow evaporation from CH_2Cl_2 solution. Crystallographic data for **2a**: crystals of bis(2,2,2-trifluoroethyl) (3*E*,5*E*)-3,5-bis[4-(dimethylamino)-benzylidene]-4-oxopiperidin-1-ylphosphonate are triclinic, space group P-1, a = 9.4914(19) Å, b = 9.6298(19) Å, c = 17.836(4) Å, α = 92.135(4)°, β = 98.602(4)°, γ = 119.344(4)°, V = 1393.4(5) Å^3, Z = 2, M = 605.51, d_{calc} = 1.443 g/m^3, μ(Mo K$_\alpha$) = 0.71073 Å, F(000) = 628. Intensities of 8698 reflections were measured with a SMART 1000 CCD diffractometer at 120 K [ω scans with a 0.3° step and 25 s per frame exposure, $2\theta < 52°$], and 5354 independent reflections (R_{int} = 0.0208) were used for further refinement. Reflection intensities were integrated using SAINT software [18] and corrected for absorption by semi-empirical method (SADABS program [19]) based on multiple measurements of identical reflections and equivalents. The positions of hydrogen atoms were calculated and included in refinement with the riding model. The presence of additional peaks on atoms in substituents at the P1 atom revealed the disordering of $-PO(OCH_2CF_3)_2$ group. We included in refinement two positions of this group with ratio 1:1.

Crystallographic data (excluding structure factors) for the structure of **2a** have been deposited to the Cambridge Crystallographic Data Centre; no. CCDC 271747. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ UK (fax: (international) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk).

Absorption and Fluorescence

Ground-state absorption spectra were recorded with a HP 8453 UV-visible spectrophotometer. Steady-state fluorescence measurements were carried out in standard quartz cuvettes with a Fluorolog Fl-3 spectrofluorimeter. To avoid re-absorption and re-emission effects all runs were made at low concentrations ((1–2.2) × 10^{-6} M).

Biological Evaluations

Cell lines used for estimation were K-562—human cell line from chronic myeloid leukemia, H9—human cell line from acute lymphoblastic leukemia, and MCF7—human mammary carcinoma.

Cells were grown in RPMI-1640 medium (Sigma-Aldrich, UK) supplemented with 10% fetal bovine serum (FBS, HyClone, USA), 2 mML-glutamine, and gentamicin.

Cell Viability Assay

Cells were plated at a density of 2×10^5 cells\mL in culture medium with increasing concentrations of drugs. The compounds were primarily dissolved in dimethylsulfoxide (DMSO) and the using solutions were in culture medium FBS free. Control preparations contained similar amounts of DMSO. Plates were incubated for 48 h at 37°C in a humidified atmosphere containing 5% CO_2. After incubation, the percentage survival of the cells was recorded. The viable cells were determined by trypan blue exclusion. Each compound was examined in triplicate, and the IC_{50} values were determined graphically. The concentrations of compounds used were 5×10^{-5}, 10^{-5}, 10^{-6}, and 10^{-7} M.

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