Regioselective Synthesis of Pyrazolo[4,5-*g*]pyrido[1,2-*a*]benzimidazoles: Cytotoxic Derivatives of Pyrido[1,2-*a*]benzimidazolic Ring System

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N-1 and N-2 substituted pyrazolo[4,5-*g*]pyrido[1,2-*a*]benzimidazoles were prepared regioselectively, and cytotoxicities evaluated *in vitro* against K562 and HL60 cells. All compounds displayed weaker activity than doxorubicin against sensitive lines, but showed the same activity against resistant cell lines (multidrug resistance +, (MDR$^+$); K562R and HL60R) indicating no resistance phenomena.

Key words pyrazolo[4,5-*g*]pyrido[1,2-*a*]benzimidazole; pyrido[1,2-*a*]benzimidazole; pyrazole; anticancer agents; multidrug resistance; glycoprotein GP 170

As part of studies related to the biological activities of tri- and tetracyclic heterocycles with a bridghead nitrogen,[1] we initiated a program aimed at examining the synthesis and cytotoxicity against resistant tumor cells of new tetracyclic derivatives of azacarbazoles.[2] Anticancer drugs still have limited efficacy against numerous tumor types because cancer cells can develop mechanisms of resistance allowing them to evade chemotherapy. One type of multidrug resistance (MDR) has been shown to be mediated by an energy dependent glycoprotein (PGP or GP 170) which possesses low substrate specificity.[3] A large number of drugs, such as anthracyclines, epipodophyllotoxins, vinca alkaloids, and taxol, are eliminated through PGP mediated efflux. In this context, the search for new drugs active towards such cells is of crucial interest for future cancer treatments. Since the pyrido[1,2-*a*]benzimidazole ring system **1** has been found to exhibit anticancer properties, a number of studies have been directed toward this heterocycle. In particular, Badaway and co-workers[4] reported the synthesis and anticancer activities of twenty pyrido[1,2-*a*]benzimidazole derivatives against sixty human tumor cell lines. These investigations showed good activities for compounds substituted on ring A. However, to our knowledge, no reports concerning modification of ring C are known. As a first approach to such modifications, herein we report the regioselective synthesis of some pyrazolo derivatives and their antitumor activities against some resistant cell lines (Chart 1).

Chemistry The starting 6,7,8,9-tetrahydropyrido[1,2-*a*]-benzimidazol-9-one (**2**) was synthesized by using a slight modification of the previously described method (dimethoxyethane as solvent).[5] Treatment of **2** with sodium hydride in tetrahydrofuran followed by addition of ethyl formate led to hydroxymethylene derivative **6** in 69% yield. Condensation of **6** with different hydrazines was then investigated: treatment of **6** with 2-nitrophenylhydrazine led to the formation of the corresponding hydrazone **7** in refluxing methanol, while the 3-nitro derivative led only to recovery of starting material. Attempts to cyclize the hydrazone **7** at higher temperatures were not effective. When the same reaction was conducted with hydrazine hydrate, the expected 2*H*-4,5-dihydropyrazolo[4,5-*g*]pyrido[1,2-*a*]benzimidazole (**8**) was isolated in 89% yield, while the use of methylhydrazine led regioselectively to one isomer **9** substituted on the N-1 position. Synthesis of derivatives substituted on the N-2 position was conducted by regioselective alkylation of the unsubstituted derivative **8**. Treatment of **8** with sodium hydride in dry dimethylformamide followed by addition of methyl iodide gave the 2-methyl derivative **10**, while the use of 3-dimethylaminopropyl chloride led exclusively to the formation of **11** (Chart 2).

The difference in reactivity between 2-nitrophenylhydrazine and methylhydrazine can be explained by steric considerations for the crucial cyclization step. Effectively, ring closure to give intermediates **13** and **14**, as well as the dehydration step to give **9** and **15** should be dramatically affected by steric interactions between the substituent on the starting hydrazine and ring A of the pyridobenzimidazole nucleus (Chart 3). In order to rationalize such considerations, these interactions were quantified by semi-empirical molecular orbital calculations (AM1 calculation within MOPAC 6.0 (PRECISE option)). Table 1 reports the heats of formation of the different species **7**, **12**, **13**, **14**, **15**, **9**. The values indicate great differences in the formation of the intermediate species **13** (ΔHf=36.34 kcal/mol) and **14** (ΔHf=17.01 kcal/mol). The high value for **13** indicates that the equilibrium is displaced toward the hydrazone form **7**, and that the formation of the pyrazole is thermodynamically controlled by this first step. Effectively, when this value is lower (17.01 kcal/mol for

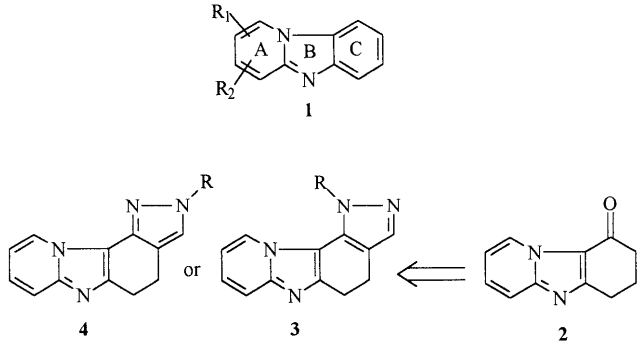

Chart 1

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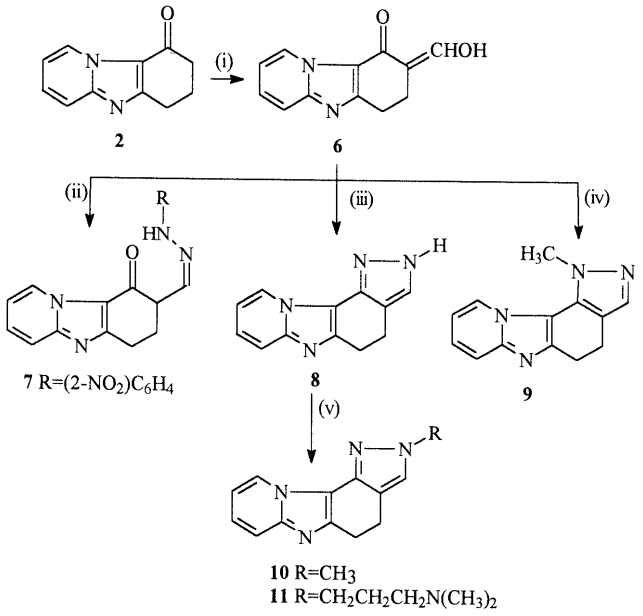
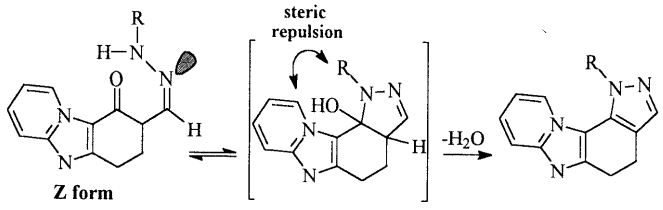


reagents and conditions

(i) a) NaH, THF, b) $HCO_2CH_2CH_3$;(ii)$(2\text{-}NO_2)C_6H_4NHNH_2$ / $(4\text{-}NO_2)C_6H_4NHNH_2$, MeOH, reflux
(iii) NH_2NH_2, MeOH, reflux;(iv) CH_3NHNH_2, MeOH, reflux
(v) a) NaH, DMF;b) for **10**, ICH_3
for **11**, $Cl(CH_2)_3N(CH_3)_2$

Chart 2



7 R = $2\text{-}NO_2C_6H_4$
12 R = CH_3 (not isolated)

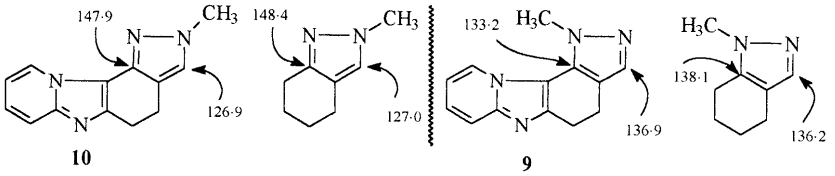
13 R = $2\text{-}NO_2C_6H_4$
14 R = CH_3

15 R = $2\text{-}NO_2C_6H_4$
9 R = CH_3

Chart 3

Table 1. Heats of Formation of the Different Species (kcal/mol)

R=$2\text{-}NO_2C_6H_4$		
7	**13**	**15**
115.99	152.33	197.50
	ΔHf=36.34	ΔHf=45.17
R=CH_3		
12	**14**	**9**
78.30	95.31	155.16
	ΔHf=17.01	ΔHf=59.85



Comparison of Chemical Shifts of C-3 in **9** and **10** with Methyltetrahydroindazoles

Chart 4

14), the equilibrium can be displaced towards the intermediate cyclized species **14** which then undergoes dehydration to give **9**. Moreover, these steric interactions do not affect the final step since calculations indicated ΔHf=59.85 kcal/mol for the methyl derivative and ΔHf=45.17 kcal/mol for the 2-nitrophenyl derivative.

Determination of the position of substituents for **8**—**11** was achieved by their ^{13}C-NMR spectra, and by comparison with methyltetrahydroindazoles.[6] When the substituent is at the N-1 position (double bond N-2/C-3), the chemical shift of C-3 is at δ 136.9 (δ 136.2 for methyltetrahydroindazole), and when the substituent is at the N-2 position (N-1/C-11b double bond), the signal shifts upfield to δ 126.9 (δ 127.0 for methyltetrahydroindazole, Chart 4).

Biological Studies Cytotoxicity of compounds **8**—**11** was evaluated against HL60 and K562 cell lines. Doxorubicin was used as a reference. The resistant sublines K562R and HL60R were established by the continuous spasm of cells to gradually increasing concentrations of daunorubicin and doxorubicin. All results are reported in Tables 2 and 3.

All compounds exhibited significant cytotoxic activities against both K562S and HL60S cell lines. However their activities were lower than the reference compound (doxorubicin) against sensitive lines. In the case of the K562 cell line, the unsubstituted compound **8** was the most active derivative against the sensitive cells ($IC_{50}=1.01\times10^{-4}$ M), while the N-1-methyl derivative **9** was the most active against the resistant line, with a small resistance factor (2.4 for **9** and 46.8 for doxorubicin). The most interesting result was obtained with the unsubstituted compound **8**, which exhibited the highest activity against both HL60S and HL60R cell lines. This activity was lower than doxorubicin on HL60S (1.03×10^{-4} and 1.72×10^{-6} M respectively), but was higher against the HL60R cell line (1.71×10^{-4} and 2.13×10^{-4} M respectively) with a resistance factor of 1.7, while the effect of doxorubicin was highly affected by the MDR phenomena, with a resistance factor of 124. In conclusion, these results indicate that these compounds represent an interesting new class of potential cytotoxic agents, active against tumor cells exhibiting the MDR phenotype (MDR+), and that introduction of substituents to the pyrazole moiety decreases the activities against both the two cell lines. Further studies are in progress to optimize activity by changing substituents on the pyrazole moiety, rather than on the pyridine ring.

Table 2. Cytotoxicity of Compounds against the K562 Cell Line

Compound	K562 S		K 562 R		
	IC 50	SD	IC 50	SD	RF
Doxorubicin	1.84×10^{-6}	1.51×10^{-6}	8.62×10^{-5}	9.15×10^{-5}	46.8
8	1.01×10^{-4}	9.92×10^{-5}	5.13×10^{-4}	3.65×10^{-4}	5.1
9	1.15×10^{-4}	7.25×10^{-5}	2.73×10^{-4}	1.21×10^{-4}	2.4
10	2.99×10^{-4}	1.33×10^{-4}	5.92×10^{-4}	5.02×10^{-4}	1.98
11	1.28×10^{-4}	3.30×10^{-5}	3.50×10^{-4}	1.52×10^{-4}	2.7

Table 3. Cytotoxicity of Compounds against the HL60 Cell Line

Compound	HL60 S		HL60 R		
	IC 50	SD	IC 50	SD	RF
Doxorubicin	1.72×10^{-6}	1.34×10^{-6}	2.13×10^{-4}	2.10×10^{-4}	124
8	1.03×10^{-4}	7.49×10^{-5}	1.71×10^{-4}	1.50×10^{-5}	1.7
9	4.81×10^{-4}	5.45×10^{-4}	4.47×10^{-4}	3.03×10^{-4}	0
10	9.60×10^{-4}	5.39×10^{-4}	4.44×10^{-4}	5.53×10^{-4}	0
11	1.36×10^{-4}	2.51×10^{-5}	3.0×10^{-4}	1.29×10^{-4}	2.2

SD, standard deviation; RF, resistance factor

Experimental

Syntheses Melting points were determined on a Büchi capillary melting point apparatus and are not corrected. Elemental analysis was performed by the Microanalytical Center, ENSCM, Montpellier. Spectral measurements were taken using the following instruments: ^{1}H-NMR spectra were taken on a Brüker AC 100 instrument; ^{13}C-NMR spectra were obtained at 26 °C with proton noise decoupling at 25 MHz with a Brüker AC 100 instrument, an asterisk (*) indicates that the values can be inversed. All NMR chemical shifts are reported in δ (ppm) values relative to tetramethysilane as an internal reference. Mass spectra were recorded on a LKB 2091 spectrometer at 15 eV [θ(source)=180 °C].

6,7,8,9-Tetrahydropyrido[1,2-*a*]benzimidazol-9-one (2) A solution of 2-aminopyridine (6.15 g, 63 mmol) and 2-bromo-1,3-cyclohexanedione (15 g, 80 mmol) in 300 ml of dimethoxyethane was refluxed overnight. After evaporation of solvent, the crude product was treated as described in the literature[5] to give **2** in 60% yield.

8-Hydroxymethylene-6,7,8,9-tetrahydropyrido[1,2-*a*]benzimidazol-9-one (6) To a stirred suspension of NaH (60% in oil, 0.62 g, 32.16 mmol) in anhydrous tetrahydrofuran (THF) (8.00 ml) at 0 °C, was added under a nitrogen stream, ethyl formate (2.14 ml, 0.027 mol). After 20 min, 1 g (5.36 mmol) of **2** in 26.0 ml of THF was added rapidly, and the mixture was stirred at room temperature overnight. Methanol (1.2 ml) and water (2 ml) were then added and the resulting solution was acidified (1 N HCl, pH 4). After extraction with dichloromethane, and evaporation of the organic layers, the crude product was chromatographed on silica gel eluting with CH_2Cl_2/MeOH (98/2) to give 790 mg of pure **6** (69%), mp: 162—164 °C (recrystallization solvent, ether). ^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 2.7 (2H, t, J_{6-7}=9.09 Hz, H_7), 2.99 (2H, t, H_6), 7.07 (t, 1H, $J_{1-2}=J_{2-3}$=5.95 Hz, H_2), 7.23 (s, CHOH), 7.5 (1H, t, $J_{3-4}=J_{2-3}$=5.95 Hz, H_3), 7.69 (d, H_4), 9.23 (d, H_1), 10.05 (s, CHO), 13.20 (s, OH). *Anal.* Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.01; H, 4.83; N, 12.98.

Hydrazone (7) To a solution of **6** (250 mg, 1.17 mmol) in methanol (9 ml) was added 231 mg (1.5 mmol) of 2-nitrophenylhydrazine. The solution was refluxed for 8 h. under a nitrogen stream. After evaporation of solvent, the resulting oil was chromatographed on silica gel eluting with CH_2Cl_2/MeOH (93/7) to give **7** (75%), mp >260 °C (recrystallization solvent, methanol); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 2.52 (2H, m, H_7), 3.24 (2H, m, H_6), 3.72 (1H, m, H_8), 6.76 (1H, m, H_{ar}), 7.08 (1H, t, $J_{1-2}=J_{2-3}$=7.5 Hz, H_2), 7.30—7.90 (5H, m), 8.12 (1H, d, J_{3-4}=8.0 Hz, H_4), 9.28 (1H, d, H_1), 10.92 (s, NH). ^{13}C-NMR ($CDCl_3$, 25 MHz) δ: 25.9 (C_6), 27.2 (C_7), 40.9 (C_8), 114.4, 115.5, 116.5, 117.6, 119.7 (C_{9a}), 125.4 (C_{3ar}), 127.9 (C_1), 129.7 (C_3), 130.3 (C_{2ar}), 135.7 (C_{5ar}), 141.6 (C_{1ar}), 144.8 (N=CH), 148.8 C_{4a}), 159.8 (C_{5a}) 195.3 CO). *Anal.* Calcd for $C_{18}H_{14}N_5O_3$: C, 62.07; H, 4.05; N, 20.10. Found: C, 62.34; H, 3.98; N, 19.99.

2*H*-4,5-Dihydropyrazolo[4,5-*g*]pyrido[1,2-*a*]benzimidazole (8) To a solution of **6** (400 mg, 1.87 mmol) in methanol (14 ml) was added 0.3 ml (6.18 mmol) of hydrazine hydrate. The solution was refluxed for 3.5 h under a nitrogen stream. After evaporation of solvents, the resulting oil was chromatographed on silica gel eluting with ether/MeOH (93/7) to give **8** (350 mg, 89%); mp: 156 °C (recrystallization solvent, methanol). MS *m/z*: 210 (100), 181 (27), 83 (96). ^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 3.1 (m , H_4 , H_5), 6.9 (1H, t , $J_{9-8}=J_{9-10}$=6.7 Hz, H_9), 7.2 (1H, dd , J_{7-8}=9.0 Hz, H_8), 7.39 (1H, s, H_3), 7.62 (1H, d, H_7), 8.71 (1H, d, H_{10}); ^{13}C-NMR ($CDCl_3$, 25 MHz) δ_{CH}: 19.3 (C_5), 23.9 (C_6), 113.2 (C_9), 116.1 (C_7), 124.7 (C_3*), 125.5 (C_8, C_{10}*). *Anal.* Calcd for $C_{12}H_{10}N_4$: C, 68.56; H, 4.79; N, 26.65. Found: C, 68.40; H, 4.89; N, 26.71.

1-Methyl-4,5-dihydropyrazolo[4,5-*g*]pyrido[1,2-*a*]benzimidazole (9) This compound was obtained according to the procedure used for **8**, using methylhydrazine (reaction time 8 h), yield 77%, mp 100—102 °C (recrystallization solvent, ethyl acetate). MS *m/z*: 244 (54), 208 (4), 83 (100). ^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 2.77 (2H, m, H_4*), 2.92 (2H, m , H_5*), 4.24 (3H, s, CH_3), 6.9 (1H, dt, $J_{9-10}=J_{9-8}$=6.8 Hz, J_{7-9}=1.3 Hz, H9), 7.19 (1H, dt, J_{7-8}=7.9 Hz, J_{8-10}=1.25 Hz, H_8), 7.65 (1H, d, H_7), 8.41 (1H, d, H_{10}). ^{13}C-NMR ($CDCl_3$, 25 MHz) δ: 20.5 (C_5), 25.5 (C_4), 40.5 (CH_3), 113.2 (C_9), 113.9 (C_{11a}*), 117.2 (C_{3a}), 118.0 (C_7), 123.7 (C_8, C_{10}), 133.2 (C_{11b}), 136.9 (C_3), 145.1 (C_{6a}*), 147.9 (C_{5a}*). *Anal.* Calcd for $C_{13}H_{12}N_4$: C, 69.63; H, 5.39; N, 24.98. Found: C, 69.82; H, 5.27; N, 12.91.

2-Methyl-4,5-dihydropyrazolo[4,5-*g*]pyrido[1,2-*a*]benzimidazole (10) To a stirred suspension of NaH (60% in oil, 80 mg, 3.43 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF) (4 ml), was added slowly **8** (180 mg, 0.86 mmol) in 4 ml of anhydrous DMF, and then 0.06 ml (1 mmol) of methyl iodide. The mixture was stirred for 2 h. under a nitrogen atmosphere. Water (30 ml) was then added and the mixture saturated with NaCl and extracted with dichloromethane. The organic layers was dried over sodium sulfate and evaporated. The crude oil was chromatographed on silica gel eluting with CH_2Cl_2/MeOH (93/7) to give **10** (47%), mp 53—55 °C (recrystallization solvent, ether). MS *m/z*: 224 (100), 209 (4), 83 (25). ^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 3.06 (H_4 , m, H_5), 3.92 (s, CH_3), 6.88 (1H, t, $J_{9-10}=J_{9-8}$=6.73 Hz, H_9), 7.15 (H_3, m, 2H, H_8), 7.6 (1H, d, J_{7-8}=6.5 Hz, H_7), 8.68 (1H, dd, J_{8-10} =1.1 Hz, H_{10}). ^{13}C-NMR ($CDCl_3$, 25 MHz) δ: 19.4 (C_5), 24.22 (C_4), 38.7 (CH_3), 112.4 (C_9), 114.84 (C_{3a}*), 115.2 (C_{11a}*), 116.6 (C_7), 123.5 (C_{10}*), 125.4 (C_8*), 126.9 (C_3*), 142.2 (C_{5a}*), 144.7 (C_{11b}*, C_{6a}*). *Anal.* Calcd for $C_{13}H_{12}N_4$: C, 69.63; H, 5.39; N, 24.98. Found: C, 69.73; H, 5.33; N, 24.94.

2-*N*,*N*-Dimethylaminopropyl-4,5-dihydropyrazolo[4,5-*g*]pyrido[1,2-*a*]benzimidazole (11) This compound was obtained according to the procedure used for **10**, using 3-dimethylaminopropyl chloride hydrochloride (reaction time, 2.5 h); chromatography: silica gel, CH_2Cl_2/MeOH (75/25); yield 53% (brown oil). MS *m/z* 295 (100), 250 (45), 237 (48), 223 (65), 58 (33). ^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 2.29 (8H, s, CH_3, $H_{13'}$), 2.96 (4H, m, H_4, H_5), 4.16 (4H, m, $H_{12'}$, $H_{14'}$), 6.83 (1H, t, $J_{9-10}=J_{9-8}$=6.66 Hz, H_9), 7.15 (2H, m, H_3, H_8), 7.54 (1H, d, J_{7-8}=8.7 Hz, H_7), 8.63 (1H, d, H_{10}). ^{13}C-NMR ($CDCl_3$ 25 MHz) δ: 18.5 (C_5), 19.5 (C_4), 24.3 ($C_{13'}$), 45.1 ($C_{16'}$, $C_{17'}$),

49.7 ($C_{14'}$*), 56.2 ($C_{12'}$*), 112.5 (C_9), 114.4 (C_{3a}*), 115.6 (C_{11a}*), 116.7 (C_7), 123,6 (C_{10}); 125.6 (C_8), 126.5 (C_3), 142.3 (C_{6a}*), 144.7 (C_{5a}*), 145.0 (C_{11b}*). *Anal.* Calcd for $C_{17}H_{21}N_5$: C, 69.13; H, 7.17; N, 23.70. Found: C, 68.85; H, 7.27; N, 23.88.

Biological Studies Doxorubicin hydrochloride (Pharmacia, St Quentin en Yvelines, France), RPMI 1640 medium and fetal calf serum (Polylabo, Paris, France) were used in this study. All other reagents were of analytical grade and were obtained from commercial sources.

Cells and Cultures: The human chronic myeloid leukaemia cell line, K562, and human promyelocytic leukaemia cell line, HL60, were obtained from the American type culture collection (Rockville, Md., U.S.A.). The doxorubicin resistant sublines K562R and HL60R were established by the continuous spasm of cells to gradually increasing concentrations of daunorubicin and doxorubicin, respectively and were maintained in medium supplemented with daunorubicin and doxorubicin at 0.1 μg/ml respectively. The MDR phenotype expression of the K562R and HL60R cell lines was assessed by an immunohistochemistry method, using the two P-glycoprotein-specific murine monoclonal antibodies C219 (Cantocor, Malvern, Pa U.S.A.) and JSB1 (Tebu, le Perray en Yvelines, France). Cultures were grown in RPMI 1640 medium supplemented with 10% fetal calf serum, antibiotics and glutamine at 37 °C in a humidified atmosphere containing 5% CO_2.

Cytotoxicity Assays: In all experiments, parental sensitive and resistant K562 and HL60 cells were seeded at a final density of 6000 cells/ well in 96 well microtiter plates and were treated with drugs (doxorubicin and compounds **8**, **9**, **10**, **11**). Ten dilutions were used for each drug. After 96 h of incubation, 20 μl of a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide solution (MTT) in Phosphate Buffer Saline (PBS) (5 mg/ml) was added to each well and the wells were then exposed to 37 °C for 4 h. This colorimetric assay is based on the ability of live and metabolically unimpaired tumor-cell targets to reduce MTT to a blue formazan product.[7] Then 100 μl of a mixture of isopropanol and 1 M hydrochloric acid (96 : 4, v/v) was then added to each well. After vigourous shaking, the absorbance was measured on a microculture plate reader (Dynatech MR5000, France) at 570 nm. IC_{50} values were defined as the concentration of drug resulting in 50% survival of the treated cells as compared with controls. For each assay, more than four experiments were performed in triplicate. The resistance factor (RF) was calculated from the ratio of the IC_{50}% growth-inhibitory concentrations (IC_{50} values) recorded for K562 R and HL60 R and K562 and HL60 cells, respectively, for all drugs tested (doxorubicin; compound **8**—**11**).

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