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### A NOVEL ROUTE TO NEW DIBENZO[b,f][1,5]DIAZOCINE DERIVATIVES AS CHEMOSENSITIZERS

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## A NOVEL ROUTE TO NEW DIBENZO[b,f][1,5]DIAZOCINE DERIVATIVES AS CHEMOSENSITIZERS

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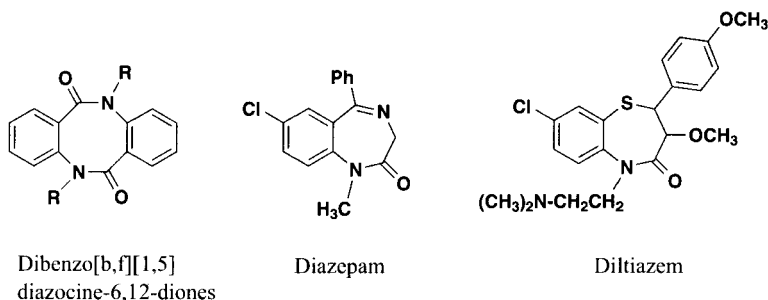
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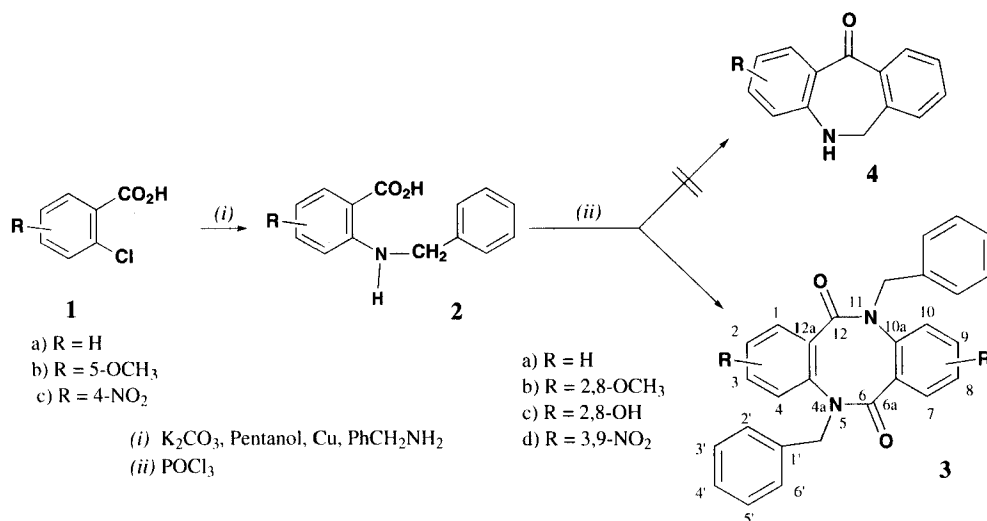
Although dibenzo[b,f][1,5]diazocine has been known for a long time,<sup>1</sup> oxo derivatives such as 5,11-dibenzylidibenzo[b,f][1,5]diazocine-6,12-dione (**3a**) were only prepared during the last decade from anthranilic acid and isatoic anhydride, in a multistep procedure.<sup>2</sup> In addition, as far as we know, until now only few substituted derivatives of **3a** have been synthesized.<sup>2,3</sup> There are common features in the molecular structure of dibenzo[b,f][1,5]diazocine-6,12-dione and those of diltiazem and benzo-diazepines such as diazepam (fig. 1), all known as calcium channel antagonists.<sup>4,5</sup>



**Fig. 1**

Thus, since calcium channel blockers may alter multidrug resistance in cancer,<sup>6</sup> we were interested in preparing a set of dibenzo[b,f][1,5]diazocine derivatives to be tested as chemosensitizers. These compounds can be readily prepared in a simple two-step procedure involving condensation<sup>7</sup> of benzylamine with substituted *o*-chlorobenzoic acids **1**, followed by cyclization with phosphorus oxychloride to give **3**. It should be noted that neither polyphosphoric acid nor thermal cyclization in diphenyl ether, was successful in effecting cyclization. Data on the compounds prepared are gathered in Table 1, including the dihydroxy derivative **3c** obtained by demethylation of the dimethoxy derivative **3b** with 62% hydrobromic acid.

The structure of compounds **3** was established by NMR spectroscopy. On the one hand, <sup>1</sup>H NMR spectra show doublets at about δ 5 ppm with *J* = 14–15 Hz. This value of coupling constant is a



typical feature for the AB figure which is due to the *gem* protons of methylene groups. On the other hand, the <sup>13</sup>C-DEPT sequence exhibits 7 CH-type carbons and 4 quaternary carbons for **3a**, while there are 6 CH-type carbons and 5 quaternary for **3b-3d**. Consequently, the dibenz[b,e]azepinone (**4**) which could have been expected to be formed, was not obtained neither as main product nor as side-product. Finally, molecular peaks determined from mass spectra support this assignment.

The drug resistance reversal effect depends on the activity of a glycoprotein (GP 170) located in the cell membrane.<sup>8,9</sup> Indeed, this protein acts as an efflux pump in order to decrease the quantity of drugs that penetrates the cell. Thus, the compounds prepared were tested on L5178 mdr cell line and activity was deduced from their capability to change Rhodamine efflux.<sup>10,11</sup> Experiments were repeated three times. The fluorescence activity ratio for some selected drug concentrations, are gathered in Table 2 with that of Verapamil used as reference drug. One may note that **3a**, **3b**, and **3c** are much more active than Verapamil in this *in vitro* test, while **3d** is nearly completely ineffective compared to its homologous derivatives. In addition, chemosensitization decreases in the following sequence of substituent on the heterocyclic moiety : OCH<sub>3</sub> > OH > NO<sub>2</sub>, i. e. in the direction as their electron-withdrawing ability.

## EXPERIMENTAL SECTION

Mps were determined on a Köfler bench. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Brüker ARX200 spectrometer with TMS as the internal reference. Elemental analyses were performed at the Service de Microanalyses (Faculté des Sciences et Techniques, Marseille, F.) on a CHN Technicon analyser. Mass spectra were obtained on a HP5987 spectrometer either by direct introduction with temperature controlled from 60° to 280° or by chemical ionization in methane as vector, under 1 torr pressure at 200° temperature of the source.

**TABLE 1.** Yields, mps, Elemental Analyses and <sup>1</sup>H NMR of Compounds **2a-c** and **3a-d**

Cmpd	Yield (%)	mp. (°C)	Elemental Analysis (Found)			<sup>1</sup> H NMR Data (δ) J (Hz)
			C	H	N	
<b>2a</b>	44	175-176	74.00 (73.87)	5.73 (5.74)	6.17 (6.14)	12.50 (unresolved signal, 1H, COOH), 8.30 (unresolved signal, 1H, NH), 7.80 (d, <i>J</i> = 1.5, 1H, Ar), 7.50 (m, 6H, Ar), 6.65 (d, <i>J</i> = 8.3, 1H, Ar), 6.55 (t, <i>J</i> = 7.2, 1H, Ar), 4.45 (s, 2H, CH <sub>2</sub> )
<b>2b</b>	36	180-181	74.69 (74.81)	6.22 (6.21)	5.81 (5.83)	7.50 (d, <i>J</i> = 3.08, 1H, Ar), 7.20-7.40 (m, 5H, Ar), 7.00 (dd, <i>J</i> = 10.15-3.09, 1H, Ar), 6.60 (d, <i>J</i> = 9.2, 1H, Ar), 4.45 (s, 2H, CH <sub>2</sub> ), 3.75 (s, 3H, OCH <sub>3</sub> )
<b>2c</b>	36	233-234	61.77 (61.71)	4.41 (4.43)	10.29 (10.28)	8.26 (unresolved signal, 1H, NH), 8.13 (dd, <i>J</i> = 8.8, 1H, Ar), 7.52 (d, <i>J</i> = 2.1, 1H, Ar), 7.36 (m, 6H, Ar), 4.45 (s, 2H, CH <sub>2</sub> )
<b>3a</b>	87 (lit.158-159) <sup>12</sup>	156-158	80.38 (80.20)	5.26 (5.28)	6.70 (6.71)	7.00-7.40 (m, 18H, Ar), 5.30 (d, <i>J</i> = 14.8, 2H, CH <sub>2</sub> ), 4.70 (d, <i>J</i> = 14.8, 2H, CH <sub>2</sub> )
<b>3b</b>	89	210-212	75.31 (75.25)	5.44 (5.43)	5.86 (5.85)	7.15-7.35 (m, 10H, Ar), 6.55-6.80 (m, 6H, Ar), 4.95 (d, <i>J</i> = 14.2, 2H, CH <sub>2</sub> ), 4.85 (d, <i>J</i> = 14.2, 2H, CH <sub>2</sub> ), 3.70 (s, 6H, OCH <sub>3</sub> )
<b>3c</b>	61	>260	74.67 (74.79)	4.88 (4.89)	6.22 (6.20)	9.82 (s, 2H, OH), 7.00-7.25 (m, 10H, Ar), 6.95 (d, <i>J</i> = 8.7, 2H, Ar), 6.60 (d, <i>J</i> = 8.6-2.6, 2H, Ar), 6.50 (d, <i>J</i> = 2.7, 2H, Ar), 5.15 (d, <i>J</i> = 14.7, 2H, CH <sub>2</sub> ), 4.64 (d, <i>J</i> = 14.7, 2H, CH <sub>2</sub> )
<b>3d</b>	46	233-235	66.14 (66.11)	3.94 (3.95)	11.02 (11.00)	8.05 (dd, <i>J</i> = 8.7, 2H, Ar), 7.80 (d, <i>J</i> = 2.02, 2H, Ar), 7.55 (d, <i>J</i> = 2.1, 2H, Ar), 7.00-7.40 (m, 10H, Ar), 5.35 (d, <i>J</i> = 14.9, 2H, CH <sub>2</sub> ), 4.85 (d, <i>J</i> = 14.9, 2H, CH <sub>2</sub> )

**TABLE 2.** Fluorescence Activity Ratio<sup>a</sup> at Several Drug Concentrations

Compd	Drug Concentrations [mmol]					
	1	2	4	10	20	40
<b>3a</b>	1.2	1.7	2.1	6.0	11.7	-
<b>3b</b>	1.6	2.5	5.0	6.5	9.9	-
<b>3c</b>	0.9	1.1	1.8	4.0	5.4	-
<b>3d</b>	0.8	-	0.7	0.8	1.2	-
Verapamil	-	-	-	-	-	4.9

a) The standard deviation is +/- 0.2.

**N-Benzylanthranilic Acids (2). General Procedure.**- A mixture of o-chlorobenzoic acid **1** (30 mmol), benzylamine (45 mmol) and potassium carbonate (48 mmol), copper powder (0.15 g) and pentanol (40 mL) was heated to reflux (140°) with stirring for 4 hrs. Excess solvent was evaporated under reduced pressure before 120 mL of warm water was added. Solution was filtered and the filtrate was neutralized with hydrochloric acid. The resulting precipitate was collected and treated with 15% aqueous potassium hydroxide (100 mL). After filtration, filtrate was neutralized with hydrochloric acid to afford **2** as solids. They were washed with water and recrystallized from absolute ethanol (Table 1).

**5-11-Dibenzylidibenzo[b,f][1,5]diazocine-6,12-dione (3).**- A mixture of anthranilic acid **2** (6 mmol) and phosphorous oxychloride (20 mL) was heated at 120° for 24 hrs, before to be poured out on ice. The diluted solution was then neutralized with 32% ammonia. The yellow precipitate obtained was recrystallized from absolute ethanol (Table 1).

**2,8-Dihydroxy-5,11-dibenzylidibenzo[b,f][1,5]diazocine-6,12-dione (3c).**- A mixture of **3b** (0.5 g, 1 mmol) and 62% hydrobromic acid (15 mL) was refluxed at 126° for 15 hrs. The solution was then poured on ice and neutralized with 32% ammonia. The precipitate obtained was washed with water (0.24 g, 61%, mp >260°) and was used without further purification.

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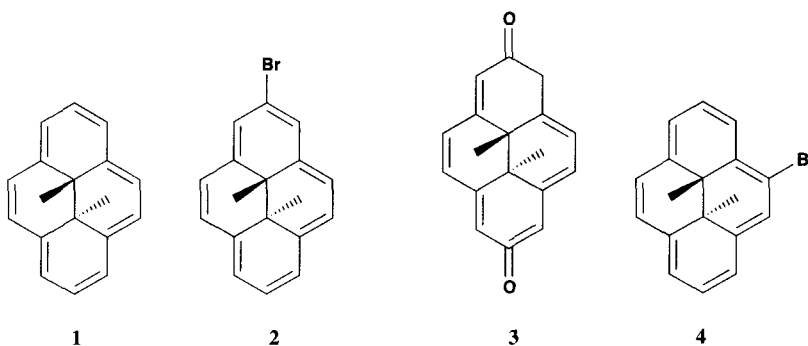
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### N-BROMOSUCCINIMIDE - CHLOROFORM, A MORE CONVENIENT METHOD TO NUCLEAR BROMINATE REACTIVE AROMATIC HYDROCARBONS

*Submitted by*                      Reginald H. Mitchell\*, Yongsheng Chen, and Ji Zhang  
(06/25/97)

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Although NBS is well known as a free radical brominating reagent for allylic and benzylic hydrogens, its use in the electrophilic bromination of aromatic rings is much less known. In 1979, we reported the use of NBS-DMF as a mild, selective nuclear monobromination reagent for reactive aromatic compounds.<sup>1</sup> Even though DMF is not the easiest solvent to handle, this reagent has since that time, found use in a variety of cases,<sup>2</sup> many of which are quite complex natural products. However, we have noted<sup>3</sup> that if the DMF is wet, problems can occur; for example, the dihydropyrene **1** gives bromide **2** with dry DMF, but quinone **3** if the DMF contains traces of water. Others<sup>4</sup> have also observed that



DMF is not an easy solvent to remove, having both a high boiling point and limited solubility in water, and thus investigated acetonitrile as an alternative solvent for methoxybenzenes and naphthalenes. In cases that are sensitive to water, the use of acetonitrile can present problems. Nevertheless, in order to obtain reasonable reaction rates at room temperature, some polarity in the solvent is