oxopropyl]glycine (8) (0.27 g) in THF were added, at 0 °C and under N_2, a solution of *N*-Boc-phenylalaninethiol (**1a**) (0.25 g) in THF, a solution of HOBt (0.14 g) in THF, and a solution of DCC (0.23 g) in $CHCl_3$. After 1 h at 0 °C, the mixture was stirred overnight at room temperature and the reaction was determined as described for compounds **5**. The crude, oily product **9** was purified by chromatography in cyclohexane/EtOAc/acetic acid 7.5/2.5/0.5: oily compound (61%); R_f (B) = 0.45. Compound **9** (0.10 g) was dissolved in 0.3 mL of CH_2Cl_2 and 0.3 mL of TFA was added at 0 °C. After 1 h at 0 °C and 3 h at room temperature, the mixture was evaporated in vacuo and the oily residue extensively washed with Et_2O/petroleum ether 50/50: oil (98%); R_f (B) 0.32; HPLC t_R (CH_3CN/TFA) 0.07% 50/50) 12 min; MS m/z = 445 (M + 1); ^1H NMR δ 2.22 (CH_3CO), centered on 2.85 [CH_2CHCH_2 (Ph) + CH_2S and CH_2 (Ph) of phenylalaninethiol moiety], 3.46 [$CH\alpha$ (Phe-thiol)], 3.93 [CH_2 (Gly)], 7.16 (Ph), 7.93 (NH_3^+), 8.70 (N*H*). Anal. ($C_{23}H_{28}N_2O_3S_2$) C, H, N.

Synthesis of *N*-[2-[[[3-[[(2-Amino-3-phenylpropyl)thio]carbonyl]propanoyl]thio]methyl]-3-phenylpropanoyl]glycine Benzyl Ester, Compound 13. To a solution of benzyl *N*-[2-(mercaptomethyl)-3-phenylpropanoyl]glycinate (0.33 g) in THF were added successively at 0 °C and under N_2, a solution of *tert*-butyl hydrogen succinate (0.17 g) in THF, a solution of HOBt (0.15 g) in THF, and a solution of DCC (0.25 g) in $CHCl_3$. After 1 h at 0 °C, the mixture was stirred overnight at room temperature, and the reaction was treated as described for compounds **5** [68%; R_f (A) 0.32]. Compound **11** (0.24 g) was dissolved in 1 mL of CH_2Cl_2, and 1 mL of TFA was added at 0 °C. After 1 h at 0 °C and 2 h at room temperature, the mixture was evaporated in vacuo and the residue extensively washed with Et_2O/petroleum ether. An oily product was obtained [84%; R_f (G) 0.79], which was used without further purification for the following step. To a solution of the preceeding compound (0.11 g) in THF were added successively a solution of Boc-phenylalaninethiol (0.07 g) in THF, a solution of HOBt (0.04 g) in THF, and a solution of DCC (0.07 g) in $CHCl_3$, at 0 °C and under N_2. After 1 h at 0 °C and overnight at room temperature, the reaction was terminated as described for compounds **5**. Compound **12** was obtained as a white solid (0.14 g, 80%) after chromatography on silica gel, using cyclohexane/EtOAc/acetic acid 8/2/0.5 as eluent [R_f (B) 0.47]. Compound **12** (0.06 g) was dissolved in 0.15 mL of CH_2Cl_2, and 0.15 mL of TFA was added at 0 °C. After 30 min at 0 °C and 3 h at room temperature, the mixture was evaporated in vacuo. The residue was extensively washed with Et_2O/petroleum ether 50/50: oily product (60%); purified by chromatography in CH_2Cl_2/MeOH 20/1; R_f (F) 0.64; HPLC t_R (CH_3CN/TFA 0.07% 50/50) 12.6 min; MS, m/z = 593 (M + 1); ^1H NMR δ 2.45 [CH_2 (succinate)], 2.58 and 2.83 [broad massifs containing CH_2S, CH_2 (Ph) of phenylalaninethiol moiety, and CH_2CHCH_2 (Ph) of the benzyl propanoyl moiety], 3.10 [$CH\alpha$ (Phe-thiol)], 3.81 ppm, [CH_2 (Gly)], 5.04 (CH_2O), 7.11 and 7.28 (Ph), 7.90 (NH_3^+), 8.47 (N*H*). Anal. ($C_{32}H_{36}N_2O_5S_2$) C, H, N.

Registry No. **1a**, 141437-85-6; **1b**, 112157-38-7; **1c**, 141437-94-7; **2a**, 141437-86-7; **2b**, 141437-95-8; **2c**, 141437-96-9; **3**, 141437-87-8; **4a**, 141437-88-9; **4e**, 141437-97-0; **5a**, 81110-69-2; **5e**, 135949-97-2; **6a**, 135949-89-2; **6b**, 135949-87-0; **6c**, 135949-90-5; **6d**, 141437-99-2; **6e**, 141437-98-1; **7a**, 135949-57-4; **7b**, 135949-54-1; **7c**, 135949-58-5; **7d**, 135949-61-0; **7e**, 135949-60-9; **7eS**, 141507-09-7; **7eR**, 141507-10-0; **8**, 76932-19-9; **9**, 141437-89-0; **10**, 141437-90-3; **11**, 141437-91-4; **12**, 141437-92-5; **13**, 141437-93-6; APN, 9054-63-1; NEP, 82707-54-8; 2,2'-dithiopyridine, 2127-03-9; 3-(acetylthio)-2-benzylpropanoic acid, 91702-98-6; *N*-[2-(mercaptomethyl)-3-phenylpropanoyl]glycinate, 15026-17-2; *tert*-butyl hydrogen succinate, 15026-17-2; (*tert*-butoxycarbonyl)phenylalaninethiol, 141437-85-6.

New Triazine Derivatives as Potent Modulators of Multidrug Resistance

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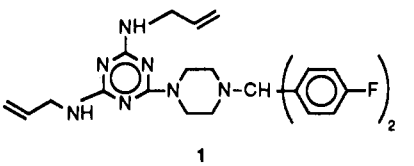
A series of 70 triazine derivatives have been synthesized and tested for their capacity to modulate multidrug resistance (MDR) in DC-3F/AD and KB-A1 tumor cells in vitro, in comparison with verapamil (VRP), a calcium channel antagonist currently used in therapy as an antihypertensive drug, which also shows MDR modulating activity. Among the 12 selected compounds, **16** (S9788) showed high MDR reversing properties in vitro (300- and 6-fold VRP at 5 μM in DC-3F/AD and KB-A1 cells, respectively) and induced a strong accumulation of adriamycin. The relationship between the increase of ADR accumulation and the fold reversal induced by these compounds and their lack of effects on the sensitive DC-3F cells suggest that they act mainly by inhibiting the P-glycoprotein (Pgp) catalyzed efflux of cytotoxic agents, as already described for a majority of MDR modulators. In vivo, in association with the antitumor drug vincristine (0.25 mg/kg), **16** (100 mg/kg) increased the T/C by 39% in mice bearing the resistant tumor cell line P388/VCR. According to these interesting properties, **16** was selected for a clinical development because it was more bioavailable than **34**, even though it was less active.

Multidrug resistance (MDR) is now recognized as a major cause of failure of cancer chemotherapy. Tumor cells having the MDR phenotype are characterized by an increased expression of an energy-dependent drug-efflux pump called P-glycoprotein (Pgp), which lowers the intracellular concentration of cytotoxic agents.[1] One current approach to circumvent this type of resistance is to inhibit this multidrug transporter by noncytotoxic compounds, thus restoring sensitivity to classical cytotoxic anticancer drugs. A wide variety of compounds have now been shown to reverse MDR in vitro, including calcium channel antagonists (verapamil, VRP), calmodulin antagonists (trifluoperazine), antihypertensive agents (reserpine), steroids (progesterone), antiparasitic agents (chloroquine), and immunosupressants (cyclosporins).[2] Among these mod-

Chart I



1

* To whom correspondence should be addressed.

(1) Endicott, J. A.; Ling, V. The biochemistry of P-glycoprotein-mediated multidrug resistance. *Annu. Rev. Biochem.* **1989**, *58*, 137-171.

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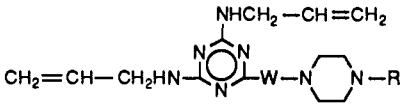
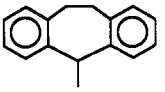
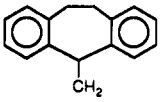
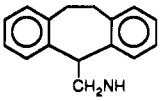
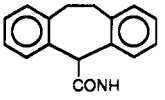
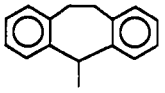
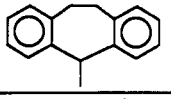
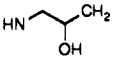
Table I. [Bis(allylamino)triazinyl]piperazine Derivatives



no.	R	W	method	mp,[a] °C	cryst[b] solvent	formula[c]
1	$(4\text{-}FC_6H_4)_2CH$		A	225–227	EtOH	$C_{26}H_{29}F_2N_7 \cdot 2CH_3SO_3H$
2	$(C_6H_5)_2CH(CH_2)_2$		A	104–108	EtOH	$C_{28}H_{35}N_7$
3	$(4\text{-}FC_6H_4)_2CH(CH_2)_3$		A	200–203	EtOH	$C_{29}H_{35}F_2N_7 \cdot C_4H_4O_4$[f]
4			A	192	EtOH	$C_{28}H_{33}N_7$
5	$(4\text{-}ClC_6H_4)_2CH$		A	236–240	EtOH	$C_{26}H_{29}Cl_2N_7 \cdot 2CH_3SO_3H$
6	$(4\text{-}FC_6H_4)_2CH$	NH	A	amorphous		$C_{26}H_{30}F_2N_8$
7			A	104–105	Et_2O	$C_{29}H_{35}N_7$
8			*d*	138–142	EtOH	$C_{29}H_{36}N_8 \cdot C_4H_4O_4$[f]
9			*e*	182–184	Et_2O	$C_{29}H_{34}N_8O$
10		$NH(CH_2)_2$	A	123–128	EtOH	$C_{30}H_{36}N_8 \cdot 2C_4H_4O_4$[f] $\cdot H_2O$
11			A	amorphous		$C_{31}H_{40}N_8O$

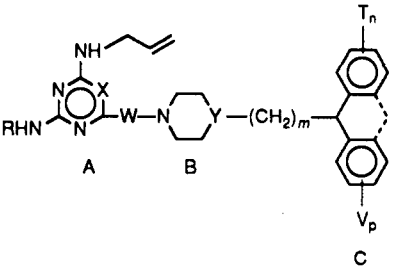
[a] All melting points were determined on a Mel Temp capillary apparatus and are uncorrected. [b] cycloH, cyclohexane; MEC, methyl ethyl ketone. [c] All compounds were purified by flash chromatography. C, H, N analyses were within 0.4% of theoretical values for the formulae given, unless otherwise stated. All compounds exhibited NMR consistent with assigned structures. [d] Synthesis described in Experimental Section. [e] For starting materials, see Experimental Section. [f] Fumaric acid.

ulators, verapamil and cyclosporin are active in animal models and in the clinic, but their relatively low potency, i.e. the high doses necessary to obtain sufficient plasma levels for effective reversal and their own pharmacological properties, induce serious side effects.[3] More potent and more specific reversing agents are urgently needed to overcome MDR in cancer.

We found, by screening, that almitrine, 1 (Chart I), a triazinylpiperazine derivative currently used for respiratory insufficiency,[4] moderately sensitized the highly resistant cell line DC-3F/AD to actinomycin D (AD). This led us to synthesize a series of analogues in order to find more potent modulators. The present work describes the chemical and biological properties of these new compounds and their ability to modulate the MDR, in vitro and in vivo.

These compounds have the general formula shown in Chart II in which X is N or CH; Y is N or CHO, CHS, CHNH; W can be a single bond, an imino, an alkylene, or an iminoalkylene chain; R an alkyl or alkenyl group; T and V, alternatively or together, represent H or Cl atoms or

Chart II



methyl or methoxy radicals. The two phenyl rings can eventually be linked in a bridge including carbon and (or) heteroatoms, m = 0–3.

Chemistry

The compounds listed in Tables I–IV have been prepared according to the methods A–E (Scheme I). Concerning the starting materials listed in Tables V–VII, most of them have been prepared according to Scheme II (parts 1 and 2).

Results and Discussion

Structure–Activity Relationships (SAR). For the discussion of SAR, the general formula has been divided in three parts (see Chart II). To obtain a potent and optimal MDR modulation on DC-3F/AD cells at nontoxic concentrations in this series (see Tables VIII and X), the following are necessary:

(1) Part A must preferably be a triazine core (X = N) rather than a pyrimidine one (X = CH) (compare toxicity of **66**, **67** vs **16**), substituted by two monoalkylamino groups

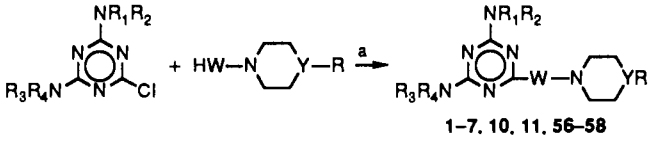
(2) Ford, J. M.; Hait, W. N. Pharmacology of drugs that alter multidrug resistance in cancer. *Pharmacol. Rev.* **1990**, *42*, 155–199.

(3) Pennock, G. D.; Dalton, W. S.; Roeske, W. R.; Appleton, C. P.; Mosley, K.; Plezia, P.; Miller, T. P.; Salmon, S. E. Systemic toxic effects associated with high dose-dose verapamil infusion and chemotherapy administration. *J. Natl. Cancer Inst.* **1991**, *83*, 105–110.

(4) Labrid, C.; Règnier, G. L.; Laubie, M. Almitrine bismesylate: Pharmacological review and structure–activity relationships. *Eur. J. Resp. Dis.* **1983**, *64* (*suppl. 126*), 185–189.

Scheme I[a]

method A: compounds **1–7**, **10**, **11** (Table I) and **56–58** (Table IV)

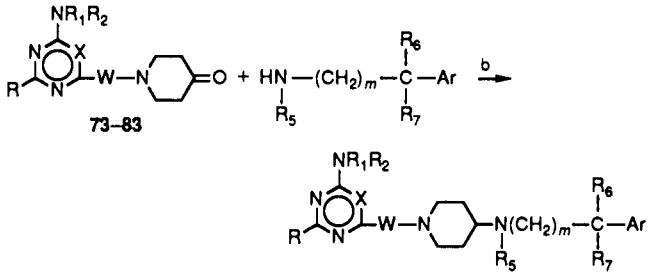


1–7, **10**, **11**, **56–58**

Y = N, CH–O, CH–S, or CH–NH

W and R have the same meaning as mentioned in Table I

method B: compounds **12–32** (Table II), **33–55** (Table III), and **59–62**, **66**, **67** (Table IV)

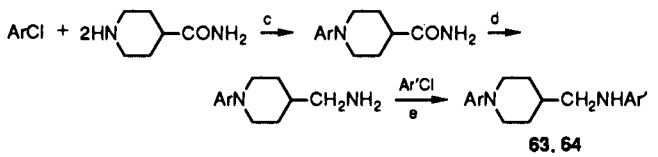


73–83

12–32, **33–55**, **59–62**, **66–67**

X can be N or CH

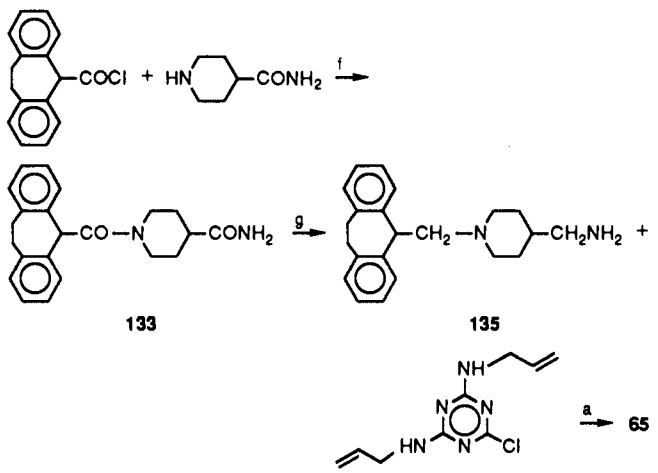
method C: compounds **63** and **64** (Table IV)



63, **64**

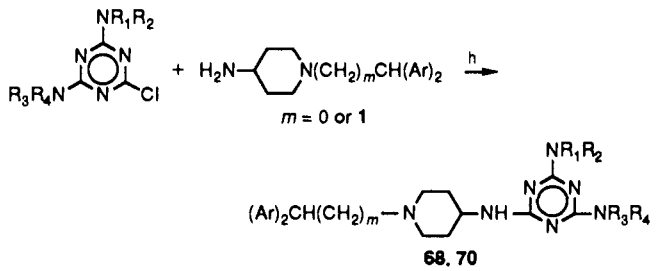
Ar and Ar' are alternatively a substituted triazinyl or dibenzosuberyl group

method D: compound **65** (Table IV)



133 **135** **65**

method E: compounds **68** and **70** (Table IV)

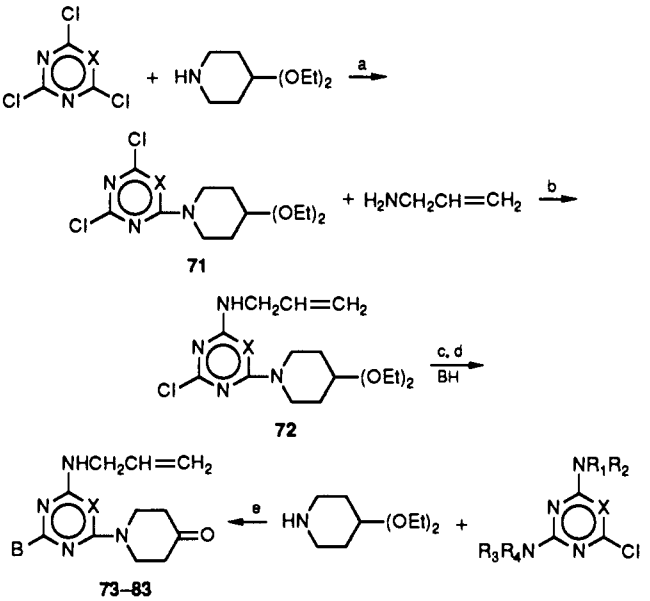


68, **70**

[a] Reagents and reaction conditions: (a) BuOH–K_2CO_3 or Et_3N at 120 °C; (b) $NaBH_3CN$–MeOH (pH 6) at room temperature; (c) toluene, at 110 °C for 16 h; (d) $LiAlH_4$–THF, at 60 °C for 3 h; (e) DMF–K_2CO_3 or Et_3N at 130 °C; (f) THF–Et_3N, at 25 °C for 16 h; (g) THF–BMS, at room temperature for 16 h, then MeOH–HCl, at 60 °C for 1 h; (h) BuOH–K_2CO_3 or Et_3N at 120 °C for 16 h.

Scheme II[a]

part 1

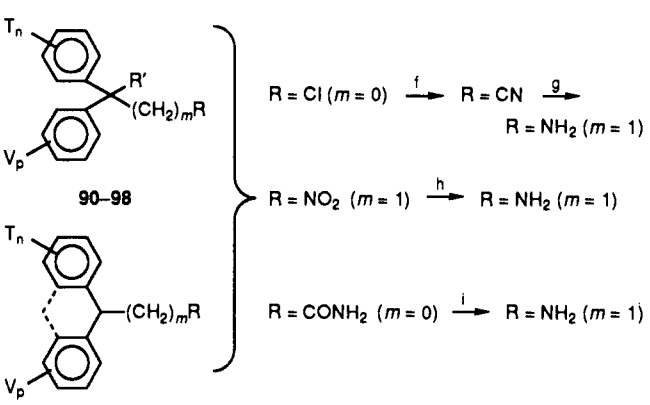


71 **72** **73–83**

B can be CH_3O, CH_3NH, C_2H_5NH, C_3H_7NH

X can be CH or N

part 2



90–98 **109–131**

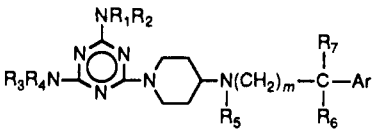
[a] Reagents and reaction conditions: (a) MEC, H_2O–$NaHCO_3$ at 0 °C; (b) DMF–allylamine excess at 20 °C for 1 h; (c) BuOH–alkylamine at 110 °C for 4 h, then 1 N HCl at 50 °C for 2 h; (d) MeOH–MeONa at 50 °C for 3 h, then 1 N HCl at 50 °C for 3 h; (e) BuOH–4,4-diethoxypiperidine excess at 110 °C for 4 h, then 1 N HCl at 50 °C for 3 h; (f) CH_3CN–AgCN excess at 80 °C for 1.5 h (see ref 11); (g) EtOH–NH_3, H_2–Raney nickel under 60 atm of pressure, at 60 °C for 5 h; (h) Et_2O–$LiAlH_4$, at room temperature for 16 h; (i) THF–$LiAlH_4$, at 60 °C for 16 h.

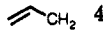
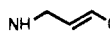
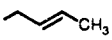
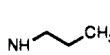
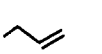
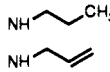
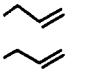
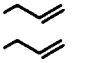
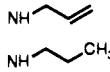
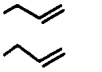
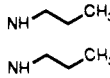
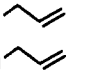
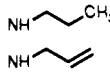
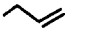
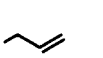
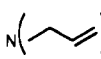
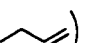
(compare respectively **28** vs **16**; **40**; **46**, **47** vs **34**; and **41** vs **34**). The first alkylamino group must be an allylamino one (other things being equal, compare **12** vs **19**) and the second can be an allyl or alkyl (in C_2–C_3) amino group (compare respectively **23** vs **16**; **35**, **45** vs **34**, and then **51**, **52** vs **42**).

(2) Part B must be a *sec*-amino-substituted piperidine core (Y = CHNR5 is better than Y = CHS or Y = CHO; compare **56** and **57** vs **16**) rather than a piperazine one (slightly less detrimental to both cellular toxicity and bioavailability) (compare respectively **12** vs **1**; and **33**, **34** vs **4** and **7**). It is better that R5 be H rather than an alkyl group (compare **53** vs **34**).

(3) The most sensitive parameter appears to be the spacer length between parts A and C (compare respectively **12** vs **16**, **57** vs **58**). **59–62**, having a spacer much longer than **34**, are completely inactive. So in the best cases,

Table II. [Bis(alkylamino)triazinyl]piperidine Derivatives



no.	NR_1R_2	NR_3R_4	R_5	R_6	R_7	Ar	m	method	mp,[a] °C	cryst[b] solvent	formula[c]
12			H	4-FC_6H_4	H	4-FC_6H_4	0	B	208–210	EtOH	$C_{27}H_{31}F_2N_7 \cdot 2C_4H_4O_4$[f]
13			H	C_6H_5	H	4-FC_6H_4	0	B[e]	242	EtOH	$C_{27}H_{32}FN_7 \cdot 2HCl \cdot 0.2H_2O$
14			H	c-C_6H_{11}	H	4-FC_6H_4	0	B[e]	228	EtOH	$C_{27}H_{36}FN_7 \cdot 2C_4H_4O_4$[f]
15			H	C_6H_5	H	C_6H_5	0	B	227	EtOH	$C_{27}H_{33}N_7 \cdot 2C_4H_4O_4$[f]
16			H	4-FC_6H_4	H	4-FC_6H_4	1	B	64–68	Et_2O	$C_{28}H_{33}F_2N_7 \cdot H_2O$
17			C_2H_5	4-FC_6H_4	H	4-FC_6H_4	0	B[e]	163	EtOH	$C_{29}H_{35}F_2N_7 \cdot 2C_4H_4O_4$[f]
18				4-FC_6H_4	H	4-FC_6H_4	0	B[e]	175	EtOH	$C_{30}H_{35}F_2N_7 \cdot C_4H_4O_4$[f]
19			H	4-FC_6H_4	H	4-FC_6H_4	0	B	228–230	EtOH	$C_{29}H_{35}F_2N_7 \cdot 2HCl \cdot 0.5H_2O$
20			H	4-FC_6H_4	H	4-FC_6H_4	0	B	250	EtOH	$C_{27}H_{33}F_2N_7 \cdot 2HCl$
21			H	C_6H_5	H	C_6H_5	1	B	69–72	EtOH, H_2O	$C_{28}H_{35}N_7 \cdot H_2O$
22			H	C_6H_5	H	C_6H_5	2	B	88–92	Et_2O	$C_{29}H_{37}N_7 \cdot 0.5H_2O$
23			H	C_6H_5	H	C_6H_5	1	B	56–58	EtOH, H_2O	$C_{28}H_{37}N_7 \cdot 1.5H_2O$
24			H	C_6H_5	H	C_6H_5	2	B	78–83	Et_2O	$C_{29}H_{39}N_7 \cdot 0.5H_2O$
25			H	2-MeC_6H_4	H	3,5-$(MeO)_2$-C_6H_3	1	B	178–184	EtOH	$C_{31}H_{41}N_7O_2 \cdot 2C_4H_4O_4$[f] $\cdot H_2O$
26			CH_3	C_6H_5	H	C_6H_5	1	B[e]	172–176	EtOH	$C_{29}H_{37}N_7 \cdot 2C_4H_4O_4$[f] $\cdot 0.5H_2O$
27			H	3,4-$(MeO)_2$-C_6H_3	H	3,4-$(MeO)_2$-C_6H_3	2	B	180–182	EtOH	$C_{33}H_{45}N_7O_4 \cdot 1.5C_4H_4O_4$[f] $\cdot 0.5H_2O$
28			H	C_6H_5	H	C_6H_5	1	B	206–210	EtOH	$C_{34}H_{43}N_7 \cdot C_4H_4O_4$[f]
29			H	C_6H_5	C_6H_5	C_6H_5	1	B[e]	135–136	AcOEt	$C_{34}H_{39}N_7$
30			H	2,6-Me_2-C_6H_3	H	2,6-Me_2-C_6H_3	1	B	205–207	EtOH	$C_{32}H_{43}N_7 \cdot 2C_4H_4O_4$[f] $\cdot H_2O$
31			H	$C_6H_5SO_2$	H	C_6H_5	1	B[e]	189–190	EtOH	$C_{28}H_{35}N_7O_2S \cdot 2C_4H_4O_4$[f]
32			H	c-C_6H_{11}	H	4-FC_6H_4	1	B[e]	72–79	Et_2O	$C_{28}H_{40}FN_7 \cdot H_2O$

[a–c,e,f] See corresponding footnotes for Table I.

where B is a 4-amino-substituted piperidine, the m value must always be 1 (compare respectively **12** vs **16**, and **33** vs **34**).

(4) The part C can be (a) either a benzhydryl group eventually substituted by halogens or alkyl or alkoxy groups [In this case, the MDR modulating activity decreases according to both the nature and the position of substitutions, in decreasing order: F ≫ H ≥ alkyl, alkoxy (compare **16**, **21**, **25**, **30**). In another case, if one exchanges the benzhydryl group for a cyclohexyl phenylmethyl group (**32** vs **16**), the toxicity increases dramatically and the activity is completely lost if the benzhydryl group is replaced by a triphenylmethyl group (**29**).] (b) or a tricyclic system in which the bridge ---- represents an alkylidene or alkylene group in C2–C3 with one or several incorporated heteroatoms, O, N, S. In a general manner, the compounds with a dibenzosuberane-like structure (Table III) are more active than those with a benzhydryl group (Table II). The order of decrease of the MDR inhibiting activity, as a function of the nature of the bridge (at a concentration of 5 μM), is **34**, CH_2-CH_2 > **43**, $(CH_2)_3$ > **44**, SO_2NCH_3 > **42**, CH_2O > **50** > **38**, CH=CH > **16**. Not at all active were **39**, **49**, and **55**.

(5) Finally, the permutation of radicals R and R′ (See Table IV) around the 4-amino-substituted piperidine B (Y = CHNH) leads to compounds less active or much more toxic (compare respectively **64** vs **34**; **69** vs **21**; and **68** vs **12**).

Biological Results. The study of the MDR-reversing properties of these new derivatives was first carried out in vitro on DC-3F/AD cells. The compounds were tested at four concentrations (1, 2.5, 5, and 10 μM) and the toxicity due to the modulator was systematically measured. Figure 1A shows a typical dose–response curve obtained with VRP, used as a reference molecule, and compounds **1**, **16**, and **34**. VRP was active from 5 μM [fold reversion (FR) = 3.1], while compound **1** had the same activity at 1 μM, and compounds **16** and **34** well below 1 μM. Table VIII gives the FR values obtained at 5 and 10 μM for all the analogues. The optimal concentration is around 5 μM, since many compounds became cytotoxic at 10 μM under these experimental conditions (4 days of exposure). Compounds toxic at 5 μM (**10**, **11**, **24**) were quite inactive at 2.5 μM (FR = 22, 24, and 17, respectively).

From Table VIII, it can be shown that compounds **34**, **44**, **45**, and **48**, the most active of this series, are about

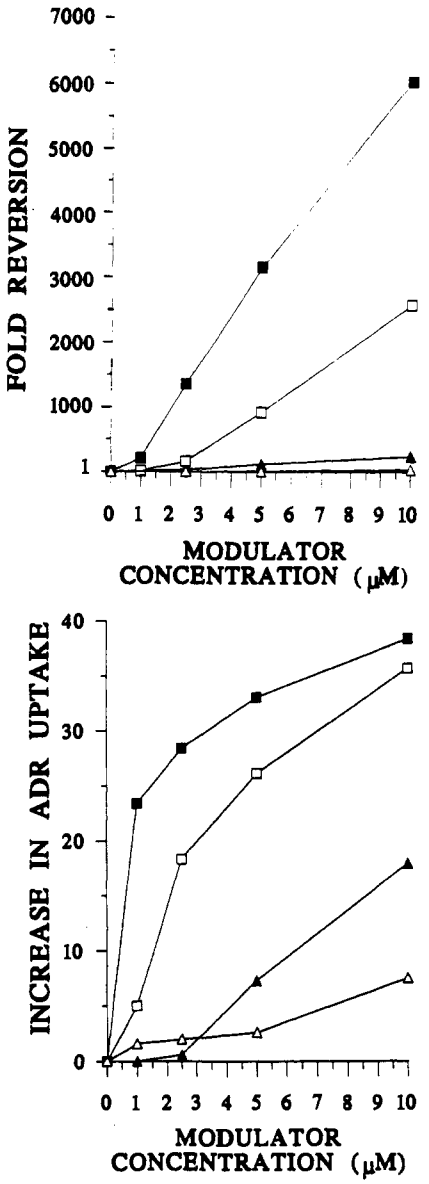


Figure 1. In vitro activity of compounds 1 (▲), 16 (□), and 34 (■) on DC-3F/AD cells compared with VRP (△): (A) Cells were exposed for 4 days to AD alone or to AD + modulator and the IC_{50} were measured by the MTT assay. Fold reversion is the ratio of the IC_{50} (AD alone)/IC_{50} (AD + modulator). (B) Cells were incubated with 50 μM ADR for 5 h with ADR alone or ADR + modulator. The increase in ADR uptake is (mean ADR fluorescence of treated cells) − (mean fluorescence of untreated cells).

300–1000-fold more active (at 5 μM) than VRP in sensitizing DC-3F/AD cells. Compounds **16**, **34**, and VRP did not modify the sensitivity of the sensitive DC-3F cells to AD (FR = 0.98–1.6). The effect of the compounds on the accumulation of ADR by DC-3F/AD cells was studied by flow cytometry, taking advantage of the strong fluorescence of ADR. Under these experimental conditions (5-h incubation), all the compounds were devoid of toxicity. Figure 1B shows that compounds **1**, **16**, and **34** increase the cellular fluorescence of ADR. Compound **34** is about 20-fold more potent (in terms of ratio of the modulator concentrations producing a similar increase in ADR fluorescence) and 5-fold more active (at 10 μM) than VRP. The relationship between the reversing activity and the increase of ADR accumulation is shown in Table VIII. The interpretation of this relationship is complicated by the fact that FR is measured with AD, while the effects of the compounds on the Pgp function was measured with ADR.

In order to verify the activity of the compounds on a human MDR line, and to better correlate the FR value with the increase of ADR uptake, some compounds were tested on KB-A1 cells (Table IX). Compounds active on DC-3F/AD cells were also able to sensitize KB-A1 cells to ADR. For some compounds (**31**, **34**, **38**, **42**, **48**, **49**, **54**) the fold reversal value was of the same order as the resistance factor of KB-A1 cells, showing a complete reversion of resistance. All these compounds induced a high increase in ADR uptake in this line (Table IX). It does seem clear that some relationship between MDR reversion and increase of ADR uptake exists in this series. This suggests that these compounds act mainly by increasing the accumulation of cytotoxic drugs, as do the majority of MDR modulators.

From the in vitro results, 12 compounds were selected and tested in vivo on sensitive P388 and vincristine-resistant P388/VCR murine leukemia. This leukemia is slightly resistant to VCR, the T/C obtained with 0.25 mg/kg VCR (QD × 4.1) being 199 ± 6% on the sensitive P388 against 146 ± 2% on the resistant line. The modulators, when administered alone, were devoid of antitumor activity, neither on the sensitive P388 nor on the resistant P388/VCR (T/C = 87–116%). None of these compounds increased the sensitivity to VCR of the sensitive parental P388 (as shown in Table X).

However, when administered at 100 mg/kg with VCR, all the selected compounds induced a significant increase in life span of the P388/VCR-bearing mice (Table X). The most active compound **34** was able to completely restore VCR sensitivity (i.e. T/C obtained with the association in the resistant line = T/C of VCR alone in the sensitive line), at 50 mg/kg.

Conclusion

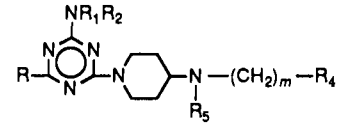
The present work deals with the synthesis and evaluation, in vitro and in vivo, of a new series of modulators of the multidrug resistance phenotype. The compounds described in this work do not belong to any of the classes of agents previously reported to reverse MDR, such as calcium channel blockers. These triazine derivatives do, however, contain chemical features known to be important for MDR reversing activity[5] i.e. a planar aromatic domain and two amino groups, one of which has a cationic charge at physiological pH.

Among the 70 compounds studied in this work, four (**34**, **44**, **45**, **48**) were about 300–1000-fold more active (at 5 μM) than VRP, the reference modulator used in this study, in sensitizing the highly resistant cells DC-3F/AD, and three (**38**, **48**, **49**) fully restore the sensitivity of KB-A1 cells to ADR.

When tested in vivo, against the P388/VCR-resistant murine leukemia, the 12 compounds selected in vitro through DC-3F/AD screening induced significant increases in the life span of mice, thus restoring their sensitivity to VCR. A relationship seems to exist between the increase of ADR accumulation and the fold reversal induced by these compounds, in that all the active compounds increase ADR accumulation in KB-A1 cells, suggesting that their effect is due, at least in part, to the inhibition of the Pgp-catalyzed efflux of cytotoxic agents, as already described for a majority of MDR modulators.[2] Moreover, the active compounds appear to be specific for the Pgp function, since they are devoid of activity in the parental

(5) Zamora, J. M.; Pearce, H. L.; Beck, W. T. Physical-chemical properties shared by compounds that modulate multidrug resistance in human leukaemia cells. *Mol. Pharmacol.* 1988, *33*, 454–462.

Table III. Other Substituted Triazinylpiperidine Derivatives



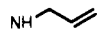
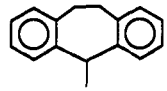
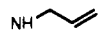
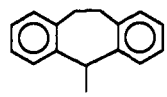
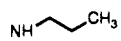
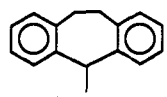
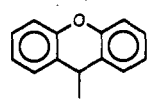
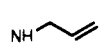
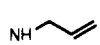
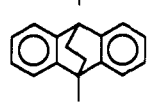
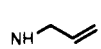
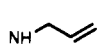
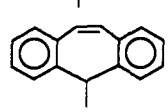
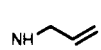
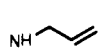
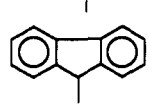
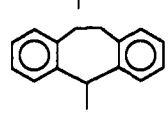
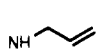
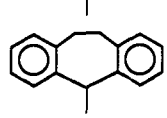
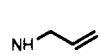
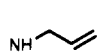
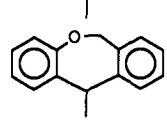
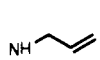
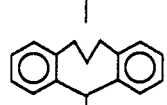
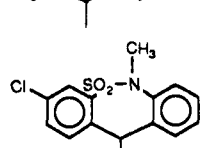
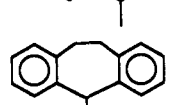
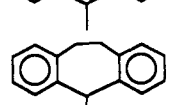
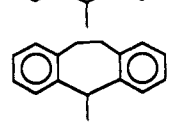
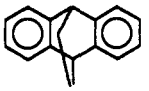
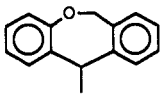
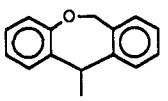
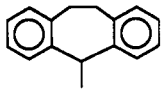
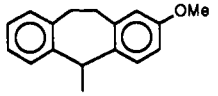
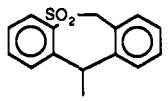
no.	R	NR_1R_2	R_5	R_4	m	method	mp,[a] °C	cryst[b] solvent	formula[c]
33			H		0	A or B	187–190	EtOH	$C_{29}H_{35}N_7 \cdot C_4H_4O_4$[f]
34			H		1	B	131–134	Et_2O	$C_{30}H_{37}N_7$
35			H		1	B	118–121	Et_2O	$C_{30}H_{39}N_7$
36			H		1	B	70–77	EtOH	$C_{28}H_{33}N_7O \cdot H_2O$
37			H		1	B[e]	148–150	Et_2O	$C_{31}H_{37}N_7$
38			H		1	B	203–205	EtOH	$C_{30}H_{35}N_7 \cdot 2C_4H_4O_4$[f]
39			H		1	B	139–144	EtOH	$C_{28}H_{33}N_7 \cdot 2C_4H_4O_4 \cdot H_2O$
40	$N(CH_3)_2$	$N(CH_3)_2$	H		1	B	234	EtOH	$C_{28}H_{37}N_7 \cdot C_4H_4O_4$[f]
41	NH_2		H		1	B	153–155	nPrOH, H_2O	$C_{27}H_{33}N_7 \cdot 2C_4H_4O_4$[f]
42			H		1	B	95–97	Et_2O	$C_{29}H_{35}N_7O$
43			H		1	B	122	Et_2O	$C_{31}H_{39}N_7$
44			H		1	B	153–155	Et_2O	$C_{29}H_{35}ClN_8O_2S$
45	NHC_2H_5		H		1	B	120–122	Et_2O	$C_{29}H_{37}N_7$
46	Cl		H		1	B	159–161	EtOH	$C_{27}H_{31}ClN_6$
47	OCH_3		H		1	B	165–167	Et_2O	$C_{28}H_{34}N_6O$
48			H		1	B	131–132	Et_2O	$C_{29}H_{35}N_7S$
49			H		1	B	185–187	EtOH	$C_{29}H_{34}N_8O$

Table III (Continued)

no.	R	NR_1R_2	R_5	R_4	m	method	mp,[a] °C	cryst[b] solvent	formula[c]
50			H		0	B[e]	amorphous		$C_{30}H_{35}N_7$
51	$NHCH_3$		H		1	B	113–116	iPrOH	$C_{27}H_{33}N_7O$
52	NHC_2H_5		H		1	B	106–107	iPrOH	$C_{28}H_{35}N_7O$
53			CH_3		1	B	105–107	iPrOH	$C_{31}H_{39}N_7$
54			H		1	B	184–187	EtOH	$C_{31}H_{39}N_7O \cdot 2C_4H_4O_4$[f]
55			H		1	B	116–119	EtOH	$C_{29}H_{35}N_7O_2S$

[a–c,e,f] See corresponding footnotes for Table I.

sensitive cell line (DC-3F) with respect to both the cytotoxicity of antitumor agent and the accumulation of ADR.[6] In addition, these active compounds do not increase the antitumor activity of VCR against the sensitive P388 leukemia in vivo.

The precise mechanism of action of these compounds, at the molecular level, is still unknown. Our preliminary results (not shown) indicating an inhibition of [^{3}H]azidopine binding to Pgp by **16** and **34** suggest a direct interaction of the modulators with Pgp, as suggested for VRP.[7] The basis for the higher potency of our compounds compared to VRP is unknown. It is possible that their affinity for Pgp is higher, or that these compounds enter cells more easily because of their high lipophilicity (log *P* of compound **16** = 4.18).

Although compound **16** is not the most potent in this series, it has been selected for further pharmacological development, because of more favorable pharmacokinetic properties in the dog. This compound has been shown to be active in different models in vitro and in vivo[8] and is currently in phase 1 clinical trial.

Experimental Section

Biological Procedures. Cell Culture and Cytotoxicity Assay. Actinomycin D (AD) and all the reversal agents were solubilized at 10^{-2} M in DMSO and diluted directly in culture medium. The maximum concentration of DMSO used (0.5%) was not cytotoxic and had no effect on chemosensitivity. verapamil (VRP) and AD were obtained from Sigma Co. Vincristine (VCR) and adriamycin (ADR) were obtained from Roger Bellon (Neuilly, France) and were dissolved in water. DC-3F/AD is a chinese hamster lung cell line, kindly provided by Dr. A. Jacquemin-Sablon, (Villejuif, France), which is highly resistant to AD (factor of resistance = 20 000) and, to a lesser extent, to ADR (factor of resistance = 375) with respect to DC-3F, the parental sensitive line. KB-A1, a human epidermoid carcinoma, was kindly provided by Dr. Gottesman (Bethesda, MD) via Dr. Charcosset (Toulouse, France) and is 340-fold resistant to ADR with respect to KB-3-1, the sensitive cell line.

These cell lines were previously characterized with respect to Pgp overexpression and cross resistance to MDR drugs.[6] Cells were cultivated in a RPMI 1640 medium supplemented with 10% fetal calf serum (Gibco), 2 mM L-glutamine, 100 units/mL penicillin, 100 μg/mL streptomycin, and 10 mM HEPES buffer, (pH = 7.4). The cytotoxicity was measured by the microculture tetrazolium assay essentially as described previously.[9] Cells were exposed for 4 days to both cytotoxic drug (nine graded concentrations in triplicate) and the reversal agent. Results are expressed as IC_{50}, the drug concentration inhibiting by 50% the absorbance with respect to untreated cells.

The activity of the reversal agents is expressed as fold reversion (FR = IC_{50} cytotoxic alone/IC_{50} cytotoxic + modulator), calculated for each concentration of modulator. To monitor the effect of the modulators on cell viability, systematic controls were performed under the same conditions, and the results are expressed as percent viability (absorbance cells grown in the presence of modulator/absorbance control cells) × 100.

ADR Uptake Studies. DC-3F/AD or KB-A1 cells (5 × 10^5/mL) were incubated with 50 μM ADR at 37 °C for 5 h with 2.5–10 μM of the tested compounds. For each sample the ADR fluorescence of 10 000 cells was analyzed, at 4 °C, on an ATC3000 flow cytometer (Bruker, Wissembourg, France) using an argon laser (Spectra-Physics, Les Ulis, France) emitting 600 mW at 488 nm. Results are expressed as the increase of the mean of ADR fluorescence of treated cells compared with the mean of ADR fluorescence of untreated cells.

Antitumor Activity. The parental sensitive P388 murine leukemia and P388/VCR, the subline resistant to VCR, were provided by NCI (Frederick, MD). Groups of 8–10 B6D2F1 female mice (Iffa Credo, Lyon, France) weighing 18–20 g were transplanted ip with 10^6 cells on day 0. The drugs were administered ip daily on days 1–4. The modulators were suspended in 0.2% (hydroxypropyl)cellulose and administered 30–60 min before VCR.

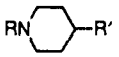
(6) Pierrê, A.; Dunn, T.; Kraus-Berthier, L.; Lêonce, S.; Saint-Dizier, D.; Rêgnier, G.; Dhainaut, A.; Berlion, M.; Bizzari, J. P.; Atassi, G. In vitro and in vivo circumvention of multidrug resistance by Servier 9788, a novel triazinoaminopiperidine derivative. In press.

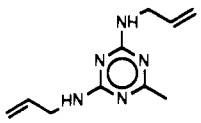
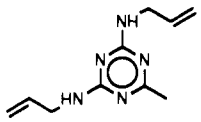
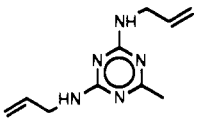
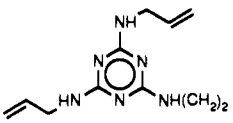
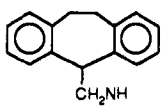
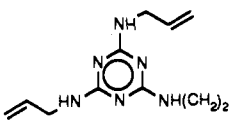
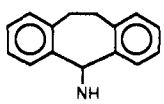
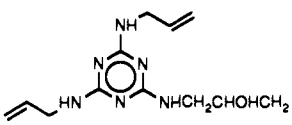
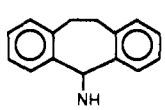
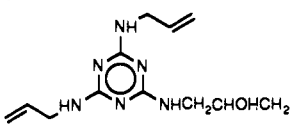
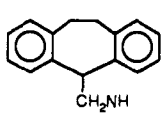
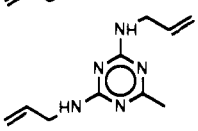
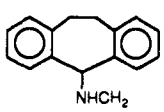
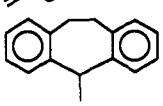
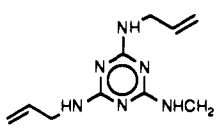
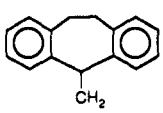
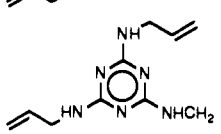
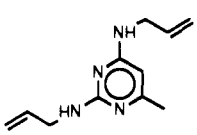
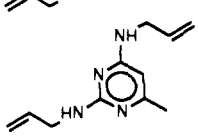
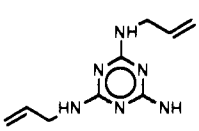
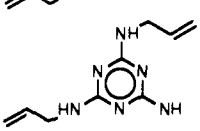
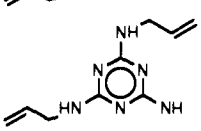
(7) Safa, A. R.; Glover, C. J.; Sewell, J. L.; Meyers, M. B.; Biedler, J. L.; Felsted, R. L. Identification of the multidrug resistance-related membrane glycoprotein as an acceptor for calcium channel blockers. *J. Biol. Chem.* **1987**, *262*, 7884–7888.

(8) Atassi, G.; Pierrê, A.; Kraus-Berthier, L.; Lêonce, S.; Rêgnier, G.; Dhainaut, A. S9788 corrects adriamycin and vincristine resistance on human and murine tumour cells in vitro and on P388 leukemia in vivo. *J. Cancer Res. Clin. Oncol.* **1991**, *117* (*Suppl. 3*), S108.

(9) Pierrê, A.; Kraus-Berthier, L.; Atassi, G.; Cros, S.; Poupon, M. F.; Lavielle, G.; Berlion, M.; Bizzari, J. P. Preclinical antitumor activity of a new Vinca alkaloid derivative. *Cancer Res.* **1991**, *51*, 2312–2318.

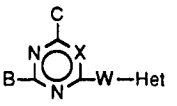
Table IV. Other Substituted Piperidine Derivatives

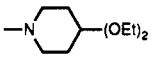
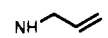
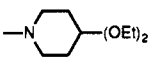
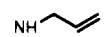
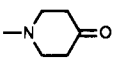
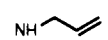
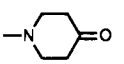
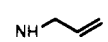
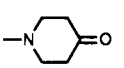
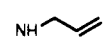
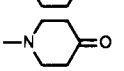
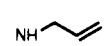
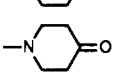
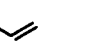
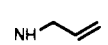
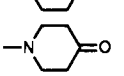
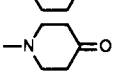
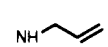
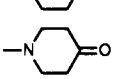
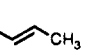
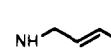
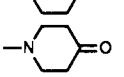
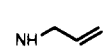
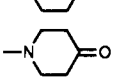
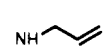
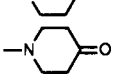
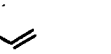
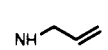
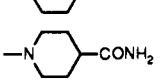
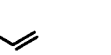
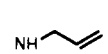
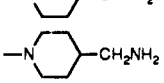
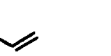
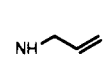
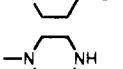
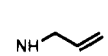


no.	R	R′	method	mp,[a] °C	cryst[b] solvent	formula[c]
56		$(4\text{-}FC_6H_4)_2CHO$	A	182–184	Et_2O	$C_{27}H_{30}F_2N_6O\cdot HCl$
57		$(C_6H_5)_2CHS$	A	172–174	EtOH	$C_{27}H_{32}N_6S\cdot C_4H_4O_4$[f]
58		$(C_6H_5)_2CH(CH_2)_2S$	A	168	EtOH	$C_{29}H_{36}N_6S\cdot C_4H_4O_4$
59			B	212	EtOH	$C_{32}H_{42}N_8\cdot 2C_4H_4O_4\cdot 0.5H_2O$
60			B	128–131	EtOH	$C_{31}H_{40}N_8\cdot 2.5C_4H_4O_4\cdot 0.5H_2O$
61			B	148–151	EtOH	$C_{32}H_{42}N_8O\cdot 2.5C_4H_4O_4\cdot 0.5H_2O$
62			B	170–173	EtOH	$C_{33}H_{44}N_8O\cdot 2C_4H_4O_4\cdot 0.5H_2O$
63			C	109–110	EtOH	$C_{30}H_{37}N_7$
64			C	amorphous		$C_{30}H_{37}N_7$
65			D	amorphous		$C_{31}H_{39}N_7$
66		$(4\text{-}FC_6H_4)_2CHNH$	B	240	EtOH	$C_{28}H_{32}F_2N_6\cdot 2HCl$
67		$(C_6H_5)_2CHCH_2NH$	B	209–211	EtOH	$C_{29}H_{36}N_6\cdot 2C_4H_4O_4$[f]
68	$(4\text{-}FC_6H_4)_2CH$		E	172	EtOH	$C_{27}H_{31}F_2N_7\cdot 2C_4H_4O_4$[f]
69	$(C_6H_5)_2CHCH_2$		E	amorphous		$C_{28}H_{35}N_7$
70	$(C_6H_5)_2CHCH_2$		E	amorphous		$C_{28}H_{37}N_7$

[a-c,f] See corresponding footnotes for Table I.

Table V. Starting Materials: Piperidine and Piperazine Derivatives



no.	B	C	W	X	Het	mp,[a] °C	cryst[b] solvent	formula[c]
71	Cl	Cl		N		89–92	Et_2O	$C_{12}H_{18}Cl_2N_4O_2$
72	Cl			N		140	H_2O	$C_{15}H_{24}ClN_5O_2$
73	OCH_3			N		153–155	Et_2O	$C_{12}H_{17}N_5O_2 \cdot HCl$
74	$NHCH_3$			N		225–228	Me_2CO	$C_{12}H_{18}N_6O \cdot HCl$
75	NHC_2H_5			N		239–241	EtOH	$C_{13}H_{20}N_6O \cdot HCl$
76				N		219–222	EtOH, H_2O	$C_{14}H_{20}N_6O \cdot HCl$
77	NHC_3H_7			N		220	EtOH	$C_{14}H_{22}N_6O \cdot HCl$
78				CH		240	EtOH	$C_{15}H_{21}N_5O \cdot C_4H_4O_4$[f]
79	$N(CH_3)_2$	$N(CH_3)_2$		N		144	Me_2CO	$C_{12}H_{20}N_6O \cdot HCl$
80	NH_2			N		214	EtOH	$C_{11}H_{16}N_6O \cdot HCl$
81				N		215	EtOH, H_2O	$C_{16}H_{24}N_6O \cdot HCl$
82			$NH(CH_2)_2$	N		amorphous		$C_{16}H_{25}N_7O \cdot HCl$
83			$NHCH_2CHOHCH_2$	N		amorphous		$C_{17}H_{27}N_7O_2 \cdot 2HCl$
84				N		159–161		$C_{15}H_{23}N_7O$
85				N		oil		$C_{15}H_{25}N_7$
86				N		100	Et_2O	$C_{13}H_{21}N_7$
87	NHC_3H_7			N		100	Et_2O	$C_{13}H_{23}N_7$
88				N		83	Et_2O	$C_{13}H_{22}N_8$
89				N		118–120	Et_2O	$C_{14}H_{23}N_7$

[a–c,f] See corresponding footnotes for Table I.

Antitumor activity is expressed in terms of T/C, where % T/C = (median survival time of treated animals/median survival time of controls) × 100.

General Methods for Preparation of Compounds. All nonaqueous reactions were carried out under an atmosphere of nitrogen. Flash column chromatography was carried out with Amicon silica gel (230–400 mesh) under a nitrogen pressure of 0.5–0.8 atm. ^1H NMR were recorded on either a Bruker AC200 or a Bruker AM400 at 200 and 400 MHz, respectively. Chemical shifts were reported as δ values in parts per million relative to tetramethylsilane (δ 0.00) used as an internal standard. IR spectra were recorded on a Bruker IFS48 infrared spectrometer. Elemental analyses were carried out on a Carlo ERBA autoanalyzer.

Starting Materials: For the Preparation of Compounds 1–11 (Table I). 1-[Bis(4-fluorophenyl)methyl]piperazine, 1-[bis(4-chlorophenyl)methyl]piperazine, and 1-[4,4-bis(4-fluorophenyl)butyl]piperazine are commercial products. 1-(3,3-Diphenylpropyl)piperazine ($bp_{0.5\ Torr}$ 162 °C) was prepared as reported.[10]

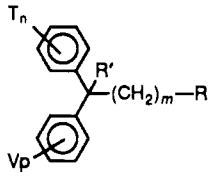
For the Preparation of Compounds 12–32 (Table II). [Bis(4-fluorophenyl)methyl]amine,[11] [(4-fluorophenyl)phenylmethyl]amine,[11] and 2-(2-methylphenyl)-2-(3,5-dimethoxyphenyl)ethylamine[12] (**94**) were prepared by reported procedures.

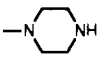
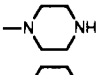
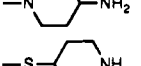
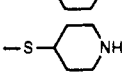
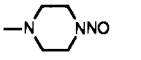
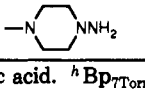
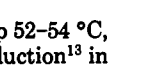
(10) Régnier, G. L.; Canevari, R. J.; Le Douarec, J. C.; Holstorp, S.; Daussy, J. Triphenylpropyl Piperazine Derivatives as New Potent Analgetic Substances. *J. Med. Chem.* **1972**, *16*, 295–301.

(11) Grisar, J. M.; Claxton, G. P.; Wiech, N. L.; Lucas, R. W.; Mackenzie, R. D.; Goldstein, S. Benzhydryl and Fluorenyl Lactamimides with Hypoglycemic, Diuretic, Blood Platelet Aggregation Inhibitory and Anti-inflammatory Activities. *J. Med. Chem.* **1973**, *16*, 885–893.

(12) Bridges, A. J.; Ortwine, D. F.; Trivedi, B. K. Preparation of N-6-aralkyladenosines having selective adenosine A2 receptor binding activity and pharmaceutical compositions containing them. PCT Int. Appl. WO 88 03147w, 1988; *Chem. Abstr.* **1989**, *111*, 97690*w*.

Table VI. Starting Materials: Diphenylalkyl Derivatives



no.	T_n	V_p	R′	R	m	mp,[a] °C	cryst[b] solvent	formula[c]
90	4-F	4-F	H	CN	0	55–57	cycloH	$C_{14}H_9F_2N$
91	4-F	4-F	H	NH_2	1	*h*		$C_{14}H_{13}F_2N$
92	H	H	C_6H_5	NH_2	1	117–120	CH_2Cl_2, MeOH	$C_{20}H_{19}N$
93	2-CH_3	3,5-$(OCH_3)_2$	H	NO_2	1	amorphous		$C_{17}H_{19}NO_4$
94	2-CH_3	3,5-$(OCH_3)_2$	H	NH_2	1	175	EtOH	$C_{17}H_{21}NO_2$
95	3,4-$(OCH_3)_2$	3,4-$(OCH_3)_2$	H	$CONH_2$	1	162–164		$C_{19}H_{23}NO_5$
96	3,4-$(OCH_3)_2$	3,4-$(OCH_3)_2$	H	NH_2	2	163–165	EtOH	$C_{19}H_{25}NO_4 \cdot C_2H_2O_4$[g]
97	2,6-$(CH_3)_2$	2,6-$(CH_3)_2$	H	CN	0	125–126	cycloH	$C_{18}H_{19}N$
98	2,6-$(CH_3)_2$	2,6-$(CH_3)_2$	H	NH_2	1	57–58		$C_{18}H_{23}N$
99	H	H	H		2	91–92[i]		$C_{19}H_{24}N_2$
100	4-F	4-F	H		3	39–41[j]		$C_{20}H_{24}F_2N_2$
101	H	H	H		1	41–45	Et_2O	$C_{19}H_{24}N_2$
102	H	H	H		0	74–76		$C_{18}H_{21}NS$
103	H	H	H		2	160	EtOH	$C_{20}H_{25}NS \cdot C_4H_4O_4$[f]
104	4-F	4-F	H		0	78–82		$C_{17}H_{17}F_2N_3O$
105	4-F	4-F	H		0	oil		$C_{17}H_{19}F_2N_3$

[a–c,f] See corresponding footnotes for Table I. [g] Oxalic acid. [h] $Bp_{7\,Torr}$ 158–160 °C. [i] $Bp_{0.5\,Torr}$ 162 °C. [j] $Bp_{1\,Torr}$ 195–200 °C.

2-(4-Fluorophenyl)-2-cyclohexylethylamine, mp 52–54 °C, was prepared by borane–dimethyl sulfide (BMS) reduction[13] in THF, for 16 h at room temperature (yield 56%), of 2-(4-fluorophenyl)-2-cyclohexylacetonitrile (oil).

2-(Phenylsulfonyl)-2-phenylethylamine, mp 112–114 °C, was prepared by BMS reduction in THF,[13] for 30 min under reflux, of 2-(phenylsulfonyl)-2-phenylacetonitrile, mp 150 °C (yield 68%), itself obtained by oxidation with an excess of MCPBA in CH_2Cl_2, at room temperature overnight, of 2-(phenylthio)-2-phenylacetonitrile, mp 50 °C (yield 85%), prepared according to the reported procedure.[14]

2,2,2-Triphenylethylamine, mp 119–121 °C, was prepared by hydrogenation under 90 atm of H_2, in EtOH–NH_3 at 60 °C for 24 h, of 2,2,2-triphenylacetonitrile, mp 127 °C[15] (yield 80%).

[(4-Fluorophenyl)cyclohexylmethyl]amine, $bp_{7\,Torr}$ 135–140 °C, was prepared by hydrogenation under 50 atm of H_2, in EtOH–NH_3 at 50 °C for 2 h, of (4-fluorophenyl)cyclohexylhydroximinomethane, mp 162 °C.

***N*-[2,2-Bis(4-fluorophenyl)ethyl]methylamine oxalate**, mp 215–216 °C, was prepared according to the reported procedure.[16]

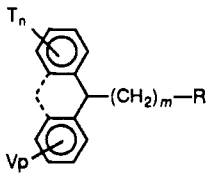
For the Preparation of Compounds 33–55 (Table III). 6-(Allylamino)-4-amino-2-chloro-1,3,5-triazine (mp 166–167 °C), 4,6-bis(allylamino)-2-chloro-1,3,5-triazine (mp 204 °C), 4-(allylamino)-2-chloro-6-(propylamino)-1,3,5-triazine (mp 210 °C), 4,6-bis(3-butenylamino)-2-chloro-1,3,5-triazine (mp 210 °C), 4,6-bis(diallylamino)-2-chloro-1,3,5-triazine ($bp_{0.6\,Torr}$ 145 °C), and 4,6-bis(dimethylamino)-2-chloro-1,3,5-triazine (mp 65 °C) were prepared by the reported methods.[17]

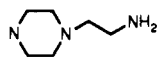
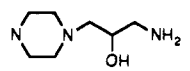
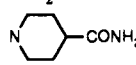
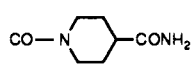
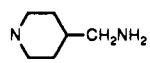
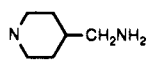
The following known compounds were also prepared according to the cited literature: 11-hydroxy-6,11-dihydrodibenzo[*b*,*e*]-thiepin,[18] 11-chloro-6,11-dihydrodibenz[*b*,*e*]oxepin,[19] 5-amino-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene,[20] 5-chloro-5*H*-dibenzo[*a*,*d*]cycloheptene,[21] 9-(aminomethyl)-9,10-ethanoanthracene,[22] and 9-cyanoxanthene.[23]

12-Chloro-5,6,7,12-tetrahydrodibenzo[*a*,*d*]cyclooctene, mp 115–116 °C, was prepared by chlorination with dry HCl in CH_2Cl_2 of the corresponding 12-hydroxy derivative, mp 77–80 °C (yield 87%), itself obtained by $NaBH_4$ reduction in MeOH of 5,6,7,12-tetrahydrodibenzo[*a*,*d*]cyclooctene-12-one, mp 138–139 °C (yield 97%).[24]

(13) Brown, H. C.; Choimoon, Y.; Narasimhan, S. Improved Procedure for Borane-Dimethylsulfide Reduction of Nitriles. *Synthesis* 1981, *8*, 605–606.
(14) Marchand, E.; Morel, G.; Foucaud, A. A Convenient Method for the Sulfenylation of Nitriles. *Synthesis* 1978, *5*, 360–361.
(15) Hoch, J. General method for the preparation of di and triarylacetonitriles. *C. R. Hebd. Seances Acad. Sci.* 1933, *197*, 770–772.
(16) Johnstone, R. A. W.; Payling, D. W.; Thomas, C. A Rapid Method of N-Alkylation of Amines. *J. Chem. Soc (C)* 1969, 2223–2224.
(17) Thurston, J. T.; Dudley, J. R.; Kaiser, D. W.; Hechenbleikner, I.; Schaefer, F. C.; Holm-Hansen, D. Cyanuric Chlorid Derivatives. I. Aminochloro-S-Triazines. *J. Am. Chem. Soc.* 1951, *73*, 2981–2986.
(18) Rajšner, M.; Protiva, M. Synthetic ataratics. VII. 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepine. *Češk. Farm.* 1962, *11*, 404–409.
(19) Boehringer, C. F. and Son. GmbH. Preparation of new dibenzoxepine. Brit. Patent 1.119.329, 1968; *Chem. Abstr.* 1969, *70*, 11583.
(20) Melloni, P.; Torre, A. D.; Meroni, M.; Ambrosini, A.; Rossi, A. C. Azetidine Derivatives of Tricyclic Antidepressant Agents. *J. Med. Chem.* 1979, *22*, 183–191.
(21) Hoffmann-La Roche and Co. Dibenzocycloheptenes. Neth Appl. 6600093, 1965. *Chem. Abstr.* 1967, *66*, 2426e.
(22) Wilhem, M.; Schmidt, P. *Helv. Chim. Acta* 1969, *145*, 1385–1395.
(23) Faust, J. A.; Sahyun, M. Xanthene and thiaxanthene cyclic amidines. US Patent 3 042674, 1962. *Chem. Abstr.* 1962, *57*, 16568 b.
(24) Winthrop, S. O.; Davis, M. A.; Herr, F.; Stewart, J.; Gaudry, R. New Psychotropic Agents. IV. Derivatives of Dibenzo[*a*,*d*]-[1,4]-cyclooctadiene. *J. Med. Chem.* 1963, *6*, 130–132.

Table VII. Starting Materials: Tricyclic Derivatives



no.	⌒	T_n	V_p	*m*	R	mp,[a] °C	cryst[b] solvent	formula[c]
106	CH_2CH_2	H	H	0		99–100	Et_2O	$C_{19}H_{22}N_2$
107	CH_2CH_2	H	H	0		70–71	EtOH	$C_{21}H_{27}N_3$
108	CH_2CH_2	H	H	0		100	Et_2O	$C_{22}H_{29}N_3O$
109	CH_2CH_2	H	H	0	NH_2	89–91	hexane	$C_{15}H_{15}N$
110	CH_2CH_2	H	H	0	CN	95	cycloH	$C_{16}H_{13}N$
111	CH_2CH_2	H	H	1	NH_2	275–280	EtOH	$C_{16}H_{17}N\cdot HCl$
112	CH=CH	H	H	0	CN	88–91	cycloH	$C_{16}H_{11}N$
113	CH=CH	H	H	1	NH_2	276	EtOH	$C_{16}H_{15}N\cdot HCl$
114	—	H	H	0	$CONH_2$	245–247	H_2O	$C_{14}H_{11}NO$
115	—	H	H	1	NH_2	272	EtOH	$C_{14}H_{13}N\cdot HCl$
116	$(CH_2)_3$	H	H	0	CN	183–185	Et_2O	$C_{17}H_{15}N$
117	$(CH_2)_3$	H	H	1	NH_2	91–93	hexane	$C_{17}H_{19}N$
118	O	H	H	0	CN	97–99	cycloH	$C_{14}H_9NO$
119	O	H	H	1	NH_2	230–235	EtOH	$C_{14}H_{13}NO\cdot HCl$
120	CH_2O	H	H	0	CN	63–65	Et_2O	$C_{15}H_{11}NO$
121	CH_2O	H	H	1	NH_2	oil		$C_{15}H_{15}NO$
122	CH_2S	H	H	0	CN	134	cycloH	$C_{15}H_{11}NS$
123	CH_2S	H	H	1	NH_2	260–266	EtOH	$C_{15}H_{15}NS\cdot HCl$
124	CH_2SO_2	H	H	0	CN	184–185	Et_2O	$C_{15}H_{11}NO_2S$
125	CH_2SO_2	H	H	1	NH_2	amorphous		$C_{15}H_{15}NO_2S$
126	CONH	H	H	0	CN	243–248	Et_2O	$C_{15}H_{10}N_2O$
127	CONH	H	H	1	NH_2	oil		$C_{15}H_{14}N_2O$
128	$SO_2N(CH_3)$	H	8-Cl	0	CN	192–194	EtOH	$C_{15}H_{11}ClN_2O_2S$
129	$SO_2N(CH_3)$	H	8-Cl	1	NH_2	127–128	EtOH, Et_2O	$C_{15}H_{15}ClN_2O_2S$
130	CH_2CH_2	2-OCH_3	H	0	CN	87–88	cycloH	$C_{17}H_{15}NO$
131	CH_2CH_2	2-OCH_3	H	1	NH_2	oil		$C_{17}H_{19}NO$
132	CH_2CH_2	H	H	0		200–203	H_2O	$C_{21}H_{24}N_2O$
133	CH_2CH_2	H	H	0		175–176	Et_2O	$C_{22}H_{24}N_2O_2$
134	CH_2CH_2	H	H	0		92–93	Et_2O	$C_{21}H_{26}N_2$
135	CH_2CH_2	H	H	1		oil		$C_{22}H_{28}N_2$
136	CH_2CH_2	H	H	1		280	EtOH	$C_{20}H_{24}N_2\cdot 2HCl$

[a–c] See corresponding footnotes for Table I.

11-Chloro-5,5-dioxo-6,11-dihydrodibenzo[*b*,*e*]thiepin (amorphous) was prepared by chlorination with dry HCl in CH_2Cl_2 of the corresponding 11-hydroxy derivative, mp 139–141 °C, itself obtained by $NaBH_4$ reduction in THF of 5,5-dioxo-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-one, mp 90 °C (yield 93%), which was prepared from 11-hydroxy-6,11-dihydrodibenzo[*b*,*e*]thiepin, by oxidation with peracetic acid in CH_3COOH (yield 50%).

11-Chloro-6-oxo-5,11-dihydro-6*H*-dibenz[*b*,*e*]azepine, mp 215–216 °C, was prepared by chlorination, with $SOCl_2$ in excess, of the corresponding 11-hydroxy derivative, mp 262–264 °C (yield 87%), obtained by $NaBH_4$ reduction in methanol of 6,11-dioxo-5,11-dihydro-6*H*-dibenz[*b*,*e*]azepine (yield 88%), prepared according to the reported procedure.[25]

5-Chloro-2-methoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene, mp 99–101 °C, was prepared by chlorination with dry HCl in CH_2Cl_2, of the corresponding 5-hydroxy derivative (oil) (yield 89%), obtained by $NaBH_4$ reduction in THF, of the 2-methoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (oil) (yield 89%), which was prepared by cyclization by means of P_2O_5 in xylene under reflux of 2-[3-(4-methoxyphenyl)propyl]benzoic acid, mp 103–105 °C (yield 55%).

5,8-Dichloro-10,10-dioxo-11-methyl-5,11-dihydrodibenzo[*c*,*f*][1,2]thiazepine, mp 245 °C, was prepared by chlorination with dry HCl in CH_2Cl_2 of the corresponding 5-hydroxy derivative (yield 89%), mp 204 °C, obtained by $NaBH_4$ reduction in THF of 8-chloro-10,10-dioxo-11-methyl-5,11-dihydrodibenzo[*c*,*f*]-[1,2]thiazepin-5-one, (yield 90%) prepared according to the reported procedure.[26]

11-Amino-9,10-dihydro-9,10-ethanoanthracene hydrochloride, mp 261–264 °C, was prepared via a Curtius reaction starting from the corresponding 11-(chlorocarbonyl) derivative, mp 104–106 °C (yield 81%), prepared by oxidation with $AgNO_3$ in EtOH–H_2O under reflux for 5 h of the commercial 11-carboxaldehyde derivative (yield 64%).

For the Preparation of Compounds 56–70 (Table IV). 4-[Bis(4-fluorophenyl)methoxy]piperidine, $bp_{0.1\ Torr}$ 155–158 °C,

(25) Caronna, G.; Palazzo, S. Reactions with hydrazoic acid in sulfuric acid solution. XII. The behavior of some anthraquinone derivatives. *Gazz. Chim. Ital.* **1953**, *83*, 533–539.

(26) Malen, C.; Laubie, M. Dibenzo-[*c*,*f*]-[1,2]-thiazepine derivatives. French Patent 1.566591, 1969; *Chem. Abstr.* **1970**, *72*, 100780j.

Table VIII. In Vitro Activity of Compounds in the DC-3F/AD Cell Line

no.	fold reversion[a] (% of viability)[b] 5 μM	fold reversion[a] (% of viability)[b] 10 μM	increase in ADR uptake[c] 5 μM	increase in ADR uptake[c] 10 μM
1	112 (65)	235 (63)	7.3	17.9
2	42 (72)	598 (64)	0.0	1.2
3	171 (50)	tox	NT	NT
4	309 (92)	455 (87)	16.9	19.3
5	42 (81)	99 (67)	NT	NT
6	1932 (82)	5344 (78)	18.3	20.7
7	464 (84)	1832 (70)	17.6	24.5
8	329 (87)	1159 (81)	21.1	28.2
9	138 (86)	2174 (67)	9.5	24.8
10	tox	tox	10.2	10.5
11	tox	tox	24.3	27.6
12	388 (76)	1212 (56)	16.0	25.1
13	732 (72)	1796 (54)	10.5	19.4
14	NT	NT	NT	NT
15	905 (75)	1828 (61)	25.9	40.0
16	918 (78)	2564 (62)	26.1	35.6
17	1008 (75)	1838 (53)	42.7	44.7
18	NT	627 (49)	22.1	33.9
19	146 (82)	339 (43)	NT	NT
20	NT	2220 (47)	19.8	25.5
21	753 (90)	1540 (77)	31.3	34.7
22	220 (50)	tox	21.5	29.8
23	965 (77)	2356 (66)	26.0	34.2
24	tox	tox	17.9	27.2
25	1224 (80)	tox	24.7	26.5
26	354 (88)	1418 (85)	20.6	27.9
27	12 (115)	12 (114)	1.6	2.9
28	1 (74)	1 (65)	NT	NT
29	57 (59)	tox	NT	NT
30	93 (100)	374 (84)	28.9	35.5
31	139 (107)	817 (92)	21.2	29.0
32	1009 (82)	tox	30.1	34.6
33	755 (99)	1626 (91)	34.3	39.7
34	3144 (98)	6021 (54)	33.0	38.3
35	2753 (85)	4452 (42)	27.3	24.9
36	844 (91)	2584 (85)	19.4	25.7
37	96 (90)	422 (87)	20.2	30.7
38	1420 (86)	tox	24.5	25.8
39	170 (78)	589 (75)	19.6	23.2
40	187 (71)	544 (66)	29.4	30.6
41	421 (92)	NT	6.7	11.0
42	1932 (82)	5344 (78)	25.5	25.3
43	2951 (105)	tox	22.3	21.6
44	2804 (91)	9570 (77)	22.8	24.1
45	2499 (114)	10684 (64)	23.1	24.9
46	850 (96)	2205 (96)	21.6	27.5
47	1092 (86)	1078 (79)	23.9	28.5
48	867 (83)	6046 (72)	33.5	32.6
49	2 (106)	583 (100)	2.2	41.5
50	1638 (98)	4264 (102)	32.9	35.9
51	600 (54)	2203 (75)	16.8	21.5
52	1327 (76)	2630 (86)	18.0	21.8
53	834 (70)	3035 (69)	17.8	21.8
54	1913 (73)	tox	30.8	NT
55	27 (90)	2536 (94)	NT	NT
56	290 (70)	969 (56)	11.4	16.1
57	380 (90)	1202 (76)	NT	28.3
58	41 (85)	248 (79)	8.0	19.7
59	120 (41)	tox	13.7	12.4
60	64 (38)	tox	10.4	18.3
61	2 (77)	NT	10.4	12.9
62	1 (98)	NT	10.5	12.6
63	173 (93)	544 (72)	14.0	20.5
64	10 (71)	46 (49)	10.1	17.4
65	353 (57)	tox	19.3	21.0
66	1174 (49)	tox	NT	NT
67	472 (67)	tox	15.1	16.3
68	1654 (38)	tox	NT	NT
69	166 (65)	240 (55)	19.9	21.6
70	374 (84)	1242 (62)	15.9	21.6
VRP	3 (43)	34 (39)	2.6	7.5

[a] Ratio of IC_{50}(AD alone)/IC_{50}(AD + modulator). [b] The percent of cell viability remaining after incubating the cells with the modulator alone is given in parentheses: tox = viability < 25%. [c] Increase in ADR uptake in modulator-treated cells relative to untreated cells. NT, not tested.

Table IX. In Vitro Activity of Compounds in the KB-A1 Cell Line

no.	fold reversion[a] (% of viability)[b]	increase in ADR uptake[c]
4	36 (108)	11.2
7	63 (121)	29.7
8	93 (96)	22.8
10	tox	26.2
11	tox	29.2
16	168 (75)	56.5
23	236 (93)	51.5
25	111 (91)	41.4
27	6 (100)	NT
28	1 (78)	NT
31	277 (115)	41.9
32	142 (71)	48.1
33	91 (74)	34.2
34	252 (68)	53.6
35	221 (55)	51.3
36	140 (106)	43.9
37	tox	22.2
38	640 (31)	59.2
39	57 (42)	20.6
40	7 (28)	16.4
41	89 (122)	16.3
42	274 (106)	53.7
43	177 (89)	44.1
44	147 (92)	39.8
45	201 (58)	45.9
46	236 (63)	33.8
47	138 (91)	40.7
48	393 (108)	57.3
49	315 (113)	48.4
50	118 (133)	43.8
51	183 (107)	35.9
52	229 (101)	38.8
53	118 (111)	25.6
54	264 (83)	72.6
59	tox	20.9
60	tox	14.5
61	tox	13
62	tox	5.5
63	126 (105)	29.8
64	10 (97)	1.9
65	12 (53)	9.8
68	22 (40)	NT
VRP	26 (75)	13.4

[a] Ratio of IC_{50}(ADR alone)/IC_{50}(ADR + modulator) at 5 μM. [b] The percent of cell viability remaining after incubating the cells with the modulator alone is given in parentheses: tox = viability < 25%. [c] Increase in ADR uptake in modulator-treated cells (5 μM) relative to untreated cells. NT, not tested.

was prepared by analogy with ref 27.

4-Benzhydrylthiopiperidine (mp 74–76 °C) and 4-[(3,3-diphenylpropyl)thio]piperidine fumarate (mp 160 °C) were prepared according to the methods described in the literature,[28,29] starting from 4-mercapto-1-methylpiperidine.[30] 2,4-Bis(allylamino)-6-chloropyrimidine, $bp_{0.1\ Torr}$ 145–150 °C, was prepared according to ref 31.

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(31) Winklemann, W. J. Several derivatives of 2,4,6-trichloropyrimidine. *J. Prakt. Chem.* **1927**, *115*, 292–314.

Table X. Potentiation by the Compounds of the Antitumor Activity of Vincristine (VCR) against P388/VCR and P388 Leukemia in Mice

no.	dose,[d] mg/kg	T/C % P388/VCR	T/C % P388
VCR alone	0	146 ± 2	199 ± 6
16	50	176 ± 10	168 ± 4
	100	185 ± 12	157 ± 6
23	50	167 ± 2	176
	100	163 ± 12	177 ± 9
34	50	208 ± 23	161 ± 2
	100	193 ± 3	167 ± 7
35	50	184	179
	100	195	176
38	50	156	196
	100	168 ± 15	172
42	50	167 ± 7	196 ± 6
	100	184 ± 7	191 ± 7
43	50	161	173
	100	174	186
44	50	154	177
	100	148	173
45	50	159	190
	100	165	174 ± 3
51	50	170	181
	100	171	163
52	50	171 ± 6	196
	100	185 ± 7	180
54	50	159	NT
	100	177	NT

[d] The compounds were administered at the indicated doses 30–60 min before 0.25 mg/kg VCR. Treatments were given ip on days 1–4. *T/C* are expressed as the mean of two independent values, or the mean of three to seven independent values ± SEM. NT, not tested.

For the Preparation of Compounds 71–89 (Table V). 1-[4-(Allylamino)-6-(ethylamino)-1,3,5-triazin-2-yl]-4-piperidone Hydrochloride (75). To a stirred solution of 2,4,6-trichlorotriazine (36.8 g, 200 mmol) in methyl ethyl ketone (200 mL) cooled at −5 °C was added crushed ice (100 g) and a solution of 4,4-diethoxypiperidine (34.6 g, 200 mmol) in methyl ethyl ketone (10 mL). To the resulting milky mixture was added at −5 °C $NaHCO_3$ powder (17 g, 200 mmol) in several batches. Then, the mixture was stirred for 16 h at room temperature and the organic layer was decanted and washed with water, dried, and evaporated in vacuo, to give **71** as a crude crystalline material which was washed with ethyl ether to give white crystals (18 g, 28%), mp 89 °C. Anal. ($C_{12}H_{18}Cl_2N_4O_2$) C, H, Cl, N.

To a stirred solution of **71** (13.2 g, 41 mmol) in anhydrous DMF (40 mL) was added allylamine (6.5 mL, 82 mmol); the internal temperature increased from 20 to 55 °C. Stirring was continued for 1 h at room temperature, the mixture was diluted with ethyl ether (200 mL), and 10% $NaHCO_3$ aqueous solution (200 mL) was added.

The resulting precipitate was filtered off, washed with water, and dried in vacuo to provide a white solid, **72** (12 g, 85%), mp 140 °C. Anal. ($C_{15}H_{24}ClN_5O_2$) C, H, Cl, N.

A solution of **72** (2.5 g, 7.3 mmol) and ethylamine (1 mL, 14.6 mmol) in butanol (30 mL) was heated under reflux for 4 h, in the presence of K_2CO_3 (1 g, 7.3 mmol) and potassium iodide (0.1 g). Then the solvent was evaporated in vacuo and the residue was treated with ethyl ether (50 mL); the organic solution was washed with water, dried, and evaporated in vacuo to give a crude oil (3 g), which was heated at 50 °C in 1 N HCl (30 mL), for 2 h. The solution was evaporated to a volume of 10 mL and compound **75** (hydrochloride) crystallized as a white solid (1.4 g, 61.3%): mp 239–241 °C; IR (Nujol) 3163 (NH), 1722 (C=O), 2800–2500 cm^{-1} (NH); ^1H NMR (DMSO-d_6, 200 MHz) δ 5.9 (m, 1 H, C*H*=), 5.2 (m, 2 H, =CH_2), 4.0 (m, 6 H, CH_2CH= and C*H*NC*H* piperidine), 3.4 (q, 2 H, CH_2CH$_3$), 2.4 (m, 4 H, CH_2COCH_2), 1.1 (t, 3 H, CH_3). Anal. ($C_{13}H_{20}N_6O$·HCl) C, H, Cl, N.

1-[2-[[4,6-Bis(allylamino)-1,3,5-triazin-2-yl]amino]-ethyl]-4-piperidone (82) was prepared by reaction of 4,6-bis-(allylamino)-2-chloro-1,3,5-triazine, in BuOH at 120 °C for 12 h in the presence of K_2CO_3, with 1-(aminoethyl)-4,4-diethoxypiperidine (oil) (yield 48%), which was obtained by hydrogenation of 1-(cyanomethyl)-4,4-diethoxypiperidine (oil) (yield 96%) in EtOH–NH_3 under 6 atm of pressure.

1-[3-[[4,6-Bis(allylamino)-1,3,5-triazin-2-yl]amino]-2-hydroxypropyl]-4-piperidone (83) was prepared by reaction of the 4,6-bis(allylamino)-2-chloro-1,3,5-triazine in BuOH at 120 °C for 7 h, in presence of K_2CO_3, with 1-(3-amino-2-hydroxypropyl)-4,4-diethoxypiperidine (oil) (yield 50%), which was obtained by hydrazinolysis in EtOH of 1-(3-phthalimido-2-hydroxypropyl)-4,4-diethoxypiperidine, mp 49–50 °C (yield 94%).

4-(Aminocarbonyl)-1-[4,6-bis(allylamino)-1,3,5-triazin-2-yl]piperidine (84). A solution of 4-(aminocarbonyl)piperidine (12.8 g, 100 mmol) and of 4,6-bis(allylamino)-2-chloro-1,3,5-triazine (22.6 g, 100 mmol) in 300 mL of butanol, was stirred in the presence of K_2CO_3 (13.8 g, 100 mmol) and potassium iodide (0.3 g), under reflux overnight. After cooling, the mixture was filtered and the solvent evaporated in vacuo to give a crude crystalline residue which was successively washed with water and ethyl ether (250 mL), to give yellowish crystals: mp 159–161 °C (28 g, 88.3%); IR (Nujol) 3450–3100 (NH_2, NH), 1664 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 200 MHz) δ 6.0–5.8 (m, 2 H, C*H*=), 5.2–5.0 (m, 4 H, =CH_2), 4.6 (m, 2 H, C*H*NC*H* piperidine), 3.8 (m, 4 H, CH_2CH=), 2.75 (m, 2 H, C*H*NC*H* piperidine), 2.3 (m, 1 H, C*H* piperidine), 1.7 (m, 2 H, CH_2 piperidine), 1.35 (m, 2 H, CH_2 piperidine). Anal. ($C_{15}H_{23}N_7O$) C, H, N.

4-(Aminomethyl)-1-[4,6-bis(allylamino)-1,3,5-triazin-2-yl]piperidine (85). A solution of $LiAlH_4$ (1 g) in anhydrous THF (50 mL) was added under reflux to a stirred solution of **84** (3.2 g, 10 mmol) in anhydrous THF (100 mL) over 30 min. Heating at 60 °C was continued for 7 h. After cooling of the mixture to 20 °C, 1 mL of water, 1 mL of 4 N NaOH and 3 mL of water were added successively; the precipitate was filtered off and the solution was evaporated in vacuo to give a pure colorless oil (3 g, 100%): IR (neat) 3425–3100 (NH_2, NH), 1643 cm^{-1} (C=N); ^1H NMR ($CDCl_3$, 200 MHz) δ 5.9 (m, 2 H, C*H*=), 5.2 (m, 4 H, =CH_2), 4.7 (m, 2 H, C*H*NC*H* piperidine), 4.0 (m, 4 H, CH_2CH=), 2.75 (m, 2 H, C*H*NC*H* piperidine), 2.6 (d, 2 H, CHCH_2NH$_2$), 1.75 (m, 2 H, CH_2 piperidine), 1.55 (m, 1 H, C*H* piperidine), 1.2–0.9 (m, 2 H, CH_2 piperidine). Anal. ($C_{15}H_{25}N_7$) C, H, N.

1-[4,6-Bis(allylamino)-1,3,5-triazin-2-yl]-4-aminopiperazine (88), mp 83 °C, was prepared by reduction with $Na_2S_2O_4$ in EtOH–H_2O, at 60 °C for 6 h, of the corresponding 4-nitroso derivative, mp 78 °C (yield 61%), prepared by reaction of 4,6-bis(allylamino)-2-chloro-1,3,5-triazine with 1-nitrosopiperazine in BuOH under reflux for 8 h, in presence of K_2CO_3 (yield 59%).

4-Amino-1-[4,6-bis(allylamino)-1,3,5-triazin-2-yl]piperidine (89) was prepared by $LiAlH_4$ reduction in anhydrous THF under reflux overnight of 1-[4,6-bis(allylamino)-1,3,5-triazin-2-yl]-4-hydroximinopiperidine, mp 180 °C (yield 42.7%), which was obtained from **76** and hydroxylamine hydrochloride in ethanol.

For the Preparation of Compounds 90–105 (Table VI). 1-(2,2-Diphenylethyl)-4-aminopiperidine (101). To a stirred solution of 2,2-diphenylacetaldehyde (10 g, 51 mmol) and 4-acetamidopiperidine in anhydrous methanol (100 mL) were successively added at 15–20 °C $NaBH_3CN$ (3.2 g, 50 mmol) and 3-Å molecular sieves. The mixture was acidified to pH 6 with a 6 N solution of dry HCl–methanol and stirring was continued for 16 h. The insoluble material was filtered off and the resulting solution was evaporated in vacuo. The residue was treated with ethyl acetate and the organic solution washed with 10% $NaHCO_3$ aqueous solution, then dried, and evaporated in vacuo. The crude product was recrystallized from ethyl ether to give 1-(2,2-diphenylethyl)-4-acetamidopiperidine, mp 147–148 °C (11.4 g, 69.5%).

This compound (10.6 g, 32.9 mmol) was heated under reflux, for 8 h, in 4 N HCl. The solution was cooled and treated with an excess of 10 N NaOH under stirring for 15 min. The amine was extracted with CH_2Cl_2 and purified by flash chromatography eluting with CH_2Cl_2–methanol (85:15) to provide an oil which crystallized on standing (6.1 g, 66.1%): mp 41–45 °C. IR (neat) 3357 cm^{-1} (NH); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.2 (m, 10 H, aromatic H), 4.2 (t, 1 H, C*H* benzhydryl), 3.0 (d, 2 H, CH_2N), 2.85 (m, 2 H, C*H*NC*H* piperidine), 2.6 (m, 1 H, C*H*NH$_2$), 2.05 (m, 2 H, C*H*NC*H* piperidine), 1.7 (m, 2 H, CH_2 piperidine), 1.3 (m, 2 H, NH$_2$), 1.25 (m, 2 H, CH_2 piperidine). Anal. ($C_{19}H_{24}N_2$) C, H, N.

1-[Bis(4-fluorophenyl)methyl]-4-aminopiperazine (105) was prepared by $LiAlH_4$ reduction in THF, for 3 h at 60 °C, of **104** (yield 72%) obtained by reaction of the bis(4-fluorophenyl)bromomethane with 1-nitrosopiperazine in toluene, for 8 h under reflux, in the presence of triethylamine (yield 67%).

For the Preparation of Compounds 106–136 (Table VII). **1-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)-piperazine (106)** was prepared from commercial 5-chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene and piperazine in dioxane, by heating at 100 °C, for 7 h, mp 99–100 °C (yield 48%).

1-(2-Aminoethyl)-4-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-5-yl)piperazine (107) was prepared by reduction with H_2 (6 atm)–Raney nickel in EtOH–NH_3 at room temperature of 1-(cyanomethyl)-4-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)piperazine, mp 112–113 °C (yield 95%), prepared by reaction of **106** with 2-hydroxyacetonitrile in dioxane at 100 °C, in the presence of NaOH, mp 70–71 °C (yield 55%).

4-(Aminocarbonyl)-1-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-5-yl)piperidine (132) was prepared by reaction of 5-chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene with an excess of 4-(aminocarbonyl)piperidine in toluene, in the presence of potassium iodide, under reflux overnight, mp 200–203 °C (yield 85%).

4-(Aminocarbonyl)-1-[(10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-5-yl)carbonyl]piperidine (133). To a stirred solution of 4-(aminocarbonyl)piperidine (5.1 g, 40 mmol) and triethylamine (5.6 mL, 40 mmol) in anhydrous THF was added dropwise over 30 min at 20 °C a solution of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-carbonyl chloride in 50 mL of THF. The mixture was stirred overnight at room temperature and the precipitate was filtered off and washed with THF (10 mL) and water (10 mL). After drying, the white crystals were treated with a mixture (50:50) of ethanol–ethyl ether to give **133** (6.8 g, 48.9%): mp 175–176 °C; IR (Nujol) 3475–3150 (NH_2), 1672 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.15 (m, 8 H, aromatic H), 5.5 (m, 2 H, [NH_2] exchangeable for D_2O), 4.8 (s, 1 H, [5H] cycloheptene), 4.5 and 4.1 (2 m, 2 H, C*H*NC*H* piperidine), 3.5 (m, 2 H, C*H*CH cycloheptene), 3.0–2.6 (m, 4 H, C*H*NC*H* piperidine, C*H*CH cycloheptene), 2.25 (m, 1 H, C*H*CO), 1.8 (m, 1 H, C*H*CH piperidine), 1.55 (m, 2 H, CH_2CH piperidine), 1.0 (m, 1 H, C*H*CH piperidine). Anal. ($C_{22}H_{24}N_2O_2$) C, H, N.

4-(Aminomethyl)-1-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-5-yl)piperidine (134) was prepared by $LiAlH_4$ reduction of **132** in anhydrous THF, under reflux for 3 h, mp 92–93 °C (yield 98%).

4-(Aminomethyl)-1-[(10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-5-yl)methyl]piperidine (135). Pure 10 N borane–dimethyl sulfide complex (9 mL, 90 mmol) was added dropwise over 2 h to a stirred solution of **133** (4.4 g, 12.6 mmol) in anhydrous THF (100 mL) under reflux. Heating was then continued for 16 h, and the mixture was cooled to 5 °C and treated with a 6 N solution of dry HCl in methanol (30 mL), dropwise over 30 min. The solution was then heated under reflux for 1 h; the resulting precipitate was filtered off after cooling and washed with THF and ethyl ether. After drying in vacuo, it was treated with 4 N NaOH (16 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The organic phase was separated, dried, and evaporated, to give **135** as a colorless oil (3.3 g, 81.7%): IR (neat) 3377 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.3–7.0 (m, 8 H, aromatic H), 4.2 (t, 1 H, [5H] cyclopentene), 3.5–3.3 (m, 2 H, C*H*CH cyclopentene), 3.0 (d, 2 H, CHCH_2N), 3.0–2.75 (m, 4 H, C*H*CH cyclopentene, C*H*NC*H* piperidine), 2.5 (d, 2 H, CHC$H_2$$NH_2$ piperidine), 1.7 (m, 2 H, CH_2 piperidine), 2.0 (m, 2 H, C*H*NC*H* piperidine), 1.3–1.0 (m, 3 H, CH_2C*H* piperidine). Anal. ($C_{22}H_{28}N_2$) C, H, N.

1-[(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)-methyl]piperazine (136) was prepared by BMS reduction in THF, at 60 °C for 7 h, of the 1-[(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)carbonyl]piperazine (yield 79%), obtained by reaction of the corresponding acyl chloride[32] with an excess of piperazine, in THF, at 60 °C, for 3 h, mp (2HCl) 280 °C (yield 45%).

Target Compounds (Methods A–E). **1-[4,6-Bis(allylamino)-1,3,5-triazin-2-yl]-4-[(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)methyl]piperazine (7) (Method A).** A solution of 4,6-bis(allylamino)-2-chloro-1,3,5-triazine (2.5 g, 11.2 mmol) and **136**·2HCl (4.1 g, 11.2 mmol) in 100 mL of butanol was stirred under reflux for 8 h, in the presence of potassium carbonate (4.5 g, 33 mmol) and potassium iodide (0.2 g). The solvent was evaporated and the residue was treated with a mixture of CH_2Cl_2 and water; the organic phase was separated, filtered, and evaporated in vacuo to provide a crude product. Purification by flash chromatography, eluting with toluene–methanol (95:5) and recrystallization from ether gave 1.9 g (35.2%) of compound **7**: mp 104–105 °C; IR (Nujol) 3421, 3271 (NH) and 1608, 1566 cm^{-1} (C=C + C=N); ^1H NMR (DMSO-d_6, 200 MHz) δ 7.0–7.3 (m, 8 H, aromatic H), 6.5–6.9 (m, 2 H, NH), 5.7–6.0 (m, 2 H, C*H*=), 4.9–5.2 (m, 4 H, =CH_2), 4.31 (t, H, [5H]), 3.7–3.9 (m, 4 H, CH_2C=), 3.5–3.7 (m, 4 H, CH_2 piperazine), 3.1–3.4 (m, 2 H, CH_2N), 2.85–3.1 (m, 4 H, CH_2 cycloheptene), 2.3–2.5 (m, 4 H, CH_2 piperazine). Anal. ($C_{29}H_{35}N_7$) C, H, N.

1-[4,6-Bis(allylamino)-1,3,5-triazin-2-yl]-4-[[(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)methyl]amino]-piperazine (8). A solution of **88** (5.5 g, 19 mmol) and of (10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)carboxaldehyde (2.8 g, 12.6 mmol) in 80 mL of methanol was acidified at pH 6.5 with dry HCl in methanol, and then $NaBH_3CN$ (0.8 g, 12.6 mmol) was added together with 3-Å molecular sieves. The mixture was stirred for 24 h, at pH 6 and room temperature, and then filtered. The solution was evaporated and the crude residue was treated with CH_2Cl_2 and water; the organic layer was separated and washed with 10% $NaHCO_3$ solution (100 mL). After drying, the solvent was evaporated in vacuo and the crude residue was purified by flash chromatography eluting with ethyl acetate–CH_2Cl_2 (1:1) to give 2 g of **8** as a pale yellow oil, which was dissolved in ethanol and treated with an excess of fumaric acid. The resulting precipitate was filtered off to provide **8** as colorless crystals (2.1 g, 27.3%): mp 138–142 °C; IR (Nujol) 3303 (NH), 1680–1670 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 200 MHz), δ 7.2 (m, 8 H, aromatic H), 6.9–6.7 (m, 2 H, [NH] exchangeable for D_2O), 6.6 (s, 2 H, C*H*=C*H* fumaric acid), 6.0–5.8 (m, 2 H, –C*H*=), 5.2–5.0 (m, 4 H, =CH_2), 4.3 (t, 1 H, [5H] cyclopentene), 3.8 (m, 4 H, CH_2C=), 3.65 (m, 4 H, C*H* piperazine), 3.3 (m, 4 H, C*H*CH cyclopentene, CH_2N), 3.0 (m, 2 H, C*H*CH cyclopentene), 2.5 (m, 4 H, C*H* piperazine). Anal. ($C_{29}H_{36}N_8$·$C_4H_4O_4$) C, H, N.

The starting carboxaldehyde (oil) was prepared by DIBAL-H reduction of **110** by analogy with ref 33, (yield 28%). IR (Nujol) 1716 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.3–7.0 (m, 8 H, aromatic H), 9.8 (s, 1 H, C*H*O), 4.6 (s, 1 H, [5H] cycloheptene), 3.25–3.0 (m, 2 H, C*H*CH cyclopentene), 2.9–2.7 (m, 2 H, C*H*CH cyclopentene). Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.2; H, 6.4.

1-[4,6-Bis(allylamino)-1,3,5-triazin-2-yl]-4-[[(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)carbonyl]amino]-piperazine (9). To a solution of **86** (4 g, 13.8 mmol) and triethylamine (2 mL, 14 mmol) in 70 mL of dry THF, was added 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-carbonyl chloride (3.6 g, 13.8 mmol), at 20 °C. The mixture was stirred overnight at room temperature then the solvent was evaporated; the crystalline residue was treated with CH_2Cl_2 and water, and the organic layer was separated, dried, filtered, and evaporated in vacuo. The crude product was recrystallized from ether to provide **9** (6 g, 85.7%): mp 182–184 °C; IR (Nujol) 3440–3000 (NH), 1662 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 200 MHz) δ 8.5 (2 s, 1 H, [N*H*] amide exchangeable for D_2O, 2 conformers), 7.0–6.6 (m, 2 H, NH), 7.4–7.0 (m, 8 H, aromatic H), 6.0–5.8 (m, 2 H, C*H*=), 5.2–5.0 (m, 4 H, =CH_2), 5.3 and 4.8 (2 s, 1 H [5H], 2 conformers), 4.4 (m, 1 H, C*H* piperazine), 3.85 (m, 4 H, CH_2C=), 3.7–3.4 (m, 4 H, CH_2 cycloheptene), 3.0–2.6 (m, 5 H, CHCH_2NCH_2 piperazine), 2.4–2.15 (m, 2 H, C*H* piperazine). Anal. ($C_{29}H_{34}N_8O$) C, H, N.

1-[4,6-Bis(allylamino)-1,3,5-triazin-2-yl]-4-[[2,2-bis(4-fluorophenyl)ethyl]amino]piperidine (16) (Method B). A solution of **76**·HCl (6.5 g, 20 mmol) and of **91** (7 g, 30 mmol) in

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50 mL of dry methanol, was acidified to pH 6 with a solution of methanol–dry HCl then cooled at 15 °C, before adding $NaBH_3CN$ (1.3 g, 20 mmol) and 3-Å molecular sieves (5 g). The mixture was stirred for 24 h at room temperature and filtered; the solvent was evaporated in vacuo and the residue treated with ether and water. The organic layer was separated and washed with 10% $NaHCO_3$ aqueous solution (50 mL). After drying, the solvent was evaporated in vacuo and the residue was purified by flash chromatography eluting with ethyl acetate, to provide a colorless oil which was dissolved in wet ether to give **16** as white crystals (5.3 g, 52.5%): mp 64–68 °C; IR (Nujol) 3450 and 3370 cm^{-1} (NH); ^1H NMR (DMSO-d_6, 200 MHz) δ 7.3 (m, 4 H, aromatic H), 7.1 (m, 4 H, aromatic H), 5.95–5.7 (m, 2 H, C*H*=), 5.15–4.9 (m, 4 H, CH_2=), 4.35 (d br, 2 H, C*H*NC*H* piperidine), 4.1 (t, 1 H, C*H* benzhydryl), 3.8 (m, 4 H, CH_2CH=), 3.15 (d, 2 H, CH_2CH), 2.85 (m, 2 H, C*H*NC*H* piperidine), 2.65 (m, 1 H, C*H*NH), 1.75 (d br, 2 H, CH_2 piperidine), 1.1 (m, 2 H, CH_2 piperidine). Anal. ($C_{28}H_{33}F_2N_7H_2O$) C, H, N.

1-[4,6-Bis(allylamino)-1,3,5-triazin-2-yl]-4-[[(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)amino]methyl]piperidine (63) (Method C). A solution of **85** (3 g, 10 mmol) and of 5-chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (2.3 g, 10 mmol) with triethylamine (1.4 mL, 10 mmol), in anhydrous butanol (100 mL) was stirred under reflux overnight, in the presence of potassium iodide (0.2 g). After cooling, the solution was washed with a 10% aqueous $NaHCO_3$ solution (50 mL). The organic layer was separated, dried, and evaporated in vacuo and the crude residue was purified by flash chromatography eluting with CH_2Cl_2–ethyl acetate (70:30), to provide 4 g (80%) of white crystals recrystallized from ethanol: mp 109–110 °C; IR (Nujol) 3435–3629 (NH), 1637 cm^{-1} (C=N); ^1H NMR (DMSO-d_6, 400 MHz) δ 7.4–7.1 (2 m, 2 H + 6 H aromatic H), 6.7 (2 m, 2 H, NH), 5.85 (tdd, 2 H, C*H*=), 5.05 (d, 4 H, =CH_2), 4.85 (sb, 1 H, [5H] cycloheptene), 4.6 (db, 2 H, C*H*NC*H* piperidine), 3.85 (sb, 4 H, CH_2CH=), 3.55–3.0 (2 mb, 4 H, C*H*C*H* cycloheptene), 2.65 (tb, 2 H, C*H*NC*H* piperidine), 2.35 (db, 2 H, $CHCH_2$), 1.75 (mb, 1 H, C*H* piperidine), 1.7–0.9 (2 mb, 4 H, CH_2CH piperidine). Anal. ($C_{30}H_{37}N_7$) C, H, N.

1-[(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)methyl]-4-[[[4,6-bis(allylamino)-1,3,5-triazin-2-yl]amino]methyl]piperidine (65) (Method D). A solution of 4,6-bis(allylamino)-2-chloro-1,3,5-triazine (1.4 g, 6.24 mmol) and **135** (2 g, 6.24 mmol) in butanol was heated under reflux in the presence of K_2CO_3 (0.9 g, 6.52 mmol) and potassium iodide (0.2 g), for 16 h. The workup was the same that for **63** and provided an amorphous product (2.4 g, 75.5%): IR (Nujol) 3419–3100 cm^{-1} (NH); ^1H NMR (DMSO-d_6, 200 MHz) δ 7.2 (m, 8 H aromatic H), 6.9–6.3 (m, 2 H, [NH] exchangeable for D_2O), 5.8 (m, 2 H, C*H*=), 5.0 (m, 4 H, =CH_2), 4.25 (t, 1 H, [5H] cycloheptene), 3.8 (m, 4 H, CH_2CH=), 3.3 (m, 2 H, C*H*C*H* cycloheptene), 3.1–2.7 (m, 8 H, C*H*C*H* cycloheptene, C*H*NC*H* piperidine, CH_2N, CH_2NH_2), 1.9 (m, 2 H, C*H*NC*H* piperidine), 1.5 (m, 2 H + 1 H, C*H* piperidine), 1.0 (m, 2 H, C*H* piperidine). Anal. ($C_{31}H_{39}N_7$) C, H, N.

4-[[4,6-Bis(allylamino)-1,3,5-triazin-2-yl]amino]-1-(2,2-diphenylethyl)piperidine (69) (Method E). A stirred solution of 4,6-bis(allylamino)-2-chloro-1,3,5-triazine (2.3 g, 10 mmol) and **101** (2.8 g, 10 mmol) in butanol (50 mL) was heated at 110 °C for 10 h, in the presence of triethylamine (1.4 mL, 10 mmol). The solution was evaporated and the residue treated with CH_2Cl_2 (100 mL) and water. The organic phase was separated, dried, and evaporated in vacuo to give a crude oil which was purified by flash chromatography eluting with ethyl acetate. The pure product (**69**) was obtained in an amorphous form (2.6 g, 55.4%): IR (Nujol) 3417–3257 cm^{-1} (NH); ^1H NMR (DMSO-d_6, 200 MHz) δ 7.4–7.1 (m, 10 H, aromatic H), 6.9–6.1 (m, 3 H, [NH] exchangeable for D_2O), 5.8 (m, 2 H, C*H*=), 5.1 (m, 4 H, =CH_2), 4.2 (t, 1 H, C*H* benzhydryl), 3.8 (m, 4 H, CH_2CH=), 3.65 (m, 1 H, C*H*N piperidine), 3.0–2.75 (m, 4 H, NCH_2, NC*H* piperidine), 1.9 (m, 2 H, C*H*NC*H* piperidine), 1.7 (m, 2 H, C*H* piperidine), 1.35 (m, 2 H, C*H* piperidine). Anal. ($C_{28}H_{35}N_7$) C, H, N.

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**49**, 141528-33-8; **50**, 141528-34-9; **51**, 141528-35-0; **52**, 141528-36-1; **53**, 141528-37-2; **54**, 141528-39-4; **55**, 141528-40-7; **56**, 88535-80-2; **57**, 141528-42-9; **58**, 140945-23-9; **59**, 141528-44-1; **60**, 141528-46-3; **61**, 141528-48-5; **62**, 141528-50-9; **63**, 141528-51-0; **64**, 141528-52-1; **65**, 141528-53-2; **66**, 88551-62-6; **67**, 141528-55-4; **68**, 141528-57-6; **69**, 141528-58-7; **70**, 141528-59-8; **71**, 141528-60-1; **72**, 141528-61-2; **73**, 141528-62-3; **74**, 141528-63-4; **75**, 141528-64-5; **76**, 88536-29-2; **77**, 141528-65-6; **78**, 141528-66-7; **79**, 141528-67-8; **80**, 141528-68-9; **81**, 141528-69-0; **82**, 141555-02-4; **83**, 141555-03-5; **84**, 141528-70-3; **85**, 141528-71-4; **86**, 29608-42-2; **87**, 141555-04-6; **88**, 141528-72-5; **89**, 88535-58-4; **90**, 37742-99-7; **91**, 98383-56-3; **92**, 109864-56-4; **93**, 141528-73-6; **94**, 120355-64-8; **95**, 108984-57-2; **96**, 141528-75-8; **97**, 54167-06-5; **98**, 141528-76-9; **99**, 20974-36-1; **100**, 5631-35-6; **101**, 140945-21-7; **102**, 128289-80-5; **103**, 141528-77-0; **104**, 141528-78-1; **105**, 141528-79-2; **106**, 69159-50-8; **107**, 141528-80-5; **108**, 141528-81-6; **109**, 7005-53-0; **110**, 1729-63-1; **111**, 7351-50-0; **112**, 13055-58-8; **113**, 19862-99-8; **114**, 7471-95-6; **115**, 34221-61-9; **116**, 24295-90-7; **117**, 24295-91-8; **118**, 85554-24-1; **119**, 5101-81-5; **120**, 21613-06-9; **121**, 141555-05-7; **122**, 1745-54-6; **123**, 82394-02-3; **124**, 141528-82-7; **125**, 141528-83-8; **126**, 24391-70-6; **127**, 141528-84-9; **128**, 141528-85-0; **129**, 141528-86-1; **130**, 141528-87-2; **131**, 141528-88-3; **132**, 141528-89-4; **133**, 141528-90-7; **134**, 141528-91-8; **135**, 141528-92-9; **136**, 141528-93-0; 2-(4-fluorophenyl)-2-cyclohexylethylamine, 141528-94-1; 2-(4-fluorophenyl)-2-cyclohexylacetonitrile, 141528-95-2; 2-(phenylsulfonyl)-2-phenylethylamine, 141528-96-3; 2-(phenylsulfonyl)-2-phenylacetonitrile, 66147-02-2; 2-(phenylthio)-2-phenylacetonitrile, 32121-59-8; 2,2,2-triphenylacetonitrile, 6639-43-6; [(4-fluorophenyl)cyclohexylmethyl]amine, 88536-30-5; (4-fluorophenyl)cyclohexylhydroximinomethane, 141528-97-4; 12-chloro-5,6,7,12-tetrahydrodibenzo[*a*,*d*]cyclooctene, 24295-89-4; 12-hydroxy-5,6,7,12-tetrahydrodibenzo[*a*,*d*]cyclooctene, 5101-32-6; 5,6,7,12-tetrahydrodibenzo[*a*,*d*]cycloocten-12-one, 1022-14-6; 11-chloro-5,5-dioxo-6,11-dihydrodibenzo[*b*,*e*]thiepin, 141528-98-5; 11-hydroxy-5,5-dioxo-6,11-dihydrodibenzo[*b*,*e*]thiepin, 5251-28-5; 5,5-dioxo-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-one, 33301-21-2; 11-hydroxy-6,11-dihydrodibenzo[*b*,*e*]thiepin, 1745-46-6; 11-chloro-6-oxo-5,11-dihydro-6*H*-dibenz[*b*,*e*]azepine, 723-86-4; 11-hydroxy-6-oxo-5,11-dihydro-6*H*-dibenz[*b*,*e*]azepine, 723-87-5; 6,11-dioxo-5,11-dihydro-6*H*-dibenz[*b*,*e*]azepine, 1143-50-6; 5-chloro-2-methoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene, 141528-99-6; 5-hydroxy-2-methoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene, 141529-00-2; 2-methoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one, 17910-72-4; 2-[3-(4-methoxyphenyl)propyl]benzoic acid, 141529-01-3; 5,8-dichloro-10,10-dioxo-11-methyl-5,11-dihydrodibenzo[*c*,*f*][1,2]thiazepine, 26638-66-4; 5-hydroxy-10,10-dioxo-11-methyl-5,11-dihydrodibenzo[*c*,*f*][1,2]-thiazepine, 26723-60-4; 8-chloro-10,10-dioxo-11-methyl-5,11-dihydrodibenzo[*c*,*f*][1,2]thiazepin-5-one, 26638-53-9; 11-amino-9,10-dihydro-9,10-ethanoanthracene hydrochloride, 35079-81-3; 11-(chlorocarbonyl)-9,10-dihydro-9,10-ethanoanthracene, 35741-60-7; 9,10-dihydro-9,10-ethanoanthracene-11-carboxaldehyde, 7673-68-9; 2,4,6-trichlorotriazine, 108-77-0; 4,4-diethoxypiperidine, 52534-66-4; 1-[4,6-bis(allylamino)-1,3,5-triazin-2-yl]-4-nitrosopiperazine, 141529-02-4; 1-nitrosopiperazine, 5632-47-3; 1-[4,6-bis(allylamino)-1,3,5-triazin-2-yl]-4-hydroximinopiperidine, 88535-67-5; 2,2-diphenylacetaldehyde, 947-91-1; 4-acetamidopiperidine, 5810-56-0; 1-(2,2-diphenylethyl)-4-acetamidopiperidine, 141529-03-5; bis(4-fluorophenyl)bromomethane, 345-90-4; 5-chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene, 1210-33-9;

piperazine, 110-85-0; 1-(cyanomethyl)-4-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)piperazine, 141529-04-6; 2-hydroxyacetonitrile, 107-16-4; 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-carbonyl chloride, 14846-34-5; 1-[(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)carbonyl]piperazine, 141529-05-7; (10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)carboxaldehyde, 24391-61-5; 4,6-bis(allylamino)-2-chloro-1,3,5-triazine, 15468-86-7; 1-(2-aminoethyl)-4,4-diethoxypiperidine, 141529-06-8; 1-(cyanomethyl)-4,4-diethoxypiperidine, 141529-07-9; 1-(3-amino-2-hydroxypropyl)-4,4-diethoxypiperidine, 141529-08-0; 1-(3-phthalimido-2-hydroxypropyl)-4,4-diethoxypiperidine, 141529-09-1; 4-(aminocarbonyl)piperidine, 39546-32-2.

Communications to the Editor

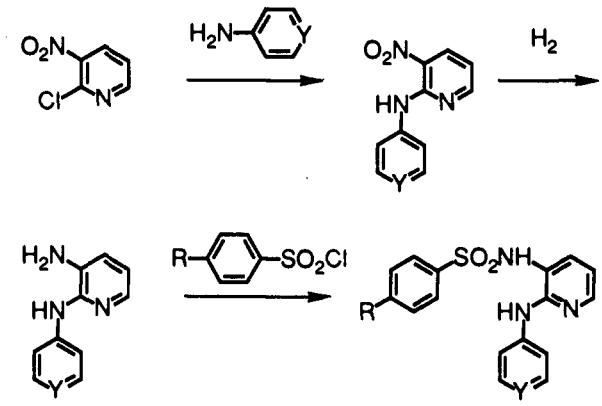
Novel Sulfonamides as Potential, Systemically Active Antitumor Agents

The discovery of new antitumor agents has truly contributed to the treatment of certain types of tumors, i.e. leukemias and lymphomas. Unfortunately, however, chemotherapeutic treatments are far from satisfactory to patients with malignant solid tumors, particularly to those with slowly growing solid tumors. Therefore, we attempted to discover clinically effective drugs against such refractory solid tumors.

It has been repeatedly noted that traditional primary in vivo screening using murine leukemias (P388 and L1210) are unsuitable for the detection of clinically active agents against solid tumors.[1-3] Our main strategy was that structurally novel synthetic compounds with significant antiproliferative activity against solid tumor cells in vitro would be tested for antitumor activity against the slowly growing, murine solid tumors in vivo. We used colon 38 (murine colon adenocarcinoma) in the primary in vivo tests because this model has the following characteristics: (a) colon 38 is a relatively slow growing, murine solid tumor,[4] (b) colon 38 is comparatively resistant to chemotherapy,[5] and (c) colon 38 is subcutaneously (sc) implanted; therefore systemic absorption and delivery of drugs are required in order to inhibit tumor growth. In the case of the traditional murine leukemia models, intraperitoneal (ip) drug treatment after ip tumor implantation has been exclusively used. For the purpose of choosing candidates for in vivo tests, we initially screened new synthetics for in vitro antiproliferative activity against two kinds of solid tumor cells, colon 38 and KB (human carcinoma of the nasopharynx) cells.

In the course of selecting various chemical structures which may be of use in designing novel antitumor agents, we were particularly interested in sulfonamides, because sulfadiazine, an antibacterial sulfonamide, was reported to preferentially accumulate in sc-implanted murine tumors after ip administration.[6] Since it has been well known that sulfonamides have a variety of biological activities such as antibacterial, insulin releasing, carbonic anhydrase inhibitory, and antithyroid,[7] there seemed to be a possibility that new antitumor sulfonamides with mechanisms different from those of known antitumor agents could be discovered. Therefore, we undertook the synthesis and screening of a number of sulfonamides with widely differing chemical structure. Although very little information had appeared in the literature regarding antitumor activity of sulfonamides, chloroquinoxaline sulfonamide (CQS) was reported to have antitumor activity[8] while our work was in progress. The mechanism of action of CQS has not yet been elucidated.[8,9]

Scheme I



2 R = CH3, Y = C-H
3 R = CH3O, Y = C-H
4 R = CH3O, Y = C-OCH3
5 R = CH3O, Y = C-OH
6 R = CH3O, Y = N

Chemistry. The syntheses of the *N*-(2-anilino-3-pyridyl)benzenesulfonamide analogs **2-6** are outlined in Scheme I. 2-Anilino-3-pyridinamine derivatives were obtained by the catalytic hydrogenation of 2-anilino-3-nitropyridine derivatives, which were prepared in good yields by heating the mixture of 2-chloro-3-nitropyridine and aniline or its derivatives at ca. 100 °C.[10] Condensation

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