Synthesis and Activity against Multidrug Resistance in Chinese Hamster Ovary Cells of New Acridone-4-carboxamides

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A number of tricyclic carboxamides have been synthesized and tested to evaluate their ability to reverse multidrug resistance in the $CH^RC/5$ cell line. Among them the acridone derivatives were the most potent. A key feature is the presence of a dimethoxybenzyl or phenethylamine cationic site, separated from the tricyclic lipophilic part by a carbamoylphenyl chain. Optimization led to compounds 2 orders of magnitude more active than the prototype inhibitors verapamil and amiodarone. On the basis of in vitro and in vivo activities, 9,10-dihydro-5-methoxy-9-oxo-*N*-[4-[2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinol-2-yl)ethyl]phenyl]-4-acridinecarboxamide (**84**) has been selected for further development.

Introduction

The occurrence of drug resistance, intrinsic or acquired, to anticancer agents in human tumor cells is a major cause of treatment failure. The multidrug resistance phenotype (MDR)[1,2] occurs when tumor cells treated with an anticancer agent eventually develop resistance to other unrelated cytotoxic compounds.

This troublesome phenomenon is now recognized to be due to the overexpression of a membrane glycoprotein of molecular weight 170 000 called P-glycoprotein.[3] Proteins of the same family have been associated with bacterial transport and resistance of malarian parasites to chloroquine.[4] P-glycoprotein, which is believed to function as an ATP dependent efflux pump, causes a decrease of anticancer drug concentration in cells to sublethal level by an outward transport process. The level of drug resistance is proportional to the level of P-glycoprotein produced in MDR cells.

It has been shown that multidrug resistance can be reversed by calcium channel blockers such as verapamil,[5,6] tiapamil, antiarrhythmic agents like amiodarone[8] as well as quinidine, reserpine, and immunosuppressants like cyclosporin.[9] Nevertheless, the full potential of MDR inhibitors in the treatment of resistant tumors is not really evaluated because existing products exhibit their activity at doses far beyond their intrinsic toxic level, and this precludes clinical use.[10] Finding more potents inhibitors of P-glycoprotein devoid of cardiovascular activity and low toxicity would thus be an interesting goal, allowing to restore the cell sensitivity to anticancer agents.

In our approach to finding new leads, we noticed, as did others,[11] that MDR inhibitory molecules, including the recently described inhibitor S 9788,[14] shared a basic structural pattern such as a cationic protonable site linked to an aromatic lipophilic part by a spacer of variable length. Nevertheless, most of the structure–activity relationships (SAR) were performed with compounds synthesized for other purposes[12,13] that do not possess a pure MDR inhibitor effect.

In our preliminary studies, we used as the cationic part a hybrid of amiodarone and verapamil side chains, linked to a variety of aromatic rings by an amide bond. We realized rapidly that the best potentialities lied in tricyclic nuclei as lipophilic moieties. We report here our studies that led to the synthesis of the potent MDR inhibitor **84**.

Chemistry

The synthetic strategy for the preparation of compounds **22–85** involved the synthesis of substituted anilines and tricyclic carboxylic acids and their coupling with an appropriate reagent (Scheme 8). Most of the substituted anilines, **7a–x**, were prepared according to Schemes 1–7. The anilines **7** containing a heteroatom in the side chain were prepared according to Scheme 1 (method A). 4-Nitrophenol (**1**) was alkylated with an (alkylbromo)alkanoate in the presence of CO_3HNa to give **2** which was saponified to give **3**. Transformation into the acid chloride and reaction with the amine **4** gave **5**. Catalytic hydrogenation of the nitro group followed by reduction of the carbonyl with $LiAlH_4$ afforded **7**.

This method was not adequate to prepare compounds **7i–n** where $n = 3$, due to the ease of alkene formation by elimination, and therefore we devised Scheme 2. 4-Nitrophenol reacted with 1,3-dibromopropane to yield **8** which reacted with amine **4** to give **9**. Subsequent catalytic hydrogenation in the presence of Pd/C afforded **7** (method B). The compounds without a heteroatom in the side chain were prepared by reaction of a nitroalkanoyl acid chloride with the appropriate benzylamine **4** to afford **11** which was hydrogenated in the presence of Pd/C to **12** followed by reduction with $LiAlH_4$ to **7** (Scheme 3) (method C). Alternatively, depending on the availability of starting products, **7q–v** were prepared according to Scheme 4, where a (nitrophenyl)-alcanoyl alcohol, **13**, was brominated with PBr_3 and the resulting bromide **14** reacted with the appropriate amine **4** to afford **15** that was reduced by **7** by catalytic hydrogenation (method D). The aniline **7w** was prepared starting from the commercially available nitrocinnamyl alcohol (**16**) which was brominated with PBr_3 in diethyl ether to yield **17**.

Condensation of **17** with **4** provided **18** that underwent selective reduction of the nitro group with Fe/HCl in methanol (Scheme 5). Compound **7x** was prepared by Merweein condensation of 4-nitrobenzenediazonium chloride with butadiene[15] in the presence of $CuCl_2$ to **19** which was condensed with **4** to give **20** that was

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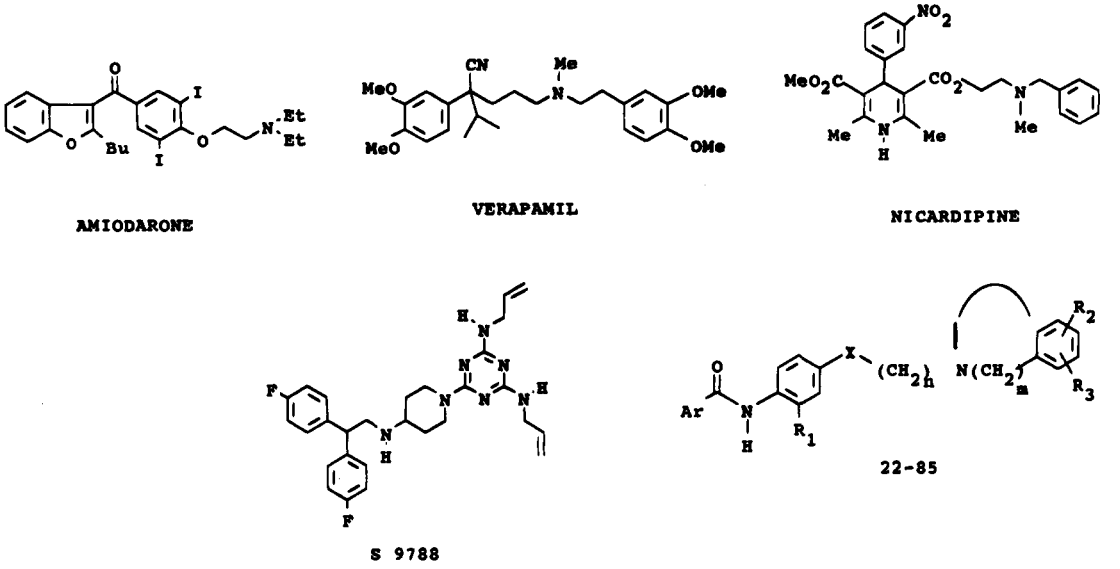
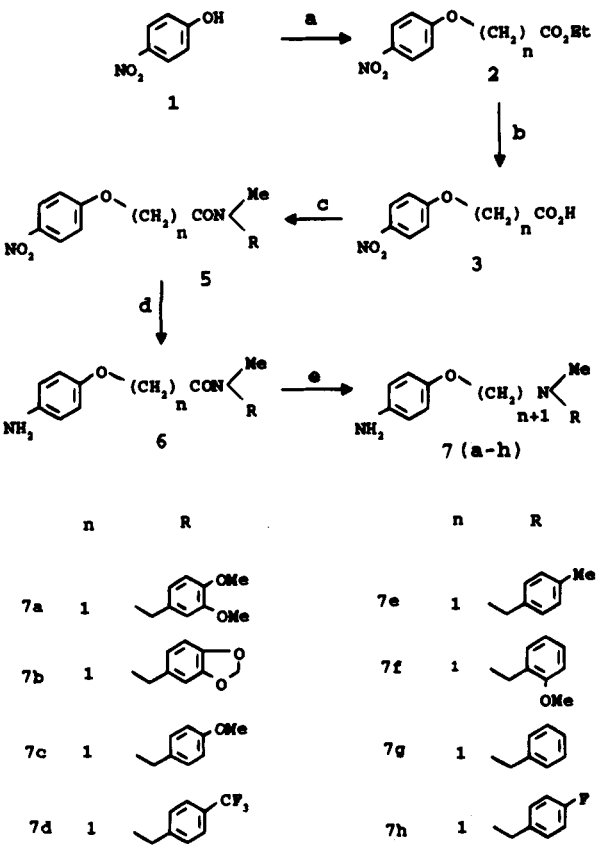
Chart 1



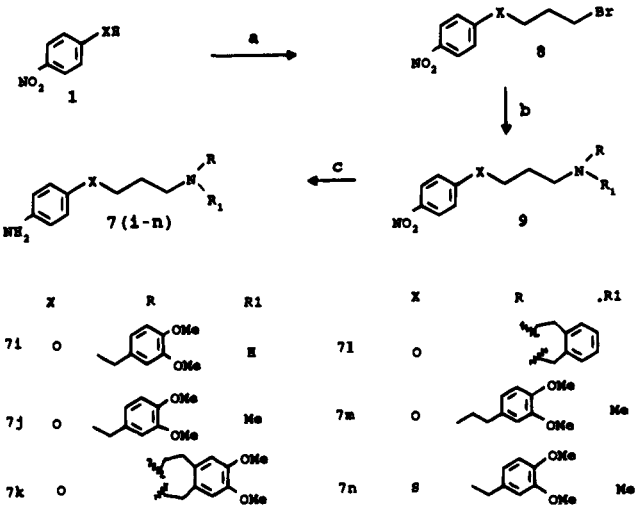
Scheme 1[a]



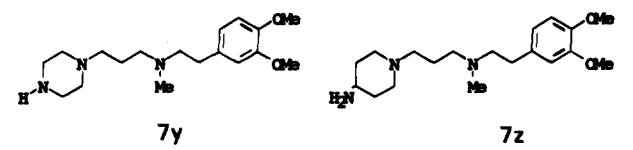
[a] Reagents: (a) $Br(CH_2)_nCO_2Et$, $NaHCO_3$, acetone; (b) NaOH; (c) i, $SOCl_2$, ii, RNHMe (**4**); (d) H_2, Pd/C; (e) $LiAlH_4$/THF.

selectively reduced to **7x** with Fe/HCl in methanol (Scheme 6). All these substituted anilines **7** are rather instable compounds which darken on storage and must be used rapidly. The compound **7y** was prepared by condensation of 1,3-bromochloropropane with **4** and reaction of the resulting product **21** with *N*-formylpiperazine followed by acid hydrolysis of the formyl group (Scheme 7). The compound **7z** was obtained by condensation of 1,3-dibromopropane with **4** and reaction of the resulting compound **21** with piperidone ethylene ketal. The keto group was regenerated by acid hydrolysis and oximated with NH_2OH·HCl. Subsequent reduction with $LiAlH_4$ led to a desired compound (Scheme 7).

Scheme 2[a]



[a] Reagents: (a) $BrCH_2CH_2CH_2Br$, CO_3K_2, DMF; (b) RR_1NH (**4**); (c) H_2, Pd/C.

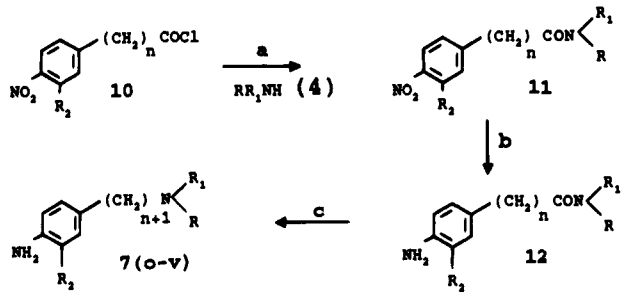


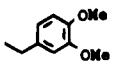
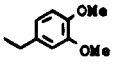
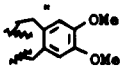
3-Methyl-4-nitrophenylacetic acid (**10**, R_2 = Me, n = 1) was prepared by Arndt and Eistert homologation of 3-methyl-4-nitrobenzoic acid. 3-Methyl-4-nitrophenylpropionic acid (**10**, R_2 = Me, n = 2) was synthesized by reaction of 3-methyl-4-nitrobenzyl bromide with diethyl malonate in the presenece of sodium ethoxide followed by decarboxylation. The necessary *N*-methylbenzyl- and phenethylamines **4** not available commercially were prepared by monomethylation of the primary amine by a modification of the procedure described by Kiefer.[16]

Results and Discussion

The compounds were assayed in vitro for the reversal of sensitivity of the multidrug resistant Chinese ham-

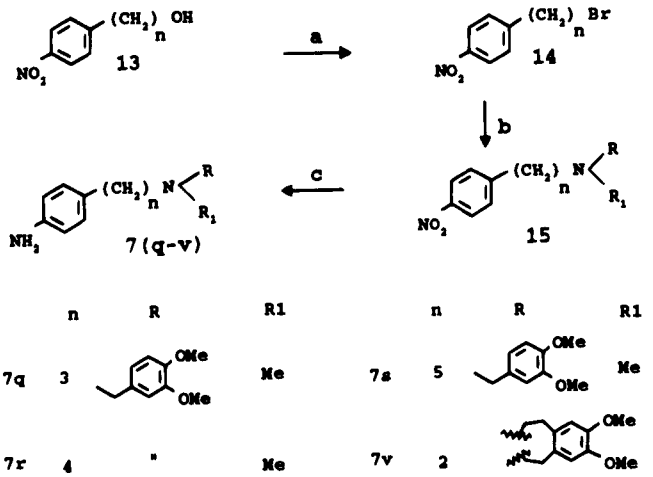
Scheme 3[a]



	n	R	R1	R2		n	R	R1	R2
7o	0		Me	H	7s	4		Me	Me
7p	1	"	Me	H	7t	1	"	Me	Me
7q	2	"	Me	H	7u	2	"	Me	Me
7r	3	"	Me	H	7v	1			H

[a] Reagents: (a) CO_3HNa, acetone; (b) H_2/Pd/C; (c) $LiAlH_4$/THF.

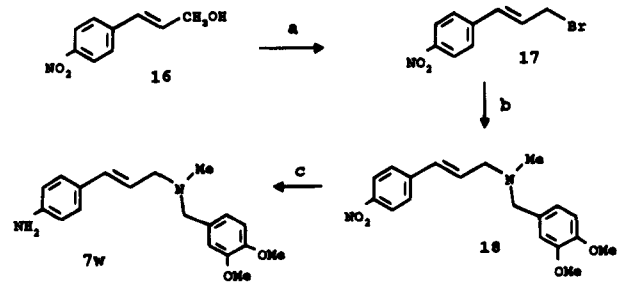
Scheme 4[a]



	n	R	R1		n	R	R1
7q	3		Me	7s	5		Me
7r	4	"	Me	7v	2		

[a] Reagents: (a) PBr_3/Et_2O; (b) R_1RNH (**4**), CO_3K_2/DMF; (c) H_2, Pd/C.

Scheme 5[a]

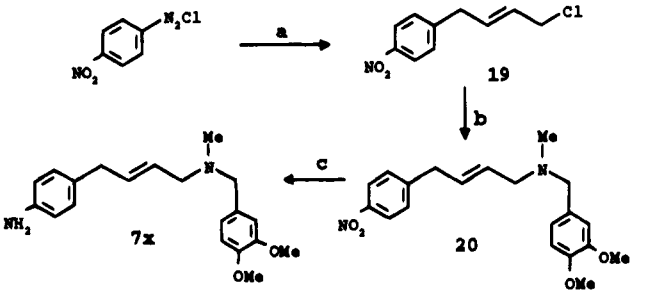


[a] Reagents: (a) PBr_3/Et_2O; (b) *N*-methylveratrylamine; (c) Fe/HCl.

ster ovary cell line $CH^RC/5$ toward doxorubicin (see the Experimental Section). Activity was expressed as the concentration that restores 50% of the cytotoxic activity of 5 μg/mL doxorubicin. In this assay the EC_{50} of amiodarone and verapamil are respectively 2.3 ± 0.6 and 3 ± 0.6 μM. Amiodarone was the standard reference in all the assays.

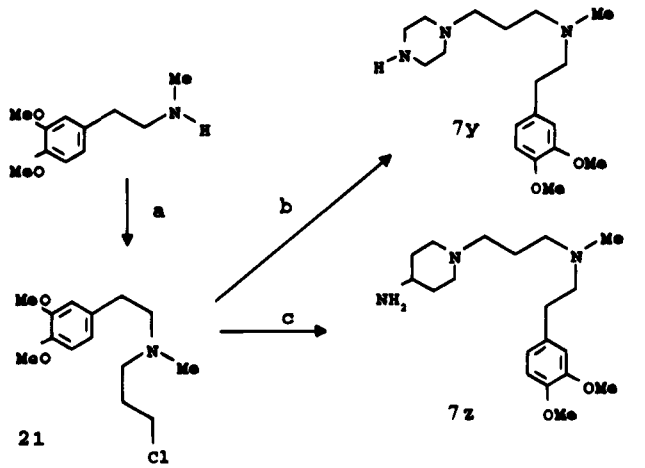
The results of the initial series of products are summarized in Table 1. We selected as the cationic part a hybrid of amiodarone and verapamil side chains

Scheme 6[a]



[a] Reagents: (a) butadiene, $CuCl_2$, CaO; (b) *N*-methylveratrylamine; (c) Fe/HCl.

Scheme 7[a]



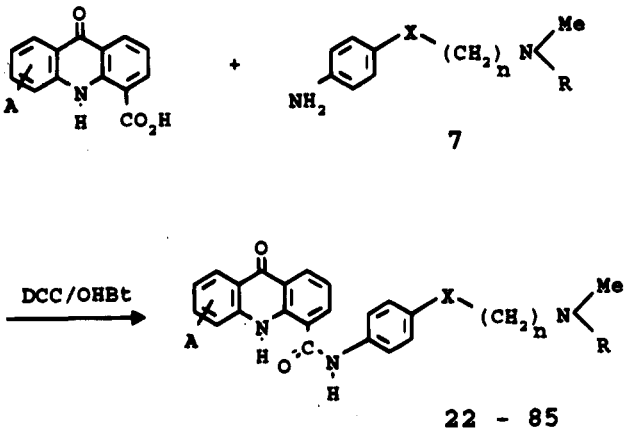
[a] Reagents: (a) $BrCH_2CH_2CH_2Cl$, CO_3K_2, DMF; (b) i, *N*-formylpiperazine, ii, HCl; (c) i, piperidone ethylene ketal, ii, HCl, iii, NH_2OH, HCl, iiii, $LiAlH_4$/THF.

linked to an array of tricyclic carboxylic acids by an amide bond. Most of the products were 10-fold more potent than verapamil with a special mention to acridone **22** and thioxanthone **24** with EC_{50} 90 nM. The replacement of sulfur by oxygen to give the xanthone **23** decreased the activity. The replacement of the acridone by 9-chloroacridine (**25**) led to an inactive compound, while an acridine (**26**) resulted in high toxicity.

The introduction of a second carbonyl to give the anthraquinone **27** was also detrimental. The phenothiazine **31** and the phenazine **30** were less potent as well as was **32** which includes a intracyclic nitrogen. The dibenzodioxin derivative **28**, which, compared to **22**, is twisted out of plane, also displayed reduced activity. The compound **29**, where the phenyl ring is taken out of the cycle, was prepared in order to give some degree of freedom to the system but was less potent. These results point to the conclusion that a planar system[11] containing a carbonyl has the best potentiality.

Since the acridone derivative **22** was the most interesting, an optimization of the cationic part (Table 2) while keeping the acridone constant was undertaken. This study demonstrated the need of a substituted benzyl- or phenethylamine derivative. Many compounds with (dialkylamino)alkyl side chains were prepared (data not shown) and were not very potent; for example, the *N*-diethylamino derivative **40** is totally inactive. Among the benzyl or phenethyl compounds, the 3,4-dimethoxy-substituted **22** and **43** showed the best potency.

Scheme 8



It is interesting to note that if the phenethylamine was constrained by forming a tetrahydroisoquinoline ring, **44**, activity was increased. On the contrary, if the cationic nitrogen was secondary, **42**, activity was decreased.

The nature and length of the spacer tethering the carboxamide function to the cationic nitrogen are also important (Tables 3 and 4). A simple eight-carbon alkyl chain (**56**) without a central phenyl ring is not adequate probably due to folding possibilities and the lack of π interactions. Compounds **48**, **49**, and **50** which include respectively a phenethyl, phenylpropyl, and phenylbutyl central chain were very potent. A decrease in activity was observed with shorter, **47**, and larger, **51**, chains, suggesting an optimal length for the spacer. We also examined the introduction of a heteroatom in the aralkyl chain as in **52** and **53**, and this did not lead to significant changes in potency. A further rigidification obtained by introduction of a double bond, **54** and **55**, was detrimental to activity.

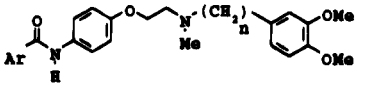
The replacement of the central phenyl by a heterocycle (piperazine **58** and piperidine **57**) in order to improve the solubility led to inactive products, suggesting that the carboamoylphenyl part does not act only as an inert spacer but also contributes to the activity of its own right, maybe by interacting with an electron acceptor site.

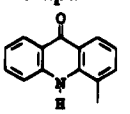
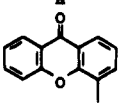
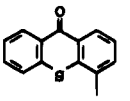
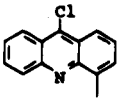
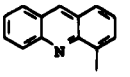
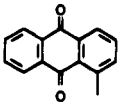
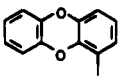
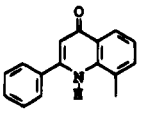
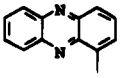
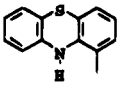
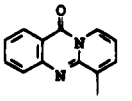
An attempt to change the position of the alkyl chain on the phenyl ring gave compounds retaining some potency, but the para position seems to be the most adequate (Table 5). As the amide linker may be considered as a possible site of metabolic cleavage, adjacent substituents were introduced in order to increase the steric crowding and proffer stability toward amidases (Table 6), and the products were found to be almost equipotent to the unsubstituted ones.

Substitutions on the acridone ring have been studied (Table 7) showing that, in most cases, a slight increase in potency was obtained with a substituent at the 5-position, the best results being attained with a methoxy, fluoro, and methyl. On the contrary, the N-methylation of the acridone ring, **77**, was detrimental.

Most of the tricyclic carboxylic acids used in this study have been shown to possess the minimal structural requirement for DNA intercalation,[19] although to a lesser extent in the case of the oxo derivatives. Nevertheless the possibility of interaction with topoisomerases can be ruled out due to the lack of cytotoxicity of the compounds. In view of the in vitro results, **84** was studied in mice implanted with the MDR P388/DOX tumor which is quite insensitive to the maximum tolerated dose of 5 mg/kg of doxorubicin. Compound **84** was administered iv at doses ranging from 1 to 20 mg/kg 1 h before administration of 5 mg/kg ip of doxorubicin. This allowed time for distribution of the compound in the intraporitoneal cavity. As result of eight pooled separate experiments with groups of 40–70 mice, which were reproducible and statistically significant, an increase of 50% of the mean survival time was obtained with a dose of 5 mg/kg of **84**. A proportion of 5–10% of the mice survived after 30 days; this is compared to a proportion of 2–5% of survivors after 15 days in the group treated with doxorubicin alone.

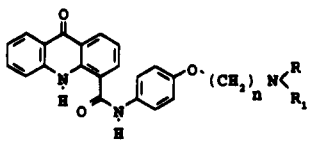
Table 1. Data and Activity of Tricyclic Compounds

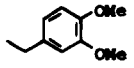
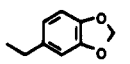
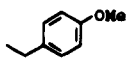
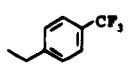
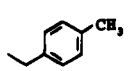
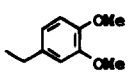
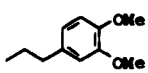
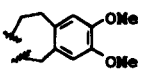
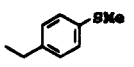


no.	Ar	*n*	formula	mp (°C)	EC_{50} (nM)[c]
	amiodarone				2300
	verapamil				3000
22		1	$C_{32}H_{31}N_3O_5$	138-9	90
23		2	$C_{33}H_{32}N_2O_6$	152	180
24		2	$C_{33}H_{32}N_2O_5S$	168	90
25		2	$C_{33}H_{32}ClN_3O_4$[a]	130	660
26		2	$C_{33}H_{33}N_3O_4$	110	TOX[b]
27		2	$C_{34}H_{32}N_2O_6$	176	1500
28		2	$C_{32}H_{32}N_2O_4$	146-8	460
29		1	$C_{34}H_{33}N_3O_5$	170	330
30		1	$C_{31}H_{30}N_4O_4$	135	330
31		2	$C_{32}H_{33}N_3O_4S$	90	180
32		2	$C_{32}H_{32}N_4O_5$	85	210

[a] HCl, $2H_2O$. [b] Toxic alone to cells at 5 μM. [c] Drug level which combined with 5 μg/mL doxorubicin results in 50% cell kill of $CH^RC/5$ (72 h exposure); expressed as the mean of three determinations.

Table 2. Variations of the Cationic Site

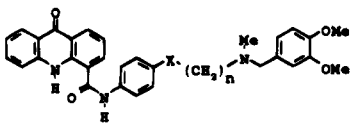


no.	n	R	R_1	formula	mp (°C)	EC_{50} (nM)
22	2	CH_3		$C_{32}H_{31}N_3O_5$	138-9	90
33	2	CH_3		$C_{31}H_{27}N_3O_5$	171	550
34	2	CH_3		$C_{31}H_{29}N_3O_4$	145-6	650
35	2	CH_3		$C_{31}H_{26}F_3N_3O_3$	156-7	800
36	2	CH_3		$C_{31}H_{29}N_3O_3$	168	240
37	2	CH_3		$C_{31}H_{29}N_3O_4$	180	510
38	2	CH_3		$C_{30}H_{27}N_3O_3$	173	720
39	2	C_2H_5		$C_{31}H_{29}N_3O_3$	156-7	110
40	2	C_2H_5	C_2H_5	$C_{26}H_{27}N_3O_3$	208	NA
41	2	CH_3		$C_{30}H_{26}FN_3O_3$	157	930
42	3	H		$C_{32}H_{31}N_3O_5$	138-9	525
43	3	CH_3		$C_{34}H_{35}N_3O_5$	140	90
44	3			$C_{34}H_{33}N_3O_5$	218	50
45	3			$C_{32}H_{29}N_3O_3$	182	210
46	2	CH_3		$C_{31}H_{29}N_3O_3S$	150	690

Conclusion

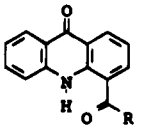
It has been possible to design P-glycoprotein inhibitors having an EC_{50} in the 10 nM range starting from general features of weak inhibitors. The compounds retain the already known, broad structure for MDR inhibition including a cationic site located at some distance from a lipophilic part. The favorable effect of a tricycle led to a new series of potent compounds. The central part linking the basic nitrogen to the tricycle proved to be of extreme importance, the key role of the central carbamoylphenyl can be assumed to be due to the hydrogen-bonding capabilities of the amide and the fixing of the nitrogen position through coplanarity with the tricycle. On the basis of activity, toxicity, and pharmacokinetics, compound **84** (GF120918) has been selected for further investigation. This compound has been shown to bind to P-glycoprotein by inhibition of [^{3}H]azidopine photoaffinity cross-linking,[17] therefore suggesting direct action on the efflux pump. Cardiovascular screening showed that Ca^{2+} antagonist activity was no longer present in this compound.

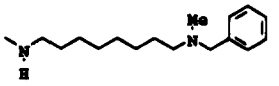
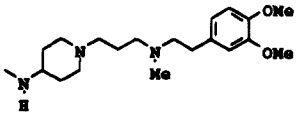
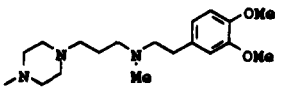
Table 3. Variation of the Central Chain



no.	x	n	formula	mp (°C)	EC_{50} (nM)
47		1	$C_{31}H_{29}N_3O_4$	175	370
48		2	$C_{32}H_{31}N_3O_4$	180	27
49		3	$C_{33}H_{33}N_3O_4$	112	60
50		4	$C_{34}H_{35}N_3O_4$	140	30
51		5	$C_{35}H_{37}N_3O_4$	108	150
52	O	3	$C_{33}H_{33}N_3O_5$	130	36
53	S	3	$C_{33}H_{33}N_3O_4S$	140	45
54	-CH=CH-	1	$C_{33}H_{31}N_3O_4$	187	270
55	$-CH_2CH=CH-$	1	$C_{34}H_{33}N_3O_4$	140	150

Table 4. Variation of the Central Chain



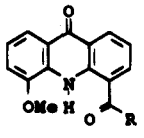
no.	R	formula	mp (°C)	EC_{50} (nM)
56		$C_{30}H_{35}N3O_2$[a]	85	1100
57		$C_{33}H_{40}N_4O_4$[b]	165	NA
58		$C_{32}H_{38}N_4O_4$[c]	145	NA

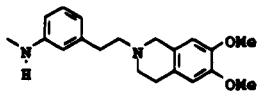
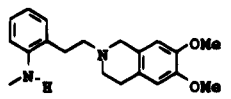
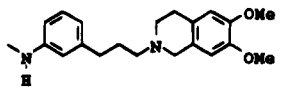
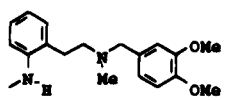
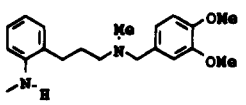
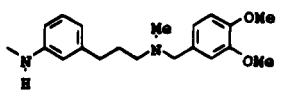
[a] 0.5 H_2O. [b] 2 oxalic acid, 1 H_2O. [c] 2 oxalic acid, 1 H_2O.

Experimental Section

The melting points were determined on a hot-stage Kofler apparatus and are not corrected. Silica gel plates (Merck F_{254}) and silica gel 60 (230–400 mesh) were used for analytical and column chromatography, respectively. Microanalyses were within ±0.4% of the theoritical values, unless stated otherwise. The IR spectra were recorded with a Perkin Elmer FTIR1600 spectrometer in KBr or neat and are expressed in cm^{-1}. The ^{1}H NMR spectra were obtained with a Bruker AC250 spectrometer at 250 MHz, and shifts are expressed in ppm with TMS as internal standard and are consistent with the proposed structures.

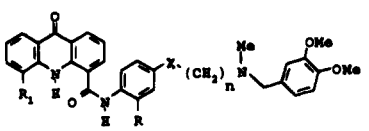
Table 5. Variation of the Chain Position on the Central Ring



no.	R	formula	mp (°C)	EC_{50} (nM)
59		$C_{34}H_{33}N_3O_5$	152	155
60		$C_{34}H_{33}N_3O_5$[a]	160	305
61		$C_{35}H_{35}N_3O_5$[b]	138-140	48
62		$C_{33}H_{33}N_3O_5$	152-3	465
63		$C_{34}H_{35}N_3O_5$	166	585
64		$C_{34}H_{35}N_3O_5$[c]	112-114	45

[a] 1 oxalic acid, 1 H_2O. [b] 1 H_2O. [c] 1 oxalic acid, 0.5 H_2O.

Table 6. Effect of Substitution on the Central Phenyl



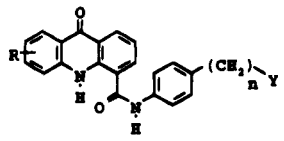
no.	R_1	R	X	*n*	formula	mp (°C)	EC_{50} (nM)
65	CH_3	CH_3	O	3	$C_{35}H_{37}N_3O_5$	146	93
66	OCH_3	CH_3	O	2	$C_{34}H_{35}N_3O_6$	178–9	280
67	F	CH_3	O	3	$C_{34}H_{34}FN_3O_5$	130	63
68	F	CH_3		2	$C_{33}H_{32}FN_3O_4$	125	88
69	F	OCH_3	O	3	$C_{34}H_{34}FN_3O_6$[a]	108	30
70	F	C_2H_5	O	3	$C_{35}H_{36}FN_3O_5$	146	90
71	OCH_3	OCH_3		3	$C_{35}H_{37}N_3O_6$	105	37
72	F	OCH_3		3	$C_{34}H_{34}FN_3O_5$[b]	105–6	43
73	CH_3	CH_3		2	$C_{34}H_{35}N_3O_4$[c]	160	80
74	CH_3	OCH_3	O	3	$C_{35}H_{37}N_3O_6$	156–7	40
75	F	OCH_3		2	$C_{33}H_{32}FN_3O_5$	161–2	21

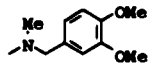
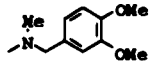
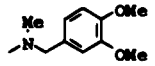
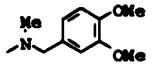
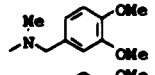
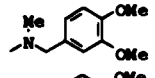
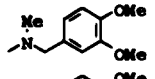
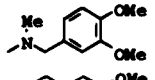
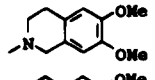
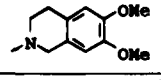
[a] 1H_2O. [b] 1H_2O. [c] 0.5H_2O.

Starting Products. The following known tricyclic carboxylic acids were prepared according to literature procedures: acridone-4-carboxylic acid,[18] 9-chloroacridine-4-carboxylic acid,[18] anthraquinone-1-carboxylic acid,[19] acridine-1-carboxylic acid,[19] xanthone-4-carboxylic acid,[19] thioxanthone-4-carboxylic acid,[19] 11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-6-carboxylic acid,[19] phenothiazine-1-carboxylic acid,[19] phenazine-1-carboxylic acid,[20] 5-substituted acridone-4-carboxylic acids,[22] and 2-phenyl-4(1*H*)quinolone-8-carboxylic acid.[21]

General Procedures for the Preparation of Anilines 7. The following typical examples are given to illustrate the general procedure for methods A–D.

Table 7. Effect of Substitutions on the Acridone Ring



no.	*n*	R	Y	formula	mp (°C)	EC_{50} (nM)
76	2	5,7-di-OMe		$C_{34}H_{35}N_3O_6$	265	22
77	2	10-CH_3		$C_{33}H_{33}N_3O_4$	182	210
78	2	5-NO_2		$C_{32}H_{30}N_4O_6$	197	195
79	2	5-F		$C_{32}H_{30}FN_3O_4$[a]	172	18
80	2	5-CH_3		$C_{33}H_{33}N_3O_4$	119	21
81	2	5-OCH_3		$C_{33}H_{33}N_3O_5$[b]	174	21
82	4	5-NH_2		$C_{34}H_{36}N_4O_4$	245	177
83	4	7-OCH_3		$C_{35}H_{37}N_3O_5$[c]	172	120
84	2	5-OCH_3		$C_{34}H_{33}N_3O_5$	224	21[e]
85	2	5-F		$C_{33}H_{30}FN_3O_4$[d]	212	33

[a] 0.5 H32O. [b] 0.25H_2O. [c] 0.5H_2O. [d] 1H_2O. [e] ±5 (means ± SD of 33 determinations).

Method A (Scheme 1): *N*-[2-(4-Aminophenoxy)ethyl]-3,4-dimethoxy-*N*-methylbenzenemethanamine (7a). A mixture of (4-nitrophenoxy)acetic acid (50 g, 0.253 mol) and thionyl chloride (150 mL) was heated for 3 h under reflux. The solution was concentrated to give the acid chloride as a solid. A solution of this chloride in acetone (250 mL) was added dropwise to a stirred solution of 3,4-dimethoxy-*N*-methylbenzenemethanamine (50 g, 0.276 mol) and CO_3HNa (23 g, 0.273 mol) in acetone (250 mL) at room temperature. Stirring was continued for 4 h, the mixture was filtered, and the filtrate was concentrated. The residue was treated with water and extracted with AcOEt. The organic phase was washed with diluted NaOH and water, dried (SO_4Na_2), and concentrated. Recrystallization from ethanol yielded 80 g of *N*-[(3,4-dimethoxyphenyl)methyl]-*N*-methyl-2-(4-nitrophenoxy)acetamide as white crystals: mp 130 °C; IR (KBr) 1650 cm^{-1} (C=O).

This product was hydrogenated in ethanol (500 mL) at 60 °C and atmospheric pressure in presence of Pd/C (10%, 8 g). After hydrogen absorbtion was completed, the catalyst was filtered and the solution concentrated to give 2-(4-aminophenoxy)-*N*-[(3,4-dimethoxyphenyl)methyl]-*N*-methylacetamide as a white solid: mp 126 °C; IR (KBr) 3346, 3406 (NH_2), 1650 (CO) cm^{-1}. A solution of this amine in anhydrous THF (500 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (30 g) in THF (300 mL) and the mixture refluxed for 3 h. The excess of $LiAlH_4$ was destroyed by careful addition of water to the cooled mixture. After filtration, the solution was evaporated and extracted with diethyl ether to give 43 g (54%) of **7a** as an oil: IR (neat) 3360–3420 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$) δ 6.55–6.95 (m, 7H, ar), 4.00 (t, 2H), 3.90 (s, 6H), 3.55 (s, 2H), 3.40 (br, 2H, NH_2), 2.80 (t, 2H), 2.30 (s, 3H, NCH_3).

Method B (Scheme 2): *N*-[3-(4-Aminophenoxy)propyl]-3,4-dimethoxy-*N*-methylbenzeneethanamine (7m). A mixture of 4-nitrophenol (69.5 g, 0.5 mol) and CO_3K_2 (83 g, 0.6 mol) in DMF (250 mL) was stirred for 1 h at room temperature, and 1,3-dibromopropane (80 mL, excess) was added. After

stirring overnight, the mixture was poured into water and extracted with dichloromethane. The organic phase was washed with diluted NaOH and water, dried (SO_4Na_2), and concentrated. The residue was recrystallized from diisopropyl oxide to give 97 g of 1-(3-bromopropoxy)-4-nitrobenzene as white crystals: mp 62–3 °C.

A mixture of this bromide (19 g, 73 mmol) and 3,4-dimethoxy-*N*-methylbenzeneethanamine (15 g, 82 mmol) was heated neat at 140 °C for 30 min and diluted with water and dilute NaOH. The mixture was extracted with dichloromethane. The organic solution was washed with water, dried (SO_4Na_2), and concentrated. The residue was purified by chromatography on silica gel 60 (240–400 mesh) (CH_2Cl_2/MeOH, 95:5) to give 18 g of 3,4-dimethoxy-*N*-methyl-*N*-[3-(4-nitrophenoxy)propyl]benzeneethanamine. This compound in solution in ethanol (200 mL) was hydrogenated at room temperature and atmospheric pressure in the presence of Pd/C (10%, 1 g). After hydrogen absorption was completed, the catalyst was filtered off and the solution concentrated to give 15 g (59.7%) of **7m** as an oil: ^{1}H NMR ($CDCl_3$) δ 6.50–6.70 (m, 7H, ar), 3.85 (t, 2H), 3.75 (s, 6H), 3.30 (br, 2H, NH_2), 2.50–2.70 (m, 6H), 2.22 (s, 3H, N-CH_3), 1.85 (m, 2H).

Method C (Scheme 3): 4-Amino-*N*-[(3,4-dimethoxyphenyl)methyl]-*N*-methylbenzeneethanamine (7p). A solution of 4-nitrophenylacetic acid (22 g, 0.12 mol) in $SOCl_2$ (200 mL) was heated under reflux for 3 h and concentrated to give the acid chloride as an oil. This oil was dissolved in acetone (100 mL) and added dropwise to a stirred mixture of 3,4-dimethoxy-*N*-methylbenzenemethanamine (22 g, 0.147 mol) and $NaHCO_3$ (15.1 g, 0.18 mol) at room temperature. Stirring was continued for 6 h, the mixture filtered, and the filtrate concentrated. The residue was extracted with ether, and the organic layer was washed with dilute NaOH and water, dried (SO_4Na_2), and evaporated to give 22 g of *N*-[(3,4-dimethoxyphenyl)methyl]-*N*-methyl-4-nitrobenzeneethanamide as an oil. This oil was hydrogenated in ethanol (250 mL) in the presence of Pd/C (10%, 2 g) at room temperature and atmospheric pressure. After hydrogen absorbtion was completed, the catalyst was filtered off on a Celite pad and the solution concentrated to give 18 g of 4-amino-*N*-[(3,4-dimethoxyphenyl)-methyl]-*N*-methylbenzeneethanamide as a white solid: mp 148 °C; IR (KBr) 3347–3447 (NH_2), 1691 (C=O) cm^{-1}.

This product in solution in anhydrous THF (150 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (8 g) in THF (250 mL) at room temperature, and the mixture was heated under reflux for 3 h. The excess of $LiAlH_4$ was destroyed by careful addition of water to the cooled mixture. After filtration on a Celite pad, the solution was concentrated and extracted with ether. The organic layer was washed with water, dried (SO_4Na_2), and concentrated to give 11 g (30.5%) of **7p** as an oil: IR (neat) 3360, 3430 (NH_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.60–7.05 (m, 7H, ar), 3.88 (s, 6H), 3.60 (br, 2H, NH_2), 3.52 (s, 2H), 2.72–2.80 (m, 2H), 2.60–2.65 (m, 2H), 2.30 (s, 3H, N-CH_3).

Method D (Scheme 4): 4-[2-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-isoquinolyl)ethyl]benzenamine (7v). A mixture of 1-(2-bromoethyl)-4-nitrobenzene (10.5 g, 43.4 mmol), 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (10.9 g, 47.5 mmol), and CO_3K_2 (13.9 g, 100 mmol) in DMF (100 mL) was heated for 6 h at 100 °C. The mixture was filtrated and evaporated, the residue taken up in water and extracted with dichloromethane, and the solution dried (SO_4Na_2) and evaporated. The resulting solid was recrystallized from diisopropyl oxide to give 14.5 g of 1,2,3,4-tetrahydro-6,7-dimethoxy-2-[2-(4-nitrophenyl)ethyl]isoquinoline as cream crystals: mp 118 °C.

This product was hydrogenated in ethanol (200 mL) at room temperature and atmostpheric pressure in the presence of Pd/C (10%, 1.4 g). After the hydrogen absorbtion was completed, the catalyst was filtered off and the solution concentrated to give 12 g (80%) of **7v** as a cream solid: mp 120 °C; IR (KBr) 3337–3403 cm^{-1} (NH_2); ^{1}H NMR ($CDCl_3$) δ 7.10 (d, 2H, ar), 6.55–6.70 (m, 4H, ar), 3.85 (s, 6H), 3.68 (s, 2H), 3.60 (br, 2H, NH_2), 2.70–2.95 (complex m, 8H).

***N*-Methylhomoveratrylamine.** A mixture of homoveratrylamine (100 g, 0.55 mol) and benzaldehyde (59 g, 0.55 mol) was stirred for 1 h at room temperature, and the water formed was rotoevaporated under reduced pressure. Methyl iodide (40 mL, 0.64 mol) was added and the mixture kept for 48 h at 40 °C; by that time, it had become a yellow solid which was boiled for 3 h with ethanol/water (8:2, 500 mL). Two-thirds of the ethanol was then evaporated and the solution diluted with diethyl ether (1 L) to give white crystals that were filtered, washed with ether, and treated with 2 N NaOH. Extraction with diethyl ether and distillation under reduced pressure gave 80 g of *N*-methylhomoveratrylamine: $bp_{0.05}$ 92–5 °C.

(*E*)-3-(4-Aminophenyl)-*N*-[(3,4-dimethoxyphenyl)methyl]-*N*-methylallylamine (7w). To a suspension of 4-nitrocinnamyl alcohol (6 g, 33.5 mmol) at room temperature in diethyl ether (50 mL) was added PBr_3 (0.5 mL, 5.4 mmol), and the mixture was stirred for 1 h. After treatment with H_2O, more diethyl ether was added and the organic layer washed with water, dried (Na_2SO_4), and concentrated to give 5.25 g of 4-nitrocinnamyl bromide as a pale yellow solid: mp 76 °C.

A mixture of this bromide (5 g, 20.7 mmol), 3,4-dimethoxy-*N*-methylbenzylamine (3.6 g, 26 mmol), and CO_3K_2 (3.5 g) was heated under reflux in methyl isopropyl ketone (60 mL) with stirring. After cooling the mixture was filtered and concentrated and the residue treated with water and extracted with dichloromethane to give an oil. This oil was purified by chromatography on silica gel (CH_2CL_2/MeOH, 95:5) to give 4.8 g of 3-(4-nitrophenyl)-*N*-[(3,4-dimethoxyphenyl)methyl]-*N*-methylallylamine as an oil. This product was mixed with methanol (100 mL) and concentrated HCl (10 mL), and iron powder (5 g) was added slowly at room temperature with stirring. The mixture was then heated for 30 min at reflux and the solution filtered and concentrated. The residue was taken up with water, basified with concentrated NaOH, and extracted with ether (3 × 100 mL). The organic phase was washed with water, dried (SO_4Na_2), and concentrated to give 3.95 g (61%) of **7w** as an oil which crystallizes by treatment with diisopropyl oxide: mp 68 °C; IR (KBr) 3346–3426 cm^{-1} (NH_2); ^{1}H NMR ($CDCl_3$) δ 7.2 (d, 2H, ar), 6.75–6.90 (m, 3H, ar), 6.70 (d, 2H, ar), 6.40 (d, 1H), 6.10 (m, 1H), 3.90 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.65 (s, 2H, NH_2), 3.45 (s, 2H), 3.13 (d, 2H), 2.20 (s, 3H, NCH_3).

(*E*)-1-[[(3,4-Dimethoxyphenyl)methyl]methylamino]-4-(4-aminophenyl)but-2-ene (7x). 4-Nitrobenzenediazonium chloride was prepared by addition of sodium nitrite (51 g, 0.73 mol) in water (100 mL) to a solution of 4-nitroaniline (100 g, 0.73 mol) in water (300 mL) and concentrated HCl (170 mL) at such a rate that the temperature did not exceed 0 °C. This solution was added dropwise to a stirred mixture of butadiene (100 mL), $CuCl_2$ (23 g), CaO (30 g) in acetone (1.4 L), and water (100 mL) maintained at −20 °C. The mixture was then stirred overnight at room temperature. The two phases were separated, and the aqueous phase was extracted with ether. The combined organic phases were washed with water, treated with charcoal, and filtered over a Celite pad. Concentration afforded a dark oil that was distillated with a short path column under reduced pressure to give a yellow oil (80 g): $bp_{0.05}$ 135–40 °C. This oil was determined by NMR and gas chromatography to be a mixture (8:2) of (*E*)-1-(4-chloro-2-butenyl)-4-nitrobenzene and (*E*)-1-(2-chloro-3-butenyl)-4-nitrobenzene that was used without further purification.

A mixture of this product (5 g) and 3,4-dimethoxy-*N*-methylbenzylamine (8 g) was heated neat for 30 min at 120 °C and poured into water. The mixture was extracted with ether; the organic phase was washed with water, dried (SO_4Na_2), and concentrated to give an oil that was dissolved in HCl (1 N), treated with charcoal, filtered, basified with NaOH, and extracted with ether to give 2.9 g of (*E*)-1-[[(3,4-dimethoxyphenyl)methyl]methylamino]-4-(4-nitrophenyl)but-2-ene. This compound was dissolved in methanol (60 mL) and concentrated HCl (4 mL); then, powdered iron (2 g) was added with stirring. After stirring at 40 °C for 2 h, the mixture was concentrated, basified with NaOH, and extracted with AcOEt (3 × 100 mL). The organic phase was washed with H_2O, dried (SO_4Na_2), and concentrated to give 2.5 g of **7x** as an oil: ^{1}H NMR ($CDCl_3$) δ 6.3–7.2 (m, 7H, ar), 5.6–6 (m, 2H), 3.8 (s, 6H), 3.5 (s, 2H), 3.4 (d, 2H), 3.15 (d, 2H), 2.15 (s, 3H, NCH_3).

1-[3-[*N*-Methyl-*N*-(3,4-dimethoxyphenethyl)amino]propyl]piperazine (7y). A mixture of 3,4-dimethoxy-*N*-methylbenzeneethamamine (10 g, 0.05 mol), 1,3-bromochloropropane (8 g, 0.05 mol), and CO_3K_2 (14 g, 0.1 mol) in DMF (50 mL) was stirred for 16 h at room temperature. The mixture was diluted with water and extracted with diethyl ether to give an oil that was refluxed with *N*-formylpiperazine (6 g, 0.052 mol) and CO_3K_2 (7 g, 0.05 mol) in methyl ethyl ketone (100 mL). The mixture was filtered and concentrated to give an oil that was heated for 2 h under reflux with concentrated HCl (50 mL) and water (200 mL). The solution was concentrated, basified with concentrated NaOH, and extracted with diethyl ether (3 × 200 mL). The organic phase was dried (SO_4Na_2) and concentrated to give 12 g of crude product that was used for the preparation of **60** without further purification: ^{1}H NMR ($CDCl_3$) δ 6.6–6.7 (m, 3H, ar), 3.75 (s, 3H), 3.80 (s, 3H), 2.75 (t, 4H), 2.45–2.55 (m, 4H), 2.15–2.45 (m, 8H), 2.15 (s, 3H, NCH_3), 1.80 (s, 1H, NH), 1.50–1.65 (m, 2H).

1-[3-[*N*-Methyl-*N*-(3,4-dimethoxyphenethyl)amino]propyl]-4-aminopiperidine (7z). A mixture of 3,4-dimethoxy-*N*-methylbenzeneethanamine (15 g, 0.075 mol), 1,3-bromochloropropane (12 g, 0.075 mol), and CO_3K_2 (21 g, 0.15 mol) in DMF (60 mL) was stirred for 2 h at room temperature. The mixture was poured into water and extracted with dichloromethane. The resulting oil (14 g) was refluxed overnight with 1,4-dioxa-8-azaspiro[4.5]decane (7.2 g, 0.05 mol) and CO_3K_2 (7 g, 0.05 mol) in methyl isopropyl ketone (150 mL). The mixture was filtered and concentrated. The residue was boiled for 2 h with HCl (250 mL), cooled, filtered, neutralized with NaOH (250 mL), and extracted with dichloromethane to give an oil. This oil was dissolved in ethanol (100 mL) and NH_2OH, HCl (3.3 g) in water (30 mL) was added, and the mixture was refluxed for 1 h. The solution was concentrated, made slightly basic with concentrated NaOH, extracted with dichloromethane (3 × 150 mL), and concentrated to give 12 g of oxime. A solution of this oxime in anhydrous THF (100 mL) was added to a stirred suspension of $LiALH_4$ (4.5 g) in anhydrous THF (150 mL), and the mixture was refluxed for 3 h. The excess of $LiALH_4$ was destroyed by careful addition of water with cooling, the mixture was filtered, and the solution was concentrated and extracted with diethyl ether to give the title compound (6.5 g) that was used for the preparation of **57** without further purification: ^{1}H NMR ($CDCl_3$ + D_2O) δ 6.70–6.82 (m, 3H, ar), 3.90 (s, 3H), 3.82 (s, 3H), 2.20–2.90 (m, complex, 12H), 2.20 (s, 3H, N-CH_3), 1.3–2.10 (m, complex, 7H).

3-Methyl-4-nitrobenzeneacetic Acid. 3-Methyl-4-nitrobenzoyl chloride (10 g, 0.05 mol) in ether (100 mL) was added dropwise to a solution of diazomethane (prepared from 30 g of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) at 0 °C. The reaction mixture was stirred at room temperature for 3 h and concentrated in vacuo to give the diazo ketone as a solid. This diazo ketone in dioxane (100 mL) was then added dropwise to a suspension of silver oxide (prepared from silver nitrate (20 g) and dilute NaOH) and sodium thiosulfate (25 g) in water (100 mL) kept at 70–5 °C. The mixture was stirred at 75–80 °C for 3 h and filtered. The filtrate was diluted with water and acidified with NO_3H and the product extracted with diethyl ether. The resulting solid was extracted twice with hot diisopropyl oxide and the solution treated with charcoal, filtered, and concentrated to give 3-methyl-4-nitrobenzeneacetic acid (6 g, 61.5%) as a cream solid: mp 95 °C. Further purification can be made by recrystallization from diisopropyl oxide: mp 95 °C; ^{1}H NMR ($CDCl_3$) δ 9.50 (s, 1H, CO_2H), 7.10–7.90 (m, 3H, ar), 3.60 (s, 2H), 2.50 (s, 3H).

General Procedure for the Coupling of Carboxylic Acids and Anilines: 9,10-Dihydro-9-oxo-*N*-[4-[2-[(3,4-dimethoxybenzyl)methylamino]ethyl]phenyl]-4-acridinecarboxamide (48). A mixture of 9,10-dihydro-9-oxo-4-acridinecarboxylic acid (1.2 g, 5 mmol) and 1-hydroxybenzotriazole hydrate (0.77 g, 5 mmol) in DMF (50 mL) was stirred at room temperature for 10 min. **7p** (1.5 g, 5 mmol) was added followed by dicyclohexylcarbodiimide (1.03 g, 5 mmol) and the mixture stirred overnight. After filtration, the solution was concentrated in vacuo, treated with dilute NaOH, and extracted with dichloromethane. The organic layer was washed with water, dried (SO_4Na_2), and evaporated to give a residue that was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 97:3) and recrystallization from 2-propanol to give **48** (0.63 g, 24%) as yellow crystals: mp 182 °C; IR (KBr) 3206, 3317 (NH), 1611, 1649 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.75 (s, 1H), 9.05 (s, 1H), 8.45 (d, 1H, ar), 8.30 (d, 1H, ar), 7.55–7.65 (m, 3H, ar), 7.35 (d, 1H, ar), 7.15–7.35 (m, 4H, ar), 6.75–6.90 (m, 4H, ar), 3.82 (s, 6H), 3.50 (s, 2H), 2.82 (t, 2H), 2.60 (t, 2H), 2.25 (s, 3H, N-CH_3).

Drug Sensitivity Assays (Described in details in references). $CH^RC/5$ cells were seeded at a density of 10^4 cells/well in Falcon microtiter plates. After 24 h, the medium was removed and replaced by 0.1 mL of fresh medium containing MDR inhibitors. A 0.1 mL volume of 2-fold dilution of doxorubicin was added. After 72 h of incubation, cell viability was assessed by the reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide to a dark blue formazan product. Briefly, 20 μL of a 5 mg/mL solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide in phosphate-buffered saline were added to each well. After 4 h of incubation at 37 °C, the medium was aspirated and replaced by 0.1 mL of DMSO. After vigorous shaking, the quantity of formazan product formed was assessed by its absorbance at 550 nm on a Dynatech MR700 instrument. The average of duplicate wells was used for the calculation. A DL_{50} for doxorubicin was then derived in the presence or absence of various MDR inhibitors.

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