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Effects of Isoquinolinesulphonamide Compounds on Multidrug-resistant P388 Cells

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Abstract—The effects of eight isoquinolinesulphonamide compounds on resistance to vinblastine in adriamycin-resistant mouse leukaemia cells (P388/ADR) which overexpress the relative molecular weight (M_r) 140 kDa P-glycoprotein in the plasma membrane were investigated. *N*-[2-(Methylamino)ethyl]-5-isoquinolinesulphonamide (H-8) and *N*-(2-aminoethyl)-5-isoquinolinesulphonamide (H-9) did not reverse vinblastine resistance. *N*-[2-[*N*-[3-(4-Chlorophenyl)-2-propenyl]amino]ethyl]-5-isoquinolinesulphonamide (H-86) and *N*-[2-[*N*-[3-(4-chlorophenyl)-1-methyl-2-propenyl]amino]ethyl]-5-isoquinolinesulphonamide (H-87) caused accumulation of intracellular vinblastine and inhibition of vinblastine efflux from the cells and reversed the resistance. Addition of an aminoethyl group to the nitrogen atom of the sulphonamide group (W-66) or a formyl group at the terminal amino group (H-85) of H-86 reduced those activities. Conversion of the chlorophenyl group of H-87 to pyridinyl (H-31) or furanyl (H-34) markedly decreased activities against the drug resistance. The activity against vinblastine accumulation closely correlated with the apparent partition coefficient of compounds. These compounds dose-dependently inhibited photoaffinity labelling of a photosensitive analogue of vinblastine, *N*-(*p*-azido-(3-[^{125}I])salicyl)-*N'*-*β*-aminoethyl-vindesine ([^{125}I]NASV), and there was a good correlation between inhibition of [^{125}I]NASV-photolabelling and hydrophobicity. Although these isoquinolinesulphonamides inhibited protein kinase A with different magnitudes, this activity did not correlate with the effect on the drug resistance. These results indicate that isoquinolinesulphonamide compounds with a hydrophobic group interact with antitumour drugs on P-glycoprotein and reverse multidrug resistance without involvement of their activity on protein kinase A.

Multidrug resistance is a major problem in cancer chemotherapy. Multidrug-resistant tumour cells overexpress P-glycoprotein in the plasma membrane, which is encoded by the mdr gene and works as a drug efflux pump, and the intracellular concentration of several antitumour drugs does not increase (Bradely et al 1985; Riordan et al 1985; Scotto et al 1986; Shen et al 1986; Gerlach et al 1987; Van der Bliek & Borst 1989; Kuwazuru et al 1990; Kaye & Kerr 1991; Weinstein et al 1991).

There are several drugs which overcome multidrug resistance in-vitro: calcium antagonists and calmodulin inhibitors such as verapamil, dihydropyridines, and trifluoperazine (Tsuruo et al 1981, 1983; Kiue et al 1990), chloroquine derivatives (Zamora & Beck 1986), Rauwolfia alkaloids (Inaba et al 1981; Miyamoto et al 1984), and cyclosporin A (Slater et al 1986). These drugs inhibit drug efflux and *N*-(*p*-azido-(3-[^{125}I]salicyl)-*N'*-*β*-aminoethyl-vindesine ([^{125}I]NASV) photolabelling of P-glycoprotein in multidrug-resistant cells (Cornwell et al 1987; Akiyama et al 1988). We have reported that an isoquinolinesulphonamide compound, *N*-[2-[*N*-[3-(4-chlorophenyl)-1-methyl-2-propenyl]amino]-ethyl]-5-isoquinolinesulphonamide (H-87), having a potent and selective inhibitory activity on protein kinase A, selectively overcame multidrug resistance of mouse leukaemia P388/ADR cells in-vitro: this compound potentiated the cytotoxicity of antitumour drugs such as adriamycin, daunorubicin, vincristine, and vinblastine in P388/ADR and vincristine-resistant P388 cells, which were resistant to these drugs, but hardly influenced the sensitivities of mitomycin C-, 5-fluorouracil-, or cisplatin-resistant P388 cells to respective antitumour drug and of the parental cells to all drugs (Miyamoto et al 1990). In this report, we investigated whether the effects of isoquinolinesulphonamide compounds on resistance to vinblastine in P388/ADR cells are provided by their inhibitory activity on protein kinases or their molecular characteristics.

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Materials and Methods

Materials

[^{3}H]Vinblastine (374 GBq mmol^{-1}) and [γ-^{32}P]ATP (110 TBq mmol^{-1}) were purchased from Amersham International, UK. Vinblastine, verapamil, and reserpine were purchased from Shionogi Co., Osaka, Japan, Sigma Chemical Co., St Louis, MO, USA, and Eisai Co., Tokyo, Japan, respectively. [^{125}I]NASV was synthesized by the methods of Safa et al (1986) and Safa & Felsted (1987). Isoquinolinesulphonamide derivatives, *N*-[2-(methylamino)ethyl]-5-isoquinolinesulphonamide (H-8), *N*-(2-aminoethyl)-5-isoquinolinesulphonamide (H-9), *N*-[2-[*N*-[3-(2-pyridinyl)-1-methyl-2-propenyl]amino]ethyl]-5-isoquinolinesulphonamide (H-31), *N*-[2-[*N*-[3-(2-furanyl)-1-methyl-2-propenyl]amino]ethyl]-5-isoquinolinesulphonamide (H-34), *N*-(2-aminoethyl)-*N*-[2-[3-(4-chlorophenyl)-2-propenyl]amino]ethyl-5-isoquinolinesulphonamide trichloride (W-66), *N*-[2-*N*-formyl-*N*-(4-chlorophenyl)-2-propenyl]amino]ethyl]-5-isoquinolinesulphonamide (H-85), *N*-[2-[*N*-[3-(4-chlorophenyl)-2-propenyl]amino]ethyl]-5-isoquinolinesulphonamide (H-86), and H-87 were synthesized by methods described previously (Hidaka et al 1984).

Enzyme assay

The catalytic subunit of protein kinase A was purified from bovine heart by the method of Beavo et al (1974). Protein kinase C was prepared from rabbit brain as described previously (Inagaki et al 1985). The activities of protein kinases were measured by [^{32}P]phosphate incorporation into a protein substrate as described by Hidaka et al (1984), in the presence of various concentrations of compounds.

Cells and culture

Parent mouse leukaemia P388 cells (P388/S) and adriamycin-resistant P388 cells (P388/ADR) were used in this study. These cells were kindly provided by the Cancer Chemotherapy Center, Japanese Foundation for Cancer Research, Tokyo, Japan. Cells were passaged weekly in the abdominal cavities of female BALB/c × DAB/2 (CDF_1) mice (Nippon SLC, Hamamatsu, Japan). To assess the effects of compounds on P388/S or P388/ADR cells in-vitro, cells were suspended in RPMI-1640 medium supplemented with 10% foetal calf serum, 20 μM β-mercaptoethanol, and 100 μM kanamycin (G-medium), and 1×10^5 cells were seeded in 24-well plastic dishes. The effects of drugs on cell growth were evaluated after consecutive culture for 48 h.

Accumulation and efflux of vinblastine

In the accumulation experiment, cells (1×10^6) were suspended in 1 mL of 20 mM HEPES-buffered G-medium (pH 7·4) and incubated in the presence of 37 kBq [^{3}H]vinblastine for 30 min at 37°C. After the incubation, the cells were chilled on ice and collected by centrifugation at 1000 *g* at 2°C. The cells were washed twice with chilled phosphate-buffered saline (PBS, pH 7·4). Vinblastine accumulated in the cells was measured by the radioactivity after solubilization with NaOH and neutralization with acetic acid. In the efflux experiment, cells were loaded with 20 nM [^{3}H]vinblastine (74 kBq) by incubation in glucose-deprived Hanks solution (pH 7·4) containing 10 mM NaN_3 for 30 min at 37°C. The cells were washed once with chilled PBS and incubated with or without test compound in 20 mM HEPES-buffered G-medium. After the incubation of the cells for designated periods at 30°C, the radioactivity remaining in the cells was measured as described above. The results were expressed as the percentage of retained vinblastine of the forced accumulated vinblastine (initial amount) in the cells.

Photoaffinity labelling with [^{125}I]NASV

The plasma membrane of the cells was prepared by the Percoll sedimentation method (Sanae et al 1988). The plasma membrane (100 μg) was incubated in 100 μL of 40 mM phosphate buffer (pH 7·4), 4% dimethylsulphoxide, and 7·4 kBq [^{125}I]NASV, with or without test compound for 20 min at room temperature (21°C) in the dark. The mixture was irradiated at 365 nm for 15 min on ice, and was centrifuged for 5 min at 13 500 *g*. The resultant pellet was solubilized by the addition of sodium dodecylsulphate (SDS) sample buffer containing 8·0 M urea and was used for SDS-polyacrylamide gel electrophoresis (7·5% gel). After being fixed and dried, gels were autoradiographed on Kodak X-Omat R film with intensifying screens (Dupont Cronex Lightening-Plus) for 24–48 h at −70°C.

Immunoblotting

Fractionated membrane proteins on gels were transferred onto nitrocellulose membrane filters (Schleicher & Schuell, Dassel, Germany). Each filter was then incubated in 3% gelatin in PBS for 2 h at room temperature for blocking, and incubated overnight with 1 μg mL^{-1} C219 monoclonal antibody against P-glycoprotein (Centocor, Inc., Malvern, PA, USA) (Kartner et al 1985). The filter was washed and incubated with horseradish peroxidase-conjugated anti-mouse IgG (Organon Teknika Corp. West Chester, PA, USA) for 1 h. Following extensive washing with PBS containing 0·05% Tween 20, the immunopositive band was made visible in a solution containing 0·5 mg mL^{-1} diaminobenzidine and 0·03% H_2O_2.

Protein was measured by the method of Lowry et al (1951) with bovine serum albumin as the standard.

Octanol-PBS partition coefficient

Each compound was dissolved in PBS or *n*-octyl alcohol at a concentration of 200 μM, and 5 mL of each solution was mixed. The mixture was vigorously shaken for 30 min and equilibrated. Concentrations of each compound in PBS phase and n-octyl alcohol phase were measured by spectrophotometry at 280 nm. The logarithmic apparent partition coefficient (log PC) was estimated as the logarithm of the concentration in the n-octyl alcohol phase over that in the PBS phase.

Statistical analysis

The regression lines in the correlation study were calculated by a nonlinear least-squares method program, MULTI (Yamaoka et al 1981).

Results

Table 1 shows the inhibitory activities of eight isoquinolinesulphonamide compounds on protein kinase A and protein kinase C. H-87 was the most potent and selective inhibitor of protein kinase A, and this activity was decreased by conversion of the chlorophenyl group to pyridinyl (H-31) or furanyl (H-34).

Table 2 shows the cytotoxicity of compounds by themselves on P388/ADR cells and the results of combination effects of a non-cytotoxic concentration of each compound with vinblastine on P388/S and P388/ADR in culture system.

Table 1. Inhibitory activities of isoquinolinesulphonamides against protein kinase A and protein kinase C.

	IC50 (μM)	
Compound	Protein kinase A	Protein kinase C
H-8	2·7	15
H-9	3·1	18
H-31	15	> 100
H-34	7·7	> 100
W-66	1·4	37
H-85	62	> 100
H-86	0·06	18
H-87	0·04	> 100

Data are the mean of two experiments, in triplicate.

Table 2. Cytotoxicities of isoquinolinesulphonamides, verapamil, and reserpine on P388/ADR cells and their in-vitro combination effects with vinblastine in P388/S and P388/ADR cells.

Compound	μM	IC50[a] of vinblastine (nM) for P388/S		P388/ADR		IC50 (μM) for P388/ADR
None	—	6·1	(1·0)[b]	51·3	(8·4)	—
H-8	10	6·1	(1·0)	48·9	(8·0)	> 100
H-9	10	5·8	(1·0)	50·3	(8·2)	—
H-31	3	6·0	(1·0)	17·0	(2·8)	68·0
H-34	3	5·9	(1·0)	15·3	(2·5)	38·6
W-66	3	4·5	(0·7)	7·8	(1·3)	5·3
H-85	3	3·3	(0·5)	9·2	(1·5)	25·8
H-86	3	5·0	(0·8)	5·2	(0·9)	5·2
H-87	3	4·9	(0·8)	3·5	(0·6)	6·1
Verapamil	3	4·9	(0·8)	6·3	(1·0)	36·2
Reserpine	3	5·2	(0·9)	3·2	(0·5)	8·9

[a] The IC50 value indicates the concentration causing 50% inhibition of cell growth. [b]Numbers in parentheses represent the relative resistance to vinblastine calculated by dividing each IC50 value by the IC50 value of vinblastine alone in P388/S cells. Data are the mean of 2–4 experiments, in triplicate.

Table 3. Effects of isoquinolinesulphonamides, verapamil, and reserpine on vinblastine accumulation and [^{125}I]NASV-photolabelling and their apparent partition coefficients.

Compound	C5[a] (μM)	I50[b] (μM)	log PC[c]
H-8	> 30	> 100	−0·67
H-9	> 30	—	−0·73
H-31	25	42	1·00
H-34	13	—	1·23
W-66	5·1	16	1·70
H-85	4·7	11	1·87
H-86	1·9	6·1	2·32
H-87	1·5	5·3	2·35
Verapamil	2·3	6·2	2·14
Reserpine	0·42	3·3	3·18

[a] The C5 value is the concentration of the compound required for a 5-fold increase of vinblastine accumulation in P388/ADR cells obtained from Fig. 1. [b]The I50 value is the concentration of the compound for 50% inhibition of [^{125}I]NASV-photolabelling to M_r 140 kDa P-glycoprotein in the plasma membrane from P388/ADR cells obtained from Fig. 4. [c]PC is the apparent partition coefficient calculated as described in Materials and Methods.

There was no difference between cytotoxicities of the compounds against the sensitive cells and the resistant cells. H-8 and H-9 did not influence the effect of vinblastine on either cell line even at 10 μM. Comparing their combination effects at 3 μM, H-86 and H-87 as well as verapamil and reserpine effectively reversed vinblastine resistance in P388/ADR cells, W-66 and H-85 performed moderately, and H-31 and H-34 were weak, but they affected the vinblastine-sensitivity only a little in P388/S cells.

Fig. 1 shows the effects of isoquinoline compounds on intracellular accumulation and efflux of vinblastine. H-31 and H-34 showed about one-tenth the potency for vinblastine accumulation than did the parent compound H-87 (Table 3). The inhibitory effect of these compounds on vinblastine efflux from the resistant cells was the same order as their potency for the drug accumulation. From these results, it is suggested that the increase in vinblastine accumulation caused by isoquinolinesulphonamides depended on the inhibition of efflux.

As shown in Fig. 2, the relative molecular weight (M_r) 140 kDa membrane protein of P388/ADR cells was labelled with

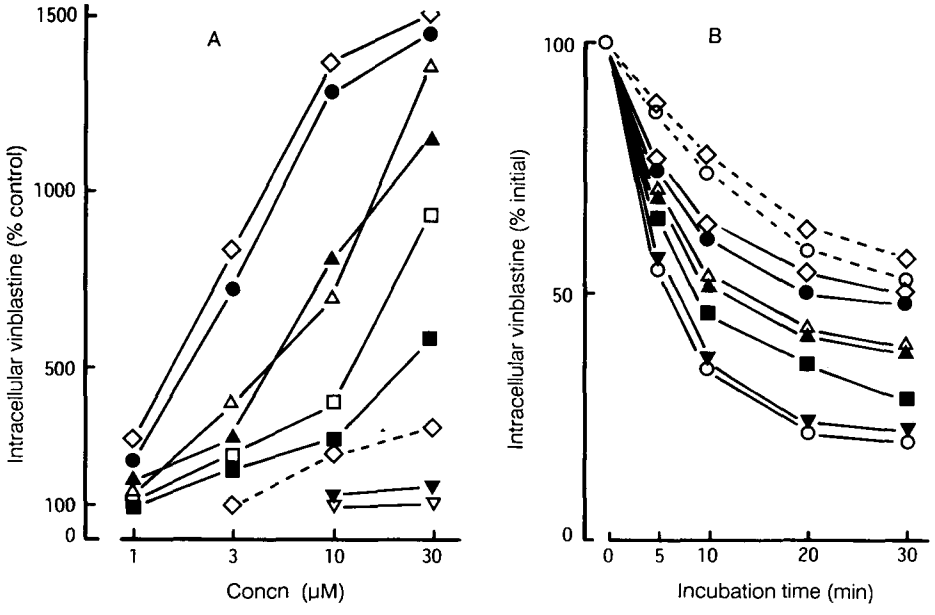

FIG. 1. Effects of isoquinolinesulphonamides on intracellular accumulation (A) and efflux of [^{3}H]vinblastine (B) in P388 cells. When cells were incubated with 20 nM [^{3}H]vinblastine for 30 min, P388/S and P388/ADR cells accumulated 436 and 31 fmol/10^6 cells, respectively, under the normal conditions and increased to 1759 and 1350 fmol/10^6 cells, respectively, under energy-deprived conditions as preload in the efflux study. In the efflux study, concentration of the compounds used was 10 μM, except for H-8, which was 30 μM. P388/S cells, - - - - -; P388/ADR cells, ——. Each point represents the mean of two experiments, in triplicate. ○ Control, ▼ H-8, ▽ H-9, ■ H-31, □ H-34, ▲ W-66, △ H-85, ● H-86, ◇ H-87.

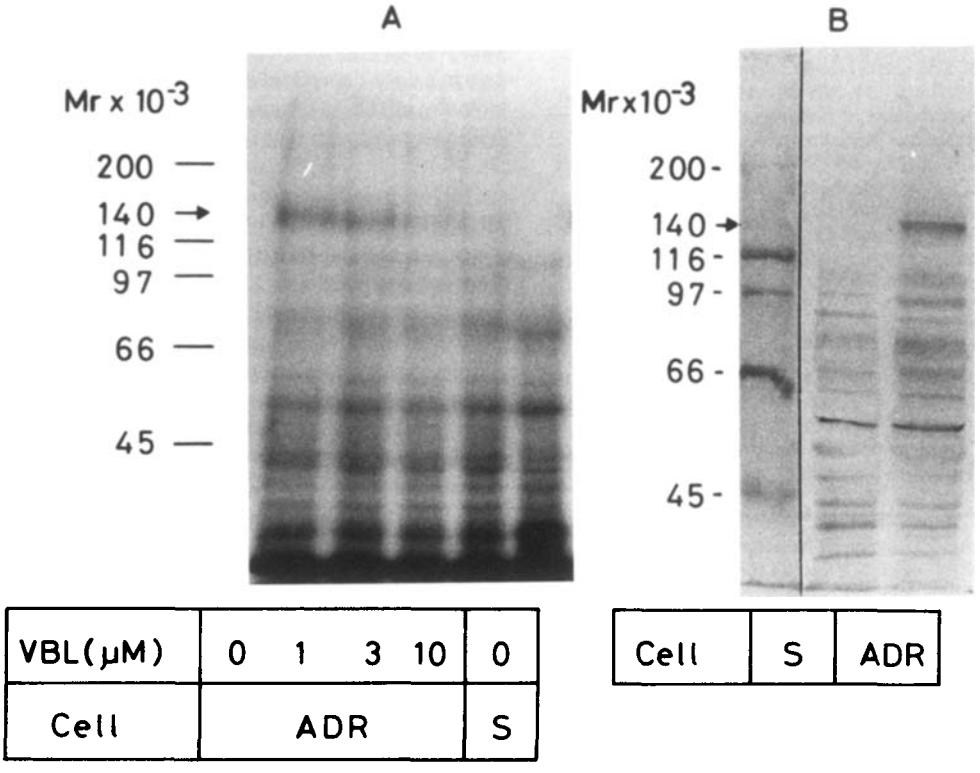

FIG. 2. Photoaffinity labelling with [^{125}I]NASV (A) and immunostaining with C219 antibody (B) of membrane vesicles from P388/S and P388/ADR cells. Positions of mol. wt (M_r) standards are indicated to the left. VBL = vinblastine.

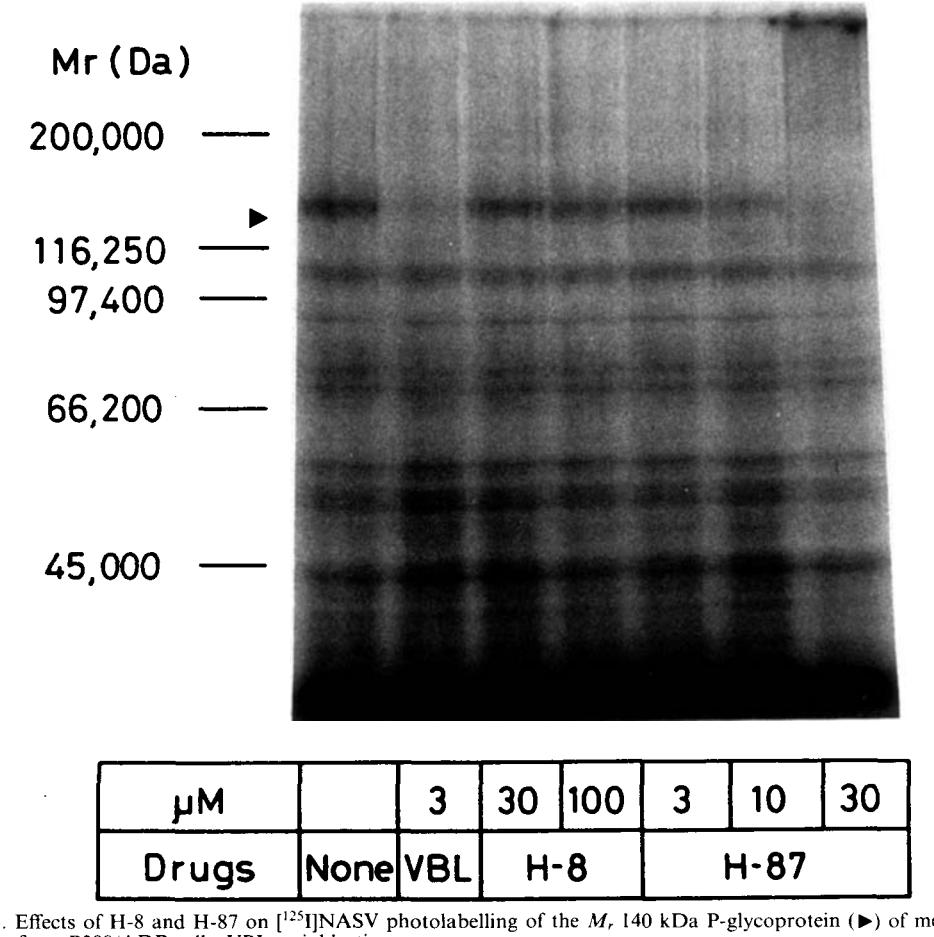

FIG. 3. Effects of H-8 and H-87 on [^{125}I]NASV photolabelling of the M_r 140 kDa P-glycoprotein (▶) of membrane vesicles from P388/ADR cells. VBL = vinblastine.

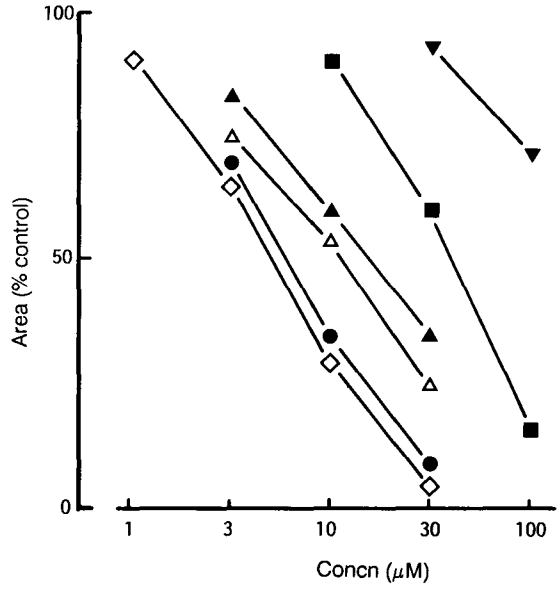

FIG. 4. Dose-dependent inhibition by isoquinolinesulphonamides of [^{125}I]NASV labelling of M_r 140 kDa P-glycoprotein in P388/ADR membrane vesicles. Abscissa, concentration of compounds. Ordinate, percentage of the integral value obtained by the densitometric analysis of the autoradiogram. Each point represents the mean of three experiments. ▼ H-8, ■ H-31, ▲ W-66, △ H-85, ● H-86, ◇ H-87.

[^{125}I]NASV, and the photolabelling was selectively inhibited by vinblastine. The M_r 140 kDa protein was immunopositive to C219 monoclonal antibody against P-glycoprotein. This protein was not detectable in the sensitive cells (P388/S). H-87 selectively inhibited [^{125}I]NASV photolabelling of M_r 140 kDa protein in a dose-dependent manner, but inhibition by H-8 was minimal even at 100 μM (Figs 3, 4). Other compounds also inhibited the photolabelling of P-glycoprotein in a dose-dependent manner (Fig. 4), and the order of the potency of these compounds for inhibition of the photolabelling agreed with that for vinblastine accumulation (Table 3).

Table 3 also shows the apparent partition coefficient (log PC) of isoquinolinesulphonamides, verapamil, and reserpine. As shown in Fig. 5, there were high correlations between the partition coefficient and vinblastine-accumulation and inhibition of photolabelling of isoquinolinesulphonamides ($r = 0.994$ and 0.993; $P < 0.01$, respectively). While verapamil and reserpine have similar or greater potencies on drug resistance than H-86 and H-87, the hydrophobicity was the same or lower for verapamil and much higher for reserpine than those of the isoquinoline compounds.

Discussion

This study investigated the mechanism of isoquinolinesulphonamides for overcoming vinblastine resistance in multidrug resistant P388/ADR cells. There was no correlation between the inhibitory activities on these protein kinases and the effects on drug resistance of these compounds. In particular, H-8 and H-9, which have only an isoquinoline ring as the hydrophobic moiety, hardly interacted with P-glycoprotein and did not reverse the vinblastine resistance. Compounds that reversed drug resistance had a hydrophobic ring at the terminus of the side chain of isoquinolinesulphonamide. These isoquinolinesulphonamide derivatives seem to bind to M_r 140 kDa P-glycoprotein in the plasma membrane from the drug-resistant cells and competitively interfere with the binding of vinblastine as reported for other

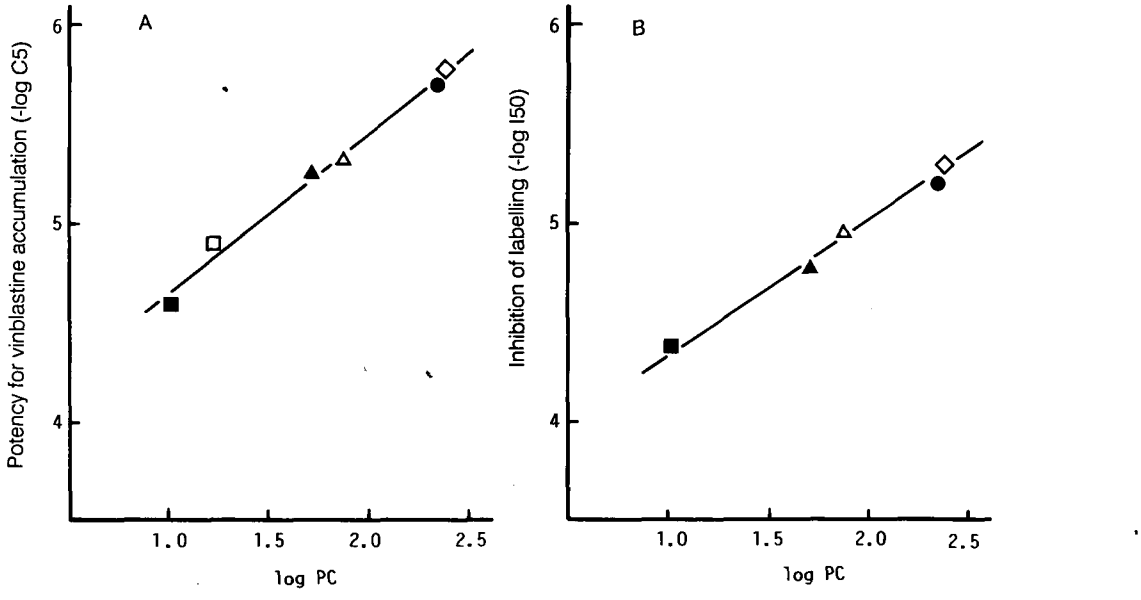

FIG. 5. Correlations of the apparent partition coefficients (log PC) of isoquinolinesulphonamides and their potencies for vinblastine accumulation in P388/ADR cells (−log C5) (A) and for inhibition of [^{125}I]NASV-photolabelling of P-glycoprotein in the plasma membranes from P388/ADR cells (−log I50) (B). ■ H-31, □ H-34, ▲ W-66, △ H-85, ● H-86, ◇ H-87.

drugs overcoming multidrug resistance, such as verapamil and reserpine (Cornwell et al 1987; Akiyama et al 1988). Thus, the suppression of the function of P-glycoprotein as a drug-efflux pump caused drug accumulation in the cells and potentiation of the antitumour effect. These effects were dependent on their hydrophobicity.

Both the isoquinoline ring and terminal ring structures seem to be necessary to interact with the hydrophobic regions of P-glycoprotein. H-87 has three sites that form hydrogen bonds: the nitrogen atom in the isoquinoline ring, the terminal amino group, and the sulphonamide moiety. The secondary amino group in the internal chain of H-87 is expected to be ionized under physiological conditions ($pK_a = 7{\cdot}8$). The introduction of a formyl group, which lowers the basicity, at the terminal amino group (H-85) and the introduction of an aminoethyl group at the nitrogen atom of the sulphonamide group (W-66) reduced the binding activity to P-glycoprotein and the inhibition of drug resistance, indicating that these secondary amino groups also act in the binding to P-glycoprotein. We also compared the effects of isoquinoline compounds with those of verapamil and reserpine. Verapamil has some similarities in biological and physical properties to the active isoquinoline compounds. Reserpine, a polycyclic indole alkaloid, has very high hydrophobicity and showed potent activity on the drug resistance. It seems that at least two hydrophobic ring structures linked by an internal chain with a suitable length containing some amino groups to confer basicity are needed to interact with P-glycoprotein.

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