Three Decades of P-gp Inhibitors: Skimming Through Several Generations and Scaffolds

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Abstract: Many tumor cells become resistant to commonly used cytotoxic drugs due to the overexpression of ATP-binding cassette (ABC) transporters, namely P-glycoprotein (P-gp). The discovery of the reversal of multidrug resistance (MDR) by verapamil occured in 1981, and in 1968 MDR Chinese hamster cell lines were isolated for the first time. Since then, P-gp inhibitors have been intensively studied as potential MDR reversers. Initially, drugs to reverse MDR were not specifically developed for inhibiting P-gp; in fact, they had other pharmacological properties, as well as a relatively low affinity for MDR transporters. An example of this first generation P-gp inhibitors is verapamil. The second generation included more specific with less side-effect inhibitors, such as dexverapamil or dexniguldipine. A third generation of P-gp inhibitors comprised compounds such as tariquidar, with high affinity to P-gp at nanomolar concentrations. These generations of inhibitors of P-gp have been examined in preclinical and clinical studies; however, these trials have largely failed to demonstrate an improvement in therapeutic efficacy. Therefore, new and innovative strategies, such as the fallback to natural products, the design of peptidomimetics and dual activity ligands emerged as a fourth generation of P-gp inhibitors. The chemistry of P-gp inhibitors, as well as their *in vitro, in vivo* and clinical trials are discussed, and the most recent advances concerning P-gp modulators are reviewed.

Keywords: ATP-binding cassette transporters, blood brain barrier, cancer, cancer stem cells, clinical trials, dual ligands, multidrug resistance, natural products, old drugs, P-glycoprotein, P-gp modulation assays, small molecules inhibitors, structure-activity relationships.

1. INTRODUCTION

Drug resistance is the major cause of failure of chemotherapy [1]. In the industrialized countries, cancer is one of the leading causes of death. Although enormous progress has been made in the field of cancer therapy, only approximately 50% of all cancers are susceptible to chemotherapy and of these, more than 50% rapidly develop drug resistance [2].

Multidrug resistance (MDR) may be defined as a phenomenum whereby cancer cells that have been exposed to just one type of drug develop cross resistance to other drugs that are structurally and functionally very dissimilar [3]. MDR is termed 'intrinsic' when the disease is refractory to chemotherapy from the outset, or 'acquired' when the disease becomes insensitive to treatment upon relapse [4].

Several mechanisms may be responsible for the complex phenomenon of MDR such as: induction of the efflux systems (MDR1/P-gp) [5, 6]; altered expression or function of target proteins (e.g. topoisomerase and tubulin) [7]; induction of detoxication pathways (e.g. glutathione-S-transferase that catalyze the conjugation of glutathione and drugs) [8]; enhanced DNA repair [3]; and alterations in the apoptotic signal pathway (e.g. p53 mutation and bcl-2 overexpression) [9, 10]. Some of these mechanisms may coexist, rendering the cell refractory to treatment with drugs acting on a single target.

P-glycoprotein (P-gp) is the best characterized efflux pump that mediates MDR and it belongs to the ATP-binding cassette (ABC) protein superfamily [11]. Other members of the ABC superfamily have also been implicated in cancer MDR, including multidrug resistance-associated protein-1 (MRP1), its homologs MRP2-8 which transport glutathione, glucuronate and sulfate-conjugated drugs, and the breast cancer resistance protein (BCRP) [12]. Multidrug transporters are present in almost every cell and protect the cell from xenobiotics through active excretion [13].

One of the best studied mechanisms of MDR reversal is the direct inhibition of the P-gp efflux pump. The three main mechanisms (Fig. **1A**) of P-gp inhibition are: (i) direct interaction with one or more of the drug-binding sites on P-gp, thus blocking transport by acting as a competitive inhibitor; (ii) inhibition of the binding of ATP to the ATP-binding site on P-gp, blocking ATP binding and hydrolysis, thus acting as a noncompetitive inhibitor [14, 15]; and (iii) interaction with an allosteric residue relevant for P-gp activity and translocation, thus also acting as a noncompetitive inhibitor [16]. An interaction with the lipid membrane of the cell perturbing the membrane environment or modifying the drug-membrane interaction was also described as a possible mechanism of inhibition of P-gp [17].

P-gp uses ATP to get energy to pump a wide variety of compounds out of the cell [18]. It is comprised of 1280 amino acids and it has two homologous halves, each one containing a transmembrane domain (TMD1 and TMD2) which spans the membrane with six α-helices (TM1-6 on TMD1, and TM7-12 on TMD2), and a hydrophilic nucleotide binding domain (NBD1 or NBD2) located at the cytoplasmatic face of the membrane (Fig. **1B**) [19, 20]. P-gp is glycosylated at the first extracellular loop, important for the integration of the protein in the membrane [21], and it is phosphorylated by protein kinase C (PKC), which modulates its transport function [22].

There is still no human P-gp structure of atomic resolution [23]. Even when a sufficient quantity and quality of the protein is available, producing crystals is not straightforward due to the amphiphilic nature of this protein. Thus, crystallization of prokaryotic membrane proteins has been helping in the structure-based drug design of P-gp [24]. Recently, the crystallographic structure of mouse P-gp has been described [25].

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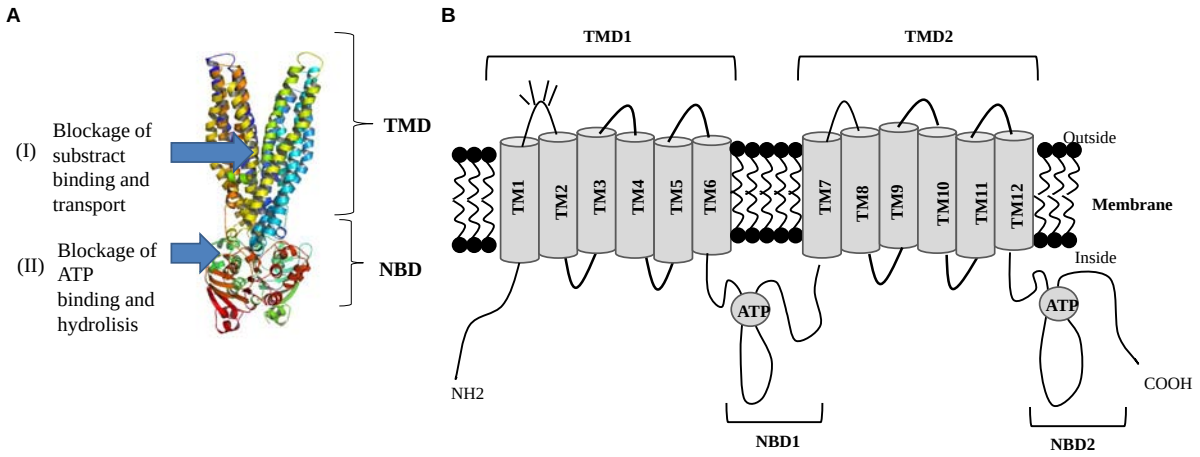


Fig. (1). (**A**) Three-dimensional representation of the open conformation P-gp and the possible binding sites for P-gp inhibitors (I, II). (**B**) Schematic representation of P-gp structure (adapted from [20]). TMD= transmembrane domains; TM= transmembrane α-helice; NBD= nucleotide binding domains; ATP= adenosine triphosphate.

A potential strategy to circumvent drug resistance is to administer a transport inhibitor when chemotherapy is initiated. Since P-gp keeps a drug out of a cell, the compounds interfering with P-gp reverse drug resistance by allowing anticancer drugs to accumulate in cells [26]. A highly effective P-gp modulator candidate should be lipophilic, possess a LogP value of 2.92 or higher (to allow hydrophobic and van der Waals interactions with P-gp residues), with a positively ionizable group such as an amine (in order to enable the establishment of ionic interactions) ,with an 18 atom long or longer molecular axis (to increase the number and strength of the interactions with P-gp), and high E_{homo} values (to favor the interaction between nucleophiles and electrophiles) [27].

The reversal of MDR through direct interaction with P-gp has been most widely investigated and the development of P-gp inhibitors or modulators has been carried out since the demonstration that verapamil could reverse MDR in 1981, indicating the possibility of identifying clinically useful reversing agents for MDR [28]. Thirteen years before, in 1968, MDR chinese hamster cell lines had been isolated for the first time [29]. Since then, a variety of compounds have been shown to reverse P-gp-mediated MDR and some MDR modulators have been undergoing clinical trials. Since the first P-gp inhibitor, verapamil, was discovered approximately thirty years ago, the aim of this review is to summarise the history of P-gp inhibitors, focusing on the three classic generations of compounds and the more recent forth generation. In the first section, a brief introduction of the main methods used in the evaluation of P-gp inhibitory activity is presented. Thereafter, P-gp inhibitors are organized into four generations according to their potency, selectivity and drug-drug interaction potential, and not according to a chronologic development. The first generation (Table **1**) includes not only the classic P-gp inhibitors such as verapamil or cyclosporine A but all compounds that had previously been described as having other main therapeutic applications other than P-gp inhibition, irrespective of the date of discovery. The second generation (Table **2**) comprises derivatives that were developed from compounds with another recognized activity, but which were subjected to structural modifications in order to decrease their "main" therapeutic activity and increase P-gp inhibitory activity. The third generation of compounds (Table **3**) is composed of the most selective and potent P-gp inhibitors to date and which were obtained by design. Many of these derivatives entered clinical trials and the results are highlighted in Table **4**. Finally, the forth generation includes P-gp inhibitors obtained by diverse strategies: compounds extracted from natural origins and their derivatives; surfactants and lipids; peptides and dual activity agents. Each generation also includes the derivatives obtained from qualitative classical SAR as well as QSAR studies which permitted a better understanding of the important substitutents for P-gp inhibitory activity.

2. ASSAYS FOR P-GP MODULATION AND LIGAND-P-GP INTERACTIONS

Several screening assays have been suggested which can help to identify P-gp inhibitors. Interactions of compounds with P-gp are complex and methods of evaluation remain controversial. However, some methods have been used over the years, giving credible results (Table **5**).

A popular method is the cytometry assay, that measures cellular efflux of a fluorescent probe that is a P-gp substrate. This method is based on the increased accumulation and/or decreased efflux of a fluorescent P-gp substrate, such as rhodamine-123 (rh123) [30], doxorubicin [85], daunorubicin [273], or calcein-AM [274], that are transported by the pump. The increased intracellular accumulation of the fluorescent compounds when co-administered with P-gp modulators is considered to be mainly due to inhibition of the efflux pumps located in the cellular membrane, such as P-gp.

Transport assays using adherent cell lines are also common. Generally, using the Caco-2 cell monolayer, these studies measure the permeability in the apical to basolateral and in the basolateral to apical directions [276]. The ratio of these measurements provides clues about P-gp involvement in absorption mechanisms.

Growth inhibition assays that provide values of GI_{50} (the concentrarion that inhibits the growth of the MDR expressing cells by 50 %) are also used frequently to evaluate effective MDR phenotype reversal. GI_{50} is determined from several concentrations of a cytotoxic drug, for example doxorucibin, in the presence or absence of a nontoxic concentration of a P-gp inhibitor, in a resistant P-gp-overexpressing cell line [30].

Certain imaging agents can be used to detect MDR tumors [277] and monitor the effectiveness of novel P-gp inhibitors in human tumor xenograft models and cell cultures [279], and in cancer patients [278]. Analysis of changes in the cellular and tissue distribution of ^{99m}Technetium-sestamibi (^{99m}Tc-sestamibi, trade name cardiolite), a synthetic gamma-emitting organotechnetium complex, a cardiac imaging agent and a P-gp substrate, permit the investigation of the effect of a potential P-gp inhibitor *in vitro* and *in vivo* in human tumor xenograft models [280].

Table 1. First Generation P-gp Inhibitors

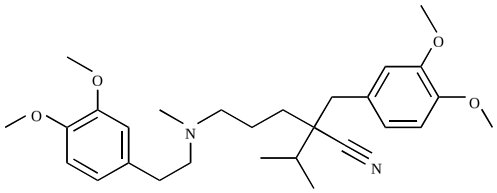
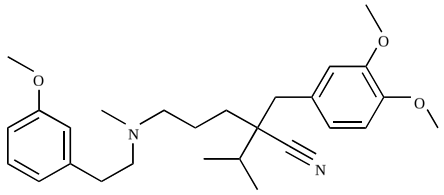
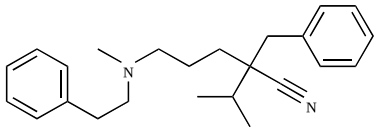
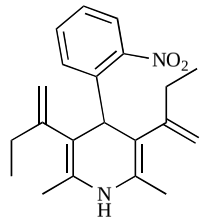
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄ *In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➔Others
					P-gp	MRP	BCRP	
A. Cardiac / circulation drugs								
1[#]	**Verapamil**		Phenylethylamine	Calcium channel blocker	+	+	-	◆Increased rh123 accumulation in K562Dox cell line [30] ✱Increased ATPase activity (Competitive P-gp inhibitor) [30] ✦Increased UIC2 binding (Competitive P-gp inhibitor) [30] ✓5.9-fold decrease in doxorubicin GI_{50} K562Dox cell line [30]
					[31, 32]			
2	**Deverapamil**		Phenylethylamine	Calcium channel blocker	+	nd	nd	◆Increased [^{3}H]vimblastine accumulation in resistant F4-6RADR cell line at μM concentrations [33]
3	**Emopamil**		Phenylethylamine	Calcium channel blocker	+	nd	nd	◆Increased [^{3}H]vimblastine accumulation in resistant F4-6RADR cell line at μM concentrations [33]
4[#]	**Nifedipine**		Dihydropyridine	Calcium channel blocker	+	+	+	✱ Increased ATPase activity (competitive P-gp inhibitor) [34, 35] ✶Photoaffinity labelling inhibited by 50 μM of nifedipine [36]
					[37]			

Table 1. Contd.…..

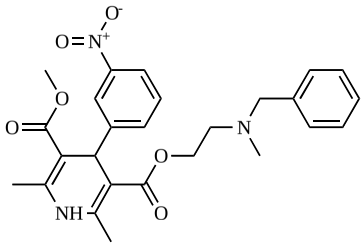
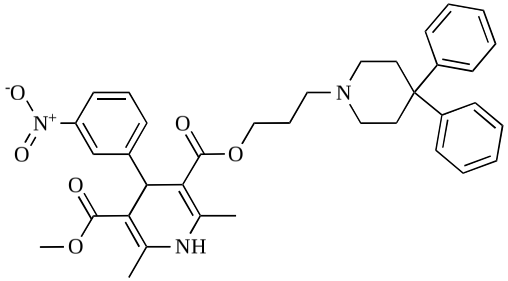
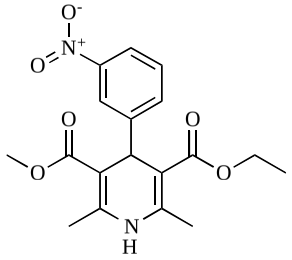
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄ *In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➞Others
					P-gp	MRP	BCRP	
5	Nicardipine		Dihydropyridine	Calcium channel blocker	+	-	+	✱Stimulated ATPase activity by 1.3- to 1.8-fold [38] ✶Photoaffinity labelling inhibited by 50 μM of nicardipine [36]
					[32]			
6	Niguldipine		Dihydropyridine	Calcium channel blockers	+	-	+	◆Increased [^{3}H]vimblastine accumulation in resistant F4-6RADR cell line at μM concentrations [33]
					[39]			
7	Nitrendipine		Dihydropyridine	Calcium channel blockers	+	-	+	◆Increased [^{3}H]vimblastine accumulation in resistant F4-6RADR cell line at μM concentrations [33] ✱ Increased ATPase activity, competitive P-gp inhibitor [35]

Table 1. Contd…..

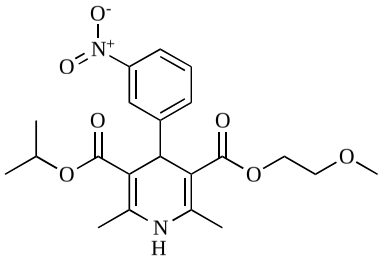
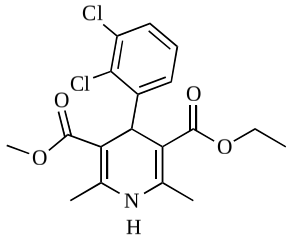
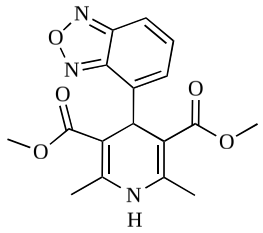
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➞Others
					P-gp	MRP	BCRP	
8	**Nimodipine**		Dihydropyridine	Calcium channel blockers	+	nd	nd	◆Increased [^{3}H]vimblastine accumulation in resistant F4-6RADR cell line at µM concentrations [33] ✱Increased ATPase activity [35] ✶Photoaffinity labelling inhibited by 50 µM of nimodipine [36]
9	**Felodipine**		Dihydropyridine	Calcium channel blockers	+	nd	nd	◆Increased [^{3}H]vimblastine accumulation in resistant F4-6RADR cell line at µM concentrations [33]
10	**Isradipine**		Dihydropyridine	Calcium channel blockers	+	nd	nd	◆Increased [^{3}H]vimblastine accumulation in resistant F4-6RADR cell line at µM concentrations [33]

Table 1. Contd…..

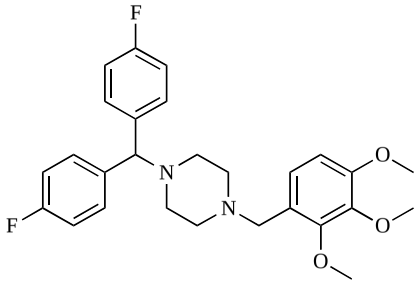
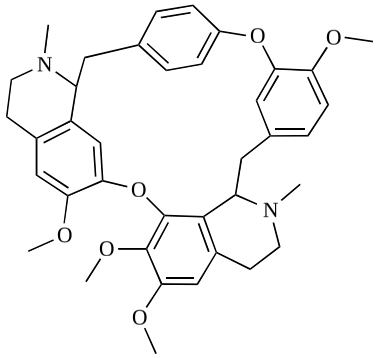
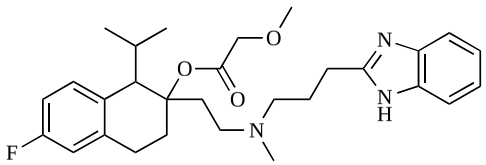
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➞Others
					P-gp	MRP	BCRP	
11	**Lomerizine**		Piperazine	Calcium channel blocker	+	nd	nd	◆Increased cellular accumulation of calcein on K562Dox ✓At 10 μM reduced the IC_{50} of doxorubicin 75-fold on K562Dox cell line [40]
12#	**Tetrandrine**		Benzylisoquinoline	Calcium channel blocker	+	nd	nd	◆Increased rh123 accumulation to the same degree as cyclosporine A (P-gp-expressing MOLT-4/DNR cells) [41] ◆Increased daunorubicin accumulation by 65% in K562Dox cell line [42] ◆Increased intracellular accumulation of [^{3}H]paclitaxel [43] ✓Combination with vincristine in KBv200 cells: tumor growth inhibition increased by 40 % [44] ✓Combination with paclitaxel and docetaxel in KBv200 cells: at 2.5 μM reversed sensitivity by around 10-fold [43] ✓Combination with paclitaxel in xenograft models bearing the intrinsically resistant KBv200 tumors: Potentiate the antitumor activity [43]
13#	**Mibefradil**		Tetrahydronaphthalene	Calcium channel blocker	+	nd	nd	✦Competitive P-gp inhibitor [30] ●Inhibition of P-gp-mediated digoxin transport through Caco-2 monolayer (IC_{50} = 1.6 μM) [45] ➞Inhibition of CYP3A-mediated oxidase activity (IC_{50} = 0.8 μM, Ki = 0.6 μM) [45]

Table 1. Contd…..

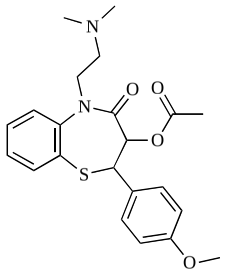
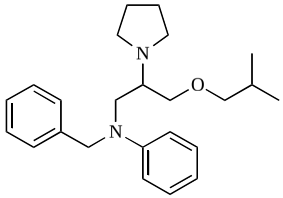
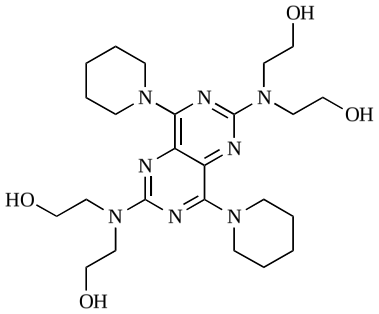
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖ Imaging Assays ➞Others
					P-gp	MRP	BCRP	
14	**Diltiazem**		Benzothiazepine	Calcium channel blocker	+	nd	-	◆Increased rh123 accumulation in K562Dox cell line [30] ✱Competitive P-gp inhibitor [30]
					[32]			
15#	**Bepridil**		Pyrrolidine	Calcium channel blocker	+	nd	-	✓Increased doxorubicin cytotoxicity in several MDR cell lines [46]
					[32]			
16#	**Dipyridamole**		Pyrimidine	Antiplatelet drug	+	+	+	◆Increased intracellular accumulation of [^{3}H]vinblastine multidrug-resistant human hepatoma PLC/PRF/5 cells (PLC/COL), but the effect was immediately diminished by its removal from the medium [47] ✓ Combination with etoposide in the MDR (CHO-Adr(r)) chinese hamster ovary cells: reversal of resistance by 2-3- fold [48] ✓ Combination with doxorubicin in B16VDXR cell line: reversal of resistance by 6.4-fold [49] ✓ Combination with doxorubicin, etoposide and methotrexate on multidrug-resistant B16VDXR cells: potentiated cytotoxicity of anticancer drugs (at 10 μM); 3.7-fold increase in total cellular level and a 4.2-fold increase in the nuclear content of doxorubicin in the resistant cells [50] ✓Combination with several antitumor drugs in MDR human hepatoma PLC/PRF/5 cells: increased cytotoxicity of antitumor drugs [47] ⅄Combination with doxorubicin in C57BL/6 mice: No alteration in the plasma pharmacokinetics of doxorubicin but resulted in a significant increase in its intratumoral accumulation [49]
					[32, 51]			

Table 1. Contd…..

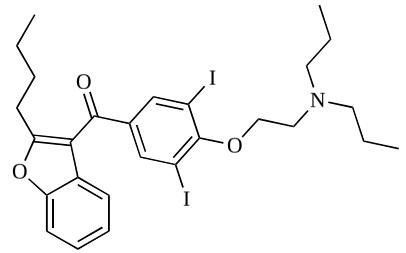
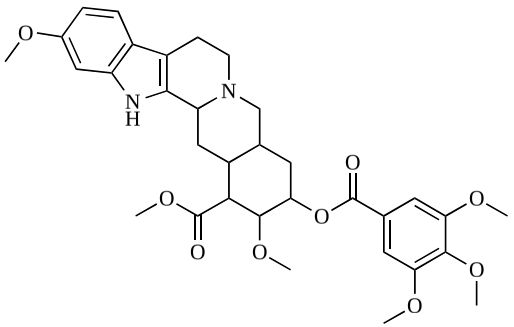
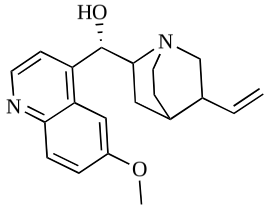
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➔Others
					P-gp	MRP	BCRP	
17	**Amiodarone**		Benzofurane	Beta blocker and potassium channel blocker	+	nd	nd	⅄Amiodarone and *N*-monodesethylamiodarone, the active metabolite of amiodarone, inhibit the P-gp-mediated digoxin transport in the intestine of rats [52]
					[53]			
18	**Reserpine**		Alkaloid	Catecho-lamine depletion	+	+	+	✶Competed with a photoactive analogue of vinblastine in the MDR human leukemia cell line CEM/VLB100 for binding to P-gp [54] ✖Increased accumulation of ^{99m}Technetium (^{99m}Tc) cations in rat brain endothelial cells (RBE4) [55]
					[56, 57]			
19	**Quinidine**		Alkaloid	Blockage of sodium and potassium currents across cellular membranes	+	+	nd	◆Increased accumulation of rh123 [30] ✱Competitive inhibitor ✓ Combination with paclitaxel in P-gp-positive MES-SA/DX5: increased the cytotoxicity of paclitaxel [58]
					[59]			

Table 1. Contd…..

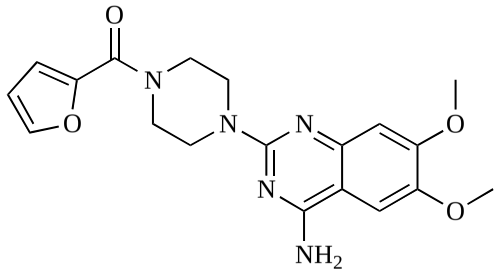
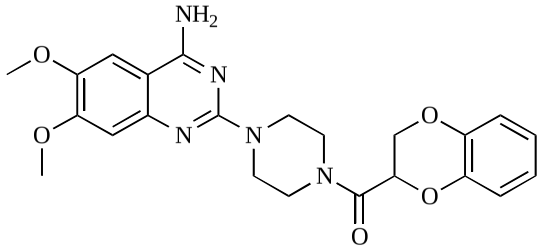
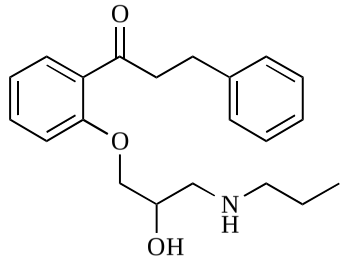
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➞Others
					P-gp	MRP	BCRP	
20	**Prazosin**		Quinazolines	Selective adrenergic α1 antagonist	+	nd	nd	◆Increased rh123 accumulation in K562Dox cell line [30] ✱ Competitive inhibitor [30, 60]
21	**Doxazosin**		Quinazoline	Selective α1 adrenergic antagonist	+	nd	+	✓ Combination with vinblastine or paclitaxel on Hvrl00-6 cells: sensitivity to vinblastine and paclitaxel was increased by 3.4- and 17.5-fold, respectively, by the addition of doxazosin (1 μM) [61]
					[62]			
22	**Propafenone**		Propiophenone	Sodium channel blocker	+	nd	+	◆Increased accumulation of rh123 on K562Dox cell line [30] ✱Competitive inhibitor [30]
					[63]			

Table 1. Contd…..

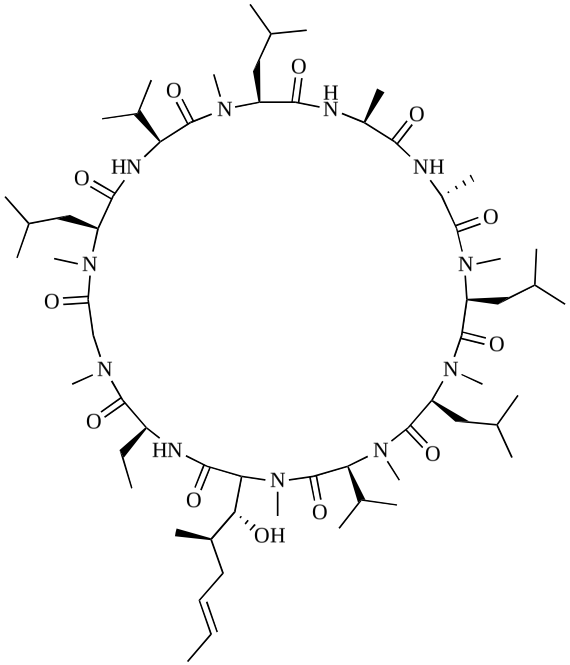
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✽ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➞Others
					P-gp	MRP	BCRP	
B. Immunossupressant Drugs								
23[#]	**Cyclosporine A**		Cyclic undecapeptide		+	+	+	✓Combination with doxorubicin on K562/A02 cells: MDR partially reversed [42] ✓Combination with doxorubicin on hepatocellular carcinoma cell lines: decreased doxorubicin IC_{50} [64] ✶Photoaffinity labelling with [^{3}H]azidopine: P-gp competitive ihibition [65]
					[66, 67]			

Table 1. Contd…..

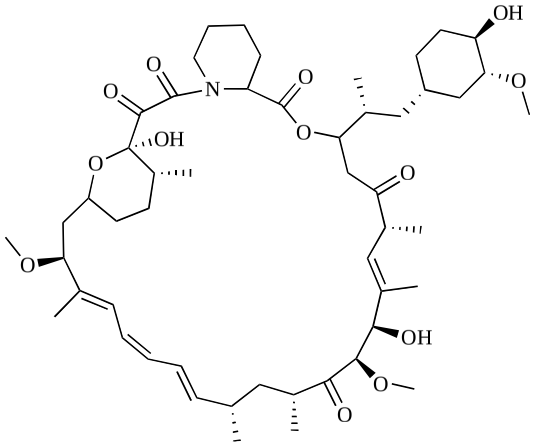
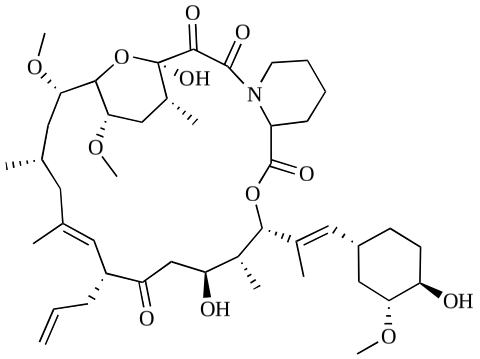
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➞Others
					P-gp	MRP	BCRP	
24[#]	**Tacrolimus**		Macrolide		+	nd	+	◆Increased accumulation of mitroxantrone in P-gp-overexpressing cells (1 μM) [66] ✓Combination with epirubicin in multidrug-resistant P388 leukemia (P388/R) cells overexpressing P-gp: increased epirubicin cytotoxicity by 4.2- and 26.7-fold (1 and 10 μM) [68] ➞Substrate of the cytochrome P450 3A (CYP3A) enzymes [69]
					[67]			
25	**Sirolimus**		Macrolide		+	+	+	◆Inhibion of rh123 efflux from human renal epithelial cells [70] ◆Enhanced cellular and nuclear drug accumulation in cells overexpressing P-gp, MRP-1 and BCRP [67] ➞Disposition is affected by both CYP3A1/2 and P-gp in rats [71]
					[67]			

Table 1. Contd…..

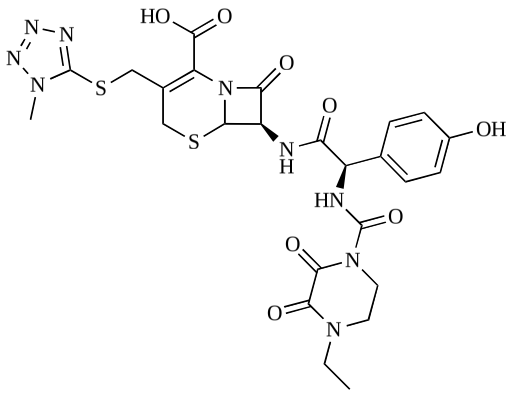
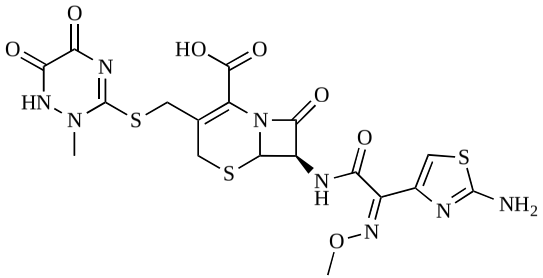
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➔Others
					P-gp	MRP	BCRP	
C. Antibiotics								
26	**Cefoperazone**		Cephalosporin		+	nd	nd	✓Decreased IC_{50} of vimblastine and doxorubicine in MDR variants of the human sarcoma line MES-SA [72]
27	**Ceftriaxone**		Cephalosporin		+	nd	nd	✓Decreased IC_{50} of vimblastine and doxorubicine in MDR variants of the human sarcoma line MES-SA [72]

Table 1. Contd…..

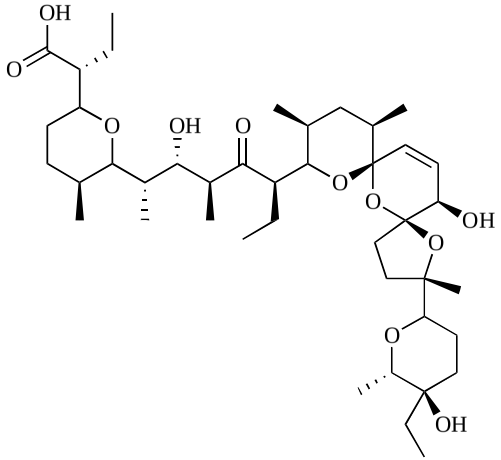
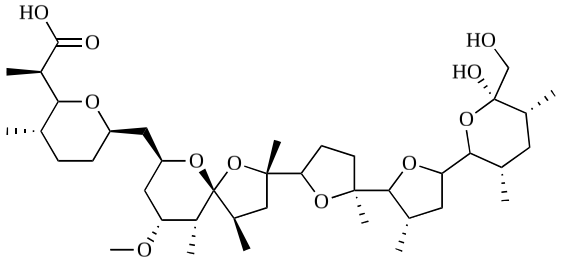
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➔Others
					P-gp	MRP	BCRP	
28	**Salinomycin**		Polyether / tetrahydropyran		+	nd	nd	◆Decreased rh123 efflux in MDR cancer cell lines overexpressing P-gp (CEM-VBL 10, CEM-VBL 100, A2780/ADR) [73] ✓Combination with bortezomib and doxorubicin in the human leukemia stem cell line KG-1a: overcomed MDR [73]
					[74]			
29	**Nigericin**		Polyether / tetrahydropyran / tetrahydrofuran		+	nd	nd	◆Increased rh123 accumulation by 1.9-fold [75]

Table 1. Contd…..

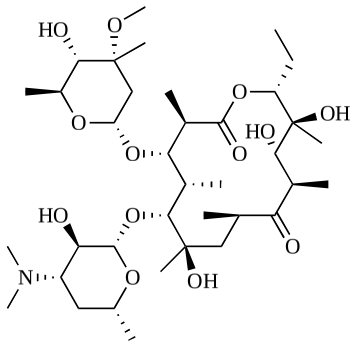
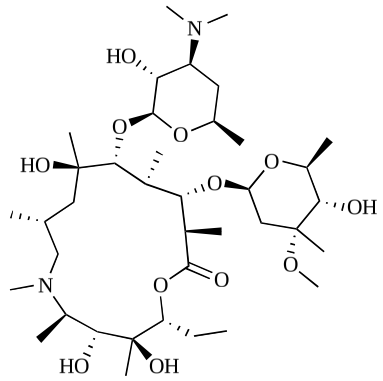
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄ *In Vivo*/*In Vtro* Pharmacokinetic Assays ✖ Imaging Assays ➞Others
					P-gp	MRP	BCRP	
30	**Erythromycin**		Macrolide		+	+	-	◆Inhibited P-gp-mediated transport of ximelagatran and melagatran *in vitro* transport through Caco-2 monolayer [76] ⅄ Decrease the biliary excretion of melagatran [76]
					[77, 78]			
31	**Azithromycin**		Macrolide		+	nd	nd	✓Combination with doxorubicin in K562/ADR cell line: reversed P-gp-dependent anticancer drug resistance ⅄ Modified the hepatobiliary excretion of doxorubicin in rats after treatment with azitromycine [79]
					[80]			

Table 1. Contd…..

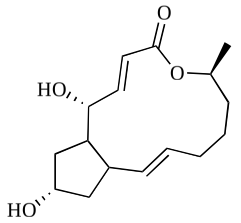
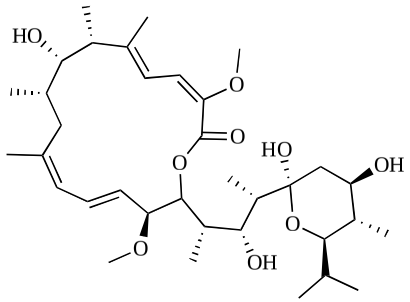
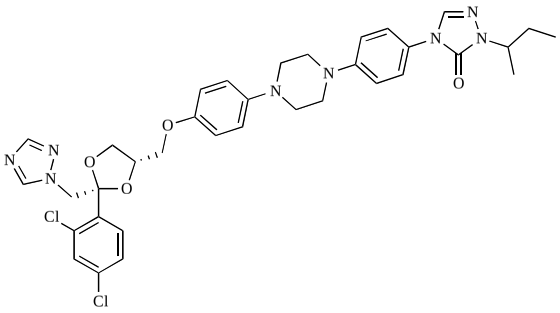
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✽ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄ *In Vivo*/*In Vtro* Pharmacokinetic Assays ✖ Imaging Assays →Others
					P-gp	MRP	BCRP	
32	**Brefeldin A**		Macrocyclic lactone		+	nd	nd	◆Increase cellular accumulation of [^{3}H]zidovudine (P-gp substrate) in the P-gp over-expressing cell line 3T3-F442A [75]
33	**Bafilomycin**		Macrolide		+	nd	nd	◆Increase cellular accumulation of [^{3}H]zidovudine (P-gp substrate) in the P-gp over-expressing cell line 3T3-F442A [75]
D. Antifungal								
34[#]	**Itraconazole**		Triazole		+	nd	+	⅄ The uptake of vincristine or vinblastine into mouse brain capillary endothelial cells was significantly increased by itraconazole [81] →Interactions between itraconazole and other CYP3A4 substrates causing inhibition of CYP-mediated metabolism [82]

Table 1. Contd…..

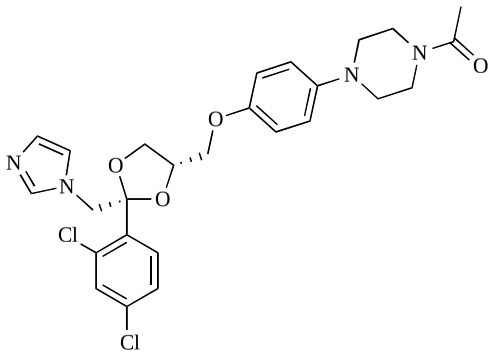
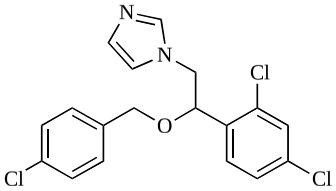
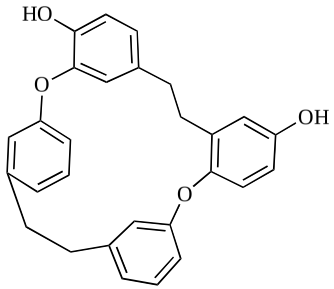
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➔Others
					P-gp	MRP	BCRP	
35	**Ketoconazole**		Imidazole		+	nd	+	● Inhibited transport of substrates through Caco-2 monolayer [83]
					[83, 84]			
36	**Econazole**		Imidazole		+	nd	-	◆Increased rh123 accumulation in K562Dox cell line ✱Noncompetitive P-gp inhibitor ✓Decreased doxorubicin GI_{50} in K562Dox cell line [30]
37	**Dihydroptychantol A**		Macrocyclic bis(bibenzyl)		+	nd	nd	◆Increased adriamycin and rh123 accumulation and decrease of rh123 efflux in the K562/A02 cell line ✓Increased adriamycin cytotoxicity in K562/A02 cells [85]

Table 1. Contd…..

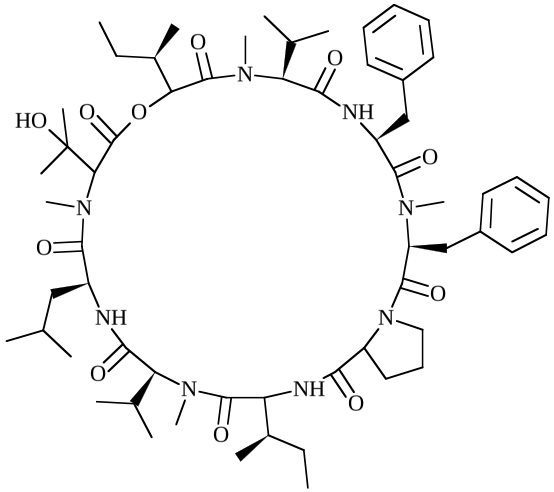
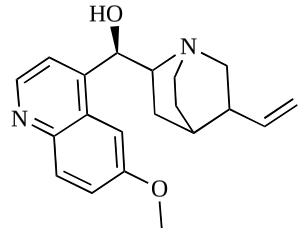
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➞Others
					P-gp	MRP	BCRP	
38	**Aureobasidin A**		Cyclic depsipeptide		+	nd	nd	✶Inhibition of azidopine photoaffinity labelling of P-gp in human cell membranes [86]
E. Antimalarial Drugs								
39#	**Quinine**		Alkaloid		+	+	nd	◆Weak effect on doxorubicin accumulation in a resistant human erythroleukemia cell line [87] ✓Completely restored doxorubicin sensitivity in the resistant human erythroleukemia cell line [88] ➞Confocal microscopy revealed that quinine was able to restore nuclear fluorescence staining of doxorubicin in resistant cells, confirming that quinine acts principally on doxorubicin redistribution within the cells, allowing the drug to reach its nuclear targets [88]
					[59]			

Table 1. Contd.…..

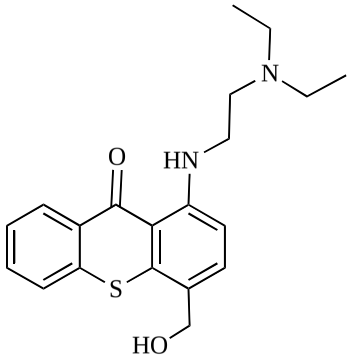
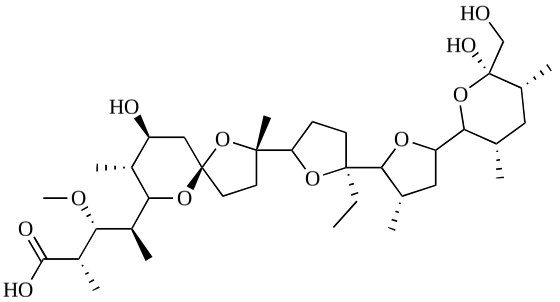
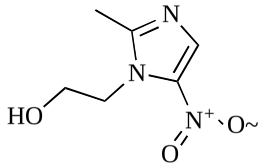
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➞Others
					P-gp	MRP	BCRP	
F. Antiprotozoal drugs								
40	**Hycanthone**		Thioxanthone	Antischistosomal agent	+	nd	nd	✓Partially circumvented resistance of doxorubicin-resistant sarcoma 180 cells [89] ✓Decreased by 1.4-fold doxorubicin GI_{50} in K562Dox [30] ✱Competitive P-gp inhibitor [30]
41	**Monensin**		Tetrahydrofuran /tetrahydropyran	Antiprotozoal agent	+	nd	nd	◆Increased accumulation of zidovudine in 3T3-F442A cells [75]
42	**Metronidazole**		Nitroimidazol	Antiprotozoal agent / antibiotic	+	nd	nd	⅄Increased imatinib accumulation in the liver, kidney and brain of mice, probably due to metronidazole-mediated inhibition of P-glycoprotein and other efflux transporters [90]

Table 1. Contd.…..

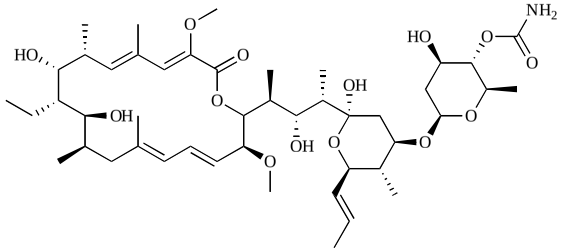
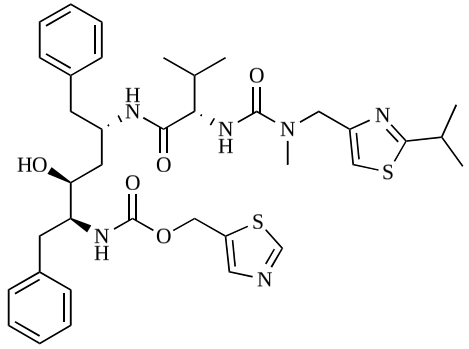
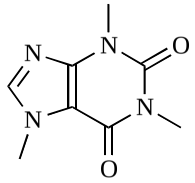
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➞Others
					P-gp	MRP	BCRP	
G. Antiviral Drugs								
43	**Concanamycin A**		Macrolide	Antiviral	+	nd	nd	◆Increased [^{3}H]zidovudine accumulation in 3T3-F442A cells (P-gp overexpressing cell line) [75]
44	**Ritonavir**		Thiazoles	HIV protease inhibitor	+	+	+	◆Inhibited P-gp-mediated extrusion of saquinavir from cultured brain endothelial cells, with an IC_{50} of 0.2 μM, indicating a high affinity of ritonavir for P-gp [91]
					[92, 93]			
H. Central nervous system stimulators								
45	**Caffeine**		Xanthine		+	nd	nd	◆Increased doxorubicin accumulation in Ehrlich ascites carcinoma cells and P388 leukemia cells [94, 95, 96]

Table 1. Contd…..

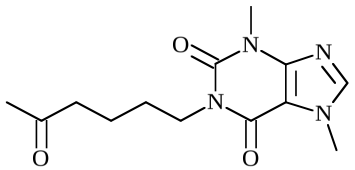
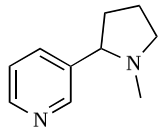
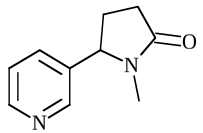
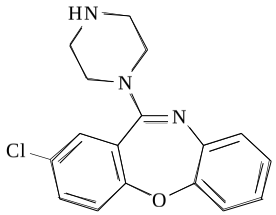
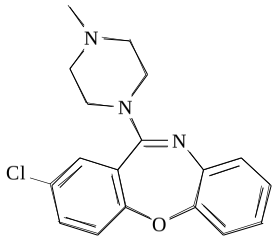
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➞Others
					P-gp	MRP	BCRP	
46	**Pentoxifylline**		Xanthine		+	nd	nd	✓Inhibited P-gp mediated MDR of the mouse leukemic cell line L1210/VCR [97, 98]
47	**Nicotine**		Pyrrolidine / pyridine		+	nd	nd	⅄Increased brain accumulation of saquinavir in rats and may cause drug-drug interaction at the BBB; it may benefit CNS antiretroviral efficacy, but also exposes the brain to potential serious neurotoxicity [99] ✱Competitive inhibitor [100]
48	**Cotinine**		Pyrrolidinone /pyridine		+	nd	nd	⅄Increased brain accumulation of saquinavir in rats and may cause drug-drug interaction at the BBB; it may benefit CNS antiretroviral efficacy, but also exposes the brain to potential serious neurotoxicity [99] ✱Competitive inhibitor [100]
49	**Amoxapine**		Tetracyclic dibenzoxazepine	Anti-depressant	+	nd	nd	◆ Reversed MDR on P388 cell line [101, 102] ✱Noncompetitive inhibitor [30] ✦Noncompetitive inhibitor [30] ✓3.5-fold decrease in doxorubicin GI_{50} in K562Dox cell line [30]
50	**Loxapine**		Tetracyclic dibenzoxazepine	Anti-depressant	+	nd	nd	◆ Reversed MDR in the P388 cell line [101, 102] ✱Noncompetitive inhibitor [30] ✓3.5-fold decrease in doxorubicin GI_{50} in K562Dox cell line [30]

Table 1. Contd…..

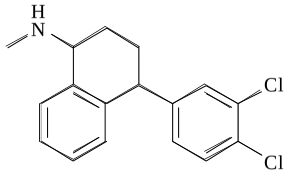
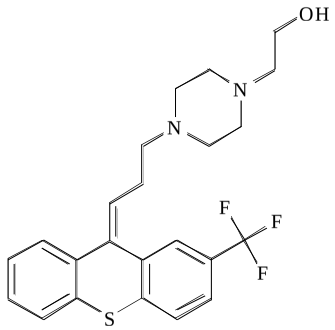
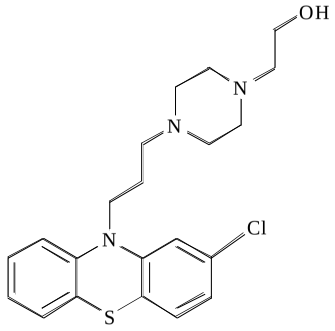
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➞Others
					P-gp	MRP	BCRP	
51	**Sertraline**		Tetrahydronaphthylamine	Anti-depressant	+	nd	nd	✱Increased ATPase activity, comparable with that of verapamil (assayed for sertraline and demethylsertraline) [103]
I. Central Nervous System Depressants								
52	**trans-Flupentixol**		Thioxanthene	Neuroleptic	+	nd	nd	✓Enhanced the cytotoxicity of anticancer drugs in UV-2237 murine fibrosarcoma MDR cells [104] ✶Inhibited [^{3}H]azidopine and [^{125}I]-*N*-(*p*-aminophenethyl)spiroperidol ([^{125}I]NAPS) binding to P-gp [105] ✦Reduce UIC2 reactivity with P-gp by blocking substrate translocation and dissociation (noncompetitive inhibitor) [106]
53	**Perphenazine**		Phenothiazine	Anti-psychotic drug Dopamine antagonist	+	nd	nd	◆Inhibitor of the rh123 efflux from resistant mouse lymphoma and MDR/COLO 320 cells [107]

Table 1. Contd…..

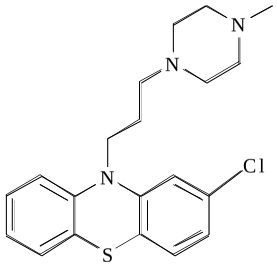
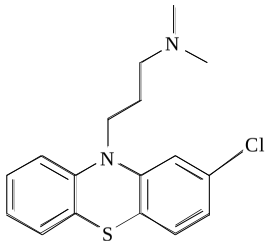
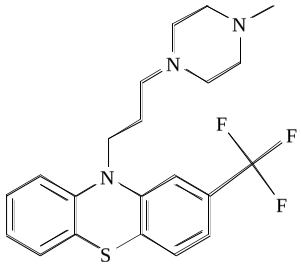
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays →Others
					P-gp	MRP	BCRP	
54	**Prochlorpromazine**		Phenothiazine	Anti-psychotic Dopamine antagonist	+	nd	nd	◆Inhibitor of the rh123 efflux from resistant mouse lymphoma and MDR/COLO 320 cells [107]
55	**Chlorpromazine**		Phenothiazine	Anti-psychotic drug Dopamine antagonist	+	-	+	✱Competitive inhibition, using membrane vesicles prepared from human CCRF-CEM leukaemia cells [108] and in vesicles prepared from vinblastine-resistant human CCRF-CEM leukaemia cells (10 μM) [109] →Chlorpromazine was shown to interact with lipidic layers leading to an increased permeability and changing the influx properties [110]
					[111]			
56	**Trifluoperazine**		Phenothiazine	Anti-psychotic and an antiemetic agent	+	nd	nd	◆Increased accumulation of rh123 in MES-SA/Dx5 cells [112] ✱Stimulated ATPase activity by 1.3- to 1.8-fold (competitive P-gp inhibitor) [38]

Table 1. Contd…..

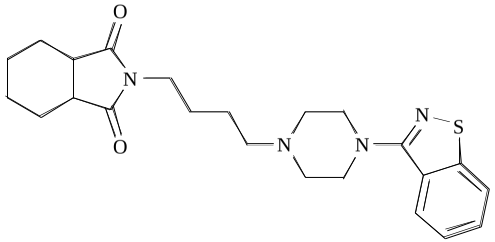
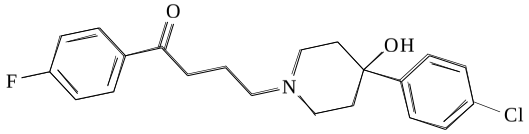
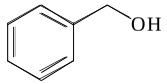
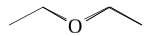
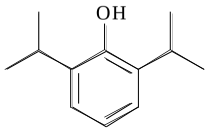
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➞Others
					P-gp	MRP	BCRP	
57	**Perospirone**		Thiazole	Anti-psychotic drug	+	nd	nd	◆Increased accumulation and inhibited P-gp-mediated efflux of rh123 in Caco-2 cells (at concentrations of 0.01-30 μM, which were found to be non-cytotoxic towards the Caco-2 cells) [113]
58	**Haloperidol**		Piperidine	Anti-psychotic drug	+	nd	nd	✓Enhanced the cytotoxic effects of vinblastine concentration-dependently in K562/VBL cells (at nontoxic concentration of haloperidol 1-30 μM) [114] ✶Inhibited binding of [^{3}H]azidopine to P-gp [114]
J. Anesthetics								
59	**Chloroform**	$CHCl_3$			+	nd	nd	• Modulate P-gp mediated MDR by acceleration of transbilayer movement of drugs by passive difusion. At higher concentrations than those required for modulation, the anesthetics accelerated the passive permeation to such an extent that it was not possible to estimate P-gp activity [115]
60	**Benzyl alcohol**				+	nd	nd	• Modulate P-gp mediated MDR by acceleration of transbilayer movement of drugs by passive difusion. At higher concentrations than those required for modulation, the anesthetics accelerated the passive permeation to such an extent that it was not possible to estimate P-gp activity [115]
61	**Diethyl ether**				+	nd	nd	• Modulate P-gp mediated MDR by acceleration of transbilayer movement of drugs by passive difusion. At higher concentrations than those required for modulation, the anesthetics accelerated the passive permeation to such an extent that it was not possible to estimate P-gp activity [115]
62	**Propofol**				+	nd	nd	• Modulate P-gp mediated MDR by acceleration of transbilayer movement of drugs by passive difusion. At higher concentrations than those required for modulation, the anesthetics accelerated the passive permeation to such an extent that it was not possible to estimate P-gp activity [115]

Table 1. Contd…..

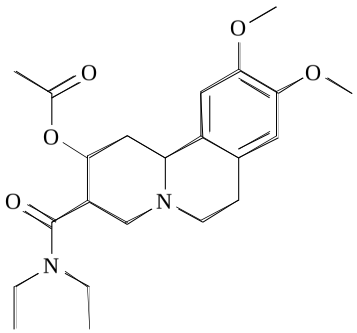
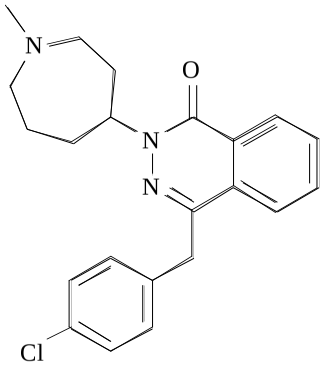
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➔Others
					P-gp	MRP	BCRP	
K. Anti-histaminics								
63	**Benzquinamide**		Quinolizine	Antagonism of muscarinic acetycholine receptors and histamine *H1* receptors	+	nd	nd	◆Increased accumulation of rh123 and [^{3}H]daunorubicin in MDR [116] ✓Increased cytotoxicity of chemotherapeutic agents in human and hamster MDR cell lines *in vitro* [116] ✶Inhibited the binding of [^{125}I]iodoarylazidoprazosin ([^{125}I]IAAP) to the P-gp in MDR cells [116]
64	**Azelastine**		Pyridazine (phthalazine)	Histamine-H1-receptor antagonist	+	nd	nd	✓Reversed MDR in the MDR P388 cell line [101, 102] ✱Competitive inhibitor [30] ✓1.8-Fold decrease in doxorubicin GI_{50} in the K562Dox cell line [30]

Table 1. Contd…..

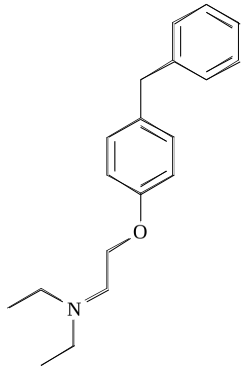
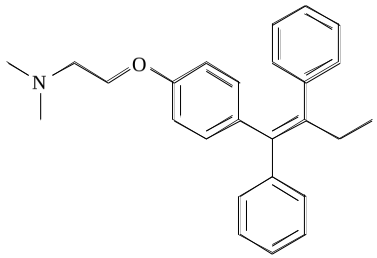
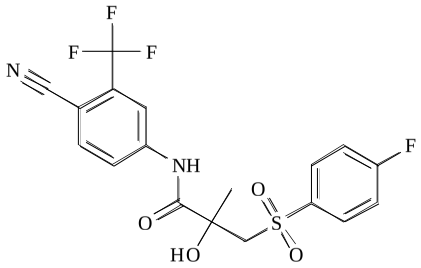
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays →Others
					P-gp	MRP	BCRP	
65[#]	**Tesmilifene**		Phenyl Ether	Histamine-H1-receptor antagonist	+	nd	nd	→Tesmilifene was found to be both a substrate and an inhibitor of P-gp responsible for the MDR cancer cell phenotype [117] →Substrate of the CYP3A subfamily [118]
L. Anticancer Drugs								
66	**Tamoxifen**		Benzylidene (stilbene)	Antagonist of the estrogen receptor in breast tissue	+	-	-	✦Competitive inhibitor [119] ⅄Increased doxorubicin accumulation in the heart and promotion of doxorubicin-induced cardiotoxicity due to the inhibitory effect of tamoxifen on the efflux activity of P-gp in the heart [120] ✓Growth inhibition and apoptosis induced by adriomicin, mitomycin, or vindesine were enhanced after pre-treatment with 5 or 10 μM tamoxifen in a cholangiocarcinoma cell line (QBC939/ADM) [119] →Inhibit CYP3A-mediated metabolism
					[121, 122]			
67	**Bicalutamide**		Tosyl compound	Non-steroidal antiandrogen approved for treatment of advanced prostate cancer	+	nd	nd	✱Noncompetitive inhibitor [30] ✓3.0-fold decrease in doxorubicin GI_{50} in the K562Dox cell line [30]

Table 1. Contd.…..

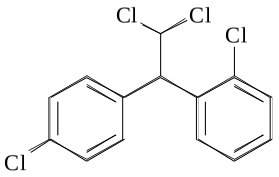
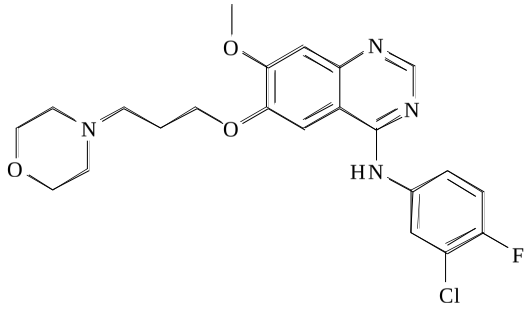
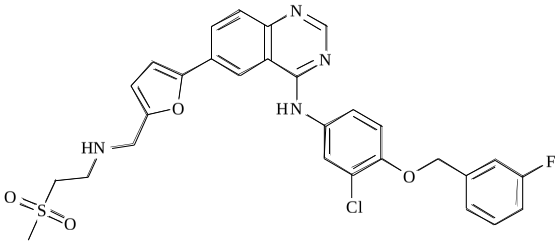
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➞Others
					P-gp	MRP	BCRP	
68[#]	**Mitotane**		Chlorophenyl compound	Anti-neoplasic used in the treatment of adreno-cortical carcinoma	+	nd	nd	✓P-gp-MDR revertion in adrenocortical cancer [123]
69	**Gefitinib**		4-Amino-quinazoline	Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI)	+	-	+	⅄Increased rat brain parenchymal extracellular fluid (ECF) accumulation of topotecan, a substrate of P-gp and breast cancer resistance protein [124] ✓Decreased IC_{50} values of paclitaxel, topotecan, doxorubicin, or etoposide in resistant MCF-7 or CL1 cells at μM concentrations [125]
					[124, 126, 127]			
70	**Lapatinib**		4-Amino-quinazoline	Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI)	+	+	+	●Decreased the Pgp-mediated transport of [^{3}H]digoxin across MDCKII-MDR1 monolayers up to 74%, yielding an IC_{50} value of 3.9 μM [128]
					[129]			

Table 1. Contd.…..

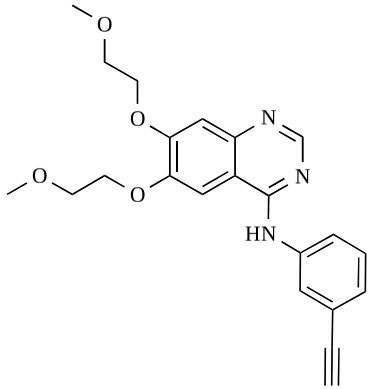
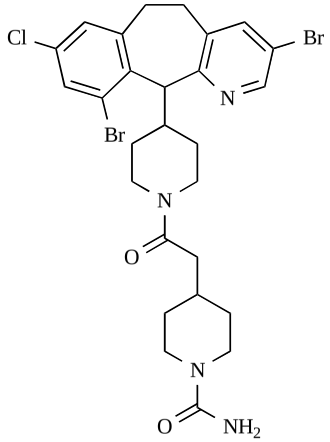
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➔Others
					P-gp	MRP	BCRP	
71	**Erlotinib**		4-Amino-quinazoline	Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI)	+	+	+	◆Erlotinib at 10 µM increased the intracellular accumulation of [^{3}H]paclitaxel in KB-C2 cells to levels 3.5-fold higher; effect comparable to that of 10 µM verapamil [130] ✓Erlotinib at 2.5 µM slightly decreased the IC_{50} values of colchicine, vinblastine, and paclitaxel in KB-C2 cells and partially reversed their resistance [130]
					[131]			
72	**SCH 66336 or lonafarnib**		Piperidine	Farnesyl-transferase inhibitor in trials	+	+	nd	◆Inhibited daunorubicin and rh123 effux from P-gp overexpressing cells with an IC_{50} of about 3 µM ✱Noncompetitive inhibitor [132]
					[133]			

Table 1. Contd…..

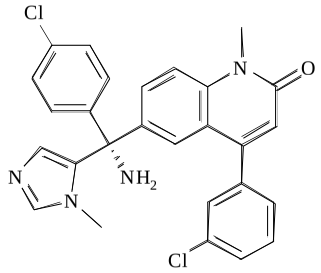
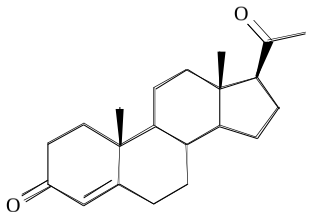
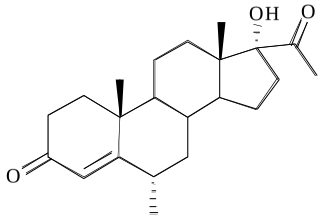
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➔Others
					P-gp	MRP	BCRP	
73	**Tipifarnib**		Quinolinone	Farnesyl-transferase inhibitor in trials	+	nd	nd	◆Inhibited daunorubucin efflux from CCRF-CEM with an IC_{50} value lower than 0.5 μM. ✓Combination with daunorubicin in CCRF-CEM: synergistic inhibition of cellular proliferation, and induction of apoptosis [134]
M. Steroid Hormones								
74	**Progesterone**		Steroid	Endogenous steroid hormone	+	+	nd	◆Increased rh123 accumulation in a sub-bronchial epithelial cell line, Calu-3 [135] ◆Increased the accumulation of vinblastine to 2100% in K562/R7 cells [136] ◆Increased daunorubicin accumulation by 25% [137] ✱Competitive inhibitor [138] ✶Progesterone reduced the photoaffinity labelling of P-gp with a photoactive analogue of vindesine in an adrenal cell line [139]
					[135, 139, 140]			
75	**Medroxiprogesterone**		Steroid	Synthetic progesta-tional hormone used in veterinary practice as an oestrus regulator	+	+	nd	◆Increased accumulation of vinblastine by 641% in human colon carcinoma SW620 Ad300 cells [136]
					[140]			

Table 1. Contd.…..

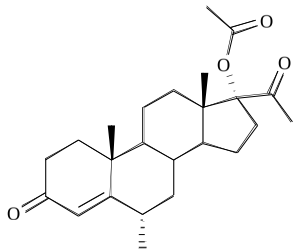
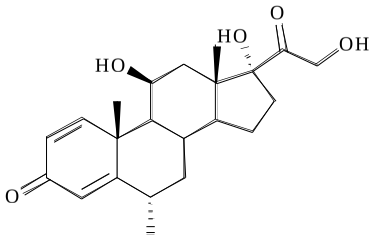
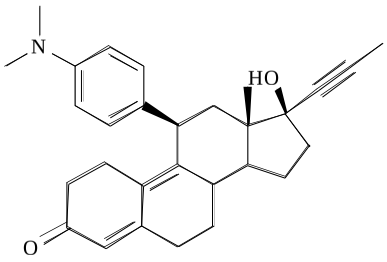
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄ *In Vivo*/*In Vtro* Pharmacokinetic Assays ✖ Imaging Assays ➔Others
					P-gp	MRP	BCRP	
76	**Medroxiprogesterone 17-acetate**		Steroid	Long-acting contraceptive Used in the treatment of breast and endometrial neoplasms	+	+	nd	◆Increased accumulation of vinblastine to 2127% in human colon carcinoma SW620 Ad300 cells [136]
					[140]			
77	**Methylprednisolone**		Steroid	Anti-inflammatory effects	+	+	nd	◆Inhibited cellular accumulation of erythromycin in rabbit primary corneal epithelial cells (rPCECs) in a dose dependent manner [140]
					[140]			
78	**Mifepristone**		Steroid	Progesterone receptor antagonist used as an abortifacient; emergency contraceptive	+	+	nd	◆Inhibited P-gp-mediated rh123 efflux in MDR1-transfected cells [141] ✶Prevented drug site photoaffinity labelling by [^{3}H]azidopine [141]
					[141, 142]			

Table 1. Contd…..

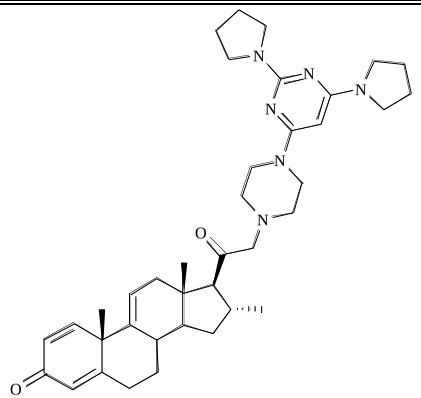
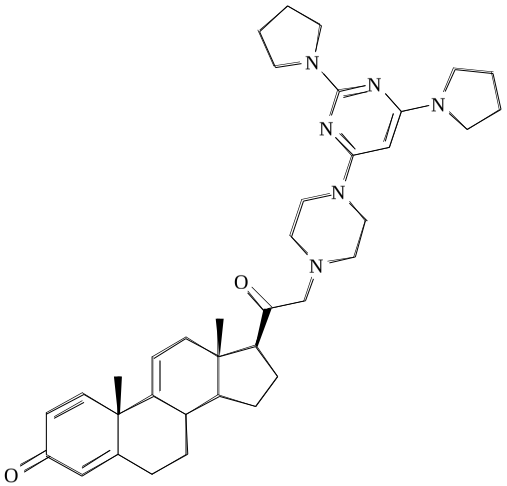
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✽ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➔Others
					P-gp	MRP	BCRP	
79	**Tirilazad**		Steroid	Potent inhibitor of lipid peroxidation Used in acute ischaemic stroke [143]	+	nd	nd	◆Increased accumulation of [^{3}H]vinblastine [144] ✶Inhibited the photoaffinity labelling of P-gp with [^{3}H]azidopine in multidrug resistant KB-V1 cells more effectively than verapamil [144] ✓Decreased vinblastine IC_{50} by 66-fold in resistant KB-V1 human cells [144]
80	**U-74389F**		Steroid	Inhibitor of lipid peroxidation in trials [145]	+	nd	nd	◆Increased accumulation of [^{3}H]vinblastine in multidrug resistant KB-V1 cells [144] ✶Inhibited the photoaffinity labelling of P-gp with [^{3}H]azidopine more effectively than verapamil [144] ✓Decreased vinblastine IC_{50} by 66-fold in resistant KB-V1 human cells [144]

Table 1. Contd…..

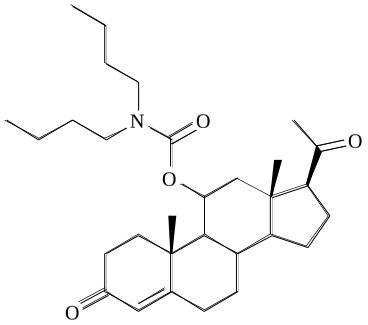
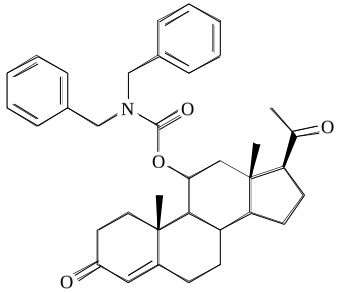
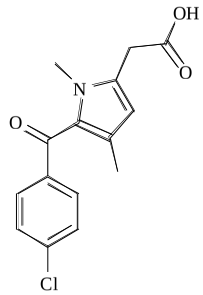
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➞Others
					P-gp	MRP	BCRP	
81	**SB4723**		Steroid carbamate	Progesterone receptor antagonist in trials	+	nd	nd	✓Increased cytotoxicity of doxorubicin (15-fold) and of paclitaxel (40-fold) in the colon cancer line HCT-15 [146] ◆Increased intracellular accumulation of 60% for doxorubicin and 300% for paclitaxel, reducing drug efflux from the cell [146]
					[146]			
82	**SB4769**		Steroid carbamate	Progesterone receptor antagonist in trials	+	nd	nd	✓Increased cytotoxicity of doxorubicin (15-fold) and paclitaxel (40-fold) in colon cancer line HCT-15 [146] ◆Increased intracellular accumulation of 60% for doxorubicin and 300% for paclitaxel, reducing drug efflux from the cell [146]
					[146]			
N. Anti-inflamatory Drugs								
83	**Zomepirac**		Pyrrole	Cyclo-oxigenase-1 (COX-1) selective inhibitor	+	nd	nd	◆Increased rh123 accumulation in the K562Dox cell line [30] ✱Noncompetitive P-gp inhibitor [30]

Table 1. Contd…..

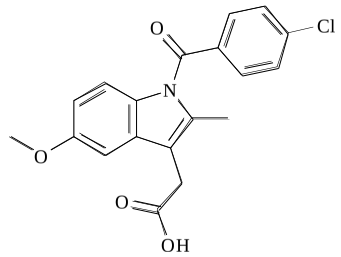
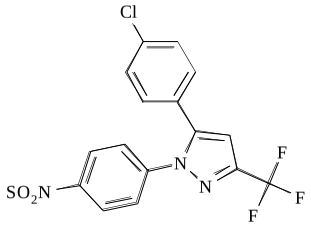
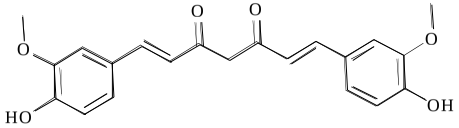
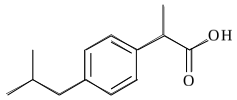
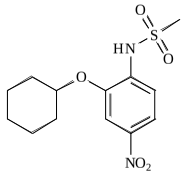
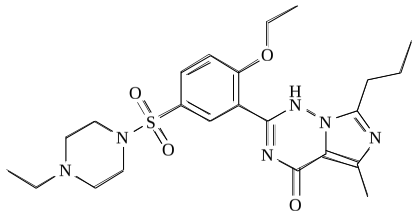
		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays →Others
					P-gp	MRP	BCRP	
84	**Indomethacin**		Indole	Cyclo-oxigenase (COX) inhibitor	+	+	+	◆Increased the intracellular retention of doxorubicin in resistant human esophageal squamous cell carcinoma cell lines, HKESC-1 and HKESC-2 [147] ✱Noncompetitive inhibitor [147] ✓Enhanced cytotoxic effects of doxorubicin in HKESC-1 and HKESC-2 cells [147]
					[148, 149]			
85	**SC236**		Sulfonamide	Cyclo-oxigenase-2 (COX-2) selective inhibitor	+	nd	nd	◆Increased the intracellular retention of doxorubicin in resistant human esophageal squamous cell carcinoma cell lines, HKESC-1 and HKESC-2 [147] ✱Noncompetitive inhibitor [147] ✓Enhanced cytotoxic effects of doxorubicin in HKESC-1 and HKESC-2 cells [147]
86	**Curcumin**		Polyphenol	COX-2 selective inhibitor	+	+	nd	◆ Significantly enhanced doxorubicin retention in resistant uterine sarcoma cells (MES-SA/Dx-5) [150] ◆Increased accumulation of rh123, calcein-AM, and bodipy-FL-vinblastine in multidrug resistant human cervical carcinoma cell line (KB-V1) [151] ✓Enhanced cytotoxicity and apoptosis of doxorubicin in MES-SA/Dx-5 when compared with doxorubicin alone [150]
					[152]			
87	**Ibuprofen**		Propanoic acid	COX inhibitor	+	nd	nd	◆ Significantly enhanced doxorubicin retention in resistant uterine sarcoma cells (MES-SA/Dx-5) [150] ✓Enhanced cytotoxicity and apoptosis of doxorubicin in MES-SA/Dx-5 when compared with doxorubicin alone [150]
88	**NS-398**		Sulfonamide	COX-2 selective inhibitor	+	nd	nd	◆ Significantly enhanced doxorubicin retention in resistant uterine sarcoma cells (MES-SA/Dx-5) [150] ✓Enhanced cytotoxicity and apoptosis of doxorubicin in MES-SA/Dx-5 when compared with doxorubicin alone [150]

Table 1. Contd.…..

		Structure	Scaffold	Therapeutic Class and/or Clinical Use	Inhibitor of			Representative P-gp assays
					P-gp	MRP	BCRP	◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄ *In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays →Others
O. Erectile Disfunction								
89	**Vardenafil**		Imidazol / piperazine	Phospho-diesterase type 5 (PDE5) inhibitor	+	-	-	◆Increases the intracellular accumulation of [^{3}H]-paclitaxel in the ABCB1 overexpressing KB-C2 cells ✱Stimulates the ATPase activity [153] ✶Inhibites the photolabelling of P-gp with [^{125}I]-IAAP [153] ✓Vardenafil when used in combination with anticancer substrates of P-gp, significantly increases their cytotoxicity in P-gp overexpressing cells in a concentration-dependent manner [153] →Incubation of cells with vardenafil for 72 h does not alter P-gp expression [153]
					[153]			

(-) means no inhibition; (+) means inhibition; (nd) means no published data. UIC2= mouse monoclonal antibody directed against an extracellular conformational epitope of P-gp.
* Clinical trials of these compounds listed in Table **4**

Table 2. Second Generation P-gp Inhibitors

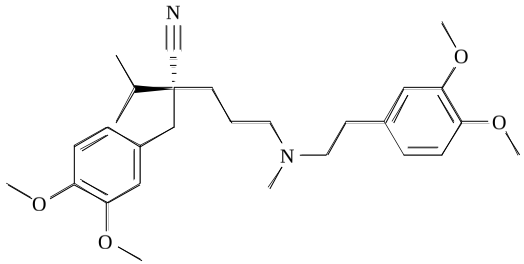
	Name	Structure	Derivative of / Stereo-isomer of	Scaffold	Inhibitor of			Representative P-gp Assays
					P-gp	MRP	BCRP	◆Accumulation/Efflux ✱ATPase assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄ *In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays →Others
90[#]	**Dexverapamil**		Verapamil	Phenilalkylamine	+	-	nd	◆Increased [^{3}H]vimblastine accumulation in theF4-6RADR cell line at μM concentrations [33] ✓Combination of dexverapamil or its metabolite, nor-dexverapamil, with DINIB, a cytotoxic natural product and P-glycoprotein substrate in the colon cancer cell line, HCT-15, and renal cell line, UO-31: reversed P-gp-mediated resistance in both cell lines, increasing DINIB cytotoxicity [154]
					[31]			

Table 2. Contd…..

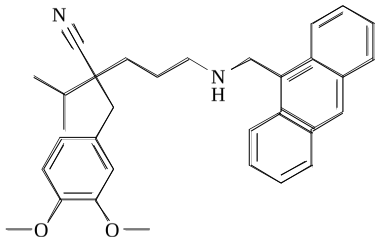
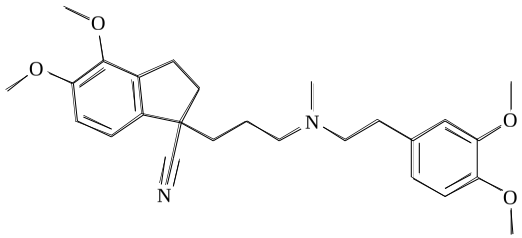
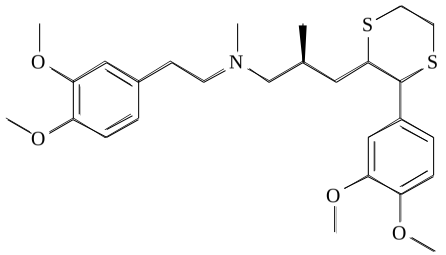
	Name	Structure	Derivative of / Stereo-isomer of	Scaffold	Inhibitor of			Representative P-gp Assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄ *In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays →Others
					P-gp	MRP	BCRP	
91	**MM36**		Verapamil	Phenilalkylamine	+	nd	nd	◆Inhibition of rh123 efflux in K562Dox and in mononuclear cells MNCs [155] ✓Reverse resistance in K562Adr cell line at nanomolar concentrations, with low cardiovascular activity [156]
92	**KR-30031**				+	nd	nd	◆Augmented paclitaxel-induced cytotoxicity in the HCT15 cell line to over 60 fold greater than verapamil [157]
93	**RO44-5912**				+	nd	nd	◆Treatment of resistant murine leukemic P388 cells (P388Dox) with doxorubicin and 3 μM verapamil decreased the IC_{50} value to 2.5 μM, whereas treatment with the same concentration of RO44-5912 decreased the IC_{50} value to 1.1 μM. No effects were seen with the parental P388 cells [158]

Table 2. Contd…..

	Name	Structure	Derivative of / Stereo-isomer of	Scaffold	Inhibitor of			Representative P-gp Assays
					P-gp	MRP	BCRP	
94[#]	**Dexniguldipine**		Niguldipine	Dihydropyridine	+	nd	nd	◆Reversed vinblastin resistance in F4-6RADR cells [33]. ◆Increased [^{3}H]vimblastine accumulation in the F4-6RADR cell line at μM concentrations [33] ✓Decreased adriamycin GI_{50} in adriamycin resistant erythroleukemia F4-6RADR cells [159]
95	**PAK-104P**		Niguldipine	Pyridine	+	nd	nd	◆Increased the accumulation of vinblastine in KB-C2 cells by about 10-fold whereas verapamil at the same concentration increased the accumulation by about 2-fold [160] ✓Combination with vinblastine in KB-8-5 and KB-C2: reversed drug resistance (at 1 and 5 μM) [160]

◆ **Accumulation/efflux**
✱ **ATPase assay**
✦ **UIC2**
✶ **Photoaffinity Labelling**
● **Cell Monolayer Transport**
✓ **Combination Assays**
⅄ ***In Vivo/In Vtro* Pharmacokinetic Assays**
✖ **Imaging Assays**
→ **Others**

Table 2. Contd…..

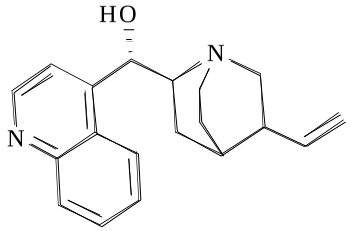
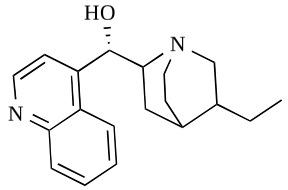
	Name	Structure	Derivative of / Stereo-isomer of	Scaffold	Inhibitor of			Representative P-gp Assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell monolayer Transport ✓Combination Assays ⅄ *In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➞Others
					P-gp	MRP	BCRP	
96[#]	**Cinchonine**		Quinidine / Quinine	Alkaloid	+	nd	nd	◆Enhanced the accumulation of rh123 in the resistant MES-SA/DX5 cell line [161] ✓Increased the cytotoxicity of paclitaxel in P-gp-positive MES-SA/DX5 [161] ✓Combination with tamoxifen in MES-SA/DX5: cleaved poly(ADP-ribose) polymerase (PARP), activated caspase-3, and downregulated P-gp expression as well as increased the sub-G1 apoptotic portion [161]. ⅄ Cinchonine did not significantly modify the pharmacokinetics of doxorubicin after intravenous administration in rats, but induced a significant increase of doxorubicin uptake in organs which express P-gp, such as liver, kidney and lung [162] ➞Co-administration with vincristine, adriamycin or dexamethasone in rats: did not significantly increase the toxicity of the cytotoxic drugs [162]
97	**Hydro-cinchonine**				+	nd	nd	◆Enhanced the accumulation of rh123 in MES-SA/DX5 [161]. ✓Increased the cytotoxicity of paclitaxel in P-gp-positive MES-SA/DX5 [161]. ✓Combination with tamoxifen in MES-SA/DX5: cleaved poly(ADP-ribose) polymerase (PARP), activated caspase-3, and downregulated P-gp expression as well as increased sub-G1 apoptotic portion [161]

Table 2. Contd…..

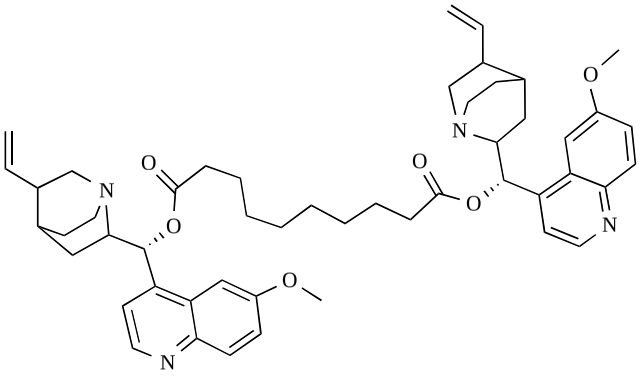
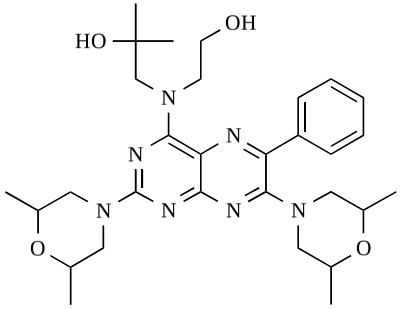
	Name	Structure	Derivative of / Stereo-isomer of	Scaffold	Inhibitor of			Representative P-gp Assays ◆**Accumulation/Efflux** ✱**ATPase Assay** ✦**UIC2** ✶**Photoaffinity Labelling** ●**Cell monolayer Transport** ✓**Combination Assays** ⅄ ***In Vivo/In Vtro* Pharmacokinetic Assays** ✖**Imaging Assays** ➔**Others**
					P-gp	MRP	BCRP	
98	**Quinine homodimer Q2**		Quinidine / Quinine	Alkaloid	+	nd	nd	◆Inhibited the efflux of several P-gp fluorescent substrates (rh123, doxorubicin, mitoxantrone, and BODIPY-FL-prazosin) from MCF-7/DX1 cell ✱Inhibitor of verapamil-stimulated ATPase activity ✓3000-fold decrease in paclitaxel IC_{50} in MDR cell lines: completely abolished the MDR phenotype [163]
99	**BIBW22BS**		Dipyridamole	Pyrimidine	+	nd	nd	◆Rh123 efflux significantly inhibited by 1 µM BIBW22 in blasts of de novo or relapsed or persistent acute myeloid leukemia [164] ⅄Combination with vincristine or doxorubicin in BRO/mdr1.1 xenografts: reduced the tumor growth at non-toxic concentrations of 1.0 µM [165, 166]

Table 2. Contd…..

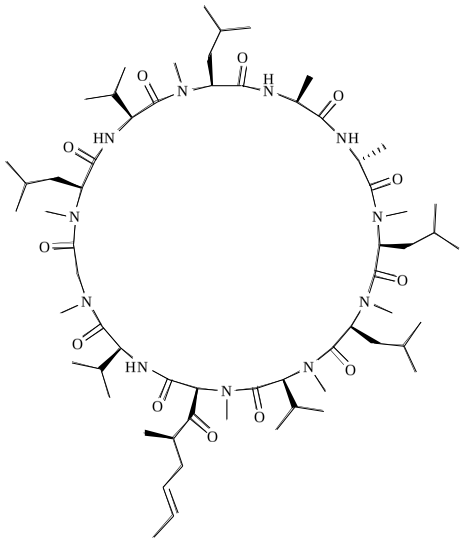
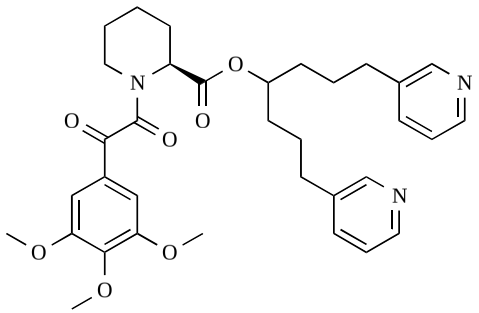
	Name	Structure	Derivative of / Stereo-isomer of	Scaffold	Inhibitor of			Representative P-gp Assays ◆Accumulation/efflux ✱ATPase assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄ *In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➝Others
					P-gp	MRP	BCRP	
100[#]	**Valspodar**		Cyclosporine	Cyclic undecapeptide	+	-	+	◆✓Decreased doxorubicin GI_{50} by increasing doxorubicin accumulation in SK-MES-1/DX1000 resistant cells, but also downregulated P-gp expression by activating JNK/c-Jun/AP-1 and suppressing NF-κB [167] ⅄Administration of valspodar to rats before mitoxantrone treatment: increased the accumulation of mitoxantrone in the MDR tumors to 94% of that in the wild-type tumors [168]
					[169]			
101[#]	**Biricodar**		Tacrolimus	Piperidine / pyridines	+	+	+	◆Increased daunorubicin and calcein accumulation in HL60/ADR cells [170] ✶Direct binding of [^{3}H]biricodar to P-gp [170]
					[171, 172]			

Table 2. Contd…..

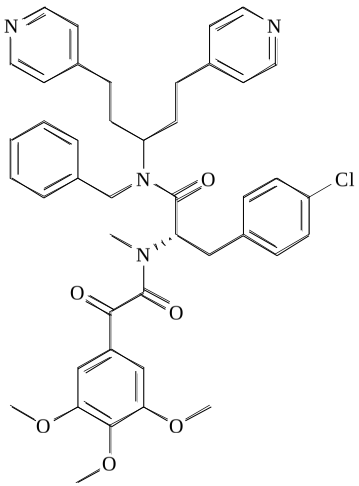
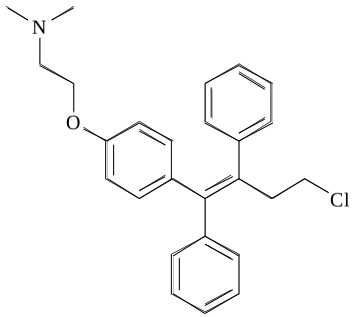
	Name	Structure	Derivative of / Stereo-isomer of	Scaffold	Inhibitor of			Representative P-gp Assays ◆Accumulation/efflux ✱ATPase assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄ *In Vivo*/*In Vtro* Pharmacokinetic Assays ✖ Imaging Assays ➔Others
					P-gp	MRP	BCRP	
102[#]	**Tincodar or VX-853**		Tacrolimus	Pyridine	+	+	nd	➔Potentiating antibiotic activity by inhibiting bacterial efflux [173]
					[174]			
103	**Toremifene**		Tamoxifen	Tribenzene	+	nd	nd	◆Increased danunorubicin accumulation in K562/D1-9 [175] ◆Addition of serum from patients on toremifene plus rh123 to MCF-7 adr cells *in vitro*: inhibited P-gp-mediated efflux of rh123 [176] ✓14- to 39-fold increase in vinblastine toxicity in MCF-7Adr cells expressing P-gp [177] ✓Restored the sensitivity of K562/A02 cells to adriamicin (2.5 μM); it was also able to increase the adriamicin concentration in K562/A02 and downregulate the expressions of P-gp and MDR1 mRNA [176]

Table 2. Contd…..

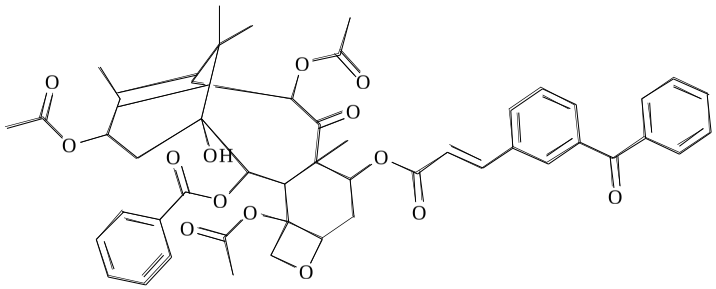
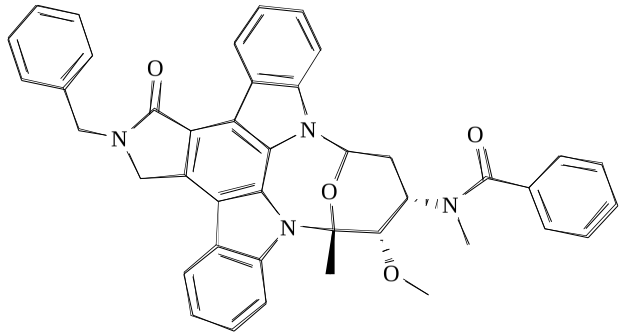
	Name	Structure	Derivative of / Stereo-isomer of	Scaffold	Inhibitor of			Representative P-gp Assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell monolayer Transport ✓Combination Assays ⅄ *In Vivo*/*In Vtro* Pharmacokinetic Assays ✖ Imaging Assays ➔Others
					P-gp	MRP	BCRP	
104	**SB-RA-31012 or tRA96023**		Paclitaxel	Taxane or diterpene	+	-	+	◆✓Increased drug retention and cytotoxicity of mitoxantrone, daunorubicin and doxorubicin in cell lines overexpressing BCRP and P-gp, but not those overexpressing MRP-1 [178]
					[178]			
105	**CGP 42700**		Staurosporine	Alkaloid	+	nd	nd	◆Increased accumulation of rhodamine G6 in the P-gp overexpressing cell line [179]

Table 2. Contd…..

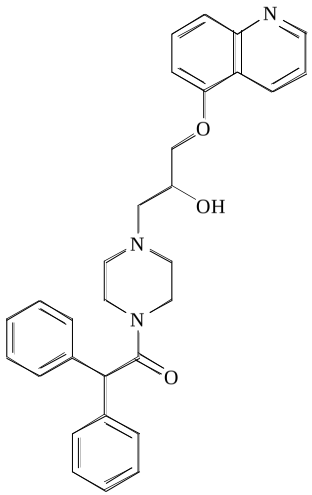
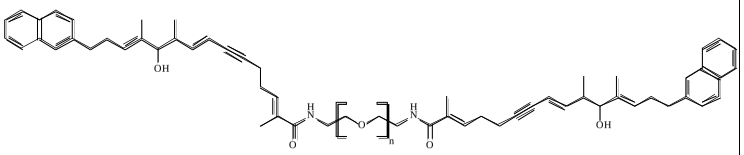
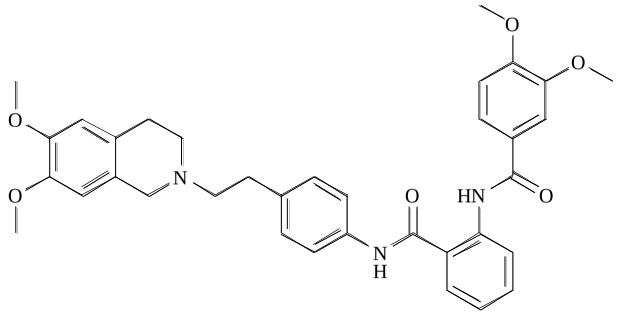
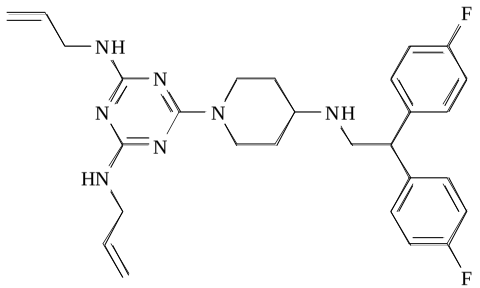
	Name	Structure	Derivative of / Stereo-isomer of	Scaffold	Inhibitor of			Representative P-gp Assays ◆**Accumulation/Efflux** ✱**ATPase Assay** ✦**UIC2** ✶**Photoaffinity Labelling** ●**Cell monolayer Transport** ✓**Combination Assays** ⅄***In Vivo*/*In Vtro* Pharmacokinetic Assays** ✖**Imaging Assays** ➞**Others**
					P-gp	**MRP**	**BCRP**	
106[#]	**Dofequidar or MS-209**		Ciprofloxacin / levofloxacin	Quinolone	+	+	-	✓Increased the efficacy of the chemotherapeutic agents adriamicin and vincristine in SBC-3/ADM and H69/VP cells [180] ✓Combination with adriamicin in SBC-3 / ADM cells (expressing P-gp): reversed the MDR of SBC-3 / ADM cells, but not SBC-3 cells, and inhibited metastasis formation *in vivo*, showing usefullness for treatment of refractory SCLC patients with multiorgan metastases [181]. ●The transport of [^{3}H]paclitaxel across the Caco-2 monolayer was markedly inhibited in the presence of MS-209 [182]
					[183, 184]			
107	**Stipiamide homodimer**		Stipiamide	Stipiamide homodimer	+			nd

Table 2. Contd…..

	Name	Structure	Derivative of / Stereo-isomer of	Scaffold	Inhibitor of			Representative P-gp Assays ◆Accumulation/Efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell monolayer Transport ✓Combination Assays ⅄*In Vivo*/*In Vtro* Pharmacokinetic Assays ✖Imaging Assays ➔Others
					P-gp	MRP	BCRP	
108	**WK-X-34**		Tetrandrine	Tetrahydroisoquinoline	+	-	+	◆Inhibited daunorubicin accumulation in A2780/Adr cells at nanomolar concentrations (IC_{50}= 82.1 nM) ✖ Uptake of ^{99m}Tc-Sestamibi in A2780/Adr xenograft tumors was significantly increased [185]. WK-X-34 caused increased ^{99m}Tc-Sestamibi levels in major organs as well as in deep tissues (e.g. muscle). Thus, pharmacokinetic alterations may be associated, imposing the need for a careful risk-benefit evaluation as well as careful toxicity monitoring [185]
					[186]			
109[#]	**S9788**		Almitrine	Triazineaminopiperidine	+	-	+	◆Restored daunorubicin accumulation in K562R cells to a level similar to that measured in sensitive cells K562S (at 5 µM) [187, 188] ✓Higher cytotoxicity of doxorubicin in the presence of S9788, compared to cyclosporin A and verapamil (reported to be due to a higher subcellular accumulation of the drugs in their nuclear sites of action and to a strong decrease of drug efflux from K562R nuclei) [188, 189]
					[188]			

(-) means no inhibition; (+) means inhibition; (nd) means no published data. UIC2= mouse monoclonal antibody directed against an extracellular conformational epitope of P-gp.

* Clinical trials of these compounds listed in Table 4

Table 3. Third Generation P-gp Inhibitors

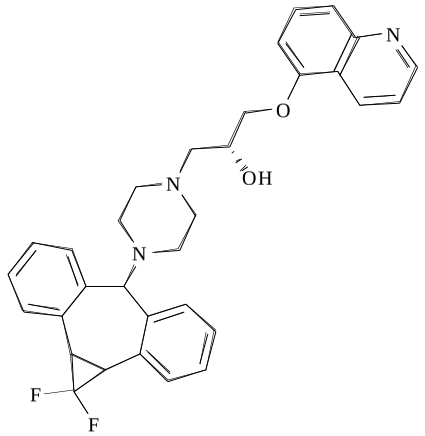
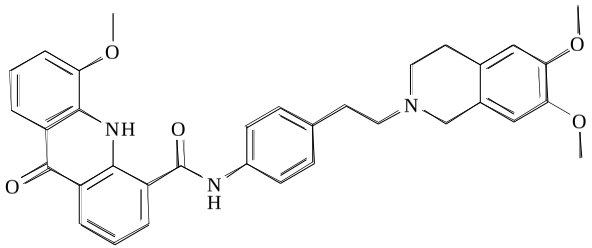
	Name	Structure	Scaffold	Inhibitor of			Representative P-gp Assays ◆Accumulation/efflux ✱ATPase assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄ *In Vivo*/*In Vtro* Pharmacokinetic Assays ✖ Imaging Assays ➞Others
				P-gp	MRP	BCRP	
110[#]	**Zosuquidar or LY335979**		Difluoro-cyclopropyl dibenzosuberane derivative	+	-	-	◆Increased accumulation of rh123 in AML blasts and NK cells from patients [190] ⅄ Increased paclitaxel levels in plasma and tissues in mice to levels similar to those observed in P-gp knockout mice, at nanomolar concentrations [191] ⅄ Combination with imatinib in mice: improved the delivery of imatinib to the brain, making it potentially more effective against malignant gliomas [192]
				[193]			
111[#]	**Elacridar or GF-120918**		Acridone carboxamide	+	-	+	⅄ ◆Increase R- [^{11}C]verapamil distribution in rat brain (which expresses P-gp) up to 11-fold over baseline at maximum effective doses, with elacridar being about three times more potent than tariquidar, with regional differences in brain uptake being related with regional differences in cerebral P-gp function and expression [194] ✓Combination with etoposide, doxorubicin, vinblastine, docetaxel and paclitaxel in MDR sarcoma MES-Dx5 cells: reversal of resistance [195] ⅄ Increase systemic concentration of imatinib [192] and paclitaxel in the brain of mice [196, 197, 198] ⅄ Significant increase of the systemic exposure of topotecan, leading to a increase of oral bioavailability [199]
				[200, 201]			

Table 3. Contd…..

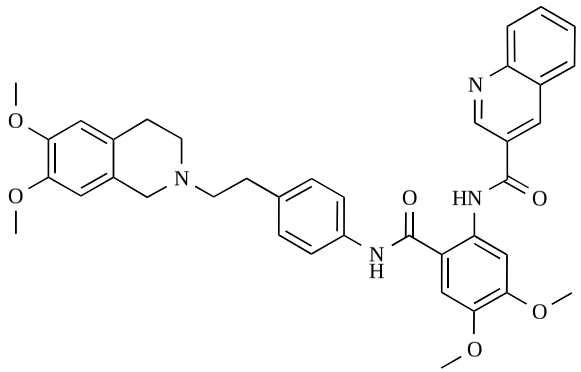
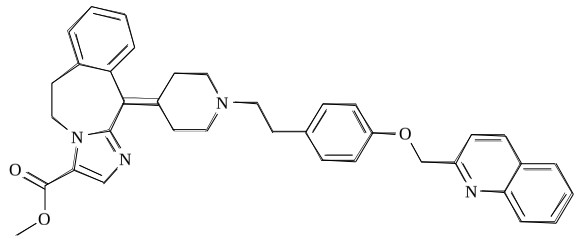
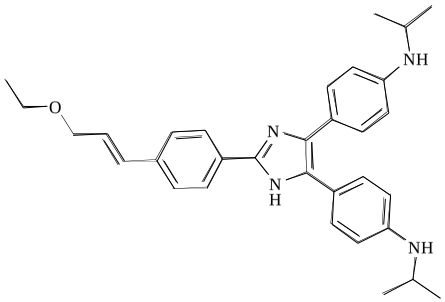
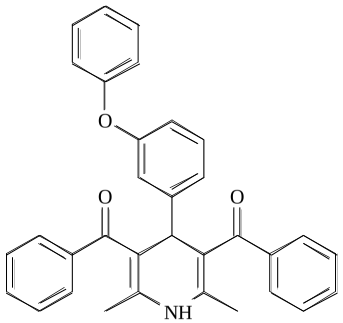
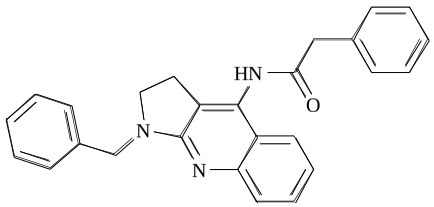
	Name	Structure	Scaffold	Inhibitor of			Representative P-gp assays ◆Accumulation/efflux ✱ATPase Assay ✦UIC2 ✶Photoaffinity Labelling ●Cell Monolayer Transport ✓Combination Assays ⅄ *In Vivo*/*In Vtro* Pharmacokinetic Assays ✖ Imaging Assays ➔Others
				P-gp	MRP	BCRP	
112 #	**Tariquidar or XR9576**		Anthranilamide	+	-	+	◆Increased accumulation of [^{3}H]vinblastine and [^{3}H]paclitaxel in CHrB30 cells [202] ✓Combination with various anticancer drugs, such as daunorubicin, doxorubicin, paclitaxel, etoposide and vincristine in human tumor xenografts (A2780AD, CH1/DOXr, H69/LX): reversed resistance (at nanomolar concentrations) [203]
				[204]			
113 #	**Laniquidar or R101933**		Tetrahydro-benzazepine and quinoline derivative	+	-	-	⅄ P-gp inhibition both in ex vivo and *in vivo* assays as indicated by the inhibition of intestinal P-gp [205] ⅄ Oral coadministration with docetaxel to mouse: does not alter the plasma pharmacokinetics of docetaxel [206]
114 #	**Ontogen or OC-144-093 or ONT.093**		Imidazol	+	nd	nd	✱Inhibited P-gp ATPase activity at μM concentration [207] ✓Combination with doxorubicin, paclitaxel, and vinblastine in human lymphoma, breast, ovarian, uterine, and colorectal carcinoma cell lines expressing P-gp: reversed MDR with an average EC_{50} of 0.032 μM. Inhibition of MDR by OC144-093 was reversible, but the effect persisted for at least 12 h after removal of compound from the culture medium [207] ✓Enhanced the antitumor activity of paclitaxel in MDR human breast and colon carcinoma cell lines [207] ✶Blocked the binding of [^{3}H]azidopine to P-gp at μM concentration [207] ⅄ Did not alter the rodent plasma pharmacokinetics of paclitaxel after IV administration [207]

Table 3. Contd…..

	Name	Structure	Scaffold	Inhibitor of			Representative P-gp Assays ◆**Accumulation/Efflux** ✱**ATPase Assay** ✦**UIC2** ✶**Photoaffinity Labelling** ●**Cell Monolayer Transport** ✓**Combination Assays** ⅄***In Vivo*/*In Vtro* Pharmacokinetic Assays** ✖**Imaging Assays** ➔**Others**
				P-gp	**MRP**	**BCRP**	
115	**DP7**		Dihydropiridine	+	nd	nd	◆ Coadministration with cytotoxic drugs in L5178 MDR cell line: reversed MDR [208]
116	**PGP-4008**		Dihydro-pyrroloquinoline	+	nd	nd	➔Animals with solid tumor (overexpressing P-gp) treated with a combination of PGP-4008 and doxorubicin: inhibition of tumor growth greater than control group [209]
117 [#]	**CBT-1**	Structure unavailable		+	+	-	◆Inhibited rh123 efflux at 1μM ✱Stimulated ATP hydrolysis at <1 μM [210] ✶CBT-1 competed with [^{125}I]IAAP labelling of P-gp with an IC_{50} of 0.14 μM ✓Combination with vinblastine, paclitaxel and depsipeptide in SW620 Ad20 cells: completely reversed Pgp-mediated resistance at 1μM
				[210]			

(-) means no inhibition; (+) means inhibition; (nd) means no published data. UIC2= mouse monoclonal antibody directed against an extracellular conformational epitope of P-gp.* Clinical trials of these compounds listed in Table 4

Table 4. MDR-Related Clinical Trials

	MDR Related Clinical Trials	Clinical Trials Results	Ongoing MDR Related Clinical Trials
Verapamil (1)	I. Verapamil combined in continuous infusion with adriamycin and vincristine in the treatment of patients with advanced and anthracycline-refractory breast cancer II. Combination of vincristine, doxorubicin, and dexamethasone alone or in combination with verapamil per os on drug resistant myeloma patients	I. Low cardiac toxicity, potentiation of neurotoxicity and hematotoxicity, response rate of only 21% [211] II. No beneficial effect observed from combination therapy regimen for the treatment of drug-resistant myeloma patients [212]	Combination of hydroxyurea and verapamil for refractory meningiomas (phase II): currently recruiting participants (www.ClinicalTrials.gov/ct/gui/show/NCT00706810)
Nifedipine (4)	Combination of nifedipine and etoposide in multidrug resistance in patients (phase I)	Cardiovascular effects of nifedipine were dose limiting but it did not interfere with the pharmacokinetics of etoposide [213]	
Tetrandrine (12)	Patients with low risk forms of AML treated with tetrandrine combined with daunorubicin, etoposide and cytarabine (TET-DEC)	TET-DEC was relatively well tolerated in these patients with poor risk AML, and had encouraging antileukemic effects [214]	
Mibefradil (13)			Mibefradil plus temozolomide phase Ib / II clinical trial beginning in 2011 (www.tautherapeutics.com/products_mibefradil.php)
Bepridil (15)	I.Combination of bepridil and anthracycline in patients with progressive advanced and resistant cancer II.Combination of vimblastine with bepridil in patients with colorectal cancer	I.No acute cardiac toxicity; bepiridil did not induce an increase or change in anthracycline toxicity, but caused chronic heart failure after treatment discontinuation (related to the total anthracycline dose received) [215] II. No response was obtained that could be attributed to MDR reversal, suggesting other mechanisms of drug resistance [216]	
Dipyridamole (16)	Combination of vinblastine and dipyridamole in the treatment of advanced renal cell carcinoma (phase II)	Combination may be administered with acceptable toxicities, but it was ineffective in the treatment of advanced renal cell carcinoma [217]	
Cyclosporine A (23)	I.Randomized (phase II) study to evaluate the potential of high doses of cyclosporine A on modulation of vinblastine resistance in patients with advanced renal cell carcinoma II.Randomized (phase II/III) trials of cyclosporine combination with vincristine, doxorubicin, etoposide, daunorubicin or dexamethasone in patients with advanced refractory cancers	I. No effects of cyclosporine A on the overall response rate [218], progression-free survival or overall survival with combinatory therapy [219]; leucopenia, transient hyperbilirubinemia and neurocortical changes [218]; dose-related cyclosporine A toxicity (reversible hyperbilirubinemia, myelosuppression and nausea hypomagnesemia, hypertension, headache and nephrotoxicity) [220] II.When used with a high-dose of cyclosporine A, etoposide doses should be reduced by approximately 50% to compensate for the pharmacokinetic effects of cyclosporine A on etoposide [221]; interference with daunorubicin pharmacokinetics [222]	Combination chemotherapy and cyclosporine followed by cryotherapy and/or laser therapy in treating patients with newly diagnosed retinoblastoma (currently recruiting participants) (www.ClinicalTrials.gov/ct/gui/show/NCT00110110) Cyclosporine and combination chemotherapy in treating patients with relapsed or refractory acute myeloid leukemia (still ongoin) (www.ClinicalTrials.gov/ct/gui/show/NCT00002688)

(Table 4). Contd…..

	MDR Related Clinical Trials	Clinical Trials Results	Ongoing MDR Related Clinical Trials
Tacrolimus (24)	Mechanisms of early response to tacrolimus treatment in combination with corticosterois in patients with P-gp mediated unresponsiveness rheumatoid arthritis (phase III/IV)	Good response to tacrolimus was noted by 20% of the patients following 2 weeks treatment. Restoration of intracellular therapeutic levels of corticosteroids and clinical improvement. Evaluation of P-gp expression on lymphocytes is potentially useful for predicting the response to rheumatoid arthritis treatment [223]. Wide spectrum of adverse effects (ex: neurotoxic effect) [224]	
Itraconazole (34)	Effect of the combination treatment with itraconazole and aliskiren, morphine, paroxetine, gemfibrozil or cimetidine on pharmacokinetics	Itraconazole raised the plasma concentrations of aliskiren [225], morphine [226], paroxetine [227], gemfibrozil [228] and cimetidine [81]; the interaction is probably mainly explained by inhibition of the P-gp-mediated efflux in the small intestine.	
Quinine (39)	I. Phase III prospective randomized multicenter study to determine whether quinine could improve the response rate of poor-risk acute leukemias to standard chemotherapy including a MDR-related cytotoxic agents such as mitoxantrone and cytarabine II. Addition of quinine to paclitaxel in patients with non-Hodgkin's lymphoma and detectable levels of P-gp III.A randomized trial of intensive chemotherapy with or without quinine in myelodysplastic syndromes IV.Continuous intravenous infusion of quinine in combination with induction chemotherapy combining idarubicine and cytarabine in adult patients with de novo acute myeloid leukemia	I.Quinine-treated patients showed increased mitoxantrone uptake in the MDR-positive cell line [229] II. Pharmacokinetic studies indicated that the MDR reversal were not due to changes in clearance of paclitaxel (which appears to increase with quinine), but more likely to the sensitization of lymphoma cells [230] III.Quinine is capable of reverting MDR phenotype, but with low complete remission rate [231] IV. Quinine did not improve the survival [232]	
Tesmilifene (65)	I.Combination with epirubicin and cyclophosphamide (phase I) and combination with docetaxel (phase II) in metastatic breast cancer II.Combination of tesmilifene with doxorubicin in metastatic breast (phase III) cancer	I.Very large survival advantage (www.ClinicalTrials.gov/ct/gui/show/NCT00364754 and www.ClinicalTrials.gov/ct/gui/show/NCT00364195) II.Addition of tesmilifene resulted in a significant improvement in overall survival and a trend toward a difference in progression-free survival [233]	
Mitotane (68)	Combination regimen of daily mitotane with infusional doxorubicin, vincristine, and etoposide in patients with metastatic adrenocortical cancer (phase II)	The side effects of mitotane made treatment difficult (neutropenia, nausea, diarrhea, fatigue, and neuropsychiatric changes) [234] and clinical trials were abandoned	

(Table 4). Contd…..

	MDR Related Clinical Trials	Clinical Trials Results	Ongoing MDR Related Clinical Trials
Dexverapamil (90)	I. Evaluation of the effects of dexverapamil on epirubicin toxicity, activity and pharmacokinetics in patients with metastatic breast cancer (phase II)	I. Increased AUC and toxicity of cytotoxic agents [235]. Significant decrease in mean heart rate and blood pressure as well as prolongation of QT time as compared to epirubicin alone. Did not require reduction of the epirubicin dose [236]. Caused myelosuppression, and mild and reversible dexverapamil-related cardiovascular side-effects, specifically hypotension [237]	
	II. Study of dexverapamil plus anthracycline in patients with metastatic breast cancer who have progressed on the same anthracycline regimen	II.Asymptomatic cardiotoxicity (hypotension, bradycardia, or prolongation of the P-R interval). Risk of acute congestive heart failure. Did not increase anthracycline toxicity. Intrinsic cardiotoxicity of dexverapamil [238]	
Dexniguldipine (94)	A phase I study using dexniguldipine alone and in combination with vinblastine in patients with a metastatic or locally advanced cancer	Cardiovascular adverse events such as a drop in blood pressure, decrease heart rate and AV block III. Most frequent adverse events were nausea, dizziness, vomiting, peripheral paresthesia, atactic gait, mild constipation, polyuria, hypocalcemia, disappeared within 24 hours after discontinuation of infusion [239]	
Cinchonine (96)	Phase I study of cinchonine combined with the CHVP regimen in relapsed and refractory lymphoproliferative syndromes	At an i.v. infusion of cinchonine might be started 12 h before MDR-related chemotherapy infusion and requires continuous cardiac monitoring but no reduction of cytotoxic drug doses [240]	
Valspodar (100)	I.A phase I study of valspodar with mitoxantrone and etoposide in refractory and relapsed pediatric acute leukemia	I. The clearance of mitoxantrone and etoposide was decreased when combined with valspodar. Dose-limiting toxicities included stomatitis, ataxia, and bone marrow aplasia. Responses were limited to a subset of patients with acute lymphoblastic leukemia whereas no patient with acute myeloid leukemia had an objective response [241]	Effectiveness of valspodar plus etoposide and mitoxantrone in treating children who have refractory or relapsed acute leukemia (phase I) (www.ClinicalTrials.gov/ct/gui/show/ NCT00002912, results not yet published)
	II. Randomized phase III trial to compare the effectiveness of combination chemotherapy with or without valspodar followed by interleukin-2 or no further therapy in treating older patients with acute myeloid leukemia (www.ClinicalTrials.gov/ct/gui/show/ NCT00006363)	II.Grade 4 toxicities during IL-2 therapy included thrombocytopenia and neutropenia, and grade 3 toxicities included anemia, infection and malaise/fatigue. Low-dose IL-2 maintenance immunotherapy is not a successful strategy in older AML patients [242]	A randomized phase II trial is being performed in order to compare the effectiveness of paclitaxel with or without valspodar in treating patients with metastatic breast cancer (www.ClinicalTrials.gov/ct/gui/show/ NCT00002937, results not yet published)
	III.Efficacy of valspodar in enhancing the effects of daunorubicin in patients receiving intensive chemotherapy (phase III) to see how well they work compared to nonintensive regimens of chemotherapy in treating older patients with acute myeloid leukemia or myelodysplastic syndrome	III. Valspodar did not improve outcomes [243]	

(Table 4). Contd…..

	MDR Related Clinical Trials	Clinical Trials Results	Ongoing MDR Related Clinical Trials
Biricodar (101)	I.Biricodar in combination with anticancer drugs such as doxorubicin [244] and paclitaxel [171] (phase I) II.Addition of biricodar to mitoxantrone or prednisone on therapy of patients with prostate cancer (phase II) III.Addition of biricodar to doxorubicin and vincristine therapy on patients with small cell lung cancer (SCLC) (phase II)	I. Fully reversed MDR, together with acceptable level of toxicity [171, 244]. Acceptable toxicity, no significant alteration in the pharmacokinetics of the cytotoxic drugs, with the exception of a reduced clearance of paclitaxel (attributed to the inhibition of CYP) [245]. II. Good safety and tolerability, but did not increase the proportion of patients with significant serum PSA reductions [246]. III. Biricodar did not significantly enhance antitumor activity or survival [247] although minimal toxicity is reported [248]	Biricodar, doxorubicin, and vincristine in treating patients with recurrent small cell lung cancer (www.ClinicalTrials.gov/ct/gui/show/NCT00003847, active, not recruiting) At present, no phase III study has been planned so far.
Timcodar (102)			A phase I/II study of the pharmacokinetics, tolerability and safety of administration of timcodar to patients receiving single agent therapy with doxorubicin (www.ClinicalTrials.gov/ct/gui/show/NCT00004030) is still ongoing
Dofequidar (106)			Dofequidar Plus Docetaxel in Treating Patients With Advanced Solid Tumors (phase I) (www.ClinicalTrials.gov/ct/gui/show/NCT00004886, no results yet)
S9788 (109)	I. Phase Ib study of doxorubicin in combination with the multidrug resistance reversing agent S9788 in advanced colorectal and renal cell cancer II.Phase I clinical and pharmacokinetic study of S9788 given alone and in combination with doxorubicin to patients with advanced solid tumors	I. MDR reversing concentrations are achieved in patients at nontoxic doses. Treatment with the combination of doxorubicin and S9788 produced a significant increase in the occurrence granulocytopenia and cardic toxicity (increase in corrected QT intervals as well as arrhythmias) [249] II.Bradycardia or clinical symptoms suggesting a vasovagal impact such as faintness or dizziness [250, 251]. Clinical trials were stopped due to cardiac toxicity (specially AV-blocks and QT prolongation, leading to ventricular arrhythmia) [250, 252]	
Zosuquidar (110)	I.The impact of zosuquidar on the pharmacokinetics of daunorubicin and daunorubicinol (phase I trial) II.A phase I/II trial of zosuquidar administered intravenously in combination with doxorubicin in patients with advanced malignancy III.Phase I study of zosuquidar administered in combination with docetaxel , vinorelbine, vincristine, daunorubicin or cytarabine in patients with advanced malignancy IV.Combinatorial treatment of daunorubicin or cytarabine plus zosuquidar in adults older than 60 years with acute myeloid leukemia or high-risk myelodysplastic syndrome (phase II)	I.Decrease in daunorubicin and daunorubicinol clearance due to inhibition of P-gp in the bile canaliculi blocking their biliary excretion [253] II.Zosuquidar can be coadministered with doxorubicin per os [254] or i.v. [255], with no effect on doxorubicin toxicity or pharmacokinetics. It can be given safely to patients with AML in combination with cytotoxic drugs [256], specially to older patients whose blasts express P-gp [257] III.Zosuquidar minimally altered the pharmacokinetics of docetaxel [258], vinorelbine [259] or vincristine [260], daunorubicin and cytarabine [190] allowing full dose administration of the cytotoxic agent. Some risk of neurotoxicity at high dosage IV.Zosuquidar did not improve outcome in older acute myeloid leukemia, in part, because of the presence P-gp independent mechanisms of resistance [261]	There is no other clinical trial planned for zosuquidar

(Table 4). Contd…..

	MDR Related Clinical Trials	Clinical Trials Results	Ongoing MDR Related Clinical Trials
Elacridar (111)	I.Effect of elacridar in the accumulation of docetaxel in the brain II.A phase I and pharmacologic study of elacridar in combination with doxorubicin in patients with advanced solid tumors III.Docetaxel and epirubicin pharmacokinetic results in a phase I combination study with the oral P-gp inhibitor elacridar in patients with locally advanced or metastatic cancer	I.Elacridar inhibits P-gp in the blood-brain barrier and increases the accumulation of docetaxel in the brain without significant effects on systemic exposure [262] II.Elacridar pharmacokinetics were not influenced by coadministration of doxorubicin and produced only minimal side effects at a dose level yielding concentrations able to inhibit the action of P-gp in vitro (hematologic toxicity, namely neutropenia, somnolence and occasional gastrointestinal complaints) [192] III.Increased systemic exposure to docetaxel and reduced clearance. This interaction limited further clinical development [263]	No phase II clinical trials with this agent have been carried out after the disencouraging results of phase I trials
Tariquidar (112)	I.Tariquidar effects on safety and its pharmacokinetics after i.v. and oral administration (phase I) II.Addition of tariquidar to chemotherapy (anthracycline or taxane) in patients with chemotherapy-resistant advanced breast (phase I) III.Tariquidar in combination with vinorelbine in breast, lung and ovarian cancer (phase I) IV.Effectiveness of combination treatment with tariquidar and docetaxel in treating patients with lung, ovarian, or cervical cancer (phase II) V.Tariquidar in combination either with paclitaxel and carboplatin or with vinorelbine as first line therapy in non-small-cell lung cancer patients (phase III)	I.Sustained inhibition of P-gp after i.v. and oral administration [264] II.Could not induce an objective tumor response yielding disappointing results [265] III.Tariquidar was shown to be a potent P-gp inhibitor, without significant side effects and much less pharmacokinetic interaction than previous P-gp inhibitors and with few nonhematologic toxicities reported (abdominal pain, anorexia, constipation, fatigue, myalgia, pain and dehydration, depression, diarrhea, ileus, nausea, and vomiting) [266] IV.Tariquidar was well-tolerated and had less observed systemic pharmacokinetic interaction than previous P-gp inhibitors. Pharmacokinetic and pharmacodynamic trial using tariquidar showed it increased the retention of co-administered docetaxel [204] V.Trial had been stopped due to increased toxicity (www.ClinicalTrials.gov/ct/show/ NCT00042302)	Phase I trial that is studying the effectiveness of tariquidar plus chemotherapy in treating children who have relapsed or refractory solid tumors (www.ClinicalTrials.gov/ct/show/ NCT00020514, still ongoing) A phase II study in order to assess if tariquidar is able to reverse primary doxorubicin or taxane resistance in advanced breast cancer in patients previously resistant to the same agents is ongoing (www.ClinicalTrials.gov/ct/show/NCT00048633, no results published yet) Another phase II clinical trial study the effectiveness of combining tariquidar with combination chemotherapy and surgery in treating patients who have recurrent, metastatic, or primary unresectable adrenocortical cancer is completed but with no published results so far (www.ClinicalTrials.gov/ct/show/NCT00073996)
Laniquidar (113)	I.Disposition of docetaxel with and without i.v. administration of laniquidar II.Oral laniquidar (R101933) in combination with i.v. docetaxel (phase I) III.Phase I study with laniquidar and escalating doses of epirubicin	I. No pharmacokinetic interaction. Minimal toxicity consisting of temporary drowsiness, somnolence and neutropenic fever [205] II. Pharmacokinetics of docetaxel were not influenced by laniquidar at any dose level tested [267] III. Toxicity consisting of leukopenia, thrombopenia and anaemia. III.Non-haematological toxicities such as with nausea, fatigue, headaches, and peripheral neuropathy. The laniquidar regimen did not influence the pharmacokinetics of epirubicine [268]	A phase II study in metastatic breast cancer patients of laniquidar in combination with taxanes (www.ClinicalTrials.gov/ct/gui/show/ NCT00028873) is still ongoing
Ontogen (114)	I.Oral bioavailability of docetaxel in combination with OC144-093 (ONT-093) II.A phase I pharmacokinetic study of ONT-093 in combination with paclitaxel in patients with advanced cancer	I.The safety of the oral combination of ontogen and docetaxel was good and the relative apparent bioavailability was most likely caused by a significant effect of ontogen on the oral uptake of docetaxel [269] II. Inhibition of P-gp and MDR reversal at nM concentrations. No effect on paclitaxel pharmacokinetics. Well tolerated. Toxicities were mainly attributable to paclitaxel (febrile neutropenia) [270]	

(Table 4). Contd…..

	MDR Related Clinical Trials	Clinical Trials Results	Ongoing MDR Related Clinical Trials
CBT-1 (117)	Paclitaxel and CBT-1TM to Treat Solid Tumors (phase I)	CBT-1 did not affect the pharmacokinetics of doxorubicin and no neurological toxicities were observed [271, 272]	A study of CBT-1 and paclitaxel with Carboplatin in patients with advanced inoperable non-small cell lung cancer is completed but still with no published results (www.ClinicalTrials.gov/ct/gui/show/NCT00437749)

i.v. = intravenous; QT= measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; AV= atrioventricular; CHVP= cyclophosphamide, hydroxydaunomycin, vm 26 (teniposide), prednisone.

Table 5. P-gp Detection Methods (adapted [291, 292, 293]**)**

Method	Measurement	P-gp Source	Reagents Required	Controls	Criteria for Activity	Advantages	Disadvantages
RNA-based (RT-PCR)	mdr1 RNA expression	Tissue, cells	Primers	Cells that express and do not express P-gp.		Highly sensitive	No detection of P-gp function
Western blotting	P-gp expression	Tissue, cells	Anti-P-gp antibody (265/F4, JSB-1, PG-13, C219, C494, CD243)	Cells that express and do not express P-gp.		P-gp molecular weight verification	Low sensitivity, no detection of P-gp function
Immuno-histochemistry	P-gp expression	Tissue, cells	Anti-P-gp antibody (265/F4, JSB-1, PG-13, C219, C494)	Cells that express and do not express P-gp.		Analysis of P-gp expression and intracellular localization	Low sensitivity, no detection of P-gp function
Caco-2 permeability	P-gp function	Caco-2 layer		Known P-gp inhibitors and substrates.	P-gp inhibitor + substrate: Papp B→A > Papp A→B		
Accumulation / efflux assay (flow cytometry)	P-gp function	Cells	P-gp substrate, e.g. rhodamine-123, doxorubicin, daunorubicin, calcein-AM, JC-1, hoechst 33342	Cells that overexpress and do not express P-gp; known P-gp inhibitor such as verapamil or cyclosporin A.	P-gp inhibitor + substrate: cellular accumulation ratio of fluorescent substrate superior in cells treated with P-gp inhibitor than in nontreated control cells	Highly sensitive detection of accumulation and/or efflux activity	No specific detection of P-gp (presence of other efflux pumps). Requires a flow cytometer.
In vitro cytotoxicity assays	P-gp function	Cells	P-gp substrate with concomitant cell growth inhibitor	Cells that overexpress and do not express P-gp; known P-gp inhibitor such as verapamil or cyclosporin A.	P-gp inhibitor + GI_{50} of cytotoxic substrate: GI_{50} of cytotoxic compound decreases	Detection of P-gp functional activity	Low sensitivity and reproducibility, no specific detection of P-gp (presence of other efflux pumps)
MDR1 shift assay (flow cytometry)	P-gp function	Cells, membranes	Antibodies for external P-gp epitopes, e.g. UIC2, MRK16, 4E3, or MM12.10; negative control IgG2a	Cells that overexpress and do not express P-gp; known P-gp inhibitors and substrates.	P-gp noncompetitive inhibitor: decreases UIC2 labeling (compared to nontreated control). P-gp substrate/ competitive inhibitor: increases UIC2 labeling (compared to nontreated control).	Detection of P-gp function, differentiation between competitive and noncompetitive inhibitors	Requires a flow cytometer

(Table 5). Contd…..

Method	Measurement	P-gp Source	Reagents Required	Controls	Criteria for Activity	Advantages	Disadvantages
ATPase assay (luciferase-based luminescence, or phosphate colorimetric assay)	P-gp function	Cells, membranes	Known P-gp substrate, luciferin, luciferase	Known P-gp competitive inhibitor (such as verapamil or cyclosporin A), known P-gp noncompetitive inhibitor (such as sodium orthovanadate), and compounds that do not interfere with P-gp (such as buthionine sulfoximine).	P-gp noncompetitive inhibitor: decreases ATPase activity (compared to nontreated control). P-gp substrate/ competitive inhibitor: increases ATPase activity (compared to nontreated control). P-gp inhibitors also decrease the maximally known substrate stimulated ATPase activity.	Detection of P-gp function, differentiation between competitive and noncompetitive inhibitors	Background ATPase activity
Imaging agents	P-gp location	Tumor xenographs, patients	^{99m}Technetiumsestamibi, PET tracers such as [^{11}C]tariquidar, [^{11}C]laniquidar, 1-[^{18}F]fluoroelacridar.		Increased labeling of areas with increased P-gp expression.	It can be used *in vivo* for diagnosis purposes.	

Papp = apparent permeability coefficient; B→A = basolateral-to-apical; A→B = apical-to-basolateral; PET = Positron emission tomography.

To elucidate the mechanism of action of the P-gp inhibitors, ATPase or UIC2 (mouse monoclonal antibody directed against an extracellular conformational epitope of P-gp) assays are often applied. The P-gp-ATPase activity may be quantified by the detection of the levels of remaining ATP by a light-generating reaction catalyzed by luciferase [30] or by colorimetric detection of levels of phosphate (Pi) liberated [281]. On the ATPase assay, the increase in ATP consumption suggests a competitive mechanism of action (when a P-gp inhibitor is also a substrate), whereas the decrease in ATP consumption is related to a noncompetitive mechanism of action [282]. Regarding the UIC2 assay, since it uses a monoclonal antibody that binds specifically to an external epitope of P-gp in its active conformation (in the process of transporting a substrate) it allows differentiation between substrates and competitive inhibitors from noncompetitive inhibitors [283].

For the characterization of the drug binding domain on P-gp, several different approaches have been used. One of these is photoaffinity labelling of P-gp with a photoactive analogue of a drug substrate (e.g. [^{3}H]azidopine [65], [^{125}I]iodoarylazidoprazosin [116], or [^{125}I]*N*-(*p*-aminophenethyl)spiroperidol [105]) followed by generation of peptides from the labelled P-gp, by chemical or proteolytic cleavage. The labelled peptides are then identified using immunological methods [284]. Labelling of the different transmembrane α-helixes with various substrate analogues helps to identify the P-gp binding site of the test molecule [285].

To identify specific residues that form the drug binding pocket, cysteine scanning mutagenesis and thiol-reactive probes may be used. Several single cysteine mutants of human P-gp are reacted with a thiol-reactive substrate, such as dibromobimane [286, 287], or a thiol-reactive analogue of a P-gp substrate, such as methanethiosulfonate (MTS)-verapamil [288, 289], or MTS-rhodamine [289, 290]. If a residue in the drug-binding pocket is modified by the thiolreactive analogue, then the presence of the test drug in the drug-binding pocket should protect the residue from being labelled.

These methods have been used alone or in combination to charactherize the four generations of P-gp inhibitors listed in the following sections.

3. FIRST GENERATION P-GP INHIBITORS

First generation P-gp inhibitors (Table **1**, **1**-**89**) are defined as drugs already in clinical use or compounds under investigation for other therapeutic indications and which were shown to have an important side effect: inhibition of ABC transporters such as P-gp. Three representatives of the first generation P-gp inhibitors are verapamil (**1**), quinidine (**19**) and cyclosporine A (**23**).

First generation P-gp inhibitors are listed in Table **1** and include drugs such as cardiac (**1**-**22**), immunossupressant (**23**-**25**), antibiotics (**26**-**33**), antifungal (**34**-**38**), antimalarial (**39**), antiprotozoal (**40**-**42**), antiviral (**43**-**44**), CNS stimulators (**45**-**51**), CNS depressants (**52**-**58**), anesthetics (**59**-**62**), anti-histaminics (**63**-**65**), anticancer (**66**-**73**), steroid hormones (**74**-**82**), anti-inflamatory (**83**-**88**), and drugs for erectile disfunction (**89**).

Therefore, the first chemosensitizers identified were themselves substrates for P-gp and thus acted by competing with the cytotoxic compounds for efflux by the P-gp pump. However, many of these chemosensitizers are substrates for other transporters and enzyme systems, resulting in unpredictable pharmacokinetic interactions in the presence of chemotherapy agents [294]. Additionaly, these modulators have low affinity for P-gp, requiring the use of high doses and resulting in unacceptable toxicity [295].

3.1. Verapamil (1)

In 1981, Tsuruo *et al.*made the first description of verapamil (**1**) as a potential MDR reversing agent, indicating the possibility of identifying clinically useful reversing agents of MDR [28]. The calcium channel blocker verapamil (**1**) was the first compound ever found which was able to enhance the intracellular accumulation of many anticancer drugs such as vincristine, vinblastine, doxorubicin and daunorubicin [296, 297]. Indeed, it was demonstrated that verapamil (**1**) inhibited the efflux of anticancer drugs from tumor cells that over-expressed P-gp, causing an increase in the intracellular concentration of the chemotherapeutic drug. Some authors suggest that verapamil (**1**) inhibits P-gp activity by direct competition with P-gp substrates [298]. Several assays confirming verapamil sensitization of tumor cell lines to cytotoxic agents have been published throughout the years [297, 298, 299, 300]. Verapamil (**1**), administered at a dose corresponding to a typical cardiovascular posology in humans, significantly increased doxorubicin cytotoxicity [301]. Clinical experience of verapamil (**1**) in combination with chemotherapy is highlighted in Table **4** and has shown that verapamil (**1**) levels in blood are associated with hypotension, heart block, neurotoxicity and hematotoxicity [211, 302].

As far as the verapamil (**1**) binding pocket is concerned, a thiol-reactive analog of verapamil (MTS-verapamil) was used with cysteine-scanning mutagenesis to identify the reactive residues within the drug-binding domain of P-gp [288]. Four mutants, S222C (TM4), L339C (TM6), A342C (TM6), and G984C (TM12) were significantly protected from inhibition by MTS-verapamil by pretreatment with verapamil (**1**). Less protection was observed in mutants I868C (TM10), F942C (TM11) and T945C (TM11). Also, reacting the mutant I306C (TM5) with thiol-reactive compounds reduced its affinity for verapamil, suggesting that this residue is close to the verapamil-binding site [303]. These results indicated that residues in TM 4, 5, 6, 10, 11, and 12 (Fig. **2A**) must contribute to the binding of verapamil (**1**) [288] and are described as providing several groups for hydrophobic and hydrogen bond interactions [304].

Structure-activity relationships (SAR) of verapamil (**1**) analogs can be summarized in Fig. **2B** and showed that a decrease in the number of methoxyl groups (replacement by H atoms) on the phenyl rings results in a considerable decrease in MDR reversal activities. No significant effect in MDR reversal potency was caused by the replacement of the phenyl ring at the position closer to the terciary amine, with long aliphatic chains, or the replacement of the methoxyl groups in the phenyl rings with Cl atoms. Finally, a drastic decrease in potency was observed by replacing the –CN group with $–CH_2NH_2$ or by replacing the of $-CH(CH_3)_2$ with the $-(CH_2)_{11}CH_3$ group [305]. *N*-Methyl derivatives are generally less potent as MDR reverters than the *N*-demethyl counterparts [156]. Other structural modifications, such as iodination, originates verapamil derivatives that restored daunorubicin activity and when used alone did not induce cell death, cell cycle perturbation and modification of calcium channel activity in comparison with verapamil [306].

3.2. Tetrandrine (12)

Tetrandrine (**12**) was charactherized by several *in vitro* assays (Table **1**) demonstrating that it possesses potent and specific activity in reversing P-gp-mediated drug resistance [43]. Besides, the P-gp protein expression can be down-regulated (by 77%) as well as the mdr1 mRNA [42]. Fe_3O_4-Magnetic nanoparticles loaded with adriamicyn and tetrandrine (**12**) can enhance the effective accumulation of the drugs in K562/A02 [307]. In a clinical trial, tetrandrine was well tolerated in patients with low risk AML [214] (Table **4**).

Bromotetrandrine derivatives (Fig. **3**) have shown significant MDR reversal activity *in vitro* and *in vivo* [309]. The substitution

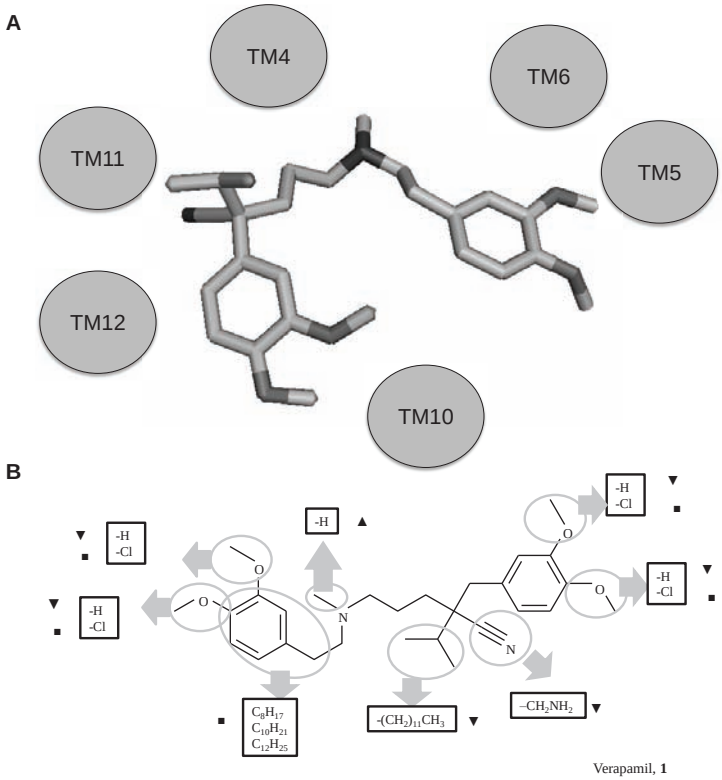
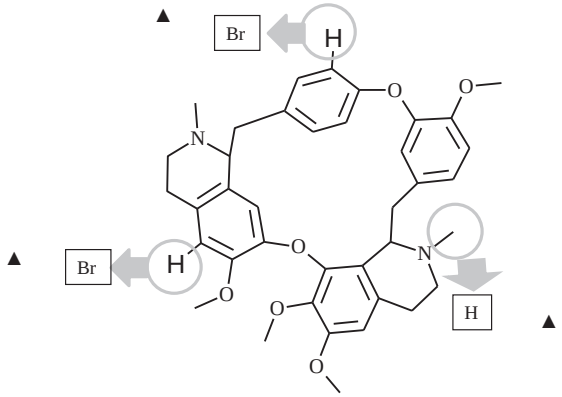


Fig. (2). **A**) Arrangement of TM cylindrical helix and verapamil (stick diagram) in the drug-binding pocket (adapted from [308]). **B**) Structure-activity relationship of verapamil (**1**). ▼= ↓ P-gp inhibition; ▲= ↑ P-gp inhibition; ■= ≈ P-gp inhibition.



Tetrandrine, **12**

Fig. (3). Structure-activity relationship of tetrandrine (**12**). ▲= ↑ P-gp inhibition.

with this bulky group, resulting in 5,14-dibromotetrandrine showed the strongest MDR-reversing effect, increasing intracellular vimblastin accumulation in P388/ADR (resistant) cells to a much greater extent than verapamil (**1**), as well as increasing vimblastin cytotoxic effect [310]. A methyl group in the piperidine nitrogen moiety may also be substituted by an H. In fact, a novel derivative of tetrandrine (**12**) with this substitution together with a bromo group, was effective in reversing P-gp-mediated MDR by inhibiting the transport function of P-gp and inhibiting its ATPase activity. This reversal of MDR may also be related with an increase in the ubiquitination of P-gp and the blockage of the MEK-ERK pathway [311].

3.3. Propafenone (22)

Propafenone (**22**) and its analogues are inhibitors of a large number of drug efflux pumps including P-gp and BCRP as well as the microbial pumps. A series of closely related structural homologues of propafenone have shown a highly significant correlation between lipophilicity and their P-gp modulation effect, and the distance between the carbonyl group and nitrogen atom was hypothised to be important [63]. Their activity is determined by the hydrogen bond donor –OH and the hydrogen bond acceptor in the amine and carbonyl groups. The alkyl or aryl chains connected to the amine seem to be involved in hydrophobic or π- π interactions, respectively [312, 313]. The merging between a pyrazole-based drug and the MDR modulator propafenone is a recent strategy for the design of hybrid molecules that interacted more effectively with P-gp, helping to decrease the P-gp mediated drug efflux [314].

3.4. Cyclosporine A (23)

In 1986, Slater *et al*. demonstrated that an immunosuppressive drug, cyclosporine A (**23**), also had the capacity to reverse resistance to anticancer drugs *in vitro* [315].

Cyclosporine A (**23**) was reported to interfere with the P-gp mediated effect (Table **1**). In fact, it has been demonstrated that cyclosporine A competed with the substrates of P-gp to bind to the drug-binding Site of P-gp [316]. These *in vitro* results originated a series of clinical trials on the combination of anticancer drugs that were MDR substrates and cyclosporine A (**23**) (Table **4**). However, contraditory results were observed concerning cyclosporine A (**23**) effects from both *in vitro* tests and from clinical trials.

At the beginning of the 90s, the first clinical trial with cyclosporin A (**23**) and anticancer drugs were started in patients with multiple myeloma and acute leukemia [220, 222, 317]. Subsequently, several other clinical trials were performed (Table **4**). Indeed, cyclosporine A (**23**) showed no selectivity towards P-gp. In fact, it increased cellular drug uptake in cells overexpressing P-gp, MRP-1 or BCRP and nuclear drug uptake in cells overexpressing LRP, at the clinically achievable concentration of 2.5 μM [66, 67].

In order to inhibit P-gp, cyclosporine A (**23**) requires a suitable lipophilicity to cross the cell membrane and conformational plasticity to gain access to P-gp binding sites. By use of photoaffinity-labeled cyclosporins and membranes from P-gp-expressing cells, it was shown that *in vitro*, P-gp could bind a large cyclosporin domain involving residues 4-9 as well as the side chain of residue 1 of cyclosporine A (**23**) [318]. P-gp inhibition was favored by larger hydrophobic side chains on cyclosporin residues 1, 4, 6, and 8, although with no effect on the residue 5 side chain (Fig. **4A**); moreover, larger hydrophobic side chains on other residues, namely 2, 3, 10, and 11, also favor the eventual inhibition of P-gp function. The *N*-demethylation of any of the seven *N*-methylated amides leads to a decreased P-gp inhibitory activity, up to its extinction if it occurs at residues 4 and 9 [319] (Fig. **4A**).

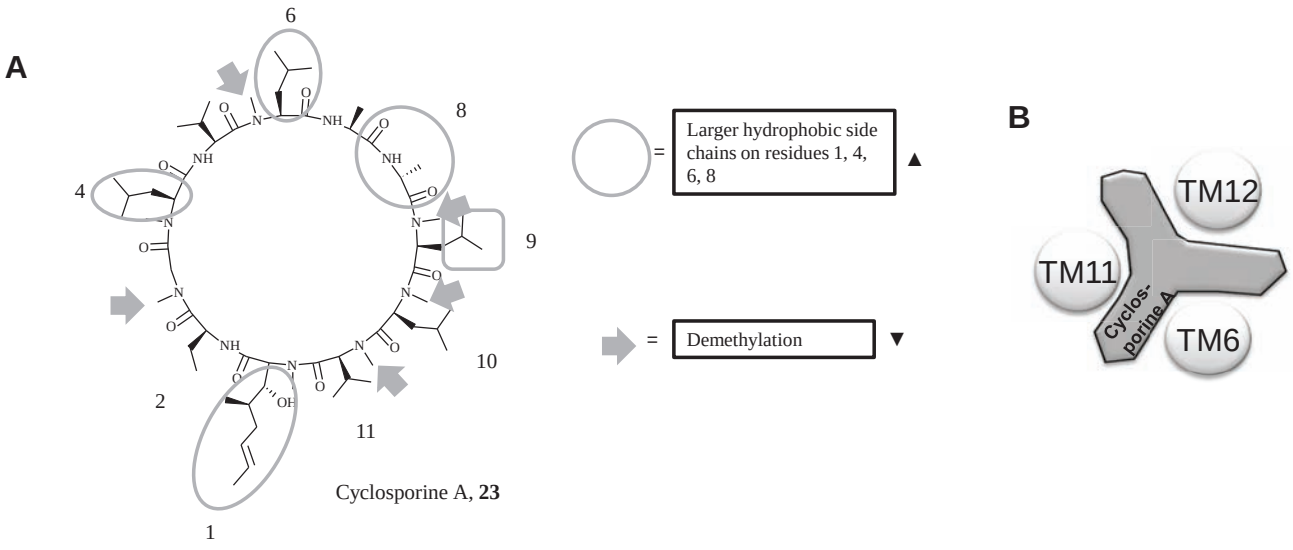


Fig. (4). **A**) Structure-activity relatioship of cyclosporine A (**23**). ▼= ↓ P-gp inhibition; ▲= ↑ P-gp inhibition. **B)** Proposed model of the cyclosporine A binding site on P-gp (adapted from [286]).

Mutagenesis studies have shown that S939 plays an important role in the cyclosporine A (**23**) specificity for the P-gp. This serine was also shown to be an important determinant in the recognition of cyclosporine A (**23**). Photolabelling P-gp with a non-radioactive cyclosporine A derivative, followed by enzymatic proteolysis and chemical cleavage of P-gp, was performed to localize the binding site of cyclosporine A (**23**) (Fig. **4B**). It has been described that the major binding site of cyclosporine A (**23**) occurs between the end of TM11 and the end of TM12 and amino acid residues 953-1007 are involved in binding [318, 320] (Fig. **4B**).

3.5. Aureobasidin A (AbA) (38)

The antifungal antibiotic aureobasidin A (AbA) (**38**) was found to be a more active P-gp inhibitor than cyclosporine A (**23**), also a cyclic compound. The replacement of the [Phe(3)-MePhe(4)-Pro(5)] tripeptide moiety by an 8-aminocaprylic acid or the *N*(7)-demethylation of MeVal(7) led to a 3.3-fold decreased capacity to inhibit P-gp function (Fig. **5**). The [2,3-dehydro-MeVal(9)] AbA derivative was the most potent P-gp inhibitory aureobasidin, described as being 13-fold more potent than AbA (**38**) and 19-fold more potent than cyclosporine A (**23**) [321].

3.6. Caffeine (45)

Various xanthines are naturally occurring compounds present in black coffee, black tea, green tea, and which have several biological activities. A xanthine derivative, caffeine (**45**), was described as a P-gp inhibitor [94, 95, 96]. Pentoxifylline (**46**), also a xanthine derivative, was found to reduce P-gp mediated MDR in the mouse leukemic cells. Long chain substituted xanthines may in fact act as P-gp modulators, although the mechanism of molecular action has not been clarified yet. One of the possible molecular mechanisms of action was hypothesized to be by direct competition with P-gp transport [97].

Structure-activity relationships allowed the discovery of more potent xanthinic P-gp inhibitors (Fig. **6**). For example, 1-methyl-3-propyl-7-butylxanthine showed great inhibitory activity of the doxorubicin efflux. In addition, it enhanced the antitumor activity of idarubicin with a reduction in the bone marrow suppression

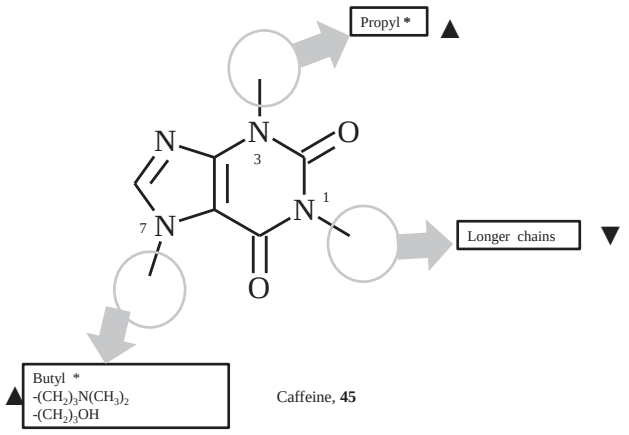
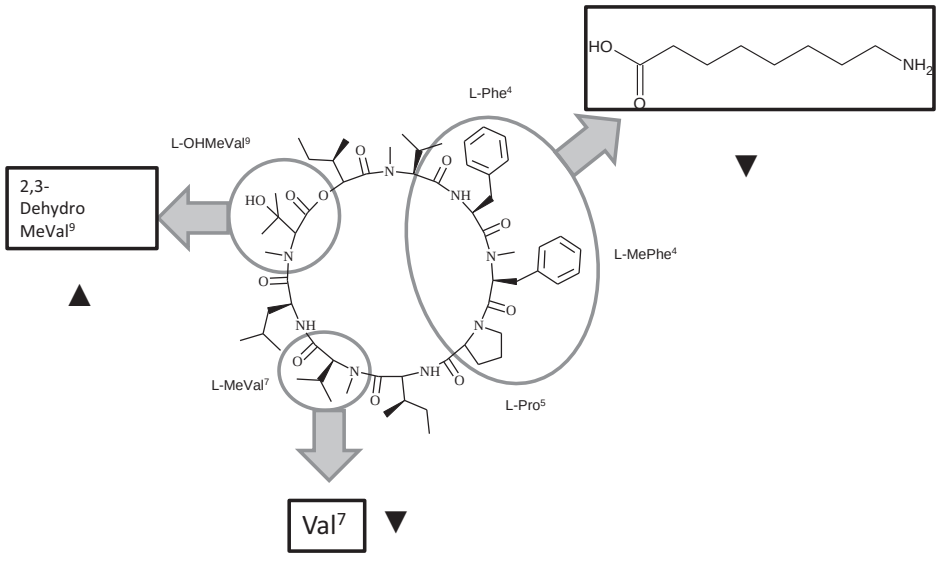


Fig. (6). Structure-activity relationship of caffeine (**45**). ▼= ↓ P-gp inhibition; ▲= ↑ P-gp inhibition; * = when together in the same molecule.

(secondary effect) induced by idarubicin [322]. It has been described that 1-substituted xanthines with longer chains facilitated the doxorubicin efflux from P388 resistant cells. In contrast, among 7-substituted xanthines, the *N*,*N*-dimethylethanamine and propanol substituted xanthines significantly inhibited the doxorubicin efflux from P388 resistant cells, possibly through their interaction with P-gp [323].

3.7. Others

P-gp modulation may be achieved not only by direct interaction with P-gp, but also by interference with its surrounding environment (the lipidic bilayer). For example, amiodarone (**17**) establishes strong interactions with phosphatidylserines. Its MDR-reversing ability is mediated through its interaction with the membrane phospholipids, changing membrane permeability and fluidity, or by changes in the conformation and functioning of the membrane-integrated proteins *via* changes in the structure organization of the surrounding membrane bilayer. Another possible mechanism of action of amiodarone (**17**) is the inhibition



Aureobasidin A, **38**

Fig. (5). Structure-activity relationship for aureobasidin A (**38**). ▼= ↓ P-gp inhibition; ▲= ↑ P-gp inhibition.

of P-gp phosphorylation *via* inhibition of the phosphatidylserine-dependent PKC [324]. Cefoperazone (**26**) and ceftriaxone (**27**) are effective modulators of P-gp and their ability to reverse P-gp is associated with lipid solubility, high protein binding, a polycyclic planar geometry, and the presence of the piperazine group in cefoperazone [72]. The anesthetics chloroform (**59**), benzyl alcohol (**60**), diethyl ether (**61**) and propofol (**62**) were described as modulators of P-gp-mediated MDR by acceleration of transbilayer movement of drugs by passive difusion. At higher concentrations than those required for modulation, the anesthetics accelerated the passive permeation to such an extent that it was not possible to estimate their P-gp activity [115]. Moreover, interaction with the phospholipid bilayer may justify the stereoselectivity observed with *trans*-flupentixol (**52**) [324]. Recent drug-membrane interaction and QSAR studies of thioxanthenes pointed to the importance of the stereoisomery for their MDR reversing activity. A molecular modeling study of *trans*- and *cis*-flupentixol showed that the electrostatic fields of the drugs have lipophilic and hydrophilic regions clearly separated in *trans*- when compared to *cis*-flupentixol. This result led to the hypothesis of a better fitting for *trans*- derivatives to the membrane due to the stronger interaction with phospholipids [325].

Other cellular mechanism may be involved in MDR reversal. Curcumin (**86**) was hypothised to contribute to the reversal of the MDR phenotype due to the suppression of P-gp expression *via* inhibition of the PI3K/Akt/NF-KB signaling pathway [326]. Trifluoperazine (**56**) also induced the downregulation of P-gp protein and mdr1b mRNA in a dose- and time-dependent manner in L1210/Adr resistant cells [327].

Not only the original drug, but also some of its metabolites, may inhibit P-gp. The major metabolite of curcumine (**86**), tetrahydrocurcumin, also inhibited P-gp [328].

Most of the first generation P-gp inhibitors lack selectivity (Table **1**, MRP and BCRP columns). Lapatinib (**70**) and erlotinib (**71**) reversed the drug efflux function of P-gp, BCRP [129] and also MRP-7 transporters [131]. Lonafarnib (**72**) was shown to inhibit the function of MRP-1 and MRP-2 with a potency similar to that of cyclosporin A (**23**) [133].

Besides improving cancer treatment, many of these P-gp inhibitors have applications to other diseases. For example, the inclusion of ritonavir (**44**) in combination regimens may greatly facilitate brain uptake of HIV protease inhibitors, which is especially important in patients suffering from AIDS dementia complex [91]. P-gp inhibitors may also potentiate the activity of antibiotics by inhibiting bacterial efflux (second generation timcodar, **102**).

One of the main issues of the first-generation P-gp inhibitors is the predominance of the original therapeutic activity of the drug. This happens not only with the well-known verapamil (**1**), whose calcium channel blocker properties potentiate the cardiotoxicity, but also, to a greater or lesser extent, with all the members of this generation. In fact, mifepristone (**78**) induces a much higher chemosensitization than the well-known verapamil (**1**), but its hormonal properties (progesterone receptor antagonist used as an abortifacient) limit its potential for clinical trials [141].

The impossibility of applying the majority of these compounds as P-gp inhibitors has been reflected from the results of phase I clinical trials (Table **4**): these drugs were eighter too toxic in their own right or not active enough and were therefore not further investigated. The only first generation P-gp inhibitors that today remain a "hope" amongst this class of compounds are tetrandrine (**12**) and tesmilifene (**65**), having proved in clinical trials to offer a major advantage in the treatment of poor risk AML and metastatic breast cancer, respectively. Tesmilifene (**65**) is a small molecule chemopotentiator under development by YM BioSciences and is described as a novel potentiator of chemotherapy which, when added to doxorubicin, achieved an unexpected and very large survival advantage. Tesmilifene (**65**) was proposed to allow chemotherapeutical drugs (e.g. anthracycline or taxane) to kill a small but critical population (clone) of aggressive, P-gp overexpressing, cells [329]. However, it is not selective for P-gp.

On the other hand, from the physiological perspective, P-gp is widely expressed in the epithelial cells of the intestine, liver and kidney, and in the endothelial cells of the brain and placenta. Despite the lack of success from this generation of P-gp inhibitors, since P-gp is widely expressed, having an important physiological role, the inhibition of this membrane transporter could have other implications related to drug absorption, distribution, metabolism, and excretion (ADME) [330]. Therefore, there remains a great need to identify not only whether an already existing drug has affinity for P-gp but also to understand the effects of P-gp on drug pharmacokinetics and pharmacodynamics, as well as efficacy and safety. In this context, our group has recently developed a pharmacophore-based screening strategy that allowed the identification of "old drugs", namely with an oxapine scaffold, that are able to inhibit P-gp function [30].

Considering the problems related to the first-generation MDR modulators, second-generation MDR modulators have been developed.

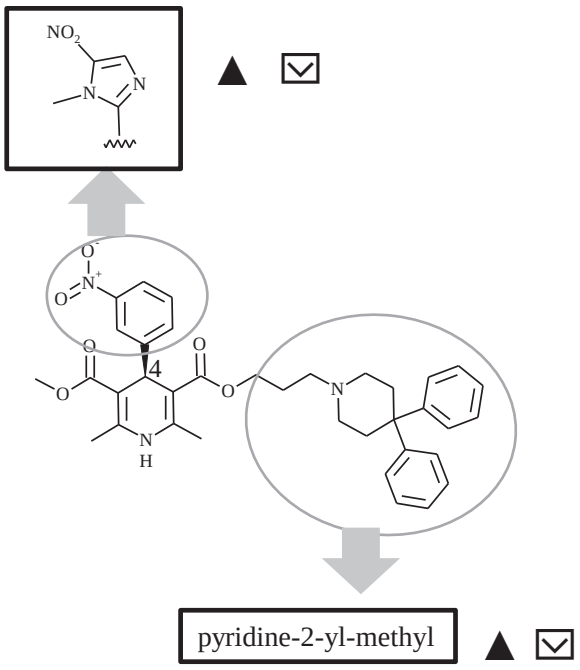
4. SECOND GENERATION P-GP INHIBITORS

On the basis of the experience with the first-generation compounds, the approach then followed was to identify analogues that were devoid of the pharmacological properties of the original molecule but could specifically inhibit P-gp, with less toxicity and greater potency [331]. Thus, the second generation of P-gp inhibitors includes derivatives of cardiovascular (**90**-**99**), imunossupressant (**100**-**102**), anticancer (**103**-**105**) and other drugs (**106**-**109**), and are represented on Table **2**.

Many of the second generation P-gp inhibitors resulted from the study of chiral drugs, through the resolution of racemic mixtures. Dexverapamil (**90**) is the *R*-enantiomer of verapamil (**1**). Dexverapamil (**90**) discovery was based on the toxicity profile and experimental potency of verapamil (**1**) [332].

The R-enantiomers of compounds with phenylalkylamine structures such as dexverapamil (**90**), and with dihydropyridine structures such as dexniguldipine (**94**), are widely described as P-gp modulators with less cardiac effects [33]. Although *R*- and *S*-enantiomers of these drugs differ markedly in their potency as calcium channel blockers, they were almost equally effective in reverting P-gp mediated drug resistance [33].

Dexniguldipine (**94**) is the *R*-enantiomer of niguldipine (**6**). Dexniguldipine (**94**) displays a 45-fold lower affinity for calcium channel binding sites than levoniguldipine, but is equally potent in inhibiting drug transport by P-gp and reversing drug resistance [33]. Studies with dexniguldipine (**94**) described that P-gp has at least two allosterically coupled drug acceptor sites: receptor site 1 which binds vinblastine, doxorubucin, etoposide and cyclosporin A (**23**), and receptor site 2 which binds dexniguldipine (**94**) and other 1,4-dihydropyridines [333]. Other study suggests that dexniguldipine (**94**) binds P-gp between residues 468-527, flanked by the Walker motifs A and B of the N-terminal ATP-binding cassette, suggesting that the mechanism of chemosensitization may be the direct interaction of dexniguldipine (**94**) with the NBD (Fig. **1A** and **B**) [334]. Furthermore, the dexniguldipine (**94**) structure-activity relationship (Fig. **7**) allowed the analysis of their Ca^{2+} channel and P-gp blocking activities and revealed a clear relationship with the moieties in C-4 and in C-3/5 positions. A 1-methyl-5-nitro-2-imidazole group in C-4, and a pyridine-2-yl-methyl directly bound to the acetate group in C-3 or in C-5 give rise to a compound with the strongest MDR reversing effect while its Ca^{2+} channel blocking



Dexniguldipine, **94**

Fig. (7). Structure-activity relationship of dexniguldipine (**94**). ▲= ↑ P-gp inhibition; ☑ = ↓ Ca^+ channel blocking.

activity was among the lowest and was only considered a side effect [335].

Other structural modifications on the first generation inhibitors are worth emphasizing in the development of second generation modulators. For example, MM36 (**91**) is a verapamil (**1**) analog with an anthracene group [155, 156]. KR-30031 (**92**) is a rigid analogue of verapamil (**1**) with a 2,3-dihydro-1*H*-indene group and an active modulator of MDR with potentially minimal cardiovascular toxicity [336]. RO44-5912 (**93**) is a phenethylamine and a tiapamil derivative structurally similar to verapamil (**1**) but with a 1,4-dithiane group. PAK-104P (**95**) is a niguldipine (**6**) analogue with a phosphate group and with more potent resistance-reversing ability than other calcium channel blockers, but it has lower calcium channel-blocking activity [160].

Dimerization was another strategy used to develop second generation modulators such as the quinine homodimer Q2 (**98**). Several homodimeric polyenes based on stipiamide (**107**) linked with polyethylene glycol ethers were also found to effectively inhibit P-gp function [337].

Molecular modifications by simplification were also used in the discovery of new members of this generation of P-gp inhibitors. SB-RA-31012 (**104**) is a taxane derivative reported to be active at 0.1 μM [338]. In contrast to the taxanes paclitaxel and docetaxel, which were shown to be substrates of P-gp (which limited theirefficacy), the synthetic taxane SB-RA-31012 (**104**) modulates P-gp without being cytotoxic (due to the removal of the tubulin-bindingside chain at the C-13 position of the taxane backbone). Biricodar (**101**) has been developed by Vertex Pharmaceuticals Inc (Cambridge, MA, U.S.A.) [339] and is a simplified analog of the immunosuppressive macrolactone tacrolimus (**24**) without immunosuppressive effects.

Valspodar or PSC-833 (**100**) was developed by Novartis and derives from cyclosporine A (**23**) due to a methylation in a lateral chain of an amino acid and an oxidation of an alcohol to a carbonyl. It is a nonimmunosuppressive cyclosporin analog which is a potent MDR modifier, 5- to 20-fold more potent than cyclosporine A (**23**) [340, 341]. The main problem associated with this compound is the interaction with the pharmacokinetics of the associate chemotherapeutic drugs, which resulted in an increase in the chemotherapeutic drug toxicity which in turn requires a reduction of its dose [342].

Some of the compounds from the second generation lack P-gp selectivity, as the compounds from the first generation. S9788 (**109**) is 1.5 to 30 times more active than verapamil (**1**) and 1.2 to 120 times more active than cyclosporine A (**23**) but was found to also inhibit BCRP [187, 188].

Several clinical trials have been performed since 1996 using valspodar (**100**) as a potential MDR reversing agent (Table **4**). However, it was found that valspodar (**100**) exerted a deleterious effect on the pharmacokinetics of co-administered anticancer drugs, including etoposide, doxorubicin, mitoxantrone or paclitaxel, which obliged a dose reduction of the anticancer drug of 30-50% [241, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353]. Despite the promising initial pre-clinical results provided by valspodar (**100**), the more recent clinical trials results (Table **4**) have confronted investigators and industry with the fact that new agents need to be explored and novel designs of clinical trials are required.

In conclusion, the second-generation of P-gp modulators have a better pharmacologic profile than the first-generation, but they also retain some characteristics that limit their use as P-gp modulators. In particular, these compounds significantly inhibit the metabolism and excretion of cytotoxic agents, thus leading to unacceptable toxicity which requires chemotherapy dose reductions. Several of the second-generation P-gp modulators, including valspodar (**100**) and biricodar (**101**), are substrates for cytochrome P450. Therefore, the competition between chemotherapeutic agents and these P-gp modulators for cytochrome P450 activity has given rise to unpredictable pharmacokinetic interactions [354]. Moreover, since the pharmacokinetic interactions between P-gp inhibitors and cytotoxic agents are unpredictable and cannot be determined in advance, reducing the dose of a cytotoxic agent may result in underdosing, thus limiting the use of these second-generation modulators in the treatment of MDR cancers [355]. Many second-generation modulators may also inhibit other transporters, particularly those of the ABC transporter family. This can lead to a decreased capacity of normal cells to extrude toxic compounds or xenobiotics in the liver, kidney, or gastrointestinal tract [356, 357]. The endothelial distribution of P-gp and other ABC transporters indicates that they are involved in physiological roles such as the regulation of the entry of certain molecules into the CNS and other anatomic compartments, such as the testis and placenta [358]. Therefore, the inhibition of transporters other than P-gp, for example, the ABC transporter BCRP, a functional regulator of hematopoietic stem cells, may lead to serious adverse effects including neutropenia and other myelotoxic effects [359]. In an effort to alleviate these problems, investigators and industry have started to focus on a new generation of P-gp inhibitors, the third generation.

5. THIRD GENERATION P-GP INHIBITORS

To overcome the limitations of the second generation P-gp modulators, a third-generation of P-gp inhibitors which specifically and potently inhibit P-gp has been developed by using quantitative structure-activity relationships (QSAR) and combinatorial chemistry [331]. This allowed the design of molecules with specific characteristics such as lipophilicity, positive charge at neutral pH

and with aromatic rings [245] (as explained in Section 1). The most studied third generation P-gp inhibitors are zosuquidar (**110**), elacridar (**111**), tariquidar (**112**), laniquidar (**113**), ontogen (**114**), DP7 (**115**), PGP-4008 (**116**) and CBT-1(**117**). Their described *in vitro/ in vivo* assays and clinical trials are summarized in Tables **3** and **4**, respectively.

Tariquidar (XR9576) (**112**) is an anthranilamide derivative and an example of a third generation P-gp inhibitor [360]. Tariquidar (**112**) had for long been described as a specific P-gp inhibitor. However, it is now accepted that tariquidar [204] (**112**) and elacridar [201] (**111**) also bind the BCRP transporter. Tariquidar (**112**) binds P-gp with a noncompetitive mechanism and with an affinity that greatly exceeds that of the transported substrates [361]. Tariquidar (**112**) inhibits the ATPase activity of P-gp; however, it is not clear whether the binding of tariquidar on P-gp is directed to the ATP binding site or to an allosteric location, thus indirectly blocking the P-gp catalytic cycle [202]. Tariquidar (**112**) is assumed to bind to the same binding site of P-gp as the P-gp substrate Hoechst 33342 [202, 362], located within the inner leaflet of the membrane [363, 364], and that combines both transport and regulatory functions [365]. The inhibitory effects of tariquidar (**112**) on P-gp greatly exceed those of first- and second-generation P-gp modulators with respect to potency and duration of action. In fact, in an *in vitro* study, the P-gp pump transport remained blocked for more than 22 hours after tariquidar had been removed from the culture medium; in the same assay, the clearance time for cyclosporine A (**23**) was only 1 hour [203]. It has been recently described that nanoparticles or liposomes delivering a combination of this P-gp modulator and an anticancer drug (paclitaxel) are a very promising approach to overcome tumor drug resistance [366, 367], which could be correlated with an increased accumulation of paclitaxel in tumor cells.

Several structure-activity studies of anthranilic derivatives have taken place in recent years, in an effort to understand important features for P-gp *versus* BCRP inhibition, with tariquidar (**112**) being an example (Fig. **8**). The most significant groups responsible for the pharmacological activity are described to be: i) the nitrogen atom (as an H bond acceptor group) in the condensed heteroaromatic quinoline ring system; ii) a hydrogen bond acceptor group such as a nitro or dimethylamine group or an electronegative atom like fluorine in the anthranilamide moiety, and iii) a hydrogen bond acceptor group in the tetrahydroisoquinoline moiety such as a methoxyl group [368, 369]. The active tetrahydroisoquinoline substructure appears as either unsubstituted (weak P-gp inhibitors) or 6,7-dimethoxysubstituted (more active P-gp inhibitors) and this substructure plays a role in the P-gp inhibitory effect [368]. Small structural changes at the benzamide core resulted in large shifts in activity and selectivity from P-gp towards BCRP [370]. By changing the amide-attached quinoline on tariquidar (**112**) from *ortho* to the *meta* position, generating a *meta*-benzamide core, the inhibitory activity against P-gp was greatly diminished, while it maintained its BCRP inhibitory activity [368]. Also, different aromatic substituents, such as 2-quinoxalinyl, 2-pyrazinyl, and 3-pyridyl and particularly 2-quinolinyl in position 2 of the benzamide ring, greatly increased selectivity against BCRP [368]. These results suggested that although sharing some general similarity, the structural requirements for binding of tariquidar (**112**) analogs to P-gp and BCRP differ, and this is probably related to differences in the topology and physicochemical properties of the protein binding sites [368].

Other third generation agents, such as zosuquidar (**110**) and laniquidar (**113**), are more specific for P-gp rather than for other ABC pumps, avoiding the risk of blockage of other transporters, which might result in altered bioavailability or excretion of the chemotherapeutic agents [203, 371]. Zosuquidar (**110**) was

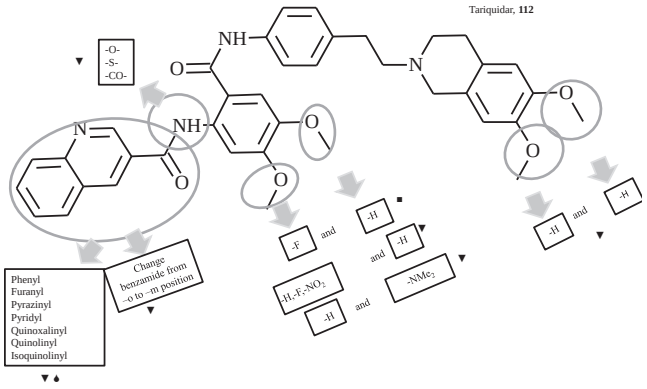


Fig. (8). Structure-activity relationship of tariquidar (**112**). ▼= ↓ P-gp inhibition; ■= ≈ P-gp inhibition; ♦= ↑ BCRP inhibitory activity.

developed by Eli Lilly and Company (Indianapolis, IN, U.S.A.) and is among the most potent modulators of P-gp known to date. In fact, it inhibits P-gp at nanomolar concentrations *in vitro* and *in vivo* [372, 373] and there is evidence that it is not an inhibitor of MRP or BCRP [193, 371]. The mechanism of action of zosuquidar (**110**) is still unclear but a noncompetitive inhibitory mechanism has been suggested since it is not a substrate and cannot be transported by P-gp [371].

The third generation P-gp inhibitors do not affect cytochrome P450 3A4 at relevant concentrations [374, 375]. Therefore, they generally do not alter the plasma pharmacokinetics of the simultaneously given antitumor agent, at least not to the extent verified with the previous generations, and consequently they do not need a chemotherapy dose reduction [203, 376]. Ontogen (**114**) was discovered *via* a high throughput cell-based screen for inhibitors, being developed from the optimization of a lead identified in a library of imidazole derivatives [377, 378] and reported to be a potent inhibitor of P-gp as well as being non toxic, causing little interference with the pharmacokinetic of other drugs as it is not a CYP3A4 substrate [379]. DP7 (**115**) also displayed weak inhibition of human CYP3A4 enzyme activity, suggesting that DP7 should not give rise to important, unpredictable pharmacokinetic interactions [380]. PGP-4008 (**116**) was identified by screening a library of synthetic compounds and has shown good systemic absorption and lack of interaction with the concomitantly administered chemotherapeutic agent [209].

In spite of all the progress that has been made in the field of multidrug resistance, namely with the discovery of the third generation MDR modulators (suggested to be more potent and more specific than their precursors) they are still far from being considered perfect MDR modulators capable of effectively and safely overcoming resistance in cancer cells.

The “wheel of Aquiles” of the third generation P-gp inhibitors was the unexpected toxic effects shown in clinical trials. For example, tariquidar (**112**) was tested on phase III clinical trials on non-small-cell lung cancer patients but had to be stopped due to high toxicity (Table **4**). Disapointing results were also obtained for zosuquidar (**110**), elacridar (**111**), laniquidar (**112**) and ontogen (**114**). However, clinical trials are still ongoing for verapamil, mibefradil and cyclosporine A from the first generation; valspodar, biricodar, timcodar and dofequidar from the second generation; and tariquidar, laniquidar and CBT-1 from the third generation (Table **4**, right column). Finally, CBT-1 (**117**) is an orally administered, bisbenzylisoquinoline alkyloid currently being developed as a P-gp inhibitor by CBA Research Inc and clinical results are promising although still preliminar.

6. NEW PERSPECTIVE: FORTH GENERATION?

Random and focused screening, systematic chemical modifications and combinatorial chemistry performed over the last three decades have given rise to the first three generations of P-gp inhibitors. However, most of those compounds did not reach the aim for which they were developed, due to several side effects and pharmacokinetic interations that limited their clinical use. Even the computational studies (namely based on docking studies, pharmacophore-based or QSAR-based screening) still have not led to any lead compound with *in vitro* and *in vivo* results that make them promising drug candidates. Therefore, new strategies to find P-gp inhibitors have been used by investigators, such as the "return" to natural products (NP) and NP mimics, peptidomimetics, surfactants and lipids, and dual ligands.

6.1. Natural Products (NP) and NP Mimics

As a result of the poor success of the three generations of P-gp inhibitors, many investigators have focused their attention on screening products of natural origin in order to find new potential P-gp inhibitors. The compounds obtained for the first time from natural sources and specifically tested for P-gp inhibition, are classified by some authors as belonging to the forth generation of P-gp inhibitors [374]. In fact, food components such as orange, grapefruit, and strawberry can interfere with the oral bioavailability of many drugs and these drug-food interactions may involve P-gp. The active components of food and plant extracts already identified were also exploited as lead compounds for chemical modifications to generate novel, selective, and high affinity P-gp inhibitors [381].

6.1.1. Flavonoids

Flavonoids are constituents of fruits and vegetables and have long been associated with a variety of biochemical and pharmacological properties, including antioxidative, antiviral, anticarcinogenic, and anti-inflammatory activities [382]. Several flavonoids are described as being able to interact with P-gp [382, 383, 384, 385, 386, 387], stimulating the P-gp-mediated efflux in tumor cells or inhibiting P-gp-mediated transport [388].

4',5,6,7,8-Pentamethoxyflavone (tangeretin, **118**), 3',4',5,6,7,8-hexamethoxyflavone (nobiletin, **119**), and 3,3',4',5,6,7,8-heptamethoxyflavone (HMF, **120**) (Fig. **9**) are methoxyflavones contained in orange juice and all have been shown to increase the steady-state accumulation of [^{3}H]vinblastine by Caco-2 cells in a concentration-dependent manner. Besides, none of these methoxyflavones inhibited CYP3A4. Methoxyflavones (**118**-**120**) enhanced vinblastine accumulation by specifically inhibiting drug efflux *via* P-gp as they increased steady-state [^{3}H]vinblastine accumulation by LLC-GA5-COL300 cells (a cell line transfected with human MDR1 cDNA) [389]. In another study, tangeretin (**118**) and nobiletin (**119**) were shown to inhibit P-gp function [390].

3',4',5,6,7-Pentamethoxyflavone (sinensetin, **121**) is a flavonoid extracted from citrus fruits. It reversed the resistance of P-gp-overexpressing AML-2/D100 to vincristine in a concentration-dependent manner. Chemosensitizing effect of sinensetin (**121**) was 10 and 18 fold higher than those of 3',4',5,7-tetramethoxyflavone and 3',4'-dimethoxy-3,7-dihydroxyflavone, respectively. This result suggested that the methoxylated pattern of substitution is more important than the hydoxylated counterpart. Sinensetin (**121**) showed high efficacy and low cytotoxicity [391].

A study using 3',4',7-trimethoxyflavone (TMF, **122**) combined with paclitaxel showed that apical transport loading of TMF (**122**) increased the paclitaxel sensitivity of paclitaxel-resistant SK-MES-1/PT4000 cells overexpressing P-gp on the basolateral side, sugesting that TMF, a low toxicity flavones, can be used as an enhancer of bioavailability of oral paclitaxel and as a P-gp inhibitor [392].

2',4'-Dihydroxy-6'-methoxy-3',5'-dimethylchalcone (DMC**,** **123**) isolated from the buds of *Cleistocalyx operculatus* potentiated the cytotoxicity of the chemotherapeutic agent doxorubicin to drug-resistant KB-A1 cells. At 5 μM, DMC decreased the doxorubicin IC_{50} on KB-A1 cells by 4-fold [393].

Baicalein (**124**), a flavone isolated from *Scutellariae baicalensis Georgi,* a skullcap native to North America was also shown to enhance the bioavailability of oral doxorubicin which could be due to the inhibition of both P-gp and the CYP3A subfamily in the intestine and/or liver [394] although other factors such as the induction of gene expression and activity of CYP3A4 and *mdr1* are also described [395].

Quercetin (**125**), a flavonol, is a plant-derived flavonoid found in fruits, vegetables, leaves and grains. Quercetin inhibits CYP3A4 enzyme activity in a concentration-dependent manner with a IC_{50} of

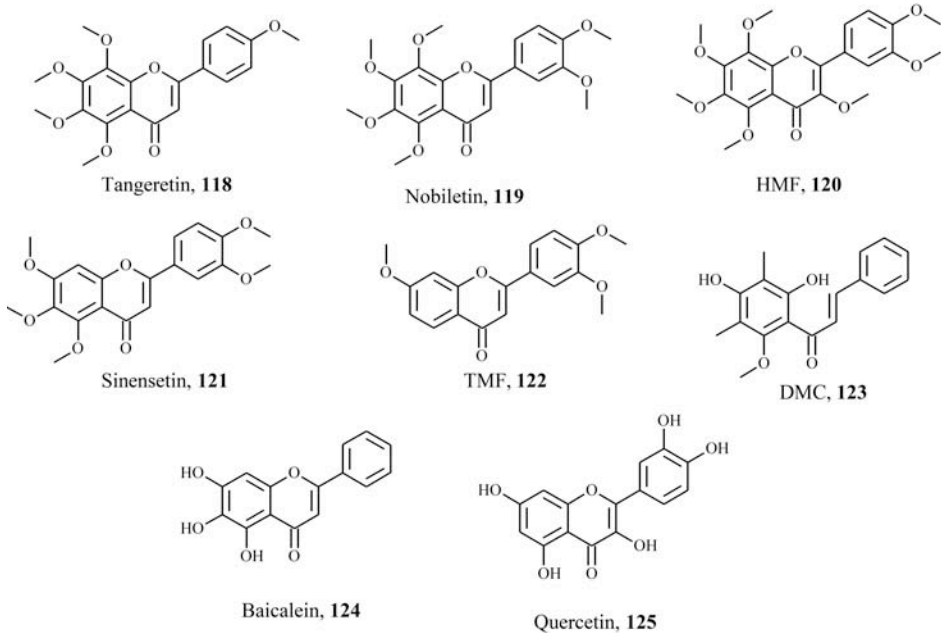


Fig. (9). Flavonoids as P-gp modulators (**118**-**125**).

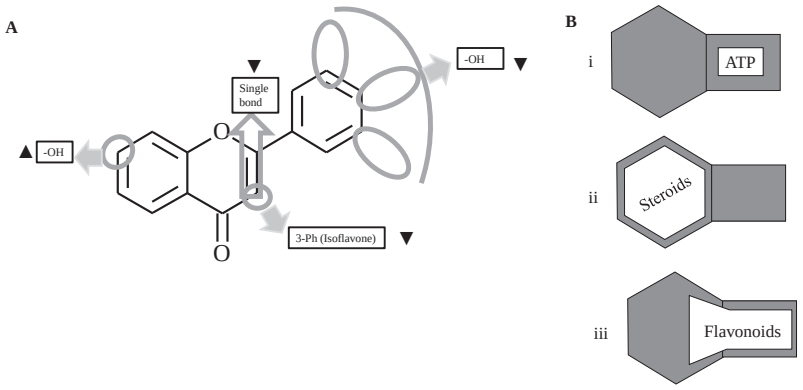


Fig. (10). A) Structure-activity relationship of flavones. ▼= ↓ P-gp inhibition; ▲= ↑ P-gp inhibition. **B**) Proposed schematic model of NBD showing the relative positions of different binding sides: i) ATP binding, ii) Steroid binding, iii) Flavonoid binding sites (adapted from [404]).

1.97 μM. In addition, quercetin significantly enhances the intracellular accumulation of rh123 in MCF-7/ADR cells overexpressing P-gp. Quercetin increases the bioavailability of oral doxorubicin, which can be attributed to enhanced doxorubicin absorption in the gastrointestinal tract *via* quercetin-induced inhibition of P-gp [396].

Structure-activity relationship for P-gp inhibition (Fig. **10A**) pointed to a specific role for the hydroxyl substitution pattern on the benzyl group. Structural units of B-ring-3'/5'-OH group, B-ring-4'-OH group, C3-ring (or isoflavones) negatively contributed to the modulation effect of flavonoids on P-gp activity, while the A-ring-7-OH group tended to enhance their inhibitory effects. Among them, the most unfavorable factor for regulating the inhibitory effect of flavonoids on P-gp function is the presence of a isoflavone scaffold [397]. From both doxorubicin sensitization assays and JC-1 accumulation experiments, these compounds can be suggested to act, at least in part, by inhibiting P-gp transport activity [398]. Lipophilic compounds containing several ring systems and a tertiary amine are good candidates for MDR modulation [399]. Hydrophobicity of both A/C and B rings plays an important role in the binding to flavonoid- and steroid-interacting binding pocket of P-gp [400]. The planar moiety of flavonoids seems to be important for their interaction with P-gp. Flavanones, which lack the double bond between the 2- and 3-position in the C ring, have a lower P-gp inhibitory activity than flavones. The double bond confers different torsion angles and a largely planar structure on flavone molecules so that they may more readily intercalate between the hydrophobic amino acid residues of P-gp [401]. Flavonoid chemosensitizers were found to bind to the ATP-binding site because of their structural similarity to the adenine moiety of ATP as demonstrated by crystallographic studies [402]. In addition, flavonoids display bifunctional interactions at the ATP-binding site and a vicinal steroid-interacting hydrophobic sequence [403] (Fig. **10B**).

6.1.2. Alkaloids

Pervilleine F (**126**) (Fig. **11**), a new tropane alkaloid aromatic ester obtained from a chloroform extract of the roots of *Erythroxylum pervillei*, was found to restore the vinblastine sensitivity of cultured multidrug-resistant KB-V1 cells, with an IC_{50} value of 0.40 μM. Pervilleine F was also able to partially reverse the cross-resistance of KB-V1 cells to anticancer agents such as actinomycin D (45.1-fold), mithramycin A (42-fold), paclitaxel (32-fold) and vincristine (74-fold) [405].

Ellipticine (**127**), an anticancer alkaloid isolated from *Ochrosia* sp, and its analogs were also found to be P-gp inhibitors [406].

6.1.3. Coumarins

Cnidiadin (**128**) (Fig. **11**) is a geranylated furocoumarin isolated from *Tetradium daniellii*. This is a cytotoxic agent capable of competitively inhibiting *in vitro* the binding and efflux of drugs by P-gp and enhancing the cell toxicity of vinca alkaloids in two cell lines (MDCK-MDR1 and mutant human carcinoma KB/VCR) overexpressing P-gp. It significantly accumulated rh123 and [^{3}H]-vimblastin and inhibited P-gp photolabelling in MDCK-MDR1 cells. However, due to its cell toxicity, clinical interest in cnidiadin (**128**) as a chemosensitizer appears to be limited [407].

Conferone (**129**) is a coumarin from *Ferula conocaula*. At 10 μM, it efficiently competes with a photoactivatable cyclosporin A analogue for binding to P-gp and accumulates [^{3}H]-vimblastine to a higher extent than cyclosporin A (**23**), supporting the hypothesis that conferone (**129**) sensitizes MDCK-MDR1 cells to vimblastine by competitively inhibiting drug efflux. Considering its high affinity for P-gp, conferone (**129**) may have an additional usefulness as a tool for the design or (hemi) synthesis of agents probing P-gp [408].

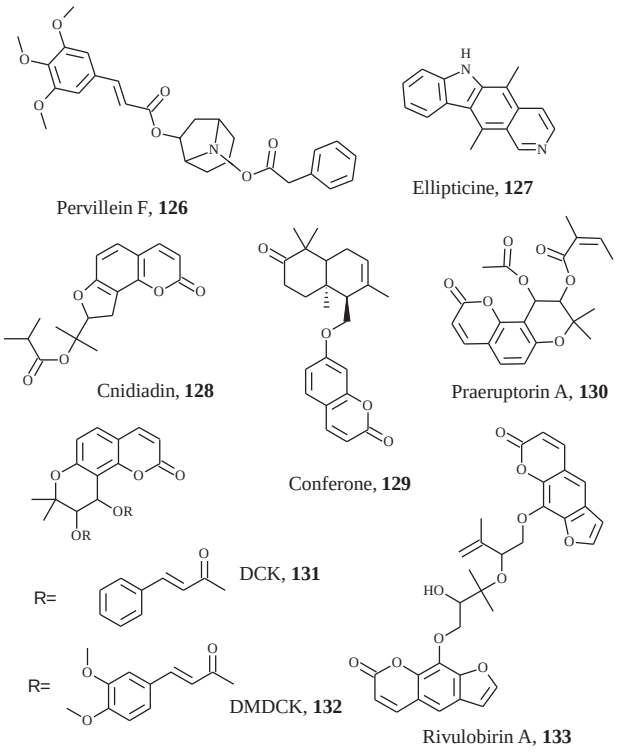


Fig. (11). Examples of P-gp modulators: alkaloids (**126** and **127**) and coumarins (**128**-**133**).

Praeruptorin A (**130**) is a naturally existing pyranocoumarin isolated from the dried root of *Peucedanum praeruptorum* Dunn and it is know to reverse P-gp-mediated MDR [409]. A praeruptorin A (**130**) derivative, (+/-)-3',4'-*O*-dicynnamoyl-*cis*-khellactone (DCK, **131**), was more potent than praeruptorin A (**130**) or verapamil (**1**) in reversing the P-gp-MDR effect. DCK (**131**) increased cellular accumulation of doxorubicin without affecting the expression level of P-gp in P-gp-MDR cells. It inhibited P-gp-ATPase and decreased the reactivity of the P-gp-specific antibody UIC2, suggesting a noncompetitive mode of inhibition [409]. Another praeruptorin A derivative, (+/-)-3',4'-bis(3,4-dimethoxy-cinnamoyl)-*cis*-khellactone (DMDCK, **132**) was able to totally inhibit P-gp ATPase activity using Pgp-enriched membrane vesicles. In fact, the co-existence of 3- and 4-methoxyl groups on cinnamoyl remarkably enhanced the P-gp-inhibitory activity. These additional methoxyl groups may allow DMDCK (**132**) to interact more efficiently with P-gp [410].

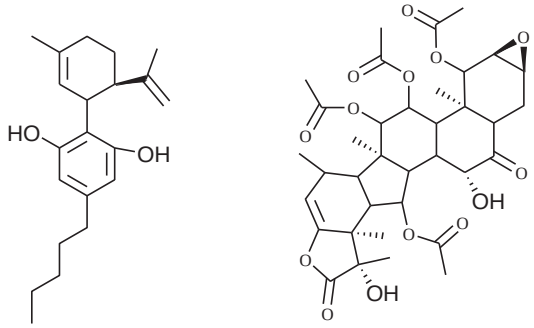
Furanocoumarins extracted from plants from Umbelliferae family strongly inhibit P-gp and CYP3A4. Kampo, a tradicional japonese medicinal extract, contains herbal compounds belonging to the Umbelliferae family, and will consequently posess furanocoumarins such as rivulobirin A (**133**) that may cause a drug-drug interaction with P-gp or CYP3A4 substrates [411] .

6.1.4. Cannabidiois

Cannabinoids are used therapeutically for the palliation of the adverse side effects associated with cancer chemotherapy. However, cannabinoids also inhibit both the *in vitro* activity and expression of P-gp. Cannabidiol (**134**) (Fig. **12**), one of the major marijuana constituents, significantly inhibits P-gp-mediated drug transport by a noncompetitive mechanism, suggesting that cannabidiol could potentially influence the absorption and disposition of other coadministered compounds that are P-gp substrates [412]. Cannabinoids also reverse MDR in CEM/VLB cells by decreasing P-gp expression [412]. Cannabinoid inhibition of MRP1 was confirmed using insect cell membrane MRP1 ATPase assays with a rank order of potency: cannabidiol>cannabinol>δ_9-tetrahydrocannabinol [413]. Cannabinoids are also BCRP inhibitors, reversing the BCRP-mediated multidrug-resistant phenotype *in vitro* [414]. Therefore, these compounds lack selectivity as they seem to be targeting several ABC transporters [414].

6.1.5. Taccalonolides

The taccalonolides are a class of microtubule-stabilizing agents isolated from *Tacca chantrieri*, structurally distinct from taxanes. Taccalonolides A (**135**) (Fig. **12**), E, B, and N were effective *in vitro* against cell lines that overexpress P-gp and MRP7. In addition, taccalonolides A and E were highly active against a



Cannabidiol, **134** Taccalonolides A, **135**

Fig. (12). Examples of P-gp modulators: cannabidiol (**134**) and taccalonolide A (**135**).

doxorubicin- and paclitaxel-resistant P-gp-expressing tumor, Mam17/ADR [415, 416].

6.1.6. Diterpenes

The taxanes are diterpenes produced by plants of the genus *Taxus*. Taxanes have been used to produce various chemotherapeutic drugs. The principal mechanism of action of the taxane class of drugs is the disruption of microtubule function [417]. It has long been reported that natural taxane diterpenes isolated from the japanese yew tree, *Taxus cuspidata*, could increase the cellular accumulation of vincristine in MDR tumor cells to the same extent as verapamil (**1**) [418].

The tetracyclic diterpene moiety of taxol, 10-deacetylbaccatin III (10-DAB**, 136**), is readily available from the renewable leaves of *Taxus baccata*. 10-DAB (**136**) (Fig. **13**) can be extracted from the leaves of this tree in high yields. Based on the 10-DAB skeleton, positions C-7 and C-13 were modified. Hydroxyl or acetyl groups at C-13 originate noncytotoxic compounds (not able to block microtubule depolymerization) with P-gp inhibitory activity. Several taxane derivatives were shown to have high level of MDR reversing activity (superior to 90%). In fact, the modification of C-7 position makes it suitable for strong MDR reversal activity (Fig. **13**). The type of substituent on C-7, namely aromaticity and length, was the determining factor for the MDR reversal activity [419]. The new noncytotoxic synthetic taxane derivatives that modulate efflux and cytotoxicity of substrate drugs in multidrug resistant cell lines overexpressing P-gp, MRP-1, and BCRP were discovered by these structure-activity studies [420].

Another series of taxane derivatives based on baccatin III (**137**) (Fig. **14**) were studied for their MDR reversal and cytotoxic potential. Baccatin III derivatives with either a C-13-hydroxyl group or C-13-acetyl group showed potent MDR reversing activities but the compound with a cetone group in C13 was shown to be more cytotoxic [421].

Taxuyunnanine-C (**138**) derivatives with 14-acyloxy substituents are a group of taxane-based MDR reversal agents isolated from callus cultures of *Taxus* species. The most effective compound has a cinnamoyloxy group at C-14. It was efficient at increasing the cellular accumulation of vincristine in MDR 2780AD cells, and it enchanced the intracellular concentration of taxol, adriamycin, and vincristine to the same extent as verapamil (**1**) in MDR 2780AD cells. However, these compounds were also cytotoxic. Other substitutions, such as an hydroxyl at C10 and an acetyl group at C5 and C14, or acetyl at C10 and C14 and hydroxyl at C5, led to MDR modulators lacking cytotoxic activity [422].

A novel class of potent P-gp inhibitors is the lathyrane-type diterpenoids from *Euphorbia lagascae*, for example jolkinol B (**139**) (Fig. **15**), which exhibited an efficacy higher than that of verapamil (**1**). These are MDR modulators as well as anticancer agents with apoptosis inducing properties [423].

The discovery of macrocyclic jatrophane diterpenes, characteristic of the *Euphorbia* species as potent inhibitors of P-gp has led to an increasing interest in researching this new class of compounds [424]. Some examples of these compounds are euphoportlandols A (**140**) and B (**141**) [425].

Euphodendroidin D (**142**) is a jatrophane polyester isolated from the Mediterranean sponge *Euphorbia dendroides* L. showing relevant P-gp inhibitory activity, outperforming cyclosporin A (**23**) by a factor of 2 to inhibit P-gp-mediated daunomycin transport. A SAR study revealed that lipophilicity and substitution pattern at positions 2, 3, and 5 are important for activity [426]. Pepluanin A (**143**) is a jatrophane isolated from *Euphorbia peplus* L., amongst others from the same class, with a P-gp inhibitory activity superior to that of cyclosporine A (**23**). Substitutions on the medium-sized ring (C 8, 9, 14, and 15) are important for activity. Activity is blocked by the presence of a free hydroxyl at C-8, and increased by

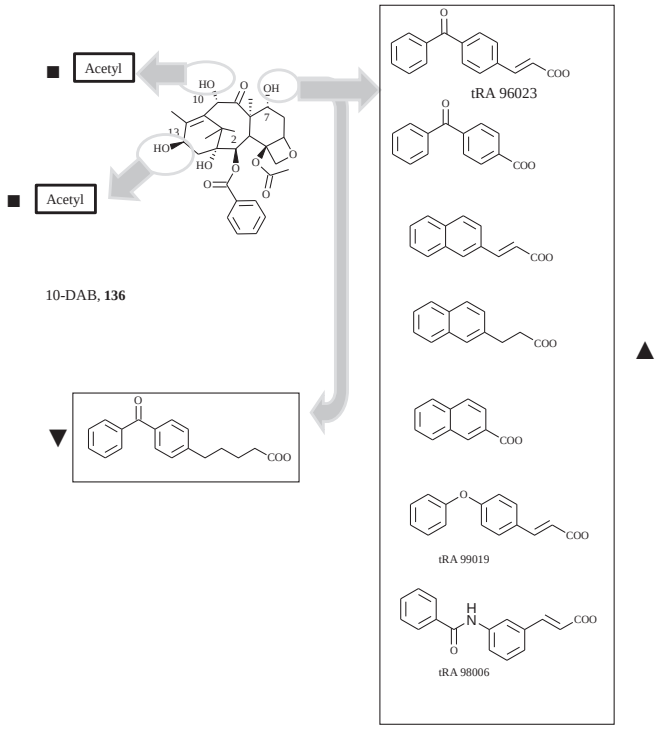


Fig. (13). Structure-activity relationship of 10-DAB (**136**). ▼= ↓ P-gp inhibition; ▲= ↑ P-gp inhibition; ■= ≈ P-gp inhibition.

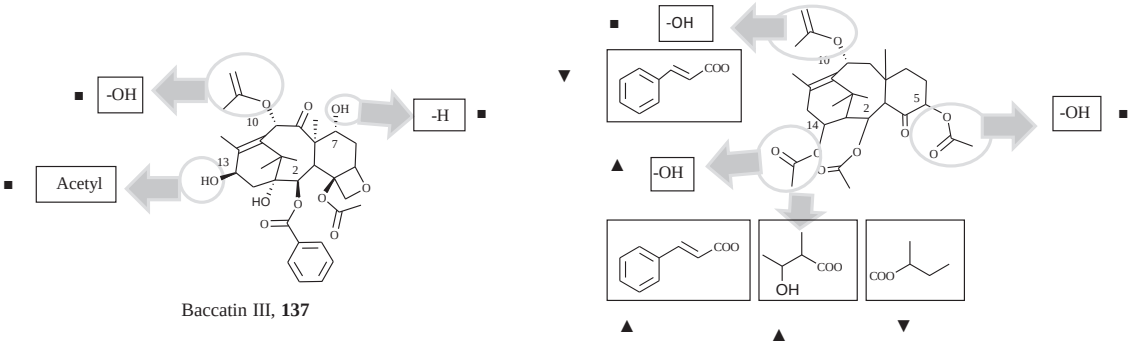


Fig. (14). Structure-activity relationship of baccatin III (**137**) (left) and taxuyunnanine-C (**138**) (right). ▼= ↓ P-gp inhibition; ▲= ↑ P-gp inhibition; ■= ≈ P-gp inhibition.

a carbonyl at C-14, an acetoxyl at C-9, and a free hydroxyl at C-15 [427]. Also, diterpenoid terracinolides from *Euphorbia dendroides L*. and euphocharacins from the mediterranean sponge *Euphorbia characias* L. [428] were discovered as being P-gp inhibitors [429].

A new abietane quinoid diterpene 16-hydroxy-abieta-8,12-diene-11,14-dione, named portlanquinol (**144**) isolated from *Euphorbia portlandica* was found to be both cytotoxic and an inhibitor of P-gp [430].

6.1.7. Sesquiterpenes

Sesquiterpenes from the *Celastraceae* family are natural compounds shown to reverse MDR in several human cancer cell lines. Moreover, they specifically inhibited drug transport activity of P-gp in a saturable, concentration-dependent manner but not that of MRP1, MRP2, and BCRP transporters [431]. There are at least two different sesquiterpene binding sites within the transmembrane domains (TMD) of P-gp: a high- and a low-affinity binding site, related in a complex allosteric manner with other drug-binding sites of the P-gp multidrug-binding pocket, which may explain the differing potential for P-gp inhibition of the different sesquiterpenes [431]. In general, the important trends of agarofuran sesquiterpenes for high P-gp inhibitory activity are the overall esterification level of the compounds, the presence of at least two aromatic-ester moieties (such as benzoate-nicotinate or benzoate-benzoate), and the size of the molecule. Sesquiterpenes tetra- or penta-substituted showed the highest potency, whereas additional esters in the molecule led to inactive compounds (Fig. **16A**). The presence of a basic tertiary nitrogen atom was shown to be non-essential for P-gp inhibition [432]. The non-substituted compounds at C-8 are less active than those with an ester group in such a position. In addition, the presence of a hydroxyl group at C-2 produced a decrease in activity [433] (Fig. **16A**). A new series of dihydro-β-agarofuran sesquiterpenes based on the celorbicol skeleton was isolated from leaves of *Celastrus vulcanicola*. The isolated compounds exhibited *in vitro* activity as inhibitors of P-gp. The most active compounds have the polyhydroxylated skeleton of dihydroxycelorbicol (**145**) and hydroxycelorbicol (**146**) (Fig. **16B**).

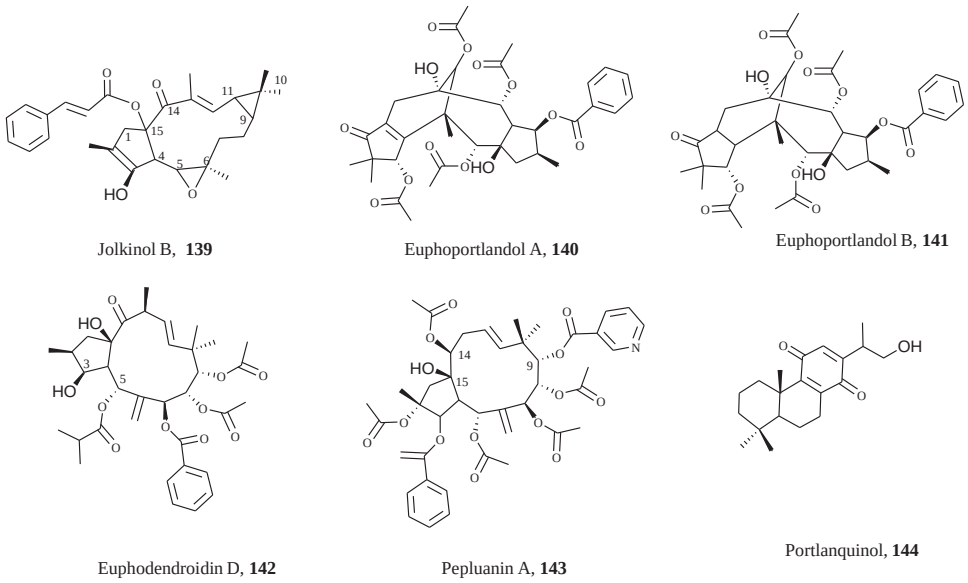


Fig. (15). Examples of P-gp modulators: diterpenes (**139**-**144**).

Sesquiterpenes did not seem to be inactivated by intracellular metabolism as they have a long intracellular half-life, and therefore they may be implied in the inhibition of P-gp for a long time both at the plasma membrane and in intracellular compartments. This may be important since P-gp is involved in other phenomenus other than MDR, such as apoptosis [434, 435, 436].

6.1.8. Triterpenes

Cycloartanes (9,19-cyclopropyltriterpenes), a class of tetracyclic triterpenes, from *Euphorbia* species were discovered as potential MDR reversing agents. However, some of the compounds were cytotoxic due to moderate induction of apoptosis [437].

Alisol B 23-acetate (ABA, **147**) (Fig. **17**) from *Alismatis orientale*, a triterpene compound with a steroid-like structure, restored the activity of vinblastine, a P-gp substrate. It stimulated ATPase activity of P-gp in a concentration-dependent manner, suggesting that ABA (**147**) could be a substrate for P-gp [438].

Several triterpenes extracted from *Betula platyphylla* were shown to increase rh123 accumulation in KB-C2 cells, and inhibited efflux of rh123 out of cells. The mechanism of action was shown to be diverse, weither by a noncompetitive or competitive inhibition of the pump [439].

Triterpenoids possessing different skeletons were isolated from the red sea sponge *Siphonochalina siphonella*. One of these, sipholenol A (**148**) (Fig. **17**), was found to be the most potent in reversing P-gp mediated MDR, increasing the sensitivity of resistant KB-C2 cells by a factor of 16 towards colchicines, and being itself nontoxic [440], inhibiting P-gp by a competitive mechanism of action [441].

Also, new sipholane triterpenoids from the red sea sponge *Callyspongia* (=Siphonochalina) *siphonella*, namely Sipholenone E

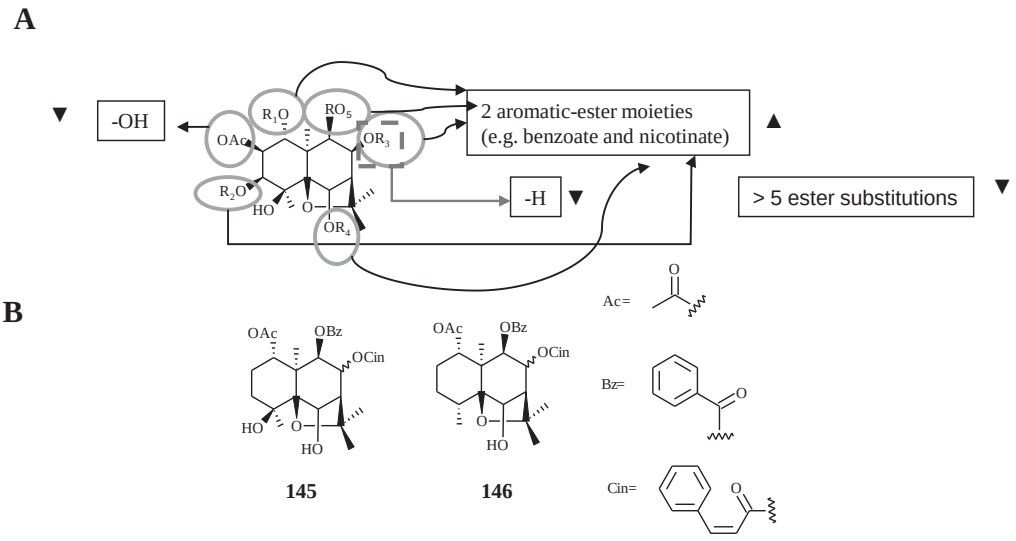


Fig. (16). **A**) Agarofuran sesquiterpene structure-activity relationship. **B**) Example of sesquiterpene that inhibit P-gp (**145** and **146**). ▼= ↓ P-gp inhibition; ▲= ↑ P-gp inhibition.

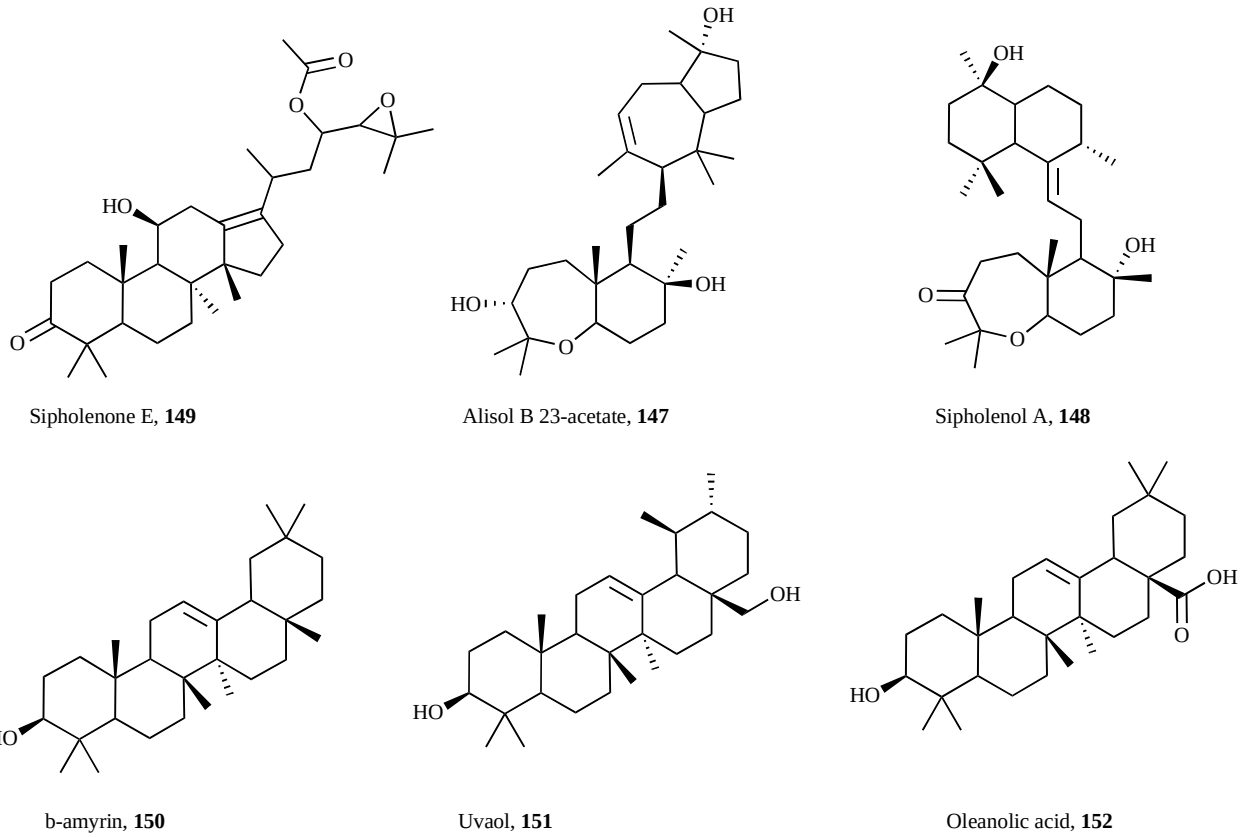


Fig. (17). Examples of P-gp modulators: triterpenes (**147**-**152**).

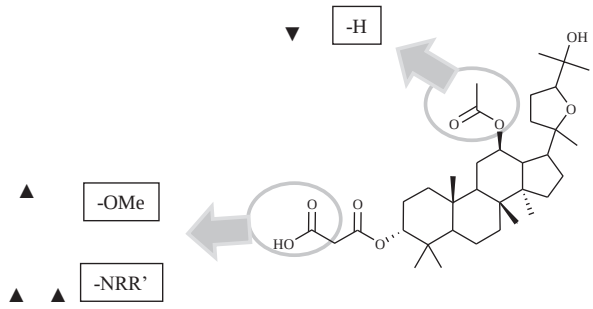


Fig. (18). Structure-activity relationship of papyriferic acid (**153**). ▼= ↓ P-gp inhibition; ▲= ↑ P-gp inhibition; ▲▲= ↑↑ P-gp inhibition. NRR' represents an amine, such as $N(CH_3)_2$, $NHCH_3$, NHC_2H_5, or morfoline group.

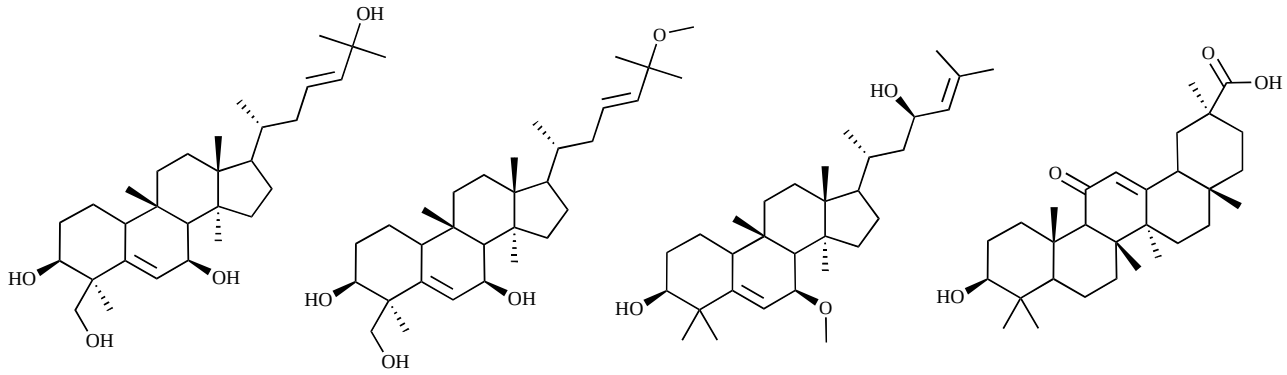
(**149**) (Fig. **17**), were able to reverse P-gp-mediated multidrug resistance in human epidermoid cancer cells [442].

Several triterpenes such as β-amyrin (**150**), uvaol (**151**), and oleanolic acid (**152**) (Fig. **17**) were extracted from *Carpobrotus edulis*, *a* creeping, mat-forming succulent species, and were found to reverse MDR in the mouse lymphoma cell line, with uvaol (**151**) being the most effective compound [443].

Derivatives of these triterpenic compounds, namely papyriferic acid (**153**) (Fig. **18**), were obtained from *Betula dahurica* ('Maurice Foster') and reversed P-gp-mediated MDR on KB-C2 cells. Among the alkyl papyriferate derivatives, methyl papyriferate (with a 3-*O*-methylmalonyl group) showed high capacity to enhance the cytotoxicity of colchicines. The enhancement of the cytotoxicity was decreased according to the chain length of the alkyl group. Removal of the 12-acetoxy group of the alkyl papyriferate derivatives reduced their MDR reversal effect. The amide derivatives of papyriferic acid, especially 3-(morpholino-β-oxopropanoyl) derivative, demonstrated more potent activity, increasing the sensitivity of colchicine against KB-C2 cells 185-fold, and thus the cytotoxicity of colchicine was recovered to almost that of sensitive cells [444].

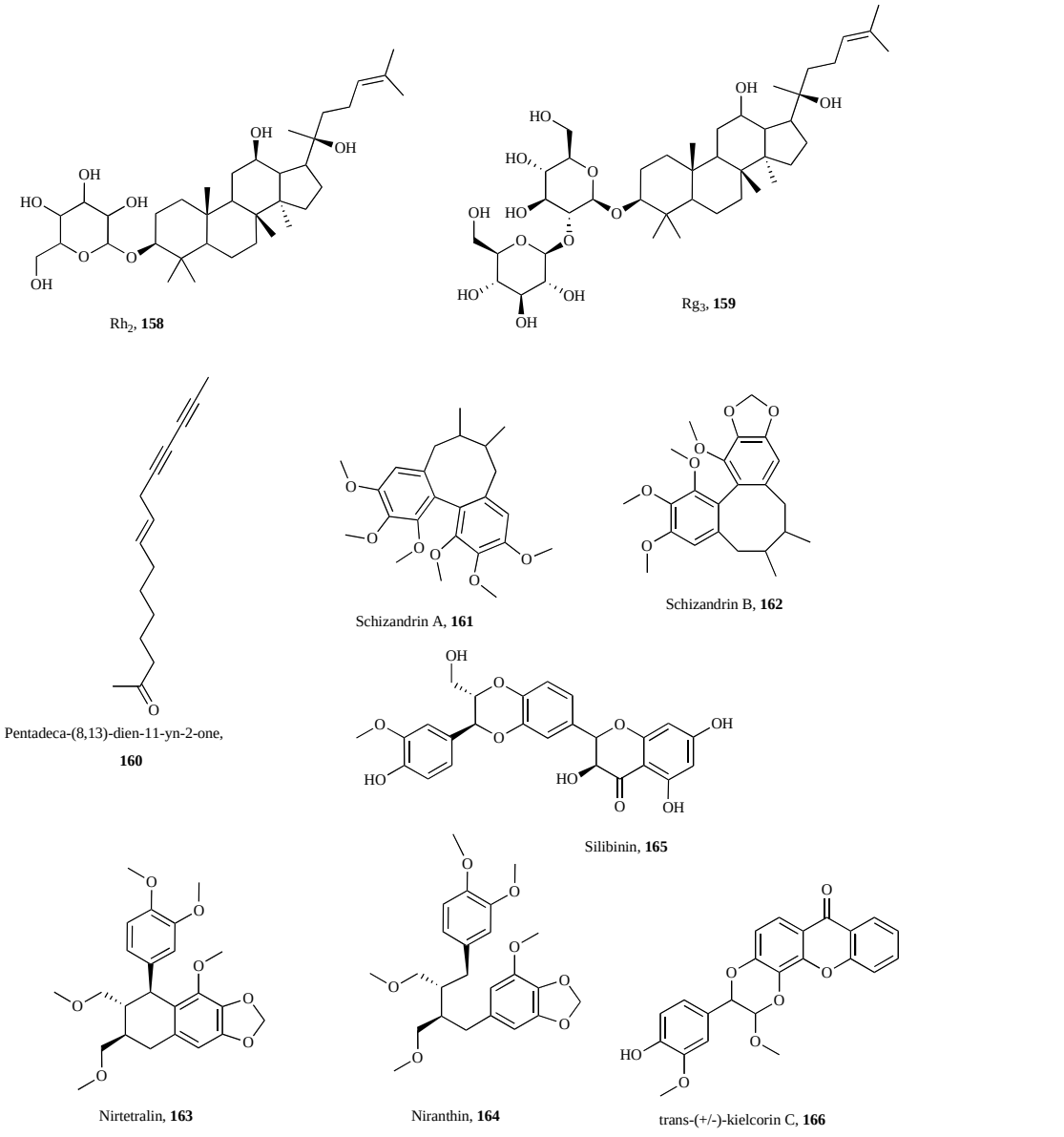
Four taraxastane-type triterpenes, 21-α-hydroxytaraxasterol, 21-α-hydroxytaraxasterol acetate, 3α,30-dihydroxy-20(21)-taraxastene and 3β-hydroxy-20-taraxasten-30-al, isolated from *Euphorbia lagascae* and *Euphorbia tuckeyana* exhibited a significant P-gp modulation activity [445].

Novel cucurbitane-type triterpenes, balsaminagenin A (**154**) and balsaminoside B (**155**), as well as the known cucurbitacin karavelagenin C (**156**) (Fig. **19**), isolated from the aerial parts of *Momordica balsamina L.* (balsam apple), reversed MDR activity on



Balsaminagenin A, **154** Balsaminagenin B, **155** Karavelagenin C, **156** Glycyrrhetinic acid, **157**

Fig. (19). Examples of P-gp modulators: triterpenes (**154**-**157**).



Rh_2, **158** Rg_3, **159**

Schizandrin A, **161** Schizandrin B, **162**

Pentadeca-(8,13)-dien-11-yn-2-one, **160**

Silibinin, **165**

Nirtetralin, **163** Niranthin, **164** trans-(+/-)-kielcorin C, **166**

Fig. (20). Examples of P-gp modulators: gingenosides (**158** and **159**), polyenes (**160**) and lignans (**161**-**166**).

mouse lymphoma cells transfected with human mdr1 gene in a similar way to verapamil (**1**) [446].

Dietary phytochemicals, such as glycyrrhetinic acid (**157**) (Fig. **19**), found in the root of *Glycyrrhiza glabra*, have dual inhibitory effects on P-gp and MRP1, with noncompetitive and competitive mechanisms of action having been suggested for those transporters, respectively [447].

6.1.9. Ginsenosides

Ginsenosides are among the active ingredients of ginseng, the root of which has been used in traditional herbal remedies in Eastern Asia for more than 2000 years and which has recently attracted attention worldwide. 20*S*-Ginsenoside (Rh_2, **158**) (Fig. **20**) could synergistically enhance the anticancer effects of conventional chemotherapeutic agents at a nontoxic dose. Unlike P-gp substrates, Rh_2 (**158**) inhibited both basal and verapamil-stimulated P-gp ATPase activities. Rh_2 (**158**) was shown to be a potent noncompetitive P-gp inhibitor, which indicates a potential herb-drug interaction when Rh_2 (**158**) is coadministered with P-gp substrate drugs [448]. However, Rh_2 (**158**) lacks selectivity, as it is also described as a BCRP inhibitor [449]. Nonetheless, ginsenoside Rh_2 (**158**) exhibited potent cytotoxicities against several cancer cells [450].

Recently, ginsenosides Rg_1, Re, Rc, and Rd were found to have a moderate inhibitory effect on P-gp in MDR mouse lymphoma, and increased rh123 accumulation. Of several ginseng components, 20*S*-ginsenoside Rg_3 (**159**) (Fig. **20**), so far found only in red ginseng, was shown to have the most potent MDR inhibitory activity on resistant human fibroblast carcinoma cells, KBV20C [451].

6.1.10. Polyenes

Polyenes are poly-unsaturated organic compounds that contain one or more sequences of alternating double and single carbon-carbon bonds [452]. Polyenes and polyacetylenes isolated from *Echinacea pallida* roots were found to be capable of reducing P-gp activity. Pentadeca-(8,13)-dien-11-yn-2-one (**160**) (Fig. **20**) was found to be the most efficient compound [453].

6.1.11. Lignans

Schizandins are derivatives of the dibenzo-[a,c]-cyclooctene lignan and may be extracted from Schisandra fruits (*Schisandraceae chinensis*). Schisandrin A (**161**) (Fig. **20**) reversed drug resistance in KBv200 cells, MCF-7/Dox cells and Bel7402 cells by factors of 309, 38, and 84, respectively, being the most potent derivative of this species [454]. *Schisandra sphenanthera* extract, which contain Schisantherin A, enhanced apical-to-basal drug-transport and decreased basal-to-apical drug-transport in the Caco-2 cell line, suggesting they could potentially increase the absorption of drugs that can act as a P-gp substrate [455]. Also, schisandrin B (**162**) (Fig. **20**), another compound from the same fruit, is also a strong inhibitor of P-gp, fully restoring the intracellular drug accumulation on four MDR cell lines with P-gp overexpression [456]. However, dibenzocyclooctadiene lignans (schisandrin A, schisandrin B, schisantherin A, schisandrol A, and schisandrol B) are not selective for P-gp, as they were also described as MRP1 inhibitors [457], and therefore proving to be dual inhibitors [458].

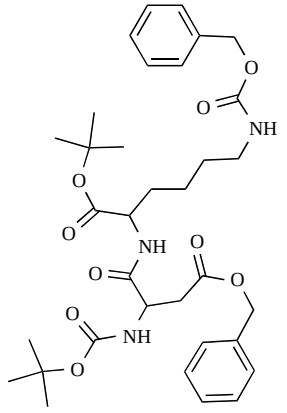
Lignans isolated from *Phyllantus amarus* were also identified as potential MDR modulating agents. Nirtetralin (**163**) and niranthin (**164**) (Fig. **20**) were found as the most potent derivatives. Concomitant incubation with the anticancer agent daunorubicin led to a reduction in cell viability of about 60% [459].

Silibinin (**165**) (Fig. **20**), also known as silybin, is the major active constituent of silymarin, the mixture of flavonolignans extracted from *Silybum marianum*. Silibinin is an inhibitor of P-gp-mediated efflux transporters and its oxidative metabolism is catalyzed by CYP3A4 [460].

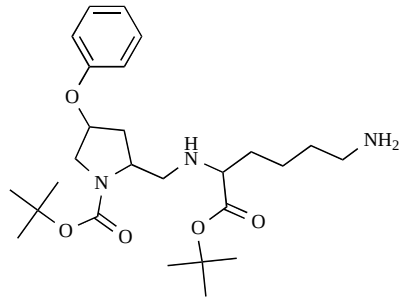
Xanthonolignoid *trans*-(+/-)-kielcorin C (**166**) (Fig. **20**), previously described as a protein kinase C inhibitor [461], was found to be also a competitive P-gp inhibitor [462].

6.2. Peptidomimetics

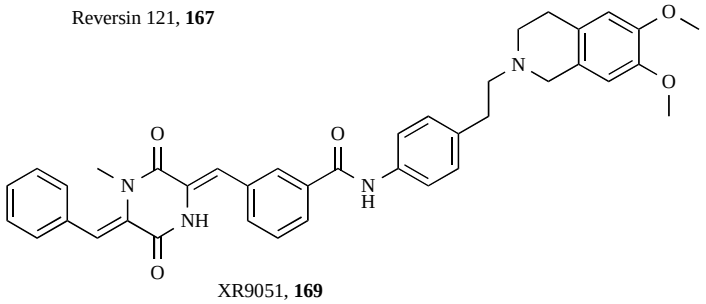
Among the known P-gp inhibitors, peptides are scarce but represent some good candidates of the forth generation of P-gp inhibitors. Valspodar (**100**), a cyclosporine A (**23**) derivative, is the best representative of compounds that have ultimately reached phase III clinical trials but were stopped because of



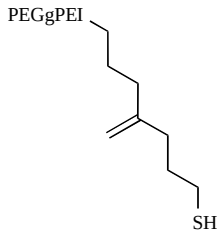
Reversin 121, **167**



Peptide 15, **168**



XR9051, **169**



Thiolated PEG-*g*-PEI co-polymer , **170**

Fig. (21). Examples of P-gp modulators: peptidomimetics (**167**-**169**) and surfactants (**170**). PEG = poly(ethylene glycol); PEI = polyethylenimine.

pharmacokinetic interactions with anticancer drugs and lack of specificity [463].

Short peptide P-gp inhibitors called reversins are di- and tripeptide derivatives sharing common physicochemical and structural features such as bulky aromatic and/or alkyl groups. Among them, reversin 121 (**167**) (Fig. **21**) is an aspartyllysine (Asp-Lys) dipeptide derivative displaying good affinity and specificity for P-gp [464]. Beneficial effects of high-affinity peptide reverin 121 (**167**) on reversing chemotherapy-induced MDR were demonstrated in pancreatic cancer in a mouse model. The addition of reversin 121 (**167**) to chemotherapeutic regimens significantly reduced the proportions of tumor cells [465].

Peptide 15 (**168**) (Fig. **21**) is a compound with high affinity and specificity for P-gp, having limited or no activity on MRP and BCRP. Besides, it has no cytotoxicity up to 10-fold its P-gp inhibitory activity $IC_{50.}$ It equally inhibited the Hoechst 33342 and daunorubicin effluxes through a typical noncompetitive inhibition mechanism, suggesting it binds to a site different from the H and R drug-transport sites [466].

XR9051 (**169**) (Fig. **21**) is a diketopiperazine (lactam ring formed by peptide bonds stablished between two amino acids) which was identified as a potent modulator of P-gp-MDR following a synthetic chemistry programme based on a *Streptomyces* product lead compound. It was found to be more potent than cyclosporin A (**23**) and verapamil (**1**) in inhibiting P-gp (EC_{50} = 1.4 nM) [467]. It inhibited the efflux of [^{3}H]daunorubicin from preloaded cells and, unlike cyclosporine A (**23**) and verapamil (**1**), remained active for several hours after removal of the resistance-modifying agent [467]. XR9051 (**169**) is rapidly distributed and accumulates in tumors and other tissues. Besides, the compound is well-absorbed after oral administration [468].

The discovery of peptide inhibitors of P-gp based on the structure of the transmembrane domains of the transporter has been a new nontoxic approach for the design of P-gp inhibitors. These peptides are thought to exert their inhibitory action by disrupting the proper assembly of P-gp. A 25-residue long retroinverse D-analogue of transmembrane domain 5 inhibited the efflux of the fluorescent P-gp substrate with an IC_{50} of 500 nM. Transmembrane peptides effectively sensitized resistant cancer cells to doxorubicin *in vitro* without demonstrating any cell toxicity of their own [469].

6.3. Surfactants and Lipids

Among the several established inhibitors of P-gp, there are a variety of surface-active agents potentially capable of accelerating drug transmembranar movement. In fact, surfactants such as Pluronic P85, Tween-20, Triton X-100 and Cremophor EL can modulate MDR by inhibition of the P-gp-mediated efflux, with no appreciable effect on transbilayer movement of drugs. Therefore, surfactants demonstrate a transporter-specific interaction rather than unspecific membrane permeabilization [115]. The drug sensitivity of K562/MDR cells to vincristine can be completely restored by Cremophor EL [470]. Poly(ethylene glycol)-300 (PEG-300) causes almost complete inhibition of P-gp activity in both Caco-2 and MDR1-MDCK cell monolayers, whereas Cremophor EL and Tween 80 only partially inhibit P-gp activity in Caco-2 cells. PEG-induced changes in P-gp activity are probably related to changes in the fluidity of the polar head group regions of cell membranes [471]. P-gp-mediated rh123 transport was inhibited by five nonionic surfactants in a concentration-dependent manner and in the order α -tocopheryl poly(ethylene glycol) 1000 succinate (TPGS) > Pluronic PE8100 > Cremophor EL > Pluronic PE6100 ~ Tween 80. In contrast, none of the surfactants showed a significant inhibition of MRP2-mediated efflux in Madin-Darby canine kidney/MRP2 cells [472]. Grafting PEG to polyethylenimine (PEI) followed by thiolation with γ-thiobutyrolactone has originated the novel thiolated PEG-g-PEI (**170**) (Fig. **21**) co-polymer which exhibited promising properties as a novel P-gp inhibitor. The thiolated co-polymer increased the accumulation of rh123 up to 3.3-fold in comparison to rh123 without any inhibitor. When applied at a concentration of 0.1 %, 0.25 % and 0. 5 % (w/v) not only did it enhance the absorption but it also decreased the secretory transport of Rh123 [473].

α-Tocopheryl poly(ethylene glycol) 1000 succinate (TPGS), added to nanoparticles, decreases the P-gp activity, increases the intracellular accumulation doxorubicin, and increases the MDR reversal of the nanoparticles [474]. However, the effective concentration range for P-gp inhibition of most surfactants is defined over a narrow concentration range, that is usually in the range of hundrends of micromolar, and therefore, they are commonly used in quantities that do not affect P-gp significantly [475].

A correlation has been shown to exist between certain molecular characteristics of surfactants such as the density of electron donor and acceptor sites and their capability to function as MDR modulators [476]. The hydrophilic-lipophilic balance and the critical micellar concentration of surfactants have been correlated with the magnitude of their MDR efflux pump modulating activity. Molar refractivity and hydrophobicity have also been associated with the magnitude of MDR inhibition [477].

Recently, the liposomal shell was discovered to be capable of directly inhibiting P-gp by two mechanisms: the liposome shell modifies the composition of rafts in resistant cells and decreases the lipid raft-associated amount of P-gp, and the doxorubicin-loaded liposomes directly impaires transport of known P-gp substrates, blocking ATPase activity. Glycine-185 is involved in the inhibition of P-gp by Lipo-Dox [478].

6.4. Dual Ligands

Recently there has been a paradigm shift in drug design moving towards developing multifunctional drugs, meaning compounds that target multiple targets related to a specific pathological condition[479, 480]. This strategy has already been used for the design of multifunctional agents for HIV [62], several neurodegenerative diseases [481, 482] and MDR cancer [483]. Indeed, a multiple target mechanism as MDR modulator and antitumor agent has already been mentioned for ellipticine (**127**), and lathyrane-type diterpenoids jolkinol B (**139**) [423]. This allows one to take advantage of both tumor-directed cytotoxicity and MDR reversal activities into one single molecule. Based on these considerations, we have investigated aminated thioxanthones as dual inhibitors of cell growth and P-gp [484]. These derivatives were designed by merging a thioxanthonic scaffold (for antitumor activity [485, 486]) with a P-gp inhibitor pharmacophore which contains a protonable group (amine) [399]. Our results showed that the most potente P-gp inhibitor, 1- [2-(1*H*-benzimidazol-2-yl)ethanamine]-4-propoxy-9*H*-thioxanthen-9-one, caused an accumulation rate of rh123 similar to verapamil in a P-gp overexpressing cell line (K562Dox) and at 10 μM caused a 12.5-fold decrease in the GI_{50} of doxorubicin in the same cell line. That compound was also a potent inhibitor of other ABC transporters, such as BCRP, MRP-1 and MRP-3 [487].

Another recently described pharmacological strategy to revert MDR was the design of dual ligands which inhibit MDR and stimulate nitric oxide synthase (iNOS) [488]. The resistance to doxorubicin can be reversed when HT29-dx resistant cells are incubated with inducers of nitric oxide (NO) synthesis. It has been postulated than nitric oxide reduces the number of functionally active P-gp, perhaps by altering the proper conformation of the transporter [489]. Following this principle, several P-gp inhibitors were shown also to stimulate NO *via* iNOS in U937, Caco-2 and MCF7-Adr cell lines [488].

Other kinds of dual activity agents are the inhibitors of more than one transporter from the ABC superfamily. In fact, several P-gp inhibitors from the four generations, even elacridar (**111**) and tariquidar (**112**), two of the most potent P-gp inhibitors found to date, interact with other ABC transporter rather than P-gp. Is this really a disadvantage? Much effort has been directed to the exploitation of "promiscuous activity" as a novel approach to treat complex disorders, such as cancer, depression and cardiovascular disease [490]. The simultaneous modulation of multiple targets is often required to alter a clinical cancer phenotype because alternative pathways may be present [491]. Attempts to develop more effective MDR reversers by discovering P-gp selective compounds (the so called "magic bullets") have, unsurprisingly, been unsuccessful. Thus, an alternative "magic-shotgun" targeting multiple efflux pumps, in some instances, may possess a higher therapeutic efficacy than a specific "magic bullet" drug [492]. A selective P-gp inhibitor would be effective if the tumor to be treated was resistant to chemotherapy through P-gp overexpression only. However, if the tumor overexpresses both P-gp and MRP1, for example, it would be of great advantage if a "promiscuous" dual activity drug targeting both transporters was available.

Besides, other advantages of this lack of selectivity may be highlighted, such as the use as radiotracers to assess the distribution of ABC transporters in tissues [493]. For example, elacridar (**111**) is active against P-gp and BCRP proteins [200, 201]. To evaluate the functions of P-gp and BCRP in tumors, a positron emission tomography (PET) study combining the administration of [^{11}C]elacridar with unlabeled elacridar (**111**) has recently proved to be a useful tool [494, 495]. 1-[^{18}F]fluoroelacridar has also been described as a PET tracer for P-gp and BCRP, although its low radiochemical yields and defluorination may limit its applicability *in vivo* [496]. Also, a PET tracer based tariquidar, [^{11}C]tariquidar (**112**), was developed and proved to interact specifically with P-gp and BCRP in the blood-brain barrier (BBB) [204], being therefore a promising approach for evaluating deficiency of the function of drug efflux transporters [497]. For a P-gp focused detection, the radiosynthetic [^{11}C]laniquidar (**113**) tracer is also available [498].

In fact, is it logical to design selective compounds for a target that is "promiscuous" itself? Indeed, in P-gp large substrate-binding cavities, binding more than one substrate/inhibitor, binding substrates in alternative orientations and locations within the binding pockets and substrate-induced conformational changes are common features. These are therefore important parameters to be considered when dealing with drug design [499]. Thus, from our point of view, the major issue is the discovery of P-gp inhibitors without toxic effects in normal tissues and an adequate choice of the MDR reversal agent, according to the cancer phenotype.

7. THE ROLE OF CANCER STEM CELLS IN MDR

Although chemotherapy is able to eliminate most cells in a tumor, it is believed that a small pool of tumor stem cells may resist and are capable of causing tumor relapse [500]. Stem-cell populations have been identified in a range of haematopoietic and solid tumors, and might represent the cell of origin of these tumors [501]. Normal and cancer stem cells express high levels of ABC transporters, such as BCRP and P-gp. These transporters have been shown to protect cancer stem cells from chemotherapeutic agents. In fact, about forty ABC transporters have been found in leukemia stem cells $CD34^{+}38^{-}$ [502]. Therapy against mature leukemia cells can improve clinical results but it is not curative as cancer stem cells are responsible for maintaining the disease and may be resistant to chemotherapy agents [503]. Therefore, ABC inhibitors can be used as sensitizers of leukemia stem cells to other chemotherapeutic drugs [504].

It is unlikely that the inhibition of one ABC transporter will be effective in cancer treatment, as not only efflux pumps overexpression but other resistance mechanisms may be present in drug resistant tumors [505]. Therefore, gaining a better insight into the mechanisms of stem cell resistance to chemotherapy might allow the development of new strategies to improve therapeutical response in cancer [501].

8. OTHER POTENTIAL USES OF P-GP INHIBITORS

The accumulation of neurotoxic β -amyloid (Aβ) within the brain is one of the causes for the progression of Alzheimer's disease [506]. P-gp is heavily expressed at the blood-brain barrier, where it mediates the efflux of Aβ from the brain [507]. Therefore, P-gp inhibitors have been used to study the link between P-gp and Aβ metabolism [508].

Concerning epilepsy, resistance to multiple antiepileptic drugs has been a common problem [509]. One prominent hypothesis to explain this resistance suggests an excess efflux of antiepileptic drugs across the blood brain barrier (BBB) as a result of overexpressed efflux transporters such as P-gp [510]. Knowledge of the cerebral expression patterns of drug transporters in normal and epileptogenic brain may provide information to trace strategies attempting to overcome drug resistance by targeting ABC transporters [511].

Besides, in the treatment of brain cancer [512] or HIV-related dementia [513], P-gp inhibitors are useful as they increase the accumulation of anticancer and protease inhibitor drugs, respectively, in the brain. Moreover, co-administration of P-gp inhibitors with protease inhibitors is an useful strategy for prophylaxis of vertical HIV transmission [514].

It has been reported that lymphocytes are able to extrude P-gp substrates in rheumatoid arthritis, immune thrombocytopenic purpura and systemic lupus erythematosus, causing a poor response to drugs that are substrates of P-gp [515, 516, 517, 518]. The overexpression of P-gp in lymphocytes might lead to exclusion of corticosteroids and disease-modifying antirheumatic drugs from lymphocytes, resulting in drug resistance in patients with autoimmune diseases [519]. Therefore, the expression of P-gp in lymphocytes not only is a promising marker of drug resistance but also is a suitable target to fight MDR in patients with active systemic autoimmune diseases [520].

9. CONCLUSION

Despite the development of new anticancer drugs, P-gp mediated MDR which protects cells from cytotoxic compounds will continue to hinder successful treatment of cancer. Various types of compounds and techniques for the reversal of P-gp-mediated MDR have been developed, and the strategy has been mainly to inhibit the function of the pump.

It has been 30 years since the discovery of the first P-gp inhibitor (in 1981) and 43 years since the isolation of the first MDR cells (in 1968). However, some pessimism still remains on the possibility of finding a "perfect" P-gp inhibitor that can efficiently modulate the pump and restore the efficacy of chemotherapy. Resources and time have been spent on the development of the third-generation P-gp inhibitors. Despite the initial enthusiasm that followed the preliminary results of tariquidar, clinical trials revealed a tragic reality. Fortunately, the story of multidrug resistant reversal is a story of convergence of different research approaches and concepts. Nowadays, by using computational techniques such as pharmacophore construction or QSAR studies, derivatives of known P-gp inhibitors have been synthetised according to the features that seem to be implied in P-gp inhibition. However, regarding the plasticity of the P-gp binding site(s), this

line of thought may become complex. In addition, new compounds extracted from natural sources are being tested for P-gp modulations. The evidence that cancer may be originated in a stem cell has been dictating a paradigm shift in the treatment of cancer, by using ABC transporter inhibitors as stem cell sensitizers to other drugs. Besides their role in reversing MDR, P-gp inhibitors have also been investigated in the treatment of other diseases such as neurodegenerative and autoimmune diseases.

Efforts of several investigators and laboratories spread all over the world, together with the adoption of new strategies, have led to an increasing number of new P-gp inhibitors, but further clinical investigations need to be done in order to accomplish the clinical reversal of P-gp-mediated MDR.

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