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Synthesis of a new inhibitor of breast cancer resistance protein with significantly improved pharmacokinetic profiles

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ABSTRACT

The design, synthesis, in vitro inhibitory potency, and pharmacokinetic (PK) profiles of Ko143 analogs are described. Compared to commonly used Ko143, the new breast cancer resistance protein (BCRP) inhibitor (compound A) showed the same potency and a significantly improved PK profile in rats (lower clearance [1.54 L/h/kg] and higher bioavailability [123%]). Ko143 on the other hand suffers from poor bioavailability. Compared to Ko143, compound A would be a useful probe for delineating the role of BCRP during in vivo studies in animals.

Resistance to anticancer agents is a major cause of chemotherapeutic failure in cancer.[1] The 75 kDa human breast cancer resistance protein (BCRP) is a polytopic plasma membrane transport protein that has been detected in many drug-resistant cell lines, solid tumors, and hematological malignancies. BCRP is one of the most important transporters involved in multidrug resistance and drug–drug interactions (DDIs).[1–3] Ko143 is a novel fumitremorgin C analog and a more potent and specific inhibitor than other known inhibitors of BCRP such as Novobiocin, XR9576, GF120918, Gefitinib, and Imatinib (Fig. 1).[4,5] More importantly, Ko143 is nontoxic at effective in vitro and in vivo concentrations, which makes it one of the most promising compounds for the development of modulators of BCRP-mediated efflux.[4] In our efforts to investigate the applications of BCRP inhibitors in the development of new anticancer agents, we developed two synthetic routes for the synthesis of Ko143.[6] Unfortunately, Ko143 exhibits high clearance (65.9 L/h/kg) and low bioavailability (3%) in rats (Table 1) perhaps due to hydrolysis of the ester moiety. According to FDA guidance, both P-gp (P-glycoprotein) and BCRP are expressed in the gastrointestinal tract, liver, and kidney, and have a role in limiting oral bioavailability. Therefore, all investigational drugs should be evaluated in vitro to determine whether they are potential substrates of P-gp or BCRP.[7] For drugs that are highly permeable and highly soluble, these requirements do not apply.[7] This exemption, however, FDA refers to does not apply to a lot of new molecular entities (NMEs) which are highly permeable but have low solubility.[8] In addition to in vitro analysis, it is equally important to check PK profiles of investigational drugs by co-administration of BCRP specific inhibitors in animals.

Synthesis of new BCRP inhibitors: To explore the SAR of Ko143 analogs, we prepared Ko134 (the demethoxy analog of Ko143) and its analogs (Scheme 1). Pictet–Spengler condensation of commercially available L-tryptophan methyl ester (**1**) with isovaleraldehyde followed by coupling of the resulting secondary amine **2** with *N*-Fmoc-5-*tert*-butyl-L-glutamic acid ester afforded **3**. Fmoc-deprotection and subsequent intramolecular cyclization/cleavage of **3** yielded Ko134.[6] Treatment of Ko134 with TFA to remove the *tert*-butyl group gave acid **4**.[9] Amidation with *tert*-butylamine and sulfamoyl chloride provided *tert*-butyl amide **5**.[10]

To synthesize a new BCRP inhibitor with better PK profiles, we decided to replace the long ester tail on the D ring of Ko143 with a more stable group (Scheme 2). To explore the SAR of the analogs with different electron-donating groups, we started with three different indoles (**6A**, **6B**, **6C**). Coupling of 6-methoxy-indole **6** with 1-benzyl-2-methyl-(*S*)-1,2-aziridinedicarboxylate and ytterbium

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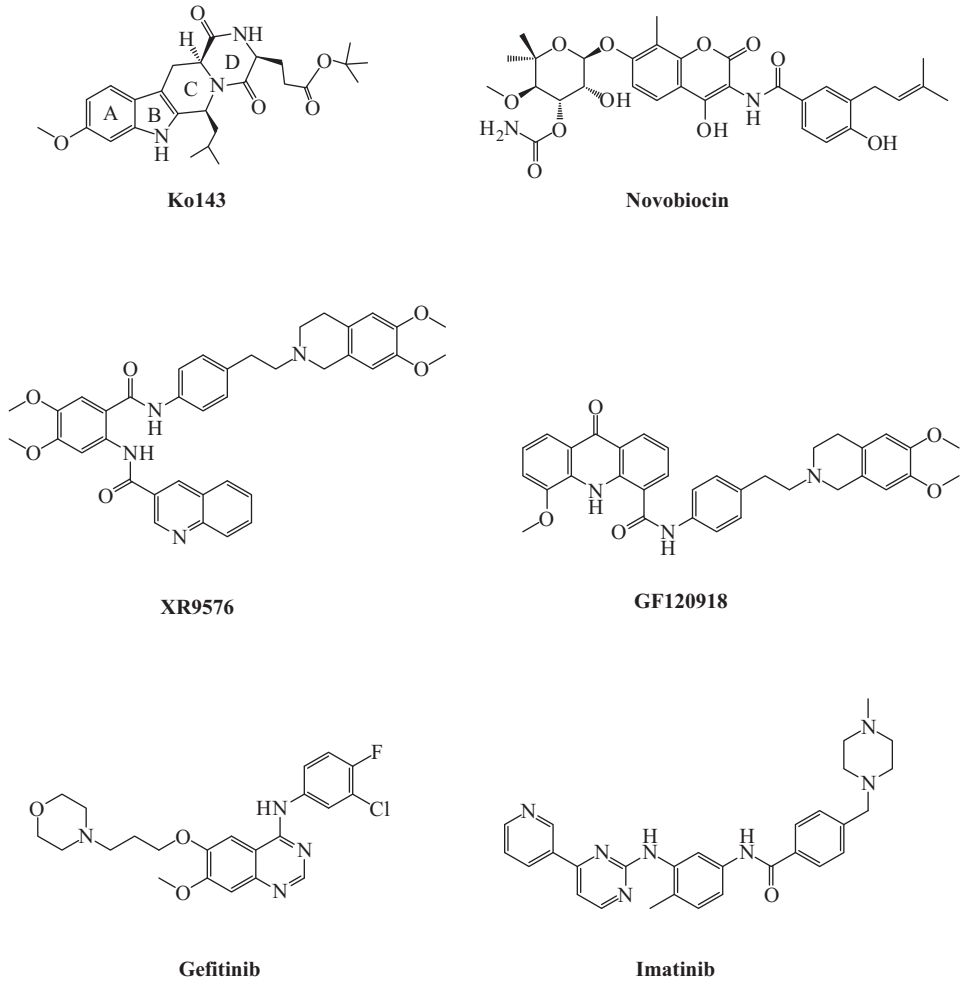
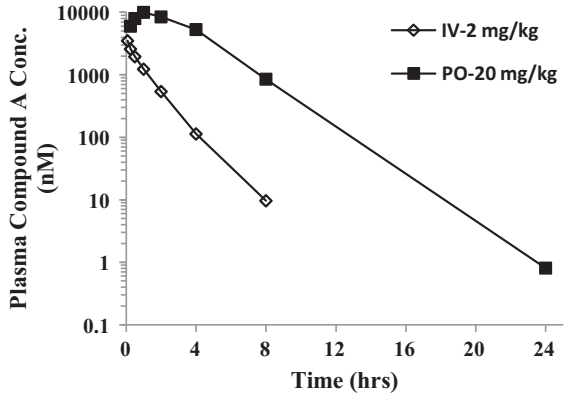


Figure 1. Structures of reported BCRP inhibitors.

Table 1
PK profiles of Ko143 in rats



Route	Dose (mg/kg)	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (nmol/L)	$AUC_{0-24\ h}$ (h nmol/L)	CL (L/h/kg)	V_{ss} (L/kg)	F (%)
iv-JVC	2	0.2			85.6	65.9	14.8	
po-JVC	50		2	21.4	72.2			3

$T_{1/2}$ = half life, T_{max} = time of maximum drug concentration, C_{max} = maximum drug concentration, AUC = area under the curve, CL = clearance, V_{ss} = volume of distribution, F (%) = bioavailability, iv = intravenous, JVC = jugular vein cannulation, po = per os (by mouth).

triflate yielded 6-methoxytryptophan derivative **7** followed by deprotection gave amino acid **8**.[5,11] To explore the SAR of two stereoisomers, we carried both isomers into the final step. More *cis* product **9A** (63.5% yield) than *trans* product **10B** (15.1% yield) was obtained during the Pictet–Spengler condensation by using dry and pure starting material **8A** and employing a low