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PRECLINICAL STUDIES

Pharmacological profiling of novel non-COX-inhibiting indole-pyran analogues of etodolac reveals high solid tumour activity of SDX-308 in vitro

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Summary SDX-308 and SDX-309 are potent indole-pyran analogues of SDX-101 (R-etodolac) which has anti-tumour activity unrelated to cyclooxygenase-2 inhibition. Their cytotoxic activity was further studied herein using a well-characterized human tumour cell-line panel containing ten cell lines, as well as in 58 primary tumour cell samples from a variety of diagnoses. The indole-pyran analogues of SDX-101 were in general considerably more active in both cancer cell lines and primary tumour samples. Low cross-reactivity with standard agents was observed, indicating a unique mechanism of action. No apparent influence on efficacy was observed via classical mechanisms of multi-drug-resistance. SDX-101 and SDX-309 showed higher relative activity in haematological compared to solid tumour samples, while SDX-308 had pronounced solid-tumour activity. High SDX-308 cytotoxic efficacy was observed in non-small cell lung cancer, renal cancer and ovarian cancer samples, and also in chronic lymphocytic leukaemia. In conclusion, the indole-pyran analogues showed a favourable pharmacological profile and represent a potentially important new class of drugs for cancer treatment.

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Introduction

There is an increasing interest in non-steroidal anti-inflammatory drugs (NSAID) for prevention and treatment of cancer. Some of the anti-tumour effects of NSAIDs are caused by their ability to inhibit cyclooxygenase-2 (COX-2), but many COX-2 inhibitors may also have COX-2 independent anti-cancer properties [1]. Thus, both celecoxib and its non-COX-inhibiting derivative OSU03012, have recently been shown to have potent anti-tumour activity unrelated to COX-inhibition [2, 3]. Recent cardiovascular safety concerns with COX-2 inhibitors, especially in adjuvant and prophylactic cancer treatment settings [4], have increased the interest in the development of novel agents which are chemically related to the non-steroidal anti-inflammatory agents, retaing the potential anti-neoplastic activity without displaying the COX-2 inhibitory effects.

Etodolac is an analgesics and non-steroidal anti-inflammatory agent, which has attracted attention for its antileukemic activity [5]. Its R-enantiomer (R-etodolac, SDX-101) is devoid of COX-2 inhibiting properties but has similar anti-tumoural potency when compared with the racemate [6]. SDX-308 and SDX-309 were chosen at Salmedix Inc. from a larger library of approximately a hundred related molecules on the basis of potent in vitro activity on primary patient B-chronic lymphocytic leukaemia (CLL) versus normal peripheral blood mononuclear cell (PBMC) samples and prostate cancer versus prostate stromal cell lines. Preliminary toxicologic testing confirmed SDX-308 and SDX-309 as leading preclinical candidates and potential second generation analogues of R-etodolac (Fig. 1). These

molecules share the indole-pyran ring system of SDX-101 but have various alkyly- or halide substituents appended to the aromatic ring. Both SDX-308 and SDX-309 display a reduction of the acetate carboxylic acid residue at the chiral center of the pyran ring to the corresponding alcohol. In a large series of analogues, generally but not without exception, reduction of the carboxylate to the corresponding alcohol was associated with significant ablation or complete removal of COX-2 inhibitory activity for the series, regardless of the chirality of the molecule. This is in distinct contrast with SDX-101, where the S but not the R isomer, is a potent COX-2 inhibitor. SDX-308 has recently shown promising activity in combination with chlorambucil in a preclinical study on primary tumour cells from CLL [7].

Since the first case report of clinical anti-tumour activity of etodolac was reported in CLL, many preclinical studies of the new analogues have been performed in this disease state [6, 8]. Activity of SDX-101 has also been shown in prostate and colon cancer cell lines [9, 10]. The choice of diagnoses to be focused upon for Phase II clinical testing is an issue of utmost importance for the development of a new anticancer agent. There is a need for valid preclinical methods for prediction of disease-specific activity of new compounds, and the use of primary tumour cells from cancer patients is gaining increasing interest. Primary tumour cells seemingly retain their disease-specific properties better than cell lines, and may be used to identify target diagnoses for Phase II testing [11].

In the current study, the cytotoxic activity of the non-COX inhibitory compound SDX-101 (R-etodolac), and that of its analogues SDX-308 and SDX-309 was studied using a cell-line panel as well as primary tumour cells from 58 cancer patients with a variety of malignant diagnoses.

Materials and methods

Primary tumour cells

Tumour cells were isolated from patients presenting with: acute myelocytic leukaemia (AML; n=4); CLL (n=7); chronic myelocytic leukaemia (CML; n=2); lymphoma (n=13); breast cancer (n=2); colorectal cancer (n=7); non-small cell lung cancer (NSCLC; n=5); ovarian cancer (n=13); and renal cancer (n=5). Tumour samples were obtained in the course of routine surgery, diagnostic biopsy or blood/bone marrow sampling, and sampling was approved by the local ethics committee at Uppsala University Hospital. For comparison, lymphocytes from normal peripheral blood of four healthy donors were used.

Leukemic cells were isolated from bone marrow or peripheral blood by Ficoll–Paque (Amersham Biosciences, Uppsala, Sweden) density gradient centrifugation [12]. Tumour tissue from solid tumours was processed as previously described and tumour cells were isolated by Percoll (Amersham Biosciences) gradient centrifugation [13]. All cell preparations were cryopreserved and stored at −150°C in fetal calf serum containing 10% dimethyl sulfoxide (DMSO, Sigma Aldrich Co) and were thawed immediately before use. The proportion of viable tumour cells was assessed on May-Grûnwald-Giemsa stained cytocentrifugates by a trained oncologist/haematologist, with a requirement of at least 70% viable tumour cells per sample prior to use in experiments.

Cell lines

A cell line panel consisting of ten human tumour cell lines was used. The panel consists of five parental cell lines and five drug resistant sublines representing different mechanisms of drug resistance, as has been described in detail previously [14]. All cell lines were maintained in RPMI-1640 culture medium (Sigma) and were passaged twice weekly. All drugs were tested in 2–3 independent experiments in each cell line and upon demonstration of similar results between experiments, one representative result was chosen for presentation and data evaluation.

Preparation of drugs and plates

SDX-101 (R-etodolac), SDX-308 (racemic mixture) and SDX-309 (racemic mixture) were kindly provided by Salmedix Inc (San Diego, CA), dissolved in DMSO to 250 mM (SDX-101) or 100 mM (SDX-308 and SDX-309) and were further diluted in sterile water. Doxorubicin, vincristine, melphalan, cytarabine and cisplatin were obtained as drug product formulations from the local

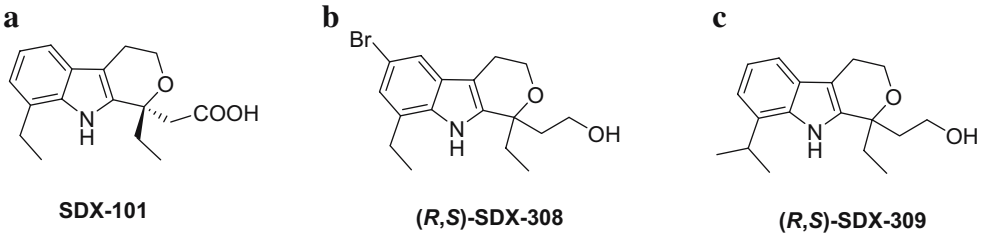

Fig. 1 Chemical structure of (**a**) SDX-101 (R-etodolac), (**b**) racemic SDX-308 and (**c**) racemic SDX-309

pharmacy, and were further diluted in phosphate buffered saline (PBS, Sigma).

Three hundred eighty-four-well microtiter plates (NUNC, Roskilde, Denmark) were prepared with 5 μl drug solution of ten times the desired drug concentration added to duplicate wells. Ten-times serial dilutions were made from each of the duplicate wells, starting from 1,000 μM for the etodolac analogues and melphalan and 100 μM for doxorubicin, cytarabine, cisplatin and vincristine. Drug dilutions were made using the pipetting robot BIOMek 2000 (Beckman Coulter, USA) and the plates were stored at − 70°C until use.

Fluorometric microculture cytotoxicity assay

The fluorometric microculture cytotoxicity assay (FMCA) measures fluorescence of fluorescein, produced by hydrolysis of viable cells with intact plasma membranes of fluorescence diacetate (FDA; Sigma) [12]. Cell suspension was seeded into the drug-containing microtiter plates using the pipetting robot Precision 2000 (Bio-Tek Instruments Inc, Winooski, VT) to a final volume of 50 μl/well. The number of cells per well was $2.5–5\times10^3$ for cell lines, $20–50\times10^3$ for patient leukemic cells and $5–10\times10^3$ for patient solid tumour cells, depending on diagnosis. Twelve wells culture medium containing only served as blanks and 36 wells containing cells but with no drug served as controls. Each plate was divided into six sections with separate control areas for increased precision. The plates were incubated at 37°C for 72 h, and were then placed the automated Optimized Robot for Chemical Analysis (Orca, Beckman Coulter, Fullerton, CA) with the software SAMI (Beckman Coulter). Medium and drug were aspirated from wells containing sedimented cells, followed by washing twice with PBS, with a 50 min sedimentation period between each step. Fifty microliter buffer was added to each well followed by 1 μl FDA solution (0.5 mg/ml; Sigma). After 50–70 min incubation, the generated fluorescence was measured at 485/520 nm using a FLUOstar Optima device (BMG Labtech GmbH, Offenburg, Germany).

Cell survival is presented as Survival Index (SI; %) defined as the mean fluorescence in duplicate test wells divided by mean fluorescence in control wells, with blank well values subtracted from each. Low SI indicates a high cytotoxic effect. A successful plate assay required a control well signal of at least five times blank and a coefficient of variation of less than 30% in the control wells. Only assays meeting these criteria are reported here.

Statistical analysis

All data was stored in an Accord HTS database (Accelrys Inc, San Diego, CA) and IC50 values were calculated using non-linear curve fit by the Hills Equation using GraphPad Prism (GraphPad Software Inc, San Diego, CA). For the cell lines or samples where a drug did not result in a SI<50%, the IC50 was reported as the highest drug concentration in the plate, if tested. IC50 values for the drug exposed cell lines were calculated from log-linear regression at 50% cell survival.

For the patient samples, the Delta values for a given disease diagnosis was defined as the mean log IC50 value for the patient samples within that diagnostic category minus the mean log IC50 values for all samples. The solid/haematological (S/H) activity ratio was defined as the fraction responders within the solid tumour group divided by the fraction responders in the haematologic tumour group, using the median IC50 value as a response cut-off. Correlations and comparisons between IC50 values were performed using logarithmic transformations of values.

For the cell line panel, the Delta value for a specific cell line and drug was defined as the log IC50 value for the individual cell line minus the mean log IC50 value for the entire cell line panel for this drug. Correlations were performed using log transformations of IC50 values. Resistance factors were defined as IC50 values in the resistant subline divided by IC50 values in the parental cell line.

Results

The ten cell lines responded to the SDX-analogues in similar ways with a narrow range of IC50 values (Fig. 2a–c). This can also be seen by the fairly small deviations in the delta graphs (Fig. 2d–f). The novel R-etodolac analogues SDX-308 and SDX-309 were however at least ten times more potent than SDX-101 in the cell-line panel (Fig. 2a–c), demonstrating a pronounced shift to the left of the dose response curves when compared with SDX-101. For all three agents, the lymphoma U937 cell lines and myeloma 8226 cell lines tended to respond better than the renal cancer cell line ACHN and leukemia CCRF-CEM cell lines. The SDX-analogues showed intermediate correlations to each other (R=0.52–0.78) with the lowest correlation coefficient found between SDX-101 and SDX-308. SDX-analogues showed low correlation (R<0.6, n s) to the standard agents tested, the highest correlations were found between doxorubicin and SDX-308 (0.58), and doxorubicin and vincristine with SDX-309 (0.58 and 0.53, respectively). The standard agents varied considerably in correlations to each other (Table 1).

The cytotoxicity of the standard agents in the cell lines confirmed the known resistance pattern of the drug resistant sublines, with for example doxorubicin sensitivity being influenced by topoisomerase II (topo II)-, P-glycoprotein 170 (Pgp)- and multidrug-resistance protein (MRP) associated resistance mechanisms, vincristine sensitivity effected by Pgp-, MRP- and tubulin associated resistance mecha-

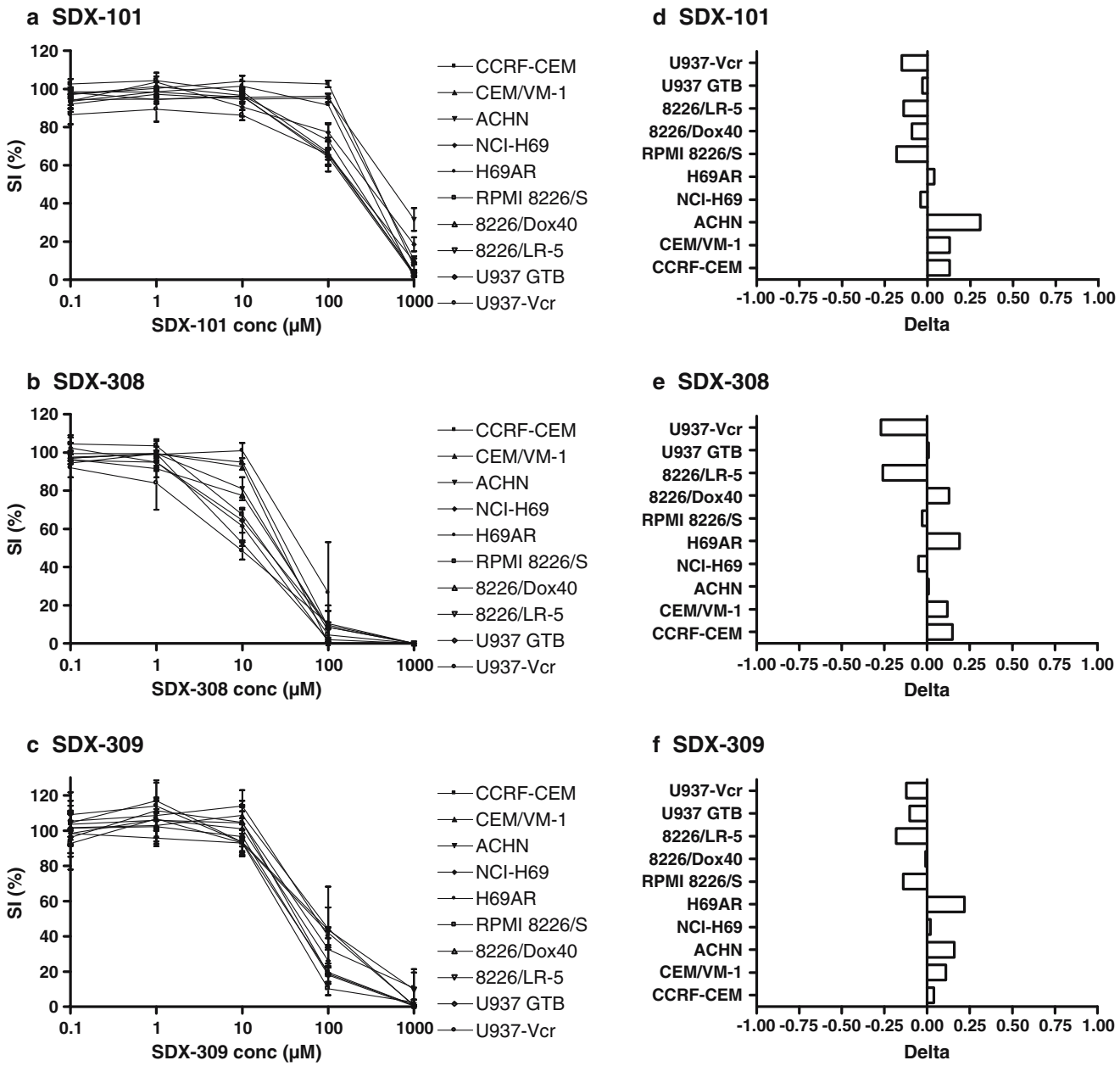

Fig. 2 Effect of the SDX-analogues in the ten different cell lines as individual dose response curves (**a**–**c**) and expressed as Delta (**d**–**f**). Delta for a cell line was defined as the log IC50 for the cell line minus the mean of the log IC50 for all ten cell lines. A deflection to the left indicates higher sensitivity than the mean

Table 1 Correlation between the activity pattern of the SDX-analoges and standard cytotoxic agents in the cell-line panel

	SDX-101	SDX-308	SDX-309	Doxorubicin	Vincristine	Melphalan	Cytarabine	Cisplatin
SDX-101	1.00	0.52	0.78	0.16	0.25	−0.60	−0.36	−0.53
SDX-308		1.00	0.73	0.58	0.18	−0.28	0.12	0.08
SDX-309			1.00	0.58	0.53	−0.34	0.06	−0.07
Doxorubicin				1.00	0.71	0.23	0.38	0.51
Vincristine					1.00	0.20	0.32	0.46
Melphalan						1.00	0.84	0.73
Cytarabine							1.00	0.72
Cisplatin								1.00

Pearson's correlation coefficient between the log IC50s of the ten cell lines is shown.

Table 2 Influence of resistance mechanisms on cytotoxic potency of the SDX-analogues and standard cytotoxic agents in the cell line panel

	TopoII-associated MDR	MRP-associated MDR	Pgp-associated MDR	GSH-associated MDR	Tubulin-associated MDR
Parental celline	*CCRF-CEM*	*NCI-H69*	*RPMI 8226/S*	*RPMI 8226/S*	*U-937 GTB*
Resistant subline	*CEM/VM-1*	*H69AR*	*8226/Dox40*	*8226/LR-5*	*U-937-Vcr*
Resistance factor					
SDX-101	0.99	1.2	1.2	1.1	0.76
SDX-308	0.94	1.7	1.4	0.60	0.52
SDX-309	1.2	1.6	1.4	0.92	0.95
Doxorubicin	5.6	33	43	0.61	2.0
Vincristine	1.0	27	398	1.1	61
Melphalan	1.1	0.55	3.2	3.5	1.6
Cytarabine	1.0	1.0	1.0	0.03	0.89
Cisplatin	0.71	0.89	4.7	1.1	1.4

The resistance factor was defined as the IC50 value in the resistant subline divided by that in its parental cell line.
TopoII topoisomerase II, *MDR* multi-drug resistance, *MRP* multidrug-resistance protein, *Pgp* P-glycoprotein 170, *GSH* glutathione

nisms and melphalan sensitivity altered by glutathione in the 8226/LR-5 subline (Table 2). None of the SDX-analogues seemed to be influenced by any of the classical resistance mechanisms investigated, with no resistance factor above 2 or below 0.5.

For SDX-101, SDX-308 and SDX-309, comparative drug effect was similar between primary tumour cells from CLL and normal lymphocytes, reflected by a ratio between the mean IC50 values in the two cell types close to 1 (1.2, 1,1 and 0.7, respectively; Fig. 3a). This property was shared with most standard agents, the only exception being vincristine which showed slight tumour cell specificity, with an IC50 ratio between normal lymphocytes and CLL of 3.7.

The relative effect of the drugs in solid compared with haematological tumour samples, expressed as the S/H ratio, is shown in Fig. 3b. SDX-101 and SDX-309 showed higher activity in haematological tumour samples, with around twice as high response rate in haematologic compared to solid samples (S/H ratio 0.54 and 0.52, respectively). SDX-308 on the other hand showed high activity in many individual solid tumour samples, resulting in an S/H ratio of 0.84. Of the five standard agents tested, cisplatin showed the greatest relative effect on solid tumours (S/H ratio 1.30), followed by doxorubicin (0.50) and melphalan (0.25). Cytarabine and vincristine were the drugs with the most pronounced haematological tumour activity pattern (0.07 and 0.16, respectively).

Figure 4 displays the relative effect of SDX-101 (Fig. 4a), SDX-308 (Fig. 4b) and SDX-309 (Fig. 4c) in the nine different malignant diagnoses. As indicated by the S/H ratio, SDX-101 and SDX-309 showed preferential activity on the haematological samples, as seen by negative Delta values for AML, CLL and lymphoma. Colon and renal cancer were the most resistant solid cancer types tested against these two agents, while SDX-101 showed the

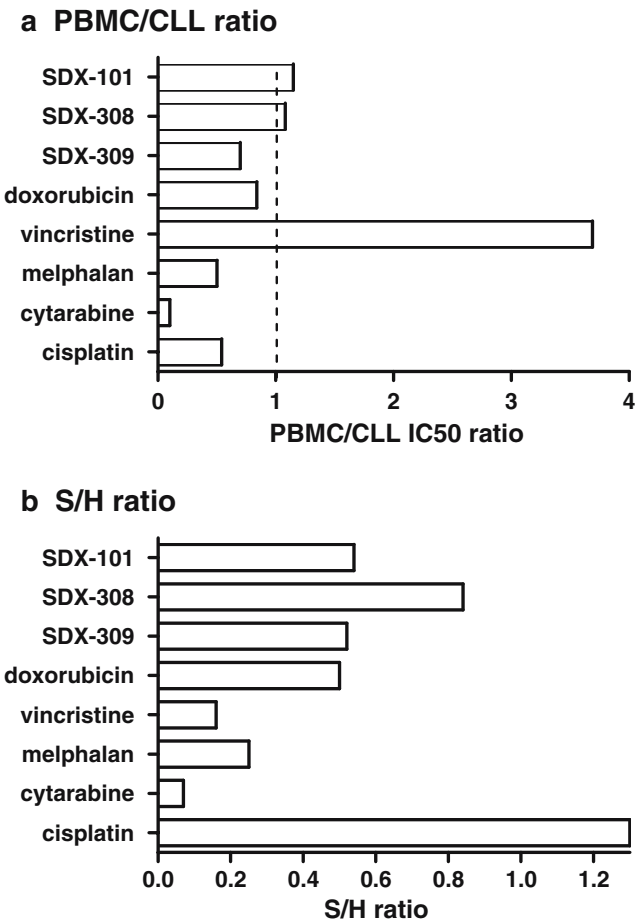

Fig. 3 Tumour cell selectivity expressed as PBMC/CLL ratio (**a**) and solid/haematological (SH) activity ratio (**b**) for the SDX-analogues and some standard cytotoxic drugs in the patient tumour cell material studied. The PBMC/CLL ratio was defined as the ratio between the geometric means of the IC50 in peripheral blood mononuclear cells (PBMC; n=4) and CLL (n=7) samples. S/H ratio was defined as the ratio between the fraction responders (below median IC50) within the solid and haematological tumour group

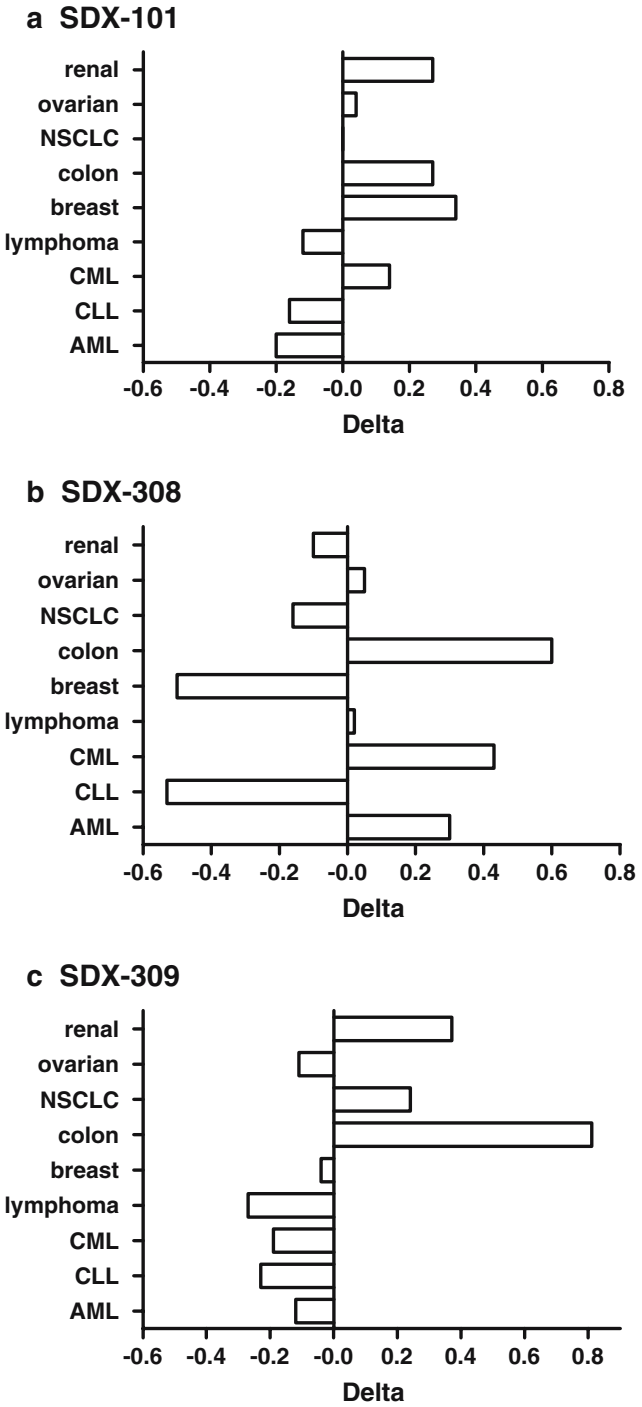

Fig. 4 Disease specific activity of (**a**) SDX-101, (**b**) SDX-308 and (**c**) SDX-309 expressed as Delta. Delta for a diagnose was defined as the mean log IC50 for all samples in a diagnose minus the mean log IC50 for all samples. Number of samples AML=4, CLL n=7, CML=2, lymphoma=13, breast=2, NSCLC=5, ovarian=13, and renal=5

highest solid tumour activity in NSCLC and SDX-309 on ovarian cancer. SDX-308 had a different Delta pattern, with activity on both solid and haematological tumour cells. CLL was the most SDX-308 sensitive haematological diagnosis whereas breast, NSCLC and renal cancer were the most SDX-308 sensitive diagnoses among the solid tumour types.

Samples responding to SDX-308 were present in all diagnoses, as shown in Fig. 5, where the IC50 for each individual is plotted. All CLL-samples responded at low concentrations whereas a large variability in drug response was seen among the lymphoma, ovarian and colon cancer samples (Fig. 5).

Discussion

R-etodolac (SDX-101) and its indole-pyran analogues SDX-308 and SDX-309 showed cytotoxic activity in a human cell line panel, and in primary tumour cells from patients with a variety of malignant diagnoses. The cell-line panel is a well established system for early evaluation of new agents, and can contribute information on relevant resistance mechanisms and mechanistic similarity to other known agents [14]. Studies using primary tumour cells, on the other hand, has better predictive capacity with respect to the relative activity of a drug in different tumour types [11].

The relatively homogenous response among the cell lines in the panel suggests that the factors determining response to etodolac analogues are expressed in a similar way in all ten cell types, although the novel analogues were on average at least tenfold more potent than SDX-101 in the various cell lines tested. The low correlations seen in the cell-line panel between the SDX compounds and standard cytotoxic agents from pharmacologically distinct groups suggest that the indole-pyran compounds may act by mechanisms different from those of clinically established agents. This is an attractive feature for new agents, which are developed as single agent alternatives to, or combination candidates for, drugs in clinical use today.

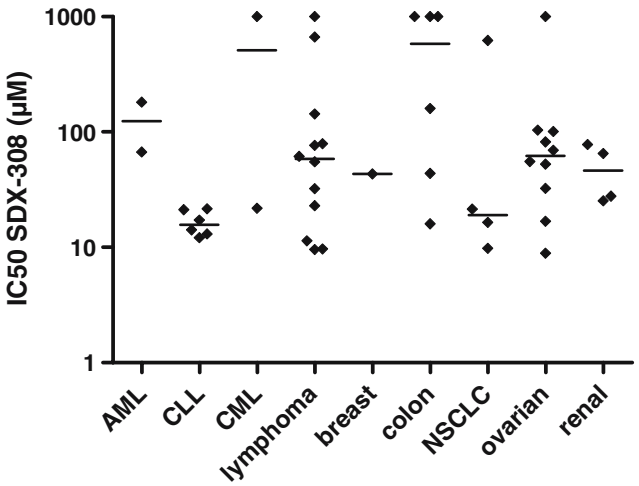

Fig. 5 Effect of SDX-308 in all individual patient samples tested, expressed as IC50. Each dot represents one sample, and the line shows the median IC50 within the diagnosis

A proposed mechanism of action of R-etodolac and its analogues is inhibition of β-catenin activity, and the upstream Wnt signaling pathway [8, 9] which is often overexpressed in certain malignancies such as CLL. It has also been shown that SDX-101 reduces the intracellular level of the anti-apoptotic protein Mcl-1 and affects the PPAR-γ and RXR- α pathway [6, 9, 10, 15]. The low effect upon cytotoxic efficacy of the indole-pyrans via the classical mechanisms of resistance represented in the panel make the compounds potentially interesting for patients with drug resistant disease.

No selectivity for tumour cells was observed for any of the three analogues, when the effect on malignant CLL-lymphocytes was compared to that on normal lymphocytes from healthy donors. This is in contrast to previously published data, where a lower toxicity in normal lymphocytes was reported [6, 15]. The discrepancy between the results of the different studies is not known, but may be connected to differences in experimental conditions. A lack of cytotoxic selectivity between malignant and normal lymphocytes is a feature shared by many antineoplastic agents, including those in clinical use as can be seen as well from results of this study. Consequently some direct toxicity in circulating normal lymphocytes could be expected when testing the SDX-analogues clinically in other malignancies although, encouragingly, clinical results generated with SDX-101 in CLL patients fail to demonstrate a significant suppressive effect on circulating platelets and neutrophils.

The appreciable activity of SDX-308 in solid tumour cells (NSCLC, breast, ovarian and renal) makes this compound interesting for further evaluation in selected solid tumour indications. Results of these studies suggest that SDX-308 displayed a similar percentage of activity among solid and haematological samples, a feature shared only by cisplatin which is one of the most active agents in many solid tumour types. SDX-101 and SDX-309 showed an average S/H activity ratio around 0.5 across various tested hematologic and solid tumor samples, which is similar to the activity profile of doxorubicin a drug with well-known solid tumour activity. The haematologically active agents vincristine and cytarabine both have S/H-ratios below 0.2, suggesting the validity of the evaluation.

While SDX-101 and SDX-309 showed highest activity in the generally more drug sensitive haematological tumour types AML, CLL and lymphoma, SDX-308 showed a more atypical activity pattern. Among the haematological tumours, CLL was by far most sensitive to SDX-308, suggesting that the focus that has been put on CLL in the literature for similar agents is relevant also for SDX-308. SDX-308 drug sensitivity can be found among examples of almost all of the solid tumour types, suggesting that further preclinical evaluation with focus for example on NSCLC and ovarian cancer might be worthwhile. As the need of new drugs to treat many solid tumour types is urgent, the choice of SDX-308 as the lead compound from among this group of indole-pyran molecules is supported by the current study.

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Conflict of Interest None declared.

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