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RESEARCH ARTICLE

Morpholine KECH-18D Restores Drug Sensitivity and Differentially Modulates Efflux Phenotypes in Cisplatin- and Paclitaxel-Resistant Cervical Cancer Cells

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Abstract

Background: Chemoresistance represents a major obstacle in cancer therapy, often associated with enhanced drug efflux. This study aimed to generate and characterize cisplatin-resistance in C-33A cells (C-33A RCDDP), and included, for comparison, a previously established paclitaxel-resistant subline (C-33A RPTX) overexpressing transporters, such as ABCB1, ABCG4, and ABCC8. In addition, we assessed whether the morpholine KECH-18D could restore drug sensitivity by enhancing intracellular drug accumulation. **Materials and Methods:** C-33A RCDDP cells were developed by stepwise cisplatin (CDDP) exposure. Cytotoxicity assays of nine morpholines were carried out to identify structural determinants of anticancer activity in the C-33A cell line. Combinatorial assays with morpholine KECH-18D and CDDP or paclitaxel (PTX) were performed to determine whether KECH-18D chemosensitizes and retains the drug in C-33A RCDDP and C-33A RPTX cells. **Results:** C-33A RCDDP cells exhibited a 4.7-fold increase in CDDP resistance. C-33A RCDDP and C-33A RPTX cells both displayed cross-resistance patterns, but C-33A RTPX cells retained lower levels of the drug than C-33A RCDDP cells. Furthermore, KECH-18D maintained strong cytotoxicity against chemoresistant cell lines and enhanced the cytotoxicity of CDDP and PTX against them. Notably, KECH-18D increased drug accumulation in C-33A RCDDP cells in a time-dependent manner, but not in C-33A RPTX cells. **Conclusion:** In summary, C-33A RCDDP and C-33A RPTX cells developed different levels, and possibly mechanisms, of resistance. Because the morpholine KECH-18D resulted highly cytotoxic in both parental and chemoresistant cells, enhanced drug retention in C-33A RCDDP cells and increased the toxicity of CDDP or PTX in chemoresistant cells, KECH-18D is a promising scaffold for overcoming multidrug resistance by selectively modulating drug efflux-related and -unrelated phenotypes, though further studies are necessary to deep its mechanisms of action.

Keywords: Chemoresistance- Cisplatin-resistant C-33A cells- Paclitaxel-resistant C-33A cells- Morpholine KECH-18D

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Introduction

Chemoresistance represents one of the main obstacles in cancer treatment worldwide, as it limits the efficacy of anticancer agents and significantly contributes to tumor recurrence, disease progression, and the high mortality associated with various types of cancer [1].

One of the most relevant and widely studied mechanisms of chemoresistance is increased drug efflux. This process is primarily mediated by transporter proteins belonging to the ABC (ATP-Binding Cassette) family, such as P-glycoprotein (P-gp/ABCB1) [2],

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MRP1 (ABCC1) [3], and BCRP (ABCG2) [4]. Similarly, low drug uptake by tumor cells constitutes a relevant resistance mechanism, associated with alterations in influx processes mediated by membrane transporters. As a result, intracellular drug uptake is limited, thereby reducing the effective intracellular concentration and, in turn, therapeutic efficacy [5].

Cisplatin and paclitaxel remain cornerstone chemotherapeutic agents in the management of cervical cancer, particularly in advanced, recurrent, or metastatic disease [6, 7], Together, this doublet has become a standard systemic option for advanced, recurrent, or metastatic disease, improving response rates and survival compared to single-agent regimens [8].

Nevertheless, resistance to cisplatin and paclitaxel remains a critical barrier. Mechanisms such as enhanced DNA repair [9, 10], altered transport [11, 12], and evasion of apoptosis [13-16] diminish drug activity, leading to frequent recurrence within two years. This resistance limits therapeutic options, reduces survival gains, and contributes to the high mortality of cervical cancer, particularly in low-resource countries [17, 18].

Morpholine-containing scaffolds have been actively explored as chemosensitizers against multidrug-resistant cancer cells. Studies have reported morpholine-bearing derivatives that inhibit pan-PI3K, DNA-PK, and ABC transporters, increase intracellular drug accumulation, and restore sensitivity to doxorubicin after its nuclear accumulation in CT26 cells overexpressing P-gp [19]. These heterocycles act as structural motifs enhancing target engagement, making them effective efflux modulators and/or other mechanisms of cytotoxicity that overcome chemoresistance [20, 21].

This study aimed to generate and characterize a C-33A RCDDP cells displaying a drug efflux-like phenotype. In addition, we sought to evaluate whether the morpholine derivative KECH-18D a compound from a series of morpholine analogs with enhanced cytotoxic activity is capable of reversing drug resistance by promoting intracellular drug retention in C-33A RCDDP cells and in C-33A RPTX cells, previously established in our laboratory.

Materials and Methods

Cell culture and drugs

The cervical cancer cell line C-33A (HTB-31) from the American Type Culture Collection (ATCC) was kindly provided by Dr. Alejandro García Carrancá from National Institute of Cancer, México. Cells were maintained in high-glucose DMEM, supplemented with 10% fetal bovine serum, at 37°C in a 5% CO_2 atmosphere. Nine new morpholines previously synthesized by collaborators were employed in this study [22]. Additional antineoplastic drugs, including cisplatin (P4394), doxorubicin (44583), and paclitaxel (T7191), obtained from Sigma-Aldrich, were used in the study.

Cell viability assay

Cancer cell lines (6×10^3; C-33A, C-33A RCDDP, or C-33A RPTX) were cultured in 96-well plates overnight. After treatment with different concentrations of CDDP, PTX, or morpholines for 72 h, cell viability was determined using the tetrazolium salt (MTS) from Promega (G3582) following the protocol of the manufacturer. Cell viability percentages for treatments with CDDP, PTX, or morpholines were calculated relative to 100% viability of were calculated relative to the control cells exposed to the vehicle (DMSO). The half inhibitory concentration (IC_{50}) was calculated from cell viability percentage data using nonlinear regression analysis under log-inhibitor vs. normalized response conditions in GraphPad Prism software version 10.4.1 by Dotmatics.

Generation of cisplatin-chemoresistance

The chemoresistant C-33A RCDDP cells were generated with treatment of a sublethal concentration of 1 μM CDDP for 72 h. Then, cells were trypsinized and maintained in fresh CDDP-free medium for 96 h for recovery. This treatment and recovery cycle was employed three times at the same concentration, followed by successive doubling (2, 4, and 8 μM) of the CDDP concentration until chemoresistance was achieved. To calculate the level of chemoresistance to CDDP, an IC_{50} assay was conducted as described above, and then, was compared to IC_{50} of the parental C-33A cells.

Chemosensitization assay

To determine whether morpholine KECH-18D chemosensitizes C-33A RPTX and C-33A RCDDP cells, toward PTX and CDDP, respectively, combinations of sublethal concentrations (IC_{20}) of KECH-18D and PTX or KECH-18D and CDDP were used. After 72 h of treatment, cell viability was determined as mentioned above.

Cellular drug accumulation assay

Parental C-33A, C-33A RCDDP, and C-33A RPTX cells were seeded in 6-well plates at a density of 2×10^5 cells per well. One day later, cells were exposed to 0.1 μM of doxorubicin (reporter drug) for 2 h. Cells were recovered by trypsinization, washed, and resuspended in PBS. Afterwards, cells were acquired by flow cytometry and cellular doxorubicin fluorescence was measured using FlowjoTM V10.10 software. The graphing and comparison of the data between cells were made in GraphPad Prism 10.4.1 by Dotmatics.

Measuring of inhibition of cellular drug accumulation

The cells C-33A RCDDP or C-33A RPTX (2×10^5/well) were cultured overnight in 6-well plates. Then, cells were treated for 2 or 24 h with KECH-18D at IC_{20} (4.50 μM for C-33A RCDDP and 8.94 μM for C-33A RPTX) and IC_{50} (7.35 μM for C-33A RCDDP and 14.93 μM for C-33A RPTX), IC_{20} of CDDP (14.47 μM) and PTX (113.3 nM), or with combinations of them. Untreated C-33A RCDDP and C-33A RPTX cells were used as a control. After the treatments, cells were stained with 0.1 μM doxorubicin for 2 h. Excess of doxorubicin

was removed, and cells were resuspended in PBS after trypsinization. Cell acquisition by flow cytometry was performed to determine doxorubicin fluorescence in the cell population by subsequent analysis in FlowjoTM V10.10 software.

Statistical analysis

All experiments were made in triplicate and graphed as media ± S.D. The data were compared using a one-way ANOVA with Dunnett's multiple-comparison test to determine statistical significance between the control and treatment groups.

Results

Half Inhibitory concentration of cisplatin in the C-33A cervical cancer cell line

To determine the sensitivity of the C-33A cervical cancer cell line (hereafter referred to as parental C-33A) to CDDP, the IC_{50} of this antineoplastic agent was determined by calculating the cell viability of parental C-33A at different concentrations of CDDP. The cell viability of parental C-33A progressively decreased with increasing concentrations of as showed in Figure 1A, resulting in an IC_{50} of 6.64 μM CDDP.

Generation of resistance to cisplatin in the C-33A cervical cancer cell line

To generate resistance to CDDP, parental C-33A cells were subjected to chronic CDDP treatment. Upon treatment, resistance to CDDP was determined by measuring the viability of C-33A RCDDP cells. The IC_{50} of C-33A RCDDP cells was 31.53 μM (Figure 1B), indicating that a 4.7-fold increased resistance to CDDP was achieved, compared to parental C-33A cells.

Cross-resistance in cervical cancer cell lines C-33A RPTX and C-33A RCDDP

In addition to the C-33A RCDDP cells generated in this study, a paclitaxel-resistant cell line, C-33A RPTX, has been established in our laboratory. To determine whether both chemoresistant C-33A cells exhibit cross-resistance, the viability of C-33A RPTX and C-33A RCDDP cells against cisplatin and paclitaxel, respectively, was assessed. The results showed that C-33A RPTX cells exhibited an IC_{50} of 12.69 μM of CDDP (Figure 2A), while C-33A RCDDP cells had an IC_{50} of 82.3 nM of PTX (Figure 2B), indicating that both resistant cells exhibited a cross-resistance phenotype, with resistance indices of 1.9 and 6.9 in C-33A RPTX and C-33A RCDDP cells, respectively, relative to the IC_{50} of cisplatin (6.64 μM) and paclitaxel (11.78 nM) in parental C-33A cells.

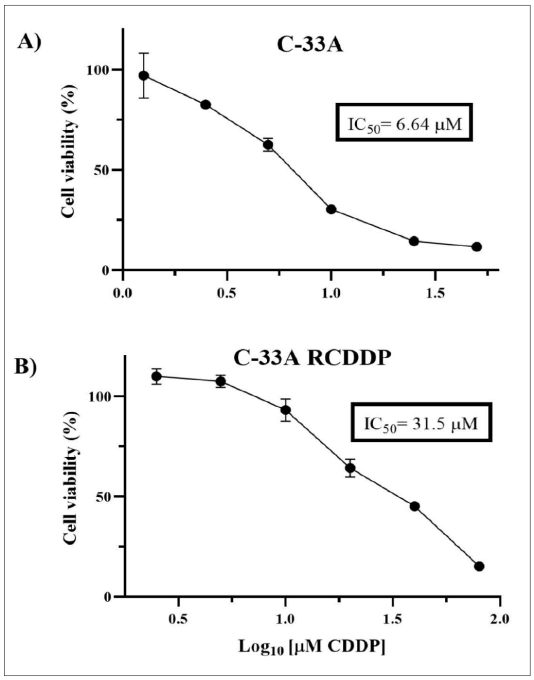
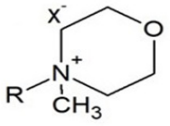


Figure 1. Percentages of the viability of parental C-33A cells treated with 1, 2.5, 5, 10, 25, and 50 μM of CDDP (A) and C-33A RCDDP cells treated with 2.5, 5, 10, 20, 40, and 80 μM of CDDP (B). The IC_{50} values are shown in the boxes.

Table 1. Cell viability of C-33A cells treated with 100 μM of each morpholine at 72 h.



Morpholine	Carbons in R group	Counterion (X)	Cell viability percentage (mean ± S.D.)
KECH-6B	12	Br	1.3% ± 0.2
KECH-10B	16	Br	2% ± 0.3
KECH-14B	18	Br	3.2% ± 1.1
KECH-18D	14	Br	0.6% ±0.4
LESM-11	1	I	96.7% ± 1.8
LESM-21	2	I	99.7% ± 2.1
LESM-24	3	I	100.8% ± 4.7
EMS-11	4	Br	106.7% ± 3.3
EMS-13	5	I	108.2% ± 10.08

S.D. Standard deviation

Table 2. Inhibitory concentration media (μM) of the most potent morpholines in parental C-33A cells

Morpholine	Half inhibitory concentration (μM)
KECH-6B	19.85
KECH-10B	4.62
KECH-14B	3.83
KECH-18D	3.07

The cytotoxity of morpholine KECH-18D is determined by the length of hydrocarbon chain

Morpholines have become key components of pharmaceutical compositions because they have a wide range of biological activities, including anticancer activity [23]. In this work, we evaluated the anticancer activity of nine new morpholines at 100 μM in parental C-33A cells for 72 h. The cell viability results revealed that the morpholines KECH-6B, -10B, -14B, and -18D showed the highest potency (Table 1). These four morpholines have a bromide counterion and an R group with 12 or more carbons. Subsequently, the IC_{50} of these four morpholines was determined. Results in Table 2 demonstrated that KECH-18D, which contains 14 carbons in the R group, had the highest cytotoxicity. A similar potency was identified for KECH-14B, while KECH-6B, which contains 12 carbons in the R group, showed the lowest potency of them. That indicates that the number of carbon chains in the R group is determinant in the activity of these morpholines. After identifying the IC_{50} of the KECH-18D in parental C-33A cells, IC_{50} values were determined in chemoresistant C-33A cells. The results in Figure 3

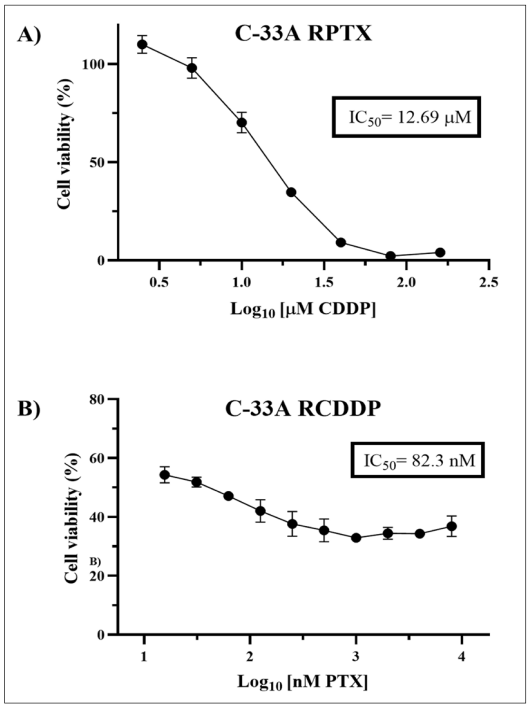


Figure 2. Percentages of the viability of C-33A RPTX cells treated with 2.5, 5, 10, 20, 40, 80, and 160 μM of CDDP (A) and C-33A RCDDP cells treated with 15.6, 31.25, 62.5, 125, 250, 500, 1,000, 2,000, 4,000, and 8,000 nM of PTX (B). The IC_{50} values are shown in the boxes.

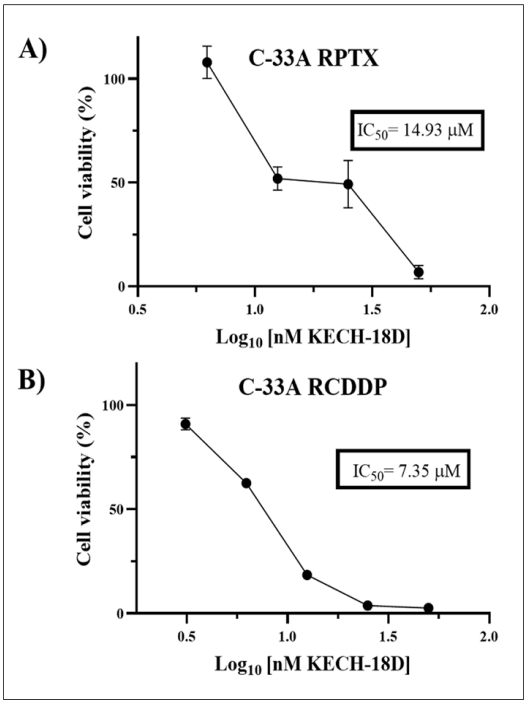


Figure 3. Percentages of the viability of C-33A RPTX (A) and C-33A RCDDP (B) cells, upon exposure to different concentrations of KECH-18D. IC_{50} values are shown in the boxes.

showed that KECH-18D yielded IC_{50} values of 14.93 and 7.35 μM in C-33A RPTX and C-33A RCDDP cells, respectively, which underscore its anticancer potency.

KECH-18D exhibited a greater chemosensitizing effect in C-33A RPTX cells than in C-33A RCDDP cells

To determine whether KECH-18D functions as a chemosensitizer on C-33A RCDDP and C-33A RPTX cells, a combination of KECH-18D/CDDP and KECH-18D/PTX was employed, respectively. The results in Figure 4A showed that the cytotoxicity of the combination of KECH-18D IC_{20} and CDDP IC_{20} on C-33A RCDDP was greater than the sum of the cytotoxicity of each drug alone. This additive effect was not seen with the combination of KECH-18D IC_{20} and PTX IC_{20} on C-33A RPTX (Figure 4B), however, the cytotoxicity resulting from the KECH-18D/PTX combination was greater than KECH-18D/CDDP combination. These results suggest differences in sensitivity and chemoresistance mechanisms between C-33A RPTX and C-33A RCDDP cells.

C-33A RCDDP and C-33A RPTX differ in the efficiency of doxorubicin retention

One mechanism of chemoresistance in cancer cells is drug efflux. In previous work from our laboratory, we identified that C-33A RPTX cells overexpressed ABCB1 and retained less doxorubicin than the parental C-33A cells [24]. Thus, we compared the ability of C-33A RCDDP and C-33A RPTX cells to reduce doxorubicin concentration. The concentration and exposure times to doxorubicin were defined based on a screening previously performed with parental C-33A and C-33A RPTX cells.

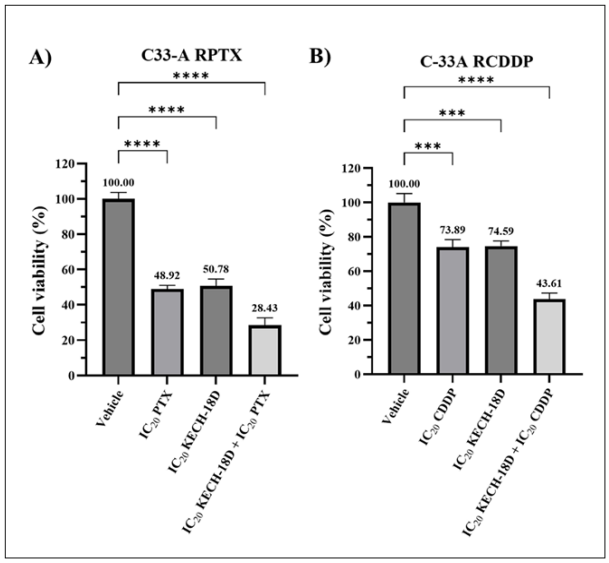


Figure 4. Percentages of the viability of C-33A RCDDP (A) and C-33A RPTX (B) cells treated for 72 h with KECH-18D and CDDP or PTX at indicated concentrations and combinations. The vehicle is the control group of cells exposed to DMSO. Bars represent mean ± SD from three independent experiments.

The results in Figure 5 showed a significantly lower doxorubicin retention in C-33A RCDDP (7.80%) and primarily in C-33A RPTX (25.15%) cells in comparison to the retention in parental C-33A cells. The drug retention rates indicated that C-33A RPTX cells are more efficient than C-33A RCDDP cells in eliminating the drug. These data indicate that both chemoresistant cells share a resistance mechanism, albeit at different levels, which corresponds to their levels of resistance to the respective antineoplastic drugs.

KECH-18D increases drug retention differentially in C-33A RCDDP and C-33A RPTX cells in a time-dependent manner

To determine whether the KECH-18D is proficient to augment the retention of doxorubicin, as a drug reporter, in C-33A RCDDP and C-33A RPTX cells; cells were treated with 0.1 µM doxorubicin for 2 or 24 h, followed by treatments with KECH-18D, PTX, and CDDP, or combinations of these (Figure 6). The results indicated that KECH-18D, alone or combined with CDDP, retains doxorubicin in C-33A RCDDP cells at both short and long times of treatment. The most significant accumulation of doxorubicin was observed with the combination of KECH-18D/CDDP, but, interestingly, exposure to CDDP alone diminished doxorubicin retention. These observations suggest that KECH-18D is responsible for drug retention in C-33A RCDDP cells, and together KECH-18D and CDDP enhance the retention. This behavior was maintained at short and long times, but at long time the effect was greater. In contrast to C-33A RCDDP cells, doxorubicin retention was only observed in C-33A PTX cells when treated for 2 h with either KECH-18D or PTX alone, but not in combination with both (Figure 6C). Moreover, for a long time, the decrease in doxorubicin was observed with any treatment. This effect was most pronounced when C-33A RPTX cells were treated with the KECH-18D alone (Figure 6D). Upon chemoresistant C-33A RCDDP or RPTX cells were treated with doxorubicin, it was evident that the level of doxorubicin retention was inversely proportional to their drug efflux ability (Figure 4). Altogether, these findings confirm the ability of KECH-18D to increase drug retention in chemoresistant cells, drug efflux-like phenotype, but this effect depends on treatment time and the efficiency of drug efflux from the chemoresistant cells.

Discussion

The present study provides new insights into behaviors of chemoresistance in cervical cancer cells and highlights the potential of morpholine derivatives, particularly KECH-18D, as a promising therapeutic agent to overcome drug resistance. Using the C-33A cervical cancer cell line as a model, a stable cisplatin-resistant C-33A RCDDP cell line was generated, and a paclitaxel-resistant C-33A RPTX cell line was included in this study. Although the generation of resistance to CDDP and PTX followed an identical treatment and recovery protocol, a highly different level of resistance was observed between C-33A RCDDP and C-33A RPTX cells, 4.7- and 55-fold, respectively. This observation suggests that differences in potency, chemical nature, targets, and mechanisms of action of the drugs CDDP and PTX are contributing to the development of resistance. This reasoning is supported by the cross-resistance result, in which C-33A RCDDP cells showed a clearly higher level of resistance to PTX (6.9-fold) than C-33A RPTX cells did to CDDP (1.9-fold). This not only shows how relevant the drug is to determining the level of resistance, but also reflects the importance of the drug recognition by cells before exposure for establishing the adaptive response to pharmacological stress. These findings are consistent with previous reports showing that chemoresistant cancer cell models frequently display multidrug resistance phenotypes due to overlapping molecular mechanisms,

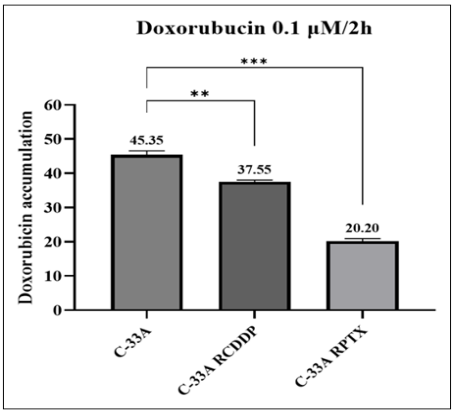


Figure 5. Percentage of doxorubicin accumulation in C-33A parental, C-33A RCDDP, and C-33A RPTX cells incubated with 0.1 µM doxorubicin for 2 h. Accumulation levels were calculated relative to control cells not incubated with doxorubicin. Bars represent mean ± SD from three independent experiments.

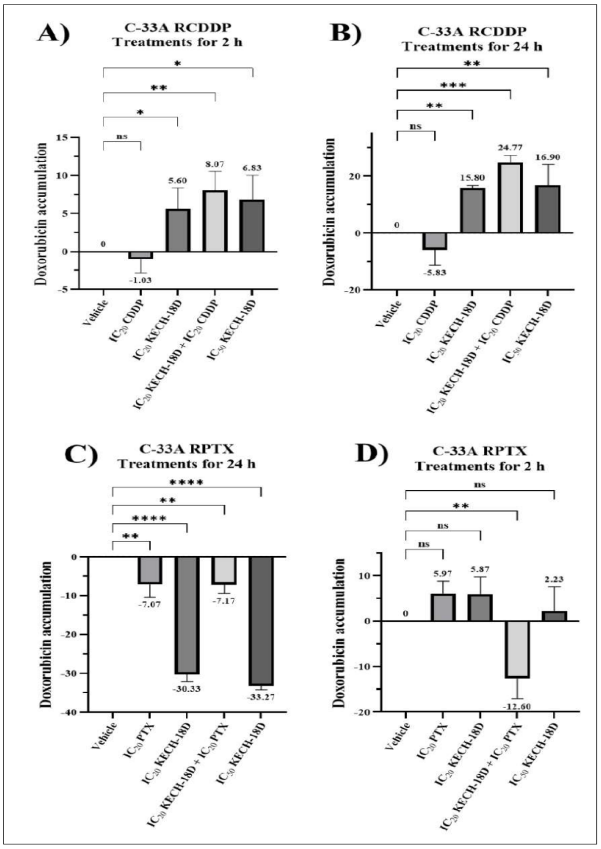


Figure 6. Graphics of percentage of doxorubicin accumulation in C-33A RCDDP and C-33A RPTX cells pre-treated for 2 (A and C) or 24 h (B and D) with KECH-18D and paclitaxel or cisplatin at indicated concentrations and combinations, followed by incubation for 2 h with 0.1 μM of doxorubicin. Accumulation levels are relative to corresponding cells exposed to doxorubicin only (without pretreatment). Bars represent mean ± SD from three independent experiments.

including alterations in drug uptake [25], efflux [26], and DNA damage repair pathways [27].

The analysis cytotoxicity of morpholine derivatives revealed structural determinants of its activity in C-33A cells. Screening demonstrated that the length of R determines cytotoxicity: those with 1-5 carbons are much less in toxicity to those with 14-18 carbons. The influence of hydrocarbon chain length on the anticancer potency of mitochondrial-targeting aryl urea derivatives through apoptotic activity has been previously reported, and this was attributed to their greater ease of mitochondrial membrane penetration [28]. The KECH-18D, carrying a 14-carbon chain in the R group, displayed the greatest potency, with an IC_{50} of 3.07 μM in parental C-33A cells, which is less than half that of CDDP in the same cells. Meanwhile, in C-33A RPTX and C-33A RCDDP cells, the IC_{50} of KECH-18D resulted in 14.93 and 7.35 μM, respectively. This revealed that the potency of KECH-18D was partially attenuated; however, its remarkable effectiveness remains in resistant cells.

The KECH-18D/CDDP combination showed a subtle additive cytotoxic effect in C-33A RCDDP cells, but this was not seen in C-33A RPTX cells with the KECH-18D/PTX. Beyond the additive effect, the cytotoxicity with KECH-18D/PTX in C-33A RPTX cells was markedly greater than KECH-18D/CDDP in C-33A RCDDP cells (71.57 % vs 56.39 %). These findings suggest that the cytotoxicity of KECH-18D relies on the drug combination and/or the resistance mechanism in the chemoresistant sublines. This assumption was addressed by comparing doxorubicin retention between C-33A RPTX and C-33A RCDDP cells, through a widely used approach to examine the drug efflux phenotype in chemoresistant cells [29-31]. Paradoxically, the lowest retention of reporter drug was found in C-33A RPTX cells, in which the cytotoxicity of the drug combination was highest. This cytotoxicity of KECH-18D/PTX in C-33A RPTX cells, even with the decreased retention/uptake of the reporter drug, could be explained because the reporter drug does not accurately reflect the trafficking behavior of KECH-18D/PTX in these cells; that is, KECH-18D/PTX together are not as good substrates as doxorubicin is for drug efflux transporters, and they manage to exhibit their cytotoxicity despite the sustained activity of the drug transporters, as described in previous studies [32, 33]. For example, as occurred in C-33A RPTX cells treated with KECH-18D, NSC-73306 compound selectively eliminated P-gp–expressing resistant cells via metal-dependent ROS-mediated mechanisms, without P-gp inhibition, illustrating how cytotoxicity can be uncoupled from drug accumulation [34]. Also, Heffeter et al. demonstrated that the lanthanum/organometallic KP772 exerts preferential toxicity toward MDR cells by inducing Bcl-2–independent apoptosis and perturbing redox/metal homeostasis; MDR cells retain functional efflux activity while remaining vulnerable to this agent [35]. Although these findings in C-33A RPTX cells treated with KECH-18D contrast with the vast majority of studies on chemoresistant cells expressing a drug efflux phenotype, when they are chemosensitized result in the inhibition of this phenotype [36-38], as occurred on C-33A RCDDP cells with KECH-18D or KECH-18D/CDDP, increased doxorubicin retention. These findings reveal the relevance of cytotoxicity of KECH-18D on C-33A RCDDP cells, and its differential effect between C-33A RCDDP and C-33A RPTX cells. These findings together indicate that differences in KECH-18D cytotoxicity between the two resistant cell sublines are not proportional to the level of cellular drug accumulation, as seen with the doxorubicin reporter, because other, more determining resistance mechanisms may be driving toxicity in each subline. These contrasting outcomes reinforce the concept that chemoresistance in C-33A RPTX and RCDDP cells relies on distinct mechanisms and/or levels of resistance. The efflux appears to be the dominant mechanism of C-33A RPTX cell resistance, but it is not sufficient to avoid cytotoxicity of KECH-18D. On the other hand, C-33A RCDDP cells may combine drug-efflux with other mechanisms of resistance, such as DNA repair [39], upregulation of GSTP1/glutathione pathway [40], and autophagy [39].

In conclusion, this study demonstrates that C-33A RCDDP and C-33A RPTX cells develop distinct levels of chemoresistance and possibly distinct mechanisms. The morpholine derivative KECH-18D displayed potent

cytotoxicity in both parental and resistant cells. Its ability to enhance drug retention and synergize with CDDP or PTX suggests a context-dependent mechanism of action. Overall, KECH-18D emerges as a promising candidate to counteract multidrug resistance in cervical cancer. However, further molecular studies should be performed to clarify its mechanisms of action and chemotherapeutic scope.

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Conflict of interest

The authors declare no conflict of interest.

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