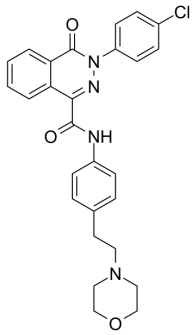
P-gp/BCRP-IN-1

Cat. No.:	HY-144393
CAS No.:	2764596-06-5
Molecular Formula:	$C_{27}H_{25}ClN_4O_3$
Molecular Weight:	488.97
Target:	BCRP
Pathway:	Membrane Transporter/Ion Channel
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	P-gp/BCRP-IN-1 (compound 19) is a potential, relatively safe, orally active and efficient efflux transporter (P-gp and BCRP) inhibitor. P-gp/BCRP-IN-1 exerts resistance reversal by inhibiting the efflux function of P-gp and BCRP. P-gp/BCRP-IN-1 can overcome the resistance and improve the oral bioavailability of PTX (Paclitaxel)[1].
IC_{50} & Target	P-gp
In Vitro	P-gp/BCRP-IN-1 (compound 19) (0-200 μM, 48 h) has a weak anti-proliferative activity against A549 cells, and shows low cytotoxicity to the K562 , K562/A02, MDCK-II, MDCK-II-BCRP cells[1]. P-gp/BCRP-IN-1 (48 h) exhibits the great reversal effect of resistance to both ADM (Adriamycin) and MX (Mitoxantrone) in K562/A02 cells and MDCK-II-BCRP cells, and increases the reversal activity of ADM (0-5 μM) and MX (0-20 μM) in a concentration-dependent manner[1]. P-gp/BCRP-IN-1 (0-5 μM, 4 h) increases drug accumulation and prevents efflux of P-gp and BCRP[1]. P-gp/BCRP-IN-1 (0-5 μM, 48 h) dose not affect the expression of P-gp as well as BCRP protein[1]. P-gp/BCRP-IN-1 (0-200 μM, 4 h) decreases the viability of Caco-2 cells, inhibits the intestinal P-gp-mediated efflux of PTX and increases its concentration in the intestinal cells, can enhance the absorption and bioavailability[1]. P-gp/BCRP-IN-1 prevents intracellular accumulation of anti-neoplastic drugs by impairing the function of P-gp and BCRP[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Proliferation Assay

Cell Line:	A549 cells, chemo-sensitive cell lines (K562, MDCK-II), chemo-resistant cell lines (K562/A02, MDCK-II-BCRP)[1]
Concentration:	200, 100, 50, 25, 12.5, 6.25, 3.125, 1.56 and 0 μM
Incubation Time:	24, 48 h
Result:	Had a weak anti-proliferative activity against A549 cells, with an IC_{50} of 46.28 μM, and showed low cytotoxicity to the K562 , K562/A02, MDCK-II, MDCK-II-BCRP cells, with IC_{50} values of 72.81, 43.29, 87.69, 81.22 μM, respectively.

Cell Viability Assay

Cell Line:	K562/A02 cells and MDCK-II-BCRP cells[1]

Concentration:	5 μM
Incubation Time:	48 h
Result:	Increased the reversal activity of ADM (0-5 μM) and MX (0-20 μM) in a concentration-dependent manner, exhibited the great reversal effect of resistance to both ADM and MX in K562/A02 cells and MDCK-II-BCRP cells, with IC_{50} values (at 5 μM) of 2.41 and 18.43 μM, RF (reversal fold, at 5 μM) of 40.51 and 37.40, and $EC_{50}$of 65.31 and 98.22 nM, respectively.

Western Blot Analysis

Cell Line:	K562/A02 cells and MDCK-II-BCRP cells, K562 and MDCK-II cells.[1]
Concentration:	0, 0.5, 1, 5 μM
Incubation Time:	48 h
Result:	Did not affect the expression of P-gp as well as BCRP protein, exerted resistance reversal without affecting the expression of P-gp as well as BCRP protein, but probably by inhibiting the efflux function of P-gp and BCRP.

Cell Viability Assay

Cell Line:	Caco-2 cells[1]
Concentration:	1.25, 5, 10, 20, 30, 50, 100, 200 μM
Incubation Time:	4 h
Result:	Decreased the viability of Caco-2 cells to less than 20% at concentrations of 30 and 50 μM respectively, significantly decreased the Papp (apparent permeability coefficient) value, inhibited the intestinal P-gp-mediated efflux of PTX and increased its concentration in the intestinal cells, which could eventually enhance the absorption and bioavailability of the orally administered drug.

In Vivo

P-gp/BCRP-IN-1 (compound 19) (Male SD rats; 5 mg/kg PTX (IV), 20 mg/kg PTX (PO), 20 mg/kg PTX and 10 mg/kg compound 19 (PO); once) increases the bioavailability of PTX when PTX is given orally[1].
Pharmacokinetic Parameters of P-gp/BCRP-IN-1 in male SD rats[1].

	PTX (5 mg/kg)	PTX (20 mg/kg)	PTX (20 mg/kg) with 19 (10 mg/kg)
$Route_{max}$ (h)	IV	PO	PO
AUC_{0-t} (ng*h/mL)	1734.95 ± 244.28	610.89 ± 45.62	3131.51 ± 63.17
C_{max} (ng/mL)	925.86 ± 31.39	112.09 ± 25.46	652.31 ± 41.93
T_{max} (h)	0.44 ± 0.05	2.00 ± 0.03	2.51 ± 0.19
$T_{1/2}$ (h)	0.12 ± 0.03	1.35 ± 0.05	1.68 ± 0.15
V_d/F (L)	5.06 ± 0.09	67.38 ± 12.54	16.04 ± 0.08

CL/F (L/h)	2.88 ± 0.14	32.74 ± 5.42	6.18 ± 0.36
F (%)	100	8.80	45.1

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Male SD rats (n = 15, three groups)[1]
Dosage:	5 mg/kg PTX (IV); 20 mg/kg PTX (PO); 20 mg/kg PTX with 10 mg/kg compound 19 (PO)
Administration:	IV, PO, once (Pharmacokinetic Analysis)
Result:	Increased the bioavailability of PTX when PTX was given orally.

REFERENCES

[1]. Shi W, Zhang P, Zou F, et al. Exploration of novel phthalazinone derivatives as potential efflux transporter inhibitors for reversing multidrug resistance and improving the oral absorption of paclitaxel. Eur J Med Chem. 2022;233:114231.

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