XK469: Selective topoisomerase II-β inhibitor

DNA topoisomerases are essential nuclear enzymes that modify DNA topology in a very precise fashion through transient DNA cleavage followed by ligation. Targeted genetic inactivation of topoisomerases is generally lethal and discussion of topological problems encountered by DNA molecules in vital cellular physiological processes, e.g. replication, transcription, recombination, condensation or segregation have been widely studied [1].

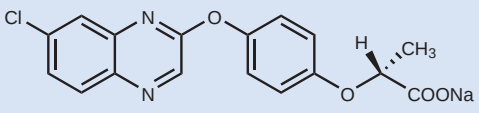
There are two classes of DNA topoisomerases, referred to as Topo I (Prod. No. **T 9069**) and Topo II, each of which is further divided into subfamilies A and B. Mammalian Topo II belongs to subfamily IIA and two isoforms exist, referred to as **Topo II-α** (p170, Prod. No. **T 8944**) and Topo II-β (p180). The α isozyme has low expression in terminally differentiated and quiescent cells. The β isozyme remains relatively constant throughout the cell cycle. Topo II exists as a dimer, requires ATP hydrolysis for DNA cleavage and thus differs from Topo I. In addition, Topo II breaks both DNA strands of the double helix simultaneously, whereas Topo I breaks one strand at a time. Accurate functioning of Topo II is essential for chromosome segregation before anaphase, which is a prerequisite for the development of normal mitosis.

XK469 (Prod. No. **X 3628**) is a selective inhibitor of Topo II-β (IC_{50} 160 µM) that has little effect on Topo II-α and no effect on Topo I [2]. It is a potent anti-proliferative agent against a broad spectrum of malignancies, in particular solid tumors and multi-drug resistant cancers.

XK469 specifically induces cell cycle arrest at G2/M. The ability to reduce cellular viability is antagonized by **cyclosporin A** (Prod. No. **C 3662**), **$NaBH_4$** (Prod. No. **45,217-3**) and NOK-1, a blocking monoclonal antibody to the Fas-Fas ligand interaction. Treatment with XK469 increases the Bax:Bcl2 ratio [3], upregulates p53-dependent proteins (such as Bax, p21, Gadd 45 and Cyclin B1) and activates **caspase 3** (Prod. No. **C 1224**) and **caspase 8** (Prod. No. **C 1099**) resulting in subsequent cleavage of **PARP** (Prod. No. **P 4730**). The effect on Cyclin B1 is correlated with inhibition of Cyclin B1 ubiquitination [4]. XK469 also blocks activation/phosphorylation of MEK and MAPK [5]. Clearly, inhibition of Topo II-β may not be the only mechanism underlying the biological effects of XK469.

Indolent B cell tumors possess undetectable levels of Topo II-α enzyme and are insensitive to standard chemotherapeutic agents, including Topo II-α poisons such as **etoposide** (VP16, Prod. No. **E 1383**). Topo II poisons are agents that stabilize Topo II-DNA cleavage complexes, leading to permanent DNA double-strand breaks. *In vitro* pre-exposure of a Waldenstrom's macroglobulinemia cell line, WSU-WM, to 5 µM XK469 induces expression of Topo II-α and increases Topo II-α mediated DNA cleavage [6]. XK469 acts synergistically with etoposide to reduce cellular viability [6]. Since XK469 does not directly target Topo II-α, it is believed to act by up-regulating Topo II-α levels, thus sensitizing indolent malignant B cells to the cytotoxic effect of etoposide.

XK469 is therefore an important isoform-specific tool for probing the function of topoisomerases in both normal and disease states.



XK469
(Prod. No. X 3628)

References

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Topoisomerase Inhibitors available from Sigma-RBI

Topo I Inhibitors

A 3145	**Apigenin**
K 0133	**Kaempferol**
R 4900	**Rebeccamycin**
C 9911	**(S)-(+)-Campothecin**

Topo II Inhibitors

A 1895	**Aurintricarboxylatic acid** (ATA)
A 2647	**AMP-PNP**
A 9809	**Amsacrine hydrochloride**
C 2659	**Chromomycin A3**
E 3380	**Ellipticine**
E 1303	**Etoposide**
N 1628	**Novobiocin**
S 4692	**Sobuzoxane**

Topo I/II Inhibitor

N 9653	**Netropsin**