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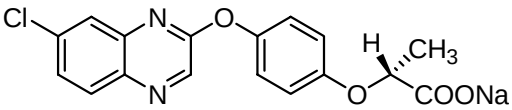
ProductInformation

XK469

Product Number **X 3628**
Store at 2-8 °C

Chemical Name: 2-[4-(7-chloro-2-quinoxalinyloxyphenoxy]-propionic acid
Synonyms: NSC 697887, NSC 656889



Product Description
Molecular formula: $C_{17}H_{12}ClN_2NaO_4$
Molecular Weight: 366.7

DNA topoisomerases are essential nuclear enzymes that perform topological changes in DNA molecules in a very precise and unique fashion through transient DNA cleavage followed by ligation. Targeted genetic inactivation of topoisomerases are generally lethal. A discussion of the topological problems encountered by DNA molecules in vital cellular physiological processes, e.g. replication, transcription, recombination, condensation or segregation, can be found in a recent review.[1]

There are two classes of DNA topoisomerases: I and II, each of which is further divided into subfamilies A and B differentiated by structure and mechanisms. Mammalian Topo II belongs to subfamily IIA and has two isoforms: Topo II-α (p170) and Topo II-β (p180). The α isozyme has low expression in terminally differentiated and quiescent cells. The β isozyme level is relatively constant throughout the cell cycle. Topo II differ from Topo I in being dimeric and requires ATP hydrolysis for DNA cleavage. In addition, Topo II breaks both DNA strands of the double helix simultaneously whereas Topo I breaks one strand at a time. The precise mechanisms and molecular models of DNA topoismerases have been reviewed.[1] Accurate functioning of Topo II is essential for chromosome segregation before anaphase, and this in turn constitutes a prerequisite for the development of normal mitosis.

XK469 is derived from the herbicide Assure and is selective for Topo II-β (IC_{50} = 160 μ) with little effect on Topo II-α and no effect on Topo I.[2] It is a potent anti-cancer, anti-proliferative agent against a broad spectrum of malignancies, in particular for solid tumors and multidrug resistant cancers. Both the R(+) and S(-) isomers of XK469 are cytotoxic, although the R-isomer is more potent. *In vivo* XK469 is converted to the R-isomer in circulation. The DNA sequence specificity of XK469 has been defined and is found to be different from that of a structurally related CQS (chloroquinoxaline sulfonamide).[3]

XK469 specifically induces cell cycle arrest at G2/M and apoptosis. Current experimental evidence points to complex mechanisms involving Fas signaling pathway, ubiquitination, p53 activation, and cytochrome c release.[4] The ability to reduce cellular viability is antagonized by cyclosporin A, $NaBH_4$ and NOK-1 (a blocking mAb to Fas-Fas ligand interaction). Treatment with this synthetic quinoxaline increases Bax: Bcl-2 ratio,[4] upregulates p53 dependent proteins such as Bax, p21, Gadd 45, and Cyclin B1, and activates caspases 8 and 3 resulting in subsequent cleavage of PARP. The effect on Cyclin B1 is correlated with inhibition of Cyclin B1 ubiquitination.[5] XK469 also blocks activation/phosphorylation of MEK and downstream MAPK.[6] Clearly, inspite of its selective inhibitory effect, inhibition of Topo II-β cannot be the primary mechanism for the biological effects of XK469.

Indolent B cell tumors have undetectable levels of Topoisomerase II-α enzyme and are refractory to standard chemotherapy including Topo II-α poisons such as Etoposide (VP16, E1383). Topo II poisons are agents that stabilize Topo II-DNA cleavage complexes leading to permanent DNA double-strand breaks and transforming the enzyme into cellular toxin without inhibiting the catalytic activity of the enzyme in contrast to classical inhibitors (Sobuzoxane, S4692). *In vitro* preexposure of a Waldenstrom's macroglobulinemia cell line, WSU-WM, to XK469 at 5μM induces expression of Topo II-α by immunofluorescence and increases

Topo II-α mediated DNA cleavage.[7] XK469 acts synergistically with VP-16 in the reduction of cellular viability.[7] This effect is dependent in the order of administration; simultaneous or reverse order results in antagonistic effect. The authors concluded that since Topo II-α is not a direct target of XK469, it must act by up-regulating Topo II-α levels and consequently sensitizes indolent malignant B cells to the cytotoxic effect of VP16.

XK469 can be employed as an isoform specific tool in probing the function of topoisomerases in normal and disease states. It has potential role in a therapeutic regiment with Topo II-α poisons such as VP16 for drug resistant indolent B cell malignancies. XK469 has been in Phase I clinical trials since 2001.

Related Products

A-281 Apigenin
A1895 ATA, Aurintricarboxylatic acid
A2647 AMP-PNP
K0133 Kaempferol
A9809 Amsacrine Hydrochloride
C2659 Chromomycin A3
E1383 Etoposide
N6106 Novobiocin
N9653 Netropsin
R4900 Rebeccamycin
S4692 Sobuzoxane

References

1. Wang, J.C., Cellular roles of DNA topoisomerases: a molecular perspective. Nat. Rev. Mol. Cell Biol., **3**, 430-440 (2002).
2. Gao, H., et al., XK469, a selective topoisomerase IIβ poison. Proc. Natl. Acad. Sci. USA, **96**, 12168-12173 (1999).
3. Gao, H., et al., DNA sequence specificity for topoisomerase II poisoning byu thye quinoxaline anticancer drugs XK469 and CQS. Mol. Pharmacol., **63**, 1382-1388 (2003).
4. Mensah-Osman, E.J., et al., XK469, a topo IIβ inhibitor, induces apoptosis in Waldenstrom's macroglobulinemia through multiple pathways. Int. J. Oncol., **23**, 1637-1644 (2003).
5. Lin, H., et al., Mitotic arrest induced by SK469, a novel antitumor agent, is correlated with the inhibition of cyclin B1 ubiquitination., Int. J. Cancer, **97**, 121-128 (2002).
6. Lin, H., et al., SK469, a novel antitumor agent, inhibits signaling by the MEK/MAPK signaling pathway. Cancer Chemother. Pharmoacol., **49**, 281-286 (2002).
7. Mensah-Osman, E.J., et al., 2-[4-(7-chloro-2-quinoxalinyloxy)phenoxy]-propionic acid (XK469), an inhibitor of topoisomerase (Topo IIβ) , up-regulates Topo IIα and enhances Topo IIα-mediated cytotoxicity. Mol. Cancer Ther., **1**, 1321-1326 (2002).

KAA 01/04