STRUCTURE-ACTIVITY RELATIONSHIP (SAR) OF NEW TORASEMIDE DERIVATIVES ON Na-K-2Cl COTRANSPORTER IN PERFUSED RABBIT THICK ASCENDING LIMB (cTAL) OF HENLE'S LOOP.

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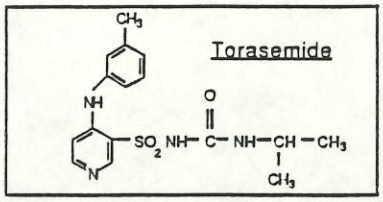
Torasemide , a diuretic sulfonylurea, inhibits the luminal Na^+ K^+ $2Cl^-$ cotransport system and basolateral Cl-channels. The aim of this study was to determine the SAR of new torasemide derivatives on the half maximal inhibition of the short circuit current (Isc) in cTAL segments after luminal or basolateral-side addition . Their lipophilicity was determined as the log of octanol/water distribution (log P).



Results show the replacement of the 3-toluyl moiety with a cycloalkyl radical (C6 - C8) preserves the affinity to the cotransporter. Moreover substitution of the isopropyl residue with a second cycloalkyl radical (C6 - C8) or a saturated nitrogen-containing ring increases this affinity. This pharmacomodulation lead us to lipophilic compounds with an Isc of ± 0.1 µM which could be new potent high ceiling diuretics.

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