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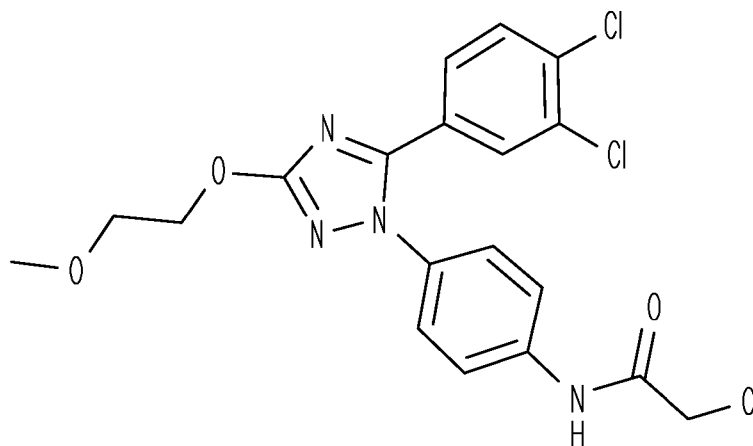


Fig. 1D

(57) Abstract: MALT1 cleavage activity is linked to the pathogenesis of activated B-cell-like diffuse large B-cell lymphoma (ABC-DLBCL), a chemo-resistant form of DLBCL. We developed a MALT1 activity assay and identified chemically diverse MALT1 inhibitors. A selected lead compound MI-2 featured direct binding to MALT1 and suppression of its protease function. MI-2 concentrated within human ABC-DLBCL cells and irreversibly inhibited cleavage of MALT1 substrates. This was accompanied by suppression of NF-κB reporter activity, inhibition of nuclear localization of c-REL and downregulation of NF-κB target gene signature. Most notably, MI-2 was non-toxic to mice, and displayed potent and specific activity against ABC-DLBCL cell lines *in vitro*, and xenotransplanted ABC-DLBCL tumors *in vivo*. The compound was also effective against primary human non-GCB-DLBCLs *ex vivo*.