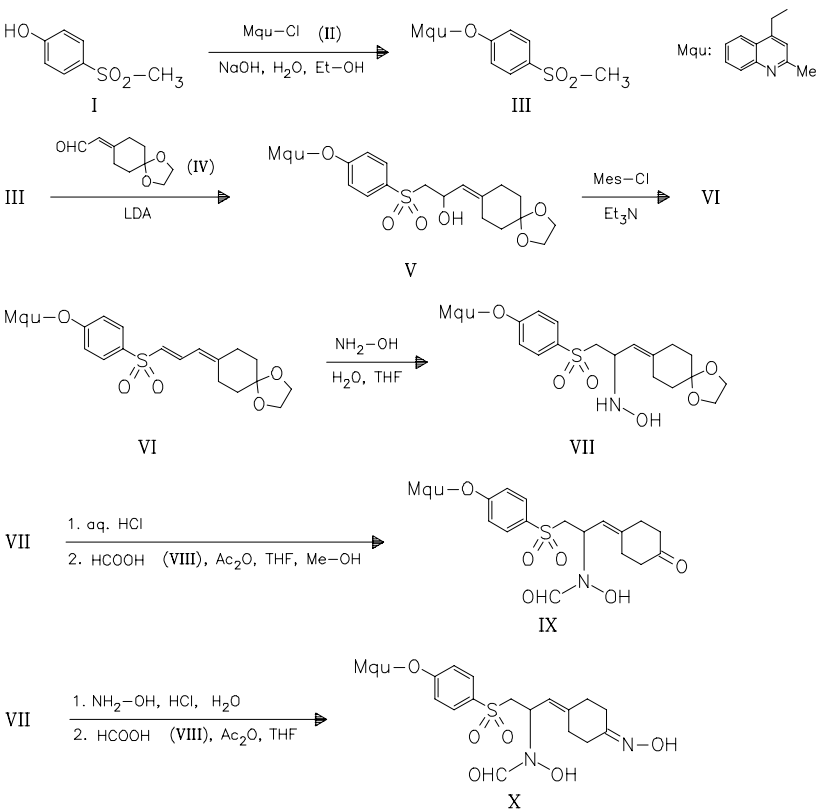
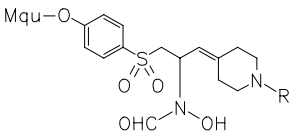
Quinoline derivatives

R 0410

39- 125

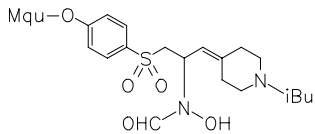
Reverse Hydroxamate-Based Selective TACE Inhibitors. — Reverse hydroxamate derivatives (IX) and (X) are prepared via the common intermediate (III). Julia coupling with aldehydes or esters provides the alcohols (V). In the case of esters, the co-existence of LiHMDS affords the corresponding β-ketosulfones with better yields, which can be reduced to alcohols in a one-pot procedure. Dehydration of (V), followed by addition of hydroxylamine to the α,β-unsaturated sulfone (VI) yield the adduct (VII), which is converted into the desired compounds (IX) and (X). The heterocycles (XI) and (XII) are prepared in the same fashion. Compounds (IX) and (X) display excellent TACE inhibitory activities and selectivities against the tested MMPs. Heterocyclic representative (XII) demonstrates excellent oral inhibitory activity of the LPS-stimulated TNF-α production. — (KAMEI, N.; TANAKA, T.; KAWAI, K.; MIYAWAKI, K.; OKUYAMA, A.; MURAKAMI, Y.; ARAKAWA, Y.; HAINO, M.; HARADA, T.; SHIMANO*, M.; Bioorg. Med. Chem. Lett. 14 (2004) 11, 2897-2900; Kaken Pharm. Co., Ltd., Yamashina, Kyoto 607, Japan; Eng.) — H. Hoennerscheid





a R: —iBu
b R: —Piv

XI



XII