3-Hydroxy-1-Azoalkenes and Their Ester Derivatives: New Cytotoxic Agents for Cancer Treatment

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Researchers are paying a lot of attention to nitrogen-containing compounds for their ability to generate organic analogs with high and diverse biological activities. 3-hydroxy-1-azoalkenes, with the azo group (N=N) in the molecule, have various biological activities such as antioxidant, anti-inflammatory and anticancer. Nevertheless, 3-hydroxy-1-azoalkenes lack stability according to the Eschenmoser-Tanabe fragmentation reaction. We built up a procedure from looking into suitable condition for the epoxidation of cyclohexenone to create epoxycycloalkanone to the condensation reaction of epoxycyclohexanone and phenylhydrazine at room temperature to synthesize stable 3-hydroxy-1-azoalkenes. After that, the esterification is implemented in DCC coupling condition with 4-DMAP. Due to the presence of a stereocenter in the structure of 3-hydroxy-1-azoalkenes, we caried out the epoxidation by using H_2O_2, (1R,2R)-(+)-diphenylethylenediamine and trifluoroacetic acid to generate stereoselective 3-hydroxy-1-azoalkene. The absolute configuration of 3S-hydroxy-1-azoalkene was established by the Mosher method and the enantiomer excess was determined by LC-MS analysis of both (S) and (R)-MTPA esters, the result showed that 3S-hydroxy-1-azoalkene has an ee of nearly 100%. As of now, our group has successfully synthesized 26 compounds, consisting of two 3-hydroxy-1-azoalkenes, one 3S-hydroxy-1-azoalkene and 23 ester derivatives. The biological activities of all compounds are evaluated on 5 cancer cell lines: Hep-G2, Lu-1, RD, HeLa and MCF-7. The result showed that nine compounds had strong cytotoxic activites with IC50 values from 0.92 to 3.86 µg/mL depending on cancer cell line. Especially, three compounds showed better cytotoxic activities toward RD cancer cell line than a standard.