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Synthesis of betulinic acid 1,2,4-triazole derivatives suitable for cyclodextrin inclusion complex formulation.

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Pentacyclic triterpenes are natural compounds with a large plethora of described pharmacotherapeutic effects. Betulinic acid (BA) stands as a widely studied compound of this class, exhibiting multiple therapeutic effects such as: antiinflammatory, antiviral and antiproliferative. The low bioavailability o BA represents a major drawback which represented a starting point of multiple research directions, having the sole purpose of increasing BA's bioavailability. One direction employed by the literature in this regard represents the synthesis of cyclodextrin (CD) inclusion complexes (1). Knowing that BA is a large pentacyclic structure herein we propose the synthesis of a BA-1,2,4-triazole derivative that can be easily incorporated into CD and can exhibit an improved antiproliferative effect as compared to BA. The proposed derivatization requires obtaining a BA halogenated derivative by allylic bromuration (C-30), that ca be subsequently used as an alkylating agent against a 3-thiol-1,2,4-triazole derivative. 30-bromo-BA was obtained according to previously reported methods using NBS (2). The obtained compound was purified by flash column chromatography. The BA derivative was later reacted to 5-(4-metoxifenil)-4H-1,2,4-triazol-3-thiol, in presence of EtOH and EtONa. The completion of the reaction was monitored by TLC. The obtained compound was purified by flash column chromatography. FT-IR and LC-MS analysis confirmed the formation of 30-[3-(4-metoxiphenyl)-1H-1,2,4-triazol-5-yl-sulfanyl]-betulinic acid. Docking studies of the BA derivative an BA using CD as targets revealed that indeed our obtained compound shows a theoretical stronger affinity towards CD as compared to BA. The obtained compound and its CD formulations will be subjected to further biological assessments.

References

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