Monensin and its Derivatives Exhibit Anti-Melanoma Activity In Vitro

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Over the last 30 years, incidences of melanoma have increased dramatically. Although, melanoma accounts only for approximately one percent of skin cancers, it is responsible for almost eighty percent of all deaths from dermatological malignancies. Current therapeutic approaches vary depending on tumor progression and patient’s health, and include tumor removal, immuno-therapy, and forms of targeted therapy. Major limitations in treating melanoma are associated with adverse side effects of treatments as well as reduced drug efficiency. Therefore, new forms of therapy are needed to overcome these limitations as well as to combat the increased incidence of melanoma.

Monensin (MON) is a naturally occurring polyether ionophore which was shown to be potent and selective towards different types of cancer cells including melanoma. In order to further explore structure-activity relationship of MON and develop more potent and selective compounds based on the scaffold of MON, we synthesized an extensive library of esters and urethanes, as well as ester-carbonates, amide carbonates, tertiary amides, and esters on the C1 atom. We have identified four derivatives more potent (IC$_{50}$ = 28.3 ± 6.0 – 132.2 ± 24.4 nM) than parent MON (IC$_{50}$ = 316.8 ± 25.7 nM) towards human melanoma A375 cell line, four derivatives more active (IC$_{50}$ = 132.2 ± 50.4 - 442.9 ± 64.8 nM) than MON (IC$_{50}$ = 794.1 ± 161.9 nM) against human melanoma SK-MEL-5 cell line, while parent MON remained to be the most potent (IC$_{50}$ = 63.2 ± 30.9 nM) towards mouse melanoma B16F10 cell line. Further studies revealed that these compounds significantly reduced A375 cell migration (23% vs 41% and 35% wound surface area after 53 hours control vs treatment respectively), increased Major Histocompatibility Complex-I and II presentation and Programmed Death - Ligand 1 expression in SK-MEL-5 cell line. Studies are ongoing to explore mechanism behind the activity of these promising novel drug candidates.

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