Synthesis and biological evaluations of putative metabolically stable analogs of VN/124-1 (TOK-001): head to head anti-tumor efficacy evaluation of VN/124-1 (TOK-001) and abiraterone in LAPC-4 human prostate cancer xenograft model.
Title: Synthesis and biological evaluations of putative metabolically stable analogs of VN/124-1 (TOK-001): head to head anti-tumor efficacy evaluation of VN/124-1 (TOK-001) and abiraterone in LAPC-4 human prostate cancer xenograft model.

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Abstract: In a continuing study of our clinical candidate 5 VN/124-1 (TOK-001) and analogs as potential agents for prostate cancer therapy, we have made a series of modifications to improve stability and bioavailability. We describe the synthesis and biological evaluation of compound 6 (3α-fluoro-) and 9 (3β-sulfamate-) designed to increase the stability and oral bioavailability of 5, respectively. These studies showed that on an equimolar basis, compound 6 was ~2-fold more efficacious versus LAPC-4 xenografts than 5, but the toxicity observed with 6 is of concern. These studies support the investigation of 6 as a potential agent for prostate cancer therapy and the continued development of VN/124-1 (TOK-001) which is currently in phase III clinical trials. In our desire to optimize the potency of 5, compounds 6 (3α-fluoro-) and 9 (3β-sulfamate-) designed to increase the stability and oral bioavailability of 5, respectively were evaluated in vivo. We showed, that on equimolar basis, compound 6 was ~2-fold more efficacious versus LAPC-4 xenografts than 5, but the toxicity observed with 6 is of concern. These studies support the investigation of 6 as a potential agent for prostate cancer therapy and the continued development of VN/124-1 (TOK-001) which is currently in phase III clinical trials.

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