Accepted Manuscript

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PII: S0960-894X(16)30776-4
DOI: http://dx.doi.org/10.1016/j.bmcl.2016.07.050
Reference: BMCL 24094

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 1 June 2016
Revised Date: 20 July 2016
Accepted Date: 21 July 2016

Please cite this article as: Li, X., Chen, G., Zhang, X., Zhang, Q., Zheng, S., Wang, G., Chen, Q-H., A new class of flavonol-based anti-prostate cancer agents: design, synthesis, and evaluation in cell models, *Bioorganic & Medicinal Chemistry Letters* (2016), doi: http://dx.doi.org/10.1016/j.bmcl.2016.07.050

A new class of flavonol-based anti-prostate cancer agents: design, synthesis, and evaluation in cell models

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Abstract — Flavonoids are a large class of polyphenolic compounds ubiquitously distributed in dietary plants with an array of biological activities. Flavonols are a major sub-class of flavonoids featuring a hydroxyl group at C-3. Certain natural flavonols, such as quercetin and fisetin, have been shown by *in vitro* cell-based and *in vivo* animal experiments to be potential anti-prostate cancer agents. However, the Achilles' heel of flavonols as drug candidates is their moderate potency and poor pharmacokinetic profiles. This study aims to explore the substitution effect of 3-OH in flavonols on the in vitro anti-proliferative potency against both androgen-sensitive and androgen-insensitive human prostate cancer cell lines. Our first lead flavonol (3',4'-dimethoxyflavonol), eight 3-*O*-alkyl-3',4'-dimethoxyflavonols, and six 3-*O*-aminoalkyl-3',4'-dimethoxyflavonols have been synthesized through aldol condensation and the Algar-Flynn-Oyamada (AFO) reaction. The WST-1 cell proliferation assay indicates i) that all synthesized 3-*O*-alkyl-3',4'-dimethoxyflavonols and 3-*O*-aminoalkyl-3',4'-dimethoxyflavonols are more potent than the parent 3',4'-dimethoxyflavonol and the natural flavonol quercetin in suppressing prostate cancer cell proliferation; and ii) that incorporation of a dibutylamino group to the 3-OH group through a three- to five-carbon linker leads to the optimal derivatives with up to 292-fold enhanced potency as compared with the parent flavonol. Flow cytometry analysis showed