Effective access to more complex drug molecules – a medicinal chemistry perspective exemplified with ingenol esters

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***Abstract*:** Exploration of bioactive compounds in plants and microorganisms has led to the identification of several of the current therapeutics. However, application of techniques such as HTS and parallel synthesis has aided the development of new chemical entities (NCEs) towards higher molecular weight and lipophilicity accompanied with development and safety issues. There is a potential to further improve the drug design strategy and capitalize more on natural products and sp^3-rich molecules associated with more favorable features. A key driver for this development is improved access to more complex molecules via scalable organic synthesis or efficient synthetic biology. For example, ingenol mebutate (ingenol 3-angelate) isolated from *Euphorbia peplus* has been developed as the active ingredient in Picato®, a new drug for field treatment of actinic (solar) keratosis. A high yielding semisynthetic route without concomitant isomerization of the angelate double bond has been developed. A number of ingenol derivatives were prepared with the purpose of investigating the chemical stability as well as the potency in assays relating to pro-inflammatory effects, cell death induction and PKCδ activation. By modifications of the ingenol scaffold several prerequisites for biological activity were determined. The chemical stability of the compounds could be linked to an acyl migration mechanism. Molecular modeling and dynamics (MD) calculations were used to illustrate the essential interactions between key compounds and PKCδ. Some key features for potent and more stable ingenol derivatives have been identified.