In silico discovery of novel Retinoic Acid Receptor agonist structures

ABSTRACT

Two novel agonists resulting from the predicted receptor model were active at 50 nM. One of them displays novel structural features which may translate into the development of new ligands for cancer therapy.

INTRODUCTION

Background The retinoic acid receptors (RAR-α, -β, and -γ) are transcription factors regulating a variety of endocrine metabolic pathways. Unlike anti-estrogens, such as tamoxifen or raloxifene, ligands targeted against the RAR isoforms can present anticancer activity against both estrogen receptor positive and negative breast tumor cells. As a result, such molecules could constitute a novel generation of drugs against breast cancer. For reasons not yet clear, both agonists and antagonists of RAR can present anti-tumor activity against breast, prostate, lung cancer or leukemia. The development of both types of ligands could therefore have important biomedical implications. We have recently demonstrated that antagonists could be discovered rationally, based on a model of the antagonist-bound conformation of the receptor. Our goal here is to discover innovative molecular structures with RAR agonist activity. Several retinoid and non-retinoid ligands have been described, which activate one or a combination of RAR isoforms. Some of them, such as the natural hormone all-trans retinoic acid (all-trans RA) (Fig. 1a), have been tested clinically, and display unacceptable side effects, such as skin dryness, cheilitis, hypertriglyceridemia and conjunctivitis. However, the compounds tested so far belong to limited series of related structures. An increasing amount of data suggests that the RAR-β isoform, which is under the transcriptional control of RAR-α, is involved in suppressing cell growth and tumorigenicity. Innovative molecules with RAR-α and RAR-β agonist activity could therefore present more favorable toxicity profile than pan-agonists. We applied a flexible virtual screening algorithm (Molsoft ICM, virtual library screening module) which rapidly docks hundreds of thousands of flexible compound structures into the ligand binding pocket of RAR, and discovered two novel RAR-β selective agonists. One of these ligands displays original structural and chemical characteristics, which could be used in the development of novel compounds for cancer prevention and therapy.

CONCLUSION

Conclusions This report details the rapid discovery of RAR agonists with novel structural features, thanks to a powerful virtual ligand screening approach, and a research strategy where considerations on existing ligands are avoided. One of the molecules presented here constitute a good framework for the development of a novel series of RAR ligands very different from all structures described so far. Such ligands could present more favorable specificity and toxicity profiles, and have important applications in cancer therapy.