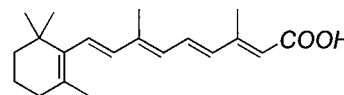


Retinoids

The Chemoprevention Working Group to the American Association for Cancer Research considers retinoids to be one of the most promising classes of cancer chemoprevention agents (1). Retinoids, which are modeled after the active vitamin A metabolite, retinoic acid (RA) [1], offer promise as cancer chemoprevention agents because of their abilities to regulate growth, differentiation, apoptosis, embryo development, angiogenesis, metastasis and immune function.

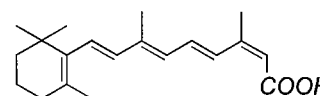


1, *all-trans-RA*

As single agents, they generally do not induce apoptosis, but when combined with DNA damaging agents, they can enhance apoptosis (2-4). RA and synthetic retinoids exert their effects through activation of two classes of nuclear retinoic acid receptors, RARs and RXRs, which act as transcription factors to regulate expression of genes that contain retinoic acid response DNA elements (RAREs). Activation of specific RARs and RXRs has been shown to be responsible for the individual toxicities and teratogenicities associated with retinoids (5, 6). The toxicities associated with chronic retinoid treatment affect the skin, mucus membranes, hair, eyes, gastrointestinal system, liver, neuromuscular system, endocrine system, kidneys and bone, and are collectively termed hypervitaminosis A (7).

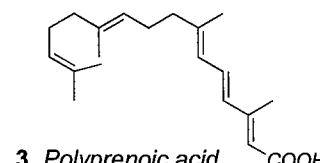
Secondary Chemoprevention Trials

The ability of retinoids to regulate growth and differentiation prompted their testing in secondary chemoprevention trials. In each of 4 trials, patients were randomized to receive either the retinoid or placebo after primary therapy for their cancer. In a trial of 103 patients with head and neck cancer, significantly fewer patients developed second primary tumors in the group treated with 13-*cis*-RA [2] (14%) in comparison to the group that received placebo (31%) with a median follow-up of 54 months (8). A similar trial of head and neck cancer using the synthetic



2, *13-cis-RA*

retinoid etretinate however, did not find a significant chemopreventative effect of the retinoid within a median follow-up of 49 months (9). In a trial of 307 patients with lung cancer, 8.6% of retinol palmitate (vitamin A)-treated patients developed second primary tumors, compared with 16% of patients that received placebo with a median follow-up of 46 months (10). In a trial of 89 patients with liver cancer, 27% of patients who received an acyclic retinoid, polyprenoic acid [3], developed recurrent or second primary tumors compared with 49% of patients who received placebo, with a median follow-up of 38 months (11). Despite this limited success, improved analogs of the retinoids are needed to improve the therapeutic ratio (efficacy/toxicity) before clinical application of a retinoid strategy for chemoprevention.

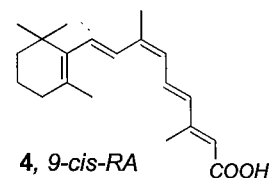


3, *Polyprenoic acid*

Design of Synthetic Retinoids

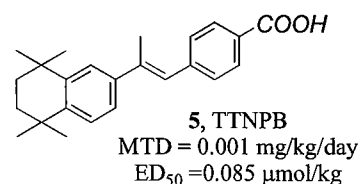
Medicinal chemists have exploited the wide range of biological activities of RA isomers, such as *all-trans*-RA [1] and 9-*cis*-RA [4], in their efforts to develop retinoid

pharmaceuticals for skin diseases, cancer, cardiovascular diseases and diabetes. Retinoids consisting of dramatic modifications of the naturally occurring all-*trans*-RA [1] structure, retain the biological activities, but also exhibit the toxicities of the natural compound. The ultimate goal in



the design of retinoids is to retain the activities specifically associated with potential therapeutic effects while eliminating activities associated with toxicity and teratogenicity. Early efforts to develop retinoids selective for the wide range of biological activities of RA were based on the premise that the flexibility of the tetraene side chain of all-*trans*-RA [1] allowed several conformations that were responsible for the individual activities and, therefore, synthetic compounds designed to be restricted in flexibility would be capable of only a subset of these activities. In the 1980's, conformationally restricted retinoids were designed by constraining the retinoid double-bonds that correspond to the tetraene side chain of all-*trans*-RA, by inclusion in an aromatic ring.

One of the first conformationally restricted retinoids, TTNPB [5], incorporated the bonds corresponding to the 5,7-double bonds and the 11,13-double bonds of *trans*-RA [1] into a tetrahydronaphthalene ring and phenyl ring systems, respectively, to restrict such bonds to planar cisoid conformations. Also, a *gem*-dimethyl group was incorporated into the tetrahydronaphthalene ring to block oxidation of the ring at the location that corresponded to the 4-position of the β -cyclogeranylidene ring of all-*trans*-RA [1]. TTNPB [5] was 10-fold more potent than all-*trans*-RA [1] in the tracheal organ culture (TOC) differentiation assay and was equally effective in the ornithine decarboxylates (ODC) induction assay (12). The clinical utility of this compound however, was prevented by a 10,000 fold greater toxicity in comparison to all-*trans*-RA [1] (13-15).



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