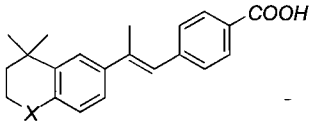
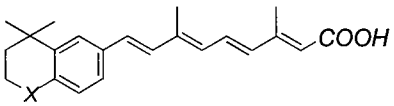
Design of Heteroarotinoids

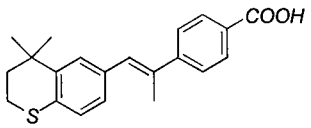
Our subsequent strategy to reducing the toxicity of arotinoids was to block metabolic oxidation of the compounds by incorporation of oxygen or sulfur heteroatoms to replace one of the *gem*-dimethyl groups in the tetrahydronaphthalene ring (heteroarotinoids [**6A** and **6B**, respectively]). Both of these heteroarotinoids exhibited the retinoid activities in TOC and ODC assays (1, 2).



6a, *X = O, MTD = 9.4 mg/kg/day*
6b, *X = S*



7a, X = O, MTD = 32 mg/kg/day
7b, X = S, MTD = 34 mg/kg/day



8, *ED_{50}= 5.0 mmol/kg*

Therapeutic ratios of heteroarotinoids in animal models.

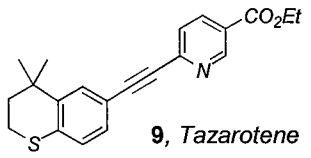
The therapeutic ratios of TTNPB [**5**] and the oxygen and sulfur heteroarotinoid derivatives [**6a** and **6b**, respectively] were compared in animal models of chemoprevention and toxicity (1). In the chemoprevention model, CD-1 mice were treated with DMBA and TPA to initiate and promote tumor formation, respectively. At concentrations of 17 and 170 n*M*, the heteroarotinoids [**6a**, **6b**] significantly inhibited tumor formation without toxic symptoms, while TTNPB [**5**] caused animal death due to hypervitaminosis A. At the lower dose of 1.7 n*M* of TTNPB [**5**], hypervitaminosis A was observed without animal death, and tumor formation was significantly inhibited. In a toxicity animal model, female Swiss mice were given intraperitoneal injections of a range of concentrations of these compounds over a period of two weeks, and the number of animal deaths was monitored. The results of this model demonstrated that, TTNPB [**5**] was far more toxic than all-*trans*-RA [**1**], and killed all of the animals at concentrations as low as 3.3 μ*M* μ*M*/kg/day, while all-*trans*-RA [**1**] did not kill the animals at concentrations as high as 100 μ*M*/kg/day. In contrast, the heteroarotinoids [**6a** and **6b**] were actually less toxic than all-*trans*-RA [**1**]. At a concentration of 200 μ*M*/kg/day, all-*trans*-RA [**1**], the oxygen heteroarotinoid [**6a**] and the sulfur heteroarotinoid [**6b**] killed 37%, 10% and 20% of the mice, respectively.

In a detailed study of toxicity, **5, 6a**, **7a** and **7b** were administered to groups of 16 animals each by gavage over a range of concentrations for 65 days (3). Mortalities, body weight, bone fracture incidence, signs of hypervitaminosis, hematologic parameters and pathology were documented. The maximum tolerated doses (MTD's) for each compound were calculated as the doses required to induce 10% weight loss in the treated animals. The MTD for TTNPB [**5**] was 0.001 mg/kg/day, which is 10,000-fold more toxic than the 10 mg/kg/day MTD of all-*trans*-RA [**1**]. In contrast, the MTD for the diaryl oxygen heteroarotinoid [**6a**] was 9.4 mg/kg/day, which is comparable to all-*trans*-RA [**1**]. The 10,000-fold difference in the MTD's for **5** and **6a** demonstrate that the heteroatom greatly decreases the toxicity of the arotinoid structure. The MTDs of 32 and 34 mg/kg/day of the monoaryl heteroarotinoids with oxygen **7a** and sulfur **7b** heteroatoms, respectively, revealed a 3-fold decrease in the toxicity of the monoaryl compounds in comparison to all-*trans*-RA [**1**]. One heteroarotinoid, **8**, was evaluated for teratogenicity in a fetal hamster model (4). The ED_{50} of **8** in this model was 5.0 μmol/kg, which is significantly less teratogenic than the ED_{50} of 0.085 μmol/kg for TTNPB [**5**] (4). Thus, inclusion of

the heteroatom in the arotinoid structure was shown to greatly improve the therapeutic ratio (efficacy/toxicity) in animal models.

Clinical Use of a Heteroarotinoid

The clinical application of a heteroarotinoid Tazarotene [**9**] produced by Allergan, has confirmed the improved therapeutic ratio predicted for compounds with heteroatoms (5). The ethyl ester form of the drug, which does not bind retinoid receptors, is used as prodrug that is readily metabolized to the receptor-active tazarotenic acid. A nicotinic acid moiety is utilized as the terminal aryl group to ensure the rapid metabolism to the acid form. The sulfur heteroatom of circulating tazarotenic acid is metabolically deactivated by oxidation, thereby producing the inactive sulfoxide and sulfone metabolites that are excreted in the urine (6). In addition, a triple bond between the two aromatic rings conformationally restricts this compound. Tazarotene is being investigated as a single agent for the treatment of acne vulgaris and in combination with corticosteroids for the treatment of psoriasis (20, 21). The mechanism of action in psoriasis is thought to occur through direct regulation of genes involved in differentiation and inflammation (7). Tazarotene is administered topically, and its good safety profile is most likely due to the low penetration through the skin to the blood system, rapid metabolism and elimination from the body (8). Tazarotene does not cause contact sensitization, and induces only mild to moderate reversible skin irritation. Since the toxic effects of retinoids in skin are associated with specific activation of RARγ, the RARβ/RARγ selectivity of Tazarotene, could explain its decreased toxicity in contrast to the severe skin irritation caused by other RARγ-selective compounds. This finding supports the theory that targeting individual receptors in retinoid drug design may not be as effective as targeting subsets of receptors or biological activities in the natural environment of the target cells.



9, *Tazarotene*

References

1. Dawson, M. I., Hobbs, P. D., Derdzinski, K., Chan, R. L.-S., Gruber, J., Chao, W.-R., Smith, S., Thies, R. W., and Schiff, L. J. Conformationally restricted retinoids. J. Med. Chem., *27:* 1516-1531, 1984.
2. Waugh, K. M., Berlin, K. D., Ford, W. T., Holt, E. M., Carroll, J. P., Schomber, P. R., and Schiff, L. J. Synthesis and characterization of selected heteroarotinoids. Pharmacological activity as assessed in vitamin A deficient hamster tracheal organ cultures. Single crystal X-Ray diffraction analysis of 1-(1-1-dioxa-3,4-dihydro-4,4-dimethyl-2*H*-1-benzothiopyra-6-yl)ethanone and ethyl (*E*)-4-[2-(3,4-dihydro-4,4-dimethyl-2*H*-1-benzothiopyran-6-yl)-1-propenyl]benzoate. J. Med. Chem., *27:* 116-124, 1985.
3. Benbrook, D. M., Madler, M. M., Spruce, L. W., Birckbichler, P. J., Nelson, E. C., Subramanian, S., Weerasekare, G. M., Gale, J. B., Patterson, M. K., Jr., Wang, B., Wang, W., Lu, S., Rowland, T. C., DiSilvestro, P., Lindamood, C., III, Hill, D. L., and Berlin, K. D. Biologically active heteroarotinoids exhibit anticancer activity and decreased toxicity. J. Med. Chem., *40:* 3567-3583, 1997.

4. Willhite, C. C., Jurek, A., Sharma, R. P., and Dawson, M. I. Structure-affinity relationships of retinoids with embryonic cellular retinoic acid-binding protein. Tox. Appl. Pharm., *112:* 144-153, 1992.
5. Chandraranta, R. A. S. Tazarotene - First of a new generation of receptor-selective retinoids. Br. J. Dermatol, *135:* 18-25, 1996.
6. Chandraratna, R. A. S. Tazarotene: The first receptor-selective topical retinoid for the treatment of psoriasis. J. Am. Acad. Dermatol., *37:* S12-S17, 1997.
7. Duvic, M., Nagpal, S., Asano, A. T., and Chandraratna, R. A. Molecular mechanisms of tazarotene action in psoriasis. J. Am. Acad. Derm., *37:* S18-S24, 1997.
8. Menter, A. Pharmacokinetics and safety of tazarotene. J. Am. Acad. Derm., *43:* S31-S35, 2000.