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Publications:

[Wagner et al. - J Med Chem - 2009](#)

[Furmick et al. -](#)

[ChemMedChem - 2012](#)

[Batie et al. - Bioorg Med Chem - 2013](#)

[Jurutka et al. - J Med Chem - 2013](#)

[Marshall et al. - Pharma Res Per - 2015](#)

Intellectual Property

Status:

[US 9,174,917 B2](#)

[US 2014/0343079 A1](#)

[JP 5784045 B](#)

[WO 2015/130973 A1](#)

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*Additional US and foreign
patents pending*

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Compounds to Modulate Retinoid X Receptors - Analogs & Derivatives of Bexarotene

AzTE Cases: M09-155L, M12-028L, M14-080L, M14-138L, M15-137L & M15-172L

Invention Description

The human retinoid X receptors (RXRs) function as transcriptional regulators, often in partnership with members of a larger nuclear receptor family of transcription factors. RXR agonists have been shown to modulate RXR transcription and activate or repress various biological pathways and effect therapeutic results for various conditions.

Bexarotene (Targretin®) is a synthetic retinoid analog used to treat cutaneous T-cell lymphoma (as well as off label to treat other types of cancer). However, recent research may show significant potential in its use for treatment of Alzheimer's disease. Bexarotene is especially effective because it has specific high affinity for RXRs. However, Bexarotene treatment has some side effects, namely hypothyroidism, hyperlipidemia, and cutaneous toxicity, which may be due to its activation of RXR in several different tissues.

Researchers at Arizona State University have developed a portfolio of compounds which are more potent analogs and derivatives of Bexarotene that may provide alternatives to Bexarotene usage. These analogs have a higher selectivity for the retinoid X receptor versus the retinoic acid receptor (RAR) and can be uncoupled from drastic lipid changes and thyroid axis variations. Additionally, in astrocytes and microglia, these Bexarotene analogs increase expression of ApoE and highly lipidated HDLs, which then promote clearance of amyloid beta in the brain.

These new analogs may provide viable and efficacious alternatives to Bexarotene for cancer, Alzheimer's disease (AD), Parkinson's disease (PD), schizophrenia, and other neurodegenerative diseases. Further, animal testing suggests that the improved PK and triglyceride profiles make these compounds compelling therapeutic candidates.

Potential Applications

- Anti-cancer treatment
 - CTCL, colon, breast, lung, pancreatic and others
- May be useful in treatment of AD & other neurodegenerative diseases
- May be useful in treatment of RXR-pathway related diseases
- May be useful in treatment of diseases associated with dopamine deficiency
 - PD, schizophrenia, depression, and other psychotic disorders
- May be useful in treatment of non-insulin dependent diabetes mellitus
- Drug discovery

Benefits and Advantages

- Several analogs demonstrate higher affinity/activation for RXR than Bexarotene
- Higher efficacies/potency/specificity may allow for lower doses thus alleviating some side effects
- Improved side effects than parent compound, Bexarotene
- May stimulate gene expression better than Bexarotene
- Some compounds may be less toxic than Bexarotene and produce statistically lower triglyceride levels
- Improved PK characteristics