Bioorganic & Medicinal Chemistry 25 (2017) 2743–2753

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Ester-to-amide rearrangement of ethanolamine-derived prodrugs of sobetirome with increased blood-brain barrier penetration

Skylar J. Ferrara [a], J. Matthew Meinig [a], Andrew T. Placzek [a], Tapasree Banerji [a], Peter McTigue [a], Meredith D. Hartley [a], Hannah S. Sanford-Crane [a], Tania Banerji [a], Dennis Bourdette [b], Thomas S. Scanlan [a,*]

[a] Program in Chemical Biology, Department of Physiology & Pharmacology, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR 97239, United States
[b] Department of Neurology, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR 97239, United States

ARTICLE INFO

Article history:
Received 24 February 2017
Revised 17 March 2017
Accepted 21 March 2017
Available online 23 March 2017

ABSTRACT

Current therapeutic options for treating demyelinating disorders such as multiple sclerosis (MS) do not stimulate myelin repair, thus creating a clinical need for therapeutic agents that address axonal remyelination. Thyroid hormone is known to play an important role in promoting developmental myelination and repair, and CNS permeable thyromimetic agents could offer an increased therapeutic index compared to endogenous thyroid hormone. Sobetirome is a clinical stage thyromimetic that has been shown to have promising activity in preclinical models related to MS and X-linked adrenoleukodystrophy (X-ALD), a genetic disease that involves demyelination. Here we report a new series of sobetirome prodrugs containing ethanolamine-based promoieties that were found to undergo an intramolecular O,N acyl migration to form the pharmacologically relevant amide species. Several of these systemically administered prodrugs deliver more sobetirome to the brain compared to unmodified sobetirome. Pharmacokinetic properties of the parent drug sobetirome and amidoalcohol prodrug **3** are described and prodrug **3** was found to be more potent than sobetirome in target engagement in the brain from systemic dosing.

1. Introduction

Thyroid hormone is an essential regulatory molecule in vertebrate physiology and homeostasis. In the central nervous system (CNS) thyroid hormone plays an integral role in development and maintenance of brain function. Myelination of nerve fibers and neuronal and glial cell differentiation are processes in which thyroid hormone plays a key regulatory role.[1] Thyroid hormone prompts the maturation of oligodendrocytes (OLs) from oligodendrocyte progenitor cells (OPCs),[2] promotes the expression of oligodendrocyte-specific genes that activate the production of myelin,[3] and has been shown to play a role in stimulating myelin repair in response to demyelination.[4–6] Currently, the only treatment options for multiple sclerosis (MS), the most prevalent demyelinating neurological disorder,[7] target the autoimmune inflammatory process of the disease that causes demyelination but do not address myelin repair.[8,9] The endogenous thyroid hormone is not a viable candidate for myelin repair as it lacks a therapeutic index (TI) separating desirable therapeutic effects from deleterious systemic thyrotoxic effects, particularly on heart, bone, and skeletal muscle.[10] The thyromimetic sobetirome (**1**, also known as GC-1) displays selective tissue action with a TI separating beneficial from adverse effects and has progressed to clinical studies in hyperlipidemia.[11] In terms of potential for CNS disorders, sobetirome has been studied in pre-clinical models of X-linked adrenoleukodystrophy (X-ALD), a lipid storage disease that produces severe neurological phenotypes involving demyelination.[12] In addition, sobetirome has been shown to promote oligodendrogenesis from human and rodent OPCs *in vitro*, and enhance oligodendrogenesis during development with attending increased production of myelin proteins *in vivo*, supporting the idea that thyromimetic agents that distribute to the central nervous system (CNS) may be useful candidates for treating demyelinating disorders.[13]

Most thyromimetics, including sobetirome, contain inner-ring, negatively charged carboxylate groups at physiological pH. These carboxylate groups are crucial for high affinity binding to the thyroid hormone receptor, but are a known liability for CNS drug distribution due to their inherent lipophobic character and

Abbreviations: ACN, acetonitrile; br, broad; Cbz, *N*-benzyloxycarbonyl; DMAP, 4-dimethylaminopyridine; DMSO, dimethyl sulfoxide; ED_{50}, median effective dose; HPLC, high performance liquid chromatography; LC-MS/MS, liquid chromatography tandem mass spectrometry; MeOH, methanol; MHz, megahertz; NMR, nuclear magnetic resonance spectroscopy; Pd/C, palladium on carbon; p.o., per os; r.t., room temperature; THF, tetrahydrofuran.

* Corresponding author.
E-mail address: scanlant@ohsu.edu (T.S. Scanlan).

http://dx.doi.org/10.1016/j.bmc.2017.03.047
0968-0896/

electrostatic repulsion at negatively charged tight junctions of blood-brain barrier (BBB) endothelial cells.[14,15] While sobetirome does distribute to the CNS,[16,17] employing a prodrug strategy which masks these carboxylate groups should, in theory, provide greater access to the CNS and could potentially limit peripheral exposure of the parent drug. After crossing the BBB, these prodrugs can be hydrolyzed to the parent drug sobetirome. Recently, an *in vivo* study evaluating the brain exposure of ester-based prodrugs of sobetirome confirmed this strategy to be effective.[18] In this study, a particular ester derivative, an ethanolamino ester (**2**), was found to have the greatest CNS penetration with minimized peripheral exposure of the parent drug. Here we report a new series of prodrugs that feature improved CNS distribution compared to the originally reported ethanolamino ester and, in the process, it was discovered that these ester promoieties undergo an intramolecular rearrangement to form the corresponding amides, which were found to be the pharmacologically active forms of the prodrugs.

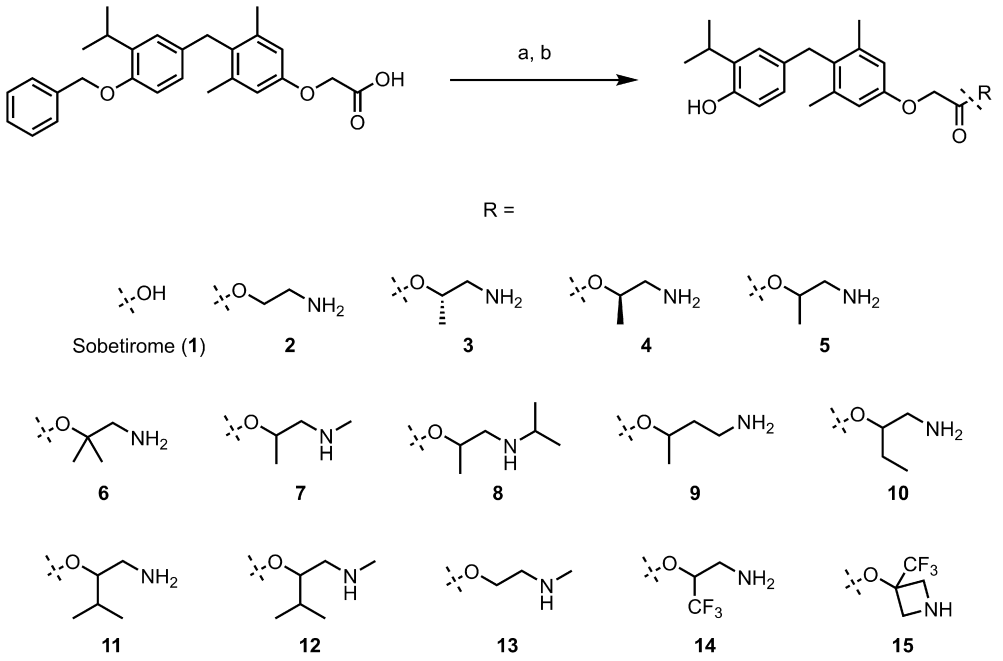
2. Results and discussion

2.1. Chemistry

In line with the recently reported successful application of an ethanolamine-based ester prodrug of sobetirome[18] and ethanolamine-based ester prodrugs of dexibuprofen,[19,20] a drug with structural similarities to sobetirome, a new series of ethanolamine-derived prodrugs of sobetirome were synthesized in an effort to expand upon these findings and improve their pharmacokinetic properties regarding CNS distribution (Scheme 1). Derivatization of the ethanolamine moiety within the series explores varying aspects of steric and electronic parameters with subtle differences in lipophilicity. Branching at the alpha carbon adjacent to the ester group was examined in an effort to impede hydrolysis via steric hindrance of the ester carbonyl (**3**–**12**, **14**–**15**). Electron withdrawing trifluoromethyl groups were incorporated to weaken the associated ester bonds (**14**–**15**), and alkylation of the amino group of the promoiety (**7**–**8**, **12**–**13**, **15**) was implemented to modulate the amino group's pKa and deter potential interactions with monoamine oxidase (MAO).[21] Additionally, degrees of freedom about the promoiety were altered by chain elongation (**9**) and incorporation of a heterocycle (**15**).

Modular synthesis of the series of ethanolamine-based prodrugs was accomplished in two steps starting with coupling of a benzyl-protected sobetirome fragment to an *N*-Cbz or *N*-(di)benzyl protected amino alcohol, followed by parallel protecting group removal by hydrogenolysis to form the ester prodrugs in moderate-to-good yield (Scheme 1). To selectively form ester species of interest, the amino alcohol's amino group was protected with Cbz, which significantly alters the polarity of the promoiety and provides for an easy separation and isolation of the *N*-protected amino alcohol. For amino alcohols that are not commercially available, zinc(II) perchlorate catalyzed nucleophilic attack of substituted epoxides by benzylated amines was employed according to a literature procedure.[22] Generation of the acid chloride of phenol-benzylated sobetirome (Scheme 1, left) is accomplished by treating phenol-benzylated sobetirome with oxalyl chloride in the presence of a catalytic amount of DMF.[18,23] Coupling of the phenol-protected sobetirome acid chloride with *N*-protected amino alcohols occurs readily in the presence of DMAP in heated THF. Global deprotection of benzyl ether, *N*-Cbz, and *N*-benzyl protected fragments follows with treatment of the protected precursors with 10% Pd/C and triethylsilane in THF/MeOH.[24] Multiple precipitations of the resulting product from hexanes yields the desired ester derivatives in excellent purity.

All compounds in the series were characterized by ^{1}H NMR spectroscopy and assessed for purity by HPLC. While all isolated final compounds were spectroscopically determined to be the desired ester derivatives, it was discovered that by eluting some derivatives on silica led to the isolation of fractions that correspond to the promoiety-rearranged amide species (Scheme 2). Formally known as an O,N acyl migration, this intramolecular rearrangement proceeds with nucleophilic attack of the ester carbonyl by the promoiety's amino group lone pair leading to facile formation of a five-membered cyclic intermediate, followed by rearrangement to the thermodynamically favored amide. Intramolecular O,



Scheme 1. Synthesis and structures of sobetirome and sobetirome prodrugs. Reagents and conditions: (a) (i) oxalyl chloride, DCM, DMF, (ii) *N*-Cbz amino alcohol or *N*-(di) benzyl amino alcohol, DMAP, THF (b) 10% Pd/C, Et_3SiH, MeOH/THF.