

RSC Chemical Biology

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: E. Kwa, C. E. Ogilvie, N. C. Kormos, A. J.E. Green, T. Smith and F. J. Gunn-Moore, *RSC Chem. Biol.*, 2026, DOI: 10.1039/D6CB00093B.



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

The inhibitors of 17 β -HSD10: are they any good?

Ernst Kwa¹, Charlene E. Ogilvie¹, Natalie C. Kormos¹, Alison J.E. Green², Terry K. Smith¹
and Frank J. Gunn-Moore^{1,3}

¹School Of Biology, University of St. Andrews, St Andrews, KY16 9ST

²Scottish Brain Sciences, Eden Campus, University of St. Andrews, Guardbridge KY16 0US

³School Of Biology, University of St. Andrews, St Andrews, KY16 9ST. fjj1@st-andrews.ac.uk

Abstract

The advent of the first disease-modifying therapies for Alzheimer's disease (AD) has renewed optimism for effective prevention and treatment strategies. Growing mechanistic insights indicate that AD pathogenesis is multifactorial and non-linear, better conceptualized as a circular vortex in which interconnected pathological processes reinforce one another. This complexity highlights the necessity for multiple druggable targets and combination-based therapeutic approaches. A hallmark of AD is reduced cerebral glucose utilization, revealed by positron emission tomography studies, reflecting profound metabolic disruption and mitochondrial dysfunction. Among mitochondrial candidates, 17 β -hydroxysteroid dehydrogenase type 10 (17 β -HSD10), encoded by *HSD17B10*, has emerged as a protein of interest. Despite debate surrounding its substrate specificity due to conflicting *in vitro* data, elevated expression in neurons and astrocytes within AD brains underscores its potential relevance. This review outlines chemical entities targeting both catalytic and non-catalytic functions of 17 β -HSD10 and examines whether its inhibition offers biological efficacy and clarifies its metabolic roles in the living brain.

Introduction

As the first disease-modifying treatments have started to appear ¹, there is renewed optimism in the development of new therapeutics for the prevention and management of Alzheimer's disease (AD). Additionally, as research continues to shape our mechanistic understanding of AD pathology ^{2,3}, it has become clear that disease triggers are multifactorial, and not simply a linear cascade of events. Consequently, we postulate that AD is a circular vortex with several entry points, and that pathogenesis rarely stems from a singular cause. Given the complex disease aetiology, identification of multiple druggable targets is imperative for effectual therapeutics. Indeed, we have previously highlighted the requirement for at least three drug types to enable the effective treatment of AD ⁴.

Previous studies using positron emission tomography (PET) scans, have revealed a substantial reduction in glucose utilisation in AD brains, despite normal levels in healthy ageing counterparts ⁵. This finding indicates major disruptions in core metabolic processes, with mitochondrial dysfunction evidently being a well-documented feature of AD pathology ⁶. While 14 different mammalian classes/types of 17- β hydroxysteroid dehydrogenase (17 β -HSD) have been identified, only 12 are present in humans ^{7,8}.

The focus of this review is 17- β hydroxysteroid dehydrogenase type 10 (17 β -HSD10), encoded by the *HSD17B10* gene ⁹⁻¹¹. This mitochondrial enzyme has piqued longstanding interest and generated much debate, with several publications disputing proper nomenclature due to contradictory *in*



in vitro findings, leading to uncertainty over substrate specificity *in vivo* ^{12–15}. Such discrepancies, however, can be attributed to wide variations in experimental parameters, which likely have little relevance to the living human brain. What is not in question, however, is that both neurons and astrocytes are involved, with each reported to have elevated 17 β -HSD10 protein expression in the AD brain ^{12,16}, although the full consequence of this has yet to be elucidated.

In the last decade, several different lines of research have suggested that modulation of 17 β -HSD10 function may have therapeutic merit. Therefore, in this review we will describe the different chemical entities that have been developed to target the catalytic and non-catalytic activities of this protein. Many of these novel compounds are now at the stage of being able to answer two critical questions:

- 1) Does inhibiting 17 β -HSD10 activity have biological efficacy in AD models (and possibly other diseases)?
- 2) Is it now possible to determine which metabolites/substrates 17 β -HSD10 modifies in the living brain?

17 β -HSD10 identification and nomenclature

As outlined above, identification of the true physiological role of 17 β -HSD10 has been a longstanding point of contention in the field, largely due to early studies relying upon heterologous expression of recombinant protein in *Escherichia coli*, with much variation in subsequent protein purification and activity assay protocols ^{12,14,17–19}. However, a combination of *in vivo* and cell culture studies in mammals, *Xenopus laevis* and *Drosophila melanogaster*, have given some insights into physiologically relevant functions, highlighting clear roles in neurosteroid oxidation, mitochondrial homeostasis and branched-chain amino acid metabolism ^{12,19,20}. For example, deletion of the 17 β -HSD10 gene in mouse models resulted in embryonic demise during gastrulation ²¹, while a tissue-specific conditional knockout led to the development of mitochondrial abnormalities, such as the loss of cristae and fragmented organelle ²¹. In *X. laevis* models, knockdown of the 17 β -HSD10 homologue reduced mitochondrial pyruvate turnover and triggered apoptosis that eliminated forebrain and eye structures ²¹. Conversely, rescue experiments demonstrated that microinjection of wild-type human 17 β -HSD10 restored mitochondrial morphology and prevented apoptosis ²¹. Furthermore, loss-of-function studies investigating the *D. melanogaster* short chain L-3-hydroxyacyl-CoA dehydrogenase, a 17 β -HSD10 homologue encoded by the *scully* (*scu*) gene, resulted in embryonic and pupal lethality, accompanied by severe defects in germline development; mutant flies also exhibited mitochondrial abnormalities in photoreceptor cells, producing phenotypes that closely resembled human β -oxidation fatty acid disorder ²². Overexpression studies have further illustrated the functional significance of 17 β -HSD10 ²³. For example, overexpression of 17 β -HSD10 in PC12, rat adrenal gland tumour-derived cells, accelerated tumour growth in both culture monolayers and in severe combined immunodeficiency (SCID) mouse xenografts; this enhanced tumorigenicity was accompanied by increased mitochondrial complex IV activity and upregulated ATP production ²³.

The broad substrate range of 17 β -HSD10 may explain why this enzyme was independently “rediscovered” several times across different fields, leading to a series of nomenclature that reflects its diverse biological roles. For example, one of the earliest identifications of 17 β -HSD10 in mammalian systems came from a yeast two-hybrid screen in HeLa cells; here it was determined to bind the amyloid beta (A β) peptide, and was reported to localise to the endoplasmic reticulum (ER), hence it was named endoplasmic reticulum amyloid binding (ERAB) protein ¹². Almost simultaneously, biochemical purification studies ¹⁴ identified a mitochondrial short-chain dehydrogenase (SCHAD) and classified it as L-3-hydroxyacyl-CoA dehydrogenase based upon its activity towards β -oxidation intermediates ^{14,18}. Shortly thereafter, the same gene product was proposed to possess alcohol dehydrogenase activity and able to bind A β directly, giving rise to the revised name A β -binding alcohol dehydrogenase (ABAD) ¹⁷. This naming was also a departure from the previously used ERAB, and the associated misconception of sole localization in the endoplasmic reticulum, which was overturned after new discoveries obtained through GFP-tagged intracellular experiments, evidently localized the protein within the mitochondria ²⁴. In parallel, clinical geneticists investigating inborn errors of metabolism, identified a male patient with X-linked neurodegenerative disease caused by mutations in the same gene²⁵. The authors coined



the protein product 2-methyl-3-hydroxybutyryl-CoA dehydrogenase (MHBD)^{15,25}, and proposed a crucial role in isoleucine catabolism. It was recognised only later, that these independently described proteins were identical entities. Previously in 1996, the enzyme was identified in bovine mitochondria²⁶, and mass spectrometry work of Ofman *et al.* (2003) later revealed that purified MHBD from bovine liver was identical to purified bovine 3-hydroxyacyl-CoA dehydrogenase type II (HADH2), resulting in the combining of science under these two names. The name HADH2 was attributed to the discovered function of catalysing the redox conversion between L-3-hydroxyacyl-CoA and 3-ketoacyl-CoA¹⁴. Ofman *et al.* (2003) recognized the human homolog of this studied bovine enzyme as being ERAB within the short-chain 3-hydroxyacyl-CoA dehydrogenase family. The unifying nomenclature, 17 β -HSD10, was subsequently adopted following the discovery that the enzyme also catalyses the oxidation of 17 β -estradiol (E2), allopregnanolone (AlloP) and 3 α -androstenediol²⁷. In 2008, the focal enzyme was also termed MRPP2 by Holzmann *et al.*, named for its association with mtrNase P activity, but was clearly also identified by its accompanying breadth of names²⁸. Although it has also been referred to as SDR5C1, denoted for its membership in the short-chain dehydrogenase/reductase superfamily^{29–31}, the focal enzyme of this review is presently identified as 17 β -HSD10³². In 2007, the gene symbol, HSD17B10, was officially adopted by the Human Gene Nomenclature Committee (HGNC)³³ and has since been used consistently across multiple studies.

Endogenous 17 β -HSD10 substrates and functions

1) Steroidal substrates

The lipid-soluble steroid hormones, oestrogens and androgens, are amongst the most important physiological substrates of 17 β -HSD10³⁴. These cholesterol-derived signalling molecules play vital roles in a wide range of processes, including reproduction, development, metabolism and immune function^{35–38}. In particular, neurosteroids are known to be crucial in brain development, neuroprotection and neurogenesis, with dysregulation strongly implicated in both HSD10 deficiency and AD³⁹. For example, AlloP, which is oxidised by 17 β -HSD10 to form 5 α -dihydroprogesterone (5 α -DHP) in an NAD⁺-dependent manner (Fig. 1A), is a potent positive allosteric modulator of γ -aminobutyric acid type A receptors (GABA_AR) and is essential for maintaining a variety of neurological functions, including normal GABAergic tone⁴⁰. Investigations have shown that excessive 17 β -HSD10 activity disrupts GABAergic signalling, which ultimately contributes to excitotoxic vulnerability via reduction in AlloP bioavailability^{19,40}.

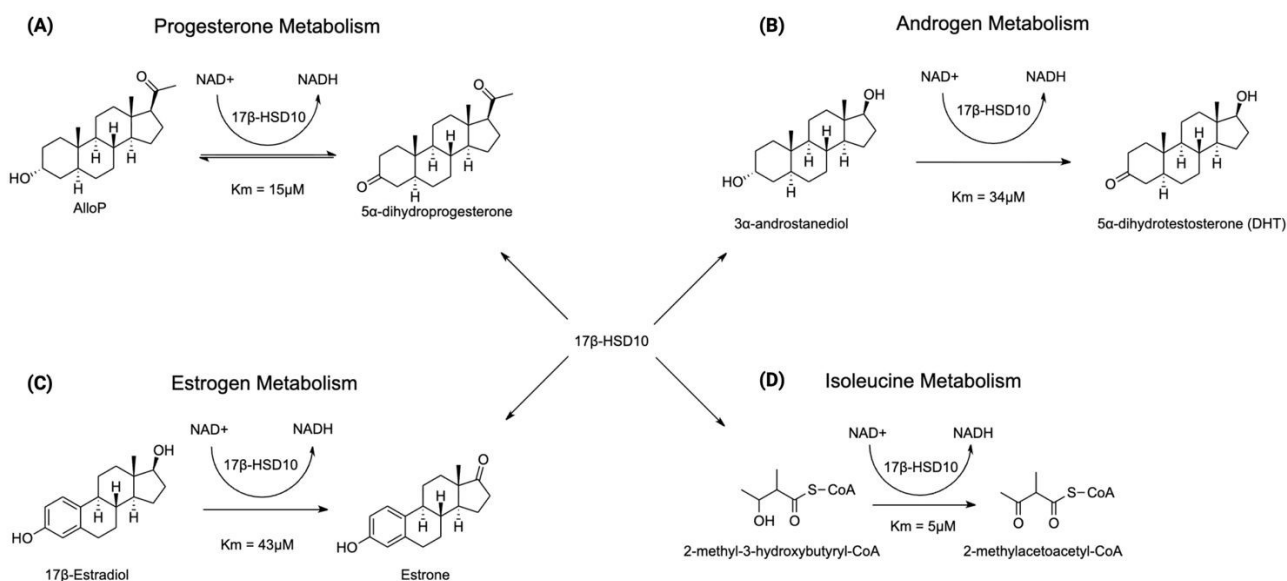


Figure 1. Reactions catalysed by 17 β -HSD10 in steroid and isoleucine metabolism. (A) In progesterone metabolism, AlloP is oxidised to form 5 α -dihydroprogesterone. (B) In androgen metabolism, 3 α -androstane-20-one is converted to 5 α -dihydrotestosterone (DHT). (C) In estrogen metabolism, 17 β -estradiol is oxidised to estrone. (D) In isoleucine catabolism, 2M3HBA is converted to 2MAA-CoA. In all reactions, NAD⁺ serves as a cofactor and is reduced to NADH. K_m values are reported by ^{19,34,35}.

Furthermore, 17 β -HSD10 also catalyses the oxidation of 3 α -androstane-20-one into dihydrotestosterone (DHT) (Fig. 1B), linking the enzyme to androgen metabolism ¹⁹. In prostate cancer, this reaction contributes to a non-classical androgen synthesis pathway, allowing tumour cells to generate DHT even under androgen-deprivation therapy ^{41,42}. This bypass mechanism provides an additional source of DHT, despite suppressed circulating testosterone, and promotes continued androgen receptor signalling, often giving rise to treatment resistance ⁴³.

One of the most significant reactions catalysed by 17 β -HSD10 is the oxidation of E2 (estradiol) to E1 (estrone) (Fig. 1C), with the former supporting essential roles in both female and male physiology, contributing to reproductive function, lipoprotein synthesis, prevention of genital atrophy, regulation of insulin sensitivity and maintenance of cognitive and neuronal function ^{44,45}. Beyond its canonical role as a sex hormone, E2 acts directly on neurons, astrocytes, microglia and neural stem cells, where it modulates ion channel activity and intracellular signalling cascades such as the cyclic adenosine monophosphate (cAMP) ⁴⁶, mitogen-activated protein kinase (MAPK) ⁴⁷ and protein kinase B (Akt) ⁴⁸ pathways. Additionally, upon binding to nuclear estrogen receptors alpha (ER α) and beta (ER β), E2 induces receptor dimerisation and translocation to the nucleus, regulating gene expression in a cell-specific manner ⁴⁹, and subsequently influencing cognition, mood, motor function and neuroprotection ^{50–52}.

Critically, a substantial portion of E2's neuroprotective effects are mediated via signalling pathways that converge on cellular survival mechanisms, particularly within the mitochondria ^{53,54}. In primary hippocampal neurons, E2 activates the phosphatidylinositol 3-kinase (PI3K/Akt) and MAPK signalling cascades to protect against glutamate-induced cytotoxicity ^{55,56}. These pathways stabilise mitochondrial calcium buffering and increase the expression of anti-apoptotic proteins, such as B cell lymphoma-2 (Bcl-2), thus preventing initiation of the apoptotic cascade ⁵³. In addition, E2 also plays a crucial role in neuronal bioenergetics, enhancing mitochondrial efficiency by upregulating key metabolic enzymes such as pyruvate dehydrogenase, complex IV of the electron transport chain (ETC) and ATP synthase, thereby expediting glycolysis and oxidative phosphorylation ^{53,57}. Consequently, E2 serves to reduce mitochondrial oxidative stress, preserve membrane potential and maintain overall mitochondrial integrity ⁵⁸. At the synaptic level, E2 rapidly enhances dendritic spine formation through ER β activation in cortical neurons ⁵⁹. This facilitates synaptic transmission and long-term potentiation (LTP) in the hippocampus by activating the RhoA/ROCK signalling pathway, facilitating actin polymerisation and stabilisation of the synaptic cytoskeleton ^{59,60}.

Collectively, these mechanisms highlight E2 as a critical neuroprotective steroid whose actions span mitochondrial regulation, synaptic plasticity and pro-survival signalling. Consequently, aberrant 17 β -HSD10 activity, be it through overexpression ²³ or A β -mediated dysregulation ¹², has the potential to disrupt E2 signalling, and therefore contribute to mitochondrial dysfunction, synaptic instability and increased vulnerability to neurodegenerative diseases such as AD. Moreover, the decline in circulating estradiol levels during menopause may further exacerbate these effects, leading to a decrease in E2-mediated neuroprotective effects and increasing susceptibility to AD in menopausal women ⁶¹.

2) Non-steroidal substrates

In addition to its roles in neurosteroid and systemic steroid metabolism, 17 β -HSD10 also mediates catabolism of branched chain amino acids (BCAAs) within the mitochondria, catalysing a key step in the isoleucine degradation pathway (Fig. 1D) via oxidation of 2-methyl-3-hydroxybutyryl-CoA (2M3HBA) to 2-methylacetoacetyl-CoA (2MAA-CoA) in an NAD⁺-dependent manner ^{25,62}. Unlike the other BCAAs, leucine and valine, isoleucine is both ketogenic and glucogenic, ultimately giving rise to acetyl-CoA and propionyl-CoA (Fig. 2), respectively ⁶³. The former is a major precursor in the synthesis of ketone bodies and fatty acids ⁶⁴, while the latter contributes to gluconeogenesis via



conversion to oxaloacetate^{65,66}, with both acting as key intermediates in the tricarboxylic acid cycle (TCA), generating high-energy electron carriers NADH/FADH₂ for oxidative phosphorylation and GTP/ATP by substrate-level phosphorylation^{15,67,68}. Evidently, the importance of isoleucine metabolism is further supported by genome-wide association studies (GWAS), which identified a positive relationship between genetic predisposition to raised plasma isoleucine levels, and the development of AD⁶⁹. This critical factor reinforces the importance of proper 17 β -HSD10 activity to sustain mitochondrial energy supply, particularly in high-demand tissues such as the brain.

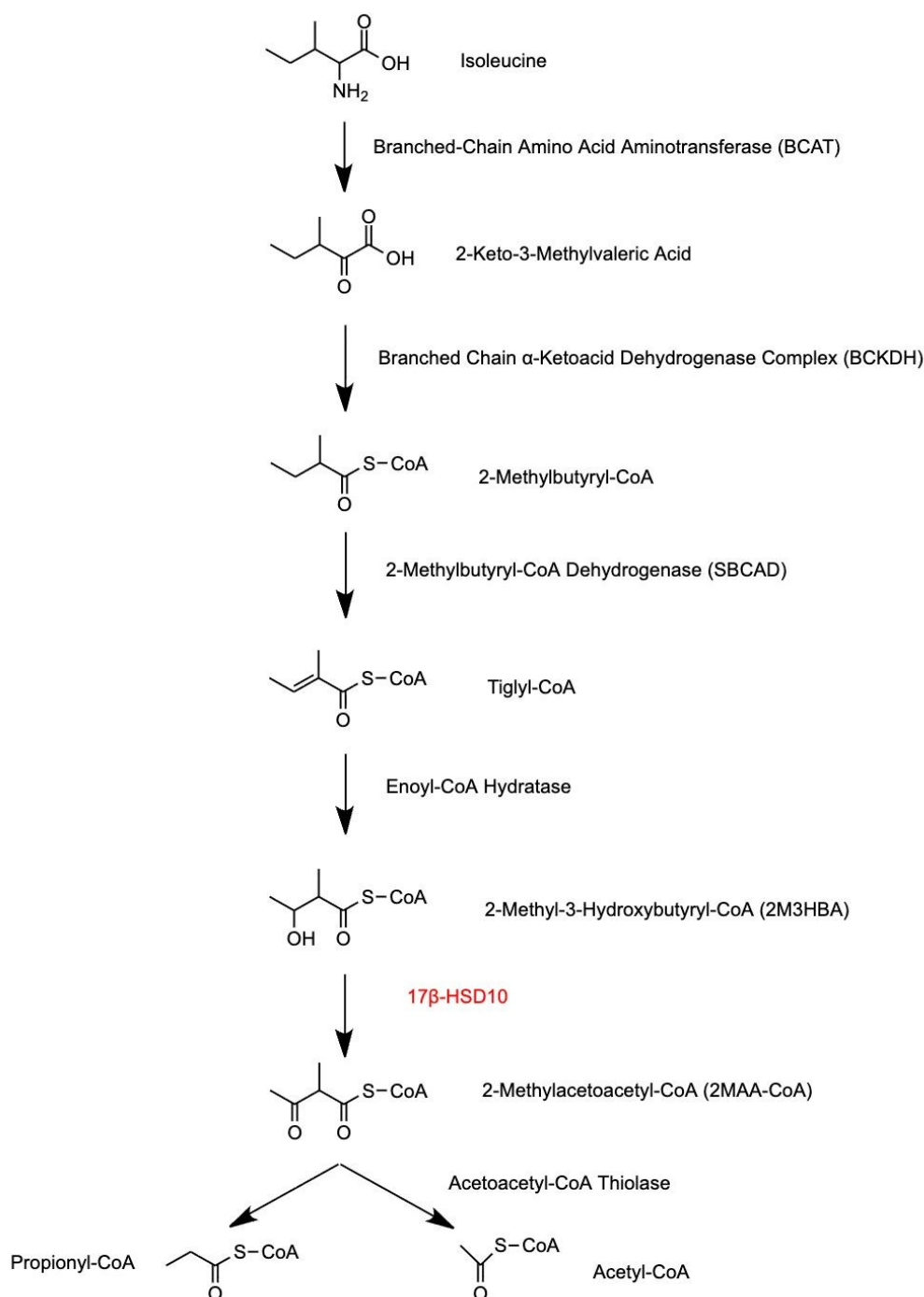


Figure 2. Schematic overview of the mitochondrial degradation of isoleucine to acetyl-CoA and propionyl-CoA. Isoleucine is first transaminated to 2-keto-3-methylvaleric acid by branched-chain amino acid aminotransferase (BCAT), followed by oxidative decarboxylation by the branched-chain α -ketoacid dehydrogenase complex (BCKDH) to yield 2-methylbutyryl-CoA. Sequential enzymatic steps catalysed by 2-methylbutyryl-CoA dehydrogenase (SBCAD) and enoyl-CoA hydratase produce tiglyl-CoA and 2M3HBA respectively. 17 β -HSD10 then catalyses the NAD⁺ dependent oxidation of



2M3HBA to 2MAA-CoA which is subsequently cleaved by acetoacetyl-CoA thiolase to generate acetyl-CoA and propionyl-CoA^{63,70}.

View Article Online
DOI: 10.1039/D6CB00093B

As briefly alluded to above, HSD10 deficiency, also referred to as HSD10 disease, 17 β -HSD10 deficiency, HSD10 mitochondrial disease and MHBD deficiency, is a rare X-chromosome-linked disease caused by missense mutations of the HSD17 β 10 gene^{71–74}. First identified in 2000, in a 2-year-old male patient through urinary metabolite analysis, this rare disease is characterized by clinical symptoms of neurodegeneration, impaired motor control, psychomotor delay, regression of previously acquired motor and cognitive skills, choreoathetosis, cardiomyopathy, abnormal metabolic function, seizures^{25,73}, cognitive impairment, epilepsy¹⁰, retinopathy⁷⁴ and mitochondrial dysfunction⁷⁵. The clinical phenotype is dependent upon the exact mutation position³². Clinical forms of this disease present as neonatal, infantile and juvenile forms, all with severely reduced patient lifespan¹⁰. It was subsequently determined that loss of enzymatic function results in the upstream accumulation of 2M3HBA, producing a toxic organic acid load that can be detected in urine as 2-methyl-3-hydroxybutyrate (2M3HB)^{15,25}. This metabolic block prevents the downstream formation of acetyl-CoA and propionyl-CoA, substantially impairing mitochondrial energy production¹⁵. There is currently no known effective treatment^{10,73,74}, and while adopting an isoleucine-restricted diet may decrease the metabolites (2M3HB and tiglyglycine) in the urine, clinical symptoms of this deficiency do not exhibit any improvement or slow in progression^{21,25,73,74,76}. While it was initially thought that HSD10 deficiency pathology arose exclusively due to inborn errors in isoleucine metabolism²⁵, this earlier hypothesis was incorrect following the discovery in human tissues that mitochondrial energy failure in HSD10 deficiency is caused by abnormal mitochondrial RNA processing⁷⁷. This came after 17 β -HSD10 was identified to be a component of the mitochondrial RNase P complex²⁸, which provides post-transcriptional processing of RNAs into mitochondrial mRNAs, tRNAs and rRNAs⁷⁷. Northern blots performed on heart tissue from control and diseased patients, revealed elevated levels of unprocessed RNA in HSD10 deficiency samples⁷⁷. The disease phenotypes ultimately arise from failure in mitochondrial energy production within the developing nervous system. Taken together, these findings demonstrate that impaired isoleucine catabolism and irregular mitochondrial RNA processing lead to augmented metabolic stress, and serve as key contributors to neuronal death.

Similarly, decreased 17 β -HSD10 levels have been measured in the brains of Parkinson's disease (PD) patients^{72,78}. PD is a neurodegenerative disease with a primary neuropathological hallmark of degradation of the dopaminergic neurons in the substantia nigra pars compacta in the ventral midbrain, a region essential for movement and motor control^{72,78}. PD is characterized by primary impairments of rest tremor, bradykinesia, limb and trunk stiffness and postural instability with freezing of gait⁷⁹. Compared to wild-type littermates, transgenic mice overexpressing human 17 β -HSD10 fourfold, were shown to be more resistant to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a toxin which impairs mitochondrial respiration and degrades dopaminergic neurons⁷⁸. In this same series of experiments, western blot analysis of human tissue samples obtained from the Parkinson Brain Bank at Columbia University, revealed reduced levels of 17 β -HSD10 in the ventral midbrain region of post-mortem samples of PD patients when compared to control subjects⁷⁸. Thus, there is evidently a required balance of the expression of this enzyme⁸⁰, in prevention of AD at one end and PD at the other²³. Further investigation could provide treatment clarity as to the more specific importance of the effects of altering expression of a catalytically inactive vs active form of the enzyme, and subsequently provide a therapeutic foundation for treatment of PD and HSD10 deficiency.

3) Non-enzymatic functions of 17 β -HSD10

While enzymatic activities in steroid and isoleucine metabolism are well established, 17 β -HSD10 has also been shown to operate via noncatalytic interactions with other proteins, including ER α , cyclophilin D (CypD) and the mitochondrial RNase (mtRNase) P complex^{23,28,81,82}.

Specifically, 17 β -HSD10 forms a crucial component of the human mitochondrial RNase P (mtRNase P) complex²⁸. This multi-subunit complex serves as a protein-only endonuclease that cleaves the 5' leader sequence from pre-transfer tRNA (tRNA) to generate mature tRNA⁸³ (Fig. 3). Human mtRNase P was long presumed to contain a trans-acting RNA component, analogous to the



ribozyme-based RNase P systems found in prokaryotes and eukaryotic nuclei⁸⁴. This assumption, however, was disproven when the mitochondrial enzyme was found to be composed entirely of three nuclear-encoded protein subunits: tRNA methyltransferase (MRPP1/TRMT10C), 17 β -HSD10 (MRPP2/SDR5C1) and Mg²⁺-dependent endoribonuclease (MRPP3/PRORP)^{28,85}. Within this complex, MRPP2 forms a stable subcomplex with MRPP1, serving as a structural platform, with ancillary roles in mitochondrial tRNA-binding and methylation, which facilitate catalytic activity of the MRPP3 subunit²⁸. The MRPP2, i.e. 17 β -HSD10 component, is comprised of a homotetramer, with each monomer adopting a Rossmann fold to yield a dehydrogenase active site capable of binding the NAD⁺ cofactor²⁸; however, within the context of mtRNase P, this domain is repurposed as a tRNA-binding motif^{28,86}. The importance of MRPP2 has been highlighted by knockdown studies, which demonstrated that MRPP2 knockdown resulted in the accumulation of unprocessed mitochondrial tRNA precursors, and impaired mitochondrial translation machinery^{28,77}. Furthermore, MRPP2 has also been identified as a critical determinant for the stable expression of MRPP1, experimentally evidenced for example, where single point mutations, such as R130C, in 17 β -HSD10, led to a reduction in MRPP2 and a concomitant loss of MRPP1, resulting in impaired RNase P activity and defective RNA processing⁸⁷.

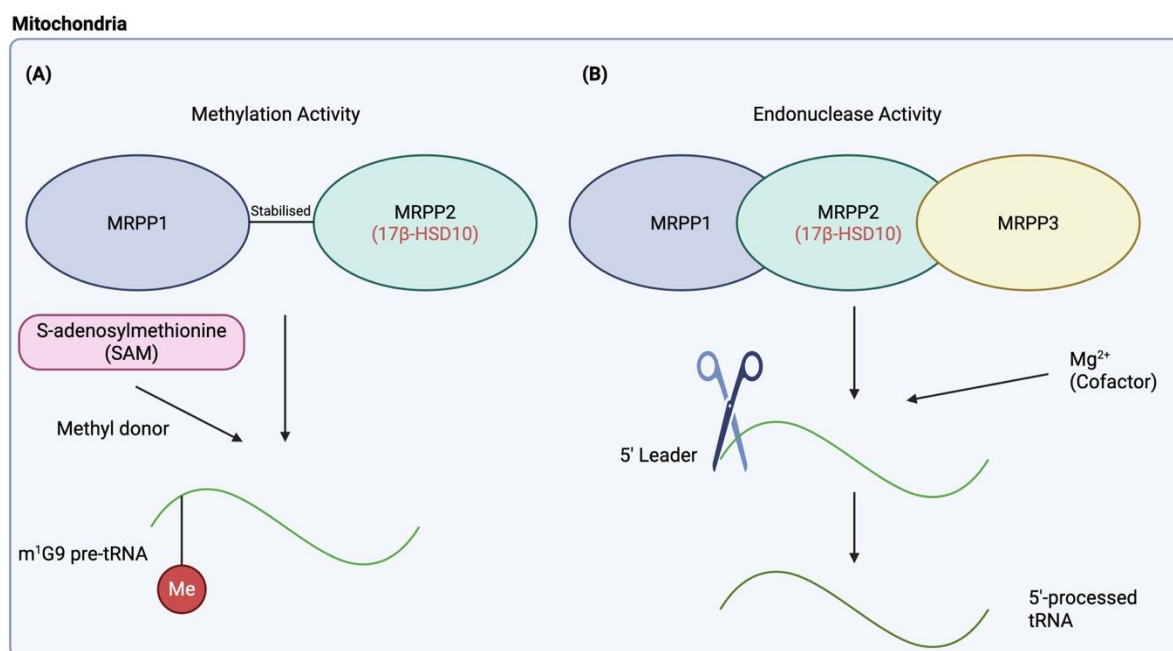


Figure 3. Non-enzymatic role of 17 β -HSD10 (MRPP2) in mitochondrial tRNA processing. 17 β -HSD10 forms a complex with MRPP1 and MRPP3 in mitochondria to regulate tRNA maturation. (A) In the methylation pathway, MRPP1-17 β -HSD10 associates to catalyse N¹-methylation of guanosine at position 9 (m¹G9) of precursor tRNA using S-adenosylmethionine (SAM) as a methyl donor⁸⁸, with 17 β -HSD10 providing a structure stabilising role²⁸. (B) In the endonuclease pathway, the MRPP1-17 β -HSD10-MRPP3 complex forms mtRNase P²⁸, where MRPP3 functions as the catalytic endonuclease, responsible for 5' cleavage of precursor tRNA²⁸. This cleavage requires Mg²⁺ as a cofactor and generates mature 5'-processed tRNA²⁸. Created in BioRender. Lab, G. (2026) <https://BioRender.com/fw89upy>

Another non-enzymatic interaction between 17 β -HSD10 and ER α (Fig. 4) within the mitochondria has been documented, suggesting the enzyme plays a role in regulating local hormone signalling. This interaction was first observed in neonatal rat cardiomyocytes, where 17 β -HSD10 was found to bind directly to the ligand-binding domain of ER α in a hormone-sensitive manner⁸¹. In these studies, the complex remained intact and 17 β -HSD10 activity was inhibited under low estrogen conditions; however, when mitochondrial E2 levels increased, ER α dissociated from the complex, allowing 17 β -HSD10 to freely oxidise E2 to E1, ultimately resulting in signal termination. This



characteristic led to a model in which 17 β -HSD10 functions as a mitochondrial estrogen sensor and regulator⁸¹.

View Article Online
DOI: 10.1039/D6CB00093B

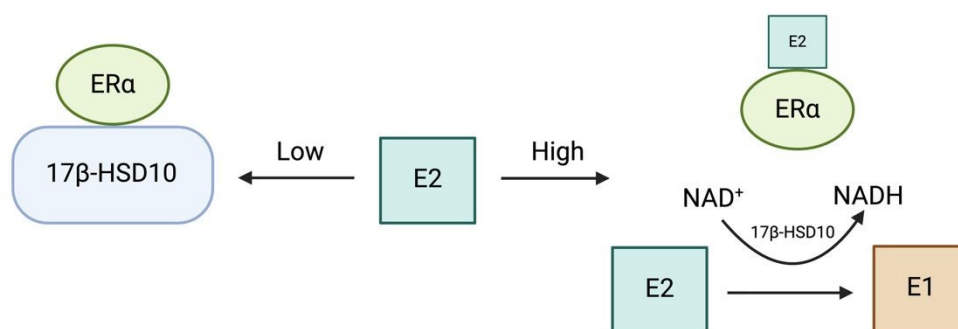


Figure 4. A diagram depicting the interaction of ER α and 17 β -HSD10. Under low concentrations of E2, 17 β -HSD10's enzymatic activity is inhibited by ER α . In the presence of high E2, ER α dissociates from 17 β -HSD10, allowing 17 β -HSD10 to catalyse the conversion of highly potent E2 to less potent E1. Figure adapted from⁸¹, *Biochemical and Biophysical Research Communications*, Vol. 384(4), V. Jazbutyte, F. Kehl, L. Neyses and T. Pelzer, Estrogen receptor alpha interacts with 17 β -hydroxysteroid dehydrogenase type 10 in mitochondria, pp. 450–454, copyright 2009, with permission from Elsevier. Created in BioRender. Lab, G. (2026) <https://BioRender.com/on5sshe>

In addition, another important binding partner of 17 β -HSD10 is the mitochondrial regulator CypD. A combination of co-immunoprecipitation and immunofluorescence studies in PC12 cells have shown that overexpression of 17 β -HSD10 increased formation of the 17 β -HSD10-CypD complex, whereas knockdown of 17 β -HSD10 yielded a reduction in CypD levels²³. Under oxidative stress, CypD typically translocates from the mitochondrial matrix into the inner mitochondrial membrane where it facilitates opening of the mitochondrial permeability transition pore (MPTP), a key event that drives apoptosis or necrosis^{23,89}. Enhanced binding of CypD by 17 β -HSD10 appears to retain CypD within the matrix, thus preventing stress-induced translocation. As such, MPTP opening is inhibited, conferring resistance to oxidative stress-induced mitochondrial dysfunction and limiting misguided apoptosis that would conversely lead to cell death. This interaction suggests that 17 β -HSD10 can modulate mitochondrial vulnerability to injury, in addition to its enzymatic activities.

Dual mechanisms of 17 β -HSD10 in Alzheimer's disease pathogenesis

The mitochondrial enzyme 17 β -HSD10 additionally plays a critical role in the pathophysiology of AD through two primary mechanisms that both contribute to neurodegeneration.

The first pathological mechanism is the overexpression of 17 β -HSD10 in AD brains, which as described above, disrupts neurosteroid metabolism and homeostasis⁷¹. Excessive enzymatic activity accelerates the degradation of E2 and AlloP, leading to decreased levels of these important protective neurosteroids^{90,91}. This reduction leads to decreased ATP production, causing dysregulation of bioenergetics and redox homeostasis, which contributes to mitochondrial dysfunction^{92,93}. Independent of AD, cellular studies have shown that overexpression of 17 β -HSD10 can itself induce cellular damage, reduce viability and impair mitochondrial function in a manner dependent upon its catalytic activity, suggesting that it acts as an independent pathological factor^{71,94}.

The second major pathological role of 17 β -HSD10, involves its interaction with one of the well-documented pathogenic hallmarks of AD, A β aggregates⁹³. The most direct link is 17 β -HSD10's ability to bind A β , particularly the plaque-forming isoforms A β (1-40) and A β (1-42)²⁰. A β enters neuronal mitochondria, where it associates with 17 β -HSD10 via a unique binding site called loop D (92-120); this region forms a short β -hairpin structure exposing key residues, Thr108, His109 and Thr110 for protein-protein interactions^{20,95}. It is thought that binding of A β to 17 β -HSD10 results in a conformational change, which prevents normal enzymatic function via blockage of the NAD⁺ cofactor and/or substrate binding sites²⁰. This binding event has been shown to be cytotoxic *in vitro*, leading to an increase in reactive oxygen species (ROS), inhibition of mitochondrial complex IV and the release



of cytochrome C and lactate dehydrogenase, ultimately leading to apoptosis^{20,95,96}. Evidence from cell viability assays and transgenic experiments, shows that disruption of the A β -17 β -HSD10 interaction leads to positive effects on mitochondria, mitigating oxidative stress and A β -induced toxicity²⁰.

View Article Online
DOI: 10.1039/D6CB00093B

Inhibitors of 17 β -HSD10

Following the above, the targeted modulation of 17 β -HSD10 presents a promising direction for the development of future therapeutics for the treatment of AD⁴³. The goal is to mitigate A β -induced cytotoxicity, while restoring neuroprotective steroidal balance in neurons. Unfortunately, the search for novel and promising inhibitors of 17 β -HSD10 has proved challenging. To date, several compounds have been repurposed or created *de novo* to target either A β -17 β -HSD10 interactions or to directly inhibit 17 β -HSD10 activity^{12,20,97}. Based upon their structure and function, these inhibitors can be broadly classified into 5 major groups: loop D mimetics, benzothiazolyl ureas, fused pyrazole compounds, steroidal compounds, and repurposed drugs and other compounds.

Loop D mimetics

Early efforts to disrupt the pathological interaction between 17 β -HSD10 and A β , focused on peptide-based mimetics derived from the loop D region of the enzyme, which forms the A β -binding interface (Fig. 5). For example, Lustbader *et al.* (2004) first synthesised a peptide dubbed ABAD-decoy peptide (ABAD-DP) using the corresponding amino acid residues (92-120). The peptide effectively inhibited binding between 17 β -HSD10, and both A β (1-40) and A β (1-42) *in vitro*, with IC₅₀ values of 4.9 μ M and 1.7 μ M, respectively. To investigate peptide activity *in vivo*, the ABAD-DP was bioengineered to incorporate additional sequences⁹⁸. The construct encoded the Tat protein transduction domain of the HIV1 virus to ensure transport across the cell membrane and blood-brain-barrier (BBB), and a mitochondrial targeting sequence (Mito) to ensure specificity translocation into neuronal mitochondria. This construct, termed Tat-Mito-DP, effectively inhibited the A β -17 β -HSD10 interaction, which preserved mitochondrial function and improved spatial memory in transgenic mouse models of AD; however, the therapeutic potential of this peptide was limited by its short *in vivo* half-life⁹⁸. To address the issue, an attempt at stabilisation was ventured via fusion to thioredoxin-1 (Trx-1)⁹⁹. This modification enhanced stability and prolonged ABAD-DP activity, allowing the conjugate to successfully protect against A β -induced cytotoxicity and re-establish redox balance in PC12 cells⁹⁹. However, later studies using the thioredoxin-fused peptide aptamers, shifted focus towards disrupting interactions between toxic A β assemblies and cellular prion proteins (PrP^c)¹⁰⁰.



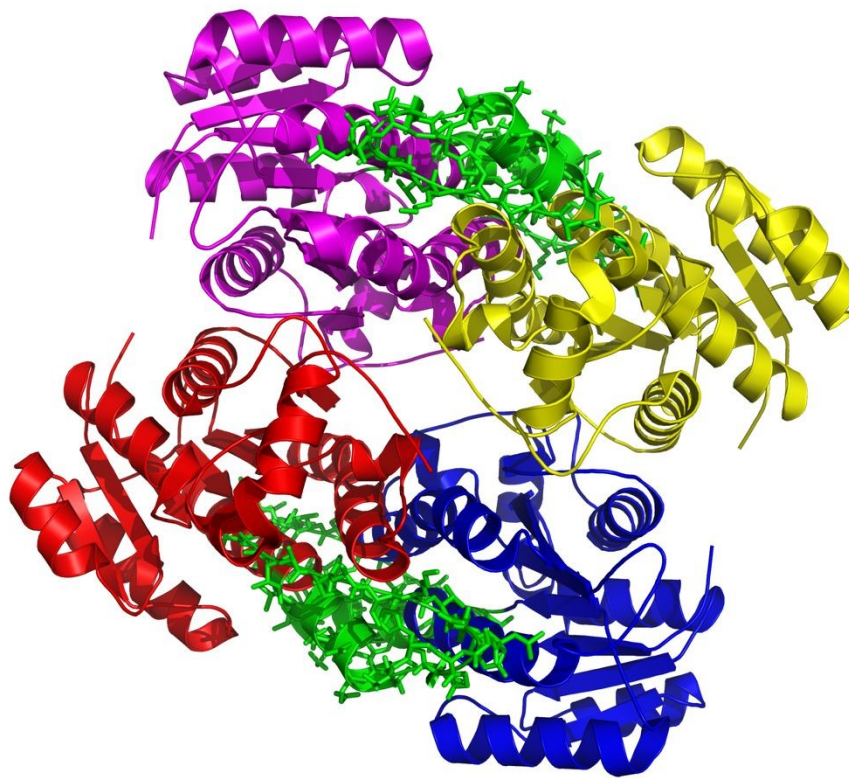
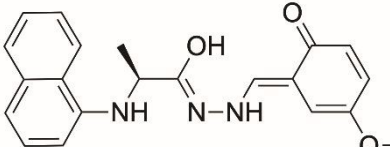
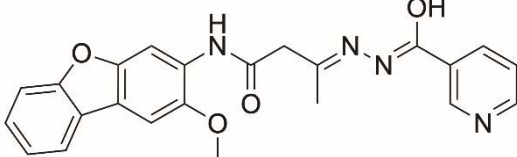


Figure 5. Crystal structure of the human 17 β -HSD10 homotetramer with each subunit represented by different colours and the loop D region highlighted in green. (PDB: 1U7T).

Given the limited bioavailability and short half-life of peptide-based mimetics, efforts were refocused on developing non-peptidyl small molecule inhibitors to target the loop D interface⁹⁵. A combination of computational and structural analyses identified three key residues: Thr108, His109 and Thr110, which act as hotspots mediating A β -17 β -HSD10 interactions⁹⁵. Virtual screening of chemical databases formed the basis of *in silico* drug discovery, followed by enzyme-linked immunosorbent assay (ELISA)-based verification of the top 20 hits, which identified 2 lead compounds, VC15 and VC19 (Table 1), with IC₅₀ values of 4.4 μ M and 9.6 μ M, respectively⁹⁵. At a structural level, the inhibitory activity of VC15 and VC19 is mediated by hydrophobic interactions and hydrogen bonding that engages with A β residues such as Phe4, Glu11 and Gln15 within the loop D pocket. The authors noted that of the two compounds, VC19 yielded a superior binding score. VC19, however, demonstrated lower *in vitro* potency compared to VC15. This difference in potency was ascribed to VC15 forming a greater number of polar interactions within the A β -binding pocket compared to VC19⁹⁵.

Table 1. Names and structures of loop D mimetic inhibitors. Inhibitor names are shown as they appear in the original literature.

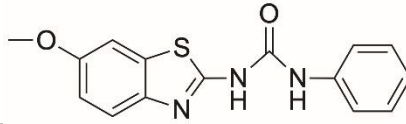
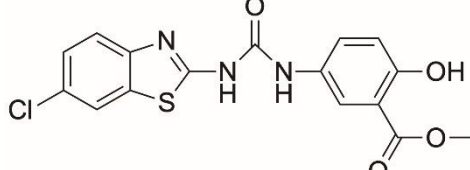
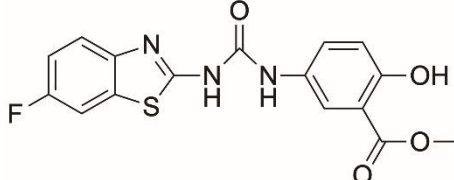
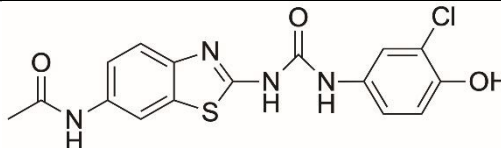


Compound	IC ₅₀ (μM)	Assay Type	Inhibition Type	Type	Sequence / Structure	Reference
ABAD-DP	1.70	Cell Based	Aβ-Interaction	Peptide	AGIAVASKTYNLLKKGQHTLTLEDFQRVLDV	View Article Online DOI: 10.1039/D6CB00093B
Tat-Mito-ABAD-93-116	-	Mice Based	Aβ-Interaction	Peptide	YGRKKRRQRRR-MAAAVRSVKGL-GIAVASKTYNLLKKGQHTLTLEDFQR	98
VC15	4.40	ELISA Based	Aβ-Interaction	Small Molecule		95
VC19	9.60	ELISA Based	Aβ-Interaction	Small Molecule		95

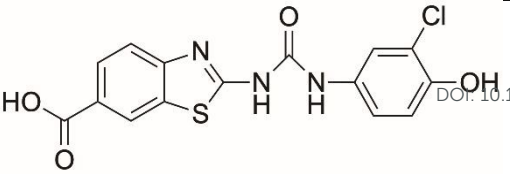
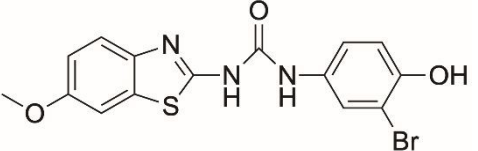
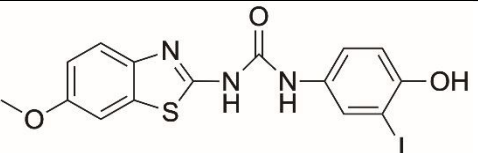
Benzothiazolyl ureas

Benzothiazolyl ureas are a class of organic compounds consisting of a benzothiazolyl heterocycle linked via a urea bridge to various aryl moieties^{101,102}. These small molecules display diverse biological activities, with their scaffolds routinely utilised in medicinal chemistry, forming the basis of various anti-cancer, anti-bacterial and AD therapeutics¹⁰³. The discovery of benzothiazolyl ureas as inhibitors of 17β-HSD10, originated from ELISA-based screening assays designed to identify 17β-HSD10 and Aβ binding partners¹⁰⁴. These investigations identified frentizole, an FDA-approved immunosuppressive drug, as a novel 17β-HSD10-Aβ inhibitor, with an IC₅₀ of 200 μM (Table 2)¹⁰⁴. Despite initially exhibiting suboptimal potency, the frentizole scaffold provided an important structural template for further optimisation, leading to the synthesis of a series of benzothiazolyl urea analogues, which enabled analysis of structure-activity relationships (SAR), with several derivatives having demonstrated up to a ~30-fold increase in potency relative to frentizole¹⁰⁴.

Table 2. Names and structures of benzothiazolyl urea inhibitors. Inhibitor names are shown as they appear in the original literature.

Compound	IC ₅₀ (μM)	Assay Type	Inhibition Type	Structure	Reference
Frentizole	200	ELISA Based	Aβ-Interaction		104
5h	6.46	ELISA Based	Aβ-Interaction		104
5l	6.56	ELISA Based	Aβ-Interaction		104
Compound 9	0.34	Recombinant Protein	Enzymatic		105



Compound 11	0.31	Recombinant Protein	Enzymatic		105 View Article Online DOI: 10.1039/D6CB00093B
Compound 5	1.28	Recombinant Protein	Enzymatic		102
Compound 6	1.86	Recombinant Protein	Enzymatic		102

These SAR studies revealed the urea, rather than an amide moiety, to be essential for inhibition of 17β -HSD10- $A\beta$ protein-protein interactions. The authors attributed this key pharmacophore element to the hydrogen-bond donor ability of the urea-NH groups. The addition of a *para*-hydroxyl group to the phenyl-urea ring, yielded a hydroxyphenyl urea derivative with increased potency, whilst further modifications combining hydroxyl and methoxycarbonyl functionalities, led to the development of the most potent compounds 5h and 5l (Table 2) ¹⁰⁴.

A later study conducted by Hroch *et al.* (2016), showed a 4-phenolic moiety with chlorine in close proximity, to be crucial for 17β -HSD10 inhibition, with a 3-halogen/4-hydroxyl substitution on the distal phenyl ring demonstrating potent inhibition. These findings provided a foundation for further optimisation and refinement of candidate compounds. Consequently, Aitken *et al.* (2019) synthesised and expanded upon this, thereby identifying compounds 5 and 6 (Table 2) as the most promising candidates featuring either a 3-bromo or 3-iodo in conjunction with a 4-hydroxyl substitution. Enzyme inhibition assays showed that both compounds act via reversible, mixed-type inhibition. This mechanism contrasts with the then “gold standard” 17β -HSD10 inhibitor, AG18051 (Table 3) (see below), which exerts inhibition via an irreversible covalent modification of the NAD^+ cofactor ⁹⁰. Thus, the benzothiazolyl ureas’ mixed reversible mode of inhibition is favourable as it implies greater selectivity and reduced off-target reactivity toward other NAD^+ -dependent short-chain dehydrogenase/reductase (SDR) family members ¹⁰².

Recent studies have further probed the effects of substitutions on the benzothiazolyl core, specifically at the C6 position ¹⁰⁵, where either a large hydrogen-bond acceptor or small hydrogen bond donor, modulates multiple electrostatic and steric interactions within the enzyme binding site. Subsequent optimisation led to the identification of submicromolar inhibitors, notably compounds 9 and 11, which have IC_{50} values of $0.34 \mu M$ and $0.31 \mu M$, respectively (Table 2) ¹⁰⁵.

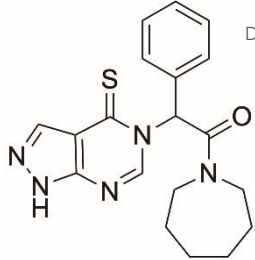
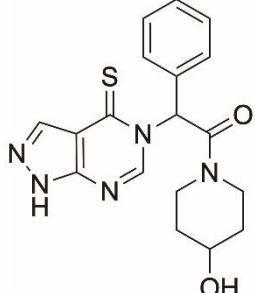
Taken together, these findings show the evolution of benzothiazolyl urea entities from a known class of compounds, repurposed into a chemically distinct class of 17β -HSD10 inhibitors with significantly improved potency and selectivity.

Pyrazole derivatives

For many years, the most potent and widely-studied inhibitor of 17β -HSD10 was AG18051 (Table 3), with an IC_{50} of 92 nM ⁹⁰. Structurally, AG18051 is 1-azepan-1-yl-2-phenyl-2-(4-thioxo-1,4-dihydro-pyrazolo[3.4-d]pyrimidin-5-yl)-ethanone, whereby its N2 atom forms a covalent adduct with the C4 carbon atom on the nicotinamide ring of the 17β -HSD10-bound NAD^+ cofactor. This irreversible modification disrupts the 17β -HSD10- NAD^+ holoenzyme, leading to suppressed activity. However, the covalent nature of this inhibition raises concerns regarding off-target reactivity and therapeutic viability.⁹⁰

Table 3. Names and structures of pyrazole derived inhibitors. Inhibitor names are shown as they appear in the original literature.



Compound	IC ₅₀ (μM)	Assay Type	Inhibition Type	Structure	Reference
AG18051	0.092	Recombinant Protein	Enzymatic		90 View Article Online DOI: 10.1039/D6CB00093B
Compound 14b	0.74	ELISA Based	Enzymatic		106

Molecular dynamic simulations provided further insight into the structural relationship between AG18051 and its binding site¹⁰⁷. These studies highlighted substantial conformational flexibility displayed by the azepane and benzene rings of AG18051, which correlates with the dynamic mobility of the 17β-HSD10 substrate-binding loop¹⁰⁷. This suggests that in the absence of a ligand, the substrate-binding loop remains highly flexible, whereas AG18051 binding leads to stabilisation of the active site¹⁰⁷. In cell culture assays, using SH-SY5Y (human neuroblastoma) cells, AG18051 was shown to reduce ROS formation, protect against Aβ-induced cytotoxicity and prevent the Aβ-mediated decrease in estradiol¹⁰⁸. Such neuroprotective effects lend significant merit to pursue 17β-HSD10 as a therapeutic target for the treatment of AD.

Despite its potency and well-documented mechanism of action, the irreversible covalent binding mode raises concerns over off-target effects, specifically for other essential NAD⁺-dependent SDR enzymes, thus limiting translational applicability and precluding AG18051 as a viable candidate for AD therapy. AG18051, however, continues to serve as the standard reference compound for both *in vitro* and *in vivo* studies and remains a valuable benchmark control for the synthesis of novel 17β-HSD10 inhibitors.

Building upon the fused-pyrazole structure of AG18051, Morsy *et al.* (2022) replaced the original azepane ring with alternative nitrogen-containing heterocycles to create a series of 'functionalised allopurinols' with improved physicochemical properties and brain penetrance. Within this series, compound 14b (LD14b) (Table 3) had the original azepane ring replaced with a piperidinyl alcohol group, markedly increasing potency and optimisation scores. *In silico* modelling suggests that LD14b stabilises 17β-HSD10 by engaging Gly199, Thr203 and Leu22 within the Aβ-interface¹⁰⁶. In E2 rescue assays, LD14b presented submicromolar inhibition with an IC₅₀ of 0.74 μM, in addition to protecting SH-SY5Y cells from Aβ-induced cytotoxicity, and preventing Aβ-induced mitochondrial dysfunction and abnormal mitochondrial morphology in cortical neurons derived from 5XFAD mice¹⁰⁶. In light of these results, Daria *et al.* (2024) conducted detailed absorption, distribution, metabolism and excretion (ADME) studies to determine pharmacokinetic (PK) parameters for LD14b, showing good metabolic stability, with ~70 % of the parent compound detected in human liver S9 fractions after 90 minutes. Caco-2 permeability assays, demonstrated that LD14b exhibits intermediate intestinal drug absorption and BBB penetration capabilities. Furthermore, LD14b also showed moderate oral bioavailability with a 3-5 hour half-life and large volume of distribution, suggesting broad tissue exposure¹⁰⁹.

Steroidal derivatives

The demonstrated ability of 17β-HSD10 to metabolise steroidal substrates³⁴, suggests that its active site could accommodate steroidal scaffolds, making steroidal derivatives a promising candidate for inhibitor development. As such, a variety of compounds were predicted to interact with the 17β-



HSD10 binding pocket, with several steroid-based inhibitors subsequently synthesised and evaluated for their ability to modulate enzymatic activity (Table 4) ⁴³.

Among the candidates, a lead compound RM-532-46 (Table 4) showed promise, with an IC_{50} of 0.55 μM ⁴³. Despite its potency, RM532-46 was deemed unsuitable due to being derived from DHT, a compound known to inhibit 17 β -HSD3. This enzyme catalyses the conversion of androstenedione to testosterone ^{42,110}, a key step in androgen biosynthesis. As prostate cancer is driven by androgen receptor signalling ¹¹¹, inhibition of 17 β -HSD3 poses as a potential therapeutic strategy to suppress androgen production. Consequently, this cross-reactivity suggests that RM-532-46 would likely be more appropriate as a drug targeting prostate cancer rather than a selective drug targeting AD ⁴³.

From the structure of RM-532-36, Boutin *et al.* (2018) synthesised a series of 15 analogues and evaluated inhibitory effects against two natural steroidal substrates, AlloP and E2. The results revealed substrate-dependent differences in inhibitory potency, where compound 5 was the most effective when assayed with AlloP and less so with E2, yielding IC_{50} s of 235 μM and 610 μM , respectively. As predicted, compound 5 also demonstrated the ability to cross the BBB, with a BBB penetration score of -2.61. In contrast, compound 8 showed the highest potency with the E2 substrate, with an IC_{50} of 300 μM , but exhibited minimal inhibition against AlloP, suggesting that certain structural features select for particular substrates ¹¹².

Further optimisation of the same RM-532-46 compound, introduced different modifications to its core scaffold, including D-ring, side chain and dual hybrid modifications ¹¹³. These investigations yielded a D-ring-modified amine derivative, known as D-3,7 (Table 4), which demonstrated excellent potency with an IC_{50} value of 0.14 μM ¹¹³. Additional selectivity testing also indicated D-3,7 had overcome the initial lack of specificity presented by RM-532-46 ¹¹³.

In contrast, other derivatives such as compound 23 (Table 4), demonstrated more moderate inhibitory activity with an IC_{50} of 5.59 μM ⁹¹, highlighting the variability in potency associated with structural modifications within steroidal derivatives.

Table 4. Names and structures of steroidal derived inhibitors. Inhibitor names are shown as they appear in the original literature.

Compound	IC_{50} (μM)	Assay Type	Inhibition Type	Structure	Reference
RM-532-46	0.55	Cell Based	Enzymatic		43
D-3,7	0.14	Cell Based	Enzymatic		113
Compound 23	5.59	Recombinant Protein	Enzymatic		91

Repurposed and other compounds



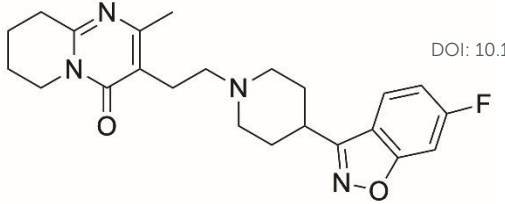
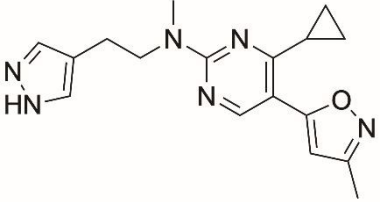
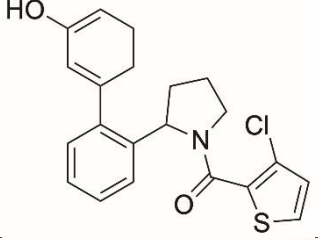
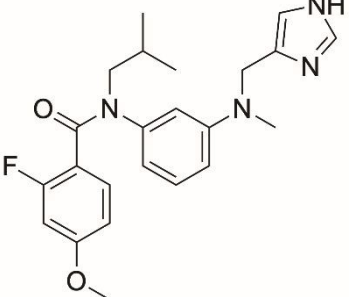
With a surge in drug repositioning, several clinically established compounds have been repurposed for the treatment of additional diseases¹¹⁴. One such compound is risperidone (Table 5), an FDA-approved drug for the treatment of schizophrenia and bipolar disorder^{115,116}. In a chemical genomic screen using a T7 bacteriophage display library, risperidone was identified as a potential 17 β -HSD10 inhibitor. Enzyme assays demonstrated that 17 β -HSD10 activity with E2 and acetoacetyl-CoA substrates, resulted in oxidation of E2 and reduction of acetoacetyl-CoA at rates of 1.0 μ M/min and 3.3 μ M/min, respectively¹¹⁷. Moreover, *in silico* computational docking experiments ranked risperidone among the highest-scoring ligands for 17 β -HSD10, and predicted the compound to act as a competitive inhibitor¹¹⁷; however, empirical pharmacodynamic parameters and inhibitor specificity are yet to be determined, with further biochemical and structural validation required.

In 2017, Aitken *et al.* conducted a pilot high-throughput screen (HTS) of 6759 compounds, which identified 16 low-micromolar inhibitors of 17 β -HSD10. Physicochemical profiling revealed that all hits exhibited favourable drug-like properties, establishing a strong foundation for subsequent SAR optimisation and *in vivo* validation, and thus enabling the development of 17 β -HSD10-targeted therapeutics¹¹⁸. Building upon this work, Dow *et al.* (2025) selected BCC0100281 (Table 5) for further investigation, in which cell-based assays displayed marked cytotoxicity in SH-SY5Y neuroblastoma cells, precluding further use in A β -induced cytotoxicity¹¹⁹. Notably, this cytotoxic effect was not observed across a broader panel of cancer and non-cancer cell lines, highlighting a degree of cell-specific vulnerability. Further analysis by differential scanning fluorimetry (DSF), revealed a decrease in 17 β -HSD10 thermal stability when assayed with BCC0100281, consistent with a non-canonical binding mode¹¹⁹. Derivatives targeting modifications of the central pyrimidine scaffold were subsequently synthesised, and found to exhibit protective effects against A β -induced cytotoxicity¹¹⁹. These compounds, however, displayed an inverse dose response relationship, indicating both mechanistic complexity and room for further optimisation. While BCC0100281 is unlikely to advance as a therapeutic lead, it nonetheless provides a valuable chemical starting point for the continued development of next-generation 17 β -HSD10 inhibitors.

In 2025, Aitken *et al.* published the first industrial-scale HTS of 350,000 drug-like molecules, generating several lead series for the potent inhibition of 17 β -HSD10. From the screen, two distinct compound series emerged for future development, a singleton hit series, ESC1002755 (Table 5) and a chemically related hit series referred to by the authors as cluster 6. From the cluster 6 series, ESC1002576 (Table 5) was selected as a lead compound. Although ESC1002576 did not exhibit the highest potency within cluster 6 (IC₅₀ = 0.25 μ M), it possessed the most favourable selection based on its overall potency and physicochemical properties⁹⁷. ESC1002755 (Table 5) yielded the highest potency against 17 β -HSD10, with an IC₅₀ of 19 nM in enzyme activity assays and an EC₅₀ of 28 nM during overexpression of the canonical form in HEK293⁹⁷. Additionally, binding site analysis supported by co-crystallography of related compounds identified a novel allosteric site on 17 β -HSD10 (Fig. 6). The novel allosteric site is bordered by residues Gln162, Gln165, Ser155 and Tyr168, with the allosteric site and residues sitting adjacent to, but not overlapping the NAD⁺ cofactor binding site, explaining the non-competitive and competitive inhibition of NADH and acetoacetyl-CoA respectively. This allosteric mode of action distinguishes ESC1002755 from classic 17 β -HSD10 active site inhibitors such as AG18051⁹⁷. Beyond its potency, ESC1002755 showed optimal selectivity and safety profiles in several cell-based assays, with minimal cell cytotoxicity⁹⁷. Moreover, screening of ESC1002755 against other SDR enzymes showed high selectivity for 17 β -HSD10, while *in vitro* ADME assessments yielded favourable pharmacokinetic profiles⁹⁷.

Table 5. Names and structures of novel and repurposed drugs as 17 β -HSD10 inhibitors. Inhibitor names are shown as they appear in the original literature.



Compound	IC ₅₀ (μM)	Assay Type	Inhibition Type	Structure	Reference
Risperidone	-	Recombinant Protein	Enzymatic		View Article Online DOI: 10.1039/D6CB00093B 117
BCC0100281	25.1	Recombinant Protein	Enzymatic		120
ESC1002755	0.019	Recombinant Protein	Enzymatic		97
ESC1002576	0.25	Recombinant Protein	Enzymatic		97

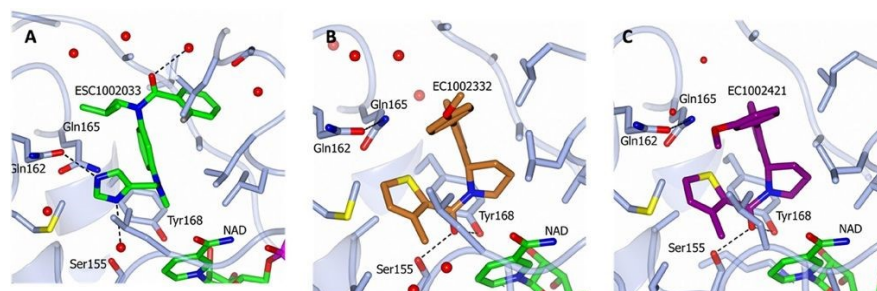


Figure 6. Interactions between 17β-HSD10 with specific novel compounds (A) ESC1002033, (B) ESC1002332 and (C) ESC1002421 sitting in a novel allosteric site. Figure taken from ⁹⁷L. Aitken *et al.*, *ACS Chem. Biol.*, 2025, **20**, DOI: 10.1021/acscchembio.5c00110. Published by the American Chemical Society under a CC BY 4.0 licence.

Future perspectives

Significant strides have been made in chemical design and optimisation of 17β-HSD10 inhibitors, which have resulted in the identification and synthesis of an array of compounds that span multiple chemical classes, with several compounds achieving submicromolar potency ^{97,105,113}. Despite this progress, relatively little work has focused on their functional evaluation in physiologically relevant neuronal systems. Cellular studies, however, are moving in the right direction, with experiments being conducted using undifferentiated or non-neuronal cell models including HEK293 and SH-SY5Y neuroblastoma cell lines, as well as primary cortical neurons from AD mouse models ^{15,20,21,94,97,106,109,119}. While these models have provided useful initial screening platforms, they still do



not capture the complexity of the true *in vivo* microenvironment; more recent investigations, however, have been developing this capability. Houfková *et al.* (2025), for example, developed stable monoclonal HEK293 cell lines overexpressing HSD10, a catalytically inactive mutant, and an Aβ-associated mutation, APPSwe/Ind variant, thus allowing direct observation of the enzymatic and non-enzymatic contributions of HSD10 to cellular pathology. Critically, the study demonstrated that HSD10 overexpression alone, is enough to induce mitochondrial dysfunction and cytotoxicity, independent of Aβ. This cytotoxicity was dependent upon HSD10 enzymatic activity, as the catalytically inactive HSD10 mutant did not present the phenotype. Importantly, cytotoxicity was only observed under glucose-deprived conditions⁹⁴, where cells are forced to rely upon mitochondrial oxidative phosphorylation, highlighting the critical role of metabolic context in modulating HSD10-driven toxicity.

Metabolic profiling further revealed that HSD10 overexpression led to broad suppression of tricarboxylic acid cycle activity and impaired β-oxidation. In contrast, the APPSwe/Ind cells exhibited increased glucose utilisation and upregulated β-oxidation, reflecting a compensatory mechanism to Aβ-induced mitochondrial stress⁹⁴.

Despite emerging insights into 17β-HSD10 function, the efficacy and safety of these inhibitors in differentiated neuronal cell types including astrocytes, oligodendrocytes and microglia, remains largely unknown, despite evidence linking 17β-HSD10 and its associated metabolic pathways to stress modulation in astrocytes and differentiation processes in oligodendrocytes¹⁶. These findings emphasise the need to extend pharmacological assessments beyond the generic immortalised models to achieve a more accurate representation of physiological context. Indeed, the rise of mass spectrometry capabilities with these new potent inhibitor compounds, will allow it to be possible to identify the metabolic changes caused by 17β-HSD10 activity in the living brain. As such, it is crucial that drug development pipelines for 17β-HSD10 inhibitors, incorporate cellular differentiation assays and human induced pluripotent neuronal stem cell models. These approaches will shed light on how candidate compounds interact with distinct neural populations, and will also provide mechanistic insights into their therapeutic action and neurotoxicity in disease-relevant contexts.

References

1. Dyck CH van, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. *N Engl J Med.* 2023;388(1):9-21. doi:10.1056/NEJMoa2212948
2. Zhang J, Zhang Y, Wang J, Xia Y, Zhang J, Chen L. Recent advances in Alzheimer's disease: mechanisms, clinical trials and new drug development strategies. *Signal Transduct Target Ther.* 2024;9(1):211. doi:10.1038/s41392-024-01911-3
3. Ivanova AV, Kutuzova AD, Kuzmichev IA, Abakumov MA. Alzheimer's Disease: From Molecular Mechanisms to Promising Therapeutic Strategies. *Int J Mol Sci.* 2025;26(19):9444. doi:10.3390/ijms26199444
4. Borger E, Aitken L, Du H, Zhang W, Gunn-Moore FJ, Du Yan SS. Is Amyloid Binding Alcohol Dehydrogenase a Drug Target for Treating Alzheimer's Disease? *Curr Alzheimer Res.* 2013;10(1):21-29.
5. Mosconi L. Brain glucose metabolism in the early and specific diagnosis of Alzheimer's disease. *Eur J Nucl Med Mol Imaging.* 2005;32(4):486-510. doi:10.1007/s00259-005-1762-7



6. DuBoff B, Feany M, Götz J. Why size matters – balancing mitochondrial dynamics in Alzheimer’s disease. *Trends Neurosci.* 2013;36(6):325-335. doi:10.1016/j.tins.2013.03.002
7. Moeller G, Adamski J. Integrated view on 17 β -hydroxysteroid dehydrogenases. *Mol Cell Endocrinol.* 2009;301(1):7-19. doi:10.1016/j.mce.2008.10.040
8. Rotinen M, Villar J, Celay J, Encío I. Type 10 17 β -hydroxysteroid dehydrogenase expression is regulated by C/EBP β in HepG2 cells. *J Steroid Biochem Mol Biol.* 2010;122(4):164-171. doi:10.1016/j.jsbmb.2010.07.003
9. Jiang T, Ouyang W, Yang H, Li S. A novel c.59 C > T variant of the HSD17B10 gene as a possible cause of the neonatal form of HSD10 mitochondrial disease with hepatic dysfunction: a case report and review of the literature. *Orphanet J Rare Dis.* 2025;20:108. doi:10.1186/s13023-024-03513-2
10. Zschocke J. HSD10 disease: clinical consequences of mutations in the HSD17B10 gene. *J Inher Metab Dis.* 2012;35(1):81-89. doi:10.1007/s10545-011-9415-4
11. Schmidt M, Benek O, Vinklarova L, et al. Benzothiazolyl Ureas are Low Micromolar and Uncompetitive Inhibitors of 17 β -HSD10 with Implications to Alzheimer’s Disease Treatment. *Int J Mol Sci.* 2020;21(6):2059. doi:10.3390/ijms21062059
12. Du Yan S, Fu J, Soto C, et al. An intracellular protein that binds amyloid- β peptide and mediates neurotoxicity in Alzheimer’s disease. *Nature.* 1997;389(6652):689-695. doi:10.1038/39522
13. Du Yan S, Zhu Y, Stern ED, et al. Amyloid β -Peptide-binding Alcohol Dehydrogenase Is a Component of the Cellular Response to Nutritional Stress*. *J Biol Chem.* 2000;275(35):27100-27109. doi:10.1016/S0021-9258(19)61485-7
14. He XY, Schulz H, Yang SY. A Human Brain l-3-Hydroxyacyl-coenzyme A Dehydrogenase Is Identical to an Amyloid β -Peptide-binding Protein Involved in Alzheimer’s Disease*. *J Biol Chem.* 1998;273(17):10741-10746. doi:10.1074/jbc.273.17.10741
15. Ofman R, Ruitter JPN, Feenstra M, et al. 2-Methyl-3-Hydroxybutyryl-CoA Dehydrogenase Deficiency Is Caused by Mutations in the HADH2 Gene. *Am J Hum Genet.* 2003;72(5):1300-1307. doi:10.1086/375116
16. Metodieva V, Smith T, Gunn-Moore F. The Mitochondrial Enzyme 17 β HSD10 Modulates Ischemic and Amyloid- β -Induced Stress in Primary Mouse Astrocytes. *eNeuro.* 2022;9(5):ENEURO.0040-22.2022. doi:10.1523/ENEURO.0040-22.2022
17. Du Yan S, Shi Y, Zhu A, et al. Role of ERAB/l-3-Hydroxyacyl-coenzyme A Dehydrogenase Type II Activity in A β -induced Cytotoxicity*. *J Biol Chem.* 1999;274(4):2145-2156. doi:10.1074/jbc.274.4.2145
18. He XY, Merz G, Mehta P, Schulz H, Yang SY. Human Brain Short Chain l-3-Hydroxyacyl Coenzyme A Dehydrogenase Is a Single-domain Multifunctional Enzyme. *J Biol Chem.* 1999;274(21):15014-15019. doi:10.1074/jbc.274.21.15014
19. He XY, Wegiel J, Yang SY. Intracellular oxidation of allopregnanolone by human brain type 10 17 β -hydroxysteroid dehydrogenase. *Brain Res.* 2005;1040(1):29-35. doi:10.1016/j.brainres.2005.01.022
20. Lustbader JW, Cirilli M, Lin C, et al. ABAD Directly Links A β to Mitochondrial Toxicity in Alzheimer’s Disease. *Science.* 2004;304(5669):448-452. doi:10.1126/science.1091230

View Article Online

DOI: 10.1039/D6CB00093B



21. Rauschenberger K, Schöler K, Sass JO, et al. A non-enzymatic function of 17 β -hydroxysteroid dehydrogenase type 10 is required for mitochondrial integrity and cell survival. *EMBO Mol Med.* 2010;2(2):51-62. doi:10.1002/emmm.200900055 View Article Online
DOI: 10.1039/D6CB00093B
22. Torroja L, Ortuño-Sahagún D, Ferrús A, Hämmerle B, Barbas JA. scully, an Essential Gene of *Drosophila*, is Homologous to Mammalian Mitochondrial Type II 1-3-hydroxyacyl-CoA Dehydrogenase/Amyloid- β Peptide-binding Protein. *J Cell Biol.* 1998;141(4):1009-1017. doi:10.1083/jcb.141.4.1009
23. Carlson EA, Marquez RT, Du F, Wang Y, Xu L, Yan SS. Overexpression of 17 β -hydroxysteroid dehydrogenase type 10 increases pheochromocytoma cell growth and resistance to cell death. *BMC Cancer.* 2015;15(1):166. doi:10.1186/s12885-015-1173-5
24. He XY, Merz G, Mehta P, Schulz H, Yang SY. Human Brain Short Chain 1-3-Hydroxyacyl Coenzyme A Dehydrogenase Is a Single-domain Multifunctional Enzyme. *J Biol Chem.* 1999;274(21):15014-15019. doi:10.1074/jbc.274.21.15014
25. Zschocke J, Ruiter JPN, Brand J, et al. Progressive Infantile Neurodegeneration Caused by 2-Methyl-3-Hydroxybutyryl-CoA Dehydrogenase Deficiency: A Novel Inborn Error of Branched-Chain Fatty Acid and Isoleucine Metabolism. *Pediatr Res.* 2000;48(6):852-855. doi:10.1203/00006450-200012000-00025
26. Kobayashi A, Jiang LL, Hashimoto T. Two Mitochondrial 3-Hydroxyacyl-CoA Dehydrogenases in Bovine Liver. *J Biochem (Tokyo).* 1996;119(4):775-782. doi:10.1093/oxfordjournals.jbchem.a021307
27. Yang SY, He XY. Role of Type 10 17 β -Hydroxysteroid Dehydrogenase in the Pathogenesis of Alzheimer's Disease. *Neuropathol Genet Dement.* 2001;487:101-110. doi:doi.org/10.1007/978-1-4615-1249-3_8
28. Holzmann J, Frank P, Löffler E, Bennett KL, Gerner C, Rossmanith W. RNase P without RNA: Identification and Functional Reconstitution of the Human Mitochondrial tRNA Processing Enzyme. *Cell.* 2008;135(3):462-474. doi:10.1016/j.cell.2008.09.013
29. Vilardo E, Rossmanith W. Molecular insights into HSD10 disease: impact of SDR5C1 mutations on the human mitochondrial RNase P complex. *Nucleic Acids Res.* 2015;43(10):5112-5119. doi:10.1093/nar/gkv408
30. Jörnvall H, Persson B, Krook M, et al. Short-Chain Dehydrogenases/Reductases (SDR). *Biochemistry.* 1995;34(18). doi:10.1021/bi00018a001
31. Kallberg Y, Oppermann U, Jörnvall H, Persson B. Short-chain dehydrogenases/reductases (SDRs). *Eur J Biochem.* 2002;269(18):4409-4417. doi:10.1046/j.1432-1033.2002.03130.x
32. Vinklarova L, Schmidt M, Benek O, Kuca K, Gunn-Moore F, Musilek K. Friend or enemy? Review of 17 β -HSD10 and its role in human health or disease. *J Neurochem.* 2020;155(3):231-249. doi:10.1111/jnc.15027
33. Korman SH, Yang SY. *HSD17B10* replaces *HADH2* as the approved designation for the gene mutated in 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency. *Mol Genet Metab.* 2007;91(1):115. doi:10.1016/j.ymgme.2007.01.001
34. Yang SY, He XY, Schulz H. Multiple functions of type 10 17 β -hydroxysteroid dehydrogenase. *Trends Endocrinol Metab.* 2005;16(4):167-175. doi:10.1016/j.tem.2005.03.006



35. Lu KH, Hopper BR, Vargo TM, Yen SSC. Chronological Changes in Sex Steroid, Gonadotropin and Prolactin Secretion in Aging Female Rats Displaying Different Reproductive States I. *Biol Reprod.* 1979;21(1):193-203. doi:10.1095/biolreprod21.1.193 View Article Online
DOI: 10.1039/D6CB00093B
36. McCarthy MM. Estradiol and the Developing Brain. *Physiol Rev.* 2008;88(1):91-124. doi:10.1152/physrev.00010.2007
37. Luine VN. Estradiol and cognitive function: Past, present and future. *Horm Behav.* 2014;66(4):602-618. doi:10.1016/j.yhbeh.2014.08.011
38. Khan D, Ansar Ahmed S. The Immune System Is a Natural Target for Estrogen Action: Opposing Effects of Estrogen in Two Prototypical Autoimmune Diseases. *Front Immunol.* 2016;6:635. doi:10.3389/fimmu.2015.00635
39. He XY, Dobkin C, Yang SY. 17 β -Hydroxysteroid dehydrogenases and neurosteroid metabolism in the central nervous system. *Mol Cell Endocrinol.* 2019;489:92-97. doi:10.1016/j.mce.2018.10.002
40. Majewska MD, Harrison NL, Schwartz RD, Barker JL, Paul SM. Steroid Hormone Metabolites Are Barbiturate-Like Modulators of the GABA Receptor. *Science.* 1986;232(4753):1004-1007. doi:10.1126/science.2422758
41. He XY, Yang YZ, Peehl DM, Lauderdale A, Schulz H, Yang SY. Oxidative 3 α -hydroxysteroid dehydrogenase activity of human type 10 17 β -hydroxysteroid dehydrogenase. *J Steroid Biochem Mol Biol.* 2003;87(2):191-198. doi:10.1016/j.jsbmb.2003.07.007
42. Luu-The V, Bélanger A, Labrie F. Androgen biosynthetic pathways in the human prostate. *Best Pract Res Clin Endocrinol Metab.* 2008;22(2):207-221. doi:10.1016/j.beem.2008.01.008
43. Ayan D, Maltais R, Poirier D. Identification of a 17 β -Hydroxysteroid Dehydrogenase Type 10 Steroidal Inhibitor: A Tool to Investigate the Role of Type 10 in Alzheimer's Disease and Prostate Cancer. *ChemMedChem.* 2012;7(7):1181-1184. doi:10.1002/cmdc.201200129
44. Cagnacci A, Soldani R, Luigi Carriero P, Maria Paoletti A, Fioretti P, Melis GB. Effects of Low Doses of Transdermal 17 β -Estradiol on Carbohydrate Metabolism in Postmenopausal Women. *J Clin Endocrinol Metab.* 1996;74(6).
45. Nelson LR, Bulun SE. Estrogen production and action. *J Am Acad Dermatol.* 2001;45(3, Supplement):S116-S124. doi:10.1067/mjd.2001.117432
46. Aronica SM, Kraus WL, Katzenellenbogen BS. Estrogen action via the cAMP signaling pathway: stimulation of adenylate cyclase and cAMP-regulated gene transcription. *Proc Natl Acad Sci.* 1994;91(18):8517-8521. doi:10.1073/pnas.91.18.8517
47. Wade CB, Robinson S, Shapiro RA, Dorsa DM. Estrogen Receptor (ER) α and ER β Exhibit Unique Pharmacologic Properties When Coupled to Activation of the Mitogen-Activated Protein Kinase Pathway*. *Endocrinology.* 2001;142(6):2336-2342. doi:10.1210/endo.142.6.8071
48. Zhang L, Rubinow DR, Xiang G, et al. Estrogen protects against β -amyloid-induced neurotoxicity in rat hippocampal neurons by activation of Akt. *NeuroReport.* 2001;12(9):1919.
49. Marino M, Galluzzo P, Ascenzi P. Estrogen Signaling Multiple Pathways to Impact Gene Transcription. *Curr Genomics.* 2006;7(8):497-508. doi:10.2174/138920206779315737
50. Kelly MJ, Moss RL, Dudley CA. Differential Sensitivity of Preoptic-Septal Neurons to Microelectrophoresed Estrogen during the Estrous Cycle. *Brain Res.* 1976;114:152-157.



51. Maggi A, Ciana P, Belcredito S, Vegeto E. Estrogens in the Nervous System: Mechanisms and Nonreproductive Functions. *Annu Rev Physiol.* 2004;66(1):291-313. doi:10.1146/annurev.physiol.66.032802.154945
52. Micevych PE, Mermelstein PG. Membrane Estrogen Receptors Acting Through Metabotropic Glutamate Receptors: An Emerging Mechanism of Estrogen Action in Brain. *Mol Neurobiol.* 2008;38(1):66-77. doi:10.1007/s12035-008-8034-z
53. Brinton RD. Estrogen regulation of glucose metabolism and mitochondrial function: Therapeutic implications for prevention of Alzheimer's disease. *Adv Drug Deliv Rev.* 2008;60(13-14):1504-1511. doi:10.1016/j.addr.2008.06.003
54. Simpkins JW, Dykens JA. Mitochondrial mechanisms of estrogen neuroprotection. *Brain Res Rev.* 2008;57(2):421-430. doi:10.1016/j.brainresrev.2007.04.007
55. Zhao L, Wu T wei, Brinton RD. Estrogen receptor subtypes alpha and beta contribute to neuroprotection and increased Bcl-2 expression in primary hippocampal neurons. *Brain Res.* 2004;1010(1-2):22-34. doi:10.1016/j.brainres.2004.02.066
56. Mannella P, Brinton RD. Estrogen Receptor Protein Interaction with Phosphatidylinositol 3-Kinase Leads to Activation of Phosphorylated Akt and Extracellular Signal-Regulated Kinase 1/2 in the Same Population of Cortical Neurons: A Unified Mechanism of Estrogen Action. *J Neurosci.* 2006;26(37):9439-9447. doi:10.1523/JNEUROSCI.1443-06.2006
57. Nilsen J, Irwin RW, Gallaher TK, Brinton RD. Estradiol In Vivo Regulation of Brain Mitochondrial Proteome. *J Neurosci.* 2007;27(51):14069-14077. doi:10.1523/JNEUROSCI.4391-07.2007
58. Nilsen J, Brinton RD. Mechanism of estrogen-mediated neuroprotection: Regulation of mitochondrial calcium and Bcl-2 expression. *Proc Natl Acad Sci.* 2003;100(5):2842-2847. doi:10.1073/pnas.0438041100
59. Srivastava DP, Waters EM, Mermelstein PG, Kramár EA, Shors TJ, Liu F. Rapid Estrogen Signaling in the Brain: Implications for the Fine-Tuning of Neuronal Circuitry. *J Neurosci.* 2011;31(45):16056-16063. doi:10.1523/JNEUROSCI.4097-11.2011
60. Kramár EA, Chen LY, Brandon NJ, et al. Cytoskeletal Changes Underlie Estrogen's Acute Effects on Synaptic Transmission and Plasticity. *J Neurosci.* 2009;29(41):12982-12993. doi:10.1523/JNEUROSCI.3059-09.2009
61. Henderson VW. Estrogen-containing hormone therapy and Alzheimer's disease risk: Understanding discrepant inferences from observational and experimental research. *Neuroscience.* 2006;138(3):1031-1039. doi:10.1016/j.neuroscience.2005.06.017
62. Luo MJ, Mao LF, Schulz H. Short-Chain 3-Hydroxy-2-methylacyl-CoA Dehydrogenase from Rat Liver: Purification and Characterization of a Novel Enzyme of Isoleucine Metabolism. *Biochem Biophys.* 1995;32(1):214-220.
63. Nelson D, Cox M. *Lehninger Principles of Biochemistry.* 7th Ed. W.H. Freeman; 2017.
64. Williamson DH, Bates MW, Page MA, Krebs HA. Activities of enzymes involved in acetoacetate utilization in adult mammalian tissues. *Biochem J.* 1971;121(1):41-47. doi:10.1042/bj1210041
65. Dimou A, Tsimihodimos V, Bairaktari E. The Critical Role of the Branched Chain Amino Acids (BCAAs) Catabolism-Regulating Enzymes, Branched-Chain Aminotransferase (BCAT) and

View Article Online
DOI: 10.1039/D6CB00093B



Branched-Chain α -Keto Acid Dehydrogenase (BCKD), in Human Pathophysiology. *Int J Mol Sci.* 2022;23(7):4022. doi:10.3390/ijms23074022

View Article Online
DOI: 10.1039/D6CB00093B

66. Bo T, Fujii J. Primary Roles of Branched Chain Amino Acids (BCAAs) and Their Metabolism in Physiology and Metabolic Disorders. *Molecules.* 2025;30(1):56. doi:10.3390/molecules30010056
67. Korman SH. Inborn errors of isoleucine degradation: A review. *Mol Genet Metab.* 2006;89(4):289-299. doi:10.1016/j.ymgme.2006.07.010
68. Doi M, Yamaoka I, Nakayama M, Sugahara K, Yoshizawa F. Hypoglycemic effect of isoleucine involves increased muscle glucose uptake and whole body glucose oxidation and decreased hepatic gluconeogenesis. *Am J Physiol-Endocrinol Metab.* 2007;292(6):E1683-E1693. doi:10.1152/ajpendo.00609.2006
69. Larsson SC, Traylor M, Malik R, Dichgans M, Burgess S, Markus HS. Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis. *The BMJ.* 2017;359:j5375. doi:10.1136/bmj.j5375
70. Conrad RS, Massey LK, Sokatch JR. D and L-Isoleucine Metabolism and Regulation of Their Pathways in *Pseudomonas putida*. *J Bacteriol.* 1974;118(1):103-111. doi:10.1128/jb.118.1.103-111.1974
71. Yang SY, He XY, Isaacs C, Dobkin C, Miller D, Philipp M. Roles of 17 β -hydroxysteroid dehydrogenase type 10 in neurodegenerative disorders. *J Steroid Biochem Mol Biol.* 2014;143:460-472. doi:10.1016/j.jsbmb.2014.07.001
72. Bertolin G, Jacoupy M, Traver S, et al. Parkin maintains mitochondrial levels of the protective Parkinson's disease-related enzyme 17- β hydroxysteroid dehydrogenase type 10. *Cell Death Differ.* 2015;22(10):1563-1576. doi:10.1038/cdd.2014.224
73. Upadia J, Walano N, Noh GS, et al. HSD10 disease in a female: A case report and review of literature. *JIMD Rep.* 2021;62(1):35-43. doi:10.1002/jmd2.12250
74. Fakoya AOJ, Abulatan I. 17-Beta-Hydroxysteroid Dehydrogenase X Deficiency. In: *Genetic Syndromes.* Springer, Cham; 2023:1-3. doi:10.1007/978-3-319-66816-1_1717-1
75. Kubo R, Iwamoto Y, Ajihara S, et al. A Case of 17 β -Hydroxysteroid Dehydrogenase Type 10 (HSD10) Disease Caused by a Novel Variant Presenting With Rapidly Progressive Cardiomyopathy Triggered by Viral Infection. *Cureus.* 17(9):e93552. doi:10.7759/cureus.93552
76. García-Villoria J, Navarro-Sastre A, Fons C, et al. Study of patients and carriers with 2-methyl-3-hydroxybutyryl-CoA dehydrogenase (MHBD) deficiency: Difficulties in the diagnosis. *Clin Biochem.* 2009;42(1):27-33. doi:10.1016/j.clinbiochem.2008.10.006
77. Chatfield KC, Coughlin CR, Friederich MW, et al. Mitochondrial energy failure in HSD10 disease is due to defective mtDNA transcript processing. *Mitochondrion.* 2015;21:1-10. doi:10.1016/j.mito.2014.12.005
78. Tieu K, Perier C, Vila M, et al. L-3-hydroxyacyl-CoA dehydrogenase II protects in a model of Parkinson's disease. *Ann Neurol.* 2004;56(1):51-60. doi:10.1002/ana.20133
79. Shulman LM. Understanding disability in Parkinson's disease. *Mov Disord.* 2010;25(S1):S131-S135. doi:10.1002/mds.22789



80. Yang SY, He XY, Olpin SE, et al. Mental retardation linked to mutations in the *HSD17B10* gene interfering with neurosteroid and isoleucine metabolism. *Proc Natl Acad Sci*. 2009;106(35):14820-14824. doi:10.1073/pnas.0902377106
81. Jazbutyte V, Kehl F, Neyses L, Pelzer T. Estrogen receptor alpha interacts with 17 β -hydroxysteroid dehydrogenase type 10 in mitochondria. *Biochem Biophys Res Commun*. 2009;384(4):450-454. doi:10.1016/j.bbrc.2009.04.139
82. Pagani L, Eckert A. Amyloid-Beta Interaction with Mitochondria. *Int J Alzheimers Dis*. 2011;2011:925050. doi:10.4061/2011/925050
83. Robertson HD, Altman S, Smith JD. Purification and Properties of a Specific *Escherichia coli* Ribonuclease which Cleaves a Tyrosine Transfer Ribonucleic Acid Precursor. *J Biol Chem*. 1972;247(16):5243-5251. doi:10.1016/S0021-9258(19)44963-6
84. Guerrier-Takada C, Gardiner K, Marsh T, Pace N, Altman S. The RNA moiety of ribonuclease P is the catalytic subunit of the enzyme. *Cell*. 1983;35(3, Part 2):849-857. doi:10.1016/0092-8674(83)90117-4
85. Oerum S, Roovers M, Rambo RP, et al. Structural insight into the human mitochondrial tRNA purine N1-methyltransferase and ribonuclease P complexes. *J Biol Chem*. 2018;293(33):12862-12876. doi:10.1074/jbc.RA117.001286
86. Hentze MW. Enzymes as RNA-binding proteins: a role for (di)nucleotide-binding domains? *Trends Biochem Sci*. 1994;19.
87. Deutschmann AJ, Amberger A, Zavadil C, et al. Mutation or knock-down of 17 β -hydroxysteroid dehydrogenase type 10 cause loss of MRPP1 and impaired processing of mitochondrial heavy strand transcripts. *Hum Mol Genet*. 2014;23(13):3618-3628. doi:10.1093/hmg/ddu072
88. Vilaro E, Nachbagauer C, Buzet A, Taschner A, Holzmann J, Rossmann W. A subcomplex of human mitochondrial RNase P is a bifunctional methyltransferase—extensive moonlighting in mitochondrial tRNA biogenesis. *Nucleic Acids Res*. 2012;40(22):11583-11593. doi:10.1093/nar/gks910
89. Schubert A, Grimm S. Cyclophilin D, a Component of the Permeability Transition-Pore, Is an Apoptosis Repressor. *Cancer Res*. 2004;64(1):85-93. doi:10.1158/0008-5472.CAN-03-0476
90. Kissinger CR, Rejto PA, Pelletier LA, et al. Crystal Structure of Human ABAD/HSD10 with a Bound Inhibitor: Implications for Design of Alzheimer's Disease Therapeutics. *J Mol Biol*. 2004;342(3):943-952. doi:10.1016/j.jmb.2004.07.071
91. Hanzlova M, Slavikova B, Morozovova M, et al. C-3 Steroidal Hemiesters as Inhibitors of 17 β -Hydroxysteroid Dehydrogenase Type 10. *ACS Omega*. 2024;9(10):12116-12124. doi:10.1021/acsomega.3c10148
92. Grimm A, Schmitt K, Lang UE, Mensah-Nyagan AG, Eckert A. Improvement of neuronal bioenergetics by neurosteroids: Implications for age-related neurodegenerative disorders. *Biochim Biophys Acta BBA - Mol Basis Dis*. 2014;1842(12, Part A):2427-2438. doi:10.1016/j.bbadis.2014.09.013
93. Grimm A, Biliouris EE, Lang UE, Götz J, Mensah-Nyagan AG, Eckert A. Sex hormone-related neurosteroids differentially rescue bioenergetic deficits induced by amyloid- β or hyperphosphorylated tau protein. *Cell Mol Life Sci*. 2016;73(1):201-215. doi:10.1007/s00018-015-1988-x



94. Houfková A, Schmidt M, Benek O, et al. New insights into the 17 β -hydroxysteroid dehydrogenase type 10 and amyloid- β 42 derived cytotoxicity relevant to Alzheimer's disease. *Alzheimers Res Ther.* 2025;17(1):170. doi:10.1186/s13195-025-01821-8 View Article Online
DOI: 10.1039/D6CB00093B
95. Viswanath ANI, Kim T, Jung SY, Lim SM, Pae AN. In silico-designed novel non-peptidic ABAD L_D hot spot mimetics reverse A β -induced mitochondrial impairments in vitro. *Chem Biol Drug Des.* 2017;90(6):1041-1055. doi:10.1111/cbdd.13065
96. Takuma K, Yao J, Huang J, et al. ABAD enhances A β -induced cell stress via mitochondrial dysfunction. *FASEB J.* 2005;19(6):1-25. doi:10.1096/fj.04-2582fje
97. Aitken L, Baillie G, Pannifer A, et al. High-Throughput Screening of Potent Drug-like Molecules Targeting 17 β -HSD10 for the Treatment of Alzheimer's Disease and Cancer. *ACS Chem Biol.* 2025;20(7):1544-1559. doi:10.1021/acscchembio.5c00110
98. Yao J, Du H, Yan S, et al. Inhibition of Amyloid- β (A β) Peptide-Binding Alcohol Dehydrogenase-A β Interaction Reduces A β Accumulation and Improves Mitochondrial Function in a Mouse Model of Alzheimer's Disease. *J Neurosci.* 2011;31(6):2313-2320. doi:10.1523/JNEUROSCI.4717-10.2011
99. Yang X, Yang Y, Wu J, Zhu J. Stable Expression of a Novel Fusion Peptide of Thioredoxin-1 and ABAD-Inhibiting Peptide Protects PC12 Cells from Intracellular Amyloid-Beta. *J Mol Neurosci.* 2007;33(2):180-188. doi:10.1007/s12031-007-0063-y
100. Ali T, Klein AN, Vu A, Arifin MI, Hannaoui S, Gilch S. Peptide aptamer targeting A β -PrP-Fyn axis reduces Alzheimer's disease pathologies in 5XFAD transgenic mouse model. *Cell Mol Life Sci.* 2023;80(6):139. doi:10.1007/s00018-023-04785-w
101. Hroch L, Benek O, Guest P, et al. Design, synthesis and in vitro evaluation of benzothiazole-based ureas as potential ABAD/17 β -HSD10 modulators for Alzheimer's disease treatment. *Bioorg Med Chem Lett.* 2016;26(15):3675-3678. doi:10.1016/j.bmcl.2016.05.087
102. Aitken L, Benek O, McKelvie BE, et al. Novel Benzothiazole-Based Ureas as 17 β -HSD10 Inhibitors, A Potential Alzheimer's Disease Treatment. *Molecules.* 2019;24(15):2757. doi:10.3390/molecules24152757
103. Law CSW, Yeong KY. Current trends of benzothiazoles in drug discovery: a patent review (2015–2020). *Expert Opin Ther Pat.* 2022;32(3):299-315. doi:10.1080/13543776.2022.2026327
104. Xie Y, Deng S, Chen Z, Yan S, Landry DW. Identification of small-molecule inhibitors of the A β -ABAD interaction. *Bioorg Med Chem Lett.* 2006;16(17):4657-4660. doi:10.1016/j.bmcl.2006.05.099
105. Benek O, Vaskova M, Miskerikova M, et al. Development of submicromolar 17 β -HSD10 inhibitors and their *in vitro* and *in vivo* evaluation. *Eur J Med Chem.* 2023;258:115593. doi:10.1016/j.ejmech.2023.115593
106. Morsy A, Maddeboina K, Gao J, et al. Functionalized Allopurinols Targeting Amyloid-Binding Alcohol Dehydrogenase Rescue A β -Induced Mitochondrial Dysfunction. *ACS Chem Neurosci.* 2022;13(14):2176-2190. doi:10.1021/acscchemneuro.2c00246
107. Marques AT, Fernandes PA, Ramos MJ. Molecular dynamics simulations of the amyloid-beta binding alcohol dehydrogenase (ABAD) enzyme. *Bioorg Med Chem.* 2008;16(21):9511-9518. doi:10.1016/j.bmc.2008.09.043



108. Lim YA, Grimm A, Giese M, et al. Inhibition of the Mitochondrial Enzyme ABAD Restores the Amyloid- β -Mediated Deregulation of Estradiol. *PLoS ONE*. 2011;6(12):e28887. doi:10.1371/journal.pone.0028887
109. Daria S, Kumar D, Gautam N, et al. *In vitro* ADME, mouse pharmacokinetics of LD14b, and bioanalysis of a novel $\alpha\beta$ 17 β -HSD10 modulator for the treatment of Alzheimer's disease. *Xenobiotica*. 2024;54(9):711-722. doi:10.1080/00498254.2024.2402033
110. Geissler W, Davis D, Ling Wu, et al. Male pseudohermaphroditism caused by mutations of testicular 17 α -hydroxysteroid dehydrogenase 3. Published online 1994. doi:10.1038/ng0594-34
111. Heinlein CA, Chang C. Androgen Receptor in Prostate Cancer. *Endocr Rev*. 2004;25(2):276-308. doi:10.1210/er.2002-0032
112. Boutin S, Roy J, Maltais R, Alata W, Calon F, Poirier D. Identification of steroidal derivatives inhibiting the transformations of allopregnanolone and estradiol by 17 β -hydroxysteroid dehydrogenase type 10. *Bioorg Med Chem Lett*. 2018;28(22):3554-3559. doi:10.1016/j.bmcl.2018.09.031
113. Boutin S, Maltais R, Roy J, Poirier D. Synthesis of 17 β -hydroxysteroid dehydrogenase type 10 steroidal inhibitors: Selectivity, metabolic stability and enhanced potency. *Eur J Med Chem*. 2021;209:112909. doi:10.1016/j.ejmech.2020.112909
114. Hua Y, Dai X, Xu Y, et al. Drug repositioning: Progress and challenges in drug discovery for various diseases. *Eur J Med Chem*. 2022;234:114239. doi:10.1016/j.ejmech.2022.114239
115. Marder R, Richard C, Meibach. Risperidone in the Treatment of Schizophrenia. Published online 1994. doi:10.1176/ajp.151.6.825
116. Sajatovic M, Subramoniam M, Fuller MA. Risperidone in the treatment of bipolar mania. *Neuropsychiatr Dis Treat*. 2006;2(2):127-138. doi:10.2147/ndt.2006.2.2.127
117. Dilly SJ, Clark AJ, Marsh A, et al. A chemical genomics approach to drug reprofiling in oncology: Antipsychotic drug risperidone as a potential adenocarcinoma treatment. *Cancer Lett*. 2017;393:16-21. doi:10.1016/j.canlet.2017.01.042
118. Aitken L, Baillie G, Pannifer A, et al. In Vitro Assay Development and HTS of Small-Molecule Human ABAD/17 β -HSD10 Inhibitors as Therapeutics in Alzheimer's Disease. *SLAS Discov*. 2017;22(6):676-685. doi:10.1177/2472555217697964
119. Dow LF, Pathirage R, Erickson HE, Amani E, Ronning DR, Trippier PC. Synthesis and biological characterization of a 17 β hydroxysteroid dehydrogenase type 10 (17 β -HSD10) inhibitor. *RSC Med Chem*. 2025;16(2):862-875. doi:10.1039/D4MD00733F
120. Aitken L, Baillie G, Pannifer A, et al. In Vitro Assay Development and HTS of Small-Molecule Human ABAD/17 β -HSD10 Inhibitors as Therapeutics in Alzheimer's Disease. *SLAS Discov*. 2017;22(6):676-685. doi:10.1177/2472555217697964





University of St Andrews

School of Biology

DOI: 10.1039/D6CB00093B

B311, BMS/BSRC annexe, St Andrews, Fife, KY16 9ST
Scotland, United Kingdom***Prof Frank Gunn-Moore FRSB, FRSE***

Tel: 01334 463525 (Direct Line)

01334 476161 (Switchboard)

Fax: 01334 463600

e-mail: fjg1@st-andrews.ac.uk12th March 2026**Re: data availability statement**

To whom it may concern,

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.

Yours sincerely,

Frank Gunn-Moore BSc PhD FRSB, FRSE,

Professor of Molecular Neurobiology.

