Bioorganic & Medicinal Chemistry Letters 25 (2015) 841–846

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

SAR-studies of γ-secretase modulators with PPARγ-agonistic and 5-lipoxygenase-inhibitory activity for Alzheimer's disease

Daniel Flesch [a], Julia Ness [b], Christina Lamers [a], Friederike Dehm [c], Sven Popella [c], Ramona Steri [a], Isabella Ogorek [b], Martina Hieke [a], Gerd Dannhardt [d], Oliver Werz [c], Sascha Weggen [b,*], Manfred Schubert-Zsilavecz [a,*]

[a] Institute of Pharmaceutical Chemistry, Goethe-University Frankfurt, Max-von-Laue-Str. 9, D-60438 Frankfurt am Main, Germany
[b] Department of Neuropathology, Heinrich-Heine-University Düsseldorf, Moorenstrasse 5, D-40225 Düsseldorf, Germany
[c] Institute of Pharmacy, Friedrich-Schiller-University Jena, Philosophenweg 14, D-07743 Jena, Germany
[d] Institute of Pharmaceutical Chemistry, Johannes-Gutenberg-University Mainz, Staudingerweg 5, D-55128 Mainz, Germany

ARTICLE INFO

Article history:
Received 7 November 2014
Revised 17 December 2014
Accepted 19 December 2014
Available online 30 December 2014

Keywords:
Alzheimer's disease
γ-Secretase
γ-Secretase-modulator
Peroxisome-proliferator-activated-receptor
5-Lipoxygenase

ABSTRACT

We present the design, synthesis and biological evaluation of compounds containing a 2-(benzylidene)hexanoic acid scaffold as multi-target directed γ-secretase-modulators. Broad structural variations were undertaken to elucidate the structure–activity-relationships at the 5-position of the aromatic core. Compound **13** showed the most potent activity profile with IC_{50} values of 0.79 μM (Aβ42), 0.3 μM (5-lipoxygenase) and an EC_{50} value of 4.64 μM for PPARγ-activation. This derivative is the first compound exhibiting low micromolar to nanomolar activities for these three targets. Combining γ-secretase-modulation, PPARγ-agonism and inhibition of 5-lipoxygenase in one compound could be a novel disease-modifying multi-target-strategy for Alzheimer's disease to concurrently address the causative amyloid pathology and secondary pathologies like chronic brain inflammation.

Alzheimer's disease (AD) is the most prevalent form of dementia, with an estimated 24 million affected individuals worldwide and projected 81 million patients in 2040.[1] AD is a progressive neurodegenerative disease, resulting in loss of memory and cognitive functions in the elderly, ultimately leading to death. According to the amyloid hypothesis, the accumulation of Aβ peptides in the brain, in particular the longer and more hydrophobic Aβ42 species, leads to the formation of soluble, neurotoxic oligomers and the characteristic extracellular amyloid plaques. These soluble and insoluble Aβ aggregates are believed to initiate pathological changes in the AD brain like synaptotoxicity, neuronal death, and chronic brain inflammation.[2,3]

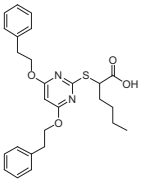
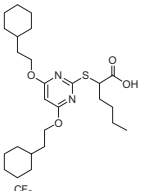
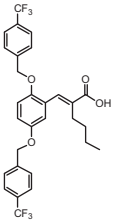
Aβ-Peptides are formed by sequential cleavage of the amyloid precursor protein (APP) by β- and γ-secretase.[2] Based on this process, approaches to modulate the proteolytic processing of APP and the generation of Aβ peptides include targeting of the aspartic proteases β- and γ-secretase.[4] For γ-secretase, γ-secretase-inhibitors (GSIs) and γ-secretase-modulators (GSMs) have been developed. GSIs reduce the overall enzymatic activity of γ-secretase. In contrast, GSMs shift the Aβ product spectrum from Aβ42 towards shorter and less aggregation-prone peptides like Aβ38. Importantly, GSMs do not affect NOTCH receptor cleavage and signalling.[5,6] Impairment of NOTCH signaling was likely at least in part responsible for the reported clinical side-effects of GSIs.[7] Thus, modulation of γ-secretase could be a safe approach to selectively target Aβ42 production and aggregation, and downstream pathological changes.

The first GSMs were discovered among non-steroidal anti-inflammatory drugs (NSAIDs) and included sulindac sulfide, ibuprofen or flurbiprofen.[6,8] The drug candidate R-flurbiprofen (tarenflurbil), which lacks undesired cyclooxygenase-(COX)-inhibition but exerts equivalent GSM activity compared to racemic flurbiprofen, failed to show efficacy in a phase III clinical trial, possibly due to substance specific limitations such as low penetration of the blood brain barrier and weak GSM activity (IC_{50}Aβ42 = 307 μM).[9,10] Despite the failure of tarenflurbil, novel GSMs have been developed that can be structurally divided in acidic, NSAID-like GSMs (e.g., the Cellzome GSM series)[5] and non-acidic tetracyclic GSMs. Potential future drug candidates have shown activity in the low nanomolar range and are evaluated in early clinical trials (for review see Ref. 11).

* Corresponding authors. Tel.: +49 211 8104506; fax: +49 211 8104577 (S.W.); tel.: +49 69 798 29339; fax: +49 69 798 29332 (M.S.-Z).
E-mail addresses: sweggen@hhu.de (S. Weggen), schubert-zsilavecz@pharmchem.uni-frankfurt.de (M. Schubert-Zsilavecz).

http://dx.doi.org/10.1016/j.bmcl.2014.12.073
0960-894X/

Table 1
Previously published compounds that act as dual γ-secretase-modulators/PPARγ-agonists[12,13]

Compound	γ-Secretase modulation		PPARγ activation		5-LO-inhibition
	IC_{50} Aβ42	EC_{50} Aβ38	EC_{50}	Max. activation	IC_{50}
1 	22.8	11.3	8.3	61%	0.6
2 	5.1	4.6	6.6	71%	0.8
3 	1.2	1.1	28% @10 μM		0.2

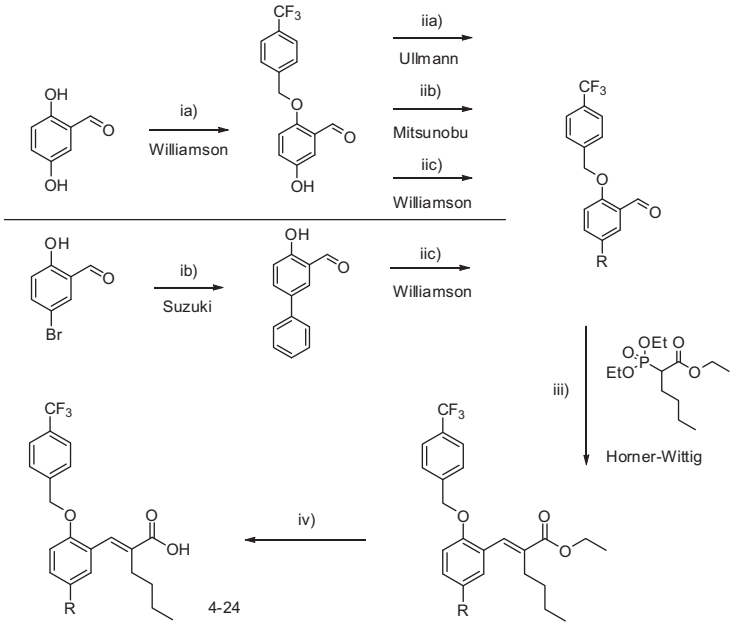
Values in μM; 100% maximal activation normalized to 1 μM pioglitazone.

We have contributed to the field with an approach to combine modulation of γ-secretase and of the peroxisome-proliferator-activated-receptor-γ (PPARγ).[12,13] PPARγ is a nuclear receptor involved in the lipid-metabolism and the response of peripheral tissues to glucose- and fatty acid uptake. PPARγ agonists were widely used as antidiabetic drugs, due to their insulin-sensitizing mode of action. Epidemiological studies have suggested a positive correlation between type 2 diabetes and the incidence of AD.[14] In addition, in vitro and in vivo investigations have demonstrated other activities of PPARγ agonists that might be beneficial in AD including down-regulation of β-secretase-(BACE1) expression, activation of insulin-degrading enzyme (IDE, which also degrades Aβ) and apolipoprotein E expression, enhancement of Aβ phagocytosis by microglia cells, improvement of hippocampus-dependent cognition, anti-inflammatory actions as well as improved glucose utilization of cerebral tissues.[15–20] Interestingly, an unbiased screen for suppressors of Aβ-induced neuronal degeneration recently identified the PPARγ agonist 5-deoxy-Δ12,14-prostaglandin J2, indicating that Aβ toxicity might, at least in part, be mediated by inhibition of PPARγ signaling.[21] Common safety liabilities of PPARγ agonists in the clinic are edema, weight gain and changes in lipid parameters. Rosiglitazone and Pioglitazone also showed substance-specific toxicity and their use was restricted.[22]

In addition to the potentially beneficial effects of modulating γ-secretase and PPARγ, 5-lipoxygenase (5-LO) could be another attractive target with implications for Aβ generation and brain inflammation.[23] Leukotrienes are products of the 5-LO-pathway, are well known mediators of inflammatory reactions and 5-LO expression appears to be upregulated in patients with AD.[24] A recently published study also showed that 5-LO and leukotrienes could promote Aβ generation, likely by transcriptional upregulation of γ-secretase subunits.[25] In other reports, the potent and selective 5-LO inhibitor zileuton reduced the amyloid and tau pathology as well as memory impairments in different mouse models of AD.[26,27] However 5-LO inhibition as a novel approach for the treatment of AD is still subject to further investigations evaluating its in vivo efficacy.

In summary, it could be a promising approach to combine GSM, PPARγ agonistic and 5-LO inhibitor activities in one compound to obtain a broad and potentially synergistic range of beneficial actions.

Our previous studies were based on the pirinixic acid derivative **1** (see Table 1), which is a moderately potent GSM with PPARγ ago-



Scheme 1. Synthesis of cinnamic acid derivatives: Reagents and conditions: (ia) 4-(Trifluoromethyl) benzyl bromide (1.0 equiv), Cs_2CO_3 (1.0 equiv), DMF, 60 °C, 2 h. (ib) Arylboronic acid (1 equiv), Cs_2CO_3 (2.5 equiv), $Pd(PPh_3)_4$ (0.1 equiv), toluene/EtOH 5:1, 80 °C, 2–3 h. (iia) Aryliodide (1.5 equiv), CuI (0.1 equiv), *N*,*N*-dimethylglycine (0.3 equiv), Cs_2CO_3 (2 equiv), DMF, 110 °C, 24 h. (iib) R-alcohol (1.3 equiv), TPP (1.3 equiv), DIAD or ADDP (1.3 equiv), THF, rt, 3–17 h. (iic) R-benzylhalide (1.3 equiv), Cs_2CO_3 (1.3 equiv), DMF, 60 °C, 2 h. (iii) Ethyl-2-diethoxy phosphorylhexanoate (1.3 equiv), NaH (1.3 equiv), THF, rt, 3–17 h. (iv) LiOH (10 equiv), THF, H_2O, MeOH, 40–60 °C, 17–72 h.