Design and synthesis of CNS-targeted drug-like flavonoid analogues with potential against Alzheimer’s disease and type 2 diabetes

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Alzheimer’s Disease

Affects over 46 million people worldwide

Currently prescribed drugs are mostly AChE and BChE inhibitors, e.g.:

- Donepezil
- Rivastigmine

\[ \uparrow \text{Acetylcholine brain levels} \]

SYMPTOMATIC RELIEF

Pathophysiology of AD

- Oxidative stress and mitochondrial dysfunction
- Neuroinflammation
- Upregulation of BACE-1, PDE, GSK-3β and BChE enzymes

The Amyloid Cascade Hypothesis:

APOE-ε4 and AChE may act as “pathological chaperones”

Synaptic dysfunction and neuronal death
Type 2 Diabetes and AD

The risk of dementia (particularly AD) is up to 73% higher in people with Type 2 Diabetes. END

Type 3 diabetes → "Diabetic brain"

Endothelial dysfunction
Brain insulin resistance
APOE-ε4 allele
↑ PDE and GSK-3β

Type 2 diabetes: an amyloid disease

Compensatory hyperinsulinemia (early stages of T2D)

Insulin + IAPP ↑
BBB

Cross-seeding with amyloid-β → Formation of brain amyloid deposits

Goal: find new multitarget leads

Broad bioactivity of natural leads

**Chrysin**

- Anti-inflammatory activity (Li et al., 2014)
- Ameliorates diabetes-induced cognitive deficits (Li et al., 2014)
- Attenuates neural loss induced by Aβ-induced oxidative stress (Aishwarya et al. 2015)
- Prevents Aβ_{1-42} fibrillization (Matos et al. unpublished results)
- AChE, BChE and BACE-1 micromolar inhibitor (Choi et al. 2014)
- Reduces BACE-1-mediated APP processing into Aβ (Sabogal-Guáqueta et al. 2015)
- Attenuates learning and memory deficits (Wang et al. 2014)
- Downregulates BACE-1 (Zhao et al. 2013)
- Decreases insoluble Aβ brain levels (Zhao et al. 2013)
- Attenuates Aβ-mediated toxicity induced by copper (Zhao et al. 2013)
- AChE and BChE micromolar inhibitor (Choi et al. 2014)

**Quercetin**

**Apigenin**
**Broad bioactivity of natural leads**

*C-glucosyl flavonoids*

- **Vitexin**
  
  (8-β-*C*-glucosyl apigenin)

- **8-β-D-glucosylgenistein**

**Neuroprotective effects** (Guimarães et al. 2015)

- AChE and BChE and BACE-1 inhibitor
  
  (Choi et al. 2014)

  +

**Antidiabetic activity**

(Farsi et al. 2014, Choo et al. 2012)

**Antidiabetic activity** (Jesus et al. 2014)

- Interaction with Aβ<sub>1-42</sub> through the same binding mode
  
  (Jesus et al. 2014)
Broad bioactivity of natural leads

Possible benefits of the sugar moiety:

- Improved **solubility** and oral bioavailability (Torres et al. 2011)
- Ability to **stabilize amyloid peptides** in their disaggregated state (synergistic effect with the aglycone) (Ladiwala et al. 2011)
- Enhanced **antioxidant and antidiabetic effects** (Xiao et al. 2015)
- Ability to act as a **drug shuttle into the CNS** through BBB GLUT-1 transporters (hypothesis)
Objectives

1. Synthesize polyphenols that are able to mimic natural flavonoids

2. Synthesize C-glucosyl ester analogues of natural flavonoids presenting differences in the position of aromatic ring B, and observe the impact on bioactivity

3. Synthesize methylated and corresponding free derivatives and study the role of the sugar in the interaction with the molecular target(s)

energy minimization and superimposition studies (Molecular Mechanics) between 8-β-D-glucosylgenistein and one rationally designed analogue
Chemistry

C-Glycosylation

Lewis Acid Promoter

Selective/Full Acylation

Base

Deprotection

R_1 = H/Me/Ac
R_2 = Bn or Me
R_3 = OH/OBz/R

Selected as rationally-designed analogue precursors

63%
37%
7%
53%
28%
66%
Chemistry

C-Glycosylation

Lewis Acid Promoter

R₁ = H/Me/Ac
R₂ = Bn or Me

Selective/Full Acylation

Base

R₂ = Bn or Me
R₃ = OH/OBz/R

Deprotection
Chemistry

C-Glycosylation → Selective/Full Acylation → Deprotection

Lewis Acid Promoter

R₁ = H/Me/Ac
R₂ = Bn or Me
R₃ = OH/OBz/R

8%
2%
Chemistry

*C*-glycosylated and non-glycosylated flavone analogues

Commercially available aldehydes: $R = \text{alkyl, aryl or heteroaryl group}$

Generation of a database of flavone analogues

Selection based on CNS drug-likeliness using the CNS-MPO Score$^a$

$^a$ Wager T., Hou X., Verhoest P.R., Villalobos A. *ACS Chem Neurosci*, 2010
Future Work

Compound screening:

1. Anti-amyloidogenic effects and BBB permeability
2. Potential to inhibit BACE-1, PDE and GSK-3β enzymes
3. Evaluation of neuroprotective and antidiabetic effects

Structure-activity relationships
focusing on the importance of the sugar moiety
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