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

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D3i4AD Diagnostic and Drug Discovery Initiative for Alzheimer's Disease

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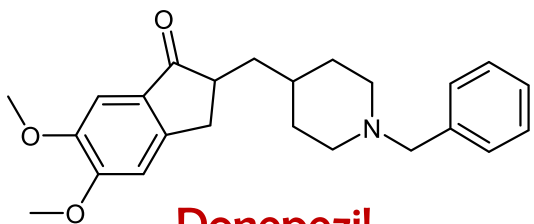
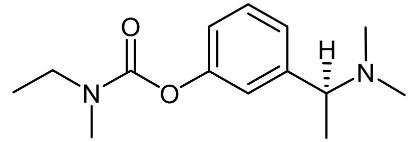
Alzheimer's Disease

Affects over **46 million** people worldwide [a]

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



Donepezil



Rivastigmine

↑ Acetylcholine brain levels

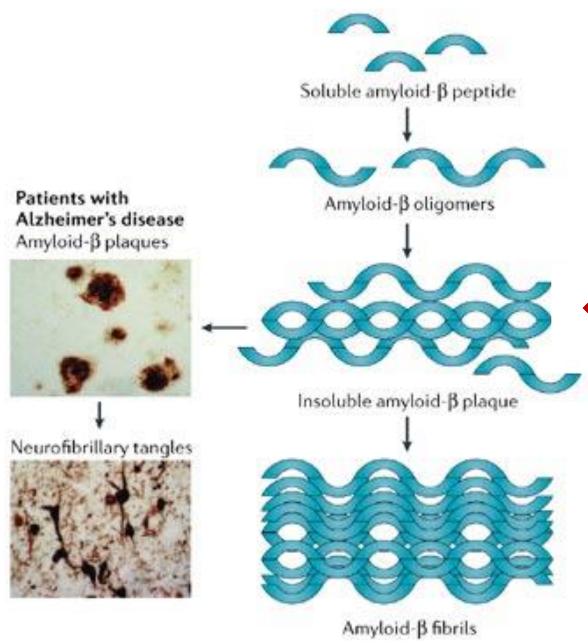
SYMPTOMATIC RELIEF

[a] Prince M., Wimo A., Guerchet M., Ali G.C., Wu Y.T., Prina M. World Alzheimer's Report 2015

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

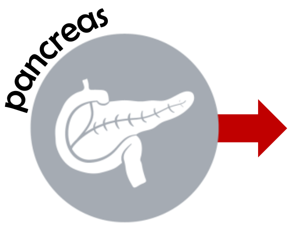
Type 2 Diabetes and AD

The risk of dementia (particularly AD) is up to **73% higher** in people with Type 2 Diabetes[b]

Type 3 diabetes ⟷ "Diabetic brain"

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

Type 2 diabetes: an **amyloid** disease



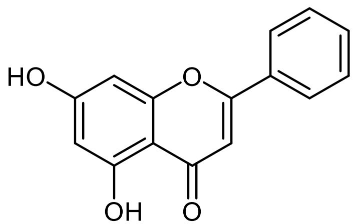
Compensatory hyperinsulinemia
(early stages of T2D)

→ ↑ Insulin + ↑ IAPP ⇢ (BBB) **Cross-seeding** with amyloid-β → **Formation of brain amyloid deposits**

Goal: find new **multitarget** leads

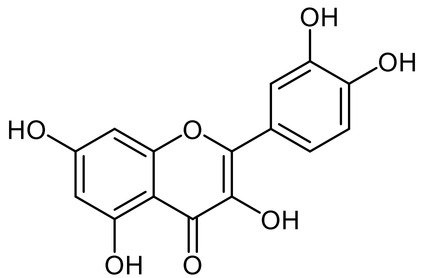
[b] P.S. Koekkoek, L.J. Kappelle, E. van den Berg, G.E.H.M. Rutten, G.J. Biessels, *Lancet Neurol.* 2015; 14(3), 329–340.

Broad bioactivity of natural leads



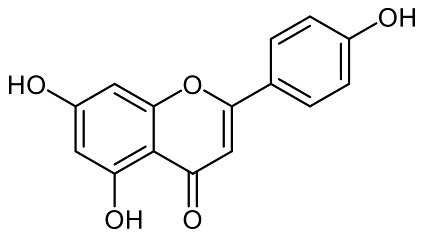
Chrysin

- Anti-inflammatory activity (Li et al., 2014)
- Amielorates diabetes-induced cognitive deficits (Li et al., 2014)
- Attenuates neural loss induced by Aβ-induced oxidative stress (Aishwarya et al. 2015)



Quercetin

- Prevents $A\beta_{1-42}$ 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)

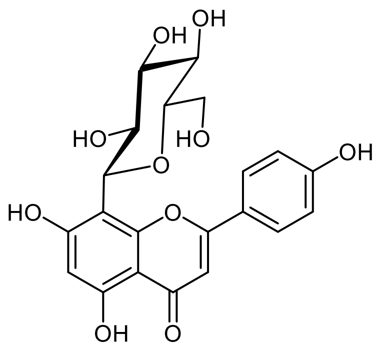


Apigenin

- Downregulates BACE-1 (Zhao et al. 2013)
- Decreases insoluble Aβ brain levels (Zhao et al. 2013)
- Attenuates Aβ-mediated toxicity incuced by copper (Zhao et al. 2013)
- AChE and BChE micromolar inhibitor (Choi et al. 2014)

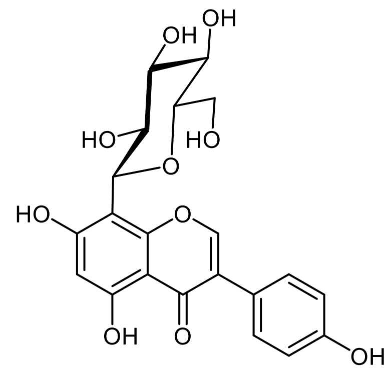
Broad bioactivity of natural leads

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

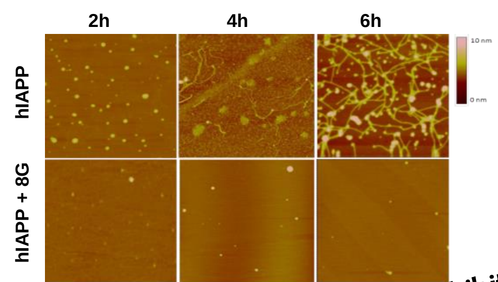
(Choi et al. 2014)

+

Antidiabetic activity

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

Antidiabetic activity (Jesus et al. 2014)



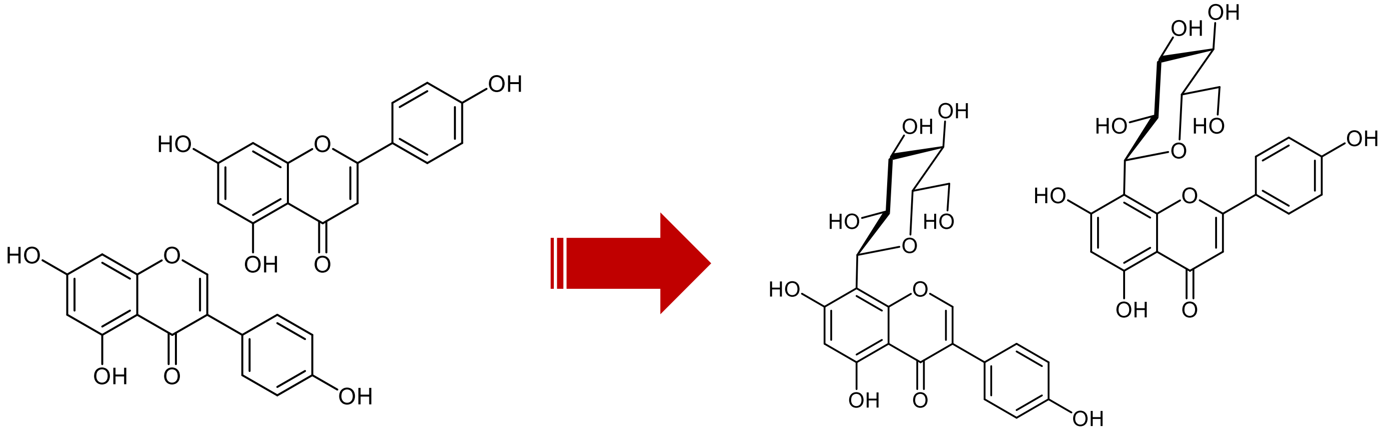
Inhibition of IAPP fibrillization

+

Interaction with Aβ_{1-42}

through the same binding mode (Jesus et al. 2014)

Broad bioactivity of natural leads



Possible benifits 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)

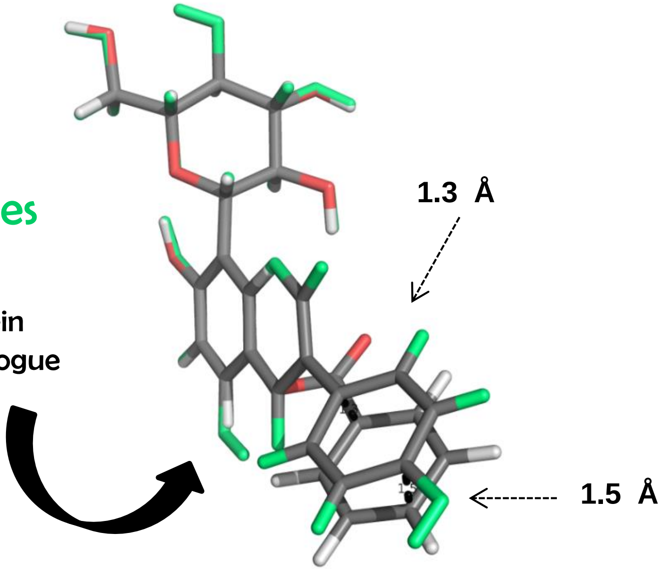
Objectives

1 Synthesize polyphenols that are able to mimic natural flavonoids

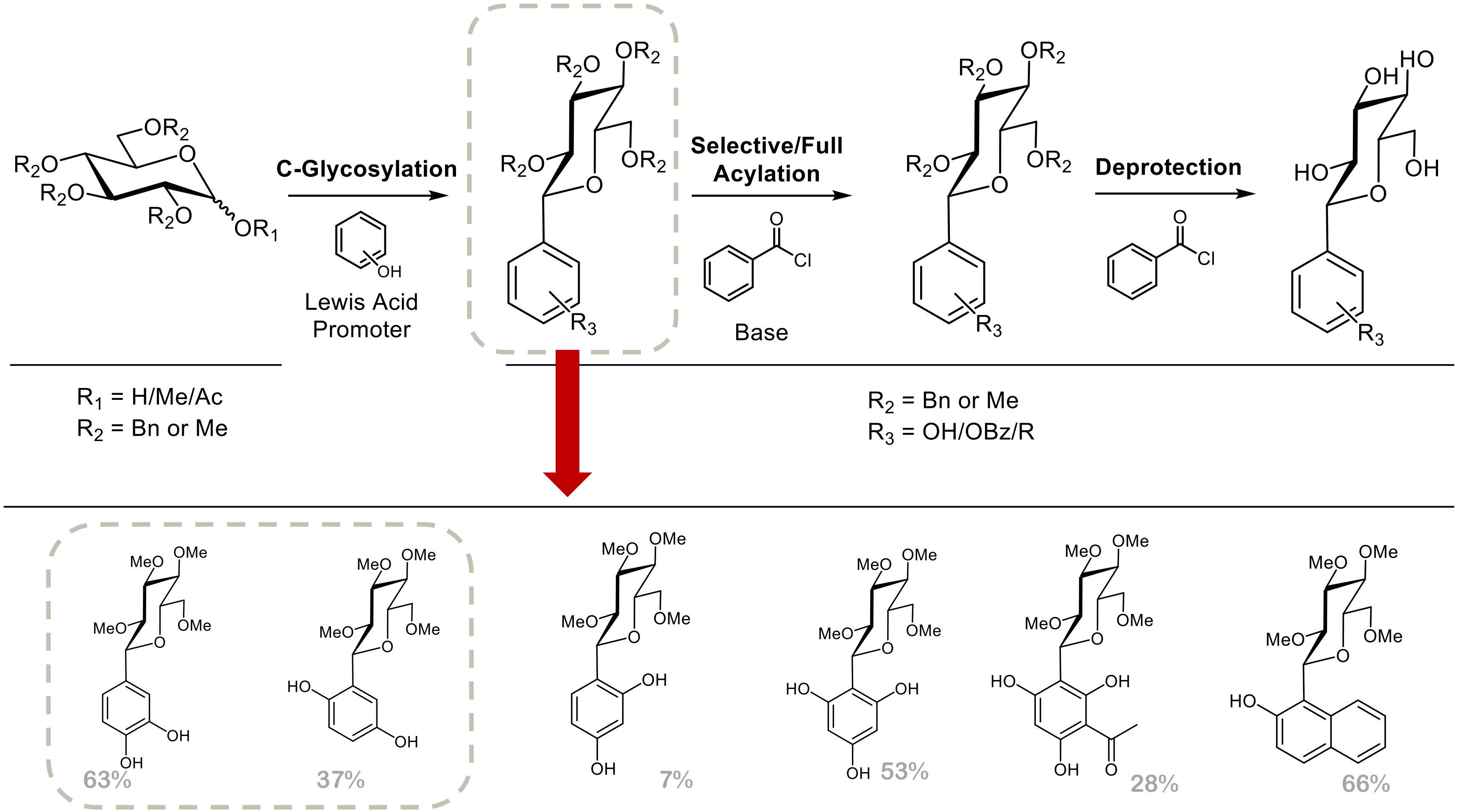
2 Synthesize *C*-glucosyl ester analogues of natural flavonoids presenting differences in the position of aromatic ring B, and observe the impact on bioactivity

3 Synthesize methylated and correnspongding 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

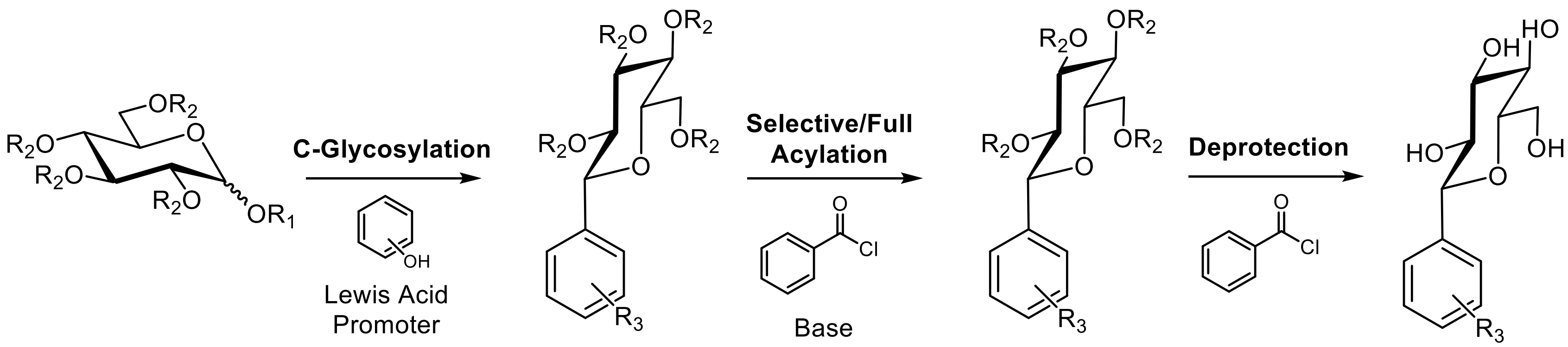


Chemistry



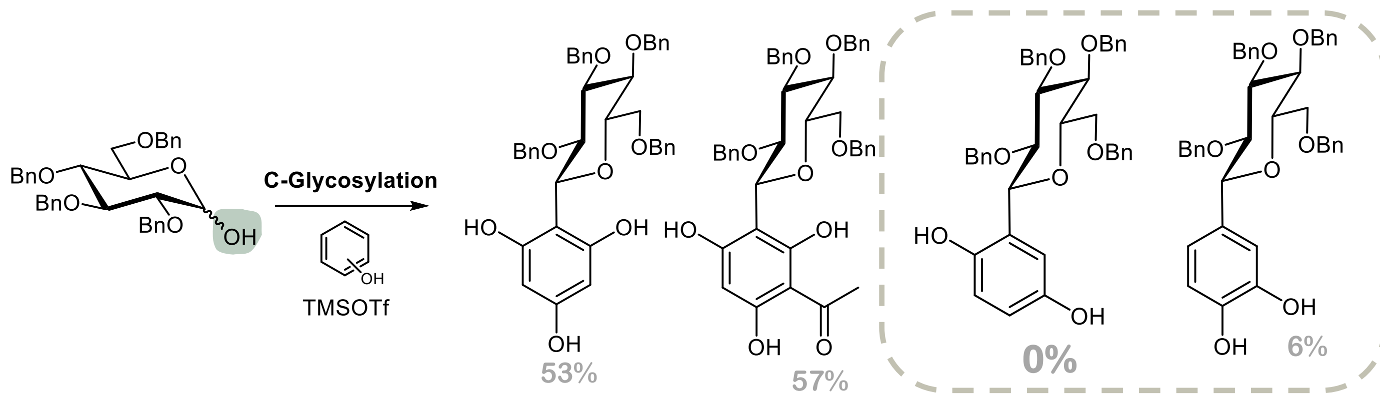
Selected as rationally-designed analogue percursors

Chemistry



R_1 = H/Me/Ac
R_2 = Bn or Me

R_2 = Bn or Me
R_3 = OH/OBz/R



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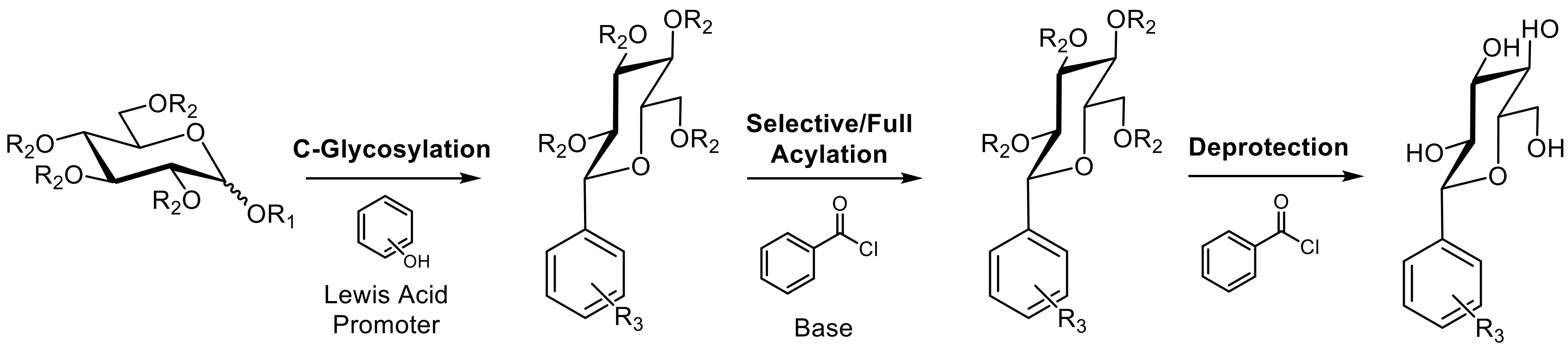

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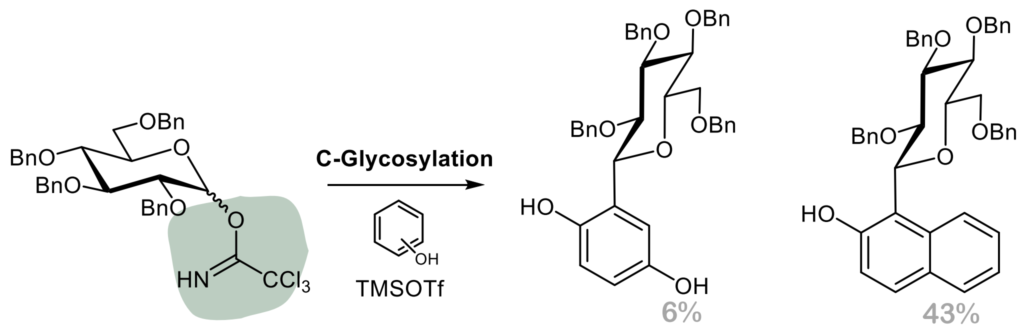

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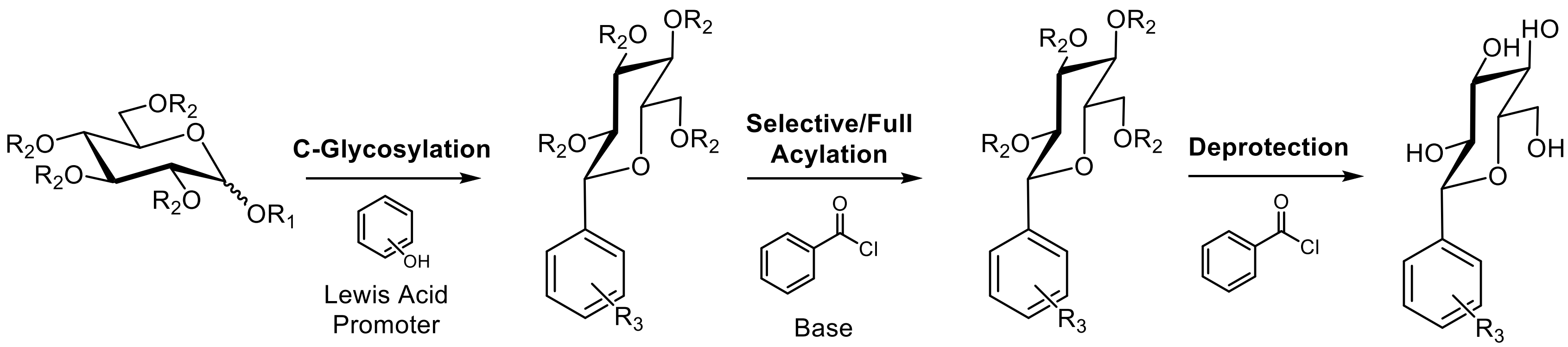

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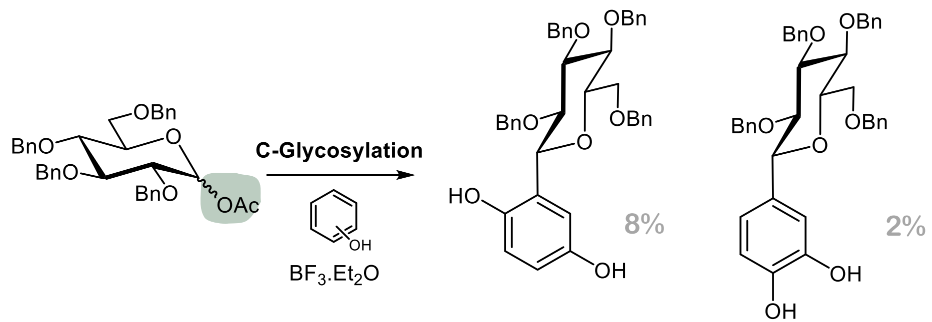
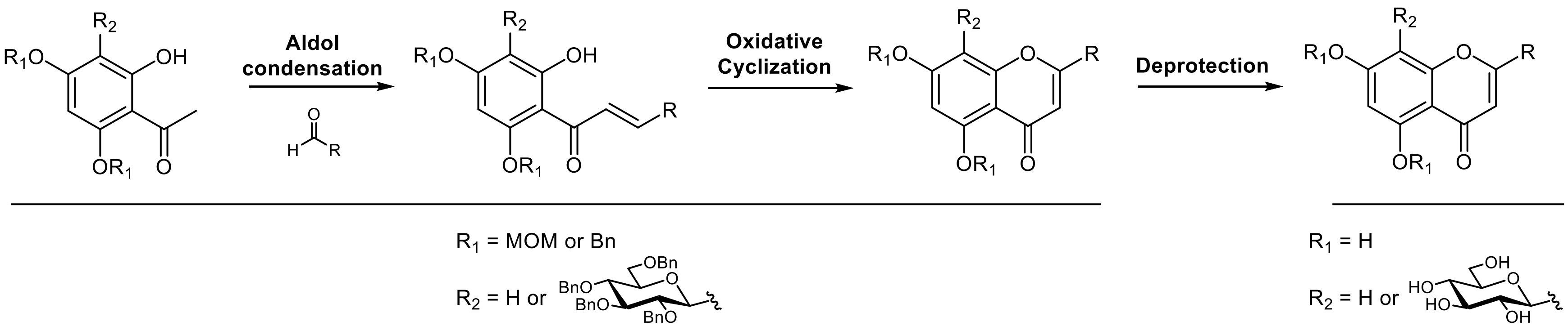
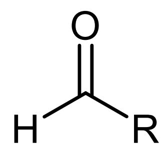


Chemistry

C-glycosylated and non-glycosylated flavone analogues



Commercially available aldehydes:  **R = 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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MARIE CURIE ACTIONS

SEVENTH FRAMEWORK PROGRAMME

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BIOFORDRUG
Diagnostics & Pharmacologicals