Synthesis of new purine nucleosides as potential metal chelators and anticholinesterase agents

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Background

Alzheimer's disease (AD) is the most common form of dementia, being a multifactorial neurodegenerative disease

Elevated levels of Cu(II)

Characteristic of both AD and some tumors

Progressive decline of the level of the neurotransmitter acetylcholine

Acetylcholine is degraded by acetylcholinesterase (AChE) or by butyrylcholinesterase (BChE)

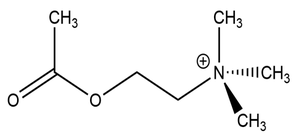


Figure 1. Structure of Acetylcholine

Mannosylpurine nucleosides

Mannosylpurines synthesized by our group already showed a potent BChE inhibition and a potent antitumor activity

Methodology

Synthesis

- **Method 1**

  Reaction of a fully protected glycoside with trimethylsilyl activated 6-benzoyladenine, catalyzed by trimethylsilyl triflate.

- **Method 2**

  Reaction of a fully protected phenyl α-D-thiomannoside with 6-benzoyladenine in the presence of iodine.

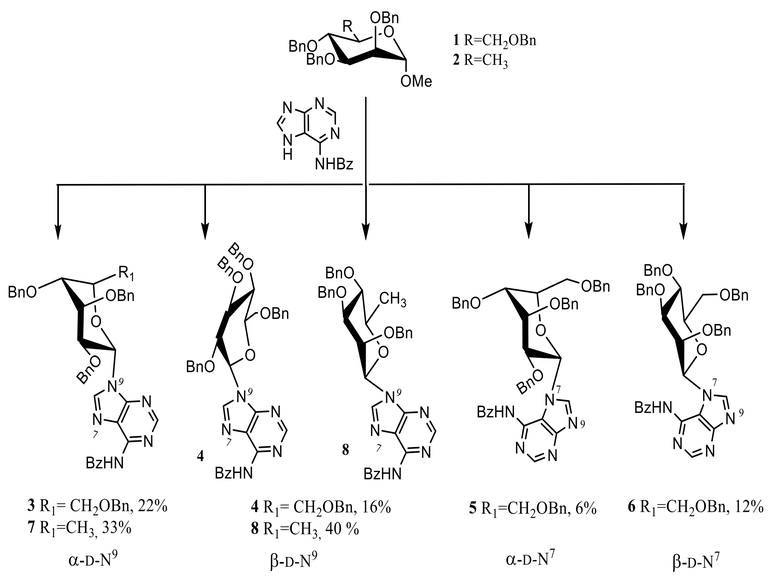
Chelating activity

Compounds **3-8**, **10**, **12**, **13** and **15** chelating activity was evaluated by recording UV-Visible spectra, since this method offers the advantage of high sensitivity towards small changes that affect electronic properties of ligand receptors.

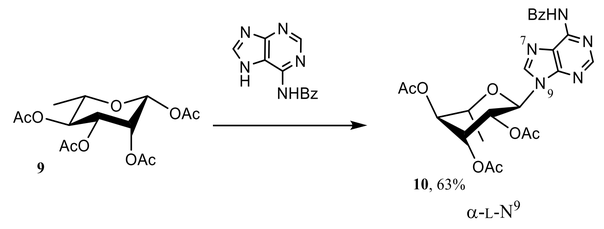
Anticholinesterase assays

Test compounds were assayed for the inhibitory activity towards electric eel AChE (*ee*AChE) and horse serum BChE (*eq*BChE) by using Ellman's colorimetric assay. Inhibition by **3-8** and **10** was tested at 20 μM final concentration. However, **12** and **13** were tested at 5 μM due to poor water solubility. Compound **15** was not tested yet.

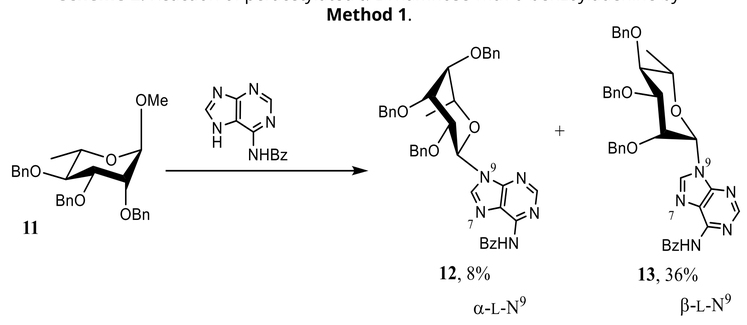
Method 1- Results



Scheme 1. Reaction of benzylated methyl α-D-mannoside and methyl α-D-rhamnoside with 6-benzoyladenine by **Method 1**.

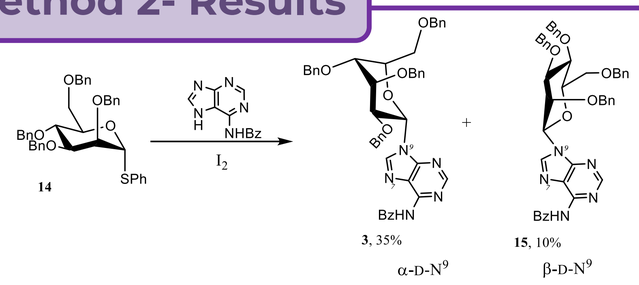


Scheme 2. Reaction of peracetylated α-L-rhamnose with 6-benzoyladenine by **Method 1**.



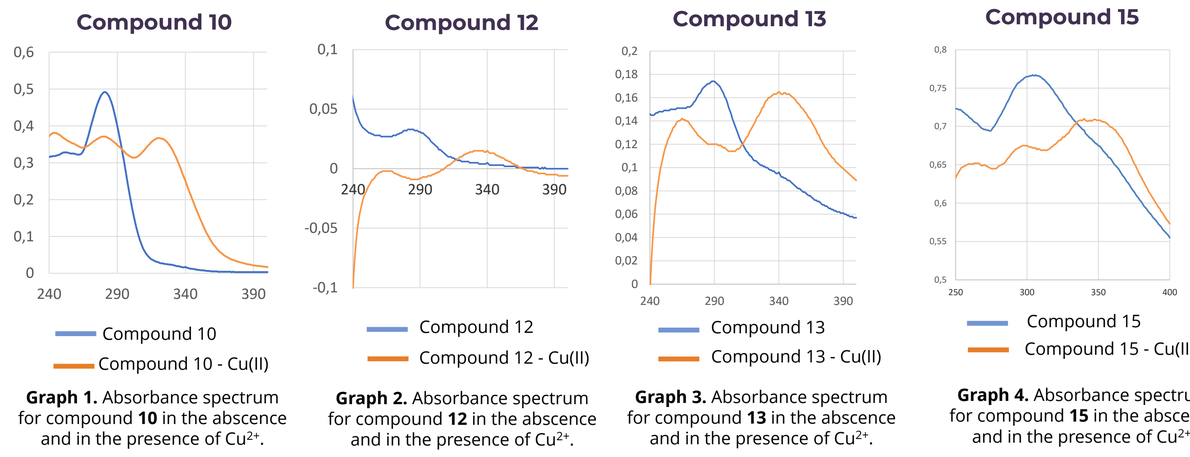
Scheme 3. Reaction of benzylated methyl α-L-rhamnoside with 6-benzoyladenine by **Method 1**.

Method 2- Results



Scheme 4. Reaction of benzylated phenyl α-D-thiomannoside with 6-benzoyladenine by **Method 2**.

Chelating activity



Graph 1. Absorbance spectrum for compound **10** in the abscence and in the presence of Cu^{2+}.

Graph 2. Absorbance spectrum for compound **12** in the abscence and in the presence of Cu^{2+}.

Graph 3. Absorbance spectrum for compound **13** in the abscence and in the presence of Cu^{2+}.

Graph 4. Absorbance spectrum for compound **15** in the abscence and in the presence of Cu^{2+}.

Amongst all the new synthesized compounds **10**, **12**, **13** and **15** showed the most interesting results.
The resulting wavelength shifts indicate a conformational rearrangement induced by interaction with Cu(II).

Anticholinesterase activity

Table 1. AChE and BChE inhibition by nucleosides **3-8** , **10**, **12** and **13**

Compound nr.	IC_{50}(μM)	
	***ee*AChE**	***eq*BChE**
3	>20	>20
4	10.60±1.10	4.29±1.70
5	>20	10.00±1.10
6	2.61±1.23	4.40±1.30
7	4.69±0.51	>20
8	15.0±2.1	11.7±1.2
10	>20	>20
12	>5	>5
13	>5	>5
Donepazil	0.137	1.50
Galantamine	0.230	11.9

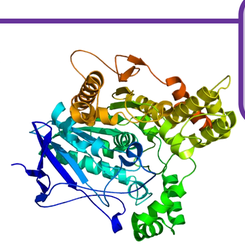


Figure 2. Structure of AChE

Compounds **4**, **6** -**8**, show IC_{50} below 15 μM.

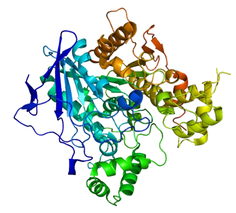


Figure 3. Structure of BChE

Conclusions

Selectivity

- Although method 1 did not allow us to obtain N^9 or N^7 selectivity for mannosides, the second method gave only N^9 isomers.
- By using method 1 with rhamnosides, it was possible to obtain N^9 selectivity.

Copper chelation studies

- Since only compounds **10**, **12**, **13** and **15** showed chelating activity, therefore N^9 purine ligation might be relevant to optimize chelating activity.

Anticholinesterase activity

- Compounds that exhibit β-D configuration are dual inhibitors, regardless of N^9 or N^7 purine ligation.
- AChE inhibition seems to be related with N^9 ligation while BChE inhibition seems to be related to with N^7 ligation.
- Aromatic rings seem to be important for anticholinesterase activity.

ACKNOWLEDGMENTS

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