CHIRAL DI- AND TRI-HYDROXYDERIVATIVES OF 1,4-MORPHOLIN-2,5-DIONE AS $\alpha$-GLUCOSIDASE INHIBITORS

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Glycosidase inhibitors play an important role not only on the study of their action mechanism, but also as therapeutic agents towards diabetes, infections, cancer, HIV. Continuing our studies directed towards producing new and more active $\alpha$-glucosidase inhibitors, we have focused our attention on a new family of optically active 1,4-morpholin-2,5-dione derivatives.

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\begin{align*}
1 & \quad \text{a}=(3S,6R,2'R,3'S) \\
2 & \quad \text{a}=(3R,6S,2'S,3'R) \\
3 & \quad \text{a}=(3S,6R,2'S,3'R) \\
4 & \quad \text{a}=(3S,6R,2'S,3'R)
\end{align*}
\]

Diols 1, 2 and triols 3 have been synthesized in good yields by following a procedure already employed starting from the (S)-phenylethylamine derived chiral synthon 1,4-morpholin-2,5-dione. The absolute configuration of C-2’ and C-3’ stereocentres was established by converting the substrates 1-3 into the respective $\gamma$-lactones through the assisted opening of the morpholinone ring previously investigated. The formation of $\gamma$-lactones (instead of $\delta$-) and their stereochemistry was then established through the IR spectroscopy and nOe measurements. All the substrates behave as non competitive inhibitors towards the $\alpha$-glucosidase from bakers yeast and bacillus stearothermophilus and show a very good inhibitor ability, the Ki values being in the range 5-1500 $\mu$M. No significant inhibition towards $\beta$-glucosidase (from almonds), $\alpha$-mannosidase (from jack beans) and $\alpha$-galactosidase (from green coffee beans) was observed.

References