PHARMACOLOGICAL EVALUATION OF THE BENZOTHIAZEPINE CGP37157 AND ISOSTERIC ANALOGUES

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Benzothiazepine CGP37157 is widely used as tool to explore the role of mitochondria in cell Ca\textsuperscript{2+} handling by its blocking effect of the mitochondria Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger (mNCX)\textsuperscript{[1]} and has recently shown to exhibit neuroprotective properties\textsuperscript{[2]}. In the trend to improve its neuroprotection profile, we have synthesized ITH12505, an isosteric analogue having a methyl instead of chlorine at C2’ of the phenyl ring.

We have also confirmed the blockade of mNCX exerted by CGP37157 and ITH12505 in permeabilized HeLa cells, transfected with mitochondrially-targeted aequorin (AEQ-Mt-Mut), and measuring mitochondrial clearance constant. By causing a mild isosteric replacement in the benzothiazepine CGP37157, we pretended to obtain a new compound, ITH12505, with improved neuroprotective properties.

As far as to prove this hypothesis in neuroprotection experiments we have used two models, SH-SY5Y cells and rat hippocampal slices. While ITH12505 elicited protection in SH-SY5Y cells stressed with oligomycin A/rotenone, CGP37157 was ineffective. In hippocampal slices subjected to oxygen/glucose deprivation plus reoxygenation, ITH12505 offered protection at 3-30 µM, while CGP37157 only protected at 30 µM. ITH12505 exerted similar neuroprotective properties to CGP37157 in hippocampal slices stressed with veratridine. Also, both compounds afforded neuroprotection in hippocampal slices stressed with glutamate.

In conclusion, these findings may inspire the design and synthesis of new benzothiazepines targeting mitochondrial Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger and L-type voltage-dependant Ca\textsuperscript{2+} channels, having antioxidant properties.

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