CHAPTER 5
CONCLUSION

The ultimate objective of the study was to create a multifunctional neuroprotective agent with the potential to halt the neuronal breakdown process, and at the same time have the ability to treat and eliminate some of the symptoms of neurodegenerative disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD).

Previous studies concluded that the neuronal loss found in certain areas of the brain in PD and AD, takes place by an intrinsic cell suicide program, known as apoptosis (Holbrook *et al.*, 1996). This cell death program consists of several pathways and cascades, with each one having an influence on the other. This ultimately leads to the death of the neuronal cells, and deterioration of the central nervous system.

PD is characterised by increased levels of MAO-B, which is responsible for the symptoms of the disease. Since MAO-B is a major catabolic enzyme of dopamine, inhibition of this enzyme leads to alleviation of the symptoms of PD. In AD increased levels of MAO-B has been shown to have a role in the pathology, not directly giving rise to the signs and symptoms, but contributing to the neurodegeneration. Therefore inhibition of MAO-B may also be beneficial in AD.

The aim was thus to create compounds with dual mechanisms, which would ultimately inhibit apoptosis as well as MAO-B. Such compounds may act as neuroprotective and symptomatic drugs. In designing the compounds we focused on the structures of rasagiline and selegiline, well known MAO-B inhibitors. Besides being potent MAO-B inhibitors, these drugs are also neuroprotective (Chen *et al.*, 2007). The neuroprotective ability of these agents has been shown to be dependent on the propargylamine moiety present in both structures (Bar-Am *et al.*, 2005). Based on this consideration the compounds studied, all contain the propargylamine functional group or a derivative thereof. These possible pharmacophores were linked to a polycyclic cage structure. Being very non-polar, these polycyclic structures would aid in the transport of the drug across the blood-brain barrier, as well as cell membranes into the cells where the drugs would be active. The highly non-polar polycyclic cage structures incorporated into the compounds studied were pentacyclo-undecane and adamantine.

To prepare the target compounds, propargylamine and propargylbromide or ethynyl magnesium bromide were reacted with either pentacyclo-undecane or amantadine. Both

conventional and modern methods were utilised to synthesise the proposed test compounds. Even though the reagents used in the synthetic routes were very similar, the experimental procedures utilised were very diverse. In most of the synthetic routes the percentage yield of the final products is very low, due to a high level of side-products. Due to this, considerable time was spent to purify intermediate and final products. The purification methods used included column chromatography, soxhlett extraction, recrystallisation as well as steam distillation.

In this study the following propargylamine derivatives were considered: Firstly the activity of a single terminal acetylene group (compound **2**) was evaluated, and secondly the activity of this group if placed between two non-polar groups (compound **3**). It was also evaluated what the activity of propargylamine would be, when it is linked to a polycyclic cage structure (compounds **4** - **7**) as a secondary amine (compound **4a**) and as a tertiary amine (compounds **5a**, **6** and **7**). Furthermore it was also investigated what effect a methyl substituent on the polycyclic structure (compounds **4b** and **5b**) would have on the activity of the polycyclic propargylamine.

Flowcytometric evaluation of the synthesised compounds for anti-apoptotic activity revealed surprising results. All the compounds had moderate to weak anti-apoptotic activity and compared favourably to the positive control, selegiline. It is important to consider the possibility that even though the compounds improved the survival of cell cultures and appear to have anti-apoptotic acivity, these observations can also be ascribed to a mechanism wherein the test compounds improve the growth of cell cultures, and thereby increased the amount of viable cells which were present in the samples analised. The pentacyclo-undecane derivatives had higher activity than the adamantane derivatives. This can possibly be attributed to solubility problems experienced with higher concentrations of the adamantane amines. It can also be attributed to the possibility that pentacyclo-undecanes may have an increased ability to pass cell membranes due to their higher lipophilicity. This would result in increased intracellular concentrations of the drugs. When compared to the control experiments, all the test compounds improved cell health between 9 and 41%. It can be concluded that all the compounds had anti-apoptotic activity, with the more effective concentration being in the micro molar range. The compound with the most significant activity was compound **2**. This compound was twice as potent as the positive control, and all cultures treated with **2** had only 0.5% apoptotic cells in the analysed samples. Slightly less active than compound **2** was compound **3**, with only 2.8% of the cells being apoptotic. Studying the results of these experiments, it is clear that the anti-apoptotic activity of propargylamine can most probably be attributed to the acetylene group, as compounds **2** and

3 have equivalent or even higher activity than compounds **4-7.** For activity, this acetylene group can either be terminal or intramolecular, with the terminal acetylene group having slightly higher activity. Due to solubility problems with compound **5b**, it can not accurately be determined whether the methyl group in position 1 of the pentacyclo-undecane cage had an effect on the anti-apoptotic activity of the compounds. Comparing the activity of compounds **4a** and **5a**, it can be concluded that the tertiary propargylamine had slightly higher activity than the secondary propargylamine. Even though all the synthesised compounds appeared to have moderate to weak anti-apoptotic activity, they can be used in further studies as lead compounds in the development of more potent inhibitors.

In the monoamine oxidase B assay, only one compound **(3)** had promising MAO-B inhibition activity. The assay revealed that the other synthesised compounds were not able to act as inhibitors of this enzyme. Considering the results of the MAO-B inhibition assay, the following can be concluded: The polycyclic propargylamines did not have promising MAO-B inhibiting activity, with pentacyclo-undecane and adamantane substituents decreasing the activity of the propargylamine moiety. The benzyl group was clearly a favourable substituent, increasing the activity of both the pentacyclo-undecane and adamantane derivatives. Having a methyl group in position 1 of the pentacyclo-undecane cage appeared to slightly increase the activity of the compounds (**4a** and **5b**). Inclusion of a second propargyl group does not significantly increase the activity of the polycyclic propargylamines. The promising activity of compound **3** can be ascribed to the benzyl group being linked to the cage structure by means of an acetylene linker. The acetylene group together with benzyl makes this part of the structure of compound **3** very planar, making it possible for this compound to move into the active site cavity of the enzyme, thereby inhibiting the enzyme.

In this study the aim was to create a drug acting via multiple mechanisms with MAO-B inhibiting as well as anti-apoptotic activity. Based on the results it can be concluded that only compound **3** exhibited dual actions. Compound **3** had a MAO-B inhibition percentage of 73.32% at 300 μM, and a percentage apoptotic cells, of only 2.78% in the samples analysed. This compound represents a lead for the discovery of new treatment strategies for neurodegenerative diseases such as PD and AD.

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