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Polycyclic propargylamine and acetylene derivatives as multifunctional neuroprotective agents

Frank T. Zindo [a], Quinton R. Barber [b], Jacques Joubert [a], Jacobus J. Bergh [b], Jacobus P. Petzer [b], Sarel F. Malan [a,b,*]

[a] Pharmaceutical Chemistry, School of Pharmacy, University of The Western Cape, Private Bag X17, Bellville 7535, South Africa
[b] Pharmaceutical Chemistry, North-West University, Private Bag X6001, Potchefstroom 2520, South Africa

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ABSTRACT

The aim of this study was to design drug-like molecules with multiple neuroprotective mechanisms which would ultimately inhibit *N*-methyl-D-aspartate (NMDA) receptors, block *L*-type voltage gated calcium channels (VGCC) and inhibit apoptotic processes as well as the monoamine oxidase-B (MAO-B) enzyme in the central nervous system. These types of compounds may act as neuroprotective and symptomatic drugs for disorders such as Alzheimer's and Parkinson's disease. In designing the compounds we focused on the structures of rasagiline and selegiline, two well known MAO-B inhibitors and proposed neuroprotective agents. Based on this consideration, the compounds synthesised all contain the propargylamine functional group of rasagiline and selegiline or a derivative thereof, conjugated to various polycyclic cage moieties. Being non-polar, these polycyclic moieties have been shown to aid in the transport of conjugated compounds across the blood–brain barrier, as well as cell membranes and have secondary positive neuroprotective effects. All novel synthesised polycyclic derivatives proved to have significant anti-apoptotic activity ($p < 0.05$) which was comparable to the positive control, selegiline. Four compounds (**12**, **15** and **16**) showed promising VGCC and NMDA receptor channel inhibitory activity ranging from 18% to 59% in micromolar concentrations and compared favourably to the reference compounds. In the MAO-B assay, 8-phenyl-ethynyl-8-hydroxypentacycloundecane (**10**), exhibited MAO-B inhibition of 73.32% at 300 μM. This compound also reduced the percentage of apoptotic cells by as much as 40% when compared to the control experiments.

1. Introduction

The pathology of neurodegenerative disorders, such as Parkinson's disease (PD) and Alzheimer's disease (AD), is caused by the abnormal loss of neuronal cells in certain areas of the brain [1]. It consequently causes an imbalance of certain neurotransmitter levels in the brain, giving rise to the characteristic signs and symptoms of these disorders [2,3]. Ultimately, it compromises the normal functionality and well-being of the individual suffering from the disease [3], thus making it an absolute necessity to create drugs which would halt this neuronal breakdown process and aid in treating the signs and symptoms of neurodegenerative disorders. The abnormal death of neurons in the central nervous system of individuals suffering from neurodegenerative diseases takes place by an intrinsic cell suicide program known as apoptosis [4–7]. This process is triggered by several stimuli, and consists of numerous pathways and cascades, each one having an influence on the other, ultimately leading to cell death [4–7]. One such pathway is the excitotoxic process which leads to apoptosis. Excitotoxicity is a result of activation of postsynaptic receptors; including NMDA receptors, 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl) propionate (AMPA), and kainate receptors. Upon their activation, these receptors open their associated ion channel to allow the influx of Ca^{2+} and Na^{+} ions. The excessive influx of calcium together with any calcium release from intracellular compartments can overwhelm Ca^{2+}-regulatory mechanisms and lead to cell death [8,9]. This mechanism of cell death suggests that the receptors and their associated calcium channels serve as drug target sites for curbing neurodegeneration. Several compounds, including polycyclic amines such as amantadine (**2**), NGP1-01 (**3**), MK-801 (**4**), and phencyclidine (PCP, **5**) have been reported to show inhibitory activities on NMDA receptors and calcium channels (Fig. 1) [10].

* Corresponding author. Present address: School of Pharmacy, University of the Western Cape, Private Bag X17, Bellville 7535, South Africa.
E-mail address: sfmalan@uwc.ac.za (S.F. Malan).

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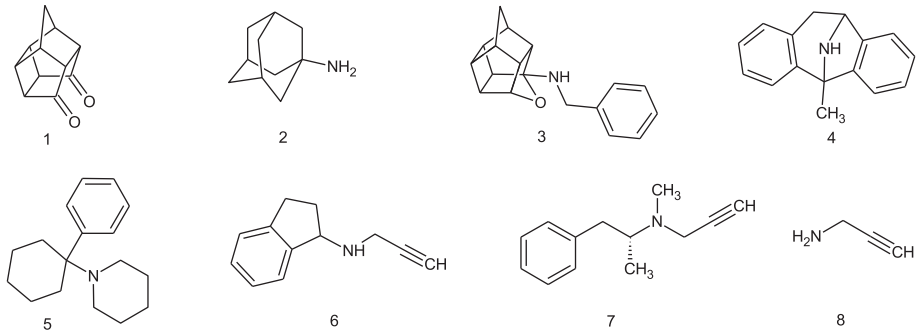

Fig. 1. Representative polycyclic cage compounds (**1**–**3**), NMDA receptor and calcium channel modulators - NGP1-01 (**3**), MK-801 (**4**) and phencyclidine (PCP, **5**), the neuroprotective MAO-B inhibitors - rasagiline (**6**) and selegiline (7), and propargylamine (**8**).

The oxidative deamination reaction catalysed by monoamine oxidase-B (MAO-B) is one of the major catabolic pathways of dopamine in the brain. Inhibition of this enzyme lead to enhanced dopaminergic neurotransmission and is currently used in the symptomatic treatment of PD [11–14]. Furthermore, MAO-B inhibitors may also exert a neuroprotective effect by reducing the concentrations of potentially hazardous by-products produced by MAO-B-catalysed dopamine oxidation [15]. In PD and AD it has been shown that there are age-related elevated levels of MAO-B, which not only act indirectly as a trigger to the apoptotic process, but also give rise to some of the signs and symptoms associated with these disorders [16–18].

In the current study, the approach was to develop multifunctional drugs which would halt the apoptotic neuronal breakdown process and eliminate some of the signs and symptoms of diseases such as AD and PD by: (a) Inhibiting NMDA receptors and blocking *L*-type voltage gated calcium channels (VGCC) thus regulating the Ca^{2+} influx mediated excitotoxic process; (b) Inhibiting the MAO-B enzyme thus allowing increase in dopamine levels in the CNS and reducing the levels of the highly oxidative products produced by the activity of this enzyme; (c) Possess anti-apoptotic activity to halt the natural neuronal cell death process. With this in mind, we focused on the structures of pentacycloundecane (**1**), amantadine (**2**), rasagiline (**6**) and selegiline (**7**, Fig. 1).

Rasagiline and selegiline are second generation propargylamine derivatives that irreversibly inhibit brain MAO-B, and have promising neuroprotective activities [19]. After several years of study and research, it has been established that the neuroprotective effects of rasagiline and selegiline can be attributed to its propargyl moiety [16–18]. This observation was made on the grounds that propargylamine (**8**), itself exerts the same neuroprotective effects as offered by rasagiline. It has also been established that the MAO-B inhibiting activity is not a prerequisite for the neuroprotection provided by rasagiline, selegiline and propargylamine as these compounds have been shown to inhibit apoptosis through other anti-apoptotic mechanisms that may contribute to their possible disease-modifying activities [20,21]. Since MAO-B activity is increased in both AD and PD, MAO-B inhibitors may be of further therapeutic benefit [22].

Polycyclic cage compounds, such as pentacyloundecane (PCU, **1**), amantadine (**2**) and NGP1-01 (**3**) have various biological applications, with special interest in the symptomatic and proposed curative treatment of neurodegenerative diseases [23]. These compounds can be used to modify and improve the pharmacokinetic and pharmacodynamic properties of drugs and it is apparent from literature that the polycyclic cage is useful as both a scaffold for side-chain attachment as well as for improving a drug's lipophilicity [23]. This lipophilicity enhances a drug's transport across cellular membranes, including the selectively permeable blood–brain barrier, and increases its affinity for lipophilic regions in target proteins [23,24]. In addition, these polycyclic moieties afford metabolic stability, thereby prolonging the pharmacological effect of a drug, leading to a reduction of dosing frequency and improving patient compliance thereof [25]. The known NMDA receptor channel antagonism of these cage compounds, combined with their *L*-type calcium channel blocking activity, suggest that these polycyclic cage moieties may potentially serve as therapeutic agents for neurodegenerative disorders [10,23,26–28].

With the focus being on the development of multifunctional drugs, it was thus a rational decision to incorporate polycyclic cage moieties and propargylamine functional groups or derivatives thereof into the structures of the novel compounds to be synthesised, thus giving rise to a series of compounds with the inherent therapeutic profiles of the contributing moieties (i.e. NMDA receptor channel antagonism, *L*-type calcium channel blocking activity, MAO-B inhibitory activity and anti-apoptotic activity). A single compound exhibiting such an array of multifunctional neuroprotective activities may curb the neurodegenerative process more effectively than a compound which functions on only one of the many drug target sites available.

2. Results and discussion

2.1. Synthesis

In synthesising the novel polycyclic compounds (**9**–**16**, Fig. 2), propargylamine, propargylbromide or ethynyl magnesium bromide was reacted with the PCU (**1**, Cookson's diketone) or amantadine (**2**) scaffold to give the final compounds (Fig. 2). Each compound was synthesised to evaluate the activity and benefit of the presence of a certain group of atoms in the molecule. These groups included the following: a terminal acetylene group (**9**), an acetylene group between two non-polar groups (**10**), a secondary propargylamine connected to an oxa-PCU structure (**11**, **12**), a tertiary propargylamine conjugated to an aza-PCU structure (**13**, **14**) and an adamantane structure (**15**, **16**).

Starting from the PCU diketone (**1**) or the methyl-diketone (**a**, Scheme 1), depending on the compound to be synthesised, the reaction proceeded by conjugation of propargylamine through reductive amination with sodium borohydride, following steps i-iv to give the oxa-derivatives, **11** and **12**. The aza derivatives, **13** and **14**, were synthesised utilising sodium cyanoborohydride as reducing agent. Compound **9** was synthesised *via* the Grignard reaction through conjugation of ethynyl magnesium bromide with the methyl-diketone producing the title compound **9** (Scheme 1).