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Inaugural Lecture

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DRUG DESIGN IN PARKINSON'S DISEASE: FROM CAFFEINE TO PROMISING LEADS

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DRUG DESIGN IN PARKINSON'S DISEASE: FROM CAFFEINE TO PROMISING LEADS

Prof JP Petzer

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1. ABSTRACT

The treatment of Parkinson's disease is insufficient and novel, more effective drugs are needed. An established molecular target for the design of drugs for the treatment of Parkinson's disease is the enzyme, monoamine oxidase (MAO), particularly the MAO-B isoform. Inhibitors of MAO-B are well-known drugs for the treatment of Parkinson's disease since these compounds block the catabolism of dopamine by the MAO-B enzyme. This prevents the depletion of dopamine reserves and enhances the duration of the physiological action of dopamine. Inhibitors of MAO-B may also act as neuroprotective agents, further cementing a role for this class of drugs in Parkinson's disease. Caffeine, a small molecule of natural origin, is an appropriate lead compound for the design of MAO-B inhibitors. This address discusses recent studies that aim to discover new caffeine-derived MAO-B inhibitors. In this respect, substitution with a relatively wide variety of moieties at C8 of caffeine yields highly potent MAO-B inhibitors. Although less frequently observed, substitution at C8 also yields highly potent MAO-A inhibitors. Since MAO-A inhibitors are used in the treatment of depression, dual-acting compounds that block the activities of both MAO-A and MAO-B may be of importance in the therapy of Parkinson's disease that is associated with depression.

2. UITTREKSEL

Die huidige terapie vir Parkinson se siekte is onbevredigend en nuwe, verbeterde geneesmiddels word benodig. Die ensiem, monoamienoksidase (MAO) B, is 'n belangrike molekulêre teiken vir die ontwerp van geneesmiddels vir die behandeling van Parkinson se siekte. MAO-B-inhibeerders word aangewend vir die behandeling van Parkinson se siekte omdat hierdie klas verbindings die MAO-B-gekataliseerde metabolisme van dopamien in die brein inhibeer. Gevolglik word die dopamienreserwes beskerm en die fisiologiese werkingsduur van dopamien word verleng. MAO-B-inhibeerders mag ook neurobeskermende eienskappe besit, 'n kenmerk wat die rol van hierdie klas verbindings in Parkinson se siekte verder beklemtoon. Die klein molekuul, kaffeïen, dien as leidraadverbinding vir die ontwerp van MAO-B-inhibeerders. Hierdie rede bespreek onlangse studies, wat gemik was daarop om kaffeïen-afgeleide MAO-B-inhibeerders te ontwerp. In hierdie opsig lei substitusie van kaffeïen, met verskeie groepe, op die C8-posisie, tot verbindings wat hoogs potente MAO-B-inhibeerders is. Alhoewel dit minder algemeen voorkom, lei substitusie op die C8-posisie soms ook tot hoogs potente MAO-A-inhibisie. Omdat MAO-A-inhibeerders antidepressiewe werking besit, kan dubbelwerkende geneesmiddels, wat beide MAO-A en MAO-B inhibeer, waardevol wees vir die behandeling van Parkinson se siekte, wat met depressie gepaardgaan.

3. INTRODUCTION

Parkinson's disease is a neurodegenerative disorder which is the result of the death of dopamine-containing neurons which project from the substantia nigra to the striatum of the brain (Olanow *et al*., 2009). This results in the depletion of dopamine at the nerve terminals of the nigrostriatal neurons in the striatum. It is the loss of functional dopamine that is responsible for the motor symptoms observed in Parkinson's disease. Since the 1960s, Parkinson's disease has been treated with the metabolic precursor of dopamine, L-3,4-dihydroxyphenylalanine (L-dopa) (Carlsson, 2002). Dopamine receptor agonist drugs and drugs that block the catabolism of dopamine and L-dopa are also used in the treatment of Parkinson's disease, and are frequently combined with L-dopa (Perdosa & Timmermann, 2013; Talati *et al*., 2009). The treatment of Parkinson's disease is, however, focussed on the symptoms of the disease and the underlying mechanism of neuronal death is not treated. Also, dopamine replacement with L-dopa almost always leads to significant side effects (Fahn *et al*., 2004). For example, L-dopa treatment frequently leads to involuntary movements, fluctuating motor responses and abnormal and neuropsychiatric alterations. The discovery of therapeutic drugs for Parkinson's disease is thus an important field in medicinal chemistry.

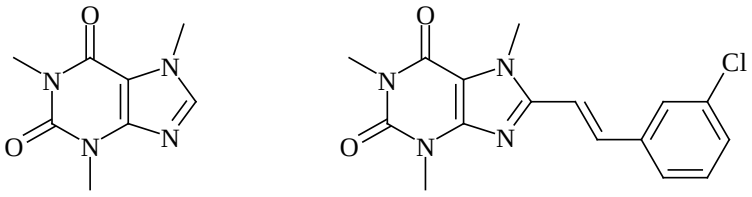
A longstanding target for the treatment of Parkinson's disease is the enzyme, monoamine oxidase (MAO), particularly the MAO-B isoform. MAO-B metabolises dopamine in the brain, and inhibitors of this enzyme are effective in the therapy of Parkinson's disease. Such compounds conserve dopamine stores in the brain. MAO-B inhibitors are thus well-known therapy for Parkinson's disease, frequently in combination with L-dopa (Youdim *et al*., 2006). It has also been suggested that MAO-B inhibitors may protect against neurodegeneration in Parkinson's disease, a property that further reinforces the role of this class of drugs in Parkinson's disease treatment (Youdim & Bakhle, 2006).

Based on this, the design and discovery of novel inhibitors of MAO-B are pursued by several research groups. Among the lead compounds that have been used in MAO-B inhibitor design is the small molecule, caffeine. Caffeine is a MAO inhibitor and an appropriate scaffold for the design of MAO

inhibitors (Petzer *et al*., 2013). This address discusses the discovery and design of caffeine-derived MAO inhibitors.

4. CAFFEINE AS SCAFFOLD FOR MAO INHIBITOR DESIGN

Caffeine (**1**) is the most commonly consumed compound with central pharmacological activity (Fig. **1**). Caffeine ingestion occurs through dietary sources, particularly via beverages such as coffee and tea (Fredholm *et al*. 1999). The ingestion of caffeine in typical dietary quantities does not result in serious side effects, and thus no or few restrictions on caffeine consumption are imposed by regulatory agencies. Among the many biochemical actions of caffeine, its effects in the brain may be of therapeutic value (Fredholm *et al*., 1999; Ribeiro & Sebastião, 2010). For example, caffeine may have value in the therapy of central disorders such as Parkinson's disease, depression and Alzheimer's disease (Ribeiro & Sebastião, 2010). Laboratory evidence suggests that caffeine acts by binding to adenosine receptors, particularly the adenosine A_1 and A_{2A} receptors (Fredholm *et al*., 1999). Caffeine also blocks the function of MAO-A and MAO-B. In this respect, caffeine inhibits the MAOs with K_i (enzyme–inhibitor dissociation constant) values of 0.70 mM (MAO-A) and 3.83 mM (MAO-B) (Petzer *et al*., 2013).



Caffeine (**1**)
MAO-A IC_{50} = 0.761 mM
MAO-B IC_{50} = 5.08 mM

CSC (**2**)
MAO-A no inhibition
MAO-B IC_{50} = 0.146 µM

Figure 1. The structures of caffeine and CSC.

Based on the above analysis, it is clear that caffeine possesses valuable central effects that may be used in the therapeutic setting. Furthermore, simple structural modifications of caffeine have been shown to enhance its activity at several central targets. For example, (E)-8-(3-chlorostyryl)caffeine (CSC, **2**), a derivative of caffeine, inhibits the MAO-B enzyme with a K_i value of 80.6 nM. This value is almost 47000-fold more potent than the MAO-B inhibition potency of caffeine (Chen *et al*., 2002; Pretorius *et al*., 2008).

Thus caffeine may also serve as an appropriate lead compound for the development of MAO inhibitors, particularly of the MAO-B isoform.

5. THE MAO-B ENZYME IN PARKINSON'S DISEASE THERAPY

As mentioned above, the enzyme MAO-B is a target for the development of treatments for Parkinson's disease (Youdim *et al*., 2006; Youdim & Bakhle, 2006). The MAO enzymes consist of two isozymes, MAO-A and MAO-B. The function of the MAO enzymes is to metabolise amine neurotransmitters by catalysing their oxidative deamination. For this purpose, MAO-A and MAO-B have diverging substrate selectivities. MAO-A catalyses the oxidation of serotonin, while MAO-B catalyses the oxidation of dietary amines, including benzylamine and β-phenethylamine. The neurotransmitters dopamine, epinephrine and norepinephrine are metabolised by both MAO isoforms (Youdim *et al*., 2006).

Inhibitors of MAO-B are frequently used for the treatment of the symptoms of Parkinson's disease (Deftereos *et al*., 2012). MAO-B inhibitors are thought to block the catabolism of dopamine, catalysed by MAO-B, in the brain and thus prevent the further depletion of dopamine. Inhibitors of MAO-B are thus used in combination with L-dopa in Parkinson's disease. In this respect, MAO-B inhibitors increase central dopamine concentrations after treatment with L-dopa, an effect that is directly associated with the blocking of the central metabolism of dopamine (Fernandez & Chen, 2007; Finberg *et al*., 1998). In early Parkinson's disease, MAO-B inhibitors may be used to delay the commencement of L-dopa therapy and possibly to allow for reduced L-dopa doses to initially be used (Shoulson *et al*., 2002; Pålhagen *et al*., 1998).

6. THE MAO-A ENZYME IN PARKINSON'S DISEASE THERAPY

The MAO-A enzyme catalyses the metabolism of the neurotransmitters, serotonin and norepinephrine, in the brain (Youdim *et al*., 2006). Since reduced concentrations of these two neurotransmitters are associated with the occurrence of depression, MAO-A inhibitors are used as antidepressant drugs (Schwartz, 2013; Lum & Stahl, 2012). Since many patients suffering from Parkinson's disease also

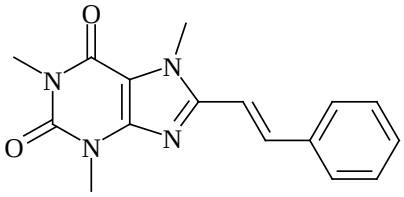
presents with depression, MAO-A inhibitors may be useful as therapy for the depression component of Parkinson's disease (Costa *et al*., 2012).

7. MAO INHIBITORS THAT ARE DERIVATIVES OF CAFFEINE

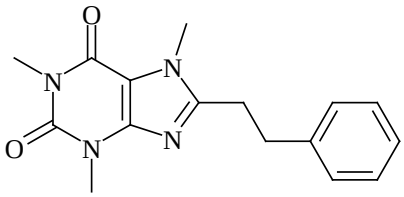
For the discovery of new treatments for Parkinson's disease, the design of inhibitors of MAO-B is the goal of a number of researchers. While a number of small molecules are suitable scaffolds for the design of MAO inhibitors, caffeine has emerged as particularly interesting since caffeine derivatives often are inhibitors of both MAO-A and MAO-B. Such dual-acting compounds that block the activities of both MAO-A and MAO-B may be of value in the therapy of Parkinson's disease that is associated with depression.

7.1. The (E)-8-styrylcaffeine class of compounds

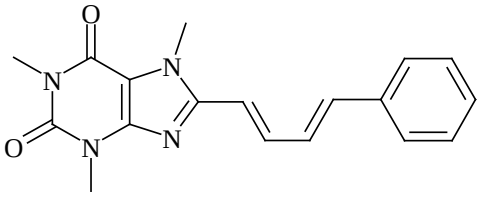
The first MAO inhibitors that contained the caffeine moiety were the (E)-8-styrylcaffeines (Fig. **2**). This is exemplified by CSC (**2**) which inhibits MAO-B with an IC_{50} value of 146 nM (K_i = 80.6 µM) (Pretorius *et al*., 2008). CSC is thus ~35000-fold more potent than caffeine (IC_{50} = 5.08 mM) as a MAO-B inhibitor. This suggests that the C8 substituent is an important structural motif for MAO-B inhibition. Further analyses show that the C3 chlorine group on the phenyl ring of CSC is an important structural feature for MAO-B inhibition. In accordance with this view, the unsubstituted homologue, (E)-8-styrylcaffeine (**3**; K_i = 2.7 µM), is a weaker MAO-B inhibitor than CSC (Petzer *et al*., 2003). Also, saturation of the double bond of CSC to yield 8-(2-phenylethyl)caffeine (**4**; K_i = 30 µM; IC_{50} = 26.0), further decreases the potency of MAO-B inhibition compared to (E)-8-styrylcaffeine. In contrast, MAO-B inhibition potency is enhanced by extending the length of the C8 side chain to yield (E,E)-8-(4-phenylbutadien-1-yl)caffeine (**5**; K_i = 0.149 µM; IC_{50} = 0.383) (Pretorius *et al*., 2008).



(*E*)-8-Styrylcaffeine (**3**)
MAO-B K_i = 2.7 µM



4
MAO-A IC_{50} = 172 µM
MAO-B K_i = 30 µM
IC_{50} = 26.0 µM



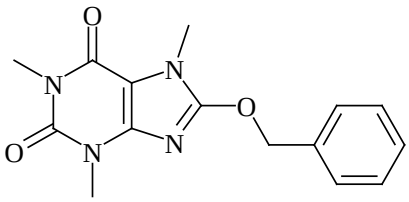
5
MAO-B K_i = 0.149 µM
IC_{50} = 0.383 µM

Figure 2. The structures of compounds discussed in the text.

7.2. The 8-benzyloxycaffeine class of compounds

The benzyloxy side chain is frequently found in the structures of MAO inhibitors (Binda *et al*., 2007; Gnerre *et al*., 2000). X-ray structure models and modelling studies suggest that the benzyloxy side chain of such inhibitors and the C8 styryl side chain of (E)-8-styrylcaffeine analogues are placed in similar space in the MAO-B active site cavity (Binda *et al*., 2007; Strydom *et al*., 2010). The styryl and benzyloxy moieties therefore are isosteric with respect to their binding to MAO-B. Based on this observation, a variety of 8-benzyloxycaffeines were investigated as potential inhibitors of MAO. The lead, 8-benzyloxycaffeine (**6**), was found to be an inhibitor of MAO-B with an IC_{50} value of 1.77 µM. This value is similar to that of (E)-8-styrylcaffeine (**3**; K_i = 2.7 µM) (Fig. **3**).

8-Benzyloxycaffeines have also been shown to be inhibitors of the MAO-A. 8-Benzyloxycaffeine is a non-specific MAO inhibitor with an IC_{50} value of 1.24 µM for MAO-A. As will be shown, 8-benzyloxycaffeines bind to MAO-A only after rotation of the benzyloxy side chain at the carbon–oxygen ether bond (Strydom *et al*., 2010).



6

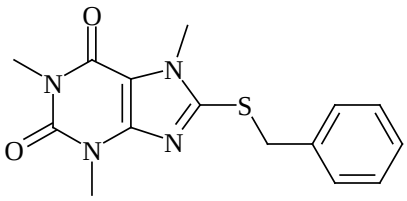
MAO-A IC_{50} = 1.24 µM
MAO-B IC_{50} = 1.77 µM

Figure 3. The structure of a compound discussed in the text.

7.3. The thio- and aminocaffeine class of compounds

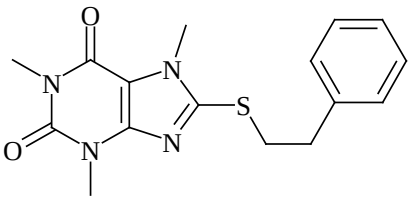
Since the benzyloxycaffeines have been found to be potent MAO inhibitors, series of thio- and aminocaffeine derivatives were also synthesized and evaluated as MAO inhibitors (Booysen *et al*., 2011). Thiocaffeine derivatives have subsequently been found to be potent MAO-B inhibitors with 8-(benzylsulfanyl)caffeine (**7**) possessing an IC_{50} value of 1.86 µM (Fig. **4**). This value is almost equivalent to that of (E)-8-styrylcaffeine (**3**; K_i = 2.7 µM) and 8-benzyloxycaffeine (**6**; IC_{50} = 1.77 µM). It is noteworthy that the caffeine derivative with a phenylethylsulfanyl side chain at C8 (**8**; IC_{50} = 0.223 µM) inhibits MAO-B with a higher potency than 8-(benzylsulfanyl)caffeine. It was concluded that **8** is an appropriate lead for the development of potent novel MAO-B inhibitors.

Aminocaffeines are, in contrast to thiocaffenes, weak MAO inhibitors. For example, the phenylethylamine derived compound **9** (IC_{50} = 17.6 µM) is a less potent MAO-B inhibitor than thiocaffeine **8** (IC_{50} = 0.223 µM) (Booysen *et al*., 2011).



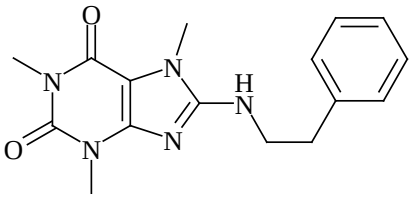
7

MAO-A IC_{50} = 8.22 µM
MAO-B IC_{50} = 1.86 µM



8

MAO-A IC_{50} = 20.5 µM
MAO-B IC_{50} = 0.223 µM



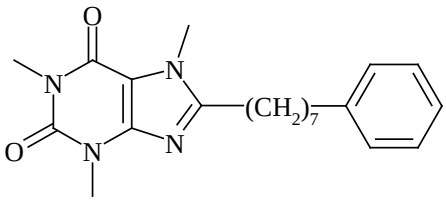
9

MAO-A IC_{50} = 45.2 µM
MAO-B IC_{50} = 17.6 µM

Figure 4. The structures of compounds discussed in the text.

7.4. The phenylalkylcaffeine class of compounds

As an extension of these studies, a series of phenylalkylcaffeines was recently examined as potential MAO inhibitors (Petzer *et al*., 2014). 8-(Phenylethyl)caffeine (**4**) was found to be a weak MAO-A (IC_{50} = 172) and MAO-B (IC_{50} = 26.0) inhibitor. In contrast, an increase of the length of the C8 side chain yielded compounds with enhanced MAO-A and MAO-B inhibition potencies. For example, 8-(7-phenylheptyl)caffeine (**10**) possesses a long C8 side chain and is thus is a potent MAO inhibitor with IC_{50} values for the inhibition of MAO-A and MAO-B of 3.01 µM and 0.086 µM, respectively (Fig. **5**). This result shows that increasing the length of the C8 side chain increases the potency of MAO inhibition of caffeine analogues.



10

MAO-A IC_{50} = 3.01 µM

MAO-B IC_{50} = 0.086 µM

Figure 5. The structure of a compound discussed in the text.

8. THE INTERACTION OF CAFFEINE DERIVATIVES WITH MAO

Three-dimensional structures of the MAO enzymes have been reported (Son *et al*., 2008; Binda *et al*., 2002). These models may be used to design novel MAO inhibitors. Using modelling, it is possible to predict the binding orientations and interactions of small molecules with the MAOs.

Molecular modelling studies have shown that the caffeine ring of 8-benzyloxycaffeine (**6**) binds in the substrate cavity of the MAO-B enzyme (Fig. **6**) (Strydom *et al*., 2010). The carbonyl oxygen at C-6 of the caffeine ring forms a hydrogen bond with the phenolic hydrogen of Tyr-435 in MAO-B, while in MAO-A the carbonyl oxygen at C-2 of the caffeine moiety and the phenolic hydrogen of Tyr-444, the residue that corresponds to Tyr-435 in MAO-B, undergo hydrogen bonding. The benzyloxy side chain is placed in the entrance cavity of MAO-B where it is stabilized via hydrophobic interactions. In MAO-A the benzyloxy side chain also projects to the entrance of the active site. In MAO-A, the benzyloxy side chains is, however, bent at the CH_2–O ether bond by about a 34 º angle from the plane of the caffeine ring. The bent conformation of **6** is necessary to avoid overlap with Phe-208. These data shows that small molecules such as **6** must possess a flexible side chain to bind to the active site of MAO-A. For binding to MAO-B, flexibility is not a requirement since small molecules bind in linear conformation. Such insight is valuable for the future design of caffeine-derived MAO inhibitors.

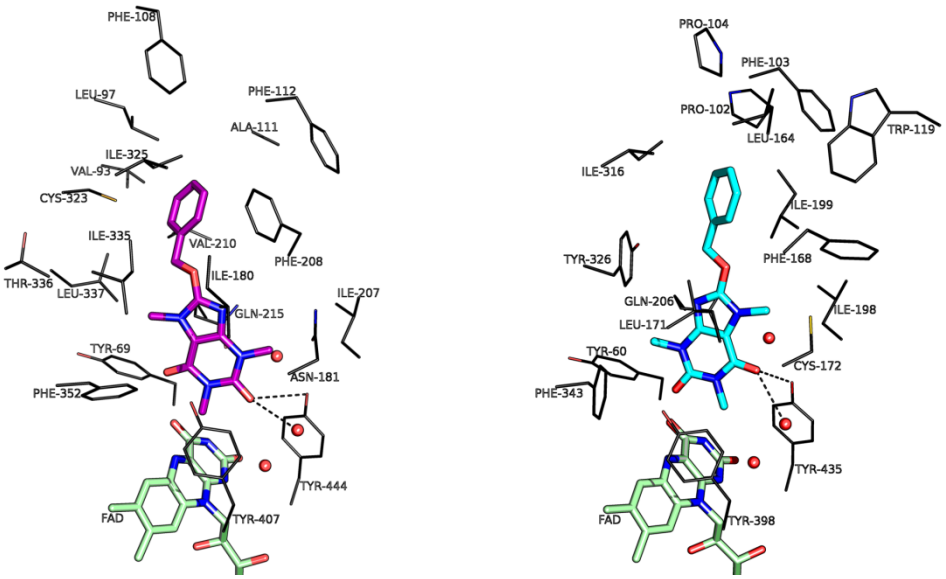


Figure 6. The binding of 8-benzyloxycaffeine to MAO-A (left) and MAO-B (right).

9. CLOSING REMARKS

This address shows that the structure of caffeine may be used as lead for the design of MAO inhibitors, particularly of the MAO-B isoform. Such inhibitors may be useful in the treatment of Parkinson's disease. It is noteworthy that a relatively wide variety of structural derivatives of caffeine are high potency inhibitors of MAO-B. In addition, structural derivatives of caffeine are also frequently found to be high potency MAO-A inhibitors. Since MAO-A inhibitors have been used in the therapy of depression, dual-acting compounds that inhibit both MAO isoforms may be particularly suitable for the treatment of Parkinson's disease where depression is frequently encountered. Since MAO-B inhibitors may also possess neuroprotective properties, these drugs may be of enhanced value for Parkinson's disease therapy.

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