Bioorganic Chemistry 69 (2016) 20–28

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

2-Heteroarylidene-1-indanone derivatives as inhibitors of monoamine oxidase

Magdalena S. Nel [a,b], Anél Petzer [a,b], Jacobus P. Petzer [a,b], Lesetja J. Legoabe [b,*]

[a] Pharmaceutical Chemistry, School of Pharmacy, North-West University, Private Bag X6001, Potchefstroom 2520, South Africa
[b] Centre of Excellence for Pharmaceutical Sciences, North-West University, Private Bag X6001, Potchefstroom 2520, South Africa

ARTICLE INFO

Article history:
Received 10 August 2016
Revised 15 September 2016
Accepted 16 September 2016
Available online 17 September 2016

Keywords:
Indanone
Monoamine oxidase
MAO
Inhibition
Chalcone
SAR
Heterocyclic

ABSTRACT

In the present study a series of fifteen 2-heteroarylidene-1-indanone derivatives were synthesised and evaluated as inhibitors of recombinant human monoamine oxidase (MAO) A and B. These compounds are structurally related to series of heterocyclic chalcone derivatives which have previously been shown to act as MAO-B specific inhibitors. The results document that the 2-heteroarylidene-1-indanones are in vitro inhibitors of MAO-B, displaying IC_{50} values of 0.0044–1.53 μM. Although with lower potencies, the derivatives also inhibit the MAO-A isoform with IC_{50} values as low as 0.061 μM. An analysis of the structure-activity relationships for MAO-B inhibition indicates that substitution with the methoxy group on the A-ring leads to a significant enhancement in MAO-B inhibition compared to the unsubstituted homologues while the effect of the heteroaromatic substituent on activity, in decreasing order is: 5-bromo-2-furan > 5-methyl-2-furan > 2-pyridine ≈ 2-thiophene > cyclohexyl > 3-pyridine ≈ 2-furan. It may therefore be concluded that 2-heteroarylidene-1-indanone derivatives are promising leads for the design of MAO inhibitors for the treatment of Parkinson's disease and possibly other neurodegenerative disorders.

1. Introduction

Monoamine oxidase (MAO) is a mitochondrial-bound flavoenzyme that regulates the levels of amine-containing compounds in the brain and peripheral tissues [1,2]. MAO is expressed as two isoforms, MAO-A and MAO-B. In mammals, these isoforms are found in all tissues but at different levels. The MAOs fulfil important biochemical functions: firstly to metabolise neurotransmitter amines thereby terminating their actions and secondly to act as metabolic barriers for the entry of sympathomimetic amines into the systemic circulation and brain [1]. With respect to the latter, MAO-A present in the gastrointestinal mucosa metabolises dietary tyramine thus limiting its levels in the circulatory system. Excess tyramine may induce the release of norepinephrine from peripheral neurons leading to a dangerous increase in blood-pressure [1,3,4]. MAO-B, in turn, is present in the microvasculature of the brain and metabolises false neurotransmitters such as benzylamine and 2-phenylethylamine, which restricts their entry into the brain [5].

It is, however, their roles in the metabolism of neurotransmitters that makes the MAOs clinically relevant drug targets [6,7]. MAO-A metabolises serotonin in the brain and MAO-A specific inhibitors are used in the clinic as antidepressants, acting by enhancing serotonin-mediated neurotransmission [8,9]. Examples of antidepressants that act by inhibiting MAO-A are phenelzine (**1**) and tranylcypromine (**2**) (Fig. 1). These are irreversible acting compounds. Examples of reversible MAO-A inhibitors for the treatment of depression are moclobemide (**3**) and toloxatone (**4**). Reversibility of MAO-A inhibition is an important consideration since irreversible inhibitors may precipitate a serious hypertensive event when combined with tyramine-containing food [3,4]. As a result, irreversible MAO-A inhibitors are used with caution in the clinic and dietary restrictions are imposed. Reversible MAO-A inhibitors, on the other hand, have good safety profiles and are not associated with blood-pressure changes when combined with dietary tyramine [10,11].

The MAO-B isoform, in turn, metabolises dopamine in the brain and specific MAO-B inhibitors are thus used for the treatment of Parkinson's disease in the clinic [6]. MAO-B inhibitors conserve the depleted dopamine supply in the Parkinsonian brain and provide symptomatic relief. In this regard, MAO-B inhibitors are mostly used in combination with L-dopa, and presumably further enhance dopamine levels in response to L-dopa therapy [12,13]. Besides providing symptomatic benefits, MAO-B inhibitors may also protect against neurodegeneration in Parkinson's disease.

* Corresponding author.
E-mail address: lesetja.legoabe@nwu.ac.za (L.J. Legoabe).

http://dx.doi.org/10.1016/j.bioorg.2016.09.004
0045-2068/

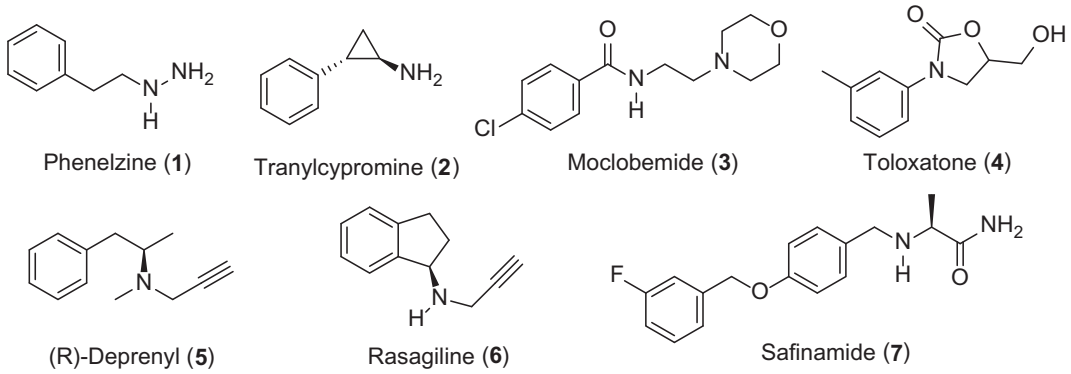

Fig. 1. The structures of known MAO inhibitors.

While the mechanism is unclear, MAO-B inhibitors may reduce the formation of injurious by-products of the MAO-B catalytic cycle [1]. These are hydrogen peroxide and aldehyde species, which may be harmful to neuronal cells if not efficiently cleared. Since MAO-B exhibits an age-related increase in the brain, the resulting enhanced formation of hydrogen peroxide and aldehydes in the aged Parkinsonian brain may significantly contribute to the degenerative processes [14]. Two irreversible MAO-B inhibitors are currently used for the treatment of Parkinson's disease, (R)-deprenyl (**5**) and rasagiline (**6**). A reversible inhibitor, safinamide (**7**), has also been developed for this purpose.

Due to their biochemical and clinical importance, the discovery and development of MAO inhibitors are being actively pursued. Recently it has been reported that a series of furanochalcones are potent MAO-B-specific inhibitors with the most active compound (**8**) exhibiting an IC_{50} value of 0.174 μM for the human form of the enzyme (Fig. 2) [15]. In a subsequent paper, a series of heterocyclic chalcone derivatives were examined as human MAO inhibitors [16]. These also were specific MAO-B inhibitors with the most potent inhibitor (**9**) exhibiting an IC_{50} value of 0.067 μM. Another inhibitor, compound **10**, also proved to be a potent MAO-B inhibitor an IC_{50} value of 0.185 μM. Based on these findings, the present study examines the MAO inhibition properties of a series of fifteen 2-heteroarylidene-1-indanone derivatives (**11a–o**). The 2-heteroarylidene-1-indanones may be considered to be the cyclic analogues of heterocyclic chalcone analogues such as **8** and **10**, and it is thus conceivable that this chemical class may, similar to the chalcones, act as MAO-B inhibitors. In support of this proposal, it was recently shown that 2-benzylidene-1-indanones (e.g. **12**) are inhibitors of the MAOs [17]. The present study is to the best of our knowledge the first investigation of the MAO inhibition properties of 2-heteroarylidene-1-indanone derivatives. For the purpose of this study, the following heteroaromatic substituents (ring B) were selected: 2-pyridine, 3-pyridine, 2-chloro-3-pyridine, 2-furan, 2-thiophene, 3-thiophene, 2-pyrrole, 5-methyl-2-furan and 5-bromo-2-furan (Table 1). For comparison, derivatives incorporating the cyclohexyl ring were also included. The A-ring was left unsubstituted or substituted with the methoxy group on C5 of the indole. In the reported study on the 2-benzylidene-1-indanones, ring A was disubstituted with the hydroxy and methoxy groups [17].

2. Results and discussion

2.1. Chemistry

The heteroarylidene-1-indanone derivatives, **11a–o**, were synthesised employing basic conditions. 1-Indanone or 5-methoxy-1-indanone was reacted with the appropriate heteroaromatic aldehyde in the presence of potassium hydroxide or sodium hydroxide (Fig. 3). Methanol served as reaction solvent. The reactions were stirred at room temperature for 2–5 h and on completion, the product was isolated by precipitation after the addition of water. Following recrystallisation from ethanol, the target heteroarylidene-1-indanones were obtained in yields of 17–79%. Structures were characterised by ^{1}H NMR, ^{13}C NMR and mass spectrometry as cited in the experimental section.

2.2. Protocol for the inhibition studies

To evaluate the MAO inhibition properties of the heteroarylidene-1-indanone derivatives, recombinant human MAO-A and MAO-B were used [18,19]. For both MAO isoforms, kynuramine served as substrate. The enzymes [0.0075 mg protein/mL (MAO-A) and 0.015 mg protein/mL (MAO-B)], substrate

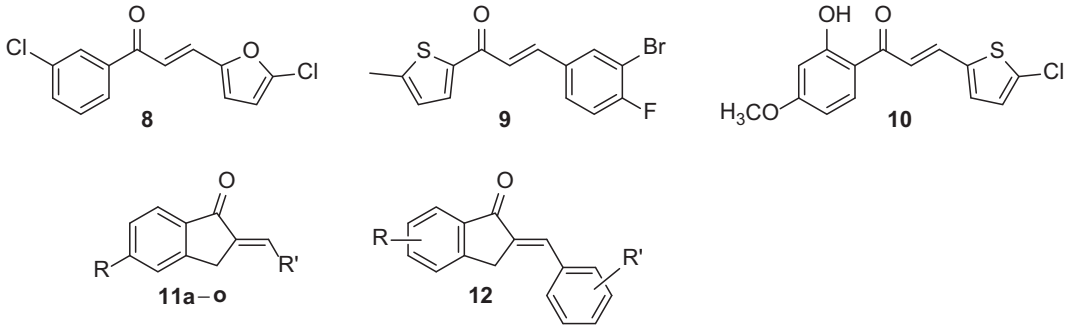

Fig. 2. The structures of heterocyclic chalcone derivatives (**8–10**) that exhibit MAO inhibition. The general structures of the 2-heteroarylidene-1-indanone derivatives (**11a–o**) that will be investigated in this study and that of a 2-benzylidene-1-indanone (**12**) are also given.