Bioorganic & Medicinal Chemistry Letters 25 (2015) 1896–1900

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

The synthesis and evaluation of sesamol and benzodioxane derivatives as inhibitors of monoamine oxidase

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ARTICLE INFO

Article history:
Received 5 February 2015
Revised 12 March 2015
Accepted 16 March 2015
Available online 20 March 2015

Keywords:
Monoamine oxidase
MAO
Inhibition
Selective
Sesamol
Benzodioxane

ABSTRACT

In the present study, series of eight sesamol (1,3-benzodioxol-5-ol) and eight benzodioxane (2,3-dihydro-1,4-benzodioxine) derivatives were synthesised and evaluated as inhibitors of recombinant human monoamine oxidase (MAO) A and B. The sesamol and benzodioxane derivatives are structurally related to series of phthalide derivatives, which have previously been found to act as potent reversible MAO inhibitors. The results document that the benzodioxane derivatives, in particular, are potent MAO-B inhibitors with IC_{50} values ranging from 0.045 to 0.947 μM. IC_{50} values for the inhibition of MAO-B by the homologous series of sesamol derivatives ranged from 0.164 to 7.29 μM. All compounds evaluated are selective for the MAO-B isoform, with IC_{50} values for the inhibition of MAO-A ranging from 13.2 to >100 μM. It is further shown that for the most potent MAO-B inhibitor, 6-[(3-bromophenyl)methoxy]-2,3-dihydro-1,4-benzodioxine, inhibition is almost completely reversed by dialysis of enzyme-inhibitor mixtures. It may be concluded that benzodioxane derivatives are promising leads for the design of selective MAO-B inhibitors for the treatment of Parkinson's disease.

Parkinson's disease is an incurable and progressive disorder that is characterised by involuntary motor symptoms and balance impairment.[1] Although the aetiology of Parkinson's disease is not known, several causes have been investigated including environmental, pathological and genetic factors.[1,2] The main pathological hallmark present in Parkinson's disease is the deficiency of dopamine at the nerve terminals in the corpus striatum, which is due to the loss of the dopamine-containing neurons which project from the pars compacta component of the substantia nigra to the corpus striatum.[1] Current treatment options for Parkinson's disease focus on the replenishment of dopamine rather than the prevention of further progression of the disease.[3] For this purpose, L-3,4-dihydroxyphenylalanine (L-dopa), the metabolic precursor of dopamine, is considered to be the most effective drug. Although replenishment therapies are of great value, L-dopa is associated with several adverse effects and eventually causes an involuntary movement disorder termed dyskinesia.[3] Several drugs are thus used to improve the therapeutic outcome of L-dopa. For example, L-dopa is frequently combined with peripheral dopa decarboxylase inhibitors or catechol-*O*-methyl transferase inhibitors.[4,5] These drugs block the peripheral metabolism of L-dopa, thus allowing for a reduced L-dopa dose to be used. This, in turn, reduces the occurrence of the debilitating adverse effects of L-dopa therapy.[6] L-Dopa is also used in combination with monoamine oxidase (MAO) inhibitors in Parkinson's disease.[7] In the central nervous system, MAO is a major metabolic pathway of dopamine, and MAO inhibitors thus conserve the depleted dopamine levels in the Parkinsonian brain.[8] MAO inhibitors may also enhance central dopamine levels derived from L-dopa and thus allow for the effective L-dopa dose to be reduced.[9–11] As monotherapy, MAO inhibitors may delay the emergence of the motor symptoms that require the initiation of L-dopa therapy.[12]

MAO consists of two distinct isoforms, MAO-A and MAO-B. These are flavin adenine dinucleotide containing enzymes, which primary functions are to metabolise amine-containing neurotransmitters and xenobiotic amines such as dietary tyramine.[8] The MAOs are important drug targets for the treatment of psychiatric and neurodegenerative disorders.[7] MAO-A metabolises serotonin in the central nervous system and inhibitors of MAO-A are thus used in the treatment of depression.[13,14] Since MAO-B is the main isoform present in the basal ganglia, the affected region in Parkinson's disease, MAO-B inhibitors are used for the treatment of Parkinson's disease.[7] Although MAO-A also metabolises dopamine in the brain, MAO-A inhibitors are not employed in the treatment of Parkinson's disease, foremost because MAO-A inhibitors may precipitate a potentially fatal hypertensive response when combined with

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http://dx.doi.org/10.1016/j.bmcl.2015.03.040
0960-894X/

tyramine-containing foods.[15] It should, however, be noted that tyramine-induced changes in blood-pressure is mostly associated with irreversible MAO-A inhibitors, and the newer generation reversible inhibitors appears to be devoid of this effect.[16,17] In spite of this, the response provoked by the combination of tyramine and MAO-A inhibitors is the major cause of the restricted therapeutic use of MAO-A inhibitors.[8] Both reversible and irreversible MAO-B inhibitors, on the other hand, have excellent safety profiles and are not associated with changes in blood-pressure.[18]

A second motivation for the use of MAO-B inhibitors in Parkinson's disease treatment is based on the possibility that MAO-B inhibitors may exert neuroprotective effects by inhibiting the formation of toxic by-products, hydrogen peroxide and aldehydic species, that are produced as a result of the MAO-B-catalysed oxidation of dopamine.[8,19] Selegiline [(*R*)-deprenyl] and rasagiline are examples of MAO-B selective inhibitors that are used in the treatment of Parkinson's disease. Clinical and preclinical evidence suggest that these drugs may protect against neurodegeneration in Parkinson's disease, an effect that may be, at least partly, attributed to the blockade of the MAO-B-catalysed generation of neurotoxins in the central nervous system.[7,8] Based on the significant role that MAO-B inhibitors play in the treatment of Parkinson's disease, the design and development of novel MAO-B inhibitors are of importance. The goal of this study is thus to discover novel MAO inhibitors which possess selectivity for the MAO-B isoform. Such drugs may possess antisymptomatic and potential neuroprotective properties for the future treatment of Parkinson's disease. Although compounds with MAO-A inhibitory properties may also be of value in Parkinson's disease, their potential for causing tyramine-associated adverse effects should be carefully considered.[11,20] In Parkinson's disease, MAO-A inhibition may protect against dopamine depletion and may offer relief of the symptoms of depression, often associated with Parkinson's disease.

Phthalide (**1**) has previously been used as a scaffold for the design of reversible MAO inhibitors (Fig. 1).[21] Phthalide is a relatively weak inhibitor of human MAO-B with an IC_{50} value of 28.6 μM. Substitution on the C6 position of phthalide, however, yields highly potent reversible MAO-B inhibitors. For example, 6-benzyloxyphthalide (**2**) exhibits an IC_{50} value of 0.024 μM for the inhibition of human MAO-B. Thus, C6-substituted phthalide derivatives may be considered as suitable leads for the design of MAO-B inhibitors. Furthermore, phthalide derivatives also exhibit MAO-A inhibition activity, with a number of phthalide derivatives acting as dual inhibitors of MAO-A and MAO-B. For example 6-(3-phenylpropoxy)phthalide (**3**) inhibits human MAO-A and MAO-B with IC_{50} values of 0.096 μM and 0.0062 μM, respectively. In the present study series of sesamol (1,3-benzodioxol-5-ol) and benzodioxane (2,3-dihydro-1,4-benzodioxine) derivatives, will be synthesised and evaluated as potential inhibitors of human MAO-A and MAO-B. The structures of sesamol (**4**) and benzodioxane (**5**) closely resemble that of phthalide, which suggests that these moieties may be useful for the design of new MAO inhibitors.

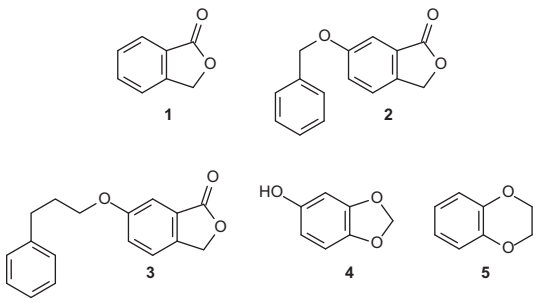


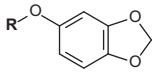
Figure 1. The structures of compounds discussed in the text.

Since substitution at C6 of the phthalide ring with a benzyloxy side chain yielded particularly potent MAO-inhibitors, the envisioned sesamol (**6a–h**) and benzodioxane (**7a–h**) (Tables 1 and 2) derivatives will also contain the benzyloxy substituent at the C5 and C6 positions, respectively.[21] The current study will also synthesise derivatives containing the phenylethoxy and phenylpropoxy moieties on C5 and C6 of sesamol and benzodioxane, respectively. In addition, the phenoxyethoxy moiety on C5 and C6 of sesamol and benzodioxane will also be considered. To further explore chemical space, selected derivatives will also be substituted in the *meta* positions of the benzyloxy ring with chlorine and bromine. Furthermore the phenoxyethoxy containing derivatives will be substituted in the *para* position of the phenyl ring with chlorine and bromine. In total 16 sesamol and benzodioxane derivatives will be synthesised. The primary goal of the study is to evaluate the synthesised compounds as inhibitors of MAO-A and MAO-B in the hope of discovering compounds with therapeutic potential in Parkinson's disease.

The sesamol (**6a–h**) and benzodioxane (**7a–h**) derivatives were synthesised in good yields by reacting sesamol (**4**) and synthesised 6-hydroxy-1,4-benzodioxane (**8**), respectively, with an appropriate alkyl bromide in the presence of K_2CO_3 in DMF (Scheme 1).[22] While sesamol is commercially available, 6-hydroxy-1,4-benzodioxane was synthesised by treating 1,4-benzodioxan-6-carboxaldehyde (**9**) with *meta*-chloroperoxybenzoic acid (mCPBA) in dichloromethane (CH_2Cl_2).[23] Hydrolysis of the resulting ester intermediate with a mixture of NaOH/methanol yields the target 6-hydroxy-1,4-benzodioxane reagent. The structures of the target sesamol (**6a–h**) and benzodioxane (**7a–h**) derivatives were verified by ^1H NMR, ^{13}C NMR and mass spectrometry.

For the inhibition studies, the activities of MAO-A and MAO-B were measured by employing the MAO-A/B mixed substrate, kynuramine, and the commercially available recombinant human MAOs.[24] Kynuramine is oxidised by both MAO-A and MAO-B to yield 4-hydroxyquinoline, a fluorescent metabolite. 4-Hydroxyquinoline fluoresces in alkaline media (λ_{ex} = 310 nm; λ_{em} = 400 nm) and may thus be conveniently measured by fluorescence spectrophotometry.[25] This method has been developed into a rapid and reliable assay for MAO activity, and was used in this study to determine whether the synthesised sesamol (**6a–h**) and benzodioxane

Table 1
The IC_{50} values for the inhibition of recombinant human MAO-A and MAO-B by sesamol derivatives **6a–h**



	R	IC_{50}[a] (μM)		SI[b]
		MAO-A	MAO-B	
6a	$C_6H_5CH_2$–	No inhibition[c]	0.513 ± 0.041	>195
6b	3-$ClC_6H_4CH_2$–	51.8 ± 4.52	0.248 ± 0.046	209
6c	3-$BrC_6H_4CH_2$–	38.4 ± 6.05	0.164 ± 0.034	234
6d	$C_6H_5(CH_2)_2$–	87.7 ± 4.41	3.31 ± 0.213	26
6e	$C_6H_5(CH_2)_3$–	77.1 ± 3.73	7.29 ± 0.140	11
6f	$C_6H_5O(CH_2)_2$–	No inhibition[c]	1.14 ± 0.080	>88
6g	4-$ClC_6H_4O(CH_2)_2$–	No inhibition[c]	1.69 ± 0.273	>59
6h	4-$BrC_6H_4O(CH_2)_2$–	No inhibition[c]	7.07 ± 0.714	>14
Methylene blue		0.07[d]	4.37[d]	0.016
Lazabemide		—	0.091[e]	—

[a] All values are expressed as the mean ± standard deviation (SD) of triplicate determinations.
[b] The selectivity index is the selectivity for the MAO-B isoform and is given as the ratio of IC_{50}(MAO-A)/IC_{50}(MAO-B).
[c] No inhibition observed at maximum tested concentration of 100 μM.
[d] Value obtained from Ref. 26.
[e] Value obtained from Ref. 27.