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Review

A comprehensive review on synthesis and designing aspects of coumarin derivatives as monoamine oxidase inhibitors for depression and Alzheimer's disease

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ABSTRACT

Monoamine oxidase (MAO) enzyme inhibition is a crucial target for the management of depression and Alzheimer disease and inhibitors of MAO are the most important drugs for their management. Coumarins are a large family of compounds, of natural and synthetic origin, that exhibit a variety of pharmacological activities, including MAO inhibition. The current review highlights the design and synthetic methods of coumarin derivatives as well as coumarins obtained from plant source as MAO inhibitors for treatment of depression and Alzheimer disease with salient finding related to structure–activity relationship. The aim of present review is to find out natural as well as synthetic coumarins as MAO inhibitors.

Contents

1. Introduction

Monoamine oxidase (MAO) is an iron containing flavoenzyme that occurs within cells, bound to the surface membrane of mitochondria and involved in the degradation of biogenic amines. Two MAO isoenzymes, MAO-A and MAO-B, are closely linked in opposite orientation on X chromosome and are expressed in the outer mitochondrial membrane. MAO-A and MAO-B oxidize neurotransmitters and xenobiotic amines by oxidative deamination, the regulation of which is important in maintaining normal mental states.[1] MAO is abundant in noradrenergic nerve terminals but is also present in many other places, such as liver and intestinal epithelium.[2] MAO-A, the primary type in fibroblasts, preferentially degrades serotonin, norepinephrine and dopamine while MAO-B, found not only in platelets but also in the brain of man and other primates, preferentially degrades phenyl ethylamine and benzylamine.

The activity of MAO helps to maintain neuron firing rates throughout the body within homeostatic limits. Part of the biochemical activity of MAO generates hydroxyl radicals, very toxic members of the oxygen free radical group that may be involved in neurodegenerative disorders such as Parkinson's disease. As mentioned above, MAO play an important role in the metabolism of several neurotransmitters and could be useful in the treatment of a number of psychiatric and neurological diseases. These properties determine the pharmacological interest of MAO inhibitors. In fact, human MAO-B inhibitors such as selegiline (*R*-(−)-deprenyl) and rasagiline are useful compounds for the treatment of

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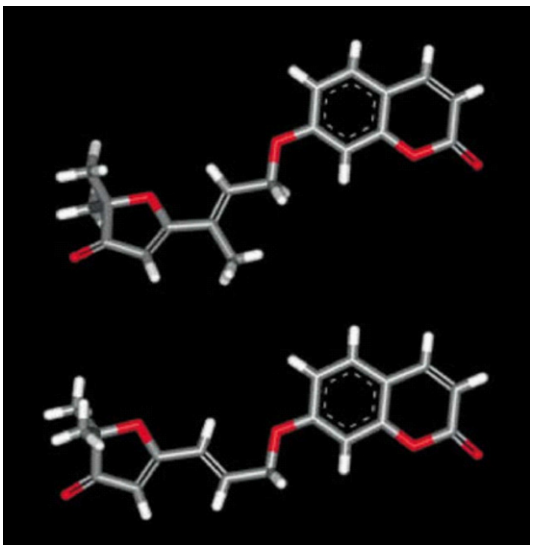


Figure 1. Molecular models, from X-ray crystallographic data, of geiparvarin **1a** (up) and desmethyl geiparvarin **1b** (down) showing two different conformations of the diene system, (s-*trans* and s-*cis*, respectively).

Parkinson[3–5] and Alzheimer's diseases[6–9] and selective MAO-A inhibitors, such as clorgyline (irreversible) and moclobemide (reversible), are useful for the treatment of neurological disorders, such as depression and anxiety.[10–12]

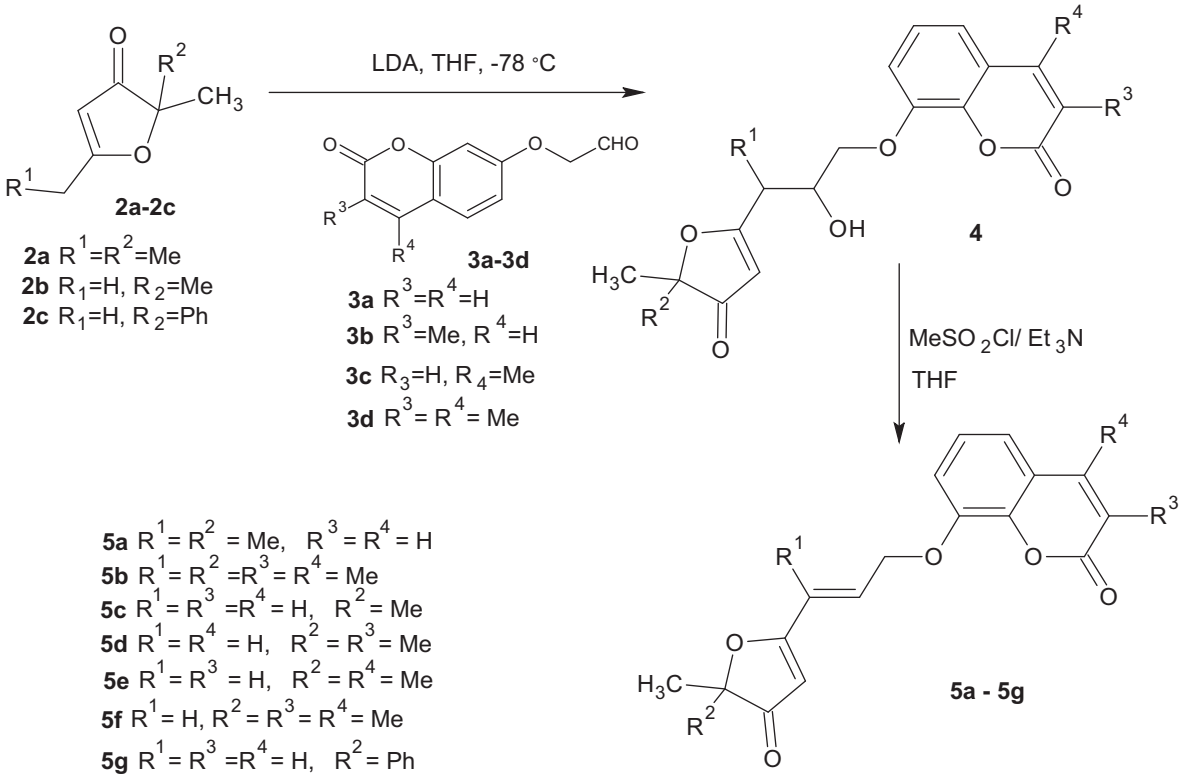
Coumarins (or benzopyrones) are a large family of compounds, of natural and synthetic origin, that exhibit a variety of pharmacological activities such as antidepressant,[13] antimicrobial,[14,15] antioxidant,[16] anti-inflammatory,[17] antinociceptive,[18] anti-tumor,[19] antiasthmatic,[20] antiviral.[21,22]

Some natural coumarins show a low MAO inhibitory potency[23,24] while properly modified natural coumarins have been characterized as potent and selective MAO inhibitors.[25,26] The identification of salient features within a coumarin template has helped in designing and synthesizing new analogs with enhanced MAO inhibition activity. Therefore, present review mainly highlights the design and synthetic methods of coumarin derivatives as MAO inhibitors with salient finding related to structure activity relationship (SAR). In current review, coumarins obtained from plant sources are also discussed.

2. Synthetic coumarin derivatives as MAO inhibitors

Natural geiparvarin (Fig. 1) and its analogues which have structural similarity with coumarin scaffold have been reported by Carotti et al.[27] and tested as inhibitors of both MAO-B and MAO-A isoforms. Structural modifications on either coumarin or the furanone moiety of geiparvarin 1a are deleterious for MAO activity. On the contrary, removal of the methyl group on the alkenoxy bridge afforded derivative **1b** displayed the highest MAO-B inhibitory potency (pIC_{50} = 7.55) with an outstanding 850-fold selectivity for the MAO-B isoform. In order to corroborate whether the observed higher activity of **1b** compared to geiparvarin **1a** could depend also on a different binding conformation. The X-ray crystallography and molecular modeling studies of **1b**, besides confirming the (E) configuration of the double bond in the bridge, showed that this compound, unlike geiparvarin **1a** crystallises in the s-*cis* conformation (Fig. 1). Therefore, the privileged activity of **1b** with regard to **1a** can be tentatively endorsed to the removal of some steric hindrance of the methyl group in the 3′position of geiparvarin.

The synthesis of 7-{[(E)-3-(5,5-dimethyl-4-oxo-4,5-dihydro-2-furanyl)-2-propenyl]oxy}-*2H*-chromen-2-one has been reported (Scheme 1). The reaction of 2,2,5-trimethyl-3*(2H)* furanone **2a–2c** and 7-(2-oxoethoxy) coumarin, afforded the corresponding aldol which, via a Stork–Kraus dehydration, afforded target derivative **5a–5g**.



Scheme 1.