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Selected chromone derivatives as inhibitors of monoamine oxidase

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ABSTRACT

A previous study has shown that a series of C6-benzyloxy substituted chromones exhibit high binding affinities for human monoamine oxidase (MAO) B. In an attempt to discover additional chromones with potent and selective MAO-B inhibitory potencies and to further examine the structure–activity relationships of MAO-B inhibition by chromones, the series was expanded with homologues containing polar functional groups on C3 of the chromone ring. The results demonstrate that 6-[(3-bromobenzyl)oxy] chromones containing acidic and aldehydic functional groups on C3 act as potent reversible MAO-B inhibitors with IC_{50} values of 2.8 and 3.7 nM, respectively. Interestingly, a 2-hydroxy-2,3-dihydro-1-benzopyran-4-one derivative as well as open-ring 2-acetylphenol analogues of the chromones also were potent MAO-B inhibitors with IC_{50} values ranging from 4 to 11 nM. Chromone derivatives containing the benzyloxy substituent on C5 of the chromone ring, however, exhibit MAO-B inhibition potencies that are several orders of magnitude weaker. High potency inhibitors of MAO-B may find application in the therapy of neurodegenerative disorders such as Parkinson's disease.

The monoamine oxidase B (MAO-B) catalyzed α-carbon oxidation of dopamine is one of the major catabolic pathways of this neurotramsmitter in the brain.[1] Inhibitors of MAO-B lead to enhanced dopaminergic neurotransmission and are therefore considered useful in the early therapy of Parkinson's disease (PD).[2] MAO-B inhibitors also enhance the levels of dopamine derived from levodopa, the metabolic precursor of dopamine, and are therefore frequently combined with levodopa in PD therapy.[3,4] Since the oxidative metabolism of dopamine yields potentially neurotoxic metabolites, which may contribute to neurodegenerative processes, MAO-B inhibitors may also provide a neuroprotective effect in PD.[5,6] Considering that MAO-B activity in the human brain increases with age, inhibition of this enzyme is especially relevant in PD therapy.[7] Based on the therapeutic value of MAO-B inhibitors, considerable effort has been devoted to the design of novel inhibitors and the elucidation of the structure–activity relationships (SAR) for MAO-B inhibition. Consequently, a variety of oxygen and nitrogen containing heterocycles have been found privileged for MAO-B inhibition.[8] Among these chromone (benzopyran-4-one) (**1**) has emerged as a useful scaffold for the design of potent and reversible MAO-B inhibitors (Fig. 1).[9–12] Substitution on C6 of the benzo-γ-pyrone moiety has been shown to yield structures with potent MAO-B inhibition activities.[12] In fact, a relatively large degree of tolerance exists for different C6 substituents and substitution patterns, and a variety of C6-substituted chromones exhibit IC_{50} values in the low nanomolar range (2–76 nM). This suggests that C6-substituted chromone derivatives are good candidates for the design of MAO-B inhibitors since structural modifications that may lead to better drug properties are less likely to be associated with a loss of activity. Interestingly, although selective for MAO-B, C6-substituted chromones also inhibit MAO-A reversibly with many derivatives exhibiting IC_{50} values in the nanomolar range. Also of interest, is a recent study which reports that carboxylic acid substitution on C3 of the γ-pyrone moiety, to yield chromone derivative **2**, results in high potency MAO-B inhibition (IC_{50} = 0.048 μM).[11] This remarkable finding suggests that the addition of simple polar functional groups to the γ-pyrone moiety of chromone may be an effective strategy to enhance the MAO-B inhibition potencies of this class of compounds. An added advantage of carboxylic acid substitution is the elimination of the MAO-A inhibition component which is frequently encountered when designing MAO-B inhibitors.[11] While MAO-A also metabolizes dopamine in the human brain, MAO-A inhibition is in general not a desired property of drugs used in PD therapy. Inhibitors of MAO-A potentiates the sympathomimetic effects of dietary amines such as tyramine, which may lead to serious adverse effects. In addition, the combination of MAO-A inhibitors and levodopa in PD therapy should be avoided since this may lead to a hypertensive response.[13]

Based on this analysis, the present study investigates the possibility of combining the favourable MAO inhibitory properties of the C6 and C3 substituents, respectively, in an attempt to design high potency MAO-B inhibitors with an acceptable selectivity profile. For this purpose, the MAO inhibitory properties of a series of

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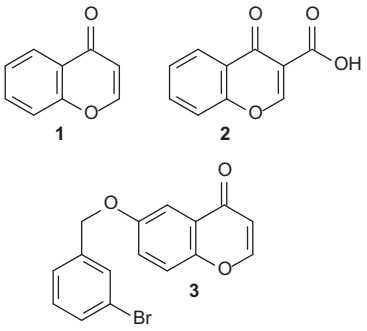

Figure 1. The structures of chromone (**1**), chromone-3-carboxylic acid (**2**) and 6-[(3-bromobenzyl)oxy]-4*H*-chromen-4-one (**3**).

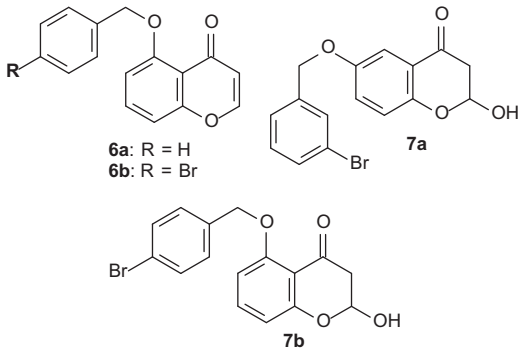

Figure 3. The structures of the C5-substituted chromones **6a**–**b**, and 2-hydroxy-2,3-dihydro-1-benzopyran-4-one derivatives **7a**–**b**.

chromone derivatives containing substituents on C6 of the benzo-γ-pyrone ring as well as polar substituents on C3 of the γ-pyrone moiety were examined. Such compounds may potentially possess high affinity for MAO-B, a property imparted by the C6 substituent, as well as improved selectivity for MAO-B, a property imparted by the polar C3 substituent. The 3-bromobenzyloxy substituent was selected as C6 substituent in this study since this moiety has been shown to be particularly favourable for MAO-B inhibition by C6-substituted chromone derivatives, with 6-[(3-bromobenzyl)oxy]-4H-chromen-4-one (**3**) exhibiting an IC_{50} value of 0.002 μM.[12] As polar C3 substituents, the carboxylic acid, formyl and methyl ester functional groups were selected. The structures of these derivatives, compounds **4a**–**c**, are illustrated in Figure 2. In addition, several other chromone derived structures were investigated with the aim of further examining the SAR of MAO inhibition. These include compounds **5a**–**f**, which are open-ring 2-acetylphenol analogues of the chromone **3**. The objective with these open-ring analogues is to examine the importance of an intact γ-pyrone moiety for MAO-B inhibition. This study also reports, for the first time, the MAO inhibitory properties of C5-substituted chromones, compounds **6a**–**b**, and 2-hydroxy-2,3-dihydro-1-benzopyran-4-one derivatives, compounds **7a**–**b** (Fig. 3). These derivatives will provide insight into the importance of the position of the substituent on C6 versus C5 for MAO-B inhibition, and the effect of saturation of the γ-pyrone moiety on the MAO inhibition properties of chromones. Unpublished observations have shown that, although not as potent as C6-substituted chromones, C7-substituted chromones also exhibit potent MAO-B inhibitory activities.[14]

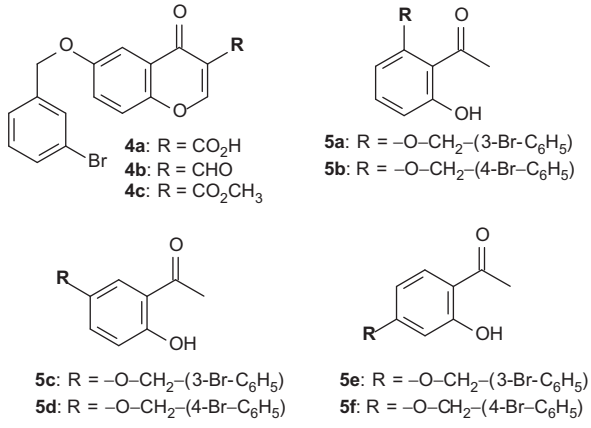

Figure 2. The structures of the target chromone derivatives **4a**–**c** and 2-acetylphenol analogues **5a**–**f**.

To synthesize the test compounds several synthetic protocols were employed. The 2-acetylphenol analogues **5a**–**f** were synthesized in low to good yields (12–91%) by reacting the appropriate dihydroxyacetophenone (**8**) with 3- or 4-bromobenzyl bromide (**9a**–**b**) in the presence of K_2CO_3 (Scheme 1). Treatment of the 2-acetylphenol analogue **5c** with phosphoryl chloride ($POCl_3$) and *N*,*N*-dimethylformamide (DMF) yielded the formyl derivative **4b** (95%). Compound **4b** was subsequently converted to the corresponding carboxylic acid **4a** with sodium chlorite ($NaClO_2$) and sulfamic acid (NH_2SO_3H) (51%). After converting **4a** to the acyl chloride with oxalyl chloride and subsequent treatment with methanol, the ester derivative **4c** was obtained (73%).[15] The 2-hydroxy-2,3-dihydro-1-benzopyran-4-one derivatives, compounds **7a**–**b**, were synthesized from the 2-acetylphenol analogues **5c** and **5b**, respectively, by reaction with ethyl formate in the presence of sodium methoxide as base (72–78%) (Scheme 2). The C5-substituted chromones, compounds **6a**–**b**, were synthesized by treating **7b** and **7c** with concentrated HCl in acetone (36–84%).[16] In each instance, the structures and purities of the target compounds were verified by ^1H NMR, ^{13}C NMR, mass spectrometry and HPLC analysis as cited in the Supplementary data.

To examine the MAO inhibitory properties of the chromone derived structures, recombinant human MAO-A and -B were employed.[17] The enzyme activity measurements were based on fluorometrically measuring the MAO-catalyzed formation of 4-hydroxyquinoline from the MAO-A/B mixed substrate, kynuramine.[18] The IC_{50} values for the inhibition of MAO-A and -B by compounds **4a**–**c** are given in Table 1. The results show that both the carboxylic acid and formyl derivatives, structures **4a** and **4b**, are highly potent MAO-B inhibitors with IC_{50} values of 0.0028 and 0.0037 μM, respectively. The potencies of these compounds are therefore similar to that of **3** (IC_{50} = 0.002 μM), the structure from which they were derived.[12] It may therefore be concluded that the additions of the carboxylic acid and formyl groups to **3** lead to neither an enhancement nor a loss of MAO-B inhibition potency. In contrast, **4a** and **4b** were found to be comparatively weak MAO-A inhibitors with IC_{50} values of 1.04 and 2.20 μM, respectively. These inhibitors are therefore 371- and 595-fold, respectively, more selective for the MAO-B isoform. The selectivity profiles of these compounds are better than that of compound **3**, which is reported to be 193-fold more selective for MAO-B [IC_{50} (MAO-A) = 0.386 μM].[12] Although not as potent as **4a**–**b**, the ester derivative **4c** also proved to be a potent MAO-B inhibitor with an IC_{50} value of 0.0774 μM. Compound **4c**, however, exhibited a lower degree of selectivity with a selectivity index (SI) of 83. These results indicate that substitution with the carboxylic acid and formyl groups on C3 of the chromone moiety results in an improved selectivity profile without a significant loss of MAO-B inhibition potency. The importance of the C3 and C6 substituents for MAO-B