Bioorganic & Medicinal Chemistry Letters xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Inhibition of monoamine oxidase by 3,4-dihydro-2(1*H*)-quinolinone derivatives

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ARTICLE INFO

Article history:
Received 28 June 2013
Revised 12 August 2013
Accepted 15 August 2013
Available online xxxx

Keywords:
Monoamine oxidase
Reversible inhibition
Selectivity
3,4-Dihydro-2(1*H*)-quinolinone
Structure–activity relationship

ABSTRACT

In the present study, a series of 3,4-dihydro-2(1*H*)-quinolinone derivatives were synthesized and evaluated as inhibitors of recombinant human monoamine oxidase (MAO) A and B. The 3,4-dihydro-2(1*H*)-quinolinone derivatives are structurally related to a series of coumarin (1-benzopyran-2-one) derivatives which have been reported to act as MAO-B inhibitors. The results document that the quinolinones are highly potent and selective MAO-B inhibitors with most homologues exhibiting IC_{50} values in the nanomolar range. The most potent MAO-B inhibitor, 7-(3-bromobenzyloxy)-3,4-dihydro-2(1*H*)-quinolinone, exhibits an IC_{50} value of 2.9 nM with a 2750-fold selectivity for MAO-B over the MAO-A isoform. An analysis of the structure–activity relationships for MAO-B inhibition shows that substitution on the C7 position of the 3,4-dihydro-2(1*H*)-quinolinone scaffold leads to significantly more potent inhibition compared to substitution on C6. In this regard, a benzyloxy substituent on C7 is more favourable than phenylethoxy and phenylpropoxy substitution on this position. It may be concluded that C7-substituted 3,4-dihydro-2(1*H*)-quinolinones are promising leads for the therapy of Parkinson's disease.

The monoamine oxidases (MAOs) are mitochondrial bound enzymes which metabolize neurotransmitter and dietary amines in the brain and peripheral tissues. The MAOs have been drug targets for numerous decades and inhibitors of these enzymes are used primarily to treat neuropsychiatric syndromes.[1,2] MAO-B inhibitors, in particular, are considered useful in the therapy of Parkinson's disease since oxidation by MAO-B represents a major catabolic pathway of dopamine in the central nervous system. MAO-B inhibitors conserve the depleted dopamine stores in the parkinsonian brain and enhance the elevation of dopamine levels after administration of levodopa, the metabolic precursor of dopamine.[3,4] The combined use of levodopa and MAO-B inhibitors allows for a reduction of the dosage of levodopa that is necessary for a therapeutic response which, in turn, leads to diminished levodopa associated side effects.[5] MAO-B may also indirectly increase extracellular dopamine concentrations by blocking the metabolism of β-phenethylamine. β-Phenethylamine is a false neurotransmitter that mediates the release of neuronal dopamine and inhibits its active uptake.[6,7] Also of interest are reports that MAO-B inhibitors may exert neuroprotective effects in Parkinson's disease by reducing the formation of potentially harmful metabolic by-products of MAO catalysis.[1,8] For example, aldehydes derived from the MAO catalytic cycle has been implicated in the aggregation of α-synuclein, a process which is associated with the pathogenesis of Parkinson's disease.[9] Hydrogen peroxide formed during MAO catalysis may lead to oxidative damage and promotes apoptotic signaling events.[9,10] Considering that MAO-B activity increases in the brain with age, the concomitant increase of these metabolic by-products may be especially relevant to the pathogenesis of Parkinson's disease.[11,12]

It should be noted that MAO-A also metabolizes dopamine in the primate and possibly human brain and, similar to MAO-B inhibitors, MAO-A inhibitors also enhance the elevation of dopamine levels derived from levodopa.[4] The clinical use of MAO-A inhibitors have, however, declined in recent years because of side effects that may arise from the combination of MAO-A inhibitors with the dietary amine, tyramine. MAO-A inhibitors block the peripheral metabolism of tyramine, and the subsequent increase in systemic tyramine concentrations leads to the release of norepinephrine from peripheral neurons, which results in a potentially severe hypertensive response.[13] Another adverse effect of MAO-A inhibitors which limits their clinical use is serotonin toxicity, a potentially fatal syndrome which develops when serotonergic agents and MAO-A inhibitors are combined.[14,15] The combination of MAO-A inhibitors, which block the MAO-A-catalyzed metabolism of serotonin, with selective serotonin reuptake inhibitors (SSRIs) and serotonin-releasing agents leads to excessive extracellular serotonin concentrations in the central nervous system and hence serotonin toxicity. Based on these considerations, inhibitors with a high degree of selectivity for MAO-B over the MAO-A isoform are generally more suitable for Parkinson's disease therapy.

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0960-894X/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2013.08.071

In addition, MAO-B inhibitors with a reversible mode of action may possess certain advantages over irreversible MAO-B inhibitors, which are currently used in Parkinson's disease therapy. The most notable advantage is an immediate recovery of enzyme activity when the inhibitor has been eliminated from the tissues. In contrast, after termination of treatment with irreversible inhibitors, the rates of recovery of enzyme activity are slow and variable, in part because the turnover rate for the biosynthesis of MAO-B in the human brain may be as much as 40 days.[16,17]

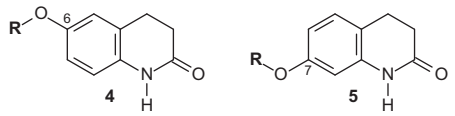
In the search for improved antiparkinsonian therapies, the design of new MAO-B inhibitors is pursued by several research groups. Based on the above analyses these inhibitors should be reversible and selective for the MAO-B isoform. In this regard, coumarin (1-benzopyran-2-one) (**1**) has emerged as a particularly promising scaffold (Fig. 1).[18] Substituted coumarins have been shown to act as competitive MAO inhibitors, with substitution on C7 of the coumarin ring yielding particularly potent MAO-B inhibitors. For example, 7-(3,4-difluorobenzyloxy)-3,4-dimethylcoumarin (**2**) was shown to inhibit rat brain MAO-B with an IC_{50} value of 1.14 nM and a 108-fold selectivity for MAO-B over the MAO-A isoform.[18] Based on the structural similarity between the coumarin moiety and 3,4-dihydro-2(1*H*)-quinolinone (**3**), the present study examines the possibility that a series of 3,4-dihydro-2(1*H*)-quinolinone derivatives (**4** and **5**) may act as reversible and selective inhibitors of recombinant human MAO-B. For this purpose substitution on the C6 and C7 positions of the 3,4-dihydro-2(1*H*)-quinolinone moiety was considered. Since alkyloxy substituents on C6 and C7 of the coumarin moiety yields compounds with good MAO-B inhibitory potencies,[18] in the present study alkyloxy substituents (benzyloxy, phenylethoxy and phenylpropoxy) were also selected for substitution on C6 and C7 of 3,4-dihydro-2(1*H*)-quinolinone ring system (Table 1). Among these, the benzyloxy side chain has been shown to be particularly suited for enhancing the MAO inhibition potencies of coumarin.[18] Furthermore, the proposal that benzyloxy-substituted 3,4-dihydro-2(1*H*)-quinolinones may act as MAO inhibitors is supported by a report, demonstrating that 7-(benzyloxy)-3,4-dihydro-2(1*H*)-quinolinone (**5a**) inhibits rat MAO-A and MAO-B with IC_{50} values of 102 μM and 1.05 μM, respectively.[18] We have therefore further explored the MAO inhibitory properties of the benzyloxy-substituted 3,4-dihydro-2(1*H*)-quinolinones by substitution on the benzyloxy phenyl ring with halogens (Cl, Br). Halogen substitution on the benzyloxy ring has previously been shown to significantly enhance the MAO-B inhibitory properties of 7-substituted benzyloxy-3,4-dimethylcoumarins as exemplified by structure **2**.[18] The aim of this study is therefore to discover novel highly potent and selective MAO-B inhibitors which may act as leads for the design of antiparkinsonian therapies.

The C6- and C7-substituted 3,4-dihydro-2(1*H*)-quinolinone derivatives **4** and **5** were synthesized according to the literature procedure (Scheme 1).[19] Commercially available 6-hydroxy-3,4-dihydro-2(1*H*)-quinolinone (**6**) and 7-hydroxy-3,4-dihydro-2(1*H*)-quinolinone (**7**), suspended in ethanol, were treated with an appropriately substituted alkyl bromide in the presence of KOH. After heating the mixture at reflux for 5 h, the reaction was poured into aqueous NaOH (1%). The crude thus obtained was purified by recrystallization and the structures of the target compounds were verified by ^{1}H NMR, ^{13}C NMR and mass spectrometry as cited in the Supplementary data.

To evaluate the MAO inhibitory properties of the 3,4-dihydro-2(1*H*)-quinolinone derivatives (**4** and **5**), the recombinant human MAO-A and MAO-B enzymes were used.[20] To measure MAO activities, the MAO-A/B mixed substrate, kynuramine, was employed. Kynuramine is oxidized by the MAOs to ultimately yield 6-hydroxyquinoline, a metabolite which fluoresces (λ_{ex} = 310 nm; λ_{em} = 400 nm) in alkaline media.[21] Using fluorescence spectrophotometry, the formation of 6-hydroxyquinoline can be readily measured in the presence of the test inhibitors since the 3,4-dihydro-2(1*H*)-quinolinone derivatives do not fluoresce under these assay conditions. From the MAO activity measurements in the presence of the test inhibitors, sigmoidal concentration–inhibition curves were constructed and the inhibition potencies, the corresponding IC_{50} values, were calculated (Fig. 2).

The IC_{50} values for the inhibition of human MAO-A and MAO-B by the 3,4-dihydro-2(1*H*)-quinolinone derivatives, **4** and **5**, are given in Table 1. The results show that the 3,4-dihydro-2(1*H*)-

Table 1
The IC_{50} values for the inhibition of recombinant human MAO-A and MAO-B by compounds **4** and **5**



	R	IC_{50} (μM)[a]		SI[b]
		MAO-A	MAO-B	
4a	$C_6H_5CH_2$–	25.3 ± 15.2	4.01 ± 1.196	6
4b	3-$ClC_6H_4CH_2$–	50.6 ± 10.3	0.620 ± 0.148	82
4c	3-$BrC_6H_4CH_2$–	12.4 ± 1.93	0.086 ± 0.029	144
4d	$C_6H_5(CH_2)_2$–	22.5 ± 9.69	2.33 ± 1.33	10
4e	$C_6H_5(CH_2)_3$–	19.7 ± 12.8	0.284 ± 0.049	69
5a	$C_6H_5CH_2$–	90.4 ± 47.1	0.038 ± 0.013	2379
5b	3-$ClC_6H_4CH_2$–	No Inh[c]	0.0062 ± 0.00063	–
5c	3-$BrC_6H_4CH_2$–	7.98 ± 1.09	0.0029 ± 0.0009	2751
5d	$C_6H_5(CH_2)_2$–	53.7 ± 12.0	0.191 ± 0.041	281
5e	$C_6H_5(CH_2)_3$–	22.5 ± 4.08	0.130 ± 0.010	173

[a] All values are expressed as the mean ± 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 at a maximum tested concentration of 100 μM.

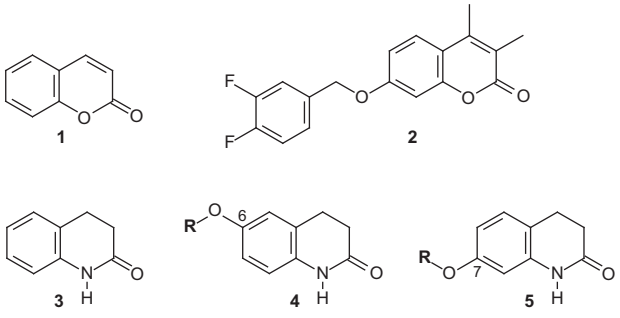
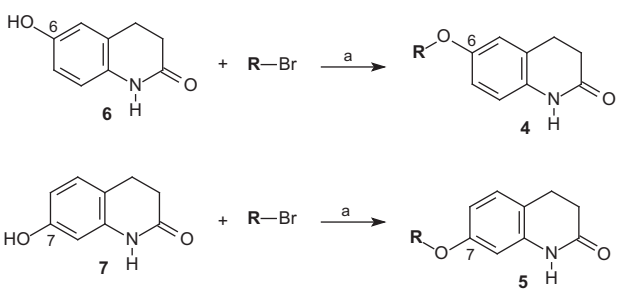


Figure 1. The structures of coumarin (**1**), 7-(3,4-difluorobenzyloxy)-3,4-dimethylcoumarin (**2**), 3,4-dihydro-2(1*H*)-quinolinone (**3**) and the 3,4-dihydro-2(1*H*)-quinolinone derivatives **4** and **5**.



Scheme 1. Synthetic route to the 3,4-dihydro-2(1*H*)-quinolinone derivatives **4** and **5**. Reagents: (a) KOH, ethanol, reflux.

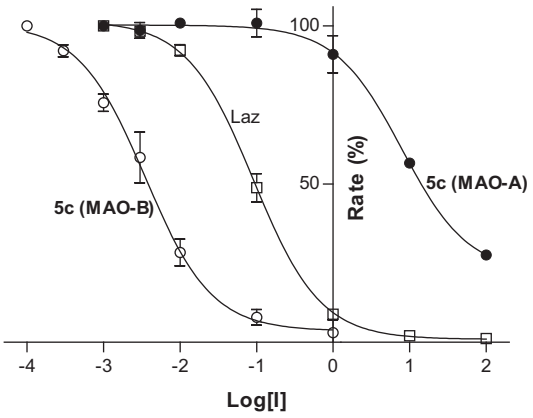


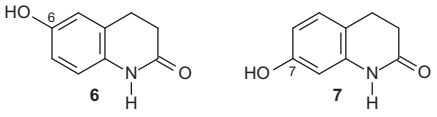
Figure 2. The sigmoidal concentration–inhibition curves for the inhibition of recombinant human MAO-A (filled circles) and MAO-B (open circles) by various concentrations of **5c**. For comparison, the sigmoidal concentration–inhibition curve (squares) for the inhibition of MAO-B by lazabemide (Laz) is also provided.

quinolinone derivatives are potent inhibitors of MAO-B with most homologues (8 of 10) exhibiting IC_{50} values in the nanomolar range. The results further demonstrate that all of the 3,4-dihydro-2(1*H*)-quinolinone derivatives are selective MAO-B inhibitors. The most potent MAO-B inhibitor, 7-(3-bromobenzyloxy)-3,4-dihydro-2(1*H*)-quinolinone (**5c**), is an exceptionally potent MAO-B inhibitor with an IC_{50} value of 0.0029 μM. Even though **5c** (IC_{50} = 7.98 μM) also was the most potent MAO-A inhibitor of the series, this compound is a highly selective inhibitor with a ~2750-fold selectivity for MAO-B over the MAO-A isoform. Another highly potent MAO-B inhibitor among the compounds evaluated is compound **5b** (IC_{50} = 0.0062 μM). Since compound **5b** did not exhibit any inhibitory activity towards MAO-A (up to a maximal tested concentration of 100 μM) it may also be considered as highly selective for MAO-B. Compared to the reversible MAO-B selective inhibitor, lazabemide (IC_{50} = 0.091 μM), compounds **5b** and **5c** are approximately 14- and 31-fold, respectively, more potent as MAO-B inhibitors under identical conditions.[22] It is interesting to note that **5a** is a relatively potent MAO-B inhibitor with an IC_{50} value of 0.038 μM. This IC_{50} value is 27-fold more potent than the previously reported value of 1.05 μM for the inhibition of rat brain MAO-B.[18] This result suggests that relatively large differences may exist between the inhibition potencies obtained with rat MAO-B and those obtained with the human isoform. The potencies by which **5a** inhibits human (IC_{50} = 90.4 μM) and rat (IC_{50} = 102 μM) MAO-A are, however, similar.

An analysis of the structure–activity relationships (SARs) for MAO-B inhibition reveals interesting trends. Substitution on the C7 position of the 3,4-dihydro-2(1*H*)-quinolinone moiety leads to significantly more potent MAO-B inhibition compared to substitution on C6. For example **5a** (IC_{50} = 0.038 μM), substituted with the benzyloxy moiety on C7, is approximately 100-fold more potent than **4a** (IC_{50} = 4.01 μM), the homologue bearing the benzyloxy moiety at C6. In fact compounds **5a–e** were in each instance more potent MAO-B inhibitors than their corresponding C6 substituted homologues **4a–e**. It may thus be concluded that C7-substituted 3,4-dihydro-2(1*H*)-quinolinones are, in general, more suitable for the design of exceptionally potent MAO-B inhibitors than C6-substituted 3,4-dihydro-2(1*H*)-quinolinones. In spite of this, with the appropriate substitution certain C6-substituted 3,4-dihydro-2(1*H*)-quinolinones such as **4c** (IC_{50} = 0.086 μM) may still be viewed as potent MAO-B inhibitors. Another interesting SAR is the finding that a benzyloxy substituent on C7 of the 3,4-dihydro-2(1*H*)-quinolinone moiety is more favourable for MAO-B inhibition than phenylethoxy and phenylpropoxy substitution on this position. For example, the C7 benzyloxy substituted homologue **5a** (IC_{50} = 0.038 μM) is at least threefold more potent than the phenylethoxy [(**5d**); IC_{50} = 0.191 μM] and phenylpropoxy [(**5e**); IC_{50} = 0.130 μM] substituted homologues. Interestingly, for the C6-substituted 3,4-dihydro-2(1*H*)-quinolinones, the benzyloxy substituted homologue **4a** (IC_{50} = 4.01 μM) was a weaker MAO-B inhibitor than the C6 phenylethoxy (**4d**) and phenylpropoxy (**4e**) substituted homologues. Reasons for the different trends observed with the C7- and C6-substituted 3,4-dihydro-2(1*H*)-quinolinones are not apparent. From a design point of view, it is noteworthy that, for the C7 benzyloxy substituted 3,4-dihydro-2(1*H*)-quinolinones, halogen (Cl, Br) substitution on the benzyloxy phenyl ring further enhances MAO-B inhibition potency. In this regard, the chlorine and bromine substituted homologues **5b** (IC_{50} = 0.0062 μM) and **5c** (IC_{50} = 0.0029 μM) are 6- to 13-fold more potent than the unsubstituted compound **5a** (IC_{50} = 0.038 μM). For those compounds with benzyloxy substituents on C6 of the 3,4-dihydro-2(1*H*)-quinolinone moiety, a similar trend was observed with the chlorine and bromine substituted homologues **4b** (IC_{50} = 0.620 μM) and **4c** (IC_{50} = 0.086 μM) exhibiting more potent MAO-B inhibition than the unsubstituted 6-benzyloxy-3,4-dihydro-2(1*H*)-quinolinone **4a** (IC_{50} = 4.01 μM). From these data it is apparent that bromine substitution yields more potent MAO-B inhibitors compared to chlorine substitution. Further investigation is necessary to evaluate the effects on MAO-B inhibition of other halogen and alkyl substituents on the benzyloxy phenyl ring. For the inhibition of MAO-A, no clear SARs are apparent. As noted above, the most potent MAO-B inhibitor of the series **5c** also was the most potent MAO-A inhibitor. Also, since **5c** as well as **4c**, the second most potent MAO-A inhibitor of the series, contain bromine on the benzyloxy phenyl ring, substitution with this halogen also enhances MAO-A inhibitory potency. To evaluate the importance of the C6 and C7 substituent for the inhibition of the MAOs by the the 3,4-dihydro-2(1*H*)-quinolinone derivatives, 6-hydroxy-3,4-dihydro-2(1*H*)-quinolinone (**6**) and 7-hydroxy-3,4-dihydro-2(1*H*)-quinolinone (**7**) were also evaluated as human MAO inhibitors. The results are given in Table 2 and show that **6** and **7** are weak MAO inhibitors with IC_{50} values >161 μM. This result demonstrates that appropriate C6 and C7 substitution is a requirement for the MAO inhibitory activities of 3,4-dihydro-2(1*H*)-quinolinone derivatives.

The reversibility of MAO-B inhibition by the most potent compound of the series **5c** was evaluated by examining the recovery of enzyme activity after the dilution of the enzyme–inhibitor complexes.[23] None of the 3,4-dihydro-2(1*H*)-quinolinone derivatives were potent MAO-A inhibitors. For this purpose, MAO-B and **5c** were combined and preincubated for 30 min at inhibitor concentrations equal to 10 × IC_{50} and 100 × IC_{50}. The reactions were sub-

Table 2
The IC_{50} values for the inhibition of recombinant human MAO-A and MAO-B by 6-hydroxy-3,4-dihydro-2(1*H*)-quinolinone (**6**) and 7-hydroxy-3,4-dihydro-2(1*H*)-quinolinone (**7**)



	IC_{50} (μM)[a]		SI[b]
	MAO-A	MAO-B	
6	161 ± 16.1	201 ± 31.3	0.8
7	183 ± 2.48	No inh[c]	—

[a–c] See Table 1 for footnotes.

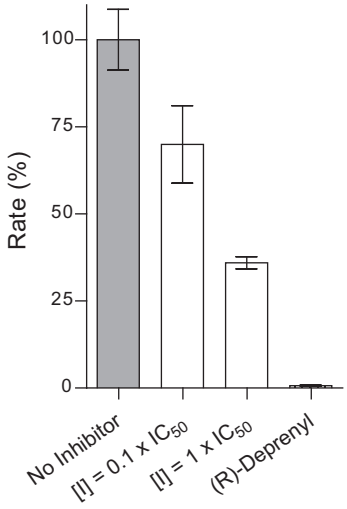


Figure 3. The reversibility of inhibition of MAO-B by compound **5c**. MAO-B was preincubated with **5c** at $10 \times IC_{50}$ and $100 \times IC_{50}$ for 30 min and then diluted to $0.1 \times IC_{50}$ and $1 \times IC_{50}$, respectively. For comparison, the irreversible MAO-B inhibitor, (*R*)-deprenyl, at $10 \times IC_{50}$, was similarly incubated with MAO-B and diluted to $0.1 \times IC_{50}$. The residual activity of MAO-B was subsequently measured.

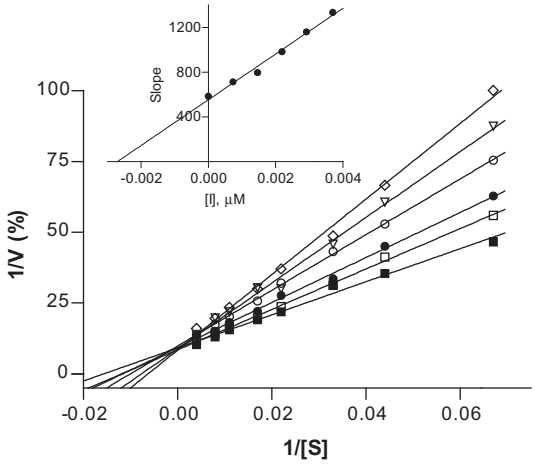


Figure 4. Lineweaver–Burk plots for the inhibition of human MAO-B by **5c**. The plots were constructed in the absence (filled squares) and presence of various concentrations of **5c**. The inset is a plot of the slopes of the Lineweaver–Burk plots versus inhibitor concentration.

sequently diluted 100-fold to yield concentrations of **5c** of $0.1 \times IC_{50}$ and $1 \times IC_{50}$, and the residual enzyme activities were measured. Control reactions conducted in the absence of inhibitor were also included in the study. The results are given in Figure 3 and show that, after dilution of **5c** to concentrations of $0.1 \times IC_{50}$ and $1 \times IC_{50}$, the catalytic activities of MAO-B are recovered to levels of 70% and 36% of the control levels, respectively. This result suggests that **5c** acts as a reversible MAO-B inhibitor since, after similar treatment of MAO-B with the irreversible inhibitor (*R*)-deprenyl at concentrations equal to $10 \times IC_{50}$, and dilution of the resulting reactions to $0.1 \times IC_{50}$, the MAO-B activities are not recovered (0.7% of control). Interestingly, after dilution of **5c** to concentrations of $0.1 \times IC_{50}$ and $1 \times IC_{50}$, the MAO-B catalytic activities are not recovered to 90% and 50%, respectively, as would be expected for reversible inhibition. This result suggests that **5c** may possess a quasi-reversible interaction or tight-binding component.

To further examine the mode of MAO-B inhibition by the 3,4-dihydro-2(1*H*)-quinolinone derivatives, a set of Lineweaver–Burk plots for the inhibition of MAO-B by **5c** was constructed. For this purpose, the MAO-B catalytic rates were recorded at eight different kynuramine concentrations (15–250 μM) in the absence of inhibitor, and presence of five different concentrations ($¼ \times IC_{50}$, $½ \times IC_{50}$, $¾ \times IC_{50}$, $1 \times IC_{50}$ and $1¼ \times IC_{50}$) of **5c**. The set of Lineweaver–Burk plots is given in Figure 4. The observation that the lines are linear and intersect on the *y*-axis suggests that **5c** is a competitive inhibitor of human MAO-B. This is further evidence that the interaction of **5c** with MAO-B is reversible. From a replot of the slopes of the Lineweaver–Burk plots versus the concentration of **5c**, a K_i value of 0.0027 μM for the inhibition of MAO-B is estimated.

In conclusion, the present study shows that a series of 3,4-dihydro-2(1*H*)-quinolinone derivatives are highly potent and selective MAO-B inhibitors, even when compared to the previously studied coumarin derivatives.[18] For example, the most potent inhibitor, compound **5c** (IC_{50} = 2.9 nM) is approximately equipotent to coumarin derivative **2**, which represents the most active MAO-B inhibitor among a large series of coumarin derivatives previously studied.[18] It should be noted that **2** was evaluated as an inhibitor of rat brain MAO while in the present study, the human enzymes were employed. Based on its high MAO-B inhibitory potency and selectivity over the MAO-A isoform, **5c** represents a suitable lead for the development of novel therapies for Parkinson's disease. In addition, **5c** interacts reversibly with MAO-B, which is a desirable property when designing antiparkinsonian therapies. The limited SARs derived for the inhibition data show that substitution on the C7 position of the 3,4-dihydro-2(1*H*)-quinolinone moiety, particularly with the benzyloxy substituent, is more favourable for MAO-B inhibition than substitution on the C6 position. In addition, halogen substituents on the benzyloxy phenyl ring further enhances MAO-B inhibition. Although a limited number of derivatives were examined, this study provides 'proof of concept' for the proposal that the 3,4-dihydro-2(1*H*)-quinolinone moiety is a promising scaffold for the design of MAO-B inhibitors. Further examination of the physicochemical properties of 3,4-dihydro-2(1*H*)-quinolinones is necessary to determine if these promising inhibitors may be acceptable as lead compounds for the treatment of central nervous system disorders.

Acknowledgments

The NMR and MS spectra were recorded by André Joubert and Johan Jordaan of the SASOL Centre for Chemistry, North-West University. This work is based on the research supported in part by the Medical Research Council and National Research Foundation of South Africa (Grant specific unique reference numbers (UID) 85642 and 80647). The Grantholders acknowledge that opinions, findings and conclusions or recommendations expressed in any publication generated by the NRF supported research are that of the authors, and that the NRF accepts no liability whatsoever in this regard.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.08.071.

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Please cite this article in press as: Meiring, L.; et al. *Bioorg. Med. Chem. Lett.* (2013), http://dx.doi.org/10.1016/j.bmcl.2013.08.071