



Inhibition of human monoamine oxidase A and B by 5-phenoxy 8-aminoquinoline analogs

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ABSTRACT

8-Aminoquinolines (8-AQs) are important class of anti-infective therapeutics. 5-Phenoxy 8-aminoquinoline analogs have shown improved metabolic stability compared to primaquine. In view of predictive role of monoamine oxidases (MAO) in metabolism of 8-aminoquinolines the 5-phenoxy analogs were evaluated in vitro for the inhibition of recombinant human MAO-A and MAO-B. The analogs were several folds more potent inhibitors of MAO-A and MAO-B compared to primaquine, the parent drug, with selectivity for MAO-B. 5-(4-Trifluoromethylphenoxy)-4-methylprimaquine (**6**) inhibited MAO-B with IC₅₀ value of 150 nM (626-fold more potent than primaquine). These results will have important implications in optimizing metabolic stability of 8-AQs to improve therapeutic value and also indicate scope for development of 8-AQs as selective MAO inhibitors.

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Monoamine oxidases (MAOs) are flavin adenine dinucleotide (FAD) containing enzymes located at the outer membrane of mitochondria in various cells found in nerve terminals, the liver, intestinal mucosa and other tissues. They regulate the levels of biogenic and xenobiotic amines in the brain and the peripheral tissues by catalyzing their oxidative deamination.¹ On the basis of their substrate specificities and inhibitor sensitivities two forms of MAOs have been identified and designated as MAO-A and MAO-B. MAO-A preferentially catalyzes the oxidation of serotonin (5-hydroxytryptamine, 5-HT) and is inhibited by low concentration of clorgyline² and RO41-1049,³ whereas MAO-B preferentially oxidizes β-phenylethylamine (PEA) and is inhibited by low concentrations of deprenyl⁴ and RO16-6491.⁵ Both isoforms utilize dopamine, epinephrine and tyramine and tranylcypromine is a non-selective inhibitor of MAO-A and MAO-B.⁶ MAO-A and MAO-B play important roles in the central nervous system and peripheral organs. Imbalances in the levels of biogenic amines have been associated with several neuronal and metabolic disorders.⁷ Abnormalities in MAO-B activities are implicated in neurological disorders such as Parkinson's and Alzheimer's disorders, whereas MAO-A plays important roles in psychiatric conditions such as depression.⁶ Elevated levels of MAO-B have been demonstrated

to induce apoptosis in neurons⁸ and kidney cells.⁹ Due to their roles in maintenance and regulation of levels of biogenic amines in neuronal and peripheral tissues. Both MAO-A and B have been of considerable pharmacological interest and the MAO inhibitors (MAOIs) have found wide clinical use for treatments of several neurological and psychiatric disorders. MAOIs although in wide use for the therapy of neuropsychiatric diseases, have various side effects. The first generation MAOIs (non-selective and irreversible) tranylcypromine, phenelzine, isocarboxazid and nilamide have serious side effects including hepatotoxicity, orthostatic hypotension, and most importantly hypertensive crises 'the cheese effect', that occurs following the ingestion of food containing tyramine.¹⁰ Selagiline, with or without levodopa, used for the control of Parkinson's disease, can cause anorexia/nausea, dry mouth, dyskinesia, orthostatic hypotension, musculoskeletal injuries and cardiac arrhythmias.¹¹ The adverse effects reported with moclobemide, a reversible inhibitor of MAO-A used for the treatment of depression, are sleep disturbance, anxiety, restlessness and headache.¹²

The role of MAO-A and MAO-B in the oxidative deamination of endogenous biogenic amines and regulation of levels of neurotransmitter amines in the neuronal tissues has been studied in detail. However, contribution of MAOs to the metabolism of xenobiotics and drugs has been largely neglected. The involvement of MAOs in the metabolism of xenobiotics has frequently been demonstrated in laboratory animals or in in vitro systems, such as animal or human hepatocytes¹³ or rat liver fractions,¹⁴ rather

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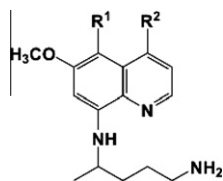


Figure 1. 8-Aminoquinoline analogs tested for inhibition (IC_{50}) of human MAO-A and MAO-B activities in vitro.

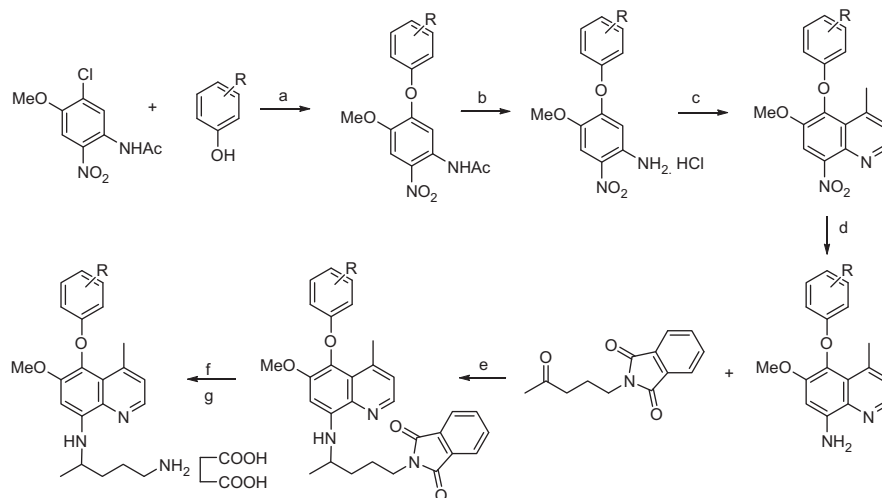
than in vivo in humans. Recently, involvement of MAOs in in vivo metabolism of citalopram,¹⁵ sertraline¹⁶ and the tryptan¹⁷ in humans has been demonstrated. Role of MAO in metabolism of primaquine and generation of carboxyprimaquine, a major plasma metabolite has also been suggested.¹⁴ Short plasma half-life and hemolytic toxicities in individuals with glucose 6-phosphate dehydrogenase deficiencies are major drawbacks, which have limited clinical use primaquine. As a part of our new 8-aminoquinoline drugs discovery program, we have synthesized several new analogs. The 5-phenoxy analogs showed significant improvement in antimalarial efficacy compared to primaquine.¹⁸ A 5-(3,4-dichlorophenoxy)-8-aminoquinoline analog (**14**) (NPC1161C) was selected for further preclinical development due its improved efficacy, metabolic stability, reduced hemolytic toxicity and selective pharmacologic profile of the enantiomers of this analogs.¹⁹ NPC1161C was observed to cause significantly more potent inhibition of human MAO-A and B in vitro than primaquine. This observation led us to test several 5-phenoxy 8-aminoquinoline analogs as a new class of MAO inhibitors.

In the present study we have determined the IC_{50} values for in vitro inhibition of human MAO-A and B with primaquine (PQ) (**15**) and its 5-phenoxy analogs (Fig. 1) (**1–13**). Compounds **1–14** were synthesized by the method outlined in Scheme 1. Appropriate halogenated phenol was coupled to commercially available *N*-(5-chloro-4-methoxy-2-nitrophenyl) acetamide to yield diphenylethers. Hydrolysis of these yielded aniline hydrochlorides, which were condensed with methyl vinyl ketone to give nitroquinoline intermediates. Catalytic hydrogenation of the nitroquinolines and subsequent attachment of the sidechain, 4-oxo-1-phthalimidopentane, afforded primaryamine-protected 8-aminoquinoline analogs. Deprotection of the terminal amine and treatment of the resulting amines with succinic acid gave compounds **1–13** as mono-succinates. Synthesis of NPC1161C (**14**) was reported previously.

Modifications at this position are considered important in view of predictive role of 5-hydroxylated metabolites, generated through CYP mediated metabolic pathways²³ and are responsible for hemolytic toxicity of primaquine. All the analogs were tested in vitro for inhibition of recombinant human MAO-A and B.^{20,21} Primaquine (**15**) showed only moderate inhibition of both MAO-A and B. Similar to findings of Bossi et al.,²⁴ who reported similar and weak inhibition of both MAO-A and B in vitro by primaquine (K_i 103–225 μ M), we observed a marginally higher inhibition of MAO-A than MAO-B by primaquine. The oxidative deamination of primaquine to carboxyprimaquine by MAO¹⁴ indicates that it also act as a substrate for this enzyme. Substitutions at C-5 position of the quinoline ring with a phenoxy group containing halides at different position and at C-4 position with methyl group produced structures that were highly more potent inhibitors of MAO-A and B compared to PQ (Table 1). The potency for MAO-B inhibition was increased much more potently (24–626 folds) than for MAO-A, for which the inhibition potency increased to only 2–19-fold when compared with inhibition of MAO-A and B by PQ (Table 1).

Among the series of 8-AQ analogs tested the most potent inhibitor for MAO-A was 5-(3-fluorophenoxy)-4-methylprimaquine (**2**) with IC_{50} of 3.2 μ M and the least active was 5-(2-fluorophenoxy)-4-methylprimaquine (**1**) with IC_{50} of 38 μ M. Similar to the finding of Van den Berg et al.,²⁵ who reported that styryl substituent's at C-8 position of caffeine with fluoro, chloro or bromo were weaker inhibitors of MAO than analogs bearing substituent trifluoromethyl group. The results presented here also indicate that 5-phenoxy substituted primaquine analogs with fluoro, chloro or bromo substitutions on the phenyl ring were less prominent inhibitors of MAO-B than the analog bearing trifluoromethyl group (**6**). It is also pertinent to mention about the findings of Ogunrombi et al.,³² that among the fluoro, chloro, bromo or trifluoromethyl derivatives of 1-methyl-3-phenyl-3-pyrrolinyl the most potent inhibitor of MAO-B was 1-methyl-3-(4-trifluoromethylphenyl)-pyrrole.

From the crystal structure of human recombinant MAO-A and MAO-B complexed with several pharmacologically important inhibitors,^{26–30} it is known that although the overall chain fold of the two isozymes is quite similar but some specific structural differences contribute to differential substrate utilization and inhibitor sensitivities of the two isoforms. There are significant similarities as well as differences in the active site of MAO-A and B.²⁹ The FAD coenzyme and two tyrosine residues constituting the 'aromatic cage' in the active site of both MAO-A and B are iden-



Scheme 1. Reagents and conditions: (a) KOH, DMF, 100 °C; (b) HCl, EtOH, reflux; (c) methyl vinyl ketone, H_3PO_4 , 100 °C; (d) $NH_2NH_2 \cdot H_2O$, Pd/C, EtOH reflux; (e) $NaBH_4$, AcOH, 20 °C; (f) $NH_2NH_2 \cdot H_2O$, EtOH, reflux; (g) succinic acid, ethanol.

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