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# ALKYLBENZYL ETHERS OF HYDROQUINONES AS MONOAMINE OXIDASE B INHIBITORS

Argyrios G. Arvanitis*, Everett L. Scholfield, Dimitri Grigoriadis[a], Peter G. Heytler, Jack Bowdle and Robert J. Chorvat

*The DuPont Merck Pharmaceutical Company, Wilmington, DE 19880-0353.*

**Abstract:** A series of alkylbenzylethers of substituted hydroquinone analogs of 4-(3-chlorophenyl methyloxy)-phenoxybutyronitrile **I**, and alcohol **II** were synthesized as monoamine oxidase (MAO) inhibitors. Incorporation of electron-withdrawing groups on the hydroquinone afforded compounds with higher levels of activity and selectivity than **I** or **II** for MAO B inhibition.

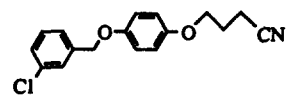
The mitochondrial monoamine oxidase enzymes (MAO's) catalyze the oxidative deamination of endogenous neurotransmitter monoamines as well as exogenous primary, secondary and tertiary amines, thereby regulating their concentration in central and peripheral tissues. In 1968, Johnston[1] discovered that MAO exists in two forms, MAO A and MAO B. While these two enzymes share about 70% homology[2] each possesses different substrate specificities and inhibitor sensitivities. In humans, MAO A is predominantly located in the outer mitochondrial membrane of aminergic neurons and primarily metabolizes norepinephrine and serotonin. MAO B, found exclusively in platelets as well as the major form present in liver and glial cells preferentially oxidizes dopamine.[3] Selective MAO B inhibition could eliminate the side effects present with non selective MAO inhibitors, which may include severe headaches, hypertensive crises and cardiac arrhythmias caused by the intake of tyramine containing foods.[4]

In humans, MAO B inhibitors have clinically demonstrated utility as an adjunct to L-dopa in the treatment of Parkinson's disease[5(a-c)], as well as showing potential for the treatment of Alzheimer's disease as cognitive enhancers.[5d] These therapeutic uses have been the basis for a renewed effort in discovering reversible and selective MAO inhibitors. Two examples of this effort are found in recent patents[6,7] in which compounds of structures **I** and **II** were reported to be potent MAO B inhibitors.

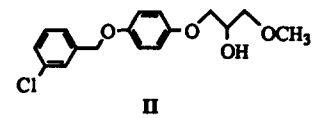
In our effort to discover potent inhibitors with high selectivity for MAO B we utilized compound **I** as a prototype molecule. We speculated that we might be able to improve on the properties of compounds like **I** by extending the chromophore system of the hydroquinone and thereby produce agents with better activity and selectivity because of

[a]Current address, Neurocrine Biosciences, Inc., San Diego, CA.

improved interaction with the flavin system of the enzyme. Thus to test this hypothesis we prepared compounds with electron withdrawing groups on the 2- and 3- positions of the hydroquinone subunit and evaluated their MAO inhibitory properties.




I

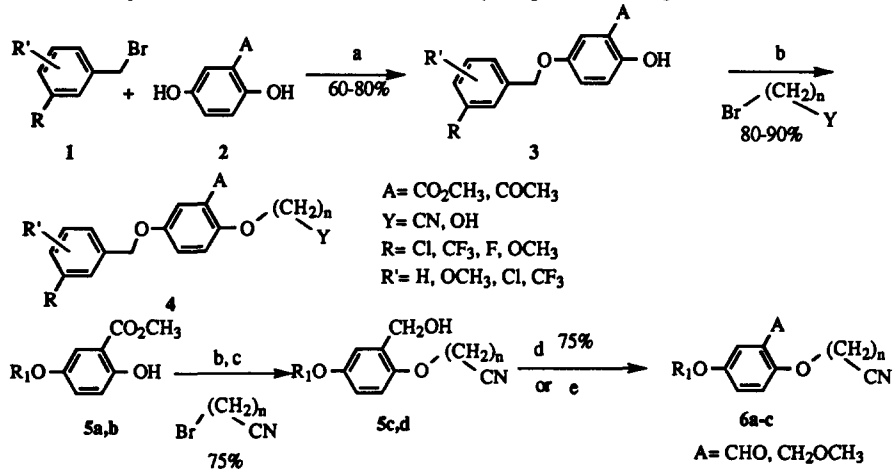



II

## Chemistry

Synthesis of various substituted hydroquinone ring compounds is described in Scheme I. Treatment of an appropriately substituted benzyl bromide **1** with a 2-substituted hydroquinone **2** afforded the 4-benzyloxyphenols **3**. These monoethers were then alkylated with various alkyl halides in refluxing $CH_3CN$ in the presence of $K_2CO_3$ to give the corresponding bis O-alkylated hydroquinones **4**. To prepare the 2-aldehyde derivative, the phenolic ester **5** was reduced with $LiAlH_4$, alkylated to **5c** or **5d**, and oxidized to the aldehyde **6a** or **6b**. Alternatively phenol **5c** was alkylated to the ether **6c** by treatment with NaH in THF, followed by $CH_3I$.

**Scheme I** Synthetic route for the 2-substituted hydroquinone analogs of **I**



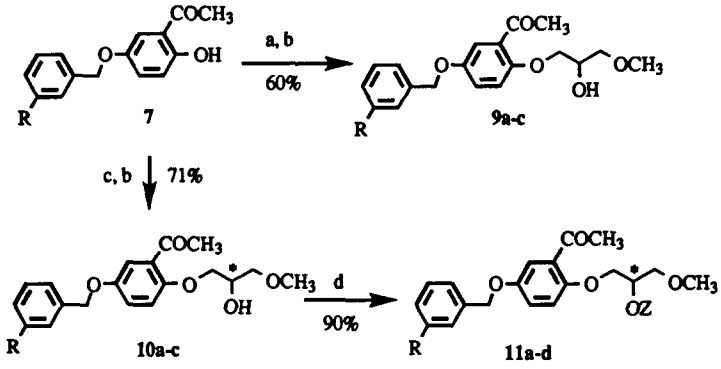

$R_1$= 3-$ClC_6H_4CH_2$

(a) $K_2CO_3$, $CH_3CN$, 25 °C, 16 h; (b) $K_2CO_3$, $CH_3CN$, Δ, 16 h; (c) $LiAlH_4$, THF, 0-25 °C; (d) pyridinium chlorochromate, Celite®, $CH_2Cl_2$, 25 °C, 3h; (e) NaH, THF, $CH_3I$.

The 3-substituted hydroquinones were synthesized by changing the order of the two alkylation reactions, first reacting **2** with an alkyl bromide, followed by treatment with a benzyl halide.

Synthesis of the racemic and chiral α-alkoxy secondary alcohols is described in Scheme II. Treatment of 2-acetyl-4-benzyloxyphenols **7** with epibromohydrin or the analogous chiral tosylate[8] **8** afforded the corresponding epoxides[9] which were opened with $CH_3ONa$ to the α-alkoxyalcohols **9** or **10**. In the case where the chiral tosylate was used, the enantiomeric excess of the alcohols was 82% as determined by HPLC analysis. These alcohols were further functionalized to esters **11a** and **11c** or carbonates **11b** and **11d**.

**Scheme II** Synthetic route to racemic and chiral secondary alcohols

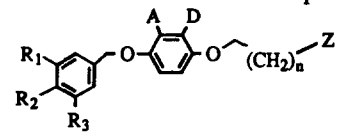



(a) $K_2CO_3$, epibromohydrin, $CH_3CN$, Δ; (b) $CH_3ONa$, $CH_3OH$, 25 °C, 16 h; (c) NaH, (2R)-(-) or (2S)-(+) glycidyl tosylate **8**, DMF, 25 °C, 16 h; (d) AcCl, Py, or $CH_3OCOCl$, Py, $CH_2Cl_2$.

## Biological Results and Discussion

The $IC_{50}$ values were obtained by measuring the inhibitory activity of the compounds using a 200 μM solution of [14-C]-phenethylamine for MAO B and a 1.0 mM solution of [14-C]-5-hydroxytryptamine for MAO A according to the previously described method.[10] In vitro MAO inhibitory activities of various substituted hydroquinone derivatives with a nitrile and primary alcohol functionalities are given in Table I.

**Table I** In vitro MAO A and B inhibition of nitriles and primary alcohols[11]

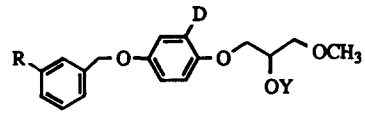



| Cmpd | $R^1,R^2,R^3$ | A | D | Z | n | $IC_{50}$ (nM)[a] | $IC_{50}A/IC_{50}B$[b] |
|---|---|---|---|---|---|---|---|
| **I** | Cl,H,H | H | H | CN | 2 | 60 | 300 |
| **5a** | Cl,H,H | H | $CO_2Me$ | CN | 2 | 6000 | ND |
| **5b** | Cl,H,H | H | $CO_2Me$ | CN | 0 | 1000 | ND |
| **5c** | Cl,H,H | H | $CH_2OH$ | CN | 2 | 1000 | ND |
| **5d** | Cl,H,H | H | $CH_2OH$ | CN | 0 | 2000 | ND |
| **6a** | Cl,H,H | H | CHO | CN | 2 | 30 | 100 |
| **6b** | Cl,H,H | H | CHO | CN | 0 | 300 | <10 |
| **6c** | Cl,H,H | H | $CH_2OMe$ | CN | 2 | 300 | 33 |
| **12** | Cl,H,H | H | COMe | CN | 2 | 30 | 333 |
| **13** | $CF_3$,H,H | H | COMe | CN | 2 | 20 | <50 |
| **14** | Cl,Cl,H | H | COMe | CN | 2 | 100 | <10 |
| **15** | F,H,H | H | COMe | CN | 2 | 100 | 100 |
| **16** | OMe,H,H | H | COMe | CN | 2 | 200 | 300 |
| **17** | Me,Me,H | H | COMe | CN | 2 | 400 | >2500 |
| **18** | H,H,H | H | COMe | CN | 2 | 500 | 100 |
| **19** | OMe,H,OMe | H | COMe | CN | 2 | 300 | 10 |
| **20** | Me,H,H | H | COMe | CN | 2 | 100 | 300 |
| **21** | Cl,H,H | COMe | H | CN | 2 | 1000 | ND |
| **22** | Cl,Cl,H | COMe | H | CN | 2 | 800 | ND |
| **23** | Cl,H,H | H | COMe | CN | 3 | 700 | ND |
| **24** | Cl,H,H | H | $CO_2Me$ | CN | 3 | 80000 | ND |
| **25** | $CF_3$,H,H | H | COMe | OH | 2 | 30 | 1667 |
| **26** | Cl,H,H | H | COMe | OH | 2 | 100 | 400 |
| **27** | F,H,H | H | COMe | OH | 2 | 100 | 100 |
| **28** | Cl,H,H | H | COEt | CN | 2 | 400 | ND |
| **29** | F,H,H | H | COEt | CN | 2 | 800 | ND |

[a] MAO B. Values for MAO B inhibition were initially determined in a primary screen (four concentrations: $10^{-4}$, $10^{-5}$, $10^{-6}$, $10^{-7}$ M). Compounds with an $IC_{50}$ of $<10^{-7}$ M were retested (five concentrations: $1x10^{-7}$, $3x10^{-8}$, $1x10^{-8}$, $3x10^{-9}$, $1x10^{-9}$ M). [b] Values for MAO A inhibition were determined at four concentrations ($10^{-3}$, $10^{-4}$, $10^{-5}$, $10^{-6}$ M). ND: not determined.

In vitro MAO inhibition data of various substituted hydroquinone derivatives with secondary alcohol, acetate and methylcarbonate functionality are given in Table II.

**Table II** In vitro MAO A and B inhibition of secondary alcohols, acetates and methyl carbonates[11]




| Compd | R | D | Y | $IC_{50}$ (nM)[a] | $IC_{50}A/IC_{50}B$[b] |
|---|---|---|---|---|---|
| **II(S)** | Cl | H | H | 20 | 100 |
| **9a**[c] | $CF_3$ | $COCH_3$ | H | 15[d] | 4700[d] |
| **9b**[c] | Cl | $COCH_3$ | H | 50 | 600 |
| **9c**[c] | F | $COCH_3$ | H | 300 | 233 |
| **10a (S)** | $CF_3$ | $COCH_3$ | H | 30[d] | ND |
| **10b (S)** | Cl | $COCH_3$ | H | 90 | 444[d] |
| **10c (R)** | $CF_3$ | $COCH_3$ | H | 25[d] | ND |
| **11a (S)** | $CF_3$ | $COCH_3$ | COMe | 30[d] | ND |
| **11b (S)** | $CF_3$ | $COCH_3$ | $CO_2Me$ | 20[d] | 30000[d] |
| **11c (R)** | $CF_3$ | $COCH_3$ | COMe | 20[d] | >2000[d] |
| **11d (R)** | $CF_3$ | $COCH_3$ | $CO_2Me$ | 200[d] | 3000[d] |

[a] See footnote a on Table I. [b]See footnote on Table I. [c]Racemic mixture. [d]Mean value of two determinations

Comparison of the inhibition data in Table I for compounds **5a-d, 6a, 6c, 12,** and **28, 29** to **I,** shows that a CHO or $COCH_3$ group on the 2-position of the hydroquinone ring, increases potency of MAO B inhibition. This is consistent with the hypothesis that an electron withdrawing substituent on the 2-position can provide a system with extended conjugation (polarizable) with either of the oxygens on that ring. This extended chromophore may interact better with the flavin portion on the enzymatic active site. Furthermore, it may also provide an additional interaction point that increases both potency and selectivity for MAO B enzyme inhibition. When this group is reduced, (**5c, 5d**), or increased in size (**5a, 5b, 28**), potency drops.

On the phenyl ring the optimal substituent is a 3-chloro or a 3-trifluoromethyl group in the case of nitriles (**12-23** Table I), and a $CF_3$ group in the case of primary and secondary alcohols (**25-27** Table I and **9a-c, 10a-c** Table II).

The secondary alcohols **9a-c** or their corresponding acetates and methyl carbonates are the optimal alkyl chain analogs. Of these compounds, the 2-acetyl analogs showed the best potency and selectivity. In particular, the propanol **9a** and the corresponding enantiomeric alcohols (**10a** and **10c**), acetates (**11a** and **11c**) and methyl carbonate (**11b**) all have $IC_{50}$'s for MAO B of 20-30 nM and $>10^2$ fold selectivity for this enzyme.

In conclusion, we have shown that extending the conjugation of the hydroquinone system can, in certain cases, increase both activity and selectivity for MAO B inhibition over unsubstituted analogs, or those with substituents that do not extend conjugation. Further exploration of this concept may provide more potent, selective and therapeutically useful agents.

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(11) Spectroscopic data of all compounds (NMR and MS) were in full agreement with their proposed structure. Elemental analyses of all compounds were within 0.4% of the calculated values, except **23** (not available) and **26** (C: calc 64.57; found 63.96).

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