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SELECTIVE INHIBITION OF MONOAMINE OXIDASE B BY AMINOETHYL SUBSTITUTED BENZYL ETHERS

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Aminoethyl 3-chlorobenzyl ether was shown previously (Ding, C.Z. and Silverman, R.B. (1993). *Bioorg. Med. Chem. Lett.*, **3**, 2077–2078) to be a potent and selective time-dependent, but reversible inhibitor of monoamine oxidase B (MAO B). Based on this result, a series of novel aminoethyl substituted benzyl ethers was synthesized and the compounds were examined as potential inhibitors of both isozymic forms of MAO. Each compound in the series inhibits both MAO A and MAO B competitively, and IC_{50} values for each compound were determined. In general, the B isozyme is much more sensitive to these inhibitors than the A isozyme (except for the *o*- and *p*-substituted nitro analogues), in some cases by more than two orders of magnitude. The selectivity in favor of MAO B inhibition is relatively high for all of the *meta*-substituted analogues and quite low for all of the *ortho*-substituted analogues. Having the substituent at the *ortho*-position is most favorable for MAO A inhibition. With MAO B the *meta*-analogues were, in general, more potent than the corresponding *ortho*- and *para*-analogues with respect to their reversible binding constants. The *meta*-iodo analogue is the most potent analogue.

Keywords: Monoamine oxidase; Inhibition; Aminoethyl benzyl ethers

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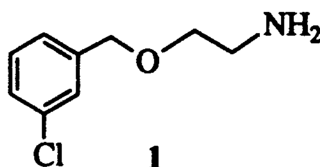
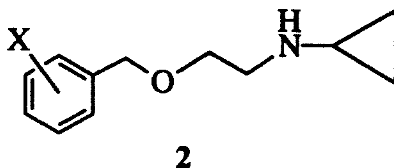
INTRODUCTION

Monoamine oxidase (MAO, EC 1.4.3.4) is a flavin-dependent enzyme located in the outer mitochondrial membrane and is responsible for the catabolism of various biogenic amine neurotransmitters and dietary amines.[1] MAO exists in two isozymic forms (MAO A and MAO B); the human liver enzymes have 70% sequence identity as deduced from their cDNA clones.[2] The genes for both MAO A and MAO B are similar, suggesting that the gene products are derived from the duplication of a common ancestral gene.[3] MAO A and MAO B differ in substrate and inhibitor selectivity. Serotonin and norepinephrine are degraded preferentially by MAO A, and inhibition of MAO A gives rise to an antidepressant effect.[4] Dopamine and phenylethylamine are preferentially degraded by MAO B, and inhibition of MAO B has been shown to be an effective treatment for Parkinson's disease.[5] Nonselective inhibitors have been shown to exhibit severe hypertensive activities as a result of blockage of the normal degradation of norepinephrine, which is involved in controlling the blood pressure.[6] Selegiline, a MAO B inactivator currently used in the treatment of Parkinson's disease,[5] has an inhibitory selectivity ratio for MAO B/MAO A of 39.[7]

Several years ago we reported results of selective inhibition of MAO B by aminoethyl 3-chlorobenzyl ether (**1**), a reversible time-dependent inactivator with a selectivity ratio $(k_{inact}/K_I)_B/(k_{inact}/K_I)_A$ of 1700.[8]



A related series of (*N*-cyclopropyl)-aminoethyl arylmethyl ethers (**2**) were reported to be time-dependent inactivators of MAO;[9] interestingly, both the *o*-chloro[9c] and *o*-iodo[9d] analogues of **2** are highly selective for MAO A. A comparison between inhibition of MAO A and MAO B was not made for the other analogues.



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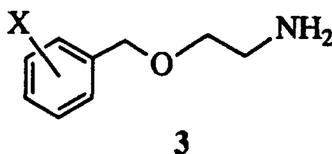
Because of the high selectivity that we observed with **1** against MAO B and the high selectivity that was observed for **2** against MAO A, we decided to make more analogues of **1** to determine the selectivity of this series with the MAO isozymes. Consequently, the novel series **3**, where X = H, F, Cl, Br, I, and NO_2, at the *o*-, *m*-, and *p*-positions of the ring, were synthesized and tested for their inhibition of both MAO A and MAO B. The results of this study are reported here.



3

MATERIALS AND METHODS

General Methods

^1H and ^{19}F NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. Chemical shifts in D_2O are reported as δ values in parts per million downfield from DSS for proton spectra and from $CFCl_3$ for ^{19}F spectra. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Oneida Research Services (Whitesboro, NY). Thin-layer chromatography was run on silica UV_{254} PE SIL G from Whatman.

Reagents

All reagents were purchased from Aldrich Chemical Co. with the exception of 4-chlorobenzyl bromide and 4-iodobenzyl bromide, which were purchased from Lancaster Synthesis, Inc. and Karl Industries, Inc. (Aurora, OH), respectively, and were used without further purification. THF was freshly distilled from sodium under argon.

General Procedure for the Synthesis of the Aminoethyl Substituted Benzyl Ether Hydrochlorides (3)

A flame-dried three-necked flask equipped with a condenser and a rubber septum was charged with 40 mL of dried THF and sodium hydride (0.31 g,

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12 mmol) under an argon atmosphere. Ethanolamine (0.61 g, 10 mmol) was added by syringe to the mixture at room temperature. After being stirred on ice for 30 min, the substituted benzyl bromide (or chloride) (10 mmol) was added dropwise via syringe if it was a liquid or by removing the septum under a positive argon pressure to add a solid bromide. The reaction was allowed to proceed for at least 2 h, after which time the reaction mixture was quenched with 10 mL of cold water. The THF was removed by rotary evaporation, and the aqueous solution was extracted with cyclohexane or methylene chloride (3× 35 mL). The organic extracts were combined and dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the organic solution was extracted with 2% HCl (3× 40 mL). The water was evaporated, the residue was taken up in water and reevaporated, then the solid product was recrystallized first from ethanol/ether, then from ethanol/ethyl acetate to give analytically pure amine hydrochloride salt products. Yields, m.p., and NMR data are given in Table IV. Elemental analyses and HRMS data are in Table V. The ^{19}F NMR resonances for the fluorine atom in the *o*-F, *m*-F, and *p*-F analogues are 41.85, 41.85, and 41.91, respectively.

X-ray Crystal Structure of Aminoethyl 4-iodobenzyl Ether Hydrochloride

A colorless needle crystal of aminoethyl 4-iodobenzyl ether, having approximate dimensions of 0.36 × 0.11 × 0.03 mm, was mounted on a glass fiber using oil (Paratone-N, Exxon). All measurements were made on a Bruker SMART-1000 CCD area detector with graphite monochromated Mo-Kα radiation. The data were collected at a temperature of -120 ± 1°C to a maximum 2θ value of 56.5°. Data were collected in 0.30° oscillations with 20.0 s exposures. The crystal-to-detector distance was 50 mm. The detector swing angle was 28.00°.

Enzymes and Assays

MAO B was purified from bovine liver mitochondria and assayed as described earlier (activity 5.2 units/mL).[10] Recombinant MAO A was purified as previously described.[11] The activity was determined to be 0.409 units/mL at 30°C by monitoring the increase in absorption at 314 nm with 1 mM kynuramine in 100 mM sodium phosphate buffer, pH 7.2 containing 20% glycerol and 0.2% Triton X-100.

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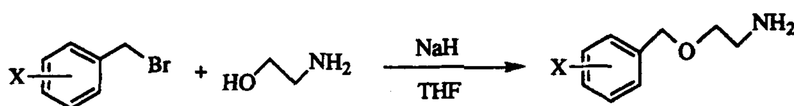
Determination of IC_{50} Values

A 5 µL aliquot of MAO B was added to a cuvette containing 495 µL of a solution of various concentrations of the inhibitor as well as 1.01 mM benzylamine in 50 mM Tris-HCl, pH 9.0. The increase in absorption at 250 nm was monitored immediately after addition of the enzyme to the substrate/inhibitor solution. Because most of these compounds are also time-dependent inactivators of MAO B, the increase in absorption from 0 to 6 s was used to calculate the activity of the enzyme. Under these conditions, little or no time-dependent inhibition occurs. The inhibitor concentrations were plotted as a function of the natural log of the enzyme activity, and the best-fit lines were extrapolated to find the concentration of inhibitor that produced 50% enzyme activity. For determination of the IC_{50} values with MAO A, 25 µL aliquots of the enzyme solution were added to 50 µL of a 10 mM kynuramine solution and sufficient inhibitor solution and buffer to bring the total volume to 500 µL. The solutions were monitored at 314 nm from 1.0 to 2.0 min and the IC_{50} values were determined as described for MAO B.

RESULTS AND DISCUSSION

Syntheses of the Aminoethyl Substituted Benzyl Ether Hydrochlorides

All of the analogues were synthesized by the reaction of the corresponding benzyl bromide or chloride with 2-aminoethanol in the presence of sodium hydride as base (Scheme 1). Small amounts of the *N*-benzylated products ((2-hydroxyethyl)benzyl amines) were removed by recrystallization. The arylmethylene protons of the undesirable side product are observed at 3.7–4.0 ppm, whereas the corresponding protons of the desired products are between 4.40 and 4.69 ppm, as expected for the more electron-withdrawing oxygen relative to nitrogen. To be certain of the structure, an X-ray crystal structure of aminoethyl 4-iodobenzyl ether was obtained, and the ether linkage was observed (Figure 1). Physical and spectral data are in Table IV; elemental analyses and HRMS data are in Table V.



SCHEME 1 Synthesis of aminoethyl substituted benzyl ethers.

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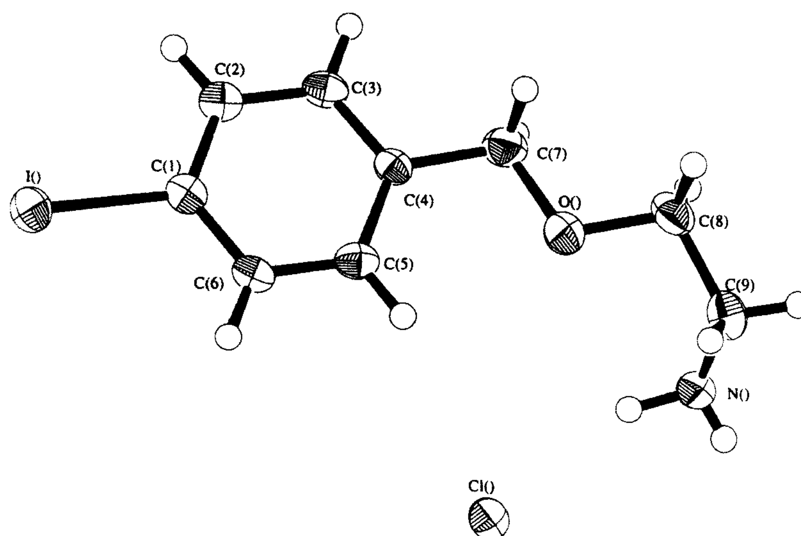

FIGURE 1 ORTEP drawing of the X-ray crystal structure of aminoethyl 4-iodobenzyl ether.

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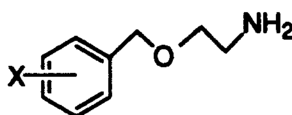
TABLE I IC_{50} values (μM) for the inhibition of MAO A by (aminoethyl) substituted benzyl ethers in the presence of 1.0 mM kynuramine as substrate[a]



MAO A

X	*ortho*	*meta*	*para*
H	1130	1130	1130
F	172	1750	1220
Cl	48.3	855	249
Br	32.9	627	173
I	70.5	545	94.5
NO_2	1730	985	459

[a]The correlation coefficients for the plots from which the data were obtained were between 0.97 and 0.99, mostly the latter; standard deviations were $< \pm 10\%$.

Inhibition of Monoamine Oxidases by the Aminoethyl Substituted Benzyl Ethers

IC_{50} values were obtained for the 16 compounds and are shown in Tables I and II; Table III summarizes the selectivities of each compound for the

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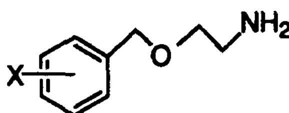
TABLE II IC_{50} values (μM) for the inhibition of MAO B by (aminoethyl) substituted benzyl ethers in the presence of 1.0 mM benzylamine as substrate[a]



MAO B

X	ortho	meta	para
H	26	26	26
F	12.9	18.7	14.3
Cl	13.1	5.6	13.7
Br	8.5	6	17.8
I	9.2	4.2	32.4
NO_2	2500	12.5	15,800

[a]The correlation coefficients for the plots from which the data were obtained were between 0.97 and 0.99, mostly the latter; standard deviations were $< \pm 10\%$.

TABLE III Selectivities of the (aminoethyl) substituted benzyl amines for monoamine oxidases MAO B/MAO A[a]

X	ortho	meta	para
H	44	44	44
F	13	94	85
Cl	4	153	18
Br	4	105	10
I	8	130	3
NO_2	0.7	79	0.03

[a]This ratio represents the inverse ratios of the IC_{50} data; a value > 1 means that the compound is a more potent inhibitor of MAO B than of MAO A.

monoamine oxidases based on the results in Tables I and II. Since the IC_{50} values for the two isozymes were obtained in the presence of different substrates, these values represent relative selectivities. The binding site about the *meta*- and *para*-positions bound to MAO A may be somewhat hydrophobic, since there is a trend of increasing binding in going from fluorine to iodine, but the nitro analogue binds less well. However, having the substituent at the *ortho*-position is most favorable (except for the nitro analogue) for MAO A inhibition, as was observed for the corresponding *N*-cyclopropyl analogues (**2**).[9] With the *N*-cyclopropyl analogues, *ortho*-iodo was a little more potent than the corresponding *ortho*-chloro compound,[9d] but in our study, the reverse was observed (and the *ortho*-bromo analogue was best).

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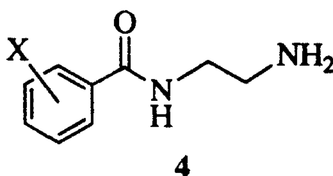
TABLE IV Physical data for the (aminoethyl) substituted benzyl ethers (**3**)

X	*Yield* (%)	*M.p.* (°C)	^1H *NMR data* (δ)
H	60	142–143[a]	7.37 (m, 4 H), 4.56 (d, 2 H), 3.70 (t, 2 H), 3.14 (t, 2 H)
o-F	63	128–130	7.48 (s, 1 H), 7.43 (dd, 1 H), 7.22 (m, 2 H), 4.69 (d, 2 H), 3.78 (t, 2 H), 3.20 (t, 2 H)
o-Cl	26	180–182[b]	7.46 (s, 1 H), 7.44 (dd, 1 H), 7.32 (m, 2 H), 4.67 (s, 2 H), 3.77 (t, 2 H), 3.17 (t, 2 H)
o-Br	27	185–187	7.66 (d, 1 H), 7.50 (d, 1 H), 7.41 (t, 1 H), 7.31 (t, 1 H), 4.69 (s, 2 H), 3.82 (t, 2 H), 3.22 (t, 2 H)
o-I	47	183–185	7.95 (d, 1 H), 7.45 (m, 2 H), 7.11 (t, 1 H), 4.63 (s, 2 H), 3.83 (t, 2 H), 3.22 (t, 2 H)
o-NO_2	5	159–161	8.28 (d, 1 H), 7.83 (t, 1 H), 7.70 (m, 2 H), 4.51 (s, 2 H), 3.90 (t, 2 H), 3.34 (t, 2 H)
m-F	47	126–128	7.41 (s, 1 H), 7.38 (d, 1 H), 7.35 (d, 1 H), 7.11 (m, 1 H), 4.57 (s, 2 H), 3.72 (t, 2 H), 3.16 (t, 2 H)
m-Cl	51	119–120[c]	7.44 (s, 1 H), 7.39 (d, 1 H), 7.38 (t, 1 H), 7.32 (t, 1 H), 4.59 (s, 2 H), 3.74 (t, 2 H), 3.2 (td, 2 H)
m-Br	60	107–109	7.59 (s, 1 H), 7.54 (d, 1 H), 7.51 (t, 1 H), 7.33 (m, 1 H), 4.56 (s, 2 H), 3.72 (td, 2 H), 3.18 (td, 2 H)
m-I	52	104–106	7.82 (s, 1 H), 7.75 (d, 1 H), 7.40 (d, 1 H), 7.19 (t, 1 H), 4.56 (s, 2 H), 3.73 (t, 2 H), 3.2 (t, 2 H)
m-NO_2	29	130–132	8.24 (d, 1 H), 8.20 (d, 1 H), 8.17 (d, 1 H), 7.66 (m, 1 H), 4.69 (s, 2 H), 3.76 (t, 2 H), 3.20 (t, 2 H)
p-F	87	140–141	7.13 (d, 2 H), 7.40 (d, 2 H), 4.55 (s, 2 H), 3.72 (t, 2 H), 3.16 (t, 2 H)
p-Cl	38	189–190	7.40 (d, 2 H), 7.34 (d, 2 H), 4.55 (s, 2 H), 3.72 (t, 2 H), 3.16 (t, 2 H)
p-Br	17	192–194	7.55 (d, 2 H), 7.28 (d, 2 H), 4.53 (d, 2 H), 3.70 (t, 2 H), 3.15 (t, 2 H)
p-I	62	202–204	7.64 (d, 2 H), 7.04 (d, 2 H), 4.40 (s, 2 H), 3.59 (t, 2 H), 3.05 (t, 2 H)
p-NO_2	60	142–143	8.29 (d, 2 H), 7.70 (d, 2 H), 4.40 (s, 2 H), 3.85 (t, 2 H), 3.25 (t, 2 H)

[a]Lit. m.p. 143–145°C (Miller, T.L., Rowley, G.L. and Steward, C.J. (1966). *J. Am. Chem. Soc.*, **88**, 2299).
[b]Lit. m.p. 182–184°C (Wellcome Foundation Ltd. (1966). *British Pat.* 1,031,165; *Chem. Abst.*, **65**, 7098e).
[c]Lit. m.p. 122–124°C (Ding, C.Z. and Silverman, R.B. (1993). *Bioorg. Med. Chem. Lett.*, **3**, 2077).

With MAO B the *meta*-analogues were, in general, more potent than the corresponding *ortho*- and *para*-analogues with respect to the reversible binding constants. Little difference in the reversible binding constants of the various halogen substituents at a particular position was observed. The *meta*-nitro analogue was found to be a potent inhibitor, but the corresponding *ortho*- and *para*-nitro analogues were the least potent of any of the compounds, based on the reversible binding efficiency. It is not clear if this is a steric or an electronic effect, but we made the same observation previously with a series of *N*-(aminoethyl)benzamide analogues (**4**).[12]



4

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TABLE V Elemental analyses and HRMS data for **3**

X	*Elemental analyses*		*HRMS data*	
	Calcd.	*Found*	*Calcd.*	*Found*
H	($C_9H_{14}ClNO$) C, 57.60%; H, 7.52%; N, 7.46%	C, 57.31%; H, 7.51%; N, 7.37%		
o-F	($C_9H_{13}ClFNO$) C, 52.56%; H, 6.37%; N, 6.81%	C, 52.45%; H, 6.30%; N, 6.69%	(M-HCl)H^+ 170.1007	170.1010
o-Cl	($C_9H_{13}Cl_2NO$) C, 48.67%; H, 5.90%; N, 6.31%	C, 48.75%; H, 6.02%, N, 6.30%	(M-HCl)H^+ 186.0686	186.0672
o-Br	($C_9H_{13}ClBrNO$) C, 40.55%; H, 4.92%; N, 5.25%	C, 40.60%; H, 4.95; N, 5.10%	(M-HCl)H^+ 230.018	230.017
o-I	($C_9H_{13}ClINO$) C, 34.47%; H, 4.18%; N, 4.47%	C, 34.27%; H, 4.30%; N, 3.97%	(M-HCl)H^+ 278.0042	278.0043
o-NO_2	($C_9H_{13}ClN_2O_3$) C,46.46%; H, 5.63%; N, 12.04%	C, 46.26%, H, 5.80%; N, 12.14%	(M-HCl) H^+ 197.0926	197.0927
m-F	($C_9H_{13}ClFNO$) C, 52.56%; H, 6.37%; N, 6.81%	C, 52.85%; H, 6.50%; N, 6.80%	(M-HCl)H^+ 170.1007	170.9890
m-Cl	($C_9H_{13}Cl_2NO$) C, 48.67%; H, 5.90%; N, 6.31%	C, 48.53%; H, 5.88%; N, 6.28%	(M-HCl)H^+ 186.0686	186.0684
m-Br	($C_9H_{13}ClBrNO$) C, 40.55%; H, 4.92%; N, 5.25	C, 40.64%; H, 5.09%; N, 5.26%	(M-HCl)H^+ 230.018	230.018
m-I	($C_9H_{13}ClINO$) C, 34.47%; H, 4.18%; N, 4.47%	C, 34.67%; H, 3.97%; N, 4.33%	(M-HCl)H^+ 278.0042	278.0043
m-NO_2	($C_9H_{13}ClN_2O_3$) C, 46.46%; H, 5.63%; N, 12.04%	C, 46.32%; H, 5.51%; N, 11.97%	(M-HCl)H^+ 197.0926	197.0925
p-F	($C_9H_{13}ClFNO$) C, 52.56%; H, 6.37%; N, 6.81%	C, 52.15%; H, 6.30%; N, 6.77%	(M-HCl)H^+ 170.1007	170.1020
p-Cl	($C_9H_{13}Cl_2NO$) C, 48.67%; H, 5.90%; N, 6.31%	C, 48.64%; H, 5.93%; N, 6.21%	(M-HCl)H^+ 186.0686	186.0681
p-Br	($C_9H_{13}ClBrNO$) C, 40.55%; H, 4.92%; N, 5.25%	C, 40.42%; H, 4.86%; N, 5.13%	(M-HCl)H^+ 230.018	230.018
p-I	($C_9H_{13}ClINO$) C, 34.47%; H, 4.18%; N, 4.47%	C, 34.68%; H, 3.98%; N, 4.27%	(M-HCl) 276.9964	276.9957
p-NO_2	($C_9H_{13}ClN_2O_3$) C, 46.46%; H, 5.63%; N, 12.04%	C, 46.36%, H, 5.55%; N, 11.93%	(M-HCl) 196.0848	196.0834

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Another similarity between the **3** and **4** series of compounds is the effect of the *meta*-iodo analogue; in both series this is the best inhibitor. Also, the *ortho*- and *para*-nitro analogues are the next-to-the-worst and worst inhibitors, respectively, in the **3** series and are the third and second worst inhibitors, respectively, in the **4** series. Unexpectedly, the *ortho*-iodo analogue is the worst inhibitor in the **4** series (even worse than the *para*-nitro analogue), but it is one of the better inhibitors in the **3** series. Unlike MAO A, in which the *meta*- and *para*-positions have a considerable negative effect on binding to MAO A relative to the *ortho*-position, there is little difference in the binding at MAO B regardless of the position of the substituent on the ring.

All but the *ortho*- and *para*-nitro analogues are selective MAO B inhibitors. This is consistent with our earlier results obtained with the *meta*-chloro analogue (**1**),[8] but is contrary to the results of Fuller and coworkers[9] for the corresponding *N*-cyclopropyl analogues (**2**), which are MAO A selective. The cyclopropyl group must participate in an important binding interaction with the active site of MAO A that is not present in MAO B. The results in the present study confirm the selectivity of the *meta*-chloro analogue; in fact, it exhibits the highest selectivity of all of the compounds in the **3** series. The selectivity in favor of MAO B inhibition is relatively high for all of the *meta*-substituted analogues of **3** and quite low for all of the *ortho*-substituted and most of the *para*-substituted analogues. Given that the antiparkinsonian drug selegiline has a reversible K_i selectivity (MAO B/MAO A) of only 39,[7] the selectivities described here are quite good.

In conclusion, aminoethyl substituted benzyl ethers (**3**) are, in general, selective inhibitors of MAO B over MAO A. The most effective and selective inhibitors in this series are the *meta*-substituted ones, which have relative selectivities of up to 153 in favor of MAO B inhibition.

Acknowledgments

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