Synthesis, Structure, and Neuroprotective Properties of Novel Imidazolyl Nitrones

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A new series of imidazolyl nitrones spin traps has been synthesized and evaluated pharmacologically. The salient structural feature of these molecules is the presence of an imidazole moiety substituted by aromatic or heteroaromatic cycles. This connectivity imparts to the nitrone superior neuroprotective properties in vivo and in parallel reduced side effects and toxicity. Thus compound **6a** (a 2-phenylimidazolyl nitrone) administered intraperitoneally protects (80%) mice from lethality induced by an intracerebroventricular administration of *tert*-butyl hydroperoxide (*t*-BHP) an oxidant capable of inducing neurodegenerative processes. Administration of the archetypal nitrone phenyl-*tert*-butyl nitrone (PBN) at an equimolar dose also affords some protection (60%) in this test. However, this activity is accompanied by hypothermia, whereas no such effect is apparent for **6a**. Moreover, previously prepared nonsubstituted or alkyl-substituted imidazolyl nitrones were shown to be extremely toxic to rats in contrast to the compounds prepared in this study. The observed activities in vivo correlate well with the calculated partition coefficients (ClogP) and HOMO energy level.

Introduction

In the past decade, extensive research efforts in pharmaceutical laboratories have been directed toward pathologies implicating an oxidative stress. This disturbance of equilibrium in favor of pro-oxidant systems (oxidative damage potential) is extremely harmful to tissues and organs, by virtue of irreversible molecular modifications of polyunsaturated membrane lipids, proteins, and nucleic acids.[1] In particular, neurones in the brain are very sensitive to oxidative damage due to high levels of 20:4 and 22:6 membrane fatty acid, high oxygen consumption, and low levels of protective antioxidant enzymes or vitamin E.

Antioxidant systems become less efficient with age due to progressive age-associated cellular damage, and therefore, oxidative stress represents one of the most critical pathophysiological factors to consider in the aging brain, in cerebral ischemia, and in other neurodegenerative conditions. The initial biochemical impairments in such diseases are caused by excessive amounts of reactive free radicals, in particular, oxygen free radicals, that can initiate chain reactions leading to the propagation of chemical modifications of macromolecules and ultimately to neuronal cell death.[2]

It has been well-established that organic molecules incorporating a nitrone moiety can act as free radical trapping agents (spin traps) and are capable of opposing oxidative challenges.[3] Indeed, addition of free radicals to the carbon−nitrogen double bond of such molecules occurs very easily, yielding nitroxide radical species, which are generally much more stable (biochemically less harmful) than the original free radical (Scheme 1).

Thus, phenyl *tert*-butyl nitrone (PBN) has been shown to possess a neuroprotective action in several animal models of brain ischemia, to decrease age-related protein oxidation, and to improve memory when administered chronically to mongolian gerbils.[3,4]

However, the operational mechanism of nitrones might not exclusively reside in their capacity to directly scavenge free radicals. Indeed, inhibition of inducible nitric oxide synthase (iNOS) expression, as well as cytokine production, modulation of calcium homeostasis, glutamate regulation, and apoptosis have been documented throughout the literature.[5]

The above chemical and biochemical properties of nitrones as well as their brain penetration and toxicity are influenced by the substitution pattern of these molecules.

For example, PBN (Figure 1) has a greater capacity to cross the blood−brain barrier (BBB) compared with pyridine *N*-oxide *tert*-butyl nitrone (POBN), an oxidated pyridine analogue, as would be expected on the basis of their lipophilicity. Moreover cyclic analogues of PBN have revealed higher activity in a rat endotoxic shock model than the parent compound.[6,7] In an effort to optimize their biological profile, a wide structural diversity of nitrones has been synthesized and investigated.[8,9]

We have recently undertaken the design, synthesis, and pharmacological evaluation of a nitrone series, typified by **6a** (Figure 1), possessing a substituted imidazole moiety as the salient feature of their chemical structure.[10] It was anticipated that the presence of a

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Scheme 1

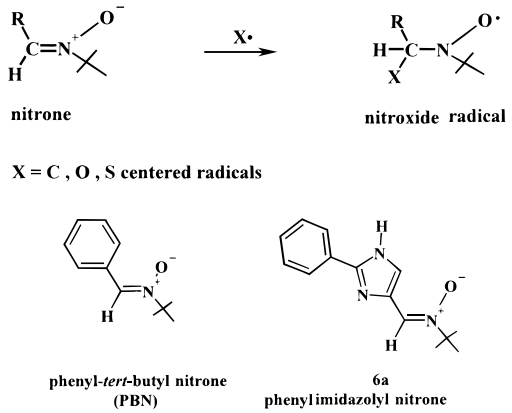


Figure 1. Spin traps: aryl and imidazolyl nitrones.

heterocyclic ring and extended conjugation would improve the bioavailability and reduce the toxicity characteristics of these nitrones in comparison to compounds described in the literature. Indeed, high-level theoretical calculations indicate that these molecules possess a higher energy HOMO (highest occupied molecular orbital) and, depending on the substitution pattern, also a lower energy LUMO (lowest unoccupied molecular orbital) in comparison with PBN (vide infra).[11] Since free radicals react via their SOMO (single occupied molecular orbital), improved spin trapping properties are expected for both heteroatom radicals (SOMO−HOMO control) and carbon atom radicals (SOMO−LUMO control). Moreover, due to its conjugation with the nitrone function, the imidazole ring might also participate in the reaction with free radical species.[12] The nitroxide radical species arising from the trapping of free radicals by these compounds are expected to be even more stable and less toxic than those derived from nitrones described in the literature. In this respect it should be stressed that the presence of an aromatic or heteroaromatic substituent on the imidazole ring is crucial. Indeed unsubstituted or alkyl-substituted imidazoles[13] turned out to be extremely toxic when administered to rats (vide infra). In addition, the BBB penetration as well as clearance and metabolism of such nitrones should be modulated by the nature of the substituent on the imidazole ring and by the hydrogen-bonding capabilities of this ring.[14]

Herein we describe the synthesis and investigation of aryl and heteroaryl substituted imidazolyl nitrones in order to delineate compounds possessing improved neuroprotective effects, a better BBB penetration, and reduced secondary effects.

Chemistry

Two pathways starting with 4-trifluoromethylimidazoles[15] have been used for the preparation of the imidazolyl nitrones described in this study.

Indeed, the transformations of 4-trifluoromethylimidazoles into the corresponding nitriles[15,16] (pathway A) or acids (pathway B) are well-known procedures. Thus 4-cyanoimidazoles **2b−q,s** were prepared in good to excellent yields by treatment of the corresponding 4-trifluoromethylimidazoles (**1b−q,s**) with dilute ammonium hydroxide. The key intermediates, **5b−q,s** (corresponding aldehydes), were then obtained by reduction with diisobutylaluminum hydride in tetrahydrofuran at low temperature (aldehyde **5a** was commercially available). Finally, reaction with *N*-*tert*-butylhydroxylamine hydrochloride in the presence of sodium bicarbonate afforded the desired nitrones **6a−q,s** in good yield.

Alternatively, 4-trifluoromethylimidazoles **1r,t** afforded on treatment with 1 N sodium hydroxide the corresponding 2-arylimidazole-4-carboxylic acids **3r,t**. The Weinreb amides[17a] obtained directly from the acid precursors by reaction with *N*,*O*-dimethylhydroxylamine using 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate as the coupling agent,[17b] led to aldehydes **5r,t** after reduction with lithium aluminum hydride in tetrahydrofuran. Nitrones **6r,t** were then obtained by the same procedure as described above.

Nitrone **11** is related to nitrone **6a** and might be thought as formally arising from the interchange of the substituents on the imidazole ring. Since unlike aldehyde **5a** the related 4-phenylimidazole-2-carboxaldehyde was not available, the procedure indicated in Scheme 3 was used to prepare the corresponding nitrone. Thus commercially available phenylimidazole **7** in *N*,*N*-dimethylformamide was reacted with trityl chloride in the presence of triethylamine [18] to afford *N*-protected imidazole **8**.

The mixture was formylated using butyllithium in *N*,*N*-dimethylformamide to afford **9**, which was then transformed into tritylated nitrone **10** in the usual manner. Removal of the protecting group under acidic conditions afforded the desired nitrone **11**.[18]

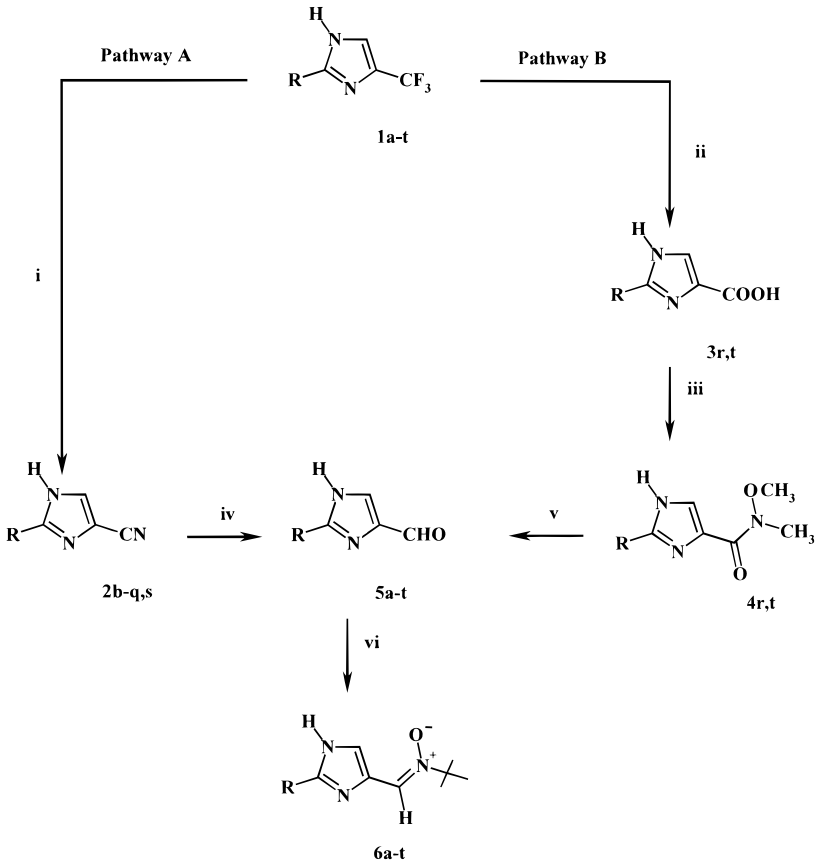
Additionally the two *N*-methylated imidazolyl nitrones were obtained as depicted in Scheme 4. Thus commercially available aldehyde **5a** reacted with dimethyl carbonate in the presence of K_2CO_3 and 18-crown-6[19] to afford the corresponding *N*-methylated π and τ aldehydes **12** and **13**. After chromatographic separation on silica each of these aldehydes was transformed by the usual procedure into nitrones **14** and **15**, respectively. All compounds synthesized in these studies showed spectroscopic characteristics and elemental analysis consistent with their indicated structure (see the Experimental Section).

Results and Discussion

In general, the in vitro antioxidative properties of nitrones are investigated by examining their capacity to protect against Fe^{2+}/H_2O_2-induced lipid peroxidation and to preserve cell viability under oxidative stress.

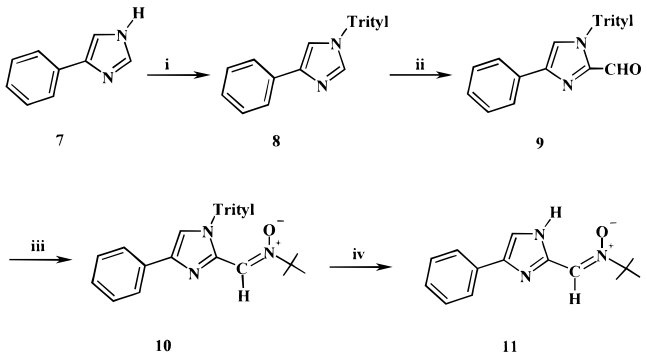
All the nitrones described in the present study demonstrated better results than PBN in a standard lipid peroxidation test (the capacity of nitrones to inhibit Fenton reaction mediated lipid peroxidation in mouse cortical membranes was examined; results are not shown). However, as already documented in the literature,[3−5] and under the present conditions, no correlation between the in vitro and in vivo profiles was found. On the other hand, and albeit a more complex interpretation of the results, it is the later in vivo profile that demonstrated interpretable information concerning the neuroprotective properties of such compounds. Consequently, in the present study we assessed the in vivo properties of the synthesized nitrones by measuring

Scheme 2[a,b]



[a] Reagents: (i) NH_4OH 5%; (ii) 1 N NaOH, Δ; (iii) TBTU/DIPEA/CH_3NHOMe/CH_2Cl_2, rt; (iv) DIBALH/THF, −78 °C; (v) $LiAlH_4$/THF, −10 °C; (vi) *t*-BuNHOH·HCl/$NaHCO_3/C_2H_5OH$, Δ. [b] Letter designation refers to substituents indicated in Table 1.

Scheme 3[a]



[a] Reagents: (i) trityl chloride/Et_3N/DMF, rt; (ii) *n*-BuLi in hexane/DMF, 0 °C; (iii) *t*-BuNHOH·HCl/$NaHCO_3$/EtOH, Δ; (iv) AcOH/EtOH, rt.

their capacity to oppose lethality induced in mice by intracerebroventricular (icv) injection of *tert*-butyl hydroperoxide (*t*-BHP), an oxidative agent known to produce apoptotic-type neurodegeneration [20] (see the Experimental Section for details). Since a major drawback of antioxidants described in the literature is the potential induction of whole-body hypothermia at neuroprotective doses, the influence of all compounds on body temperature was investigated (see the Experimental Section for details). Table 1 below summarizes the biological results obtained with the various nitrones described in this study, as well as their respective HOMO energies[21] and calculated partition coefficients (ClogP).[22]

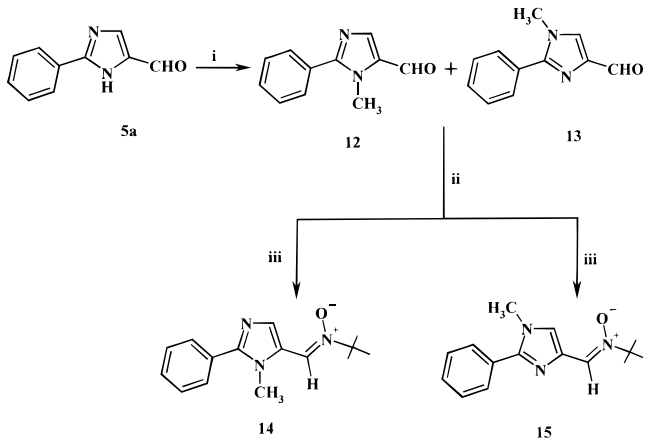
An ideal nitrone would provide a significant protection in the *t*-BHP test but without generating hypothermia at protective doses. Thus compound **6a** produced in the above test nearly 80% survival without any significant hypothermia at the tested doses, whereas the percentage survival provided by PBN (≅60%) is accompanied by a lowering of body temperature (≅−1 °C).

Interestingly, compound **11**, a regioisomer of **6a**, is devoid of any protective effects and also generates hypothermia (≅−1.5 °C). Moreover this compound, found to be the most potent antioxidant in the lipid peroxidation assay, is the best example for the fact that such experiments are poorly representative when considering whole animals. Similarly, striking differences are also observed when analyzing the results obtained with the *N*-methylated imidazole regioisomers **14** and **15**. Indeed, while no protection, but significant hypothermia, was obtained with the former, a marked protective effect (lower than with **6a** but comparable with PBN) with slight hypothermia was observed with the latter; both these compounds demonstrated very low activity in the lipid peroxidation test.

A close examination of the structures, indicated in Table 1, reveals a clear dependence of the protective effect and of the hypothermia on the nature of the imidazole substituent. Thus compounds bearing naphthyl substituents (**6b,c**) demonstrated excellent protection but also significant hypothermia.

Molecules possessing heteroaromatic substituents on the imidazole ring demonstrated an important decrease in protection, despite the presence of hypothermia (**6d**−

Scheme 4[a]



[a] Reagents: (i) $(CH_3O)_2CO$, K_2CO_3, 18-crown-6, Δ; (ii) chromatographic separation SiO_2, 230−400 mesh, toluene/AcOEt/THF, 94:5:1; (iii) *t*-BuNHOH·HCl/$NaHCO_3$/EtOH, Δ.

k). Finally, substitution of the phenyl ring in **6a** maintained a high degree of protection with variable levels of hypothermia (**6l**−**t**). It should be emphasized that in our hands nitrones lacking substituents or having alkyl substituents on the imidazole ring[13] not only were ineffective in the *t*-BHP test but also demonstrated major toxicity. Indeed black urines, myorelaxation, catatonia and tremors, were observed after oral administration of these nitrones to rats (600 mg/kg). No such effects were observed for our compounds tested at an equivalent dose.

To gain a deeper understanding of the biological behavior of these compounds, the dependence of the neuroprotection and hypothermia on calculated physicochemical parameters (ClogP and HOMO energies, Table 1) was examined. The above correlations can be conveniently visualized as in Figure 2, whereby the area of the circle is directly proportional to the magnitude of the determined biological effect (compounds without any activities do not appear).

Two principal subsets can be distinguished (convergent dotted lines): the first subset includes PBN and phenylimidazolyl nitrones substituted by electron-withdrawing groups. These compounds are characterized by their relatively low energy HOMO. The level of neuroprotection observed in this subset is comparatively large, PBN being the least effective; the second subset includes unsubstituted phenylimidazolyl nitrones, phenylimidazolyl nitrones substituted by electron-donor groups, heteroaryl-substituted imidazolyl nitrones and *N*-methylated imidazolyl nitrones. All these molecules have a higher energy HOMO. Marked levels of protection were observed for **6a** and related compounds, whereas low or negligible central activities were observed for the heteroaryl-substituted imidazolyl nitrones.

The two naphthyl isomers **6b** and **6c**, situated near the convergence of the two dotted lines, have a high-energy HOMO and exhibit excellent levels of protection.

There is clearly a trend toward higher protection when the HOMO energy is higher and this is particularly apparent for the second subset described above.

In general, lipophilic compounds are known to possess higher central nervous system (CNS) activities and this trend is also observed in Figure 2. Indeed the more active compounds in the *t*-BHP test have ClogP values above 1, the optimum value being situated between 1.5 and 2.

Partial least squares algorithm (PLS, see Experimental Section) led to the following quantitative structure−activity relationship equation for the *t*-BHP test:

$$\%\ \text{neuroprotection} = 33.2 \times \text{ClogP} - 2.15 \times E_{HOMO} - 379.43 \quad (1)$$

$$n = 23 \quad r^2 = 0.73 \quad r = 0.85 \quad q^2 = 0.62$$

$$\text{standard error of estimate} = 19.38$$

$$\text{standard error of prediction cross-validated} = 22.71$$

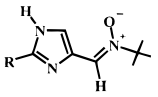
The ClogP parameter alone explains 64% of the activity variation in the *t*-BHP test ($r^2 = 0.64$), whereas no correlation was observed with only HOMO energies. A different perspective of the data was obtained by plotting calculated protection levels (from eq 1) versus measured activities (Figure 3, $r^2 = 0.76$, $r = 0.87$). The major outlier(s) from the fitted line appear to be compounds **11** and **14**, regioisomers of **6a** and **15**, respectively. Besides the possible difference in experimental lipophilicity, the different connectivity found in **11** and **14** might also induce changes in metabolic and clearance factors which are not apparent in the above equation. From a strictly quantitative point of view, better correlations could be obtained by ignoring PBN and outlier(s). However, it is more general and realistic to take into consideration all studied nitrones and to emphasize factors impacting on the pharmacological profile.

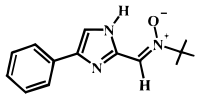
The correlation involving hypothermia is shown in Figure 4. Again the same two subsets, previously described, can be distinguished. Molecules in the first subset (PBN and substituted phenylimidazolyl nitrones) display larger hypothermia effects than molecules in the second subset. Electron-withdrawing-group substitution in phenylimidazolyl nitrones leads to a dramatic increase in hypothermia (e.g. **6l**). The differences between regioisomers (e.g. **6b** and **6c**, **6a** and **11**) are again clearly apparent. Contrary to the *t*-BHP test, no meaningful quantitative structure−activity relationship (QSAR) could be obtained for the hypothermia effect. However, the protective effect, as seen in the *t*-BHP test, and hypothermia are clearly distinguishable, where the best profile in this respect was demonstrated by **6a**, **6c**, **6t**, and **15**.

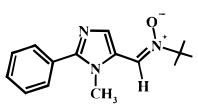
Conclusion

A series of new aryl-substituted imidazolyl nitrones was synthesized and evaluated in two in vivo tests. These compounds proved to be better neuroprotective agents (*t*-BHP test) with less hypothermia and toxicity than previously described spin trappers (e.g. PBN and unsubstituted and alkyl-substituted imidazolyl nitrones). The neuroprotective profile in vivo is strongly dependent on ClogP calculated partition coefficient. An additional parameter influencing biological behavior is the HOMO energy level. A meaningful structure−activity equation that links the above two parameters with the percentage of neuroprotection could be obtained

Table 1. Structure−Activity Profile


6a-t


11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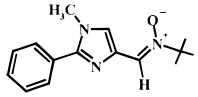

15

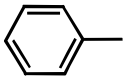
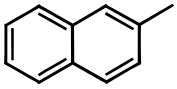
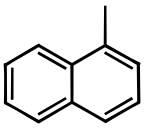
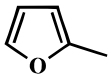
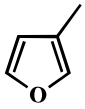
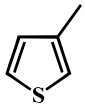
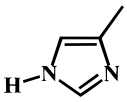
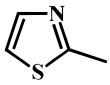
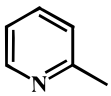
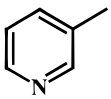
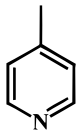
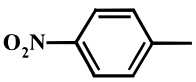
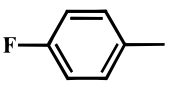
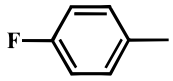
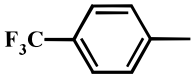
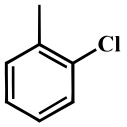
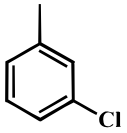
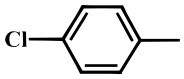
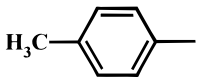
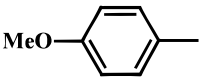
Compound	R	ClogP	HOMO (Kcal/mol)	% Neuroprotection measured [a,e]	% Neuroprotection predicted [b,e]	Hypothermia [c,e] (°C)
6a		1.25	-179	78	47	0.33
6b		2.43	-176	94	80	-1.62
6c		2.43	-177	75	82	-0.52
6d		0.64	-179	15	26	-0.72
6e		0.43	-182	30	26	-0.78
6f		0.93	-180	40	39	-0.48
6g		-0.58	-173	0	0 (-25.66)[d]	-0.13
6h		-0.14	-184	0	12	-0.38
6i		0.05	-180	0	10	-0.36
6j		-0.16	-184	0	10	-0.75
6k		-0.16	-187	24	18	-0.49
6l		1.01	-191	93	64	-1.89
6n		1.4	-182	67	58	-2.01

Table 1 (Continued)

Compound	R	ClogP	HOMO (Kcal/mol)	% Neuroprotection measured [a,e]	% Neuroprotection predicted [b,e]	Hypothermia [c,e] (°C)
6n		1.4	-182	67	58	-2.01
6o		2.15	-187	80	95	-2.16
6p		1.72	-184	71	74	-1.91
6q		1.97	-184	89	81	-1.66
6r		1.97	-183	89	70	-1.32
6s		1.75	-177	66	59	-1.24
6t		1.27	-174	53	37	-0.53
11	-	1.25	-177	0	42	-1.42
14	-	1.2	-175	0	38	-0.69
15	-	1.2	-178	50	44	-0.3
PBN	-	1.23	-191	57	73	-0.90

[a] See also the Experimental Section. Nitrones were administered at 150 mg/kg, 30 min before injection of *t*-BHP. Indicated are percentage survival at 2 h. [b] Calculated from eq 1. [c] See also the Experimental Section. Indicated are temperature differences 30 min after 150 mg/kg ip administration of the corresponding nitrone. [d] Negative value set to 0%. [e] To take into consideration differences in molecular weight, figures in these columns were obtained by multiplying the actual measured values by the ratio of the molecular weight for the compound under consideration and the highest molecular weight in the series (compound **6o**).

for the *t*-BHP test. Finally, it could be shown that the neuroprotective effect and the hypothermia effect can be separated.

Experimental Section

Abbreviations: pyridine *N*-oxide *tert*-butyl nitrone (POBN), *tert*-butyl hydroperoxide (*t*-BHP), phenyl *tert*-butyl nitrone (PBN), inducible nitric oxide synthase (iNOS), single occupied molecular orbital (SOMO), lowest unoccupied molecular orbital (LUMO), highest occupied molecular orbital (HOMO), intracerebroventricular (icv), blood-brain barrier (BBB), diisobutylaluminum hydride (DIBALH), 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), central nervous system (CNS), partial least squares (PLS), quantitative structure−activity relationships (QSAR), thin-layer chromatography (TLC), flash chromatography (FC), Austin Method 1 (AM_1), diisopropylethylamine (DIPEA), *N*,*N*-dimethylformamide (DMF), and tetrahydrofuran (THF).

Chemistry. Unless indicated otherwise, reagents and solvents were obtained from commercial sources and used as received. When required, reactions were conducted under an inert atmosphere. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F-254 plates, spots being visualized by UV, light, or I_2 vapors. HPLC analyses were performed using Rainin pumps, a UV detector, and Hypersil preparative columns. Normal and flash chromatography (FC) was carried out using Merck silica gel (70−230 or 230−400 mesh). All final products were obtained as crystalline solids. Yields are of purified compound and were not optimized. Melting points were determined on a Büchi 535 capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a AC 200, AM 300 or AMX 500 Bruker spectrometer using $CDCl_3$ or DMSO-d_6 as solvent; chemical shifts (δ) are reported in ppm relative to tetramethylsilane (0 ppm) and the following multiplicity abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Elemental analyses were obtained on a Carlo Erba 1108 combustion apparatus; chlorine elemental analyses were performed with a Metler DL 70 titration potentiometer.

Preparation of 4-Trifluoromethylimidazoles 1 (General Procedure A). Compounds **1i**, **1j**, **1k, 1l, 1m, 1n, 1p,**

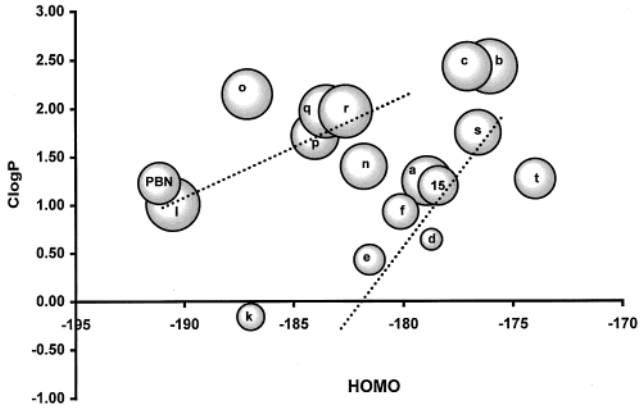


Figure 2. Plot of neuroprotective action vs ClogP and HOMO energy for nitrones in Table 1. The circle area is proportional to the percentage of protection in the *t*-BHP test. Labels correspond to compounds **6a**−**f** and **6k**−**t**. (Compounds **6g**−**j,m**, **11**, and **14**, which do not reveal any protection, are not shown.)

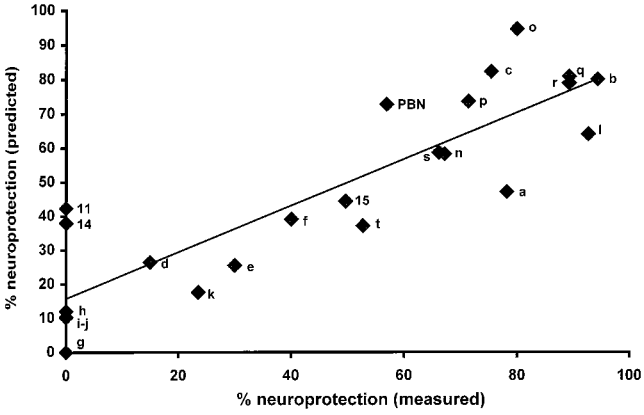


Figure 3. Plot of measured vs predicted neuroprotection (*t*-BHP test, percentage survival). Predicted values were calculated from eq 1. Labels correspond to nitrones **6a**−**t**.

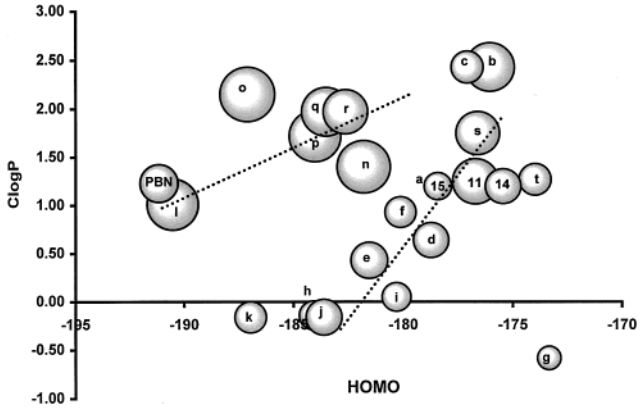


Figure 4. Plot of induced hypothermia vs Clog P and HOMO energy for nitrones in Table 1. The circle area is proportional to the hypothermia effect (absolute value). Labels correspond to compounds **6a**−**t**.

1q, 1r, and **1t** are described in the literature. Other compounds described in this work have been synthesized in the same manner using the procedure described below.

1,1-Dibromo-3,3,3-trifluoroacetone (1 equiv) is added to a solution of $NaOAc \cdot 3H_2O$ (2 equiv) in H_2O (∼40 mL/100 mmol), and the mixture is stirred and heated on a steam bath for 30 min. After cooling, the appropriate aldehyde (0.8 equiv) in methanol (∼40 mL/100 mmol) containing concentrated ammonium hydroxide (∼10 mL/100 mmol) is added and the reaction is stirred for 20 h at room temperature. The precipitated product is filtered, washed with water, and dried.

2-(2-Naphthyl)-4-trifluoromethyl-*1H*-imidazole (1b): Yield 4.5 g (53%); mp 142−144 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 8.6 (s, 1H), 8.2 (d, 1H), 8.1 (m, 4H), 7.6 (m, 2H). Anal. ($C_{14}H_9F_3N_2$) C, H, N.

2-(1-Naphthyl)-4-trifluoromethyl-*1H*-imidazole (1c): Yield 7.2 g (43%); mp >240 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.3 (bs, 1H), 8.8 (m, 1H), 8.1 (m, 3H), 7.85 (d, 1H), 7.6 (m, 3H). Anal. ($C_{14}H_9F_3N_2$) C, H, N.

2-(2-Furyl)-4-trifluoromethyl-*1H*-imidazole (1d): Yield 3.7 g (61%); mp 221−225 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) 10.0 (m, 1H), 7.45, 7.35 (dd, 2H), 7.0 (d, 1H), 6.5 (dd, 1H). Anal. ($C_8H_5F_3N_2O$) C, H, N.

2-(3-Furyl)-4-trifluoromethyl-*1H*-imidazole (1e): Yield 7.5 g (79%); mp 177 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.1 (bs, 1H), 8.25 (m, 1H), 7.85 (m, 1H), 7.6 (m, 1H), 6.93 (m, 1H). Anal. ($C_8H_5F_3N_2O$) C, H, N.

2-(3-Thienyl)-4-trifluoromethyl-*1H*-imidazole (1f): Yield 7.1 g (51%); mp 222−223 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.1 (bs, 1H), 8.1 (dd, 1H), 7.87 (m, 2H), 7.65 (m, 1H). Anal. ($C_8H_5F_3N_2S$) C, H, N, S.

2-(4-*1H*-Imidazolyl)-4-trifluoromethyl-*1H*-imidazole (1g): Yield 5.9 g (65%); mp 137−138 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.0−12.0 (bs, 2H), 7.75, 7.65, 7.60 (3s, 3H). Anal. ($C_7H_5F_3N_4$) C, H, N.

2-(2-Thiazolyl)-4-trifluoromethyl-*1H*-imidazole (1h): Yield 4.5 g (50%); mp 197−198 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.70 (bs, 1H), 8.05−7.9 (m, 2H), 8.0 (m, 1H). Anal. ($C_7H_4F_3N_3S$) C, H, N, S.

2-(2-Pyridyl)-4-trifluoromethyl-*1H*-imidazole (1i): Yield 4.4 g (33%); mp 160−161 °C (lit.[15] mp 156−157 °C); ^{1}H NMR (DMSO-d_6, 300 MHz) 13.5 (bs, 1H), 8.65 (ddd, 1H), 8.10 (dt, 1H), 7.95 (td, 1H), 7.8 (dd, 1H), 7.45 (ddd, 1H). Anal. ($C_9H_6F_3N_3$) C, H, N.

2-(3-Pyridyl)-4-trifluoromethyl-*1H*-imidazole (1j): Yield 7.3 g (55%); mp 228−229 °C (lit.[15] mp 228−228.5 °C); ^{1}H NMR (DMSO-d_6, 300 MHz) 13.5 (bs, 1H), 9.1 (dd, 1H), 8.6 (dd, 1H), 8.3 (ddd, 1H), 8.0 (d, 1H), 7.55 (ddd, 1H). Anal. ($C_9H_6F_3N_3$) C, H, N.

2-(4-Pyridyl)-4-trifluoromethyl-*1H*-imidazole (1k): Yield 3.2 g (48.5%); mp 210−214 °C (lit.[15] mp 211−212 °C); ^{1}H NMR (DMSO-d_6, 200 MHz) 13.6 (bs, 1H), 8.7 (d, 2H), 8.1 (s, 1H), 7.9 (d, 2H). Anal. ($C_9H_6F_3N_3$) C, H, N.

2-(4-Nitrophenyl)-4-trifluoromethyl-*1H*-imidazole (1l): Yield 6.2 g (25%); mp 197 °C (lit.[15] mp 195−196.5 °C); ^{1}H NMR (DMSO-d_6, 200 MHz) 13.59 (bs, 1H), 8.4 (d, 2H), 8.2 (d, 2H), 8.05 (bs, 1H). Anal. ($C_{10}H_6F_3N_3O_2$) C, H, N.

2-(4-Dimethylaminophenyl)-4-trifluoromethyl-*1H*-imidazole (1m): Yield 2.1 g (13%); mp >240 °C (lit.[15] mp 264−265 °C); ^{1}H NMR (DMSO-d_6, 200 MHz) 12.75 (bs, 1H), 7.81 (d, 1H), 7.77 (s, 1H), 7.75 (d, 2H), 6.79 (d, 1H), 2.97 (s, 6H). Anal. ($C_{12}H_{12}F_3N_3$) C, H, N.

2-(4-Fluorophenyl)-4-trifluoromethyl-*1H*-imidazole (1n): Yield 5.2 g (58%); mp 203−205 °C (lit.[15] mp 206.5−207.5 °C); ^{1}H NMR (DMSO-d_6, 200 MHz) 13.2 (bs, 1H), 8.0 (dd, 2H), 7.9 (bs, 1H), 7.3 (dd, 2H). Anal. ($C_{10}H_6F_4N_2$) C, H, N.

2-(4-Trifluoromethylphenyl)-4-trifluoromethyl-*1H*-imidazole (1o): Yield 6.7 g (39%); mp 223 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 13.5 (bs, 1H), 8.2 (d, 2H), 8.02 (m, 1H), 7.82 (d, 2H). Anal. ($C_{11}H_6F_6N_2$) C, H, N.

2-(2-Chlorophenyl)-4-trifluoromethyl-*1H*-imidazole (1p): Yield 7.7 g (66%); mp 168−170 °C (lit.[15] mp 165−167 °C); ^{1}H NMR (DMSO-d_6, 200 MHz) 12.90 (bs, 1H), 7.9 (s, 1H), 7.8 (m, 1H), 7.6 (m, 1H), 7.5 (m, 2H). Anal. ($C_{10}H_6ClF_3N_2$) C, H, Cl, N.

2-(3-Chlorophenyl)-4-trifluoromethyl-*1H*-imidazole (1q): Yield 8.9 g (88%); mp 189−191 °C (lit.[15] mp 186.5−187.5 °C); ^{1}H NMR (DMSO-d_6, 200 MHz) 12.3 (m, 1H), 8.1 (s, 1H), 8.0 (s, 1H), 7.9 (dd, 1H), 7.7 (s, 1H), 7.6 (b, 1H). Anal. ($C_{10}H_6ClF_3N_2$) C, H, Cl, N.

2-(4-Chlorophenyl)-4-trifluoromethyl-*1H*-imidazole (1r): Yield 7.2 g (88%); mp 218−221 °C (lit.[15] mp 228−230 °C); ^{1}H

NMR (DMSO-d_6, 200 MHz) 13.0 (m, 1H), 8.0 (d, 2H), 7.95 (s, 1H), 7.6 (d, 2H). Anal. ($C_{10}H_6ClF_3N_2$) C, H, Cl, N.

2-(*p*-Tolyl)-4-trifluoromethyl-*1H*-imidazole (1s): Yield 3.4 g (48%); mp 221−222 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.0 (bs, 1H), 7.9 (m, 3H), 7.3 (d, 2H), 2.4 (s, 3H). Anal. ($C_{11}H_9F_3N_2$) C, H, N.

2-(4-Methoxyphenyl)-4-trifluoromethyl-*1H*-imidazole (1t): Yield 3.8 g (51%); mp 201−203 °C (lit.[15] mp 204−206 °C); ^{1}H NMR (DMSO-d_6, 200 MHz) 12.01 (bs, 1H), 7.9 (d, 2H), 7.8 (m, 1H), 7.05 (d, 2H), 3.8 (s, 3H). Anal. ($C_{11}H_9F_3N_2O$) C, H, N.

Preparation of 4-Cyanoimidazoles 2 (General Procedure B). Compounds **2d**, **2f**, **2g**, and **2j** are described in the literature. Other compounds described in this work have been synthesized in the same manner using the procedure described below.

The 4-trifluoromethylimidazoles **1** (1 equiv) in MeOH (10 mL/mmol) containing 5% ammonium hydroxide (20 mL/mmol) were heated and stirred at 60 °C for 24 h, followed by concentration of the reaction mixture under reduced pressure. The precipitated product is filtered washed with water and dried.

2-(2-Naphthyl)-4-cyano-*1H*-imidazole (2b): Yield 2.4 g (87%); mp 219 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.6 (bs, 1H), 8.6 (s, 1H), 8.4 (s, 1H), 8.10 (m, 4H), 7.60 (m, 2H). Anal. ($C_{14}H_9N_3$) C, H, N.

2-(1-Naphthyl)-4-cyano-*1H*-imidazole (2c): Yield 3.3 g (62%); mp 239 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.5 (bs, 1H), 8.75 (m, 1H), 8.35 (s, 1H), 8.05 (d, 1H), 8.00 (m, 1H), 7.82 (dd, 1H), 7.60 (m, 3H). Anal. ($C_{14}H_9N_3$) C, H, N.

2-(2-Furyl)-4-cyano-*1H*-imidazole (2d): Yield 4.8 g (63%); mp 225−229 °C (lit.[16a] mp 229−232 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) 13.5 (bs, 1H), 8.2 (s, 1H), 7.9 (d, 1H), 7.0 (dd, 1H), 6.7 (dd, 1H). Anal. ($C_8H_5N_3O$) C, H, N.

2-(3-Furyl)-4-cyano-*1H*-imidazole (2e): Yield 0.4 g (51%); mp 177−180 °C (lit.[16b] mp 198−202 °C); ^{1}H NMR (DMSO-d_6, 200 MHz) 13.3 (bs, 1H), 8.25 (d, 1H), 8.25 (s, 1H), 7.75 (t, 1H), 7.0 (d, 1H). Anal. ($C_8H_5N_3O$) C, H, N.

2-(3-Thienyl)-4-cyano-*1H*-imidazole (2f): Yield 5.6 g (95%); mp 175 °C (lit.[16b] mp 198−202 °C); ^{1}H NMR (DMSO-d_6, 200 MHz) 13.2 (bs, 1H), 8.1 (s, 1H), 8.02 (m, 1H), 7.55 (m, 2H). Anal. ($C_8H_5N_3S$) C, H, N, S.

2-(4-*1H*-Imidazolyl)-4-cyano-*1H*-imidazole (2g): Yield 2.0 g (77%); mp >240 °C (lit.[16b] mp >260 °C); ^{1}H NMR (DMSO-d_6, 300 MHz) 13.05, 12.4 (bs, 2H), 8.3 (s, 1H), 8.05 (d, 1H), 7.95 (d, 1H). Anal. ($C_7H_5N_5$) C, H, N.

2-(2-Thiazolyl)-4-cyano-*1H*-imidazole (2h): Yield 2.1 g (76%); mp >240 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 14.1 (bs, 1H), 8.3 (s, 1H), 8.05 (d, 1H), 7.95 (d, 1H). Anal. ($C_7H_4N_4S$) C, H, N, S.

2-(2-Pyridyl)-4-cyano-*1H*-imidazole (2i): Yield 2.7 g (84%); mp 233 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.7 (bs, 1H), 8.7 (d, 1H), 8.25 (s, 1H), 8.15 (d, 1H), 8.0 (t, 1H), 7.5 (m, 1H). Anal. ($C_9H_6N_4$) C, H, N.

2-(3-Pyridyl)-4-cyano-*1H*-imidazole (2j): Yield 4.8 g (86%); mp 247 °C (dec) (lit.[16b] mp 215−218 °C); ^{1}H NMR (DMSO-d_6, 200 MHz) 13.6 (bs, 1H), 9.1 (d, 1H), 8.65 (dd, 1H), 8.35 (s, 1H), 8.30 (dt, 1H), 7.5 (s, 1H). Anal. ($C_9H_6N_4$) C, H, N.

2-(4-Pyridyl)-4-cyano-*1H*-imidazole (2k): Yield 2.1 g (84%); mp >240 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 14.0 (bs, 1H), 8.8 (m, 2H), 8.4 (s, 1H), 7.95 (m, 2H). Anal. ($C_9H_6N_4$) C, H, N.

2-(4-Nitrophenyl)-4-cyano-*1H*-imidazole (2l): Yield 3.8 g (74%); mp >240 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 13.6 (bs, 1H), 8.32 (d, 2H), 8.3 (s, 1H), 8.15 (d, 2H). Anal. ($C_{10}H_6N_4O_2$) C, H, N.

2-(4-Dimethylaminophenyl)-4-cyano-*1H*-imidazole (2m): Yield 2.0 g (50%); mp >240 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.1 (bs, 1H), 7.7 (s, 1H), 7.45 (d, 2H), 6.80 (d, 2H), 2.9 (s, 6H). Anal. ($C_{12}H_{12}N_4$) C, H, N.

2-(4-Fluorophenyl)-4-cyano-*1H*-imidazole (2n): Yield 2.7 g (67%); mp 216−218 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.7 (bs, 1H), 8.21 (s, 1H), 8.0 (dd, 2H), 7.35 (dd, 2H). Anal. ($C_{10}H_6FN_3$) C, H, N.

2-(4-Trifluoromethylphenyl)-4-cyano-*1H*-imidazole (2o): Yield 3.9 g (72%); mp 220−222 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 13.75 (bs, 1H), 8.35 (s, 1H), 8.2 (d, 2H), 7.9 (d, 2H). Anal. ($C_{11}H_6F_3N_3$) C, H, N.

2-(2-Chlorophenyl)-4-cyano-*1H*-imidazole (2p): Yield 3.0 g (52%); mp 153−154 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.3 (bs, 1H), 8.25 (s, 1H), 7.8−7.4 (m, 4H). Anal. ($C_{10}H_6ClN_3$) C, H, N, Cl.

2-(3-Chlorophenyl)-4-cyano-*1H*-imidazole (2q): Yield 3.1 g (42%); mp 173−175 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.5 (bs, 1H), 8.25 (s, 1H), 7.99 (b, 1H), 7.90 (m, 1H), 7.48 (m, 2H). Anal. ($C_{10}H_6ClN_3$) C, H, N, Cl.

2-(*p*-Tolyl)-4-cyano-*1H*-imidazole (2s): Yield 2.3 g (75%); mp 226 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.4 (bs, 1H), 8.2 (s, 1H), 7.85 (d, 2H), 7.3 (d, 2H), 2.3 (s, 3H). Anal. ($C_{11}H_9N_3$) C, H, N.

Preparation of 4-Carboxyimidazoles 3 (General Procedure C). The 4-trifluoromethylimidazoles **1** (1 equiv) are added to 2 N NaOH (∼2.5 mL/mmol) followed by stirring at 90 °C during 1 h. The reaction mixture is brought to pH 6 using 2 N HCl and the precipitated product is filtered, washed with water, and dried.

2-(4-Chlorophenyl)-4-carboxy-*1H*-imidazole (3r): Yield 0.5 g (57%); mp 218 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 8.1 (d, 2H), 7.6 (s, 1H), 7.5 (d, 2H). Anal. ($C_{10}H_7ClN_2O_2$) C, H, N, Cl.

2-(4-Methoxyphenyl)-4-carboxy-*1H*-imidazole (3t): Yield 2.9 g (85%); mp 233−235 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 8.0 (d, 2H), 7.85 (s, 1H), 7.1 (d, 2H), 3.85 (s, 3H). Anal. ($C_{11}H_{10}N_2O_3$) C, H, N.

Preparation of Weinreb Amides 4 (General Procedure D). To a solution of the corresponding carboxylic acids **3** (1 equiv) in dichloromethane (∼10 mL/mmol) were added TBTU (0.4 g/mmol, 1.1 equiv), diisopropylamine (0.64 mL/mmol), and *N*,*O*-dimethylhydroxylamine (0.13 g/mmol, 1.8 equiv), followed by stirring during 20 h at room temperature. The reaction mixture is diluted with dichloromethane (15 mL/mmol) and washed with water. The organic phase is dried on magnesium sulfate, filtered, and concentrated in vacuo. After trituration in diethyl ether the residue is filtered to afford the desired product.

2-(4-Chlorophenyl)-4-(*N*-methyl-*N*-methoxyaminocarbonyl)-*1H*-imidazole (4r): Yield 6.4 g (78%); mp 188−190 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) 11.4 (bs, 1H), 8.0 (d, 2H), 7.8 (s, 1H), 7.4 (d, 2H), 4.85 (s, 3H), 3.4 (s, 3H). Anal. ($C_{12}H_{12}ClN_3O_2$) C, H, N, Cl.

2-(4-Methoxyphenyl)-4-(*N*-methyl-*N*-methoxyaminocarbonyl)-*1H*-imidazole (4t): Yield 2.7 g (78%); mp 138−139 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) 7.9 (d, 2H), 7.7 (s, 1H), 6.95 (d, 2H), 3.9 (s, 6H), 3.4 (s, 3H). Anal. ($C_{13}H_{15}N_3O_3$) C, H, N.

Preparation of Imidazolcarbaldehydes 5. With the exception of **5a**, which is commercially available, all described imidazolcarbaldehydes have been synthesized by one of the two pathways described below.

Pathway A: **From Cyanoimidazoles 2 (General Procedure E).** The corresponding cyanoimidazole (1 equiv) in anhydrous THF (∼2 mL/mmol) is treated under argon at − 78 °C with 1.5 equiv of DIBALH (1.0 M in toluene), followed by stirring for 30 min at − 45 °C and 1 h at 0 °C. Ethanol (0.5 mL/mmol) is added and the stirring is continued for 1 h at 0 °C. The reaction mixture is concentrated to dryness and the residue is flash chromatographed to afford the desired product.

2-(2-Naphthyl)-*1H*-4-imidazolcarbaldehyde (5b): FC with a mixture of dichloromethane and ethanol (99:1); Yield 0.9 g (36%); mp 216 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 13.7 (bs, 1H), 9.85 (s, 1H), 8.55 (s, 1H), 8.3−7.95 (m, 4H), 8.04 (s, 1H), 7.57 (m, 2H). Anal. ($C_{14}H_{10}N_2O$) C, H, N.

2-(1-Naphthyl)-*1H*-4-imidazolcarbaldehyde (5c): FC with a mixture of dichloromethane and ethanol (99:1); Yield 3.4 g (39%); mp >240 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.5 (bs, 1H), 9.7 (s, 1H), 8.3−7.65 (m, 7H), 8.1 (s, 1H). Anal. ($C_{14}H_{10}N_2O$) C, H, N.

2-(2-Furyl)-*1H*-4-imidazolcarbaldehyde (5d): FC with a mixture of dichloromethane and ethanol (97:3); Yield 0.5 g

(49%); mp 215 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.3 (bs, 1H), 9.8 (s, 1H), 8.4 (s, 1H), 8.3−7.3 (m, 3H). Anal. ($C_8H_6N_2O_2$) C, H, N.

2-(3-Furyl)-*1H*-4-imidazolcarbaldehyde (5e): FC with a mixture of dichloromethane and ethanol (97:3); Yield 1.9 g (51%); mp 225 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.5 (bs, 1H), 9.7 (s, 1H), 8.4 (s, 1H), 8.2 (s, 1H), 7.7 (d, 1H), 7.0 (d, 1H). Anal. ($C_8H_6N_2O_2$) C, H, N.

2-(3-Thienyl)-*1H*-4-imidazolcarbaldehyde (5f): FC with a mixture of dichloromethane and ethanol (99:1); Yield 0.6 g (32%); mp 226 °C (dec); ^{1}H NMR (DMSO-d_6, 200 MHz) 13.6 (bs, 1H), 9.8 (s, 1H), 8.4 (s, 1H), 7.9 (d, 1H), 7.7 (m, 2H). Anal. ($C_8H_6N_2OS$) C, H, N, S.

2-(4-*1H*-Imidazolyl)-*1H*-4-imidazolcarbaldehyde (5g): FC with a mixture of dichloromethane and 2N ammoniacal methanol (95:5); Yield 1.9 g (41%); mp >240 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.0, 12.4 (bs, 2H), 9.9 (s, 1H), 8.3 (s, 1H), 7.8 (s, 1H), 7.6 (s, 1H). Anal. ($C_7H_6N_4O$) C, H, N.

2-(2-Thiazolyl)-*1H*-4-imidazolcarbaldehyde (5h): FC with a mixture of dichloromethane and ethanol (98:2); Yield 2.3 g (45%); mp 199−201 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 14.0 (bs, 1H), 9.85 (s, 1H), 8.15 (bs, 1H), 8.0 (d, 1H), 7.9 (d, 1H). Anal. ($C_7H_5N_3SO$) C, H, N, S.

2-(2-Pyridyl)-*1H*-4-imidazolcarbaldehyde (5i): FC with a mixture of dichloromethane and methanol (98:2); Yield 1.2 g (46%); mp 170 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.7 (bs, 1H), 9.8 (s, 1H), 8.7 (d, 1H), 8.15 (td, 1H), 8.12 (s, 1H), 7.9 (td, 1H), 7.5 (dd, 1H). Anal. ($C_9H_7N_3O$) C, H, N.

2-(3-Pyridyl)-*1H*-4-imidazolcarbaldehyde (5j): FC with a mixture of dichloromethane and ethanol (95:5); Yield 1.3 g (51%); mp 175 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.2 (bs, 1H), 9.7 (s, 1H), 9.1 (s, 1H), 8.65 (m, 1H), 8.4 (m, 1H), 8.2 (s, 1H), 7.6 (m, 1H). Anal. ($C_9H_7N_3O$) C, H, N.

2-(4-Pyridyl)-*1H*-4-imidazolcarbaldehyde (5k): FC with a mixture of dichloromethane and ethanol (95:5); Yield 1.1 g (55%); mp 204 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.8 (bs, 1H), 9.8 (s, 1H), 8.7 (d, 2H), 8.15 (s, 1H), 7.9 (d, 2H). Anal. ($C_9H_7N_3O$) C, H, N.

2-(4-Nitrophenyl)-*1H*-4-imidazolcarbaldehyde (5l): FC with a mixture of dichloromethane and ethanol (95:5); Yield 1.4 g (36%); mp >240 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.8 (bs, 1H), 9.8 (s, 1H), 8.5 (d, 2H), 8.35 (s, 1H), 8.2 (d, 2H). Anal. ($C_{10}H_7N_3O_3$) C, H, N.

2-(4-Dimethylaminophenyl)-*1H*-4-imidazolcarbaldehyde (5m): FC with a mixture of toluene and methanol (95:5); Yield 1.0 g (70%); mp 220 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.5 (bs, 1H), 9.8 (s, 1H), 7.85 (d, 2H), 7.75 (s, 1H), 7.6 (d, 2H), 3.0 (s, 6H). Anal. ($C_{12}H_{13}N_3O$) C, H, N.

2-(4-Fluorophenyl)-*1H*-4-imidazolcarbaldehyde (5n): FC with a mixture of dichloromethane and ethanol (95:5); Yield 2.0 g (67%); mp 202−203 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.5 (bs, 1H), 9.8 (s, 1H), 8.15 (s, 1H), 8.15 (dd, 2H), 7.4 (dd, 2H). Anal. ($C_{10}H_7FN_2O$) C, H, N.

2-(4-Trifluoromethylphenyl)-*1H*-4-imidazolcarbaldehyde (5o): FC with a mixture of dichloromethane and ethanol (95:5); Yield 3.7 g (51%); mp 221 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 14.0 (bs, 1H), 9.8 (s, 1H), 8.25 (d, 2H), 8.15 (s, 1H), 7.9 (d, 2H). Anal. ($C_{11}H_7F_3N_2O$) C, H, N.

2-(2-Chlorophenyl)-*1H*-4-imidazolcarbaldehyde (5p): FC with a mixture of dichloromethane and methanol (96:4); Yield 1.5 g (54%); mp 184−185 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 13.2 (bs, 1H), 9.75 (s, 1H), 8.15 (bs, 1H), 7.9 (dd, 1H), 7.62 (dd, 1H), 7.57 (td, 1H), 7.53 (td, 1H). Anal. ($C_{10}H_7ClN_2O$) C, H, N, Cl.

2-(3-Chlorophenyl)-*1H*-4-imidazolcarbaldehyde (5q): FC with a mixture of dichloromethane and methanol (95:5); Yield 1.4 g (45%); mp 178−180 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 13.55 (bs, 1H), 9.76 (s, 1H), 8.1 (d, 1H), 8.1 (s, 1H), 7.98 (m, 1H), 7.5 (m, 2H). Anal. ($C_{10}H_7ClN_2O$) C, H, N, Cl.

2-(*p*-Tolyl)-*1H*-4-imidazolcarbaldehyde (5s): FC with a mixture of dichloromethane and ethanol (96:4); Yield 0.15 g (49%); mp 199−200 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.5 (bs, 1H), 9.8 (s, 1H), 8.1 (m, 3H), 7.3 (d, 2H), 2.3 (s, 3H). Anal. ($C_{11}H_{10}N_2O$) C, H, N.

Pathway B: From Weinreb Amides (General Procedure F). A solution of the corresponding amide **4** (1 equiv) in THF (∼8 mL/mmol) is cooled under argon at −10 °C followed by addition of $LiAlH_4$ (4 equiv, 110 mg/mmol) in one portion. The reaction mixture is stirred for 2 h at 0 °C and then hydrolyzed by addition of wet Na_2SO_4. All solids are filtered out, the liquid is concentrated in vacuo, and the residue is chromatographed to afford the desired product.

2-(4-Chlorophenyl)-*1H*-4-imidazolcarbaldehyde (5r): FC with a mixture of dichloromethane and ethanol (99:1); Yield 0.5 g (20%); mp 207 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 13.5 (bs, 1H), 9.76 (s, 1H), 8.1 (bs, 2H), 8.1 (bs, 1H), 7.6 (d, 2H). Anal. ($C_{10}H_7ClN_2O$) C, H, N, Cl.

2-(4-Methoxyphenyl)-*1H*-4-imidazolcarbaldehyde (5t): FC with a mixture of dichloromethane and methanol (99:1); Yield 0.6 g (48.3%); mp >240 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) 11.0 (m, 1H), 9.75 (s, 1H), 8.0 (d, 2H), 7.85 (s, 1H), 7.0 (d, 2H), 3.85 (s, 3H). Anal. ($C_{11}H_{10}N_2O_2$) C, H, N.

Preparation of Imidazolylnitrones 6 (General Procedure G). The corresponding imidazocarbaldehydes **5** (1 equiv), *tert*-butylhydroxylamine hydrochloride (1.5 equiv, 180 mg/mmol), and $NaHCO_3$ (1.5 equiv, 120 mg/mmol) in ethanol (0.6 mL/mmol) are stirred under argon at 60 °C during 16 h.

The reaction mixture is diluted with dichloromethane (6 mL/mmol). The organic phase is washed with water, dried on $MgSO_4$, and then concentrated in vacuo. The residual oil, quickly taken up into diethyl ether, crystallizes to afford after filtration the desired product.

(*Z*)-α-(2-Phenyl-*1H*-imidazol-4-yl) *N*-*tert*-butyl nitrone (6a): Yield 10.8 g (91%); mp 209−210 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) 13.0 (bs, 1H), 7.95 (s, 1H), 7.8 (d, 2H), 7.65 (dd, 1H), 7.4−7.15 (m, 3H), 1.5 (s, 9H). Anal. ($C_{14}H_{17}N_3O$) C, H, N.

(*Z*)-α-[2-(2-Naphthyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6b): Yield 1.2 g (99%); mp 200−202 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) 13.0 (bs, 1H), 8.4 (s, 1H), 8.1 (dd, 1H), 7.95 (d, 1H), 7.9−7.5 (m, 4H), 7.6 (s, 1H), 7.5 (s, 1H), 1.6 (s, 9H). Anal. ($C_{18}H_{19}N_3O$) C, H, N.

(*Z*)-α-[2-(1-Naphthyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6c): Yield 3.0 g (70%); mp 95 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 12.85 (bs, 1H), 9.05 (m, 1H), 8.5 (s, 1H), 8.05 (dd, 2H), 8.0 (s, 1H), 7.8 (dd, 1H), 7.65 (m, 3H), 1.55 (s, 9H). Anal. ($C_{18}H_{19}N_3O$) C, H, N.

(*Z*)-α-[2-(2-Furyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6d): Yield 1.3 g (49%); mp 103 °C (dec); ^{1}H NMR (DMSO-d_6, 200 MHz) 12.9 (bs, 1H), 8.4 (bs, 1H), 7.9 (s, 1H), 7.9 (d, 1H), 7.0 (d, 1H), 6.7 (m, 1H), 1.55 (s, 9H). Anal. ($C_{12}H_{15}N_3O_2$) C, H, N.

(*Z*)-α-[2-(3-Furyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6e): Yield 1.0 g (71%); mp 160 °C (dec); ^{1}H NMR ($CDCl_3$, 200 MHz), 7.89 (d, 1H, J = 1.5 Hz), 7.58 (s, 1H), 7.37 (m, 1H, J = 1.2 Hz), 7.17 (s, 1H), 6.72 (d, 1H), 1.49 (s, 9H). Anal. ($C_{12}H_{15}N_3O_2$) C, H, N.

(*Z*)-α-[2-(3-Thienyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6f): Yield 0.6 g (58%); mp 197−198 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 12.7 (bs, 1H), 8.4 (d, 1H), 8.0 (d, 1H, J = 4.8 Hz), 7.85 (s, 1H), 7.6 (m, 2H, J = 2.0 Hz), 1.5 (s, 9H). Anal. ($C_{12}H_{15}N_3OS$) C, H, N, S.

(*Z*)-α-[2-(4-*1H*-Imidazolyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6g): Yield 0.75 g (27%); mp 220 °C (dec); ^{1}H NMR (DMSO-d_6, 200 MHz) 12.35 (bs, 2H), 8.2 (bs, 1H), 7.75 (bs, 1H), 7.75 (bs, 1H), 7.5 (bs, 1H), 1.45 (s, 9H). Anal. ($C_{11}H_{15}N_5O$) C, H, N.

(*Z*)-α-[2-(2-Thiazolyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6h): Yield 1.40 g (52%); mp 170 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 13.4 (bs, 1H), 8.4 (s, 1H), 7.95 (d, 1H), 7.9 (s, 1H), 7.85 (d, 1H), 1.5 (s, 9H). Anal. ($C_{11}H_{14}N_4OS$) C, H, N, S.

(*Z*)-α-[2-(2-Pyridyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6i): Yield 0.85 g (55%); mp 172−173 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.0 (bs, 1H), 8.65 (m, 1H), 8.35 (d, 1H), 8.15−7.75 (m, 3H), 7.45 (m, 1H), 1.5 (s, 9H). Anal. ($C_{13}H_{16}N_4O$) C, H, N.

(*Z*)-α-[2-(3-Pyridyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6j): Yield 1.1 g (60%); mp 174−176 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.1 (m, 1H), 9.1 (s, 1H), 8.65 (m, 1H),

8.5 (m, 1H), 8.3 (m, 1H), 7.9 (s, 1H), 7.5 (m, 1H), 1.5 (s, 9H). Anal. ($C_{13}H_{16}N_4O$) C, H, N.

(*Z*)-α-[2-(4-Pyridyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6k): Yield 0.9 g (57%); mp 239−241 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.2 (m, 1H), 8.7 (d, 2H, J = 6.0 Hz), 8.5 (bs, 1H), 7.9 (d, 2H), 7.9 (s, 1H), 1.5 (s, 9H). Anal. ($C_{13}H_{16}N_4O$) C, H, N.

(*Z*)-α-[2-(4-Nitrophenyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6l): Yield 1.0 g (61%); mp 253 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.2 (bs, 1H), 8.5 (bs, 1H), 8.4 (d, 2H, J = 8.5 Hz), 8.2 (d, 2H), 7.9 (m, 1H), 1.5 (s, 9H). Anal. ($C_{14}H_{16}N_4O_3$) C, H, N.

(*Z*)-α-[2-(4-Dimethylaminophenyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6m): Yield 1.0 g (70%); mp 190−192 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 12.45 (bs, 1H), 8.3 (bs, 1H), 7.8 (s, 1H), 7.75 (d, 2H), 6.75 (d, 2H), 2.95 (s, 6H), 1.45 (s, 9H). Anal. ($C_{16}H_{22}N_4O$) C, H, N.

(*Z*)-α-[2-(4-Fluorophenyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6n): Yield 2.0 g (73%); mp 192−194 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 12.81 (bs, 1H), 8.4 (bs, 1H), 7.98 (dd, 2H), 7.85 (s, 1H), 7.3 (t, 2H), 1.49 (s, 9H). Anal. ($C_{14}H_{16}FN_3O$) C, H, N.

(*Z*)-α-[2-(4-Trifluoromethylphenyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6o): Yield 2.0 g (86%); mp 226 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.1 (bs, 1H), 8.5 (m, 1H), 8.2 (d, 2H), 7.8 (s, 1H), 7.8 (d, 2H), 1.5 (s, 9H). Anal. ($C_{15}H_{16}F_3N_3O$) C, H, N.

(*Z*)-α-[2-(2-Chlorophenyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6p): Yield 1.3 g (73%); mp 132−134 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.2 (bs, 1H), 8.05 (bs, 1H), 8.05 (d, 1H), 7.66−7.4 (m, 4H), 1.5 (s, 9H). Anal. ($C_{14}H_{16}ClN_3O$) C, H, N, Cl.

(*Z*)-α-[2-(3-Chlorophenyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6q): Yield 1.5 g (79%); mp 181−183 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 12.95 (bs, 1H), 8.45 (bs, 1H), 8.02 (t, 1H), 7.92 (dt, 1H), 7.87 (s, 1H), 7.5 (t, 1H), 7.42 (ddd, 1H), 1.49 (s, 9H). Anal. ($C_{14}H_{16}ClN_3O$) C, H, N, Cl.

(*Z*)-α-[2-(4-Chlorophenyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6r): Yield 0.48 g (72%); mp 212−215 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.0 (bs, 1H), 8.5 (d, 1H), 8.0 (d, 2H), 7.85 (s, 1H), 7.6 (d, 2H), 1.5 (s, 9H). Anal. ($C_{14}H_{16}ClN_3O$) C, H, N, Cl.

(*Z*)-α-[2-*p*-Tolyl-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6s): Yield 10.8 g (86%); mp 174−176 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) 12.7 (bs, 1H), 7.8 (d, 2H), 7.7 (bs, 1H), 7.5 (bs, 1H), 7.2 (d, 2H), 2.35 (s, 3H), 1.6 (s, 9H). Anal. ($C_{15}H_{19}N_3O$) C, H, N.

(*Z*)-α-[2-(4-Methoxyphenyl)-*1H*-imidazol-4-yl] *N*-*tert*-butyl nitrone (6t): Yield 0.8 g (97%); mp 198−201 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 12.7 (bs, 1H), 8.4 (bs, 1H), 7.95 (d, 2H, J = 8.8 Hz), 7.85 (s, 1H), 7.05 (d, 2H), 3.8 (s, 3H), 1.5 (s, 9H). Anal. ($C_{15}H_{19}N_3O_2$) C, H, N.

(*Z*)-α-[4-Phenyl-*1H*-imidazol-2-yl] *N*-*tert*-butyl nitrone (11). (a) Tritylated Imidazole 8. To a solution containing 9.9 g (6.9 mmol) of commercially available 4-phenyl-*1H*-imidazole (**7**) in 50 mL of DMF and 10 mL of triethylamine was added under an argon atmosphere 21.3 g (7.6 mmol) of trityl chloride in 150 mL of DMF. After stirring for 4 h at room temperature 2.5 L of water is added and the obtained gummy precipitate is triturated with ether. Filtering followed by drying affords 25.0 g (94%) of the expected compound: mp 198−190 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) 7.80 (d, 1H), 7.74 (s, 2H), 7.55 (s, 1H), 7.40 (m, 18H). Anal. ($C_{28}H_{22}N_2$) C, H, N.

(b) Tritylated Carbaldehyde 9. 25 mL of *n*-BuLi (1.6 M in hexane) is added over a 15 min period to a solution of 9.93 g (25.7 mmol) of **8** dissolved in 250 mL of anhydrous THF, and the mixture is stirred under argon at 0 °C. After 2 h, 8 mL of DMF is added at 0 °C over a period of 5 min, followed by stirring for 2 h more at room temperature. The THF is removed in vacuo, water (250 mL) is added, followed by extraction with dichloromethane. Drying ($MgSO_4$), concentration in vacuo, and crystallization from diethyl ether afford 7.3 g (68.5%) of carbaldehyde **9**: mp 187 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 9.20 (s, 1H), 7.79 (d, 2H), 7.54 (s, 1H), 7.43 (m, 11H), 7.32 (t, 1H), 7.17 (m, 6H). Anal. ($C_{29}H_{22}N_2O$) C, H, N.

(c) Tritylated Nitrone 10. A solution of 7.3 g (17.6 mmol) of **9**, 3.2 g of *tert*-butylhydroxylamine hydrochloride, and 2.1 g of sodium bicarbonate in 20 mL of ethanol is heated and stirred overnight at 60 °C. The reaction mixture is diluted with 200 mL of dichloromethane, followed by washing with water. Drying of the organic phase ($MgSO_4$), removal of the solvent in vacuo, and crystallization from diethyl ether afforded 5.8 g (68%) of the desired compound: mp 224−225 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) 7.68 (d, 2H), 7.45 (m, 13H), 7.33 (t, 1H), 7.16 (m, 6H), 0.95 (s, 9H). Anal. ($C_{33}H_{31}N_3O$) C, H, N.

(d) Nitrone 11. A solution of 5.6 g (11.5 mmol) of **10** in 60 mL of ethanol containing 5 mL of acetic acid is heated at reflux during 5 h. The reaction mixture is concentrated under reduced pressure, and dichloromethane is added, followed by washing with 5% $NaHCO_3$ and then with water. The organic phase is dried over $MgSO_4$ and concentrated. Crystallization of the residual oil from diethyl ether affords 2.0 g (71%) of the final compound **11**: mp 166 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) 13.1 (bs, 1H), 7.95 (s, 1H), 7.8 (d, 2H), 7.65 (dd, 1H), 7.4−7.15 (m, 3H), 1.5 (s, 9H). Anal. ($C_{14}H_{17}N_3O$) C, H, N.

(*Z*)-α-[1-Methyl-2-phenyl-*1H*-imidazol-5-yl] *N*-*tert*-butyl nitrone (14) and (*Z*)-α-[3-Methyl-2-phenyl-*1H*-imidazol-5-yl] *N*-*tert*-butyl nitrone (15). (a) Carbaldehydes 12 and 13. Commercially available **5a** (6.3 g, 36.6 mmol) in 70 mL of dimethyl carbonate containing 7.7 g of potassium carbonate and 0.5 g of crown ether (18-crown-6) are stirred at 80 °C for 80 h. After cooling to room temperature, the insolubles are filtered off and washed with a mixture of dichloromethane and methanol (8:2). The filtrate and washings are concentrated, and the residue is flash chromatographed (SiO_2, 230−400 mesh) using a mixture of toluene, ethyl acetate, and tetrahydrofuran (94:5:1) to afford 1.5 g (22%) of carbaldehyde **12** [mp 87−89 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 9.74 (s, 1H), 8.0 (s, 1H), 7.72 (m, 2H), 7.5 (m, 3H), 3.91 (s, 3H). Anal. ($C_{11}H_{10}N_2O$) C, H, N] and 1.2 g (17.6%) of carbaldehyde **13** [mp 98−100 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) 9.85 (s, 1H), 8.15 (s, 1H), 7.75 (dd, 2H), 7.5 (m, 3H), 3.8 (s, 3H). Anal. ($C_{11}H_{10}N_2O$) C, H, N].

(b) Nitrone 14. Carbaldehyde **12** (1.4 g, 7.5 mmol), 1.4 g of *tert*-butylhydroxylamine hydrochloride, and 1 g of sodium bicarbonate in 10 mL of ethanol are heated and stirred at 60 °C during 16 h under an argon atmosphere. The reaction mixture is diluted with 100 mL of dichloromethane, and the organic phase is washed with water, dried ($MgSO_4$), and then concentrated under reduced pressure. The oily residue is quickly taken up in ether to afford after crystallization 1.2 g (62%) of product **14**: mp 155−157 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 8.4 (s, 1H), 7.8 (s, 1H), 7.7 (dd, 2H), 7.55 (m, 3H), 3.75 (s, 3H), 1.55 (s, 9H). Anal. ($C_{15}H_{19}N_3O$) C, H, N.

(c) Nitrone 15. The procedure described for **14** was again employed: Yield 1.0 g (51%); mp 178−180 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 8.45 (s, 1H), 7.8 (s, 1H), 7.7 (dd, 2H), 7.5 (m, 3H), 3.8 (s, 3H), 1.5 (s, 9H). Anal. ($C_{15}H_{19}N_3O$) C, H, N.

Pharmacology. *tert*-Butyl Hydroperoxide-Mediated Lethality. The induction of lethality in mice via icv injection of *t*-BHP was based on the method of Adams.[20] Male NMRI mice (30−35 g) were administered an icv injection of a 70% solution of *t*-BHP (22 mg/kg/μl). The lethality was then assessed at 1, 2, 5, and 24 h postinjection. In general, icv injection induced convulsive behavior followed by progressive mortality (6−10 animals) between 1 and 24 h. The protective action of drugs on *t*-BHP-induced lethality was estimated by a 30 min pretreatment with drug administered at 150 mg/kg (ip), in 0.2 mL saline/Tween solution. Results are expressed as the percentage survival estimated from the number of lethalities of the *t*-BHP-treated group relative to *t*-BHP/drug-treated group; n = 10 animals per group, at the respective time intervals.

Effect on Body Temperature. The total body temperature of NMRI mice (25−30 g) was assessed, with the aid of a rectal probe, at 30, 60, 90, and 120 min following intraperitoneal (ip) injection of the tested antioxidants (150 mg/kg ip/0.2 mL Tween/saline solution). Results are expressed as the maximal

temperature difference, at a given time, between saline-treated (control) animals relative to drug-treated mice.

Molecular Modeling and Calculations. Structures discussed within this study were modeled using standard bond lengths and angles, as implemented in the SYBYL version 6.41 molecular modeling software running on an Indigo^2 R4400 Extreme Silicon Graphics workstation. Initial geometries, as well as HOMO and LUMO energies, were first obtained by AM1 semiempirical calculations with the Gaussian 92 package (Gaussian 92/DFT, Revision F.3). The above geometries were then fully optimized at the ab initio HF/3-21G* level (Gaussian 92) and frontier orbitals energies were recalculated.[21]

ClogP was calculated with the program available from Daylight Chemical Information System,[22] and regression analysis was performed using the PLS method implemented within the SYBYL Software.

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Supporting Information Available: Analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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