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## ELECTRONIC SUPPLEMENTARY INFORMATION

## for the paper entitled

# Synthesis, Physicochemical Characterization and Neuroprotective Evaluation of Novel 1-hydroxypyrazin-2(1H)-one Iron Chelators in an In Vitro Cell Model of Parkinson's Disease 

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## 1. Organic Synthesis

## Discussion

The target 1-hydroxypyrazin- $2(1 \mathrm{H})$-ones $\mathbf{6}$ were synthesized in two steps from amino acid ethyl esters following the literature procedures as shown below in Scheme S1. ${ }^{1}$ Initially, reaction of glycine ethyl ester hydrochloride 4a with hydroxylamine hydrochloride in alkaline water afforded the known glycine hydroxamic acid 5a in $64 \%$ yield. ${ }^{1 a, 2}$ Condensation reaction of 5a with 2,3-butanedione afforded the known 1-hydroxypyrazin-2(1H)-one $\mathbf{6 a}^{1 \mathrm{lb}, 3-5}$ in $24 \%$ yield (Scheme S1). Unfortunately, application of this two-step procedure to the synthesis of $\mathbf{6 b}$ from alanine ethyl ester $\mathbf{4 b}$ failed to give the desired product, due to the high solubility of the hydroxamic acid $\mathbf{5 b}$ in water. We subsequently modified this procedure by using methanol as the solvent and we were able to obtain $\mathbf{5 a}$ from $\mathbf{4 a}$ in 56 \% yield (Scheme S1). However, application of this modified procedure to the synthesis of alanine hydroxamic acid $\mathbf{5} \mathbf{b}^{2 b, 2 c, 6}$ from alanine ethyl ester $\mathbf{4 b}$ gave a mixture of $\mathbf{5 b}$ and another compound (presumed to be the corresponding diketopiperazine) in low yield as judged by ${ }^{1} \mathrm{H}$ NMR spectroscopy. Reaction of this mixture with 2,3-butanedione gave an intractable mixture of products from which the novel 1-hydroxypyrazin- $2(1 H)$-one $\mathbf{6 b}$ could not be isolated by chromatography. However, 1-hydroxypyrazin- $2(1 H)$-ones $\mathbf{6 c}$ and $\mathbf{6 d}$ were successfully obtained by this modified procedure from the known hydroxamic acids $\mathbf{5 c}{ }^{1 \mathrm{lb}, 2 \mathrm{~b}, 7}$ and $\mathbf{5 d},{ }^{8}$ albeit in only $13 \%$ and $14 \%$ overall yields from $\mathbf{4 c}$ and 4d, respectively (Scheme S1). There are some reports of multifunctional hydroxypyridinone metal chelators containing phenolic antioxidant moieties that show promising efficacy against neurodegenerative diseases by acting as radical traps as well as metal chelators. ${ }^{9}$ Accordingly, we synthesized 1-hydroxypyrazin- $2(1 H)$-one $\mathbf{6 d}$ that contains a phenol moiety which could provide a beneficial antioxidant mode of action in addition to iron chelation. Unfortunately, all our attempts to isolate hydroxamic acids $\mathbf{5 e}-\mathbf{5 g}$ from amino esters $\mathbf{4 e}-\mathbf{4 g}$ met with no success.


Scheme S1. Synthesis of 1-hydroxypyrazin-2(1H)-ones 6a-6g.
Due to the low yields obtained above and the failure to synthesize certain 1-hydroxypyrazin-2(1H)ones $\mathbf{6}$ by the procedure shown in Scheme S1, we sought a more general synthetic method which could be applied to the synthesis of a broader range of these compounds. The synthesis of 1-hydroxypyrazin$2(1 H)$-ones 6 in 4 steps from $N$-Boc amino acids via their protected hydroxamic acid benzyl esters was previously reported. ${ }^{3-5,10}$ Inspired by this approach, we explored a new synthesis of 1-hydroxypyrazin$2(1 H)$-ones 6 from activated $N$-Boc amino acid $N$-hydroxysuccinimide esters $\mathbf{7}$ as shown below in Scheme S2.

Reaction of $N$-Boc-protected $N$-hydroxysuccinimide esters 7a, 7b, 7c, 7e and 7f with $O$ benzylhydroxylamine generated the Boc-protected aminohydroxamic acid benzyl esters $\mathbf{8 a}, \mathbf{8 b}, \mathbf{8 c}, 8 \mathbf{8 e}$ and $\mathbf{8 f}$ in high yields. Subsequent $N$-Boc deprotection (TFA in DCM) gave the free aminohydroxamic acid benzyl esters $\mathbf{9 b}, \mathbf{9 c}, \mathbf{9 e}$ and $\mathbf{9 f}$ in excellent yields. However, despite the known formation of $\mathbf{6} \mathbf{9}$ from 9a (as HCl salt) and 2,3-butanedione reported in the literature, ${ }^{5,11}$ attempted condensation reactions of compounds $\mathbf{9 b}, \mathbf{9 c}, \mathbf{9 e}$ and $\mathbf{9 f}$ with 2,3-butanedione in our hands failed to generate the desired 1-benzyloxypyrazin-2(1H)-ones $\mathbf{6}^{\prime} \mathbf{b}, \mathbf{6}^{\prime} \mathbf{c}$, $\mathbf{6}^{\prime} \mathbf{e}$ and $\mathbf{6}^{\prime} \mathbf{f}$. This synthetic approach was subsequently abandoned in favour of the approach outlined above in Scheme S1.


Scheme S2. Attempted synthesis of 1-hydroxypyrazin-2(1H)-ones 6a-6f.
We also explored the reactions of glycine hydroxamic acid 5a with both aromatic and aliphatic $\alpha$ ketoaldehydes (glyoxals) as shown below in Scheme S3. Reaction of 5a with phenylglyoxal in ethanol/water at reflux afforded the novel 1-hydroxypyrazin- $2(1 \mathrm{H})$-one 10a in $30 \%$ yield as a single regioisomer. Similarly, reaction of 5a with 4-methoxyphenylglyoxal and 4-fluorophenylglyoxal gave 10b and 10c as single regioisomers in $27 \%$ and $24 \%$ yields, respectively. As with 1-hydroxypyrazin$2(1 H)$-one $\mathbf{6 d}$, we sought to convert 10b into a 1-hydroxypyrazin-2( $1 H$ )-one bearing a phenol moiety with potential antioxidant activity. Accordingly, deprotection of the methoxy group of $\mathbf{1 0 b}$ with boron tribromide in DCM afforded the novel 1-hydroxypyrazin-2 $(1 \mathrm{H})$-one $\mathbf{1 0 d}$ in $21 \%$ yield. Reaction of 5a with pyruvaldehyde gave the novel 1-hydroxypyrazin- $2(1 \mathrm{H})$-ones 11a and 12a as a 12:1 mixture of regioisomers, as judged by ${ }^{1} \mathrm{H}$ NMR spectroscopy (Scheme S3). The major regioisomer was tentatively assigned as 11a on the basis that the free primary amino group of 5a would preferentially react with the aldehyde carbonyl group of the glyoxal, rather than the less electrophilic ketone carbonyl group. These regioisomers proved inseparable by recrystallisation or chromatography, and were studied without further purification.


5a

reflux


11a $\mathrm{R}_{1}=\mathrm{H}, \mathrm{R}_{2}=\mathrm{Me}$
12a $R_{1}=M e, R_{2}=H$

Scheme S3. Synthesis of 1-hydroxypyrazin-2(1H)-ones 10a-10d, 11a and 12a

## 2. Experimental Procedures

## Synthesis of $\boldsymbol{N}$-Boc hydroxamic acid benzyl esters 8a-8f: General procedure



To a solution of the appropriate $N$-Boc amino acid $N$-hydroxysuccinimide ( OSu ) ester $7(1.47 \mathrm{mmol})$ in DCM ( 20 mL ) at room temperature was added $O$-benzylhydroxylamine ( $1.47 \mathrm{mmol}, 1 \mathrm{eq}$ ). The solution was allowed to stir at room temperature for 24 hours. The solvent was evaporated to afford the crude N -Boc hydroxamic acid benzyl ester $\mathbf{8}$ as an oil that crystallised contaminated with N hydroxysuccinimide. This mixture was used in the next step without further purification.
$N$-Boc glycine hydroxamic acid benzyl ester $8 \mathbf{a n}^{3-5,11} \delta_{\mathrm{H}}\left(399.8 \mathrm{MHz}, \mathrm{CDCl}_{3}, \mathrm{Me}_{4} \mathrm{Si}\right) 1.40(9 \mathrm{H}, \mathrm{s}$, $\left.\left(\mathrm{CH}_{3}\right)_{3}\right), 3.67\left(2 \mathrm{H}, \mathrm{s}, \mathrm{CH}_{2} \mathrm{NHBoc}\right), 4.82(1 \mathrm{H}, \mathrm{br} \mathrm{s}, \mathrm{NH}), 4.88(2 \mathrm{H}, \mathrm{s}, \mathrm{OCH} 2 \mathrm{Ph}), 5.25(1 \mathrm{H}, \mathrm{br} \mathrm{s}, \mathrm{N} H \mathrm{Boc})$, 7.36 (5H, s, ArH).
$N$-Boc alanine hydroxamic acid benzyl ester $\mathbf{8 b}{ }^{11} \delta_{\mathrm{H}}\left(399.8 \mathrm{MHz}, \mathrm{CDCl}_{3}, \mathrm{Me}_{4} \mathrm{Si}\right) 1.28(3 \mathrm{H}, \mathrm{d}, J 6.8$, $\left.\mathrm{CH}_{3} \mathrm{CH}\right), 1.38\left(9 \mathrm{H}, \mathrm{s},\left(\mathrm{CH}_{3}\right)_{3}\right), 4.05\left(1 \mathrm{H}\right.$, app t, $\left.J 6.8, \mathrm{CH}_{3} \mathrm{CH}\right), 4.86\left(2 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{2} \mathrm{Ph}\right), 5.29(1 \mathrm{H}, \mathrm{d}, J$ 6.4, NHBoc), 7.27-7.36 (5H, m, ArH).
$N$-Boc phenylalanine hydroxamic acid benzyl ester $\mathbf{8 c}^{12,13} \delta_{\mathrm{H}}\left(399.8 \mathrm{MHz}, \mathrm{CDCl}_{3}, \mathrm{Me}_{4} \mathrm{Si}\right) 1.36(9 \mathrm{H}$, $\left.\mathrm{s},\left(\mathrm{CH}_{3}\right)_{3}\right), 2.96-3.06\left(2 \mathrm{H}, \mathrm{m}, \mathrm{CHCH}_{2} \mathrm{Ph}\right), 4.20(1 \mathrm{H}, \mathrm{q}, J 7.6, \mathrm{CHNHBoc}), 4.62-4.84\left(2 \mathrm{H}, \mathrm{m}, \mathrm{OCH}_{2} \mathrm{Ph}\right)$, 5.26 (1H, d, J 7.6, CHNHBoc), 7.17-7.36 (10H, m, ArH).
$N$-Boc valine hydroxamic acid benzyl ester $8 \mathbf{e}^{12,13} \delta_{\mathrm{H}}\left(399.8 \mathrm{MHz}, \mathrm{CDCl}_{3}, \mathrm{Me}_{4} \mathrm{Si}\right) 0.88(3 \mathrm{H}, \mathrm{d}, J 6.4$, $\left.\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CH}\right), 0.90\left(3 \mathrm{H}, \mathrm{d}, J 6.4,\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CH}\right), 1.39\left(9 \mathrm{H}, \mathrm{s},\left(\mathrm{CH}_{3}\right)_{3}\right), 1.96-2.02\left(1 \mathrm{H}, \mathrm{m},\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CH}\right), 3.70$ $(1 \mathrm{H}, \mathrm{t}, J 8.4, \mathrm{CHNHBoc}), 4.88\left(2 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{2} \mathrm{Ph}\right), 5.28(1 \mathrm{H}, \mathrm{d}, J 8.4, \mathrm{CHNHBoc}), 7.28-7.37(5 \mathrm{H}, \mathrm{m}$, $\mathrm{ArH}), 9.45\left(1 \mathrm{H}, \mathrm{br}\right.$ s, $\left.\mathrm{NHOCH}_{2} \mathrm{Ph}\right)$.
$N$-Boc leucine hydroxamic acid benzyl ester $8 \mathbf{f f}^{11} \delta_{\mathrm{H}}\left(399.8 \mathrm{MHz}, \mathrm{CDCl}_{3}, \mathrm{Me}_{4} \mathrm{Si}\right) 0.85-0.87(6 \mathrm{H}, \mathrm{m}$, $\left.\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CH}\right), 1.39\left(9 \mathrm{H}, \mathrm{s},\left(\mathrm{CH}_{3}\right)_{3}\right), 1.41-1.47\left(1 \mathrm{H}, \mathrm{m},\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CH}\right), 1.54-1.60\left(2 \mathrm{H}, \mathrm{m},\left(\mathrm{CH}_{2} \mathrm{CH}\left(\mathrm{CH}_{3}\right)_{2}\right)\right.$,
3.97 ( $1 \mathrm{H}, \mathrm{q}, J 8.0, \mathrm{CHNHBoc}), 4.88$ ( $2 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{2} \mathrm{Ph}$ ), 5.17 ( $1 \mathrm{H}, \mathrm{d}, J 8.0, \mathrm{CHNHBoc}$ ), 7.24-7.37 (5H, $\mathrm{m}, \mathrm{Ar} H), 9.45\left(1 \mathrm{H}, \mathrm{br} \mathrm{s}, \mathrm{NHOCH}_{2} \mathrm{Ph}\right)$.

## Synthesis of hydroxamic acid benzyl ester TFA salts 9b-9f: General procedure



The appropriate crude $N$-Boc hydroxamic acid benzyl ester $\mathbf{8}(1.47 \mathrm{mmol})$ was dissolved in DCM (10 $\mathrm{mL})$ and trifluoroacetic acid ( 10 mL ) was added. The solution was allowed to stir at room temperature for 24 hours. The solvents were evaporated to afford the crude TFA salt $\mathbf{9}$ as a clear oil. The oil was triturated with diethyl ether $(10 \mathrm{~mL})$ and the resulting white solid was filtered and washed with diethyl ether $(10 \mathrm{~mL})$ and allowed to dry in air to afford the pure TFA salt $\mathbf{9}$ as a white solid.

Alanine hydroxamic acid benzyl ester TFA salt 9b ${ }^{4,11}$ Obtained from 7b in $87 \%$ overall yield. $\delta_{\mathrm{H}}\left(399.8 \mathrm{MHz}, \mathrm{DMSO}-d_{6}\right) 1.24\left(3 \mathrm{H}, \mathrm{d}, J 7.2, \mathrm{CH}_{3} \mathrm{CH}\right), 3.64\left(1 \mathrm{H}, \mathrm{br} \mathrm{s}, \mathrm{CH}_{3} \mathrm{CH}\right), 4.77(1 \mathrm{H}, \mathrm{d}, J 11.2$, $\left.\mathrm{OCH}_{2} \mathrm{Ph}\right), 4.81\left(1 \mathrm{H}, \mathrm{d}, J 11.2, \mathrm{OCH}_{2} \mathrm{Ph}\right), 7.34-7.38(5 \mathrm{H}, \mathrm{m}, \mathrm{ArH})$.

Phenylalanine hydroxamic acid benzyl ester TFA salt 9c ${ }^{12,13}$ Obtained from 7c in $78 \%$ overall yield. $\delta_{\mathrm{H}}\left(399.8 \mathrm{MHz}, \mathrm{D}_{2} \mathrm{O}\right) 2.91\left(1 \mathrm{H}, \mathrm{dd}, J 14.0\right.$ and $\left.8.4, \mathrm{CHCH}_{2} \mathrm{Ph}\right), 2.99(1 \mathrm{H}, \mathrm{dd}, J 14.0$ and 6.8 , $\left.\mathrm{CHCH}_{2} \mathrm{Ph}\right), 3.82\left(1 \mathrm{H}, \mathrm{dd}, J 8.4\right.$ and $\left.6.8, \mathrm{CHCH}_{2} \mathrm{Ph}\right), 4.41\left(1 \mathrm{H}, \mathrm{d}, J 11.0, \mathrm{OCH}_{2} \mathrm{Ph}\right), 4.59(1 \mathrm{H}, \mathrm{d}, J 11.0$, $\left.\mathrm{OCH}_{2} \mathrm{Ph}\right), 7.06-7.13(4 \mathrm{H}, \mathrm{m}, \mathrm{Ar} H), 7.20-7.26(6 \mathrm{H}, \mathrm{m}, \mathrm{ArH})$.

Valine hydroxamic acid benzyl ester TFA salt $9 \mathbf{e}^{12,13}$ Obtained from 7e in $91 \%$ overall yield. $\left.\left.\delta_{\mathrm{H}}\left(399.8 \mathrm{MHz}, \mathrm{D}_{2} \mathrm{O}\right) 0.69\left(3 \mathrm{H}, \mathrm{d}, J 6.4,\left(\mathrm{CH}_{3}\right)_{2}\right) \mathrm{CH}\right), 0.73\left(3 \mathrm{H}, \mathrm{d}, J 6.4,\left(\mathrm{CH}_{3}\right)_{2}\right) \mathrm{CH}\right), 1.88(1 \mathrm{H}, \mathrm{sp}, J$ $\left.6.4,\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CH}\right), 3.38\left(1 \mathrm{H}, \mathrm{d}, J 6.4, \mathrm{CHNH}_{3}{ }^{+}\right), 4.75\left(1 \mathrm{H}, \mathrm{d}, J 11.2, \mathrm{OCH}_{2} \mathrm{Ph}\right), 4.80(1 \mathrm{H}, \mathrm{d}, J 11.2$, $\mathrm{OCH}_{2} \mathrm{Ph}$ ), 7.27-7.32 (5H, m, ArH).

Leucine hydroxamic acid benzyl ester TFA salt $9 \mathbf{f}^{11}$ Obtained from $7 \mathbf{f}$ in $84 \%$ overall yield. $\delta_{\mathrm{H}}(399.8$ $\left.\mathrm{MHz}, \mathrm{D}_{2} \mathrm{O}\right) 0.65\left(3 \mathrm{H}, \mathrm{d}, J 6.0,\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CH}\right), 0.67\left(3 \mathrm{H}, \mathrm{d}, J 6.0,\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CH}\right), 1.01-1.10(1 \mathrm{H}, \mathrm{m}$, $\left.\left(\mathrm{CH}_{3}\right)_{2} \mathrm{CH}\right), 1.37\left(2 \mathrm{H}, \mathrm{t}, J 7.2, \mathrm{CH}_{2} \mathrm{CH}\left(\mathrm{CH}_{3}\right)_{2}\right), 3.56\left(1 \mathrm{H}, \mathrm{t}, J 7.2, \mathrm{CHNH}_{3}{ }^{+}\right), 4.74(1 \mathrm{H}, \mathrm{d}, J 11.2$, $\left.\mathrm{OCH}_{2} \mathrm{Ph}\right), 4.82\left(1 \mathrm{H}, \mathrm{d}, J 11.2, \mathrm{OCH}_{2} \mathrm{Ph}\right), 7.25-7.34(5 \mathrm{H}, \mathrm{m}, \mathrm{ArH})$.

## 3. NMR Spectra

Glycine hydroxamic acid 5a


Alanine hydroxamic acid 5b


Phenylalanine hydroxamic acid 5c


Tyrosine hydroxamic acid 5d


1-Hydroxy-5,6-dimethylpyrazin-2(1H)-one $\mathbf{6 a}$





1-Hydroxy-3-benzyl-5,6-dimethylpyrazin-2(1H)-one $\mathbf{6 c}$



1-Hydroxy-3-(4-hydroxybenzyl)-5,6-dimethylpyrazin-2(1H)-one 6d


$N$-Boc glycine hydroxamic acid benzyl ester $\mathbf{8 a}$

$N$-Boc alanine hydroxamic acid benzyl ester $\mathbf{8 b}$

$N$-Boc phenylalanine hydroxamic acid benzyl ester 8c

$N$-Boc valine hydroxamic acid benzyl ester $\mathbf{8 e}$

$N$-Boc leucine hydroxamic acid benzyl ester $\mathbf{8 f}$


Alanine hydroxamic acid benzyl ester TFA salt 9b


Phenylalanine hydroxamic acid benzyl ester TFA salt $9 \mathbf{c}$


Valine hydroxamic acid benzyl ester TFA salt 9e


Leucine hydroxamic acid benzyl ester TFA salt 9f


1-Hydroxy-6-phenylpyrazin-2(1H)-one 10a



1-Hydroxy-6-(4-methoxyphenyl)-pyrazin-2(1H)-one 10b




1-Hydroxy-6-(4-fluorophenyl)-pyrazin-2(1H)-one 10c




1-Hydroxy-6-(4-hydroxyphenyl)-pyrazin-2(1 H )-one 10d





1-Hydroxy-6-methylpyrazin-2(1H)-one 11a and 1-Hydroxy-5-methylpyrazin-2(1H)-one 12a





## 4. Mass Spectra

1-Hydroxy-3-(4-hydroxybenzyl)-5,6-dimethylpyrazin-2(1H)-one 6d



1-Hydroxy-6-phenylpyrazin-2(1H)-one 10a


1-Hydroxy-6-(4-methoxyphenyl)-pyrazin-2(1H)-one 10b



1-Hydroxy-6-(4-fluorophenyl)-pyrazin-2(1H)-one 10c



1-Hydroxy-6-(4-hydroxyphenyl)-pyrazin-2(1H)-one 10d


1-Hydroxy-6-methylpyrazin-2(1H)-one 11a and 1-Hydroxy-5-methylpyrazin-2(1H)-one 12a


## 5. Determination of pKa Values of the Ligands and Stability Constants of the

 Complexes
## Protonation studies with ligand 11a



Figure S1. Spectrophotometric titrations vs pH of ligand 11a between (A) $-0.5<\mathrm{pH}<2.08$ (batch titration, $[\mathbf{1 1 a}]=2.57 \times 10^{-4} \mathrm{M}$ ) and $(\mathbf{B}) 2.61<\mathrm{pH}<10.17$ (direct titration, $[\mathbf{1 1 a}]=2.55 \times 10^{-4} \mathrm{M}$ ). (C) Electronic spectra and (D) distribution curves ([11a] $\left.=2.55 \times 10^{-4} \mathrm{M}\right)$ of the protonated species of ligand 11a. Solvent: $\mathrm{H}_{2} \mathrm{O}, \mathrm{I}=0.1 \mathrm{M}\left(\mathrm{NaClO}_{4}\right), \mathrm{T}=25.0^{\circ} \mathrm{C}$.

## Protonation studies with ligand 10a in water



Figure S2. Spectrophotometric titrations vs pH of ligand 10a between (A) $-0.75<\mathrm{pH}<2$ (batch titration, $\left.[\mathbf{1 0 a}]=1.95 \times 10^{-4} \mathrm{M}\right)$ and $(\mathbf{B}) 2.12<\mathrm{pH}<11.79$ (direct titration, $[\mathbf{1 0 a}]=1.02 \times 10^{-4} \mathrm{M}$ ). (C) Electronic spectra and (D) distribution curves $\left([\mathbf{1 0 a}]=1.95 \times 10^{-4} \mathrm{M}\right)$ of the protonated species of ligand 10a. Solvent: $\mathrm{H}_{2} \mathrm{O}, \mathrm{I}=0.1 \mathrm{M}\left(\mathrm{NaClO}_{4}\right), \mathrm{T}=25.0^{\circ} \mathrm{C}$.

Protonation studies with ligand 10a in $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}(80 / 20 \mathrm{w} / \mathrm{w})$


Figure S3. Spectrophotometric titrations vs pH of ligand $\mathbf{1 0 a}$ between (A) $-0.37<\mathrm{pH}<0.63$ (batch titration, $\left.[\mathbf{1 0 a}]=1.02 \times 10^{-4} \mathrm{M}\right)$ and $(\mathbf{B}) 2.43<\mathrm{pH}<11.88$ (direct titration, $[\mathbf{1 0 a}]=1.01 \times 10^{-3} \mathrm{M}$ ). (C) Electronic spectra and $(\mathbf{D})$ distribution curves $\left([\mathbf{1 0 a}]=1.02 \times 10^{-4} \mathrm{M}\right)$ of the protonated species of ligand 10a. Solvent: $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}(80 / 20 \mathrm{w} / \mathrm{w}), \mathrm{I}=0.1 \mathrm{M}\left(\mathrm{NaClO}_{4}\right), \mathrm{T}=25.0^{\circ} \mathrm{C}$.

## Protonation studies with ligand 6d



Figure S4. Spectrophotometric titrations vs pH of ligand $\mathbf{6 d}$ between (A) $-0.36<\mathrm{pH}<2.36$ (batch titration, $\left.[\mathbf{6 d}]=3.0 \times 10^{-4} \mathbf{M}\right)$ and $(\mathbf{B}) 1.78<\mathrm{pH}<11.47$ (direct titration, $\left.[\mathbf{6 d}]=9.98 \times 10^{-5} \mathrm{M}\right)$. (C)

Electronic spectra and (D) distribution curves $\left([\mathbf{6 d}]=3.0 \times 10^{-4} \mathrm{M}\right)$ of the protonated species of ligand 6d. Solvent: $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}(80 / 20 \mathrm{w} / \mathrm{w}), \mathrm{I}=0.1 \mathrm{M}\left(\mathrm{NaClO}_{4}\right), \mathrm{T}=25.0^{\circ} \mathrm{C}$.

## Protonation studies with ligand 6c



Figure S5. Spectrophotometric titrations vs pH of ligand $\mathbf{6 c}$ between (A) $-0.04<\mathrm{pH}<2.11$ (batch titration, $[\mathbf{6 c}]=3.0 \times 10^{-4} \mathbf{M}$ ) and (B) $2.49<\mathrm{pH}<11.74$ (direct titration, $[\mathbf{6 c}]=9.98 \times 10^{-5} \mathrm{M}$ ). (C) Electronic spectra and $(\mathbf{D})$ distribution curves $\left([\mathbf{6 c}]=1.54 \times 10^{-4} \mathrm{M}\right)$ of the protonated species of ligand 6c. Solvent: $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}(80 / 20 \mathrm{w} / \mathrm{w}), \mathrm{I}=0.1 \mathrm{M}\left(\mathrm{NaClO}_{4}\right), \mathrm{T}=25.0^{\circ} \mathrm{C}$.
$\mathrm{Fe}^{3+}$ complexation studies with ligand 6a


Figure S6. Spectrophotometric titration vs pH of $\mathrm{Fe}^{3+}$ complexes of ligand $\mathbf{6 a}$ between (A) $-0.5 \leq$ $\mathrm{pH} \leq 1.25$ (batch titration, $[\mathbf{6 a}]=3.78 \times 10^{-4} \mathrm{M},\left[\mathrm{Fe}^{3+}\right]=1.26 \times 10^{-4} \mathrm{M}$ ) and (B) $1.97 \leq \mathrm{pH} \leq 12.04$ (direct titration, $\left.[\mathbf{6 a}]=2.38 \times 10^{-4} \mathrm{M},\left[\mathrm{Fe}^{3+}\right]=7.14 \times 10^{-5} \mathrm{M}\right)$. (C) Electronic spectra and (D) distribution curves $\left([\mathbf{6 a}]=2.38 \times 10^{-4} \mathrm{M},\left[\mathrm{Fe}^{3+}\right]=7.14 \times 10^{-5} \mathrm{M}\right)$ of the $\mathrm{Fe}^{3+}$ complexes of $\mathbf{6 a}$.

$$
\text { Solvent: } \mathrm{H}_{2} \mathrm{O}, \mathrm{I}=0.1 \mathrm{M}\left(\mathrm{NaClO}_{4}\right), \mathrm{T}=25.0^{\circ} \mathrm{C} \text {. }
$$

$\mathrm{Fe}^{3+}$ complexation studies with ligand 10a


Figure S7. Spectrophotometric titration vs pH of $\mathrm{Fe}^{3+}$ complexes of ligand 10a between (A) $-0.36 \leq$ $\mathrm{pH} \leq 1.80$ (batch titration, $[\mathbf{1 0 a}]=1.02 \times 10^{-4} \mathrm{M},\left[\mathrm{Fe}^{3+}\right]=3.20 \times 10^{-5} \mathrm{M}$ ) and (B) $2.34 \leq \mathrm{pH} \leq 8.03$ (direct titration, $\left.[\mathbf{1 0 a}]=1.02 \times 10^{-3} \mathrm{M},\left[\mathrm{Fe}^{3+}\right]=3.12 \times 10^{-4} \mathrm{M}\right) .(\mathbf{C})$ Electronic spectra and (D) distribution curves $\left([\mathbf{1 0 a}]=1.02 \times 10^{-4} \mathrm{M},\left[\mathrm{Fe}^{3+}\right]=3.20 \times 10^{-5} \mathrm{M}\right.$ ) of the $\mathrm{Fe}^{3+}$ complexes of $\mathbf{1 0 a}$.

Solvent: $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}(80 / 20 \mathrm{w} / \mathrm{w}), \mathrm{I}=0.1 \mathrm{M}\left(\mathrm{NaClO}_{4}\right), \mathrm{T}=25.0^{\circ} \mathrm{C}$.
$\mathrm{Fe}^{3+}$ complexation studies with ligand 6d


Figure S8. Spectrophotometric titration vs pH of $\mathrm{Fe}^{3+}$ complexes of ligand $\mathbf{6 d}$ between (A) $-0.36 \leq$ $\mathrm{pH} \leq 2.36$ (batch titration, $[\mathbf{6 d}]=3.0 \times 10^{-4} \mathrm{M},\left[\mathrm{Fe}^{3+}\right]=8.0 \times 10^{-5} \mathrm{M}$ ) and (B) $1.97 \leq \mathrm{pH} \leq 12.04$ (direct titration, $\left.[\mathbf{6 d}]=1.04 \times 10^{-4} \mathrm{M},\left[\mathrm{Fe}^{3+}\right]=3.23 \times 10^{-5} \mathrm{M}\right)$. (C) Electronic spectra and (D) distribution curves $\left([\mathbf{6 d}]=1.04 \times 10^{-4} \mathrm{M},\left[\mathrm{Fe}^{3+}\right]=3.23 \times 10^{-5} \mathrm{M}\right)$ of the $\mathrm{Fe}^{3+}$ complexes of $\mathbf{6 d}$. Solvent: $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}(80 / 20 \mathrm{w} / \mathrm{w}), \mathrm{I}=0.1 \mathrm{M}\left(\mathrm{NaClO}_{4}\right), \mathrm{T}=25.0^{\circ} \mathrm{C}$.
$\mathrm{Fe}^{3+}$ complexation studies with ligand 6c


Figure S9. Spectrophotometric titration vs pH of $\mathrm{Fe}^{3+}$ complexes of ligand $\mathbf{6 c}$ between (A) $-0.36 \leq$ $\mathrm{pH} \leq 1.83$ (batch titration, $[\mathbf{6 c}]=3.0 \times 10^{-4} \mathrm{M},\left[\mathrm{Fe}^{3+}\right]=9.38 \times 10^{-5} \mathrm{M}$ ) and (B) $1.97 \leq \mathrm{pH} \leq 12.04$ (direct titration, $\left.[\mathbf{6 c}]=1.02 \times 10^{-4} \mathrm{M},\left[\mathrm{Fe}^{3+}\right]=3.12 \times 10^{-5} \mathrm{M}\right)$. (C) Electronic spectra and (D) distribution curves $\left([\mathbf{6 c}]=1.02 \times 10^{-4} \mathrm{M},\left[\mathrm{Fe}^{3+}\right]=3.12 \times 10^{-5} \mathrm{M}\right)$ of the $\mathrm{Fe}^{3+}$ complexes of $\mathbf{6 c}$.

Solvent: $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}(80 / 20 \mathrm{w} / \mathrm{w}), \mathrm{I}=0.1 \mathrm{M}\left(\mathrm{NaClO}_{4}\right), \mathrm{T}=25.0^{\circ} \mathrm{C}$.

## 6. BBB Penetration Scores

Table S1. Predicted BBB score of compound 6a.

| 6a |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: |
| Property | Value | $\mathbf{T}_{\mathbf{0}}$ |  |  |
| Number of Aromatic Rings (Aro_R) | 1 | 0.82 |  |  |
| Number of Heavy Atoms (HA) | 10 | 0.65 |  |  |
| Molecular Weight (MW) | 140.14 |  |  |  |
| Number of Hydrogen Bond Acceptor (HBA) | 3 |  |  |  |
| Number of Hydrogen Bond Donor (HBD) <br> MWHBN [MWHBN = (MW^(-0.5)*HBN), <br> where HBN=HBA+HBD] | 1 |  |  |  |
| Topological Polar Surface Area(TPSA) | 55.34 | 0.71 |  |  |
| pKa | 0.62 |  |  |  |
| BBB SCORE | 4.58 | 0.23 |  |  |
|  |  |  |  | 3.88 |

Table S2. Predicted BBB score of compound $\mathbf{6 c}$.

| 6c |  |  |
| :---: | :---: | :---: |
| Property | Value | $\mathbf{T}_{\mathbf{0}}$ |
| Number of Aromatic Rings (Aro_R) | 2 | 1.00 |
| Number of Heavy Atoms (HA) | 17 | 0.98 |
| Molecular Weight (MW) | 230.26 |  |
| Number of Hydrogen Bond Acceptor (HBA) | 3 |  |
| Number of Hydrogen Bond Donor (HBD) | 1 |  |
| MWHBN [MWHBN = (MW^(-0.5)*HBN), <br> where HBN=HBA+HBD] | 0.26 | 0.93 |
| Topological Polar Surface Area(TPSA) | 65.42 | 0.54 |
| pKa | 5.53 | 0.47 |
| BBB SCORE | 4.70 |  |

Table S3. Predicted BBB score of compound $\mathbf{6 d}$.

| 6d |  |  |
| :---: | :---: | :---: |
| Property | Value | $\mathbf{T}_{\mathbf{0}}$ |
| Number of Aromatic Rings (Aro_R) | 2 | 1.00 |
| Number of Heavy Atoms (HA) | 18 | 0.99 |
| Molecular Weight (MW) | 246.26 |  |
| Number of Hydrogen Bond Acceptor (HBA) | 4 |  |
| Number of Hydrogen Bond Donor (HBD) | 2 |  |
| MWHBN [MWHBN = (MW^(-0.5)*HBN), <br> where HBN=HBA+HBD] | 0.38 | 0.55 |
| Topological Polar Surface Area(TPSA) | 75.35 | 0.47 |
| pKa | 5.96 | 0.58 |
| BBB SCORE | 4.05 |  |

Table S4. Predicted BBB score of compound 10a.

| 10a |  | Value |
| :---: | :---: | :---: |
| Property | $\mathbf{T}_{\mathbf{0}}$ |  |
| Number of Aromatic Rings (Aro_R) | 2 | 1.00 |
| Number of Heavy Atoms (HA) | 14 | 0.89 |
| Molecular Weight (MW) | 188.18 |  |
| Number of Hydrogen Bond Acceptor (HBA) | 3 |  |
| Number of Hydrogen Bond Donor (HBD) | 1 |  |
| MWHBN [MWHBN = (MW^(-0.5)*HBN), <br> where HBN=HBA+HBD] | 0.29 | 0.87 |
| Topological Polar Surface Area(TPSA) | 51.48 | 0.64 |
| pKa | 3.18 | 0.00 |
| BBB SCORE | 4.47 |  |

Table S5. Predicted BBB score of compound 10d.

| 10d |  |  |
| :---: | :---: | :---: |
| Property | Value | $\mathbf{T}_{\mathbf{0}}$ |
| Number of Aromatic Rings (Aro_R) | 2 | 1.00 |
| Number of Heavy Atoms (HA) | 15 | 0.93 |
| Molecular Weight (MW) | 204.18 |  |
| Number of Hydrogen Bond Acceptor (HBA) | 4 |  |
| Number of Hydrogen Bond Donor (HBD) | 2 |  |
| MWHBN [MWHBN = (MW^(-0.5)*HBN), | 0.42 | 0.40 |
| where HBN=HBA+HBD] |  |  |
| Topological Polar Surface Area(TPSA) | 53.5 | 0.63 |
| pKa | 4 | 0.11 |
| BBB SCORE | 3.83 |  |

Table S6. Predicted BBB score of compound 11a.

| 11a |  |  |
| :---: | :---: | :---: |
| Property | Value | $\mathbf{T}_{\mathbf{0}}$ |
| Number of Aromatic Rings (Aro_R) | 1 | 0.82 |
| Number of Heavy Atoms (HA) | 9 | 0.56 |
| Molecular Weight (MW) | 126.11 |  |
| Number of Hydrogen Bond Acceptor (HBA) | 3 |  |
| Number of Hydrogen Bond Donor (HBD) | 1 |  |
| MWHBN [MWHBN = (MW^(-0.5)*HBN), <br> where HBN=HBA+HBD] | 0.36 | 0.65 |
| Topological Polar Surface Area(TPSA) | 31.01 | 0.78 |
| pKa | 3.98 | 0.11 |
| BBB SCORE | 3.97 |  |

Table S7. Predicted BBB score of compound 2.

| 2 |  |  |
| :---: | :---: | :---: |
| Property | Value | $\mathbf{T}_{\mathbf{0}}$ |
| Number of Aromatic Rings (Aro_R) | 1 | 0.82 |
| Number of Heavy Atoms (HA) | 10 | 0.65 |
| Molecular Weight (MW) | 141.12 |  |
| Number of Hydrogen Bond Acceptor (HBA) | 3 |  |
| Number of Hydrogen Bond Donor (HBD) | 2 |  |
| MWHBN [MWHBN = (MW^(-0.5)*HBN), <br> where HBN=HBA+HBD] | 0.42 | 0.39 |
| Topological Polar Surface Area(TPSA) | 34.37 | 0.76 |
| pKa | 6.02 | 0.60 |
| BBB SCORE | 3.87 |  |

Table S8. Predicted BBB score of compound 3.

| 3 |  |  |
| :---: | :---: | :---: |
| Property | Value | $\mathbf{T}_{\mathbf{0}}$ |
| Number of Aromatic Rings (Aro_R) | 1 | 0.82 |
| Number of Heavy Atoms (HA) | 11 | 0.72 |
| Molecular Weight (MW) | 155.11 |  |
| Number of Hydrogen Bond Acceptor (HBA) | 4 |  |
| Number of Hydrogen Bond Donor (HBD) | 2 |  |
| MWHBN [MWHBN = (MW^(-0.5)*HBN), <br> where HBN=HBA+HBD] | 0.48 | 0.00 |
| Topological Polar Surface Area(TPSA) | 79.53 | 0.44 |
| pKa | 3.7 | 0.06 |
| BBB SCORE | 2.46 |  |

Table S9. Predicted BBB score of DFP 1.

| DFP 1 |  | Value |
| :---: | :---: | :---: |
| Troperty | 1 | 0.82 |
| Number of Aromatic Rings (Aro_R) | 10 | 0.65 |
| Number of Heavy Atoms (HA) | 139.15 |  |
| Molecular Weight (MW) | 2 |  |
| Number of Hydrogen Bond Acceptor (HBA) | 1 |  |
| Number of Hydrogen Bond Donor (HBD) <br> MWHBN [MWHBN = (MW^(-0.5)*HBN), <br> where HBN=HBA+HBD] | 0.25 | 0.95 |
| Topological Polar Surface Area(TPSA) | 38.95 | 0.73 |
| pKa | 3.68 | 0.06 |
| BBB SCORE | 4.37 |  |

Table S10. Comparison of predicted BBB scores with percentage neuronal rescue from 6-OHDA neurotoxicity at $100 \mu \mathrm{M}$ dose of the compound.

| Compound | BBB Score | \% 6-OHDA Rescue <br> (at $\mathbf{1 0 0} \boldsymbol{\mu M}$ ) |
| :---: | :---: | :---: |
| $\mathbf{6 a}$ | 3.88 | 100 |
| $\mathbf{6 c}$ | 4.70 | 89 |
| $\mathbf{6 d}$ | 4.05 | 64 |
| $\mathbf{1 0 a}$ | 4.47 | 63 |
| $\mathbf{1 0 d}$ | 3.83 | 76 |
| $\mathbf{1 1 a}$ | 3.97 | 60 |
| DFP 1 | 4.37 | 117 |
| $\mathbf{2}$ | 3.87 | 93 |
| $\mathbf{3}$ | 2.46 | 84 |



Figure S10. Plot of predicted BBB scores versus percentage neuronal rescue from 6-OHDA neurotoxicity at $100 \mu \mathrm{M}$ dose of the compound, showing no clear correlation between the two properties $(\bullet=\mathbf{6 a}-\mathbf{6 d}, \mathbf{1 0 a}, \mathbf{1 0 d}$ and 11a, $\boldsymbol{\square}=\mathbf{2}$ and $\mathbf{3}, \boldsymbol{\Delta}=$ DFP $\mathbf{1})$.

## 7. DPPH Antioxidant Assay



Figure S11. Percentage inhibition of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical by ligand 6a after 24 hours (24h) and 48 hours (48h).


Figure S12. Percentage inhibition of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical by ligand 11a after 1 hour (1h), 24 hours (24h) and 48 hours ( 48 h).


Figure S13. Percentage inhibition of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical by ligand 10a after 1 hour (1h), 24 hours (24h) and 48 hours (48h).


Figure S14. Percentage inhibition of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical by ligand $\mathbf{6 d}$ after 24 hours (24h) and 48 hours (48h).


Figure S15. Percentage inhibition of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical by ligand $\mathbf{6 c}$ after 1 hour (1h), 24 hours (24h), 48 hours (48h) and 72 hours ( $72 h$ ).

## 8. Trolox Equivalent Antioxidant Capacity (TEAC) Assay



Figure S16. Percentage of ABTS inhibition (TEAC) by ligand $\mathbf{6 a}$ (ABTS $=2,2^{\prime}$-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)).


Figure S17. Percentage of ABTS inhibition (TEAC) by ligand 11a (ABTS $=2,2^{\prime}$-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)).


Figure S18. Percentage of ABTS inhibition (TEAC) by ligand 10a (ABTS $=2,2^{\prime}$-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)).


Figure S19. Percentage of ABTS inhibition (TEAC) by ligand 6d (ABTS $=2,2$ '-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)).


Figure S20. Percentage of ABTS inhibition (TEAC) by ligand $\mathbf{6 c}$ (ABTS $=2,2$ '-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)).


Figure S21. Percentage of ABTS inhibition (TEAC) by Trolox (ABTS $=2,2$ '-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)).

## 9. Neuroprotection against 6-OHDA Neurotoxicity



Figure S22. Comparison of the percentage neuroprotection against 6-hydroxydopamine (6-OHDA) neurotoxicity in SH-SY5Y neuroblastoma cells by compounds 6a, 6c, 2, $\mathbf{3}$ and DFP $\mathbf{1}$ (at $100 \mu \mathrm{M}$ compound dose).

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