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# Synthesis and antioxidant properties of substituted 2-phenyl-1*H*-indoles

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ABSTRACT

In this study, we report the design, synthesis and antioxidant activity of a series of substituted 2-(4-aminophenyl)-1*H*-indoles and 2-(methoxyphenyl)-1*H*-indoles. The new compounds are structurally related to the known indole-based antioxidant lead compound melatonin (MLT), and the antitumour 2-(4-aminophenyl)benzothiazole and 2-(3,4-dimethoxyphenyl)benzothiazole series. Efficient access to the target 2-phenylindoles was achieved via Fischer indole synthesis between substituted phenylhydrazines and acetophenones. 2-(4-Aminophenyl)indoles (such as the 6-fluoro analogue **3b**) in particular showed potent antioxidant activity in the DPPH and superoxide radical scavenging assays (80% and 81% inhibition at 1 mM concentration of **3b**, respectively), at a level comparable with the reference standard MLT (98% and 75% at 1 mM).



The design of small molecule agents to combat cellular oxidative stress has become an important therapeutic objective, given the wide-ranging damage to cellular macromolecules caused by reactive oxygen (and reactive nitrogen) radical species (ROS). Oxidative stress that gives rise to generation of ROS and related radicals has been associated with a wide range of diseases including those of cardiovascular, inflammatory, neurodegenerative and autoimmune origin.[1] The naturally occurring hormone melatonin (*N*-acetyl-5-methoxytryptamine, Fig. 1) has been known since 1993 as a potentially useful lead compound due to its wide-ranging free radical scavenging and antioxidant properties,[2,3] in addition to its common use for controlling circadian rhythms that regulate the sleep-wake cycle.[4]

Melatonin (MLT) represents one example amongst many indole-based compounds with therapeutic activity; other indole derivatives with notable biological activity include antitumour agents, particularly modulators of tubulin dynamics.[5] A number of studies have been published on the discovery of melatonin analogues, mainly designed to improve free radical scavenging antioxidant properties,[6–12] including 2-phenylindoles that have particular relevance to the present study (Fig. 1).[13] Previous studies have established that both the methoxy and amide side chains of MLT contribute to the antioxidant activity of MLT in addition to the indole ring. 2-(4-Aminophenyl)-1*H*-indole, a compound previously reported to possess inhibitory activity against lipid peroxidation (ex vivo) and DPPH (2,2-diphenyl-1-picrylhydrazyl) free radical scavenging ability,[13] provided the starting point for this study.

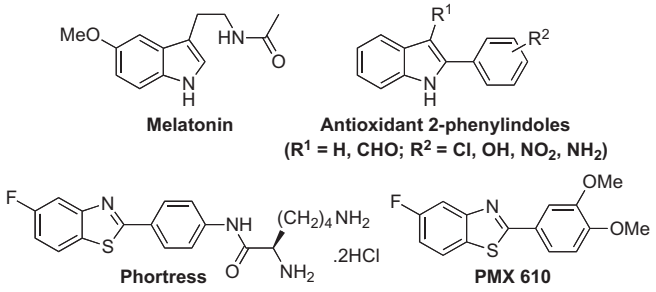


**Figure 1.** Antioxidant and antitumour lead compounds relevant to this study.

Substituted 2-(4-aminophenyl)benzothiazoles were found to possess potent and selective antitumour activity within certain in vitro and in vivo cancer cell models containing inducible cytochrome P450 1A1,[14–18] culminating in the identification of the 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole prodrug Phortress (Fig. 1) as a clinical trial candidate.[19,20] The related 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (PMX 610, Fig. 1) was also found to possess potent and selective antitumour activity;[21] extension of this work to related 2-phenyl-benzoxazoles[22] and -benzimidazoles[23] led to antitumour agents with lower potency.

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Given the previously reported moderate antioxidant properties of 2-(4-aminophenyl)-1*H*-indole,[13] and the exciting biological properties associated with the structurally related 2-(4-aminophenyl)- and 2-(3,4-dimethoxyphenyl)-benzothiazoles, we have herein prepared and studied the antioxidant properties of a series of 2-phenyl-1*H*-indole derivatives (eight of which are novel compounds). Our chosen 2-phenylindole substitution patterns are here based on the known antitumour fluorinated 2-(4-aminophenyl)benzothiazole and 2-(3,4-dimethoxyphenyl)benzothiazole series.

Substituted 2-phenyl-1*H*-indoles (**3a**–**q**) were prepared via the acetic acid-promoted Fischer indole synthesis[24] between substituted -phenylhydrazines (**1a**–**g**) and -acetophenones (**2a**–**f**) in refluxing ethanol (Scheme 1), followed by heating with polyphosphoric acid (PPA).[25] Purification by column chromatography gave the required 2-phenylindoles[26] in low to moderate yields (10–74%). For the 4-substituted phenylhydrazine starting materials (**1a**, **d**, **f** and **g**) the synthetic method resulted in a single regioisomer of 2-(4-aminophenyl)-1*H*-indole product (**3a**, **3e**, **3h**, **3j**, **3m**, **3n**, **3o**, **3p** and **3q**). However in the case of the 3-chlorophenylhydrazine starting material **1e** (but not 3-fluorophenylhydrazine **1b**), cyclisation of the intermediate enamine to either of the two positions ortho to nitrogen resulted in a regioisomeric mixture of products (**3f** and **3g**) that required careful separation by column chromatography. For the reaction sequence starting with 2-fluorophenylhydrazine (**1c**), cyclisation and subsequent aromatisation resulted in the 7-fluoroindole product (**3c**) plus unsubstituted 2-(4-aminophenyl)-1*H*-indole (**3d**) via fluoride displacement, following chromatographic separation.

Three different in vitro assays, previously described and established by Süzen and co-workers,[6–13] were carried out to assess the antioxidant capacity of the newly synthesised compounds, using MLT as a positive control. The results of the antioxidant test assays are shown in Table 1. Initially, the free radical scavenging activities of indole derivatives were tested by their ability to bleach the stable radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) at 517 nm.[27] Compounds were also tested spectrophotometrically for their ability to scavenge xanthine/xanthine oxidase generated superoxide anion formation, as measured by the nitroblue tetrazolium (NBT) reduction method.[28,29] Assessment of hydroxyl radical formation in vivo was carried out by measuring the ability of the indole analogues to inhibit malondialdehyde (MDA) formation through lipid peroxidation, as detected using thiobarbituric acid.[30] Unsubstituted 2-phenyl-1*H*-indole (commercially available) was initially tested as a reference compound but found to be completely inactive in our test assays. All data were recorded as the average of at least triplicate analyses, and full protocols for the antioxidant assays can be found in the Supplementary data.

Free radical scavenging abilities of the new 2-phenylindole derivatives as determined by the DPPH assay revealed a number of compounds with inhibitory activity approaching that of the reference standard MLT. For example, compounds **3b**–**h** showed similar activity to MLT particularly at the 1 mM test concentration (well in excess of 50% inhibition). In general the 2-(methoxyphenyl)indole derivatives (**3i**–**p**) and 2-(4-nitrophenyl)indole compound (**3q**) showed lower antioxidant activity at the test concentrations (1 mM and 0.1 mM) compared to MLT.

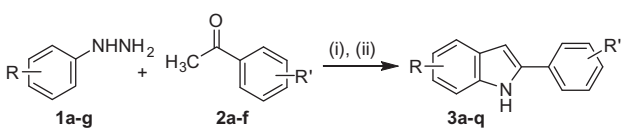
The results of the superoxide radical scavenging assay revealed some potent novel compounds. In particular, compound **3b** presented a higher level of radical scavenging (81% inhibition at 1 mM) compared to reference compound MLT (75% inhibition at 1 mM) at the two concentrations studied, while **3i** was found to have a similar activity and **3j**–**m** showed moderate inhibitory activity. Among the 2-(4-aminophenyl)indole derivatives, only the 6-fluoro analogue **3b** was very active, whilst among the (methoxyphenyl)indole derivatives, a number of compounds (**3i**–**m**) showed moderate to high superoxide anion scavenging activity. There remains the possibility that MLT or the active indole analogues inhibit xanthine oxidase directly, in turn reducing superoxide radical formation by an alternative mechanism; however further experimental studies would be required to test this hypothesis.

In the lipid peroxidation assay, the newly synthesized 2-phenylindole analogues showed rather weaker inhibitory effects on MDA formation at the test concentrations. In general, the 2-(4-aminophenyl)indole compounds **3b**–**h** containing Cl, F and $OCH_3$ groups on the indole ring showed moderate activity in the lipid peroxidation assay. Activity of 2-(4-aminophenyl)indoles was comparable with the previously reported inhibitory activity of compound **3d** (26% at 1 mM in this study), although activities were lower than reference compound MLT. However compounds **3i**–**p** containing (methoxyphenyl) groups or 2-(4-nitrophenyl)indole **3q** showed weak lipid peroxidation inhibitory activity.

Overall the most active compound across the three antioxidant assays was found to be 2-(4-aminophenyl)-6-fluoro-1*H*-indole (**3b**), with radical scavenging activities at a similar level to MLT, as judged by the DPPH and superoxide radical scavenging assays. In general, most of the substituted 2-(4-aminophenyl)-1*H*-indoles (particularly **3b**–**h**) displayed higher levels of antioxidant activity compared to their 2-(methoxyphenyl)indole counterparts.

In our earlier studies various modifications were made on MLT and many significant antioxidant results were obtained.[8,9,12,13] However the effect of the methoxy group still remains unclear. In this study replacement of the 5-methoxy group of MLT by F, Cl or H did not increase the antioxidant activity significantly except in the case of **3b**. Similar to our earlier findings[8,13] and those of Poeggeler et al.,[31] 2-(4-aminophenyl)-5-methoxyindole (**3h**) showed lower antioxidant activity overall activity compared to MLT.

The mechanism by which the indole ring interacts with reactive species is still not entirely understood. Although it is thought that melatonin interacts with free radicals by donation of an electron to form the melatoninyl cation radical through a radical addition at




| 1 | R |
|---|---|
| a | 4-F |
| b | 3-F |
| c | 2-F |
| d | 4-Cl |
| e | 3-Cl |
| f | 4-OMe |
| g | 2-Cl,4-F |

| 2 | R' |
|---|---|
| a | 4-$NH_2$ |
| b | 3,4-diOMe |
| c | 4-OMe |
| d | 3,4,5-triOMe |
| e | 3,F,4-OMe |
| f | 4-$NO_2$ |

| 3 | R | R' |
|---|---|---|
| a | 5-F | 4-$NH_2$ |
| b | 6-F | 4-$NH_2$ |
| c | 7-F | 4-$NH_2$ |
| d | H | 4-$NH_2$ |
| e | 5-Cl | 4-$NH_2$ |
| f | 4-Cl | 4-$NH_2$ |
| g | 6-Cl | 4-$NH_2$ |
| h | 5-OMe | 4-$NH_2$ |

| 3 | R | R' |
|---|---|---|
| i | H | 3,4-diOMe |
| j | 5-F | 3,4-diOMe |
| k | H | 4-OMe |
| l | H | 3,4,5-triOMe |
| m | 5-F | 3,4,5-triOMe |
| n | 5-F,7-Cl | 4-OMe |
| o | 5-F,7-Cl | 3,4-diOMe |
| p | 5-F | 3,F,4-OMe |
| q | 5-F,7-Cl | 4-$NO_2$ |

**Reagents:** (i) AcOH (catalytic), EtOH, reflux; (ii) polyphosphoric acid,120ºC

**Scheme 1.** Synthesis of substituted 2-phenyl-1*H*-indoles **3a**–**q**. Reagents: (i) AcOH (catalytic), EtOH, reflux; (ii) polyphosphoric acid, 120 ºC

**Table 1**
Antioxidant activity of synthesised 2-phenylindole derivatives, represented as % mean inhibition

| Compound[a] | Concn. (mM) | DPPH assay[b] | Superoxide radical scavenging assay[b] | Lipid peroxidation assay[b] |
|---|---|---|---|---|
| Melatonin | 1 mM | 98 ± 2 | 75 ± 4 | 85 ± 3 |
| | 0.1 mM | 81 ± 3 | 19 ± 3 | 45 ± 3 |
| **3a** | 1 mM | 28 ± 2 | 35 ± 2 | 19 ± 2 |
| | 0.1 mM | 18 ± 3 | 20 ± 1 | 17 ± 2 |
| **3b** | 1 mM | 80 ± 2 | 81 ± 2 | 35 ± 3 |
| | 0.1 mM | 65 ± 2 | 35 ± 2 | 22 ± 3 |
| **3c** | 1 mM | 77 ± 3 | 23 ± 3 | 30 ± 3 |
| | 0.1 mM | 43 ± 2 | 15 ± 0.5 | 26 ± 3 |
| **3d** | 1 mM | 74 ± 2 | 30 ± 2 | 26 ± 4 |
| | 0.1 mM | 43 ± 2 | 16 ± 2 | 13 ± 3 |
| **3e** | 1 mM | 70 ± 4 | 22 ± 3 | 31 ± 2 |
| | 0.1 mM | 23 ± 1 | NA | 30 ± 3 |
| **3f** | 1 mM | 69 ± 2 | 18 ± 2 | 30 ± 2 |
| | 0.1 mM | 44 ± 3 | NA | 30 ± 2 |
| **3g** | 1 mM | 77 ± 5 | 20 ± 3 | 35 ± 2 |
| | 0.1 mM | 50 ± 3 | 17 ± 2 | 35 ± 3 |
| **3h** | 1 mM | 85 ± 2 | 35 ± 3 | 42 ± 3 |
| | 0.1 mM | 69 ± 2 | 14 ± 0.5 | 33 ± 3 |
| **3i** | 1 mM | 44 ± 0.7 | 70 ± 3.5 | 27 ± 4.2 |
| | 0.1 mM | 12 ± 2.1 | 12 ± 2.1 | 13 ± 1.4 |
| **3j** | 1 mM | 21 ± 0.7 | 51 ± 4.2 | 24 ± 0.7 |
| | 0.1 mM | 2.0 ± 1.4 | NA | 10 ± 1.4 |
| **3k** | 1 mM | 38 ± 2.8 | 43 ± 2.8 | 24 ± 2.1 |
| | 0.1 mM | 6.0 ± 1.4 | 12 ± 1.4 | 14 ± 3.5 |
| **3l** | 1 mM | 35 ± 3.5 | 42 ± 3.5 | 28 ± 2.8 |
| | 0.1 mM | 9.0 ± 2.1 | q13 ± 0.7 | 33 ± 2.8 |
| **3m** | 1 mM | 23 ± 1.4 | 50 ± 4.2 | 19 ± 3.5 |
| | 0.1 mM | 3.0 ± 0.7 | 9 ± 0.7 | 10 ± 2.1 |
| **3n** | 1 mM | NA | 32 ± 2.1 | 33 ± 1.4 |
| | 0.1 mM | NA | NA | 6.0 ± 1.4 |
| **3o** | 1 mM | 10 ± 2.8 | 39 ± 1.4 | 24 ± 2.8 |
| | 0.1 mM | NA | NA | 13 ± 0.7 |
| **3p** | 1 mM | NA | NA | 13 ± 2.1 |
| | 0.1 mM | NA | NA | 7.0 ± 1.4 |
| **3q** | 1 mM | 5.0 ± 0.7 | 39 ± 2.1 | 20 ± 3.5 |
| | 0.1 mM | NA | NA | 5.0 ± 1.4 |

[a] Compound was dissolved in DMSO (solvent expressed no antioxidant activity).
[b] Values are means ± standard deviation ($n \geqslant 3$). NA = No Activity.

C3, other possibilities include hydrogen donation from the nitrogen atom or substitution at position C2, C4 and C7 on the indole ring.[3,32] It is possible that the 4-aminophenyl side chain may help the formation of an indolyl cation radical during scavenging free radicals in the in vitro assays. Results showed that for antioxidant activity of melatonin analogue indole derivatives, both the indole ring and side chain are important. These results suggest a new approach for the in vitro antioxidant activity properties and structure activity relationships of substituted indole rings.

Oxidative stress may initiate molecular events in the cancer formation, and reduction of oxidative stress may protect against carcinogenesis.[1] The new compounds synthesized herein are structurally related to the known indole-based antioxidant lead compound melatonin (MLT) and the antitumour 2-(4-aminophenyl)benzothiazole and 2-(3,4-dimethoxyphenyl)benzothiazole series. The lead compounds emerging with the most potent antioxidant activity in this study (such as **3b**, **3h** and **3i**) will be further structurally modified towards the discovery of a compound with optimal combined antioxidant and anticancer activities.

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## Supplementary data

Supplementary data (compound characterization data (**3a–q**); detailed protocols for antioxidant test assays) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.02.090.

## References and notes

1. Dröge, W. *Physiol. Rev.* **2002**, *82*, 47.
2. Tan, D. X.; Chen, L. D.; Poeggeler, B.; Manchester, L. C.; Reiter, R. J. *Endocrinol. J.* **1993**, *1*, 57.
3. Tan, D-X.; Reiter, R. J.; Manchester, L. C.; Yan, M-T.; El-Sawi, M.; Sainz, R. M.; Mayo, J. C.; Kohen, R.; Allegra, M.; Hardeland, R. *Curr. Top. Med. Chem.* **2002,** *2,* 181.
4. Lemoine, P.; Zisapel, N. *Expert Opin. Pharmacother.* **2012**, *13*, 895.
5. Brancale, A.; Silvestri, R. *Med. Res. Rev.* **2007**, *27*, 209.
6. Suzen, S. *Comb. Chem. High Throughput Screen.* **2006**, *9*, 409.
7. Suzen, S.; Cihaner, S. S.; Coban, T. *Chem. Biol. Drug Des.* **2012**, *79*, 76.
8. Gurkok, G.; Coban, T.; Suzen, S. *J. Enzyme Inhib. Med. Chem.* **2009**, *24*, 506.
9. Shirinzdeh, H.; Eren, B.; Gurer-Orhan, H.; Suzen, S.; Ozden, S. *Molecules* **2010**, *15*, 2187.
10. Ates-Alagoz, Z.; Coban, T.; Suzen, S. *Med. Chem. Res.* **2005**, *14*, 169.
11. Das-Evcimen, N.; Yildirim, O.; Suzen, S. *Arch. Biol. Sci.* **2009**, *61*, 697.
12. Yilmaz, A. D.; Coban, T.; Suzen, S. *J. Enzyme Inhib. Med. Chem.* **2012**, *27*, 428.
13. Suzen, S.; Bozkaya, P.; Coban, T.; Nebioglu, D. *J. Enzyme Inhib. Med. Chem.* **2006**, *21*, 405.
14. Hutchinson, I.; Chua, M.-S.; Browne, H.; Trapani, V.; Fichtner, I.; Bradshaw, T. D.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **2001**, *44*, 1446.

15. Hutchinson, I.; Bradshaw, T. D.; Matthews, C. S.; Stevens, M. F. G.; Westwell, A. D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 471.
16. Kashiyama, E.; Hutchinson, I.; Chua, M.-S.; Stinson, S. F.; Phillips, L. R.; Kaur, G.; Sausville, E. A.; Bradshaw, T. D.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **1999**, *42*, 4172.
17. Weekes, A. A.; Westwell, A. D. *Curr. Med. Chem.* **2009**, *16*, 2430.
18. Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. *Curr. Med. Chem.* **2001**, *8*, 203.
19. Hutchinson, I.; Jennings, S. A.; Vishnuvajjala, B. R.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **2002**, *45*, 744.
20. Bradshaw, T. D.; Westwell, A. D. *Curr. Med. Chem.* **2004**, *1009*, 11.
21. Mortimer, C. G.; Wells, G.; Crochard, J.-P.; Stone, E. L.; Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. *J. Med. Chem.* **2006**, *49*, 179.
22. Aiello, S.; Wells, G.; Stone, E. L.; Kadri, H.; Bazzi, R.; Bell, D. R.; Stevens, M. F. G.; Matthews, C. S.; Bradshaw, T. D.; Westwell, A. D. *J. Med. Chem.* **2008**, *51*, 5135.
23. Kadri, H.; Matthews, C. S.; Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. *J. Enzyme Inhib. Med. Chem.* **2008**, *23*, 641.
24. Patil, S. A.; Patil, R.; Miller, D. D. *Curr. Med. Chem.* **2011**, *18*, 615.
25. *General method for synthesis of 2-(4-aminophenyl)-1H-indoles (***3a–q***).* The appropriate substituted phenylhydrazine (**1a–g**, 1.0 mmol) and substituted acetophenone (**2a–f**, 1.0 mmol) were mixed in ethanol (20 mL) and a few drops of glacial AcOH were added. The solution was heated under reflux at 80 °C for 1–2 h. The solvents were evaporated in vacuo to give a solid that was added to polyphosphoric acid (PPA) (30 mL), and the mixture slowly heated to 120 °C and kept at this temperature for a few hours until the reaction was complete (TLC monitoring). The mixture was allowed to cool and then poured into cold water (50 mL). The acidic solution was neutralised by the slow addition of 1 M NaOH (aq) and the solid precipitate of crude product was collected. Purification by column chromatography (hexane/ethyl acetate) gave the required product(s) (**3a–q**).
26. *Representative characterization data: (a) 2-(4-Aminophenyl)-5-fluoro-1H-indole (***3a***).*[13] (74% yield). Mp 196–199 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 11.27 (1H, s, indole-NH), 7.52 (2H, d, $J$ = 8.5 Hz, H-2′, H-6′), 7.29 (1H, dd, $J$ = 8.6, 4.7 Hz, H-7), 7.17 (1H, dd, $J$ = 10.1, 2.5 Hz, H-4), 6.82 (1H, dt, $J$ = 9.2, 2.6 Hz, H-6), 6.64 (2H, d, $J$ = 8.5 Hz, H-3′, H-5′), 6.57 (1H, s, H-3), 5.32 (2H, s, $NH_2$); $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 157.11 (d, $J$ = 230.1 Hz, C-5-indole), 148.70, 141.18, 133.29, 129.32 (d, $J$ = 10.5 Hz), 126.18, 119.47, 113.93, 111.40 (d, $J$ = 9.7 Hz, C-7-indole), 107.98 (d, $J$ = 25.8 Hz), 103.66 (d, $J$ = 23.5 Hz), 95.69 (d, $J$ = 4.5 Hz, C-3-indole); MS (EI+), $m/z$ (%) 226.09 (100) ($M^+$), 198.07 (18). *(b) 2-(3,4-Dimethoxyphenyl)-5-fluoro-1H-indole (***3j***).* Yellow solid, 55% yield. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 11.51 (1H, s, indole-NH), 7.45 (1H, d, $J$ = 2.0 Hz, H-2′), 7.38 (1H, dd, $J$ = 8.5, 2.0 Hz, H-6′), 7.36 (1H, dd, $J$ = 9.0, 5.0 Hz, H-7), 7.25 (1H, dd, $J$ 10.0, 2.5 Hz, H-4), 7.04 (1H, d, $J$ = 8.5 Hz, H-5′), 6.90 (1H, dt, $J$ 9.0, 2.5 Hz, H-6), 6.81 (1H, s, H-3), 3.87 (3H, s, $OCH_3$), 3.80 (3H, s, $OCH_3$); MS (ESI+), $m/z$ 272.1 ($M^+$+1). Anal. calcd. for $C_{16}H_{14}FNO_2$; C, 70.84; H, 5.20; N, 5.16; found C, 70.82; H, 5.10; N, 5.17.
27. Blois, M. S. *Nature* **1958**, *181*, 1199.
28. Cheng, Z. J.; Kuo, S. C.; Chan, S. C.; Ko, F. N.; Teng, C. M. *Biochim. Biophys. Acta* **1998**, *1392*, 291.
29. Huong, N. T.; Matsumoto, K.; Kasai, R.; Yamasaki, K.; Watanabe, H. *Biol. Pharm. Bull.* **1998**, *21*, 978.
30. Mihara, M.; Uchiyama, M.; Fukuzawa, K. *Biochem. Med.* **1980**, *23*, 302.
31. Poeggeler, B.; Pappolla, M. A.; Hardeland, R.; Rassoulpour, A.; Hodgkins, P. S.; Guidetti, P.; Schwarcz, R. *Brain Res.* **1999**, *815*, 382.
32. Rosenstein, R. E.; Estrin, D. A.; Turjanski, A. G. *J. Med. Chem.* **1998**, *41*, 3684.