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New Quinolinic Derivatives as Centrally Active Antioxidants

Gilbert Dorey,* Brian Lockhart, Pierre Lestage and Patrick Casara*

Institut de Recherches Servier, 125 Chemin de Ronde, Croissy-sur-Seine, F78290, France

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Abstract—A series of new 1,2-dihydro and 1,2,3,4-tetrahydroquinolines, synthesized from the corresponding propargylaniline intermediates, have been developed as antioxidants for the potential treatment of pathologies implicating central oxidative stress.

Introduction

Oxidative damage of cellular components such as proteins, unsaturated fatty acids and DNA have been associated with biological disorders such as cancer, stroke, and post-ischaemic or age-related neuronal degeneration.[1,2] Furthermore, the high levels of oxygen consumption, unsaturated fatty acids and iron stores, combined with the low antioxidant capacity and absence of neuronal regeneration, make the brain extremely susceptible to radical-mediated damage. Paradoxically, despite numerous strategies aimed at inhibiting this damaging process,[3] only a small number of centrally acting synthetic antioxidants, including tBPN,[4] edaravone[5] and ebselen,[6] have been proposed as candidates for clinical development (Fig. 1).

Ethoxyquin (1,2-dihydro-6-ethoxy-2,2,4-trimethylquinoline), a synthetic molecule prepared nearly 80 years ago by Knoevenagel[7] (Scheme 1), has been described as a powerful antioxidant[8] and lipid peroxidation inhibitor in different in vitro paradigms[9] as well as a dual cyclooxygenase/lipoxygenase inhibitor in a model of in vivo renal inflammation.[10] However, despite its potent radical scavenger activity, the significant hypothermic effect[11,12] of ethoxyquin (ETQ) in rodents (Table 4), precludes its selection as a potential candidate for central nervous system (CNS) protection.

In this report, we have outlined the synthesis and biological evaluation of a new class of centrally active antioxidants **II**, based on the ETQ backbone **I** (Fig. 2), showing moderate or negligible hypothermia.

*Corresponding authors. E-mail: gdorey@netgrs.com and pcasara@netgrs.com

Chemistry

The reaction first reported by Knoevenagel (Scheme 1), involving the condensation of 2 mol of acetone per mol of aniline, is somewhat limited in terms of chemical diversity on either the phenyl or piperidyl portion of the molecule. Moreover, this approach gives exclusive access to 2,2,4-trisubstituted-1,2-dihydroquinolines where $R_5 = H$. Furthermore, all attempts to condense a ketone, with a 3,5-disubstituted aniline were unsuccessful.

In order to circumvent such limitations, the two-step synthesis reported by Easton[13] and further ameliorated by Ward[14] was developed. This approach permitted the preparation of R_2, R'_2, R_5, R_6, R_7 and R_8 modified analogues of ETQ with $R_4 = H$ in moderate yields. The general synthetic pathway for the preparation of compounds listed in Table 1 is shown in Schemes 2 and 3.

The 2,2′-dimethylquinoline (ETQ-related series) as well as the 2,2′-cyclohexylquinoline series were selected, the latter being designed to enhance the lipophilicity[15] and thereby facilitate CNS penetration.

The 3-chloro-3-methyl-1-butyne or 1-ethynyl-1-chlorocyclohexane, obtained from the corresponding tertiary alcohol[16] were coupled to various synthetic[17,18] or commercially available anilines with copper catalysis.[19] The resulting *N*-1,1-disubstituted propargylanilines were then refluxed in toluene, containing a catalytic amount of cuprous chloride, to give the desired dihydroquinolines.[37] In order to enhance the solubility in water, compounds with *gem* 2,2′-piperidine were also prepared. A different approach was used due to the difficulties experienced in the synthesis of the key intermediate 4-ethynyl-4-chloro-1-Boc-piperidine (Scheme 3).

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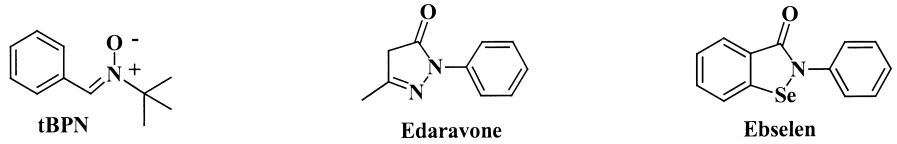
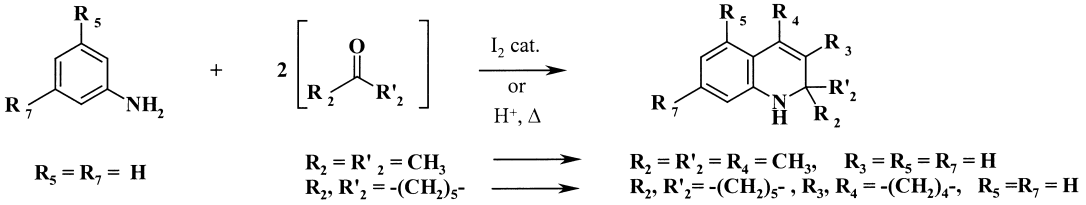


Figure 1.



Scheme 1. Knoevenagel methodology.

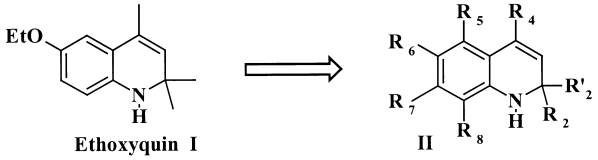
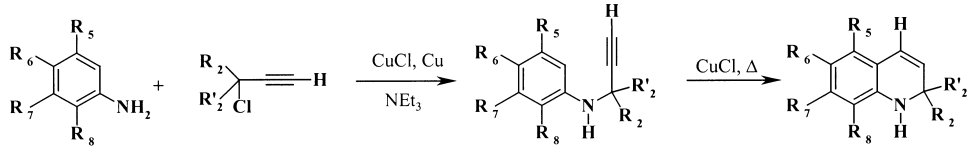


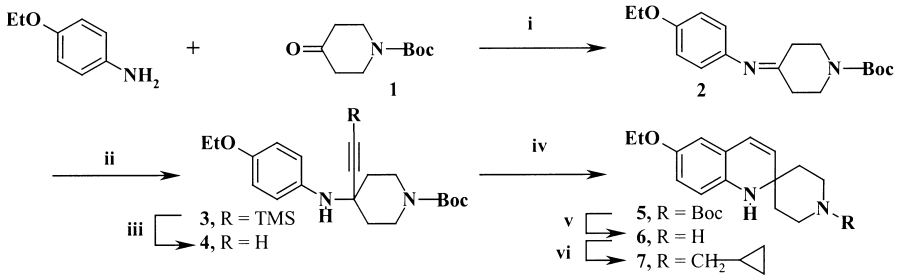
Figure 2.

Table 1. Structure of representative 1,2-dihydroquinolines

Compound	R_2	R'_2	R_4	R_5	R_6	R_7	R_8	Yield (%)	Compound	R_2 R'_2	R_4	R_5	R_6	R_7	R_8	Yield (%)
ETQ	Me	Me	Me	H	OEt	H	H	See ref 20	**16**	$CH_2(CH_2)_3CH_2$	H	Me	OEt	Me	H	42
8	Me	Me	H	H	OEt	H	H	39	**17**	$CH_2(CH_2)_3CH_2$	H	Me	OEt	Me	Me	39
9	Me	Me	H	H	H	H	OEt	24	**18**	$CH_2(CH_2)_3CH_2$	H	iPr	OEt	iPr	H	19
10	Me	Me	H	Me	OEt	Me	H	32	**19**	$CH_2(CH_2)_3CH_2$	H	H	OMe	H	H	34
11	Me	Me	H	Me	OEt	Me	Me	35	**20**	$CH_2(CH_2)_3CH_2$	H	H	OPh	H	H	17
12	Me	Me	H	iPr	OEt	iPr	H	19	**21**	$CH_2(CH_2)_3CH_2$	H	H	OtBu	H	H	19
13	Me	Me	H	tBu	OEt	tBu	H	12	**22**	$CH_2(CH_2)_3CH_2$	H	H	OPiv	H	H	6
14	$CH_2(CH_2)_3CH_2$		H	H	OEt	H	H	34	**6**	$(CH_2)_2NH(CH_2)_2$	H	H	OEt	H	H	15
15	$CH_2(CH_2)_3CH_2$		H	H	H	H	OEt	12	**7**	$(CH_2)_2NCH_2cPr(CH_2)_2$	H	H	OEt	H	H	7



Scheme 2. Easton/Ward methodology.



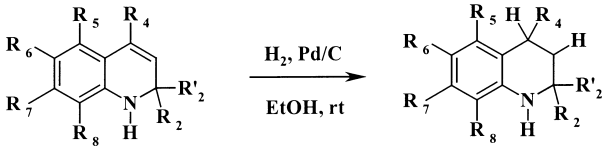
Scheme 3. (i) mol. sieves 5 Å, Et_2O, rt, 33%; (ii) (trimethylsilyl)acetylene, *n*-BuLi, THF, −78 °C to rt, 48%; (iii) TBAF, THF, 0 °C, 80%; (iv) CuCl, toluene, reflux, 45%; (v) HCl, EtOH, 90%; (vi) (bromomethyl)cyclopropane, K_2CO_3, CH_3CN, reflux, 50%.

N-Boc-4-piperidone (**1**) was condensed under dehydrating conditions with *p*-phenetidine to give the expected Schiff base **2**. Nucleophilic addition of lithium (trimethylsilyl)acetylide to the carbon/nitrogen double bond of imine **2** gave the desired propargylaniline **3** which, upon subsequent desilylation with fluoride ions afforded **4** in good yield.

The final copper cyclisation, as previously shown (supra), yielded the expected *N*-Boc protected 1,2-dihydroquinoline **5**. Removal of the *tert*-butoxycarbonyl group with hydrochloric acid afforded **6,** which was regioselectively alkylated under standard conditions to give **7**.[37] To our knowledge, no 1,2,3,4-tetrahydroquinolines have been so far described and used as antioxidants, for these reasons, the contribution of C3–C4 unsaturation on the antioxidant profile of our compounds was investigated. In this aim, catalytic hydrogenation of selected 1,2-dihydroquinolines (Scheme 4) was performed, giving the desired 1,2,3,4-tetrahydroquinolines **23**–**29** (Table 2) in good yield.[37]

Biological Results and Discussion

In order to select compounds with reasonable safety profiles for in vivo evaluation, dihydroquinolines and tetrahydroquinolines listed in Tables 1 and 2 were examined in vitro, for their intrinsic toxicity[21] on HT-22 hippocampal cell lines as well as their antioxidant activities.[22] The results were compared to Vitamin E and synthetic antioxidants depicted in Figure 1. The PC_{50} and TC_{50} (concentration producing 50% protection and 50% toxicity, respectively) as well as the MTC (maximum tolerated concentration) were determined via the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) reduction assays[23] (Table 3).



Scheme 4.

Initially, substitution of the 4-methyl group of ETQ for a hydrogen atom enhanced the neuroprotective level of the molecule (compare **8** with ETQ) without any significant modification of the safety ratio. On the basis of these results, the development of 4-desmethyl analogues of ETQ, was undertaken in order to permit the introduction of R_5 substituents.

The effect of the 2,2′-substitution in compound **8** was next examined. Introduction of a lipophilic cyclohexyl moiety as in **14** gave an equipotent molecule (compare **14** with **8**) with a reduced safety ratio. Hydrophilic homologues **6** and **7** of potent antioxidant **14** exhibited lowered activities (compare **6** and **7** with **14**) or safety ratio (SR), thus confirming the need of hydrophobicity for a high level of neuroprotection in this model.

In order to assess the contribution of the 6-ethoxy group to the potency of the compounds, C-8-ethoxy regioisomers **9** and **15** were prepared, and their activity compared to parent compounds **8** and **14**. The results indicated that 8-ethoxy analogues were less active than their 6-ethoxy congeners (compare **9** with **8** and **15** with **14**), arguing in favor of the development of a C-6 positional isomer series.

The effect of various groups at C-6 in the 2,2′-cyclohexyl family, in the aim of improving the safety profile of **14** was also examined. In this aim, replacement of the ethoxy moiety with either a methoxy, phenoxy, *tert*-butoxy or

Table 2. Structure of representative 1,2,3,4-tetrahydroquinolines

Compound	R_2	R'_2	R_4	R_5	R_6	R_7	R_8	Yield (%)
23	Me	Me	Me	H	OEt	H	H	91
24	Me	Me	H	Me	OEt	Me	H	88
25	Me	Me	H	Me	OEt	Me	Me	79
26	Me	Me	H	iPr	OEt	iPr	H	85
27	$CH_2(CH_2)_3CH_2$		H	H	OEt	H	H	66
28	$CH_2(CH_2)_3CH_2$		H	Me	OEt	Me	H	91
29	$CH_2(CH_2)_3CH_2$		H	Me	OEt	Me	Me	88

Table 3. Protection against L-HCA-mediated neurotoxicity and intrinsic toxicity of 1,2-dihydro and 1,2,3,4-tetrahydroquinolines

	Protection	Toxicity				Protection	Toxicity		
Compound	PC_{50} (μM)	MTC (μM)	TC_{50} (μM)	Safety ratio MTC/PC_{50}	Compound	PC_{50} (μM)	MTC (μM)	TC_{50} (μM)	Safety ratio MTC/PC_{50}
ETQ	0.41	50	103	122	**16**	0.03	10	19.3	333
Vitamin E	0.80	>200	—	>250	**17**	0.17	10	17.8	59
tBPN	>200	>200	—	Not relevant	**18**	0.12	10	16.9	83
Edaravone	70.4	200	> 200	2.8	**19**	0.49	5	46.9	10
Ebselen	1	10	20	10	**20**	4.75	10	11.2	2.1
6	0.51	10	139	20	**21**	0.13	10	13.2	77
7	0.77	200	200	260	**22**	0.73	1	1.61	1.4
8	0.19	25	56	132	**23**	0.86	50	137	58
9	1.00	100	200	100	**24**	0.16	100	186	625
10	0.35	50	182	143	**25**	0.20	50	128	250
11	0.46	50	123	109	**26**	0.06	10	18.2	167
12	0.07	10	200	143	**27**	0.16	25	74.5	156
13	0.10	25	36.5	250	**28**	0.01	10	17.6	1000
14	0.18	5	17.1	28	**29**	0.15	10	17.2	67
15	0.37	10	17.9	27					

tert-butylcarbonyloxy group gave, respectively, **19**, **20**, **21** and **22**. The results showed that electron-donating substituents (e.g. OtBu ⩾ OEt >OMe >OPiv≫OPh) enhanced the neuroprotective activity of the molecules with a negative impact on the safety ratio (**21** being, however, the exception; compare **14** with **21**). This effect being possibly due to stabilization, of the N-1 aminyl radical,[24] by delocalization of the unpaired electron to the *p*-type lone pair of oxygen in position 6 as reported earlier for Vitamin-E-related antioxidants.[25]

The effect of electron-donor groups (i.e. methyl, isopropyl, *t*-butyl) at C-5, C-7 and/or C-8 on both protection and toxicity was next examined. In the 2,2′-dimethyl-1,2-dihydroquinoline series, no linear dependence of antioxidant activity on the electron density of the aromatic ring was found (compare **8** with **10**, **11**, **12** and **13**). Within this series the safety ratio was found either identical (i.e. **10**, **11**, **12**) or improved (i.e. **13**) to parent compound **8**. In contrast, in the 2,2′-cyclohexyl family, electron donating substituents, resulted in a safer profile to the molecules (compare **14** with **16**, **17** and **18**).

The effect of the C-3, C-4 double bond in both 2,2′-dimethyl and 2,2′-cyclohexyl-1,2-dihydroquinoline series was finally investigated. Hydrogenation of 2,2′-dimethyl-1,2-dihydroquinolines **10**, **11** and **12** gave tetrahydro analogues **24**, **25** and **26** with comparable or enhanced activities as well as higher safety ratio values. A similar effect was observed upon reduction of 2,2′-cyclohexyl-1,2-dihydroquinoline **15**, **16** and **17** resulting in tetrahydroquinolines, **27**, **28** and **29** displaying remarkable neuroprotective levels. It is interesting to note, however, that hydrogenation of ETQ gave tetrahydroquinoline **23** with a decreased antioxidant activity.

These data showed that, neither the electronic density of the aromatic ring nor the lipophilicity of the molecule could account for the considerable biological differences observed. However, within a series of compounds, it is noteworthy that 5,7-dimethyl-quinolines i.e. **10**, **16**, **24** and **28** displayed a considerably enhanced safety ratio compared to their 5,7,8-trimethyl congeners **11**, **17**, **25** and **29**. As previously reported[26] for the parent ETQ, the C-8 position could be implicated in the anti-oxidative process.

In vivo model of CNS-induced oxidative stress: *tert*-butylhydroperoxide-mediated lethality in NMRI mice[27]

Compounds with a protective level (e.g. $PC_{50} \cong 0.50\ \mu M$) and/or a safety ratio (SR >100) comparable to ETQ were tested in an acute neurodegenerative model implicating oxidative stress in vivo. Thus, the ability of a selection (supra) of 1,2-dihydro and 1,2,3,4-tetrahydroquinolines to protect mice from a lethal intracerebroventricular injection of *tert*-butylhydroperoxide (*t*-BuO_2H) was examined. Concomitantly, the effect of selected antioxidants on body temperature in mice[28] was assessed and compounds showing significant dose-related hypothermia (i.e. $\Delta T > 1.0\,^{\circ}C$ at 150 mg/kg) were not suitable for further in vivo evaluation. Data are presented in Table 4.

Table 4. Effects of selected compounds and references on *t*-BuO_2H-mediated lethality and body temperature in NMRI mice

Compound	*t*-BuO_2H survival % (5 h) 150 mg/kg ip	Body temperature (°C) (30 min) 150 mg/kg ip	Compound	*t*-BuO_2H survival % (5 h) 150 mg/kg ip	Body temperature (°C) (30 min) 150 mg/kg ip
ETQ	80	−1.85	**16**	70	−0.30
tBPN	30/60	−2.10	**17**	50	−0.80
Ebselen	20	−1.85	**19**	100	−1.00
Edaravone	80	−2.40	**21**	30	−0.20
8	100	−1.70	**22**	30	−2.80
10	100	−0.90	**24**	80	−0.50
11	70	−2.50	**25**	100	−0.20
12	50	−0.05	**26**	40	−0.50
13	60	−1.00	**27**	60	−0.70
14	80	−0.20	**28**	80	−2.20
15	60	−1.00	**29**	60	−0.80

Despite the reported low central bioavailability,[29] parent ETQ had potent in vivo antioxidative activity in the *t*-BuO_2H model (80% protection) associated with a considerable hypothermic effect. Desmethyl homologues **8**, **11** and **28** showed data closely related to ETQ in term of both protection and hypothermia. In contrast, 4-desmethyl-2,2′-cyclohexyl analogue **14**, although as equally active as ETQ, was shown to possess moderate hypothermia (compare **14** ($\Delta T = 0.2\,^{\circ}C$) with ETQ ($\Delta T = 1.85\,^{\circ}C$)). Compound **19**, unexpectedly, from the primary in vitro screening, demonstrated an improved level of protection to its 6-ethoxy congener **14** but was associated, with a ΔT of 1 °C. To corroborate the dissociation between hypothermic and neuroprotective effects, compound **22** was found to dramatically lower the body temperature at 150 mg/kg ($\Delta T = 2.8\,^{\circ}C$) whereas no significant neuroprotection was observed. On the other hand, tetrahydroquinoline **25**, devoid of hypothermia ($\Delta T = 0.2\,^{\circ}C$), was able to protect mice completely against *t*-BuO_2H-mediated lethality. Moreover, 6-*tert*-butoxydihydroquinoline **21**, a very powerful in vitro antioxidant (e.g. $PC_{50} = 0.13\ \mu M$), was devoid of both protective activity (e.g. 30% protection) and hypothermia ($\Delta T = 0.2\,^{\circ}C$). The data obtained in the present study illustrates the complexity in establishing the criteria for selection of potent antioxidants based exclusively on their in vitro profile. Indeed, the noticeable lack of antioxidants demonstrating therapeutic activity in different neurodegenerative disorders,[30] highlights the inherent difficulties in the selection of centrally acting antioxidants lacking toxic side effects. Nevertheless, a group of antioxidants (**10**, **14**, **19**, **24** and **25**) with high radical scavenger capacities and moderate hypothermia have been selected for further evaluation and are currently being tested on different in vivo models of delayed neuronal degeneration.

Acknowledgements

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22. L-Homocysteic acid-mediated neurotoxicity: L-HCA depletes intracellular glutathione levels in certain cell lines, and the subsequent oxidative stress-mediated cell death can be attenuated with antioxidants.[33] HT-22 cell culture were pre-incubated (1 h) with different concentrations of the studied antioxidant. Cells were then exposed to 2 mM L-HCA, in the presence of antioxidant, for 48 h, and neurotoxicity was estimated relative to 2 mM L-HCA plus 200 μM vitamin E-treated cells (0% toxicity), and 2 mM L-HCA alone (100% toxicity). PC_{50} was estimated via MTT cellular reduction assay[34] by linear regression analyses.
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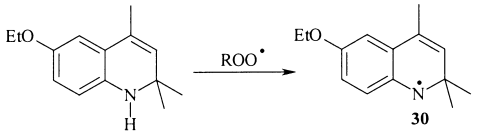

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28. Body temperature measurement in NMRI mice: The rectal temperature was measured in male NMRI (28–35 g) mice with a rectal probe (Physitemp, Bat-12) at $T=0$ h. Animals were then injected intraperitoneally (150 mg/kg in Tween-saline; 20 mL/kg) with either vehicle or the compound under study. Rectal temperature was assessed at 30 min post-injection.
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37. All the compounds described in Tables 1 and 2 gave spectroscopic data (IR, NMR) and acceptable analysis (CHN) in agreement with the assigned structures.