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Synthesis And Free Radical Scavenging Activity of 4-(2H-1,2,4-Benzothiadiazine-1,1-dioxide-3-yl)-2,6-bis(1,1-dimethylethyl)phenols

Annalisa Tait, Stefano Ganzerli, Maria Di Bella*

Dipartimento di Scienze Farmaceutiche- University of Modena, via Campi 183, 4100 Modena, Italy.

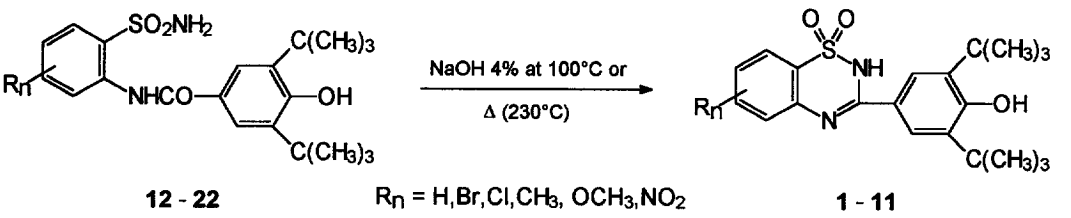
Abstract : 4-(2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-2,6-bis(1,1-dimethylethyl)phenols (**1-11**) were prepared by cyclization of the corresponding 3,5-bis(1,1-dimethylethyl)-4-hydroxy-N-2-(sulphamoylphenyl)benzamides (**12-22**). Compounds **1-22** were tested as free radical scavengers by reaction with DPPH using UV and ESR spectrometry and the formation of stable phenoxy radicals by their oxidation with lead tetraacetate was also studied.

INTRODUCTION

The oxidative metabolites of arachidonic acids and their subsequent derivatives have been implicated as important mediators in a variety of diseases including stroke, myocardial infarction, inflammation, ulcerative colitis, and rheumatoid arthritis.[1] In addition a lot of reports suggest that active oxygen species mediate cell damage in a variety of pathological conditions.[2]

Intensive research in the perturbation of the arachidonate cascade system resulted in the discovery of many interesting agents, some of which have found therapeutic application. Recently two related isoenzymes of cyclooxygenase have been identified in mammalian cells:[3] COX-1 is expressed constitutively while COX-2 is induced in cells exposed to proinflammatory agents, including cytokines, mitogens and endotoxin. The identification of selective isoenzyme inhibitors may eventually lead to safer drugs for inflammation therapy.
Furthermore extensive research has been undertaken to develop dual inhibitors of cyclooxygenase and 5-lipoxygenase with the expectation of superior effectiveness and an improved safety profile.[4]
One of the possible approaches to identifying dual inhibitors has focused on the use of antioxidant in which a 2,6-di-*tert*-butylphenol moiety is linked either directly or to a two-carbon chain linkage or is part of a benzylidene linked to a heterocyclic ring.[5]

This paper describes the synthesis of a series of 4-(2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-2,6-bis(1,1-dimethylethyl)phenols **1** - **11**. These compounds were obtained by cyclization of the corresponding 3,5-bis(1,1-dimethylethyl)-4-hydroxy-N-(2-sulphamoylphenyl)benzamides (**12** -**22**),[6] some of which exhibit a good antiinflammatory activity in carrageenan induced rat paw edema. Cyclization was afforded either by heating with aqueous NaOH or by pyrolysis (Scheme 1).



12 - 22 R_n = H,Br,Cl,CH_3, OCH_3,NO_2 **1 - 11**

Scheme 1

To acquire preliminary information about the antioxidant activity of both series of compounds the stable free radical 2,2-diphenyl-1-(2,4,6-trinitrophenyl)hydrazil (DPPH) was used and the scavenging effect was determined by UV spectrometry. The radical scavenging activity of each compound was expressed by the ratio of lowering of the absorption of DPPH relative to the absorption of DPPH solution in the absence of compound (control). Furthermore the time courses of the decrease of DPPH concentration was evaluated at different concentrations for selected compounds. Selected compounds were evaluated by electron spin resonance (ESR) spectrometry also. Moreover the stable phenoxy radicals obtained by oxidation with lead tetraacetate of compounds **1 - 22** were studied.

RESULTS AND DISCUSSION

The cyclization of 3,5-bis-(1,1-dimethylethyl)-4-hydroxy-N-(2-sulphamoylphenyl)benzamides (**12 - 22**) by heating with aqueous NaOH (Method A) afforded the title compound except **3**, **4**, **7** and **11** which were obtained by direct heating (Method B) of the corresponding benzamides.

UV measurements of free radical scavenging activity (S.A.%) for 1.0 x 10^{-4}M solution, after storage for 6 hours (Table 1) show that all the studied compounds scavenge the DPPH radical. The DPPH absorbances show a non-linear dose dependant exponential decay (Fig. 1-3). Between the two examined series that of 4-(2-H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-2,6-bis(1,1-dimethylethyl)phenols (**1-11**) is proved to be the most active even though it is less effective than 4-methyl-2,6-bis-(1,1-dimethylethyl)phenol (BHT) which under these conditions shows a 100% scavenging effect.

The influence of the substituents at the benzene ring on the parameter under investigation is negligible in the series of benzamides (**12 - 22**). In the case of the series of the most active compounds **1 - 11** the bz-substitution plays a most significant role. 6-Methyl and 6-methoxy-substitution (compounds **9** and **10**) reduces the scavenging activity, while 5,7-dihalogensubstitution (compounds **3** and **7**) improves it.

Table 1. Absorbance decrease at 514 nm versus control (ΔA) and (S.A.%) for 1.0 x 10^{-4}M solutions of compounds **1 - 22** after 6 hours

Comp	R_n	ΔA	S.A.%	Comp	R_n	ΔA	S.A.%
1	6-Br	0.154± 0.02	29,09	**12**	5-Br	0.041 ± 0.02	7,90
2	7-Br	0.147 ± 0.02	27,67	**13**	4-Br	0.047 ± 0.03	9,10
3	5,7-diBr	0.331 ± 0.03	62,32	**14**	4,6-diBr	0.059 ± 0.01	11,35
4	6,7-diBr	0.177 ± 0.02	33,42	**15**	4,5-diBr	0.042 ± 0.01	8,10
5	6-Cl	0.155 ± 0.01	29,18	**16**	5-Cl	0.041 ± 0.02	7,81
6	7-Cl	0.143 ± 0.03	26,92	**17**	4-Cl	0.044 ± 0.03	8,43
7	5,7-diCl	0.309 ± 0.02	58,17	**18**	4,6-diCl	0.043 ± 0.01	8,34
8	6-CF_3	0.168 ± 0.01	31,63	**19**	5-CF_3	0.036 ± 0.02	6,85
9	6-CH_3	0.075 ± 0.03	14,12	**20**	5-CH_3	0.033 ± 0.01	6,28
10	6-OCH_3	0.077 ± 0.03	14,50	**21**	5-OCH_3	0.040 ± 0.01	7,60
11	7-NO_2	0.168 ± 0.01	31,63	**22**	4-NO_2	0.039 ± 0.03	7,43

Fig. 1 : Time courses of decrease in DPPH concentration for compound **3**

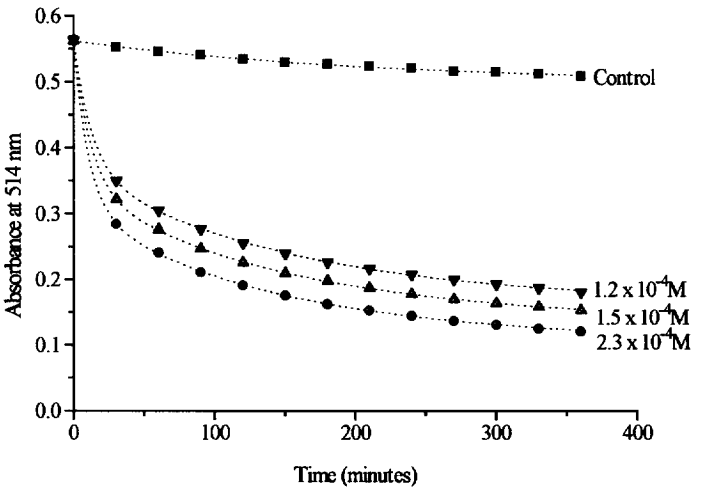


Fig.2 : Time courses of decrease in DPPH concentration for compound **6**

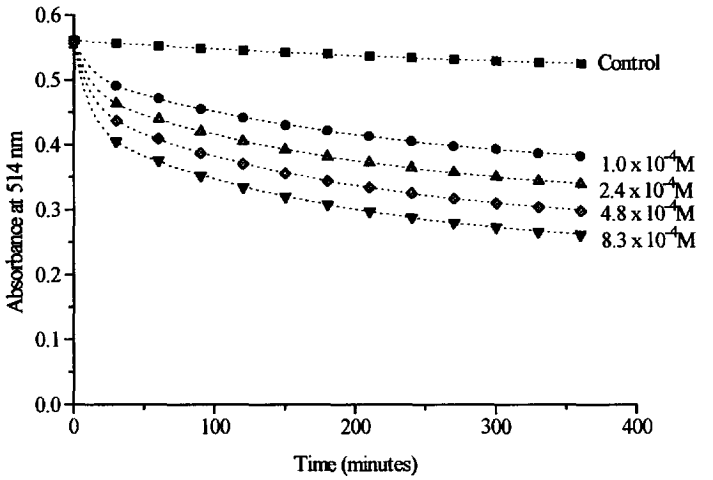
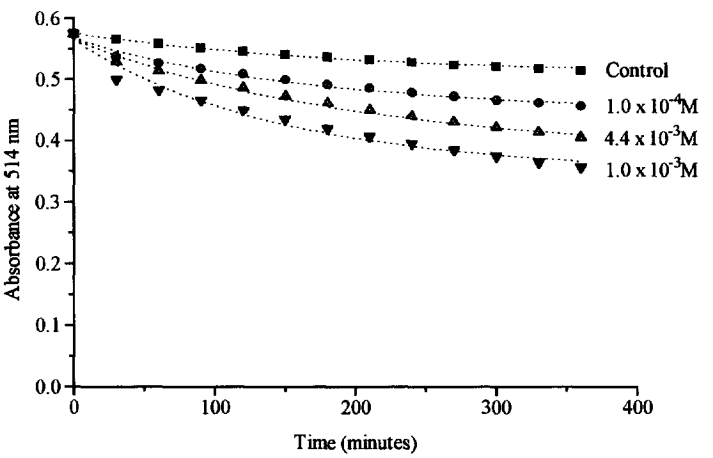


Fig. 3 : Time courses of decrease in DPPH concentration for compound **14**



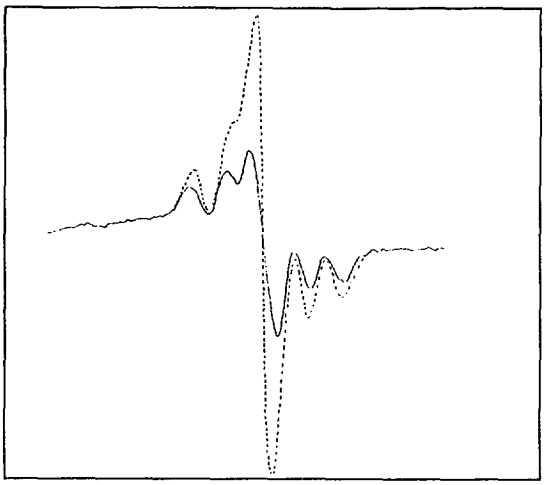
Data obtained by ESR measurements for compounds **1**, **3** and **22** are in agreement with UV data (± 2%). The scavenging activity was calculated according to the equation (1) :

$$S.A.\ \% = \frac{100 \times \Delta h_x}{h_t} \qquad (1)$$

where h_t is the control signal height and Δh_x the difference between h_t and signal height obtained with the mixture DPPH and tested compound.

During ESR experiments with 4-(2-H-5,7-dibromo-1,2,4-benzothiadiazine-1,1-dioxide -3-yl)-2,6-bis-6-(1,1-dimethylethyl)phenol (**3**), which proved to be the most reactive in the series, the appearance of an overlapping signal due to the formation of another radical in addition to the decrease of signal intensity of the DPPH radical was observed. The intensity of the overlapping signal decays in a time dependant manner [Fig.4]. The newly appeared signal may be attributable to the phenoxy radical derived from the tested compound. This assignment was supported by the g value of the phenoxy radical obtained by oxidation of compound **3** with lead tetracetate (Table 2).

Fig.4 ESR spectra of 1:1 (v/v) DPPH and compound **3** after 1 [---] and 6 hours [–]



Condition : magnetic field 3420 Gauss, power 2 mW, response 0.5 sec., modulation 0.16 Gpp, room temperature, amplitude 4 x 10^5, scan time 200 sec.

Table 2. ESR parameters of free radicals produced by oxidation of **1 - 22** with lead tetraacetate

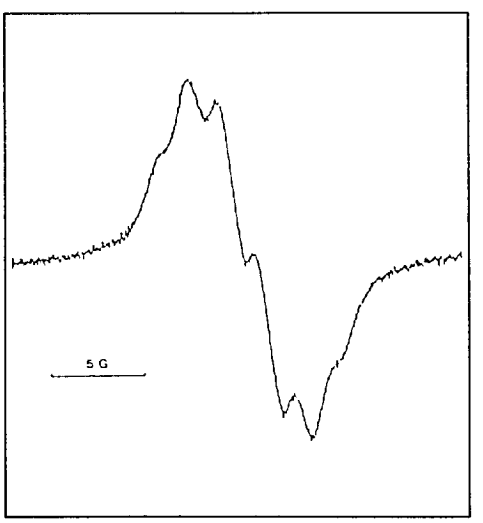
Comp	R_n	g	Comp	R_n	g	a_{m-H}
1	6-Br	2.00805	**12**	5-Br	2.00674	2.3
2	7-Br	2.00430	**13**	4-Br	2.00785	2.3
3	5,7-diBr	2.00641	**14**	4,6-diBr	2.00476	2.2
4	6,7-diBr	2.00480	**15**	4,5-diBr	2.00483	2.3
5	6-Cl	2.00738	**16**	5-Cl	2.00240	2.2
6	7-Cl	2.00435	**17**	4-Cl	2.00233	2.3
7	5,7-diCl	2.00767	**18**	4,6-diCl	2.00382	2.2
8	6-CF_3	2.00492	**19**	5-CF_3	2.00483	2.3
9	6-CH_3	2.00474	**20**	5-CH_3	2.00470	2.2
10	6-OCH_3	2.00463	**21**	5-OCH_3	2.00477	2.3
11	7-NO_2	2.00508	**22**	4-NO_2	2.00503	2.3

The spectra of phenoxy radicals derived from compounds **12 - 22** show a triplet attributable to the coupling of the unpaired electron with the meta protons of the phenolic ring (a_{m-H}). The a_{m-H} values for phenoxy radicals

derived from compounds **1** - **11** were not assigned because their spectra under moderate resolution consist of approximately 6 lines. This splitting pattern derives from the delocalization of the unpaired electron on the benzothiadiazine ring. This wider delocalization accounts for the longer lifetime of radicals generated from compounds **1** - **11** and also for their stronger scavenger activity compared with the parent compounds **12** - **22**. As example Fig. 5 and 6 show the ESR spectrum of the phenoxy radical obtained from oxidation of **3** and **14** respectively.

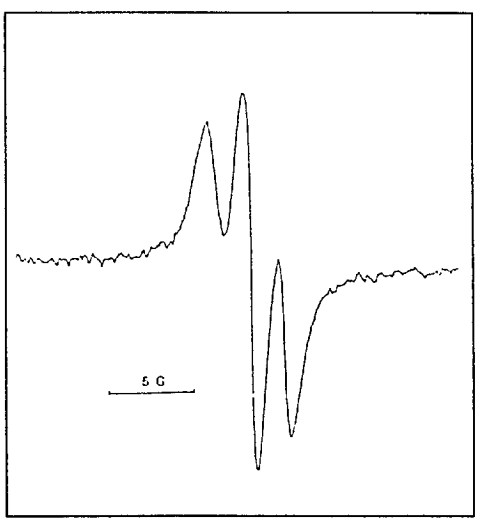
The obtained data show that cyclization of sulfamides **12** - **22** affords compounds with improved antioxidant profile.

Fig. 5 : The ESR spectrum of radical obtained from compound **3**



Condition : magnetic field 3420 Gauss, power 2 mW, response 0.2 sec., modulation 0.125 Gpp, room temperature, amplitude 5 x 10^5, scan time 200 sec.

Fig. 6 : The ESR spectrum of radical obtained from compound **14**



Condition : magnetic field 3420 Gauss, power 2 mW, response 0.5 sec., modulation 0.16 Gpp, room temperature, amplitude 4 x 10^5, scan time 200 sec.

EXPERIMENTAL

General M.P. Electrothermal apparatus, uncorr.. ^{1}H-NMR spectra were recorded with a Varian XL-200 spectrometer using $DMSO_{d6}$ and $CDCl_3$ as solvents and tetramethylsilane (TMS) as external standard. Chemical

shifts are in ppm (δ) and coupling constants (J) in Hz. Multiplicities are abbreviated as follows: s, singlet; d, doublet; b, indicates a broadening of the signal; *, D_2O changeable. IR spectra were recorded on a Perkin-Elmer mod.681 and UV spectra on a Perkin Elmer Lambda 15 UV/VIS spectrophotometers. The spectra were in agreement with the proposed structures. Purity was checked by TLC performed on aluminium sheets silica gel 60 F_{254} , 0.2 mm thick: solvent chloroform-acetone 95:5. Flash chromatography was performed on Silica gel Merck (230-400 mesh). Elemental analyses were performed in Microanalysis Laboratory of Dipartimento di Scienze Farmaceutiche of Modena University on a Carlo Erba Elemental Analyzer 1106 apparatus.

4-(2H-1,2,4-Benzothiadiazine-3-yl)-2,6-bis-(1,1-dimethylethyl)phenols 1,1-dioxide 1 - 11

Method A: The starting 2-(acylamino)benzensulfonamide dissolved in 4% NaOH (100 ml per g of substance) was heated on a boiling waterbath for 7 hours. After cooling, the alkaline solution, first saturated with a current of CO_2 to separate possible decomposition products, supplied the title compounds on acidification with HCl. The crude phenol was washed with H_2O, dried in vacuo and then purified by fractional crystallization from acetone/petrol ether b.p. 80 - 100°C.

Method B: The starting 2-(acylamino)benzensulfonamide was heated at 230°C for 5 - 10 minutes. After cooling the residue was percolated on silica gel column (eluent: chloroform-acetone 95:5) following the flash chromatography procedure. The selected fractions were collected and evaporated under reduced pressure then the residue crystallized from acetone/petrol ether b.p. 80 - 100°C to give the title compounds.

4-(6-bromo-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-2,6-bis-(1,1-dimethylethyl)phenol (1) : Method A, 58%, mp 385°C dec ; ^{1}H-NMR ($DMSO_{d6}$) : 1.43 (18H, s), 7.63 (1H, dd, J = 8.4, 1.8 Hz), 7.75 (2H, s), 7.77 (1H, d, J = 8.4 Hz), 7.83 (1H, d, J = 1.8 Hz), 11.92 (1H, b s*); IR (Nujol) ν_{max} 3594, 3367, 1605, 1550, 1375, 1169 cm^{-1}; UV λ_{max}(EtOH) nm (log ε) 302.2 (9.97) ; Anal.Calcd. for $C_{21}H_{25}BrN_2O_3S$:C, 54.20 ; H, 5.42 ; N, 6.02 ; Found : C, 53.99 ; H, 5.41 ; N, 5.91.

4-(7-bromo-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-2,6-bis-(1,1-dimethylethyl)phenol (2) : Method A, 46%, mp 336°C dec ; ^{1}H-NMR ($DMSO_{d6}$) : 1.43 (18H, s), 7.56 (1H, d, J = 8.8 Hz), 7.75 (2H, s), 7.89 (1H, dd, J = 8.8, 2.2 Hz), 7.96 (1H, d, J = 2.2 Hz), 12.05 (1H, b s*); IR(Nujol) ν_{max} 3557, 3254, 1601, 1537, 1378, 1162 cm^{-1}; UV λ_{max}(EtOH) nm (log ε) 304.1 (9.96) ; Anal.Calcd. for $C_{21}H_{25}BrN_2O_3S$:C, 54.20 ; H, 5.42 ; N, 6.02 ; Found : C, 54.09 ; H, 5.66 ; N, 5.81.

4-(5,7-dibromo-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-2,6-bis-(1,1-dimethylethyl)phenol (3) : Method B, 31%, mp 321°C dec ; ^{1}H-NMR ($CDCl_3$) : 1.49 (18H, s), 5.58(1H, s*), 7.82 (2H, s), 7.95 (1H, d, J = 2.1 Hz), 8.09 (1H, d, J = 2.1 Hz), 8.95 (1H, b s*); IR(Nujol) ν_{max} 3575, 3358, 1597, 1542, 1496, 1372, 1171

cm^{-1}; UV λ_{max}(EtOH) nm (log ε) 312.7 (9.86); Anal.Calcd. for $C_{21}H_{24}Br_2N_2O_3S$:C, 46.34 ; H, 4.44 ; N, 5.15 ; Found : C, 46.29 ; H, 4.39 ; N, 5.02.

4-(6,7-dibromo-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-2,6-bis-(1,1-dimethylethyl)phenol (4) : Method B, 36%, mp 340°C dec ; ^{1}H-NMR ($DMSO_{d6}$) : 1.42 (18H, s), 7.79 (2H, s), 7.95 (1H, s), 8.11 (1H, s), 11.54 (1H, b s*); IR(Nujol) ν_{max} 3556, 3259, 1600, 1587, 1371, 1160cm^{-1}; UV λ_{max}(EtOH) nm (log ε) 326.0 (9.99), 280.2 (9.52) ; Anal.Calcd. for $C_{21}H_{24}Br_2N_2O_3S$:C, 46.34 ; H, 4.44 ; N, 5.15 ; Found : C, 46.49 ; H, 4.51 ; N, 5.22.

4-(6-chloro-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-2,6-bis-(1,1-dimethylethyl)phenol (5) : Method A, 35%, mp 374°C dec ; ^{1}H-NMR ($DMSO_{d6}$) : 1.44 (18H, s), 7.51 (1H, dd, J = 8.5, 2.0 Hz), 7.66 (1H, d, J = 2.0 Hz), 7.75 (2H, s), 7.85 (1H, d, J = 8.5 Hz), 11.95 (1H, b s*); IR(Nujol) ν_{max} 3598, 3366, 1608, 1551, 1374, 1170 cm^{-1}; UV λ_{max}(EtOH) nm (log ε) 301.2 (9.98) ; Anal.Calcd. for $C_{21}H_{25}ClN_2O_3S$:C, 59.92 ; H, 5.99 ; N, 6.65 ; Found : C, 59.77 ; H, 5.98 ; N, 6.61.

4-(7-chloro-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-2,6-bis-(1,1-dimethylethyl)phenol (6) : Method A, 42%, mp 315°C dec ; ^{1}H-NMR ($DMSO_{d6}$) : 1.43 (18H, s), 7.63 (1H, d, J = 9.0 Hz), 7.75 (2H, s), 7.77 (1H, dd, J = 9.0, 2.4 Hz), 7.87 (1H, d, J = 2.4 Hz), 12.05 (1H, b s*); IR(Nujol) ν_{max} 3612, 3345, 1607, 1550, 1380, 1172 cm^{-1}; UV λ_{max}(EtOH) nm (log ε) 301.8 (10.10) ; Anal.Calcd. for $C_{21}H_{25}ClN_2O_3S$:C, 59.92 ; H, 5.99 ; N, 6.65 ; Found : C, 59.68 ; H, 6.01 ; N, 6.51.

4-(5,7-dichloro-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-2,6-bis-(1,1-dimethylethyl)phenol (7) : Method B, 38%, mp 338°C dec ; ^{1}H-NMR ($DMSO_{d6}$) : 1.42 (18H, s), 7.72 (2H, s), 7.92 (1H, d, J = 1.9Hz), 8.02 (1H, s*), 8.11 (1H, d, J = 1.9Hz), 11.54 (1H, b s*); IR(Nujol) ν_{max} 3556, 3354, 1598, 1545, 1378, 1175 cm^{-1}; UV λ_{max}(EtOH) nm (log ε) 320.8 (9.90), 273.4 (9.47), 205.9 (9.66) ; Anal.Calcd. for $C_{21}H_{24}Cl_2N_2O_3S$:C, 55.39 ; H, 5.31 ; N, 6.15 ; Found : C, 55.58 ; H, 5.40 ; N, 6.21.

4-(6-trifluoromethyl-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-2,6-bis-(1,1-dimethylethyl)phenol (8) : Method A, 38%, mp 365°C dec ; ^{1}H-NMR ($DMSO_{d6}$) : 1.44 (18H, s), 7.78 (1H, dd, J = 8.3, 1.5 Hz), 7.80 (2H, s), 7.98(1H, d, J = 1.5 Hz), 8.07(1H, d, J = 8.3 Hz), 12.07 (1H, b s*); IR(Nujol) ν_{max} 3605, 3243, 1616, 1558, 1374, 1158cm^{-1}; UV λ_{max}(EtOH) nm (log ε) 302.6 (9.94); Anal.Calcd. for $C_{22}H_{25}F_3N_2O_3S$:C, 58.14 ; H, 5.54 ; N, 6.16 ; Found : C, 58.37 ; H, 5.84 ; N, 5.98.

4-(6-methyl-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-2,6-bis-(1,1-dimethylethyl)phenol (9) : Method A, 77%, mp 322°C dec ; ^{1}H-NMR ($CDCl_3$) : 1.46 (18H, s), 2.29 (3H, s), 5.75 (1H, s*), 6.95 (1H, s), 6.97 (1H, d, J = 7.9 Hz), 7.67 (1H, d, J = 7.9 Hz), 7.69 (2H, s), 8.96 (1H, b s*); IR(Nujol) ν_{max} 3612, 3535, 1617, 1598, 1376, 1162cm^{-1}; UV λ_{max}(EtOH) nm (log ε) 294.4 (9.97); Anal.Calcd. for $C_{22}H_{28}N_2O_3S$:C, 65.96 ; H, 7.04 ; N, 6.99 ; Found : C, 65.87 ; H, 6.94 ; N, 6.82.

4-(6-methoxy-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-2,6-bis-(1,1-dimethylethyl)phenol (10) : Method A, 73%, mp 365°C dec ; ^{1}H-NMR ($DMSO_{d6}$) : 1.43 (18H, s), 3.85 (3H, s), 7.02 (1H, dd, J = 8.8, 2.1 Hz), 7.08 (1H, d, J = 2.1 Hz), 7.72 (1H, d, J = 8.8 Hz), 7.73 (2H, s), 11.75 (1H, b s*); IR(Nujol) ν_{max} 3602, 3369, 1616, 1562, 1374, 1159cm^{-1}; UV λ_{max}(EtOH) nm (log ε) 299.3 (10.04); Anal.Calcd. for $C_{22}H_{28}N_2O_4S$:C, 63.44 ; H, 6.77 ; N, 6.72 ; Found : C, 63.67 ; H, 6.79 ; N, 6.92.

4-(7-nitro-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-2,6-bis-(1,1-dimethylethyl)phenol (11) : Method B, 30%, mp 315°C dec ; ^{1}H-NMR ($DMSO_{d6}$) : 1.43 (18H, s), 7.80 (1H, d, J = 8.4 Hz), 7.81 (2H, s), 7.96 (1H, b s*), 8.51 (1H, dd, J = 8.4, 2.4 Hz), 8.52 (1H, d, J = 2.4 Hz), 12.43 (1H, b s*); IR(Nujol) ν_{max} 3588, 3263, 1617, 1555, 1375, 1172cm^{-1}; UV λ_{max}(EtOH) nm (log ε) 397.6 (9.80), 248.4.(9.61), 207.8 (10.86); Anal.Calcd. for $C_{21}H_{25}N_3O_5S$:C, 58.45 ; H, 5.84 ; N, 9.74 ; Found : C, 58.61 ; H, 5.79 ; N, 9.92.

Radical Scavenging Effect on DPPH Radical

UV measurements : 2 ml of an ethanolic solution of the tested compound was added to 2 ml of a DPPH solution (1 x 10^{-4} M) (Sigma), and the reaction mixture was shaken vigorously and kept at 37°C ± 0.02 (Haake F 3-C Thermocriostat) in air. DPPH absorption was measured at 514 nm every thirty minutes. The mean values were obtained from quadruplicate experiments.

ESR measurements : reaction mixtures of DPPH and tested compounds were prepared as reported for UV experiments. Aliquots of the mixtures were placed in a special aqueous flat cell (WG-808Q Wilmad) and DPPH radical spin resonance was analysed by ESR spectrometry [Bruker ER 200-SRC]. Conditions of ESR spectrometry for measurements were as follows : magnetic field 3420 Gauss ; power 2mW ; response 0.5 sec. ; scan time 200 sec..

Oxidation with lead tetraacetate : a 10^{-3}M solution in dichloromethane of the tested compounds was treated with solid lead tetraacetate (ratio 1:1 Mol for **1 - 11** and 1:10 for **12 - 22**). The ESR spectra of radicals obtained were recorded and the g-factor of each radical was estimated using DPPH as g-factor reference. The hyperfine splitting constants $a_{m\text{-}H}$ are given in mT.

References

1. (a) Samuelsson, B. *Science*, **1983**, *220*, 568.(b) Ford-Hutchinson, A.W. *Fed.Proc.***1985**, *44*,25.
2. (a) Fridvich, I. *Annu.Rev.Pharmacol.Toxicol.***1983**, *23*, 239. (b) McCord, J.M. *N.Engl.J.Med.***1985**, *312*, 159. (c)Halliwell,B. ; Gutteridge, J.M. *Trends Biochem.Sci. (Pers.Ed.)* **1986**, *11*, 372 (d) Youngman, R.Y. Ibid. **1984**, *9*, 280.
3. (a) Xie, W. ; Robertson, D.L. ; Simmonson, D.L.*Drug Develop.Res.***1992**, *25*, 249-265. (b) DeWitt, D.L. ; Smith, W.L. *Am.J.Med.***1993**, *95*(Suppl.2A), 2A-40S-2A-44S. (c) Mitchell J.A. ; Akarasereenont P. ; Thiemermann C., Flower R.J. ; Vane J.R. *Proc.Natl.Acad.Sci.USA*, **1994**, *90*, 11693-11697.
4. (a) Carty T.J. ; Marfat A. ; Masamune, H. . In *Annual Reports in Medicinal Chemistry ;* Allen, R.C., Ed. ; Academic press : New York, 1988 ; Vol.23, pp 181-9. (b) Laufer, S.A. ; Augustin,J. ; Dannhardt, G. ; Kiefer, W. *J.Med.Chem.***1994**, *37*, 1894-7. (c) Boscelli, D.H. ; Connor, DE.T. ; Bornemeier, D.A. ; Dyer, R.D. ; Kennedy,J.A. ; Kuipers, P.J. ; Okonkwo, G.C. ; Schrier, D.J. ; Wright,C.D. *J.Med.Chem.***1993**, *36*, 1802-10. (d) Bonne, C.; Muller, A.; Latour, E.; Tissie, G.; Emerit I.; Modat, G.; Dornand, J, Roch, M.; Giroud, J.P.; Grisworld, D.E.; Marshall, P.J.; Coquelet, C. *Arzneim. Forsc.***1989**, *39*, 1242. (e) Marshall, P.J.; Grisword, D.E.; Breton, J.; Webb, E.F.; Hillegass, L.M.; Sarau, H.M.; Newton, J.,Jr.; Lee, J.C.; Bender, P.E.; Hanna,N. *Biochem. Pharmacol.* **1991**, *42*, 813-824. (f) Grisword, D.E.; Marshall, P.J.; Lee, J.C.; Webb, E.F.; Hillegass, L.M.; Wartell, J.; Newton, J., Jr.; Hanna, N. *Biochem. Pharmacol.* **1991**, *42*, 825-831.(d) Mylari, B.; Carty, T.J.; Moore, P.F.; Zembrowski, W.J. *J.Med.Chem.* **1990**, *33*, 2019-2024.
5. (a) Ikuta, H.; Shirota, H.; Kobayashi, S.; Yamagishi, Y.; Yamada, K.; Yamatsu, I.; Katayama, K. *J.Med.Chem.* **1987**, *30*, 1995-1998.(b) Unangst,P.C. ; Shrum, G.P. ; Connor,D.T. ; Dyer, R.D. ; Schrier, D.J. *J.Med.Chem.***1992**, *35*, 3691-8. (c) Flyn, D.L. ; Belliotti, T.R. ; Boctor, A.M. ; Connor, D.T. ; Kostlan, C.R. ; Nies, D.E. ; Ortwine, D.F. ; Schrier, D.J. ; Sircar, J.C. *J.Med.Chem.* **1991**, *34*, 518-25. (d) Unangst,P.C. ; Connor,D.T. ; Cetenko, W.A. ; Sorenson, R.J. ; Kostlan, C.R. ; Sircar,J.C. ; Wright, D.C. ; Schrier, D.J. ; Dyer, R.D. *J.Med.Chem.***1994**, *37*, 322-8. (e) Calhoun, W. ; Carlson, R.P. ; Crossley, R. ; Datko, L.J. ; Dietrich, S. ; Heatherington, K. ; Marshall, L.A. ; Meade, P.J. ; Opalko, A. ; Shepard, R.G., *J.Med.Chem.***1995**, *38*, 1473-1481.
6. Tait, A. ; Parenti, C. ; Zanoli, P. ; Veneri, C. ; Truzzi, C. ; Brandoli, C. ; Baraldi, M. ; Di Bella, M. *Il Farmaco,* **1993**, *48*, 1463-73

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