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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and pharmacological evaluation of antioxidant chalcone derivatives of 2(3*H*)-benzoxazolones

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Abstract Chalcones featuring an analgesic/anti-inflammatory pharmacophore, i.e., the 2(3*H*)-benzoxazolone heterocycle, on the one hand, and a radical scavenger moiety, i.e., 2,6-di-*t*-butylphenol, on the other hand were synthesized by condensation of a ketone 2(3*H*)-benzoxazolone precursor with 3,5-di-*t*-butyl-4-hydroxybenzaldehyde. Among the various methods explored (acid homogenous or heterogenous catalysis, base catalysis), heterogenous catalysis conditions using KSF Montmorillonite were found to be the most convenient. The *E*-geometry of the so-obtained chalcones was ascertained both by ^{1}H and ^{13}C-nuclear magnetic resonance (NMR) spectroscopy as well as B3LYP/6-31G** quantum mechanics calculations. Chalcones **1**–**8** were pharmacologically evaluated in vitro for their ability to prevent human low-density lipoprotein (LDL) copper-induced oxidation using Cu^{2+} as oxidizing agent. Compound **4** emerged as the most promising agent as it was able to inhibit copper-mediated human LDL oxidation with an activity ten times greater than that of Probucol, a reference antioxidant drug.

Keywords 2(3*H*)-benzoxazolone · Chalcone derivatives · Synthesis · Antioxidant evaluation

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Introduction

The pharmacology of 6-acyl-2(*3H*)-benzoxazolones has been extensively investigated because these compounds were found to posses interesting anti-inflammatory and analgesic properties (Poupaert *et al.*, 2005; Yous *et al.*, 2001, 2005; Safak *et al.*, 1992; Pilli *et al.*, 1993; Blanc-Delmas *et al.*, 2006). In particular, 6-benzoyl–2(*3H*)-benzoxazolone (CERM 10194) and its sulfur bioisoster 6-benzoyl-2(*3H*)-benzothiazolone (S-14080) were found to exhibit potent analgesic activity in several in vivo tests [acetic acid writhing, Koster, carrageenan, and prostaglandin E_2 (PGE_2) hyperalgesia] (Yous *et al.*, 2005). In these tests, the most active compound of this series, i.e., 6-benzoyl-2(3*H*)-benzothiazolone, was found to be superior to acetylsalicylic acid and equivalent to glafenine. As such, the 2(*3H*)-benzoxazolone (BOA) and benzothiazolone (BZT) heterocycles are endowed with antioxidant properties mediated by their radical scavenger ability (Orhan *et al.*, 1999). On the other hand, the 1,6-di-*t*-butylphenol moiety has long been known as a potent radical scavenging system (Sgaragli *et al.*, 1993). In an effort to design a compound endowed both with anti-inflammatory/analgesic and radical scavenger properties, the BOA/BZT heterocycle was linked to the 1,6-di-*t*-butylphenol moiety via a chalcone linker. Additionally, the chalcones studied here can be considered as vinylogous structures of CERM 10194 and S-14080 (Fig. 1).

Chalcone structures have been employed to generate pharmacomolecules active as anti-inflammatory, antineoplastic, etc. agents. The CH=CH–C=O chain allows for electronic delocalization of a free-radical position via extensive mesomeric effects and free-radical stabilization through the so-called capto-dative effect, a concept introduced in the 1980s by Viehe and coworkers (Stella *et al.*, 1978). The capto-dative effect is based on the following concept: while carbocations are stabilized by electron-donating substituents and carbanions are stabilized by electron-withdrawing substituents, radicals gain stability when flanked by a push–pull system.

In this paper, we report the detailed synthetic approach of the chalcones designed as illustrated in Fig. 2, their structure assignment by spectroscopy [^{1}H and ^{13}C-NMR, infrared (IR)] and theoretical calculations [hypergeometric-type function (HTF) quantum mechanics method] and their pharmacological evaluation as antioxidants.

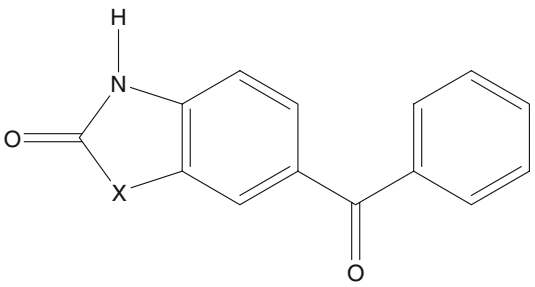


Fig. 1 Structure of CERM 10194 (X = O) and S-14080 (X = S)

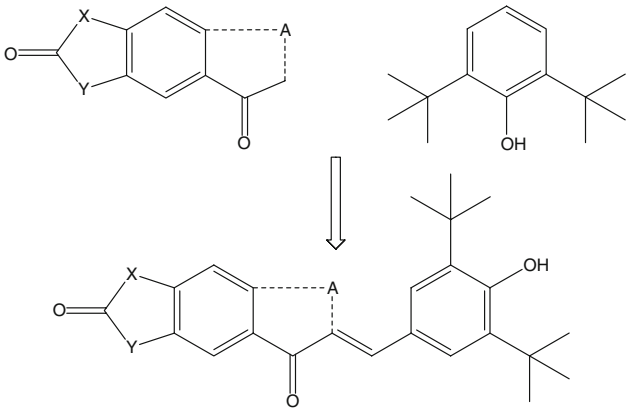


Fig. 2 Design of the chalcones: the analgesic/anti-inflammatory pharmacophore I is connected to the radical scavenger moiety II resulting in the general structure III featuring a chalcone linkage

Results and discussion

Chemistry

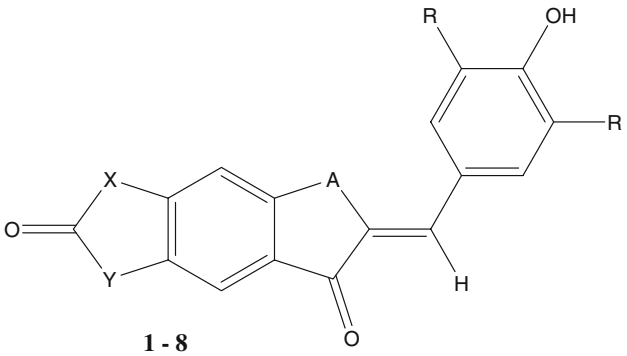
Most chalcone syntheses are performed in general using the base-catalyzed Claisen–Schmidt condensation to yield the *E* species in good to excellent yield. In some more rare cases, the reaction is carried out under acid-catalyzed conditions, especially when one of the partners, either the aldehyde or the acetophenone, is base sensitive (Rendy *et al.*, 2004). BOA, and to a lesser extent BZT, are considered base sensitive (Ilieva *et al.*, 2003). As a consequence, the acid-catalyzed approach appears a priori more favorable.

A model chalcone was first prepared by condensing 4-hydroxybenzaldehyde with 6-acetyl-2(*3H*)-benzoxazolone both under basic and acid conditions (Table 1). This work was undertaken to optimize reaction conditions and to verify the *E* configuration of the chalcone double bond. It is indeed known that the ratio *E*/*Z* varies as a function of the reaction conditions. It has been reported (Climent *et al.*, 2004) that, under basic conditions, condensation for 2 h at 80°C of acetophenone and benzaldehyde in a biphasic system (benzene/water) using sodium hydroxide and tetraethylammonium hydroxide as a phase transfer catalyst gave the corresponding chalcones in 96:4 *E*/*Z* ratio. In acidic conditions, also at 80°C in benzene for 3 h and using HY zeolite as a proton source, the resulting *E*/*Z* ratio was found to be 92:8. Owing to the phase transfer conditions used, the chalcone formation is virtually irreversible (kinetic control) while in acidic homogeneous conditions equilibration between the *Z* and *E* species remains possible (thermodynamic control). On the other hand, the chalcones isolated by crystallization (see the "Experimental Section") were found to possess the *E* configuration as judged on the basis of the coupling constant $^{3}J_{H-H}$ of 16 Hz. Quantum-mechanical calculations performed with the basis set B3LYP/6–31G** on benzylideneacetophenone revealed that there was an energy difference of 6.1 kcal/mol in favor of the *E*

species. Similar calculations performed on our benchmark compounds, i.e., 6-(*E*)-3-((4-hydroxyphenyl)acryloyl)benz[d]oxal-2(*3H*)-one (**1**) and 6-(E)-3-((3,5-di-t-butyl-4-hydroxyphenyl)acryloyl)benz[d]oxal-2(*3H*)-one (**2**), the chalcones arising from condensation of 2(*3H*)-benzoxazolone with 4-hydroxybenzaldehyde or 3,5-di-t-butyl-4-hydroxybenzaldehyde, gave similar figures of 5.8 and 6.2 kcal/mol, respectively, again in favor of the *E* species. These calculations reinforced the concept of the superior thermodynamic stability of the *E*-chalcones. Lutz and Jordan prepared *Z*-chalcones in the 1950s by photoisomerization and the so-obtained *Z*-benzalacetophenone could be easily isomerized thermally to the *E*-species (Lutz and Jordan, 1950). This observation thus validates our calculations.

All the compounds reported here were prepared initially using a hydrochloric-acid-saturated ethanolic solution as reaction medium (see experimental method A). While this procedure proceeds well to give fair to good yields, we found an alternative reported technique that takes advantage of the clay Montmorillonite KSF, which acts as a strong acidic catalyst in this process. This very promising procedure, inspired by "green" chemistry, is solvent free, and the catalyst can be recovered at the end of the reaction and reused, but presents the disadvantage of being rather slow (12 h) even at the relatively high temperature employed (130°C) (Ballini *et al.*, 2001). These reaction conditions were explored with our substrates and optimized, particularly in terms of temperature. Indeed, the condensation reaction was found to proceed to completion within 24 h at 85°C, provided that the

Table 1 Structure of compounds **1–8**



1 - 8

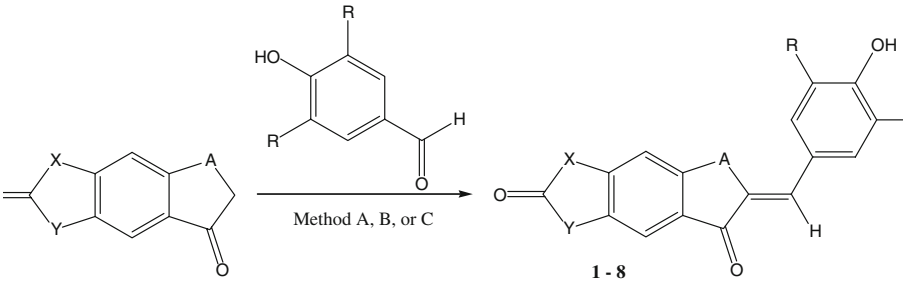
Compound	X	Y	A	R
1	NH	O	–	H
2	O	NH	–	*t*-C_4H_9
3	O	N–CH_3	–	*t*-C_4H_9
4	N–CH_3	O	$CH(CH_3)$	*t*-C_4H_9
5	O	N–CH_3	$CH(CH_3)$	*t*-C_4H_9
6	O	N–CH_3	CH_2–$CH(CH_3)$	*t*-C_4H_9
7	NH	O	$CH(CH_3)$	*t*-C_4H_9
8	O	NH	CH_2–$CH(CH_3)$	*t*-C_4H_9

amount of KSF was kept relatively high. In our hands, the optimum acetophenone derivative/KSF ratio by weight was nearly 1 (see experimental method B). In view of the ease of the procedure and the simplicity of the recovery of the final product, method B was tested on our benchmark compounds. While the method proceeded well for synthesis of **1**, it was found to be less efficient for synthesis of **2** due to extensive sublimation of the aldehyde component. The base-catalyzed method (method C) was found to be even less efficient, presumably due to the extensive oxidation of the aldehyde partner, especially in the case of 3,5-di-*t*-butyl-4-hydroxybenzaldehyde.

Another structural problem was evident when we condensed indanone (i e., 2,7-dioxo-3-methylcyclopenta[f]benzoxazole) with 3,5-di-*t*-butyl-4-hydroxybenzaldehyde (Scheme 1) under acid-catalyzed conditions. After crystallization from toluene, a single stereoisomer was obtained [thin-layer chromatography (TLC), NMR]. However, on the basis of ^{1}H- and ^{13}C-NMR, it was difficult to assign the *Z* or *E* configuration to the resulting adduct **4** (which is 2-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)-2,3-dihydro-3-methylinden-1-one benzoxazolin'one derivative). HTF ab initio quantum mechanics calculations performed in the same conditions as above on compound **4** gave an energy difference of 3.63 kcal/mol in favor of the (*E*)-species. Additionally, the $^{3}J(^{13}C\text{-}^{1}H)$ coupling constant between the indanone carbonyl and the olefinic carbon was found to be 1.5 Hz, which is consistent with the proposed geometry; an *E* geometry would produce indeed a significantly higher figure on the order of 2.4 Hz (Leyrer *et al.*, 1986).

Pharmacological evaluation

As a proof of concept, chalcones **1**–**8** were pharmacologically evaluated in vitro for their ability to prevent human LDL copper-induced oxidation using Cu^{2+} as oxidizing agent. All compounds were tested at a concentration of 10 μM. One of them, compound **4** (also referred to as S20478) emerged as the most promising agent and was found to be able to inhibit the initiation and the propagation of copper-mediated LDL oxidation as determined by time- and dose-dependent inhibition of the formation of conjugated dienes and thiobarbituric acid-reactive substances, as well as the conservation of the net electric charge of LDL. Indeed



Scheme 1 Synthesis of compounds **1–8**

Table 2 In vitro antioxidant activity of compound **4**

LDL type separated with HPLC	A	B	C	D	E
Blank without Cu^{2+}	78%	22%	–	–	–
Blank with Cu^{2+} + (5 μg, 24 h, 37°C)	–	–	–	38%	62%
Probucol (3×10^{-5} M)	–	–	–	48%	52%
Compound **4** (3×10^{-6} M)	–	84%	8%	8%	–

A and B refer to native forms of LDL

C, D, and E refer to oxidized forms of LDL, E being the most oxidized ones

compound **4** conserved cholesteryl esters in their native form up to 24 h. Compound **4** was more efficient in inhibiting copper-mediated LDL oxidation as compared with Probucol at the same concentration (Table 2). LDL preparation, Cu(II) reduction measurement, and fast protein liquid chromatography (FPLC) method were adapted from the report by Lebeau *et al.* (2000).

Moreover, in the model of inhibition of malondialdehyde formation by LDL oxidation (Cu^{2+}, 5 μM, 3 h incubation), compound **4** was found to be ten times more active than the reference drug Probucol [compound **4**, 505% inhibition concentration (IC_{50}) = 3.10^{-6} M; Probucol IC_{50} = 3.10^{-5} M]. This inhibition was maintained over 24 h. In an ex vivo model of copper-induced LDL oxidation in Watanabe rabbits, after a single oral dose of 50 mg/kg, compound **4** protected for 48 h. In the same conditions, an oral dose of 250 mg/kg of Probucol was necessary to achieve the same level of protection. Taken together, these findings suggest that compound **4** may be of potential interest in a new antioxidant approach to therapeutic stabilization and regression of atherosclerotic plaques (Lebeau *et al.*, 2000).

Conclusion

Herein, we report the synthesis of chalcones featuring an analgesic/anti-inflammatory pharmacophore, i.e., the 2(3*H*)-benzoxazolone heterocycle, on the one hand, and a radical scavenger moiety, i.e., 2,6-di-*t*-butylphenol, on the other. These compounds were synthesized by condensation of a ketone 2(3*H*)-benzoxazolone precursor with 3,5-di-*t*-butyl-4-hydroxybenzaldehyde in yields ranging from 69% to 92%. The *E*-geometry of the so-obtained chalcones was ascertained both by ^{1}H- and ^{13}C-NMR spectroscopy and density functional theory (DFT) quantum mechanics calculations. After screening of chalcones **1**–**8**, compound **4** (also referred to as S20478) emerged as the most promising agent and was found able to inhibit copper-mediated LDL oxidation both in vitro and ex vivo. Moreover, compound **4** was found to be ten times more active than the reference antioxidant drug Probucol.

Experimental

Melting points were determined using an electrothermal melting point apparatus and are reported uncorrected. IR spectra were recorded on a Perkin-Elmer 457

spectrometer using KBr pellets. Wave numbers are expressed in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra were recorded at ambient temperature on a Bruker 400 spectrometer. Compounds were dissolved in dimenthyl sulfoxide (DMSO)-d_6. Chemical shifts are expressed in the δ scale with tetramethylsilane (TMS) as internal standard. Thin-layer chromatography analyses were performed on Merck TLC plates (silica gel, 60 F 254, E. Merck, Darmstadt, ref. 5735). All the compounds reported here were routinely checked in two standard solvents, i.e., acetone/toluene/cyclohexane (solvent A, 5:2:3, v/v/v) and purity reverse-phase thin-layer chromatography conditions were: HPTLC plates RP-18 F-254 S (Merck), methanol: water (75/25, v/v). All compounds reported were found homogenous under such TLC and HPLC conditions. All reagents were purchased from Aldrich. All solvents were of American Chemical Society (ACS) reagent grade (Aldrich). KSF Montmorillonite was used as received from the provider (Aldrich). Elemental analyses were obtained from the Service Central d'Analyses of the CNRS at Solaise Vernaison, France. The theoretical calculations were performed using Becke-style three-parameter density functional theory with the Lee–Yang–Parr correlation functional (B3LYP) and 6-31G** basis set (Becke, 1998; Vosko *et al.*, 1980).

(*E*)-5-[3-[4-hydroxyphenyl]-1-oxo-2-propenyl]-2(*3H*)-benzoxazolone (**1**)

Method A: homogenous acid catalysis

To a stirred solution of 1.77 g (10 mmol) 5-acetyl-2(*3H*)-benzoxazolone in 150 ml hydrochloric-acid-saturated ethanol was added in one portion 1.22 g (10 mmol) of 4-hydroxybenzaldehyde. The reaction medium was kept at room temperature for 12 h, and concentrated to one-quarter. The resulting thin white precipitate was collected, air dried, and recrystallized from toluene to give 2.51 g of the title compound (yield 89%). This material was similar in all respects to the compound previously reported (Aichaoui *et al.*, 1992; Depreux *et al.*, 1993).

Method B: heterogenous acid catalysis

A blend of 1.7 g (10 mmol) 6-acetyl-2(*3H*)-benzoxazolone and 1.22 g (10 mmol) 4-hydroxybenzaldehyde was obtained by grinding. The blend was melted and kept at a temperature of 85°C in an oven for 24 h. Progress of the reaction was regularly monitored by TLC. After cooling, the hard cake was dissolved in boiling ethanol and filtered to discard the catalyst. The filtrate was evaporated to dryness and the residue was crystallized from toluene. Yield: 92%. This material was similar in all respects to the compound previously reported (Aichaoui *et al.*, 1992).

Method C: homogenous base catalysis

To a stirred solution of 1.77 g (10 mmol) 6-acetyl-2(*3H*)-benzoxazolone in 30 ml 2-propanol containing 0.5 ml of piperidine was added in one portion 1.22 g (10 mmol) 4-hydroxybenzaldehyde. The reaction medium was refluxed for 12 h,

and concentrated to dryness in vacuo. The residue was recrystallized twice from toluene to give the title compound with 78% yield.

(*E*)-5-[3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1-oxo-2-propenyl]-2(*3H*)-benzoxazolone (**2**) (method A)

Yield: 89%. M.p. 206–207°C. IR (KBr) 3610, 3145, 1780, 1665, 1615, 1570 cm^{-1}. ^{1}H-NMR 1.50 (18H, s), 5.60 (1H, s, (He)), 7.28 (1H, d, J = 8.8 Hz H(7)), 7.35 (1H, d, J = 16 Hz, H(b)), 7.50 (2H, s, H(2′), H(6′)), 7.73 (1H, d, J = 1.5 Hz H(4)), 7.74 (1H, dd, J = 8,8 Hz, J = 1,5 Hz H(6)), 7.84 (1H, s, H(e)), 9.77 (1H, s, (Ha)).

(*E*)-3-methyl-5-[3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1-oxo-2-propenyl]- 2(3H)-benzoxazolone (**3**) (method B)

Obtained from 3-methyl-5-acetyl-2(3H)-benzoxazolone and 3,5-di-*t*-butyl-4-hydroxybenzaldehyde. Yield: 92%. M.p. 246–247°C (toluene). IR (KBr) 3520, 1785, 1665, 1615, 1580, 1560 cm^{-1}. ^{1}H-NMR 1.44 (18H, s), 3.44 (3H, s), 7.27 (1H, d, J = 16.18 Hz H(b)), 7.45 (1H, d, J = 8,5 Hz, H(7)), 7.57 (2H, s, H(2′), H(6′)), 7.83 (1H, d, H(e)), 7.88 (1H, s, H(4)), 7.96 (1H, dd, J = 8.5 Hz, J = 1,6 Hz H(5)).

(*E*)-6-(4-hydroxy-[[3,5-bis(1,1-dimethylethyl)-phenyl]methylene]-5,6-dihydro-3,5-dimethyl-*2H*-Indeno[5,6-d]oxazole-2,7(*3H*)-dione (**4**) (method A)

Obtained from 3-methyl-6-acetylbenzo[d]oxal-2(*3H*)-one and 3,5-di-*t*-butyl-4-hydroxybenzaldehyde. Yield: 78%. M.p. 215–216°C (toluene). IR (KBr) 3650, 2980, 1800, 1680, 1630, 1610 cm^{-1}. ^{1}H-NMR 1.34 (18H, s), 1.44 (3H, d, J = 5.6 Hz), 3.42 (3H, s, N–CH3), 4.43 (1H, q, J = 5.6 Hz), 7.42 (1H, s, H(4)), 7.52 (2H, s, H(2′), H(6′), 7.58 (1H, s, H(8)), 7.64 (1H, s, ethylenic H).

(*E*)-*2H*-Indeno[5,6-d]oxazole-2,5(*3H*)-dione, 6-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-6,7-dihydro-3,7-dimethyl- (**5**) (method A)

Yield: 76%. M.p. > 270°C. IR (KBr) 3655, 1790, 1675, 1610 cm^{-1}. ^{1}H-NMR 1.34 (18H, s), 1.43 (3H, d, J = 5.6 Hz), 3.39 (3H, s, N–CH3), 4.39 (1H, q, J = 5.6 Hz), 7.18 (2H, s, H(2′), H(6′), 7.49 (1H, s, H(8)), 7.55 (1H, s, H(4)), 7.70 (1H, s, ethylenic H).

(*E*)-*2H*-Indeno[5,6-d]oxazole-2,7(*3H*)-dione,6-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-5,6-dihydro-3,5-dimethyl- (**6**) (method A)

Yield: 72%. M.p. 224–226°C. IR (KBr) 3620, 2960–2865, 1795, 1655, 1630, 1580 cm^{-1}. ^{1}H-NMR 1.18 (3H, d, J = 6.6 Hz), 1.40 (18H, s), 3,09 (2H, s), 3.33 (4H, s, N–CH3, H8), 7.32 (2H, m, H(2′), H(6′), 7.39 (1H, s, H(9)), 7.72 (2H, s, H(4), H(c)), 7.78 (1H, s, ethylenic H).

(*E*)-2H-Indeno[5,6-d]oxazole-2,7(3H)-dione, 6-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-5,6-dihydro-3,5-dimethyl- (**7**) (method A)

Yield: 69%. M.p. > 260°C. IR (KBr) 3610, 3100, 2960, 1770, 1660, 1620, 1580 cm^{-1}. ^{1}H-NMR 1.50 (21H, s), 4.36 (1H, m, H(5)), 5.60 (1H, s), 7.20 (1H, s, H(4)), 7.30–7.52 (2H, m, H(2′), H(6′), 7.65 (1H, s, H(8)), 7.74 (1H, s, ethylenic H), 10,11 (1H, s, H(a)).

(*E*)-*2H*-Indeno[5,6-d]oxazole-2,7(*3H*)-dione,6-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-5,6-dihydro-3,5-dimethyl- (**8**) (method A)

Yield: 70%. M.p. 228–229°C. IR (KBr) 3620, 3260, 1775, 1665, 1600, 1580 cm^{-1}. ^{1}H-NMR 1.37 (3H, d, J = 5.5 Hz), 1.50 (18H, s), 3.17 (3H, s), 5.50 (1H, s), 7.14 (1H, s, H(9)), 7.20–7.38 (2H, m, H(2′), H(6′), 7.90 (1H, s, H(4)), 8.00 (1H, s, H(c)), 9.32 (1H, s, H(a)).

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