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Studies on the Synthesis and Anti-Inflammatory Activity of 2,6-Di-*tert*-butylphenols with a Heterocyclic Group at the 4-Position. II [1)]

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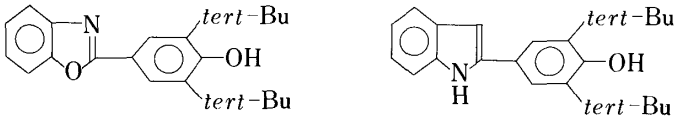
2,6-Di-*tert*-butylphenols with an imidazo[2,1-*b*]thiazole or 2,3-dihydroimidazo[2,1-*b*]thiazole group at the 4-position were prepared. Substituents were introduced at the 5-position of 6-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (Ia) by means of the Vilsmeier reaction and Mannich reaction. 6-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole 1-oxide (IVa) and the 1,1-dioxide (IVb) were obtained by oxidation of Ia. The above compounds were examined for anti-inflammatory activity in adjuvant-induced arthritis in rats, and some compounds were further tested for activity in the carrageenin-induced rat paw edema assay and in the AcOH-induced writhing assay in mice. Some of the compounds showed potent anti-inflammatory and analgesic activities. The most potent compound, IVa (25 mg/kg, *p.o.*), had about the same anti-inflammatory activity as indomethacin (2 mg/kg, *p.o.*), but IVa (50 mg/kg, *p.o.*) had weaker analgesic activity than aminopyrine (50 mg/kg, *p.o.*).

Keywords——anti-inflammatory activity; imidazo[2,1-*b*]thiazole; 2,3-dihydroimidazo[2,1-*b*]-thiazole; 2,6-di-*tert*-butylphenol; Vilsmeier reaction; Mannich reaction

In the previous paper, we reported that 2,6-di-*tert*-butylphenols with a benzoxazole or indole group at the 4-position had potent anti-inflammatory and analgesic (AcOH-induced writhing assay) activities and that the anti-inflammatory activity of 2,6-di-*tert*-butylphenol derivatives depended largely on the substituents at the 4-position.



tert-Bu = $C(CH_3)_3$

Fig. 1

Since anti-inflammatory activity of 2,3-dihydroimidazo[2,1-*b*]thiazole[2-5)] and imidazo-[2,1-*b*]thiazole[6)] was reported by several workers, we investigated the anti-inflammatory activity of 2,6-di-*tert*-butylphenols with a 2,3-dihydroimidazo[2,1-*b*]thiazole or imidazo-[2,1-*b*]thiazole group at the 4-position.

Synthesis

6-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazoles (Ia—c) were prepared from 4-(2-bromoacyl)-3,5-di-*tert*-butylphenols[7)] and 2-aminothiazoline by using a modification of the procedure described by Kano.[8)]

6-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)imidazo[2,1-*b*]thiazole (II) and the benzo analogue (III) of II were prepared by a similar method.

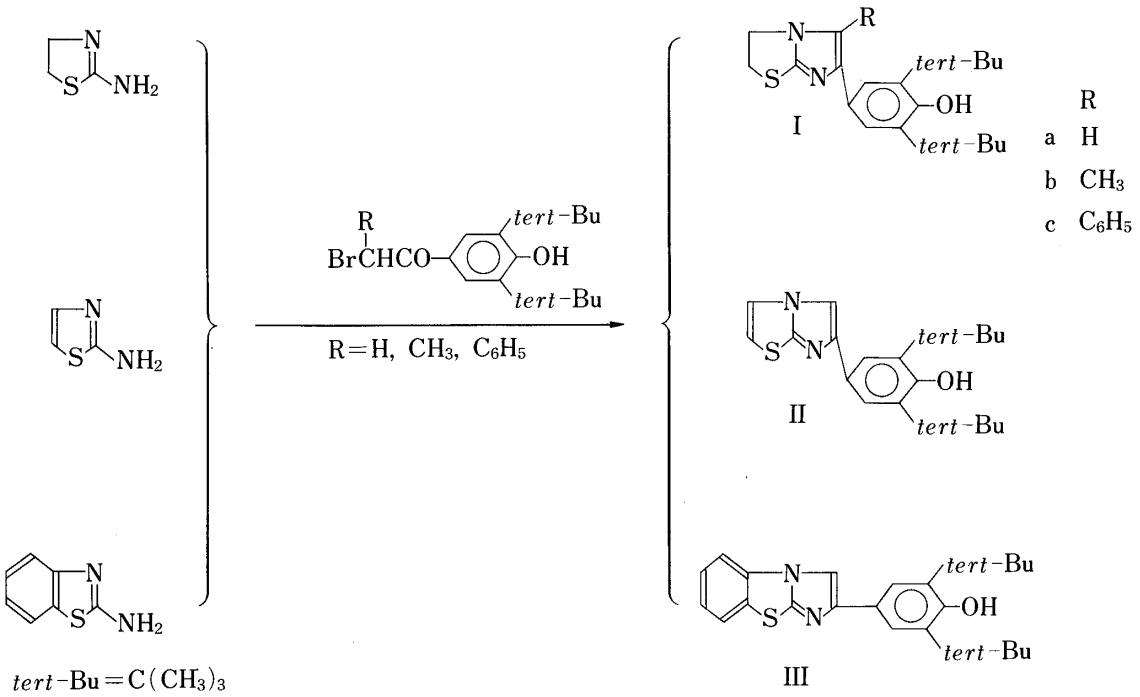


Chart 1

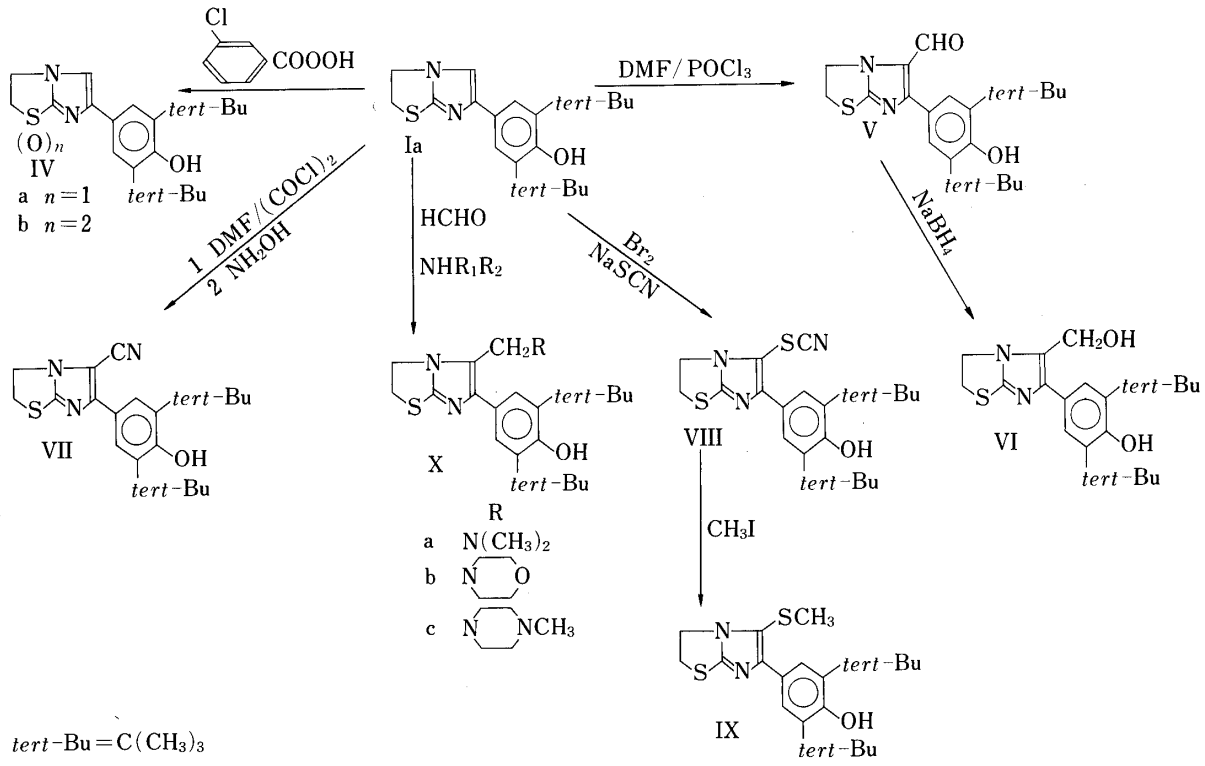


Chart 2

Compound Ia showed potent anti-inflammatory activity, so various derivatives of Ia were prepared and examined for activity. Treatment of Ia with *m*-chloroperbenzoic acid at room temperature yielded the corresponding sulfoxide (IVa) and sulfone (IVb). Since Kano reported bromination and thiocyanation of 6-phenyl-2,3-dihydroimidazo[2,1-*b*]thiazole, some electrophilic substitution reactions were carried out in order to introduce various substituents into the 5-position of Ia.

6-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-5-formyl-2,3-dihydroimidazo[2,1-*b*]thiazole (V) was prepared by reacting Ia with Vilsmeier reagent which was prepared from *N,N*-dimethylformamide and phosphorus oxychloride. Compound V was then converted to the alcohol derivative (VI) by reduction with sodium borohydride. 5-Cyano-6-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (VII) was prepared by reacting Ia with Vilsmeier reagent which was prepared from *N,N*-dimethylformamide and oxallyl chloride, followed by treatment with hydroxylamine in pyridine.[9]

6-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-5-thiocyano-2,3-dihydroimidazo[2,1-*b*]thiazole (VIII) was prepared by reacting Ia with bromine and sodium thiocyanate in AcOH. Compound VIII was then converted to the methylthio derivative (IX) by methylation with methyl iodide. 5-Dimethylaminomethyl-6-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (Xa) was prepared by reacting Ia with dimethylamine and formalin in the presence of AcOH in dioxane. Compounds Xb and Xc were prepared by a similar method. The compounds thus prepared are listed in Table I.

Pharmacology and Discussion

These compounds were evaluated for anti-inflammatory activity (chronic phase) by using the adjuvant-induced arthritis (A.A) assay described by Pearson[10] at 25 mg/kg (*p.o.*) and the results were compared with that for indomethacin (2 mg/kg, *p.o.*).

The biological activity of compounds I—X is listed in Table I. Among these compounds, IVa had the most potent inhibitory activity in the A.A assay. Compound II, which has a double bond between the 2- and 3-positions of Ia, had no activity at the screening dose. When a substituent was introduced at the 5-position of Ia, all compounds except Ib lost the activity. This finding suggested that there is no relationship between the electrostatic character of the substituent and the anti-inflammatory activity, and that the steric factor is important for the biological activity. The oxidation products of Ia, IVa and IVb, had augmented activity compared with Ia.

The anti-inflammatory activity of IVa, IVb and Ia decreased in that order. Compounds IVa, b and Ia were further tested for prophylactic activity in the A.A assay and the carrageenin-induced rat paw edema assay described by Winter *et al.*[11] The potency of these compounds was compared with that of indomethacin. The analgesic activity of these compounds was tested in the AcOH-induced writhing assay in mice as described by R. Koster *et al.*,[12] and the results were compared with that for aminopyrine (Table II). Compound IVa showed potent activity in these tests. Compound IVa (25 mg/kg, *p.o.*) had about the same anti-inflammatory activity as indomethacin (2 mg/kg, *p.o.*) and IVa (50 mg/kg, *p.o.*) had about half the analgesic activity of aminopyrine (50 mg/kg, *p.o.*).

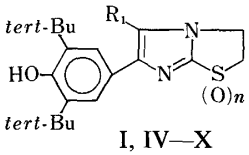
Experimental

All melting points were determined by using a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were obtained with a Hitachi 215 spectrometer. The ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectra were obtained with a JEOL-MH 100 or a JEOL-FX 90 spectrometer using $(CH_3)_4Si$ as an internal standard.

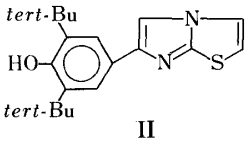
Mass spectra (MS) were obtained with an RMU-6MG spectrometer.

6-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (Ia)——4-(2-Bromoacetyl)-2,6-di-*tert*-

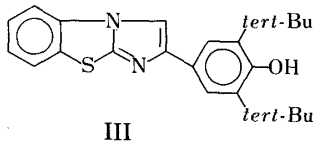
TABLE I.



I, IV—X



II



III

Compd. No.	R_1	n	AA[a] 25 mg/kg *p.o.*	mp (°C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
Ia	H	0	(+)	212—214	EtOH	71.2	$C_{19}H_{26}N_2OS$	69.05 (69.11	7.93 8.04	8.48 8.43)
Ib	CH_3	0	(±)	258—261	CH_3CN	28.2	$C_{20}H_{28}N_2OS$	69.73 (69.62	8.19 8.22	8.13 8.11)
Ic	C_6H_5	0	(−)	251—253	MeOH–H_2O	14.5	$C_{25}H_{30}N_2OS \cdot 1/2H_2O$	73.85 (73.29	7.44 7.47	6.89 6.39)
II			(−)	184—185	EtOH	38.4	$C_{19}H_{24}N_2OS$	69.48 (69.31	7.36 7.65	8.53 8.38)
III			(−)	117—119	MeOH	35.0	$C_{23}H_{26}N_2OS \cdot MeOH$	70.21 (70.17	7.36 7.63	6.82 6.91)
IVa	H	1	(+++)	211—212	EtOH	72.7	$C_{19}H_{26}N_2O_2S \cdot 1/2EtOH$	65.01 (65.11	7.91 7.91	7.58 7.82)

IVb	H	2	(++)	267—269	EtOH–H_2O	35.5	$C_{19}H_{26}N_2O_3S$	62.96 (62.77	7.23 7.35	7.73 7.60)
V	CHO	0	(−)	210—212	EtOH	61.5	$C_{20}H_{26}N_2O_2S$	67.01 (66.82	7.31 7.20	7.81 7.80)
VI	CH_2OH	0	(−)	227—229	EtOH–H_2O	74.6	$C_{20}H_{28}N_2O_2S$	66.63 (66.55	7.83 8.04	7.77 7.73)
VII	CN	0	(−)	207—208	EtOH	15.3	$C_{20}H_{25}N_3OS$	67.57 (67.52	7.09 6.92	11.82 11.74)
VIII	SCN	0	(−)	178—179	EtOH	37.9	$C_{20}H_{25}N_3OS_2$	61.98 (62.05	6.50 6.50	10.84 10.66)
IX	SCH_3	0	(−)	170—171	EtOH	14.3	$C_{20}H_{28}N_2OS_2$	63.79 (63.49	7.49 7.60	7.44 7.36)
Xa	$CH_2N(CH_3)_2$	0	(−)	188—189	EtOH–H_2O	38.3	$C_{22}H_{33}N_3OS \cdot 1/4H_2O$	67.39 (67.49	8.61 8.70	10.72 10.48)
Xb	$CH_2N\square O$	0	(−)	231—233	MeOH	39.6	$C_{24}H_{35}N_3O_2S$	67.10 (67.08	8.21 8.32	9.78 9.67)
Xc	$CH_2N\square NCH_3$	0	(−)	211—212	MeOH–H_2O	58.7	$C_{25}H_{38}N_4OS \cdot H_2O$	65.18 (65.28	8.75 8.61	12.16 12.00)
Indomethacin (2 mg/kg, *p.o.*) 70—80%[b]										

a) Adjuvant-induced arthritis. Test compounds and reference drugs were administered to rats ($n=3$—6) with established arthritis on days 15 through 27 after the injection of the adjuvant. +++: Therapeutic effect was larger than or equal to that of indomethacin. ++: Therapeutic effect was less than that of indomethacin but more than half that of indomethacin. +: Therapeutic effect was less than half that of indomethacin. ±: Therapeutic effect was noted but was not statistically significant. −: Inactive at 25 mg/kg.

b) Inhibition (%) of edema formation induced by adjuvant.

TABLE II

Compd. No.	CIPE[a] (25 mg/kg, *p.o.*) (%)	Analgesic[b] (50 mg/kg, *p.o.*) (%)	Adjuvant arthritis (25 mg/kg, *p.o.*)[c] Therapeutic[d] $\lvert\Delta FT\rvert \times 10^{-2}$ mm test compd/IM	Prophylactic[e] (%)
Ia	24.5	35.0	177±31/225±61	77.8
IVa	33.8	43.0	245±57/177±40	71.5
IVb	12.0	25.3	141±60/177±40	N.T.[f]
Indomethacin	25.8 (2 mg/kg)	N.T.		81.3 (2 mg/kg)
Phenylbutazone	33.2 (50 mg/kg)			
Aminopyrine	N.T.	83.2	N.T.	N.T.

a) Inhibition (%) of edema formation induced by carrageenin in rats ($n=6$).
b) Inhibition (%) of writhing induced by AcOH in mice ($n=8$—10).
c) Compounds were administered to rats ($n=6$) on days 15 through 27 (therapeutic) or on days 0 through 20 (prophylactic) after the injection of the adjuvant.
d) The change of foot thickness was calculated as the difference between the values on day 15 and day 28.
e) Inhibition (%) of adjuvant-induced right plantars edema formation in rats.
f) N.T.: not tested.

butylphenol (32.7 g) was added portionwise to a solution of 10.2 g of 2-aminothiazoline in methyl ethyl ketone (300 ml) at room temperature. After being stirred for 0.5 h, the reaction mixture was refluxed for 1 h, then the solvent was evaporated off *in vacuo*. Ethanol (200 ml) was added to the residue and the mixture was again refluxed for 24 h. The solution was basified by the addition of NH_4OH and H_2O (200 ml). The resulting precipitate was collected by filtration and recrystallized from ethanol to give 23.5 g of Ia. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (18H, s, $-C(CH_3)_3$, 3.76 (2H, td, $J=8$, 2 Hz), 4.14 (2H, td, $J=8$, 2 Hz), 5.14 (1H, s, OH), 7.08 (1H, s, C_5-H), 7.48 (2H, s, aromatic-H). MS *m/z*: 330 (M^+). Ib and Ic were prepared in a manner similar to that described above.

6-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)imidazo[2,1-*b*]thiazole (II)——A mixture of 1.2 g of 2-aminothiazole, 3.9 g of 4-(2-bromoacetyl)-2,6-di-*tert*-butylphenol and 20 ml of ethanol was refluxed for 2 h. After neutralization, H_2O (30 ml) was added and the resulting precipitate was collected. The precipitate was recrystallized from ethanol to give 1.5 g of II. ^{1}H-NMR ($CDCl_3$) δ: 1.84 (18H, s, $-C(CH_3)_3$, 5.20 (1H, s, OH), 6.72 (1H, d, $J=6$ Hz,), 7.34 (1H, d, $J=6$ Hz), 7.58 (3H, s, aromatic-H and C_5-H). MS *m/z*: 328 (M^+).

III was prepared in a manner similar to that described above.

6-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole 1-Oxide (IVa)——*m*-Chloroperbenzoic acid (1 g) was added to a solution of 1.6 g of Ia in 10 ml of $CHCl_3$. After being stirred for 10 min, the reaction mixture was washed with sodium bicarbonate (5%), dried and concentrated, and the residue was recrystallized from ethanol to give 1.3 g of IVa. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (18H, s, $-C(CH_3)_3$), 4.26—4.45 (2H, m), 4.68—4.96 (2H, m), 5.26 (1H, s, OH), 7.36 (1H, s, C_5-H), 7.54 (2H, s, aromatic-H). MS *m/z*: 346 (M^+).

6-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole 1,1-Dioxide (IVb)——*m*-Chloroperbenzoic acid (0.4 g) was added to a solution of 0.6 g of IVa in 10 ml of $CHCl_3$. The mixture was stirred for 0.5 h, then a further 0.4 g of *m*-chloroperbenzoic acid was added. The reaction mixture was stirred for 1 h then washed with sodium bicarbonate (5%), dried and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography with $CHCl_3$. The eluate was concentrated *in vacuo* and the residue was recrystallized from aqueous ethanol to give 0.2 g of IVb. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (18H, s, $-C(CH_3)_3$), 3.92 (2H, t, $J=8$ Hz), 4.50 (2H, t, $J=8$ Hz), 5.28 (1H, s, OH), 7.24 (1H, s, C_5-H), 7.54 (2H, s, aromatic-H). MS *m/z*: 362 (M^+).

6-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-5-formyl-2,3-dihydroimidazo[2,1-*b*]thiazole (V)——Phosphorus oxychloride (1.1 g) was added to a solution of 1.5 ml of *N,N*-dimethylformamide in 10 ml of $CHCl_3$ under cooling and then the reaction mixture was stirred for 1 h at room temperature. Next, 1.5 g of Ia was added and the whole was refluxed for 4 h. After addition of 20 ml of 10% potassium carbonate, the reaction mixture was stirred for 15 min, then the $CHCl_3$ layer was dried and concentrated *in vacuo*. The residue was recrystallized from ethanol to give 1.0 g of V. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (18H, s, $-C(CH_3)_3$), 3.88 (2H, t, $J=8$ Hz), 4.54 (2H, t, $J=8$ Hz), 5.40 (1H, s, OH), 7.44 (2H, s, aromatic-H), 9.60 (1H, s, CHO), MS *m/z*: 358 (M^+).

6-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-5-hydroxymethyl-2,3-dihydroimidazo[2,1-*b*]thiazole (VI)——V (0.4 g) was dissolved in 10 ml of ethanol and 40 mg of sodium borohydride was added to the solution. The mixture was stirred for 10 min, then 10 ml of acetic acid and 30 ml of H_2O were added to yield a precipitate, which was collected by filtration and recrytallized from aqueous ethanol to yield 0.3 g of VI. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (18H, s, $-C(CH_3)_3$), 3.80 (2H, t, $J=8$ Hz), 4.14 (2H, t, $J=8$ Hz), 4.36 (1H, t, $J=6$ Hz, OH), 4.62 (2H, t, $J=6$ Hz, $-CH_2OH$), 5.12 (1H, s, OH), 7.40 (2H, s, aromatic-H). MS *m/z*: 387 (M^+).

5-Cyano-6-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (VII)——A solution of 0.9 g of

oxallyl chloride in 5 ml of ethylene dichloride ($C_2H_4Cl_2$) was added to a solution of 0.5 g of *N,N*-dimethylformamide in 10 ml of $C_2H_4Cl_2$ under cooling with an ice bath. The mixture was stirred for 15 min at room temperature, then a solution of Ia in 3 ml of *N,N*-dimethylformamide and 10 ml of $C_2H_4Cl_2$ was added to it. The whole was stirred for 2 h, then a solution of hydroxylamine hydrochloride in 1.5 ml of *N,N*-dimethylformamide and 0.6 ml of pyridine was added, and the mixture was heated under reflux overnight. The reaction mixture was washed with sodium bicarbonate (5%), dried and concentrated *in vacuo*. The residue was applied to a column of silica gel and eluted with $CHCl_3$. The crude product was recrystallized from ethanol to give 0.33 g of VII. ^{1}H-NMR (DMSO-d_6) δ: 1.40 (18H, s, $-C(CH_3)_3$), 3.96 (2H, t, J=8 Hz), 4.34 (2H, t, J=8 Hz), 7.28 (1H, s, OH), 7.64 (2H, s, aromatic-H). MS *m/z*: 355 (M^+). IR ν_{max}^{KBr} cm^{-1}: 2200 (CN).

6-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-5-thiocyanato-2,3-dihydroimidazo[2,1-*b*]thiazole (VIII)——A solution of 1.35 g of Ia and 0.64 g of sodium thiocyanate in 10 ml of AcOH was cooled with an ice bath, then bromine (0.7 g) was added dropwise under cooling. The mixture was stirred for 1 h at room temperature, then 30 ml of H_2O was added and the resulting precipitate was collected by filtration. The precipitate was added to a mixture of 30 ml of $CHCl_3$ and 10 ml of aqueous K_2CO_3 (10%), and stirred for several minutes. Then the $CHCl_3$ layer was separated, dried and concentrated *in vacuo*. The residue was purified by silica gel column chromatography and recrystallized from ethanol to give 0.6 g of VIII. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (18H, s, $-C(CH_3)_3$), 3.86 (2H, t, J=8 Hz), 4.30 (2H, t, J=8 Hz), 5.32 (1H, s, OH), 7.60 (2H, s, aromatic-H). MS *m/z*: 387 (M^+). IR ν_{max}^{KBr} cm^{-1}: 2150 (SCN).

6-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-5-methylthio-2,3-dihydroimidazo[2,1-*b*]thiazole (IX)——A solution of 1.3 g of VIII in 10 ml of methanol was cooled to 0 °C. Methyl iodide (0.65 g) was added under stirring and then a solution of 0.2 g of potassium hydroxide in 50% methanol–H_2O was added. After being stirred for 0.5 h, the reaction mixture was poured into 30 ml of H_2O and extracted with $CHCl_3$. The extract was dried and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography and eluted with $CHCl_3$. The eluate was concentrated and the residue was recrystallized from ethanol to give 0.18 g of IX. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (18H, s, $-C(CH_3)_3$), 3.80 (2H, t, J=8 Hz), 4.18 (2H, t, J=8 Hz), 5.20 (1H, s, OH), 7.84 (2H, s, aromatic-H). MS *m/z*: 376 (M^+).

5-Dimethylaminomethyl-6-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (Xa)——A mixture of 0.9 g of dimethylamine (40% in H_2O), 0.6 g of formalin (35%), 1.5 ml of AcOH, 5 ml of dioxane and 0.66 g of Ia was refluxed for 6 h. The solvent was evaporated off *in vacuo*, then 20 ml of aqueous K_2CO_3 (10%) was added to the residue, which was extracted with $CHCl_3$. The extract was dried and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography with $CHCl_3$. The eluate was concentrated *in vacuo* and the residue was recrystallized from aqueous ethanol to give 0.3 g of Xa. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (18H, s, $-C(CH_3)_3$), 2.24 (6H, s, $-N(CH_3)_2$), 3.46 (2H, s, $-CH_2N$), 3.76 (2H, t, J=8 Hz), 4.16 (2H, t, J=8 Hz), 5.12 (1H, s, OH), 7.40 (2H, s, aromatic-H). MS *m/z*: 387 (M^+). Compounds Xb, c were prepared in the same manner.

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