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# Synthesis of new substituted 2,2-bis-(3,5-di-*t*-butyl-4-hydroxybenzyl)benzocycloalkanones, bromopropiophenones, and their alcohol analogs

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A new series of substituted 2,2-bis-(3,5-di-*t*-butyl-4-hydroxybenzyl) benzocycloalkanones, bromopropiophenones, and their alcohol analogs were synthesized. The corresponding alcohols may act as potential allosteric modulators of $GABA_B$ receptors.

**Key Words:** Benzocycloalkanone, allosteric modulator, $GABA_B$ receptor, propiophenone

## Introduction

$\gamma$-Aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the central nervous system.[1,2] GABA is involved in the regulation of a variety of physiological mechanisms[3,4] and is implicated in the pathophysiology of several central nervous system diseases.[5] Therefore, a variety of GABA analogs have been investigated,[6–8] essentially GABA agonists, GABA antagonists, and GABA uptake inhibitors. Two subclasses of receptors for GABA have been defined and designated as $GABA_A$ and $GABA_B$ receptors.[9,10] $GABA_A$ receptors are selectively activated by the GABA analog muscimol and blocked by convulsants such as bicuculline or picrotoxin. A selective agonist for the $GABA_B$ receptor is $\beta$-p-chlorophenyl-GABA **1** (baclofen, Figure 1).[10] Until recently, investigation has concentrated on agonists and antagonists for the $GABA_A$ receptor; by contrast,

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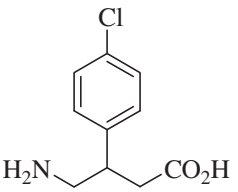
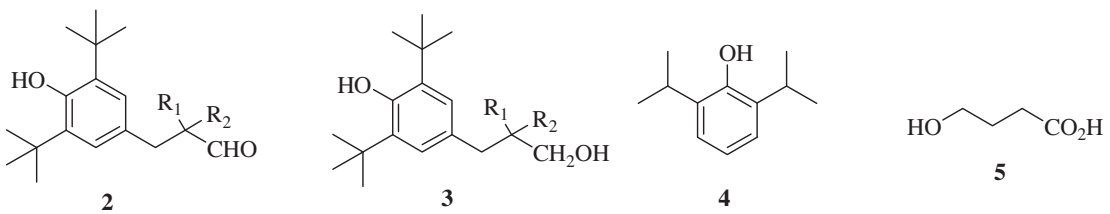
few compounds have been studied for the $GABA_B$ receptor, and its activities and consequently its structure-activity relationships have remained practically unknown.[11]




**1**

**Figure 1.** Structure of baclofen.

Following a random mass screening, Urwyler et al.[12] recently reported that 2,6-di-*t*-butyl-4-(3-hydroxyphenyl)-2,2-dimethylpropionaldehyde, CGP 13501, **2** ($R_1$, $R_2$ = Me), acted as a positive allosteric modulator for $GABA_B$ receptors,[13,14] and its reduction product, the corresponding alcohol CGP 7930 **3** ($R_1$, $R_2$ = Me), regarded as a hybrid of propofol **4** and $\gamma$-hydroxybutyric acid (GHB, **5**) was found to be even more potent (Figure 2). Propofol[15,16] is a short-acting hypnotic agent ($GABA_A$ modulator), effective for induction and maintenance of anesthesia when administered intravenously either as repeated bolus injections or by continuous infusion. GHB is best known as a drug of abuse[17] and is a GABA analog.




**2** **3** **4** **5**

**Figure 2.** Structures of CGP 13501, CGP 7930, propofol, and GHB.

Accordingly, we recently synthesized a series of modifications of structure **3**, all of which acted as positive modulators at $GABA_B$ receptors.[18,19] The present paper describes the synthesis of new substituted 2,2-bis-(3,5-di-*t*-butyl-4-hydroxybenzyl) benzocycloalkanones (**6**), bromopropiophenones (**7**), and their alcohol analogs (**8-9**) as potential allosteric modulators of $GABA_B$ receptors (Figure 3). The basic synthetic approach continues to be basically that of Urwyler et al.[12]

# Experimental

All solvents used were freshly distilled and dried according to the methods of Perrin and Armarego.[20] Melting points were determined on a Reichert hot-stage microscope. $^1$H-NMR (300 MHz) and $^{13}$C-NMR (75.5 MHz) spectra were recorded on a Bruker 300 spectrometer in deuteriochloroform with tetramethylsilane as the internal standard. Infrared spectra were recorded on a Thermo Nicolet (Nexus 670) FT-infrared spectrophotometer, measured as films or KBr disks. Microanalyses were performed on a LECO Analyzer 932.

## Synthesis of 2,6-(di-*t*-butyl-4-methoxymethyl)phenol (10)

2,6-Di-*t*-butylphenol **11** (5.2 g, 0.025 mol), 36% formaldehyde (5 mL), and absolute methanol (50 mL) were dissolved in a 3-necked round-bottom flask, and a solution of potassium hydroxide (2 g) in water (2 mL) was added under a nitrogen atmosphere. The solution was refluxed for 30 min under an atmosphere of nitrogen, and it turned deep purple. After the mixture had cooled to room temperature, the precipitate was collected and washed with cold water. The pale yellow product was recrystallized several times from methanol to yield colorless crystalline plates (5.01 g), mp 99-100 °C (lit. mp 99.5 °C). $^{211}$H-NMR ($CDCl_3$): $\delta$ 1.44 (s, 18H, t-Bu), 3.40 (s, 3H, $CH_3$), 4.34 (s, 2H, $CH_2$), 5.10 (s, 1H, OH), 7.14 (s, 2H, Ar) ppm. $^{13}$C-NMR ($CDCl_3$): $\delta$ 30.21, 34.37, 58.10, 75.54, 125.29, 128.65, 135.84, 153.01 ppm.

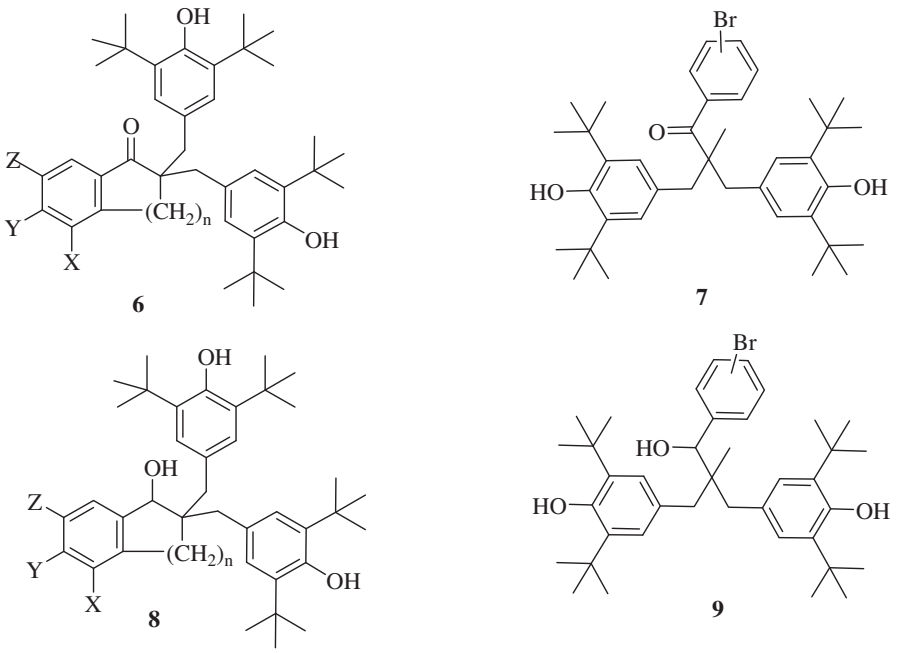



**Figure 3.** Structures of benzocycloalkanones, bromopropiophenones, and their alcohol analogs.

## Typical procedure for synthesis of 2,2-bis-(3,5-di-*t*-butyl-4-hydroxybenzyl) benzocycloalkanones

A solution of 2,6-(di-*t*-butyl-4-methoxymethyl)phenol **10** (1 g, 4 mmol) and potassium hydroxide (0.04 g) in methanol (4 mL) was heated to 60 °C. The corresponding benzocycloalkanone (2 mmol) was then added to the solution over a period of 10 min and the reaction mixture was refluxed for 4 h. The mixture was cooled to room temperature and poured into 1% acetic acid (10 mL) to solidify. The resulting solids were washed with water and dried. Recrystallization from n-hexane gave the final products in good yields.

**2,2-Bis(3,5-di-*t*-butyl-4-hydroxybenzyl)-4-chloro-2,3-dihydroinden-1-one (17)** Yellow solid, 93%, mp 224-225 °C. Anal calcd for $C_{39}H_{51}ClO_3$: C 77.65%; H 8.52%. Found: C 77.76%, H 8.60%. $^1$H-NMR ($CDCl_3$): $\delta$ 1.34 (s, 36H, 12 × $CH_3$), 2.79 (d, $J$ = 13.5 Hz, 2H, $CH_2$), 3.03 (s, 2H, $CH_2$), 3.24 (d, $J$ = 13.5 Hz, 2H, $CH_2$), 4.95 (s, 2H, 2 × OH), 6.87 (s, 4H, Ar), 7.06 (t, $J$ = 7.8 Hz, 1H, Ar), 7.26 (d, $J$ = 7.5 Hz, 1H,

Ar), 7.39 (d, $J$ = 7.5, 1H, Ar) ppm. $^{13}$C-NMR ($CDCl_3$): $\delta$ 30.17, 34.10, 34.26, 44.19, 56.36, 121.13, 126.39, 127.47, 128.02, 131.85, 133.48, 135.34, 139.34, 150.97, 152.23, 210.55 ppm. FT-IR (KBr): $\upsilon$ 3642, 2954, 2911, 2872, 1712, 1599, 1460, 1435, 1391, 1360, 1318, 1248, 1235, 1213, 1153, 1122, 960, 881, 770, 758 cm$^{-1}$.

**2,2-Bis(3,5-di-*t*-butyl-4-hydroxybenzyl)-6-methoxy-2,3-dihydroinden-1-one (18)** Yellow solid, 92%, mp 194-195 °C. Anal calcd for $C_{40}H_{54}O_4$: C 80.22%, H 9.09%. Found: C 80.17%, H 9.16%. $^1$H-NMR ($CDCl_3$): $\delta$ 1.34 (s, 36H, 12 × $CH_3$), 2.78 (d, $J$ = 13.5 Hz, 2H, $CH_2$), 2.93 (s, 2H, $CH_2$), 3.21 (d, $J$ = 13.5 Hz, 2H, $CH_2$), 3.74 (s, 3H, $CH_3$), 4.95 (s, 2H, 2 × OH), 6.86 (s, 4H, Ar), 6.92-7.00 (m, 3H, Ar) ppm. $^{13}$C-NMR ($CDCl_3$): $\delta$ 30.25, 34.10, 34.56, 44.14, 55.42, 56.69, 104.22, 123.42, 126.43, 126.46, 127.95, 135.19, 138.91, 146.50, 152.12, 158.76, 211.30 ppm. FT-IR (KBr): $\upsilon$ 3642, 3551, 2955, 2920, 2873, 1740, 1666, 1501, 1435, 1261, 1256, 1215, 1121, 844 cm$^{-1}$.

**2,2-Bis(3,5-di-*t*-butyl-4-hydroxybenzyl)-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (19)** White solid, 81%, mp 214-215 °C. Anal calcd for $C_{41}H_{56}O_4$: C 80.35%, H 9.21%. Found: C 80.45%, H 9.31%. $^1$H-NMR ($CDCl_3$): $\delta$ 1.39 (s, 36H, 12 × $CH_3$), 1.89 (t, $J$ = 7 Hz, 1H, CH), 2.06 (d, $J$ = 7 Hz, 1H, CH), 2.55 (d, $J$ = 13.5 Hz, 2H, $CH_2$), 2.82 (t, $J$ = 7 Hz, 2H, $CH_2$), 3.28 (d, $J$ = 13.5 Hz, 2H, $CH_2$), 3.82 (s, 3H, $CH_3$), 5.04 (s, 2H, 2 × OH), 6.58 (d, $J$ = 2.4 Hz, 1H, Ar), 6.80 (dd, $J_1$ = 8.4 Hz, $J_2$ = 1.2 Hz, 1H, Ar), 6.94 (s, 4H, Ar), 8.03 (d, $J$ = 8.7 Hz, 1H, Ar) ppm. $^{13}$C-NMR ($CDCl_3$): $\delta$ 25.87, 28.66, 30.25, 34.19, 42.76, 50.80, 55.35, 111.96, 113.15, 125.16, 127.41, 128.29, 130.18, 135.15, 145.81, 152.18, 163.18, 200.65 ppm. FT-IR (KBr): $\upsilon$ 3642, 3551, 2955, 2920, 2873, 1740, 1666, 1601, 1435, 1261, 1256, 1215, 1121, 844 cm$^{-1}$.

**2,2-Bis(3,5-di-*t*-butyl-4-hydroxybenzyl)-7-methoxy-3,4-dihydronaphthalen-1(2H)-one (20)** White solid, 86%, mp 215-217 °C. Anal calcd for $C_{41}H_{56}O_4$: C 80.35%, H 9.21%. Found: C 80.43%, H 9.26%. $^1$H-NMR ($CDCl_3$): $\delta$ 1.41 (s, 36H, 12 × $CH_3$), 1.91 (t, $J$ = 6 Hz, 2H, $CH_2$), 2.62 (d, $J$ = 13.5 Hz, 2H, $CH_2$), 2.85 (t, $J$ = 6 Hz, 2H, $CH_2$), 3.27 (d, $J$ = 13.5 Hz, 2H, $CH_2$), 3.85 (s, 3H, $CH_3$), 5.06 (s, 2H, 2 × OH), 6.95 (s, 4H, Ar), 6.99-7.08 (m, 2H, Ar), 7.55 (d, $J$ = 2.4 Hz, 1H, Ar) ppm. $^{13}$C-NMR ($CDCl_3$): $\delta$ 24.67, 29.03, 30.36, 34.20, 42.56, 50.92, 55.47, 109.62, 121.33, 127.41, 128.15, 129.69, 133.92, 135.20, 135.90, 152.22, 158.2, 201.69 ppm. FT-IR (KBr): $\upsilon$ 3637, 3568, 2954, 1655, 1495, 1434, 1237, 1199, 1097, 1033, 882, 776 cm$^{-1}$.

**2,2-Bis(3,5-di-*t*-butyl-4-hydroxybenzyl)benzosuberone (21)** Yellow solid, 83%, mp 195-196 °C. Anal calcd for $C_{41}H_{56}O_3$: C 82.50%, H 9.46%. Found: C 82.62%, H 9.55%. $^1$H-NMR ($CDCl_3$): $\delta$ 1.42 (s, 36H, 12 × $CH_3$), 1.71 (t, $J$ = 6 Hz, 2H, $CH_2$), 2.06 (m, 2H, $CH_2$), 2.73-2.78 (m, 4H, CH), 3.08 (d, $J$ = 13.5 Hz, 2H, $CH_2$), 5.07 (s, 2H, 2 × OH), 6.58 (d, $J$ = 7.5 Hz, 1H, Ar), 6.91-6.98 (m, 6H, Ar), 7.17 (dd, $J_1$ = 7.5 Hz, $J_2$ = 2.7 Hz, 1H, Ar) ppm. $^{13}$C-NMR ($CDCl_3$): $\delta$ 23.41, 28.21, 30.33, 31.14, 34.21, 43.29, 54.61, 125.91, 126.73, 127.36, 127.53, 127.57, 130.32, 135.21, 136.65, 141.92, 152.33, 214.98 ppm. FT-IR (KBr): $\upsilon$ 3638, 3584, 2955, 2866, 1669, 1434, 1377, 1358, 1235, 1213, 1155, 1113, 957, 757 cm$^{-1}$.

## Typical procedure for synthesis of 2-(3,5-di-*t*-butyl-4-hydroxybenzyl) bromopropiophenones

A solution of 2,6-(di-*t*-butyl-4-methoxymethyl)phenol **10** (1 g, 4 mmol) and potassium hydroxide (0.04 g) in methanol (4 mL) was heated to 60 °C. The corresponding bromopropiophenone (4 mmol) was then added to the solution over a period of 10 min and the reaction mixture was refluxed for 3 h. The mixture was cooled to room temperature and poured into 1% acetic acid (10 mL) to solidify. The resulting solids were washed with

water and dried. Recrystallization from n-hexane gave the final products in good yields.

**2-(3,5-Di-*t*-butyl-4-hydroxybenzyl)-1-(4-bromophenyl)propan-1-one (24)** Yellow solid, 86%, mp 83-84 °C. Anal calcd for $C_{24}H_{31}BrO_2$: C 66.82%, H 7.24%. Found: C 66.72%, H 7.22%. $^1$H-NMR ($CDCl_3$): $\delta$ 1.24 (d, $J$ = 6.9 Hz, 3H, $CH_3$), 1.38 (s, 18H, 6 × $CH_3$), 2.68 (dd, $J_1$ = 13.8 Hz, $J_2$ = 7.5 Hz, 1H, CH), 3.01 (dd, $J_1$ = 13.8 Hz, $J_2$ = 7.5 Hz, 1H, CH), 3.64 (sex., $J$ = 6.9 Hz, 1H, CH), 5.03 (s, 1H, OH), 6.90 (s, 2H, Ar), 7.53 (d, $J$ = 8.4 Hz, 2H, Ar), 7.68 (d, $J$ = 8.4 Hz, 2H, Ar) ppm. $^{13}$C-NMR ($CDCl_3$): $\delta$ 17.52, 30.32, 34.18, 40.23, 43.02, 125.42, 127.78, 129.77, 130.11, 131.68, 135.71, 135.79, 152.15, 203.53 ppm. FT-IR (KBr): $\upsilon$ 3569, 2957, 2870, 1683, 1584, 1434, 1238, 1216, 1133, 974, 754 cm$^{-1}$.

**2-(3,5-Di-*t*-butyl-4-hydroxybenzyl)-1-(3-bromophenyl)propan-1-one (25)** Yellow solid, 88%, mp 76-77 °C. Anal calcd for $C_{24}H_{31}BrO_2$: C 66.82%, H 7.24%. Found: C 66.75%, H 7.20%. $^1$H-NMR ($CDCl_3$): $\delta$ 1.25 (d, $J$ = 6.9 Hz, 3H, $CH_3$), 1.38 (s, 18H, 6 × $CH_3$), 2.69 (dd, $J_1$ = 13.5 Hz, $J_2$ = 7.5 Hz, 1H, CH), 3.01 (dd, $J_1$ = 13.5 Hz, $J_2$ = 7.5 Hz, 1H, CH), 3.64 (sex., $J$ = 6.9 Hz, 1H, CH), 5.03 (s, 1H, OH), 6.90 (s, 2H, Ar), 7.26 (t, $J$ = 7.50 Hz, 1H, Ar), 7.62 (d, $J$ = 7.8 Hz, 1H, Ar), 7.74 (d, $J$ = 7.8 Hz, 1H, Ar), 7.90 (d, $J$ = 1.8 Hz, 1H, Ar) ppm. $^{13}$C-NMR ($CDCl_3$): $\delta$ 17.49, 30.26, 34.19, 40.38, 43.26, 122.78, 125.42, 126.68, 127.31, 129.98, 131.36, 135.44, 135.82, 138.87, 152.19, 203.33 ppm. FT-IR (KBr): $\upsilon$ 3576, 2957, 1684, 1566, 1433, 1359, 1203, 1118, 987, 733, 667 cm$^{-1}$.

## Typical procedure for synthesis of 2,2-bis(3,5-di-*t*-butyl-4-hydroxybenzyl) bromopropiophenones

A solution of 2,6-(di-*t*-butyl-4-methoxymethyl)phenol **10** (0.25 g, 1 mmol) and potassium hydroxide (0.02 g) in methanol (2 mL) was heated to 60 °C. The corresponding 2-(3,5-di-*t*-butyl-4-hydroxybenzyl)bromopropiophenone (1 mmol) was then added to the solution over a period of 10 min and the reaction mixture was refluxed for 4 h. The mixture was cooled to room temperature and poured into 1% acetic acid (10 mL) to solidify. The resulting solids were washed with water and dried. Recrystallization from n-hexane gave the final products in good yields.

**2,2-Bis(3,5-di-*t*-butyl-4-hydroxybenzyl)-1-(4-bromophenyl)propan-1-one (26)** White needles, 92%, mp 76-77 °C. Anal calcd for $C_{39}H_{53}BrO_3$: C 72.09%, H 8.22%. Found: C 72.19%, H 8.29%. $^1$H-NMR ($CDCl_3$): $\delta$ 1.14 (s, 3H, $CH_3$), 1.39 (s, 36H, 12 × $CH_3$), 2.67 (d, $J$ = 13.2 Hz, 2H, $CH_2$), 3.42 (d, $J$ = 13.2 Hz, 2H, $CH_2$), 5.10 (s, 2H, 2 × OH), 6.27 (d, $J$ = 8.4 Hz, 2H), 6.92 (s, 4H, Ar), 7.20 (d, $J$ = 8.4 Hz, 2H, Ar) ppm. $^{13}$C-NMR ($CDCl_3$): $\delta$ 22.22, 30.27, 34.2, 47.88, 54.84, 123.94, 127.25, 127.51, 128.03, 130.50, 135.65, 140.37, 152.52, 211.12 ppm. FT-IR (KBr): $\upsilon$ 3635, 2056, 1698, 1583, 1434, 1363, 1237, 1154, 1120, 1065, 967, 937, 824, 771 cm$^{-1}$.

**2,2-Bis(3,5-di-*t*-butyl-4-hydroxybenzyl)-1-(3-bromophenyl)propan-1-one (27)** White needles, 84%, mp 229-230 °C. Anal calcd for $C_{39}H_{53}BrO_3$: C 72.09%, H 8.22%. Found: C 72.04%, H 8.26%. $^1$H-NMR ($CDCl_3$): $\delta$ 1.15 (s, 3H, $CH_3$), 1.41 (s, 36H, 12 × $CH_3$), 2.66 (d, $J$ = 12.9 Hz, 2H, $CH_2$), 3.42 (d, $J$ = 12.9 Hz, 2H, $CH_2$), 5.13 (s, 2H, 2 × OH), 6.11 (d, $J$ = 1.5 Hz, 1H, Ar), 6.20 (dd, $J_1$ = 7.5 Hz, $J_2$ = 0.9 Hz, 1H, Ar), 6.90 (d, $J$ = 7.8 Hz, 1H, Ar), 6.95 (s, 4H, Ar), 7.29 (d, $J$ = 8.1 Hz, 1H, Ar) ppm. $^{13}$C-NMR ($CDCl_3$): $\delta$ 22.15, 30.30, 34.21, 48.07, 55.00, 121.69, 123.72, 127.31, 127.93, 128.24, 128.94, 132.07, 135.76, 143.74, 152.63, 211.42 ppm. FT-IR (KBr): $\upsilon$ 3631, 2955, 2910, 1697, 1466, 1434, 1236, 1148, 1119, 974, 888, 771, 731 cm$^{-1}$.

## Typical procedure for preparation of alcohol analogs of 2,2-bis-(3,5-di-*t*-butyl-4-hydroxybenzyl)benzocycloalkanones and 2,2-bis(3,5-di-*t*-butyl-4-hydroxybenzyl) bromopropiophenones

A mixture of 2,2-bis-(3,5-di-*t*-butyl-4-hydroxybenzyl)benzocycloalkanone or 2,2-bis(3,5-di-*t*-butyl-4-hydroxybenzyl)bromopropiophenone (1 mmol) and lithium aluminum hydride (4 mmol) in dry THF (5 mL) was refluxed for 1 h under a nitrogen atmosphere. After cooling the mixture to room temperature, water (10 mL) was added and then the mixture was extracted with dichloromethane (20 mL), which was dried over sodium sulfate. Removal of the solvent gave the corresponding alcohols in good yields.

**2,2-Bis(3,5-di-*t*-butyl-4-hydroxybenzyl)-4-chloro-2,3-dihydro-1H-inden-1-ol (32)** Colorless crystals, 96%, mp 187-188 °C. Anal calcd for $C_{39}H_{53}ClO_3$: C 77.39%, H 8.83%. Found: C 77.50%, H 8.90%. $^1$H-NMR ($CDCl_3$): $\delta$ 1.46 (s, 36H, 12 × $CH_3$), 2.51-2.83 (m, 4H), 2.95-3.05 (m, 2H), 5.08 (s, 1H, CH), 5.12 (s, 1H, OH), 5.18 (s, 1H, OH), 6.94-7.14 (m, 7H, Ar) ppm. $^{13}$C-NMR ($CDCl_3$): $\delta$ 30.19, 30.34, 30.36, 34.22, 34.27, 37.13, 38.19, 42.54, 53.44, 80.52, 121.68, 126.89, 127.30, 127.49, 128.00, 128.89, 129.03, 135.25, 135.92, 138.53, 146.70, 152.05, 152.33 ppm. FT-IR (KBr): $\upsilon$ 3630, 2955, 2870, 1434, 1232, 1212, 1148, 1120, 882, 775 $cm^{-1}$.

**2,2-Bis(3,5-di-*t*-butyl-4-hydroxybenzyl)-6-methoxy-2,3-dihydro-1H-inden-1-ol (33)** Colorless crystals, 79%, mp 164-165 °C. Anal calcd for $C_{40}H_{56}O_4$: C 79.96%, H 9.39%. Found: C 80.03%, H 9.32%. $^1$H-NMR ($CDCl_3$): $\delta$ 1.42 (s, 18H, 6 × $CH_3$), 1.46 (s, 18H, 6 × $CH_3$), 2.49-2.79 (m, 5H), 2.98 (d, $J$ = 13.8 Hz, 1H, CH), 3.80 (s, 3H, $CH_3$), 5.08 (s, 1H, CH), 5.11 (s, 2H, 2 × OH), 6.73 (dd, $J_1$ = 8.1 Hz, $J_2$ = 2.4 Hz, 1H, Ar), 6.89 (d, $J$ = 2.1 Hz, 1H, Ar), 6.97-7.00 (m, 3H, Ar), 7.05 (s, 2H, Ar) ppm. $^{13}$C-NMR ($CDCl_3$): $\delta$ 29.72, 30.40, 34.24, 34.27, 37.31, 37.47, 41.87, 54.26, 55.37, 80.21, 108.73, 113.90, 125.11, 127.03, 127.31, 129.33, 129.36, 132.28, 135.20, 135.82, 145.95, 151.97, 152.22, 158.83 ppm. FT-IR (KBr): $\upsilon$ 3643, 3568, 2955, 1613, 1489, 1434, 1390, 1361, 1315, 1282, 1234, 1214, 1152, 1120, 1030, 885, 757 $cm^{-1}$.

**2,2-Bis-(3,5-di-*t*-butyl-4-hydroxybenzyl)-6-methoxy-1,2,3,4 tetrahydronaphthalen-1-ol (34)** Viscous colorless oil, 69%. Anal calcd for $C_{41}H_{58}O_4$: C 80.08%, H 9.51%. Found: C 80.20%, H 9.58%. $^1$H-NMR ($CDCl_3$): $\delta$ 1.46 (s, 18H, 6 × $CH_3$), 1.49 (s, 18H, 6 × $CH_3$), 1.89 (t, $J$ = 6.3 Hz, 2H, $CH_2$), 2.33 (s, 1H, OH), 2.45-3.07 (m, 5H), 3.83 (s, 3H, $CH_3$), 4.42 (s, 1H, CH), 5.10 (s, 1H, OH), 5.15 (s, 1H, OH), 6.70 (s, 1H, Ar), 6.81 (d, $J$ = 8.4 Hz, 1H, Ar), 7.03 (s, 2H, Ar), 7.10 (s, 2H, Ar), 7.45 (d, $J$ = 8.4 Hz, 1H, Ar) ppm. $^{13}$C-NMR ($CDCl_3$): $\delta$ 26.03, 27.80, 30.37, 30.44, 34.24, 34.34, 37.59, 41.10, 41.36, 55.26, 72.56, 112.23, 113.22, 125.54, 127.38, 128.53, 128.73, 129.14, 131.79, 135.26, 135.51, 137.00, 152.11, 152.22, 158.53 ppm. FT-IR (KBr): $\upsilon$ 3630, 2955, 2870, 1434, 1232, 1212, 1148, 1120, 882, 775 $cm^{-1}$.

**2,2-Bis(3,5-di-*t*-butyl-4-hydroxybenzyl)-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (35)** Viscous colorless oil, 69%. Anal calcd for $C_{41}H_{58}O_4$: C 80.08%, H 9.51%. Found: C 80.15%, H 9.60%. $^1$H-NMR ($CDCl_3$): $\delta$ 1.47 (s, 18H, 6 × $CH_3$), 1.48 (s, 18H, 6 × $CH_3$), 1.64 (t, $J$ = 6.6 Hz, 2H, $CH_2$), 2.50 (d, $J$ = 12.9 Hz, 1H, CH), 2.65 (d, $J$ = 13.5 Hz, 1H, CH), 2.75-3.16 (m, 4H), 3.85 (s, 3H, $CH_3$), 4.45 (s, 1H, CH), 5.10 (s, 1H, OH), 5.15 (s, 1H, OH), 6.81 (d, $J$ = 8.1 Hz, 1H, Ar), 7.06-7.14 (m, 6H, Ar) ppm. $^{13}$C-NMR ($CDCl_3$): $\delta$ 24.91, 28.44, 29.72, 30.44, 34.24, 34.32, 37.50, 41.30, 41.73, 55.29, 73.08, 111.30, 113.38, 125.54, 127.34, 127.41, 128.60, 129.05, 129.56, 135.30, 135.59, 140.84, 152.14, 152.28, 158.14 ppm. FT-IR (KBr): $\upsilon$ 3566, 3547, 3448, 2955, 2926, 2869, 1434, 1377, 1236, 1096, 872 $cm^{-1}$.

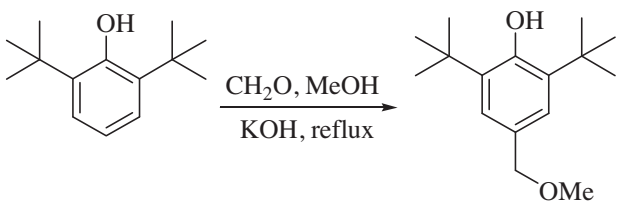
**2,2-Bis(3,5-di-*t*-butyl-4-hydroxybenzyl)benzosuberol (36)** Viscous colorless oil, 89%. Anal calcd for $C_{41}H_{58}O_3$: C 82.22%, H 9.76%. Found: C 82.33%, H 9.74%. $^1$H-NMR ($CDCl_3$): $\delta$ 1.45 (s, 36H, 12 × $CH_3$), 1.62-2.62 (m, 10H), 4.74 (s, 1H, CH), 5.08 (s, 1H, OH), 5.12 (s, 1H, OH), 7.04-7.35 (m, 8H, Ar) ppm. $^{13}$C-NMR ($CDCl_3$): $\delta$ 24.23, 29.72, 30.41, 30.45, 34.29, 34.31, 35.12, 44.06, 125.73, 126.99, 127.32, 127.44, 129.11, 129.39, 129.57, 135.13, 135.71, 152.00 ppm. FT-IR (KBr): $\upsilon$ 3641, 3501, 2955, 2870, 1434, 1235, 1214, 1154, 1121, 1024, 756 cm$^{-1}$.

**2,2-Bis(3,5-di-*t*-butyl-4-hydroxybenzyl)-1-(4-bromophenyl)propan-1-ol (37)** Viscous colorless oil, 88%. Anal calcd for $C_{39}H_{55}BrO_3$: C 71.87%, H 8.51%. Found: C 71.94%, H 8.55%. $^1$H-NMR ($CDCl_3$): $\delta$ 0.76 (s, 3H, $CH_3$), 1.27 (s, 18H, 6 × $CH_3$), 1.44 (s, 18H, 6 × $CH_3$), 2.26-2.40 (m, 2H, $CH_2$), 2.89-2.98 (m, 2H, $CH_2$), 4.41 (s, 1H, CH), 5.08 (s, 2H, 2 × OH), 6.93 (s, 2H, Ar), 7.03 (s, 2H, Ar), 7.21 (d, $J$ = 7.5 Hz, 2H, Ar), 7.42 (d, $J$ = 7.5 Hz, 2H, Ar) ppm. $^{13}$C-NMR ($CDCl_3$): $\delta$ 14.10, 21.05, 22.67, 29.49, 30.42, 31.43, 34.25, 40.74, 42.32, 126.95, 127.29, 127.51, 128.81, 128.50, 129.11, 130.34, 131.27, 135.33, 142.14, 144.47, 153.00 ppm. FT-IR (KBr): $\upsilon$ 3641, 3421, 2058, 1484, 1435, 1362, 1234, 1213, 1157, 1120, 1072, 1010, 874, 770 cm$^{-1}$.

**2,2-Bis(3,5-di-*t*-butyl-4-hydroxybenzyl)-1-(3-bromophenyl)propan-1-ol (38)** Viscous colorless oil, 80%. Anal calcd for $C_{39}H_{55}BrO_3$: C 71.87%, H 8.51%. Found: C 71.87%, H 8.51%. $^1$H-NMR ($CDCl_3$): $\delta$ 0.79 (s, 3H, $CH_3$), 1.46 (s, 36H, 6 × $CH_3$), 2.29-2.43 (m, 2H, $CH_2$), 2.91-3.01 (m, 2H, $CH_2$), 4.43 (s, 1H, CH), 5.10 (s, 2H, 2 × OH), 6.95 (s, 2H, Ar), 7.05 (s, 2H, Ar), 7.18-7.29 (m, 2H, Ar), 7.43 (d, $J$ = 7.5 Hz, 2H, Ar) ppm. $^{13}$C-NMR ($CDCl_3$): $\delta$ 21.09, 29.70, 30.45, 30.48, 34.27, 40.79, 42.37, 42.59, 76.59, 121.90, 125.68, 126.96, 127.31, 127.52, 128.63, 128.84, 129.13, 130.36, 131.29, 135.30, 135.37, 144.49, 152.14 ppm. FT-IR (KBr): $\upsilon$ 3643, 3422, 2923, 2855, 1462, 1434, 1363, 1234, 1213, 1158, 1120, 883, 783 cm$^{-1}$.

## Results and discussion

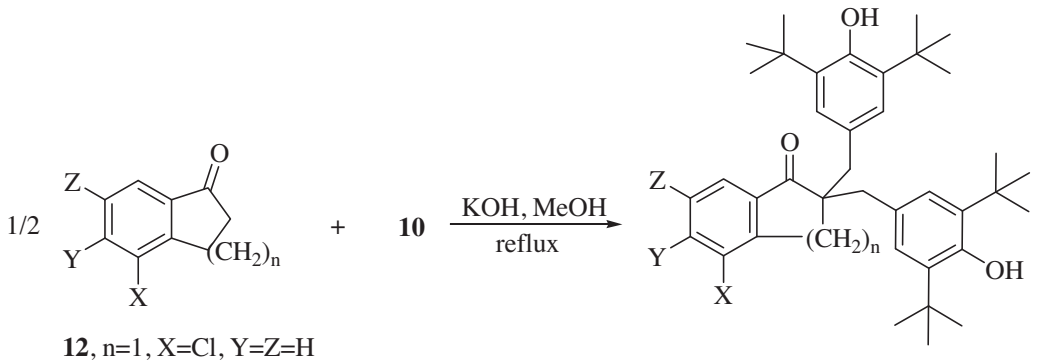
2,6-Di-*t*-butyl-4-methoxymethylphenol **10**[21] was prepared by the reaction of 2,6-di-*t*-butylphenol **11** and formaldehyde in the presence of potassium hydroxide in methanol at reflux conditions (Scheme 1).




**11** **10**

**Scheme 1.**

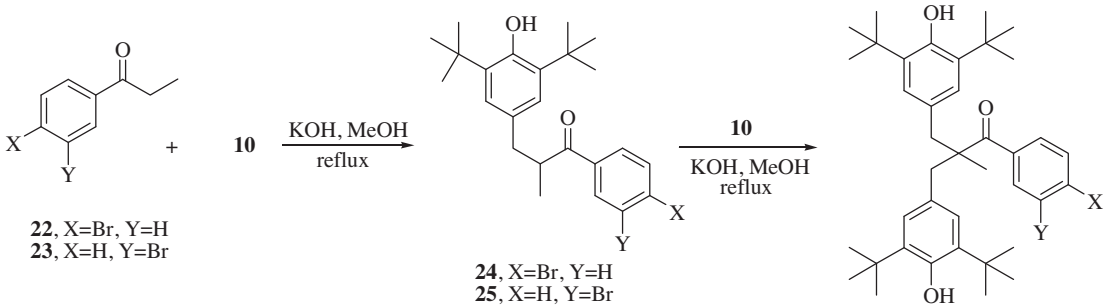
As shown in Schemes 2 and 3, compound **10**, presumably a precursor of *p*-quinonemethide, was reacted with a number of substituted benzocycloalkanones and bromopropiophenones in the presence of potassium hydroxide in methanol at 65 °C. For cyclic ketones, i.e. indanones **12-13**, tetralones **14-15**, and benzosuberone **16**, the resulting products were the substituted 2,2-bis-(3,5-di-*t*-butyl-4-hydroxybenzyl) benzocycloalkanones **17-21**, whereas in the case of acyclic ketones, i.e. *p*- and *m*- bromopropiophenones **22-23**, the 2-(3,5-di-*t*−butyl-4-hydroxybenzyl)propanones **24-25** were formed initially, but further reaction with compound **10** gave the *bis* products **26-27**.




**12**, n=1, X=Cl, Y=Z=H
**13**, n=1, X=Y=H, Z=$OCH_3$
**14**, n=2, X=Z=H, Y=$OCH_3$
**15**, n=2, X=Y=H, Z=$OCH_3$
**16**, n=3, X=Y=Z=H

**17**, n=1, X=Cl, Y=Z=H
**18**, n=1, X=Y=H, Z=$OCH_3$
**19**, n=2, X=Z=H, Y=$OCH_3$
**20**, n=2, X=Y=H, Z=$OCH_3$
**21**, n=3, X=Y=Z=H

**Scheme 2.**




**22**, X=Br, Y=H
**23**, X=H, Y=Br

**24**, X=Br, Y=H
**25**, X=H, Y=Br

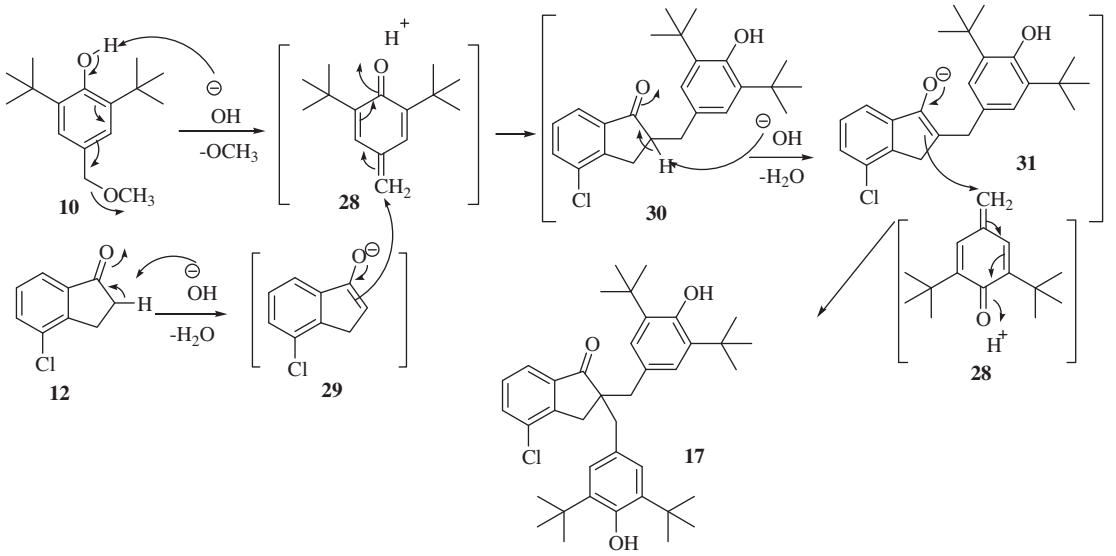
**26**, X=Br, Y=H
**27**, X=H, Y=Br

**Scheme 3.**

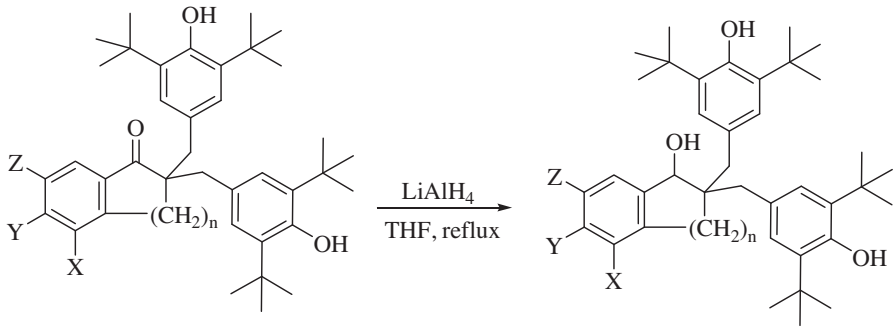
The proposed mechanism for the formation of *bis* product **17** involves in situ formation of *p*-quinonemethide **28**, then the nucleophilic attack by the preformed enolate **29** to form the mono-substituted ketone **30** and the subsequent nucleophilic attack of its enolate **31** on a second molecule of *p*-quinonemethide **28** to afford the final product **17**, as shown in Scheme **4**.

It is notable that all of the cycloalkanone derivatives reacted with 2 equivalents of *p*-quinonemethide **28** and directly formed the *bis* alkylated products; we were unable to isolate any mono-substituted products even under moderate reaction conditions. This was probably because of the high reactivity of the remaining *alpha* hydrogen on the mono-substituted cycloalkanone intermediates (e.g. **30**), which is easily removed with KOH to form a reactive enolate that readily reacts with a second molecule of quinonemethide. In contrast with the cyclic ketones, with acyclic ketones the initial mono-substituted ketones **24-25** were unreactive, even under harsh reaction conditions.

All of these alkylated ketones were reduced to their corresponding alcohols (Schemes 5 and 6). As mentioned previously, it is hoped that such alcohols will act as positive allosteric modulators of $GABA_B$ receptors as propofol analogs, with the hydroxyphenyl group corresponding to the carboxyl group of $\gamma$-hydroxybutyric acid.



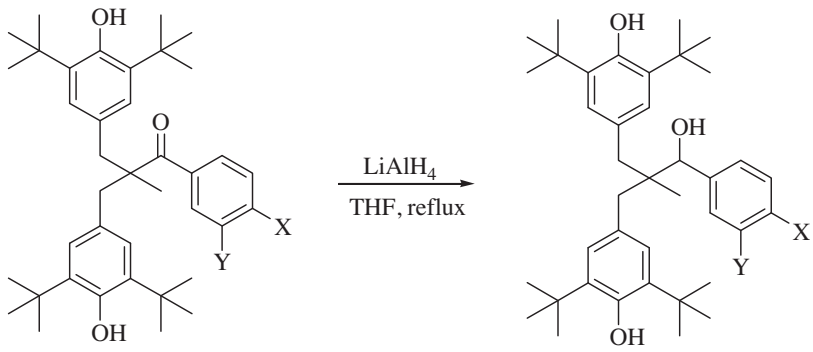
**Scheme 4.**



**17**, n=1, X=Cl, Y=Z=H
**18**, n=1, X=Y=H, Z=$OCH_3$
**19**, n=2, X=Z=H, Y=$OCH_3$
**20**, n=2, X=Y=H, Z=$OCH_3$
**21**, n=3, X=Y=Z=H

**32**, n=1, X=Cl, Y=Z=H
**33**, n=1, X=Y=H, Z=$OCH_3$
**34**, n=2, X=Z=H, Y=$OCH_3$
**35**, n=2, X=Y=H, Z=$OCH_3$
**36**, n=3, X=Y=Z=H

**Scheme 5.**



**26**, X=Br, Y=H
**27**, X=H, Y=Br

**37**, X=Br, Y=H
**38**, X=H, Y=Br

**Scheme 6.**

## Conclusion

In conclusion, we have synthesized a series of new substituted 2,2-bis-(3,5-di-*t*-butyl-4-hydroxybenzyl)indanones, tetralones, propiophenones, and benzosuberone, and their alcohol analogs. These alcohols are potential allosteric modulators of $GABA_B$ receptors. Due to the presence of 2 phenolic hydroxyl groups in these derivatives, they may exhibit better binding properties than those previously synthesized.

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