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Novel thyroid hormone receptor antagonists with an N-alkylated diphenylamine skeleton

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Abstract—Thyroid hormones play important roles in growth, development and homeostasis, and disruption of their functions induces serious disease, so novel synthetic thyroid hormone analogues are candidates for clinical application. We designed and synthesized novel diphenylamine derivatives with a thiazolidinedione moiety as the terminal polar group as thyroid hormone receptor (TR) antagonists. Compounds bearing an appropriately sized *N*-alkyl group showed antagonistic activities towards both the hTRα1 and hTRβ1 subtypes.

1. Introduction

Thyroid hormones (THs), 3,3′,5-triiodothyronine (T_3, Fig. 1) and 3,3′,5,5′-tetraiodothyronine (T_4), are produced by the thyroid gland and peripheral tissues, and regulate various physiological processes associated with growth, homeostasis and development.[1] They regulate gene transcription through binding with thyroid hormone receptors (TRs),[2] which are ligand-inducible transcriptional factors belonging to the nuclear receptor superfamily, and they also influence basal and adaptive metabolism, lipid levels, bone and muscle metabolism and heart rate. Disruption of these regulatory functions causes various diseases. For example, abnormal elevation of circulating TRs results in hyperthyroidism, which manifests clinically as weight loss, lowering of serum lipid levels, cardiac arrhythmias and heart failure. Present clinical treatment of hyperthyroidism involves direct reduction of TH production by inhibiting the synthesizing enzymes, or by ablating the thyroid gland surgically or with radioiodine, but because of the long half-life of THs, these therapies take several weeks to restore a normal state. In contrast, the direct suppression of TR functions is expected to be quick. Therefore, in addition to TR agonists,[3–11] such as Triac,[3,4] GC-1[5] and **1**,[6] several TR antagonists have been synthesized (Fig. 2).[12–21] Most of them, except for a few compounds such as HY-4, are analogues of Triac or GC-1 bearing a bulky group at the 5′-position of the phenol moiety (outer ring). However, the structure-activity relationship study of GC-14[16] and NH-3[17] showed that the agonist/antagonist activity balance varied depending on the substituent on the phenyl or phenylethynyl group, which means that the bulkiness of the 5′-substituent is not the only factor determining the activity of these types of TR antagonists.[18] In this article, we designed and synthesized a series of novel TR antagonists, and elucidated their activities towards the TR subtypes.

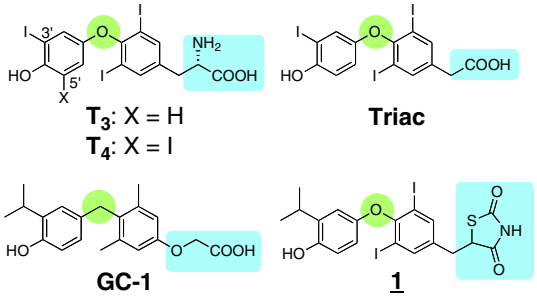

Figure 1. Structures of endogenous and synthetic TR agonists.

Keywords: Thyroid hormone; Antagonist; Diphenylamine; Thiazolidinedione.
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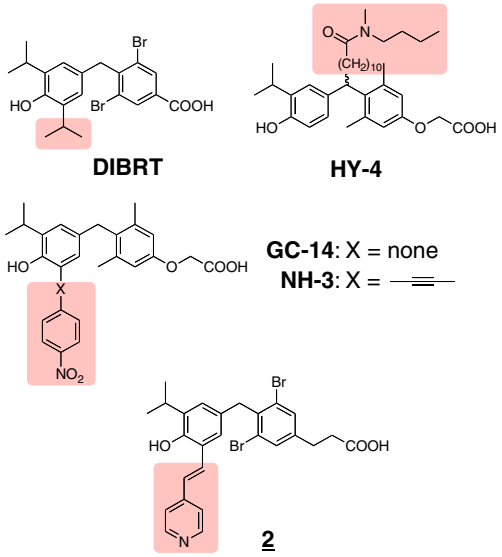


Figure 2. Structures of typical TR antagonists.

2. Results

2.1. Design of new antagonist candidates

The crystal structures of several nuclear receptor ligand-binding domains (LBD) indicated that in binding with agonists, the C-terminal helix 12 (H12) forms a lid over the ligand-binding pocket, thereby providing an accessible surface structure suitable for coactivator binding.[22–24] Prevention of this proper packing of H12 by a bulky group introduced into the structure of some antagonists could explain the antagonistic activity.

In the case of TRs, the crystal structures of holo-receptors with some agonists, including T_3, have already been reported.[25,26] In these structures, the 5′ position of the ligand is oriented in the direction of the loop between helix 11 and H12, so the introduction of a bulky group at this position might yield antagonists. Based on this concept, several synthetic TR antagonists, such as DIBRT,[19] GC-14, NH-3 or **2**,[20] were reported. However, modification at the 5′ position also caused variation in the TR agonist/antagonist activity ratio, and therefore we designed different types of TR antagonist candidates.

TR ligands consist of three parts, that is, a phenolic outer ring, another benzene ring (inner ring) bearing the terminal polar group and their linking atom. The terminal polar group is significant for the interaction with TRs and may be associated with the selectivity between TRα and β subtypes.[27] The linking atom in the endogenous ligand is oxygen. Recently, various TR analogues with a methylene linker have been developed, and introduction of a long substituent on the methylene linker afforded antagonistic activity in the case of HY-4. Considering these results, we designed compounds **3** as TR antagonist candidates (Fig. 3). In the structure of **3**, the nitrogen atom was used as the linker between the outer and inner rings, and antagonistic activity was expected to be generated by the introduction of an appropriately sized *N*-alkyl group. As for the terminal polar group, we previously reported that compound **1** is as active as T_3,[6] and a thiazolidinedione group is a good bioisoster for carboxylic acid, as has also been found with ligands of other nuclear hormone receptors.[28,29] Thus, we designed and synthesized **3a**–**3g** as TR antagonist candidates.

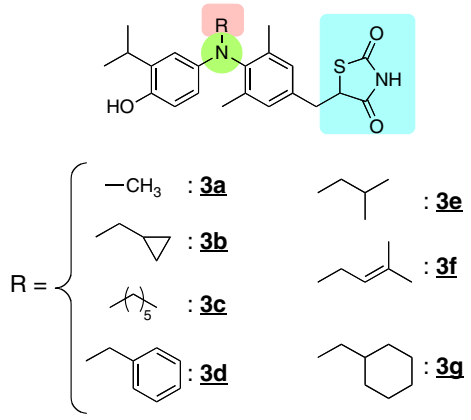


Figure 3. Structures of newly synthesized TR antagonist candidates.

2.2. Synthesis

For the synthesis of **3a**–**3g**, we planned to derive the thiazolidinedione group from an aldehyde group at the final stage in the synthesis. The diphenylamine compound **4** can be synthesized by Buchward's amination reaction between a protected 4-bromo-2-isopropylphenol, **6a** or **6b**, and aniline derivatives with an aldehyde (**7a**), a protected aldehyde (**7b**) or a cyano group as the precursor for aldehyde (**7c**) (Fig. 4).

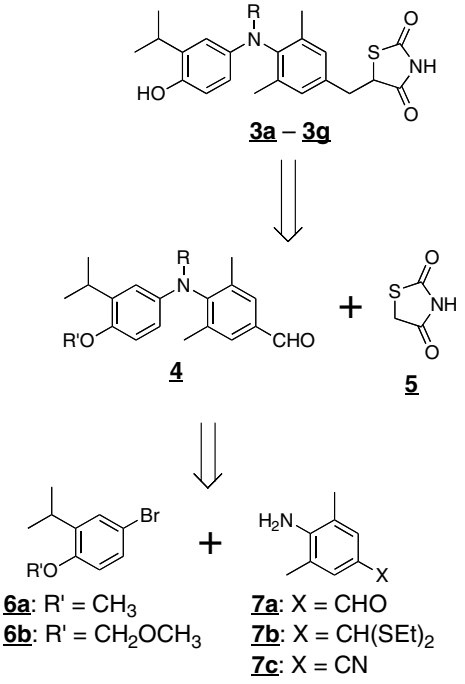
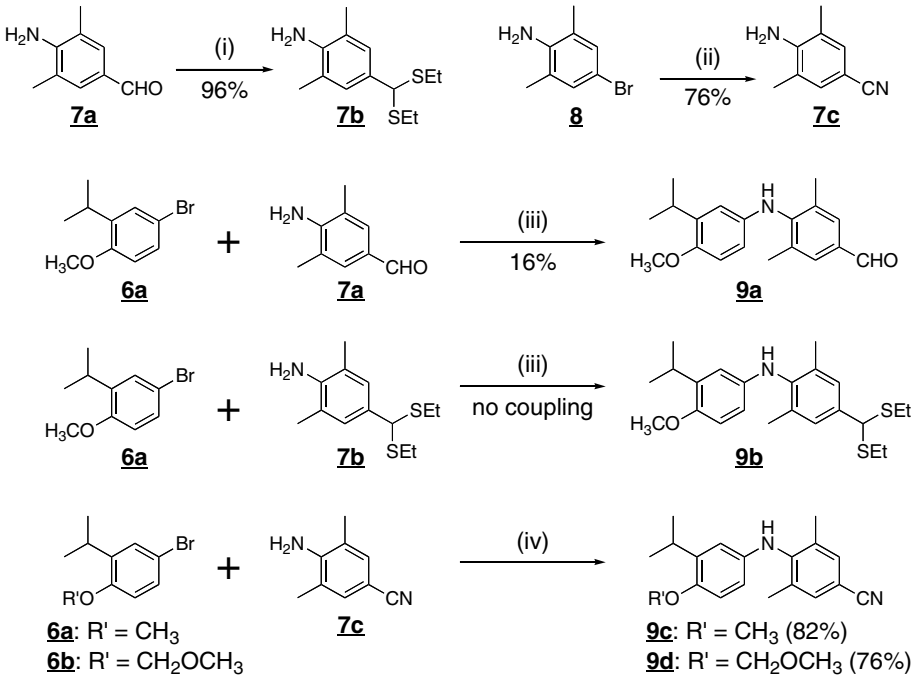


Figure 4. Synthetic strategy for **3**.



Scheme 1. Reagents: (i) EtSH, TMSCl, $CHCl_3$; (ii) CuI, KI, CuCN, *N*,*N*′-dimethylethylenediamine, DMF; (iii) $Pd_2(dba)_3$, *t*-BuONa, 2-(di-*tert*-butylphosphino)biphenyl, toluene; (iv) $Pd_2(dba)_3$, *t*-BuONa, 2-(di-cyclohexylphosphino)biphenyl, toluene.

The methyl-protected *p*-bromophenols **6a** and **7a** were prepared by the method in the literature[5,30] (Scheme 1). However, the coupling reaction of **6a** and **7a** proceeded only in low yield (16%), mainly due to the high reactivity of the aldehyde group. To prevent side reactions, the aldehyde group was protected with thiolate to form a thioacetal moiety, **7b**, but this could not be coupled with **6a**, probably because the sulfur atoms would chelate palladium, preventing the catalytic reaction.[‡] Thus, a cyano group (**7c**) was used as a precursor of aldehyde. The cyano derivative **7c** was synthesized from **8** via a Sonogashira-like reaction.[31] The coupling reaction of **7c** with **6a** proceeded to afford **9c** in 82% yield. In this reaction, the phosphine ligand, 2-(di-cyclohexylphosphino)biphenyl, is important for high yield. The methoxymethyl-protected molecule **6b** was also coupled with **7c** to afford the diphenylamine **9d** in 76% yield.

After methylation of **9c**, **10** was reduced to the aldehyde (**11**) via Knoevenagel condensation with thiazolidinedione (**5**) to afford **12** (Scheme 2). The reduction of **12** with Pd/C or $LiBH_4$ was unsuccessful because of decomposition or slow reaction, but the method using cobalt–dimethylglyoxime complex successfully reduced **12** to **13**. However, demethylation of **13** proved difficult. Therefore, we used the methoxymethyl group for protection of the phenolic hydroxyl group. Starting from **6b**, the same reactions proceeded to afford **17a**, and deprotection of the methoxymethyl group proceeded easily to give **3a**. Compounds **3b**–**3g** were similarly synthesized.

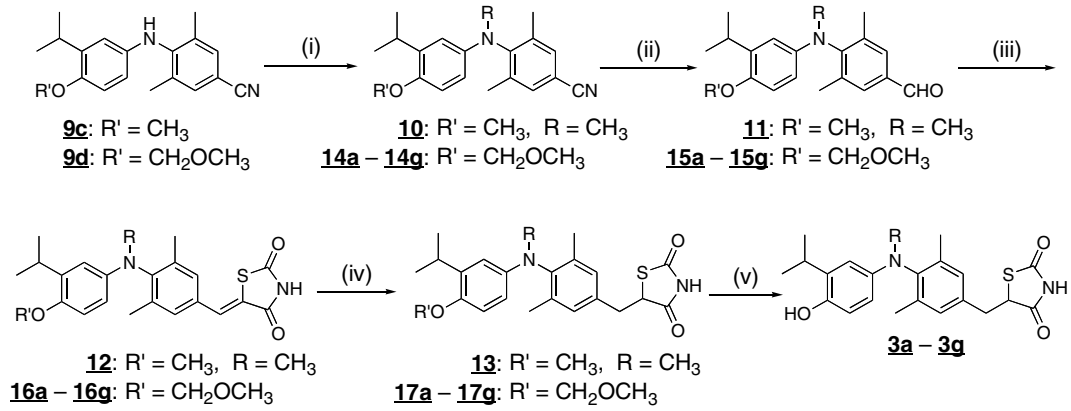
[‡] The compound **7a** could not be converted to the acetal derivatives by the typical reaction conditions.

2.3. Biological activity

The activity of the synthesized molecules was examined by means of transient transactivation assay in COS-1 cells transfected with hTRα1 or hTRβ1. None of the compounds activated transcription via either of the subtypes, except that **3a** had a slight agonist activity towards TRα1 and TRβ1, being less than one-tenth as potent as T_3 at the concentration of 10^{-6} M (data not shown). Then, the antagonistic activities towards T_3 in TR activation were examined. All the compounds, except for **3a**, exhibited antagonistic activity (Fig. 5). The difference in the activity depending upon the N-substituent was small, and the similar tendency was observed between two TR subtypes. Compounds with a bulky *N*-alkyl group, such as a benzyl (**3d**) and cyclohexylmethyl group (**3g**), were moderately effective among the synthesized compounds.

3. Discussion

Compounds **3b**–**3g** showed antagonist activities towards both subtypes of TRs, while **3a** exhibited very weak partial-agonistic activity, and this difference must be due to the difference of substituents at the nitrogen atom. Among the TR antagonists so far known, only HY-4 has a bulky substituent on the linker atom.[12] However, HY-4 has an extremely long chain, and compounds with a shorter allyl group, such as **18** (Fig. 6), show weak agonistic activity. In our case, such a long substituent is unnecessary, and a C4–C8 alkyl group is sufficient for antagonist activity against both TR subtypes. A possible reason for this difference is the difference of the linker atom, carbon in HY-4 and **18**, and nitrogen in our



Scheme 2. Synthesis of **3a**–**3g**. In compounds **3** and **14**–**17**, R is (a) CH_3, (b) cyclopropylmethyl, (c) *n*-hexyl, (d) benzyl, (e) *iso*-butyl, (f) prenyl and (g) cyclohexylmethyl. Reagents: (i) NaH, R–X (Cl, Br or I), DMF; (ii) DIBAL-H, toluene; (iii) **5**, piperidine, EtOH; (iv) 1—Co-DMG, DMF; 2—$NaBH_4$, H_2O; (v) HCl, CH_3OH–CH_2Cl_2.

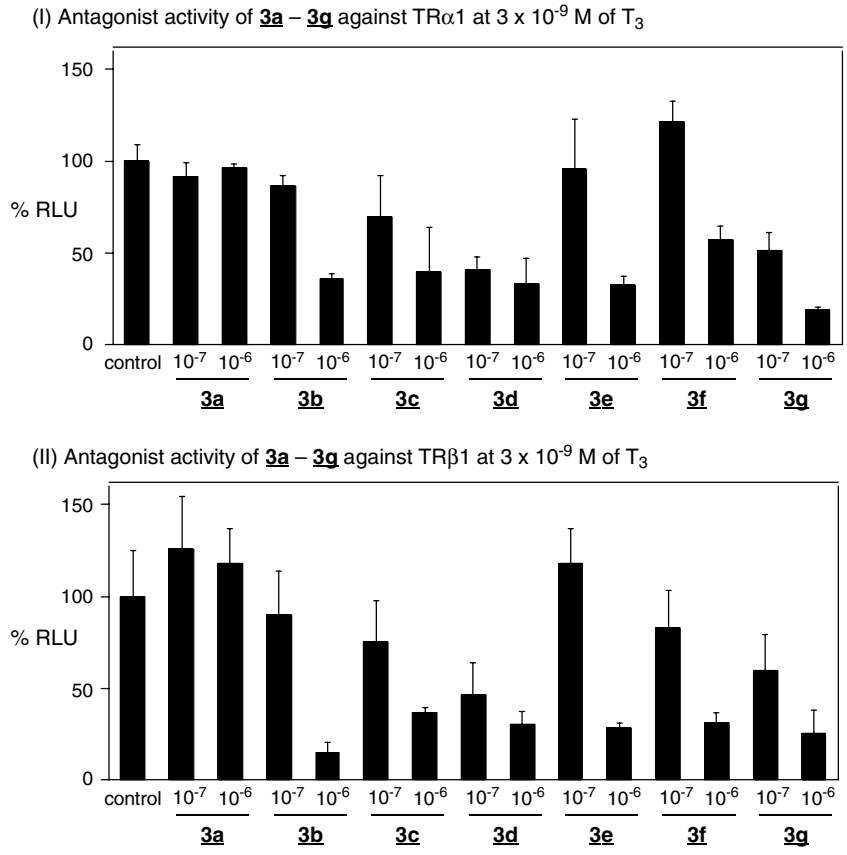


Figure 5. Transactivation profile for **3** with (I) TRα1 and (II) TRβ1. COS-1 cells were transfected with TR expression vector and luciferase reporter genes, and were treated with the indicated concentration of **3** in the presence of 3×10^{-9} M T_3. The values were normalized to β-galactosidase activities and expressed relative to that obtained when 3×10^{-9} M T_3 was added, and the results are shown as percentages, with the value for T_3 taken as 100%. Values are means ± SD for separate experiments ($n = 3$).

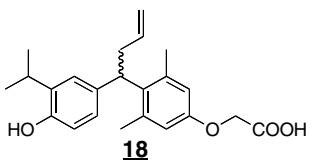


Figure 6. Structure of **18**.

molecules. The orientation of the substituent would be different in the two cases, and this might account for the difference of threshold between agonist and antagonist. Crystal structures of holo-TR ligand binding domains show that the introduction of the bulky substituent at 5′-position of T_3 may disturb the proper conformation of helix 12 that is significant for the active form

of TR. If the compounds **3** bind to TRs with similar conformation with that of T_3 or GC-1, the substituent on the linker nitrogen atom was thought to face to helix 7 or 8. The further study for elucidation of the structural factors for the antagonism of novel compounds **3** is ongoing.

The key intermediate **9d** should be a convenient synthetic intermediate for obtaining various derivatives with different N-substituents. In addition, the cyano (**9d**) or aldehyde group (**15**) can be easily transformed to other polar groups. Crystallographic studies have shown that only one amino acid residue is different (Ser277 in hTRα1, Asn331 in hTRβ1) in the ligand binding cavities of the two TR subtypes.[32] Although these residues do not directly contact the ligand, they participate in a hydrogen-bonding network with the terminal polar group. In the study of GC-1, a β-selective agonist, the terminal polar group (oxoacetic acid) was found to be important for its β-selectivity. In our case, although no subtype selectivity was observed, it is possible that modification at the terminal polar group may afford potent TR subtype-selective antagonists. We are now developing a TR ligand library by using **9d** as the key intermediate. It is also possible that other combinations of linker atom and terminal polar group may yield selective TR agonists and antagonists.

4. Conclusion

We have designed and synthesized novel TR antagonists, **3b**–**3g**. This new class of antithyroid compounds should provide candidate drugs for clinical application and tools for elucidation of the physiological functions of thyroid hormone receptors.

5. Experimental

5.1. General information

All reagents were purchased from Sigma–Aldrich Chemical Co., Tokyo Kasei Kogyo Co., Wako Pure Chemical Industries and Kanto Kagaku Co., Inc. Silica gel for column chromatography was purchased from Kanto Kagaku Co., Inc. ^{1}H and ^{13}C NMR spectra were recorded on Bruker ARX400 or Bruker Avance 500 spectrometer. Mass spectral data were obtained on a Bruker Daltonics microTOF-2focus in the positive and negative ion detection modes.

5.2. Synthesis

5.2.1. Synthesis of 4-[bis(ethylthio)methyl]-2,6-dimethylaniline (7b). To a solution of **7a** (202 mg, 1.36 mmol) in anhydrous chloroform (5.0 mL) at room temperature were added trimethylsilyl chloride (0.43 mL, 3.36 mmol) and ethanethiol (0.25 mL, 3.38 mmol) under argon atmosphere. The reaction mixture was stirred for 2 h. After the addition of aqueous NaOH, the aqueous phase was extracted with chloroform. The organic fractions were washed with brine, dried over sodium sulfate and concentrated in vacuo. Purification by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:1) yielded the **7b** as a brown solid (332 mg, 96%).

Compound **7b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 2H), 4.82 (s, 1H), 2.56 (q, 4H, J = 7.4 Hz), 2.23 (s, 6H), 1.23 (t, 6H, J = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 129.4, 127.6, 121.6, 52.3, 26.3, 17.7, 14.3; HRMS (ESI) calcd for $C_{13}H_{21}N_1Na_1S_2$ ($M+Na^+$) 278.1008; found 278.0996.

5.2.2. Synthesis of 4-amino-3,5-dimethylbenzonitrile (7c). An oven-dried, round-bottomed flask was charged with CuCN (5.85 g, 65.3 mmol), CuI (1.04 g, 5.46 mmol), **8** (10.8 g, 54.2 mmol) and KI (1.91 g, 11.5 mmol) under argon. Anhydrous DMF (39 mL) and *N*,*N*′-dimethylethylenediamine (5.80 mL, 54.4 mmol) were added, and the reaction mixture was stirred at 100 °C for 24 h. The resulting suspension was allowed to warm to room temperature, diluted with 28% aqueous ammonia and extracted with ethyl acetate. The organic fractions were washed with brine, dried over sodium sulfate and concentrated in vacuo. Purification by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:3) yielded the **6c** as a white solid (6.05 g, 76%).

Compound **7c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (s, 2H), 4.04 (br s, 2H), 2.17 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 130.5, 123.6, 109.4, 17.4; HRMS (ESI) calcd for $C_9H_9N_2$ ($M-H^+$) 145.0761; found 145.0768.

5.2.3. Synthesis of 4-[(3-isopropyl-4-methoxyphenyl)-amino]-3,5-dimethylbenzaldehyde (9a). An oven-dried, round-bottomed flask was charged with $Pd_2(dba)_3$ (4.4 mg,4.25 μmol), 2-(di-*tert*-butylphosphino)biphenyl (4.3 mg, 14.4 μmol), *t*-BuONa (63.0 mg, 0.656 mmol) and **7a** (82.0 mg, 0.550 mmol) under argon. A separate flame-dried, two-necked, pear-shaped flask was charged with **6a** (103 mg, 0.451 mmol) and dry toluene (1.7 mL) under argon. This solution was added to the round-bottomed flask via cannula. The resulting mixture was stirred for 3 days at 100 °C. After the addition of water and aqueous HCl to the reaction mixture at 0 °C, the aqueous phase was extracted with ethyl acetate. The organic fractions were washed with brine, dried over sodium sulfate and concentrated in vacuo. Purification by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:9) yielded the **9a** as a brown oil (21.4 mg, 16%).

Compound **9a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.58 (s, 2H), 6.71 (d, 1H, J = 8.6 Hz), 6.66–6.48 (m, 2H), 3.79 (s, 3H), 3.28 (septet, 1H, J = 6.9 Hz), 2.20 (s, 6H), 1.16 (d, 6H, J = 6.9 Hz); HRMS (ESI) calcd for $C_{19}H_{22}N_1O_2$ ($M-H^+$) 296.1645; found 296.1633.

5.2.4. Synthesis of 4-[(3-isopropyl-4-methoxyphenyl)-amino]-3,5-dimethylbenzonitrile (9c). An oven-dried, round-bottomed flask was charged with $Pd_2(dba)_3$ (104 mg, 0.100 mmol), 2-(di-cyclohexylphosphino)biphenyl (48.9 mg, 0.140 mmol), *t*-BuONa (0.633 g, 6.59 mmol) and **7c** (0.751 g, 5.14 mmol) under argon. A

separate flame-dried, two-necked, pear-shaped flask was charged with **6a** (1.31 g, 5.72 mmol) and dry toluene (29 mL) under argon. This solution was added to the round-bottomed flask via cannula. The resulting mixture was stirred for 19 h at 100 °C. After the addition of water and aqueous HCl to the reaction mixture at 0 °C, the aqueous phase was extracted with ethyl acetate. The organic fractions were washed with brine, dried over sodium sulfate and concentrated in vacuo. Purification by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:4) yielded the **9c** as a white solid (1.24 g, 82%).

Compound **9c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 2H), 6.70 (d, 1H, J = 8.6 Hz), 6.61 (d, 1H, J = 2.8 Hz), 6.41 (dd, 1H, J = 8.6 Hz, 2.8 Hz), 5.35 (s, 1H), 3.78 (s, 3H), 3.27 (septet, 1H, J = 6.9 Hz), 2.15 (s, 6H), 1.16 (d, 6H, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 144.8, 138.2, 137.3, 132.6, 132.1, 119.6, 116.3, 115.1, 111.3, 105.7, 55.9, 26.9, 22.6, 18.7; HRMS (ESI) calcd for $C_{19}H_{21}N_2O_1$ ($M-H^+$) 293.1648; found 293.1646.

5.2.5. Synthesis of 4-[[3-isopropyl-4-(methoxymethoxy)-phenyl]amino]-3,5-dimethylbenzonitrile (9d). Compound **9d** was prepared from **7c** (3.81 g, 26.2 mmol) and **6b** (6.01 g, 23.2 mmol) according to the procedure described for **9c** in yield 76% (5.73 g, white solid).

Compound **9d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (s, 2H), 6.92 (d, 1H, J = 8.6 Hz), 6.56 (d, 1H, J = 2.7 Hz), 6.39 (dd, 1H, J = 8.6 Hz, 2.8 Hz), 5.34 (s, 1H), 5.13 (s, 2H), 3.49 (s, 3H), 3.29 (septet, 1H, J = 6.9 Hz), 2.16 (s, 6H), 1.17 (d, 6H, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 144.5, 139.0, 138.5, 132.6, 132.6, 119.6, 115.5, 115.5, 114.9, 106.2, 95.4, 56.0, 27.0, 22.8, 18.7; HRMS (ESI) calcd for $C_{20}H_{23}N_2O_2$ ($M-H^+$) 323.1754; found 323.1751.

5.2.6. Synthesis of 4-[*N*-(3-isopropyl-4-methoxyphenyl)-*N*-methylamino]-3,5-dimethylbenzonitrile (10). To a suspension of NaH (25.7 mg, 1.07 mmol) in dry DMF (1.0 mL) under argon, **9c** (200 mg, 0.679 mmol) was slowly added at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 30 min. To the mixture, iodomethane (140 μL, 2.25 mmol) was slowly added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. After the addition of water to the reaction mixture at 0 °C, the aqueous phase was extracted with ethyl acetate. The organic fractions were washed with brine, dried over sodium sulfate and concentrated in vacuo. Purification by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:6) yielded the **10** as a brown oil (196 mg, 94%).

Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 2H), 6.72 (d, 1H, J = 8.8 Hz), 6.28 (d, 1H, J = 1.9 Hz), 6.19 (dd, 1H, J = 8.3 Hz, 1.9 Hz), 3.75 (s, 3H), 3.24 (septet, 1H, J = 6.9 Hz), 3.15 (s, 3H), 2.11 (s, 6H), 1.12 (d, 6H, J = 6.9 Hz).

5.2.7. Synthesis of 4-[*N*-(3-isopropyl-4-methoxyphenyl)-*N*-methylamino]-3,5-dimethylbenzaldehyde (11). To a solution of **10** (196 mg, 0.637 mmol) in dry toluene (3.0 mL) under argon, DIBAL-H (0.99 M solution in toluene, 0.90 mL, 0.891 mmol) was slowly added at 0 °C. The reaction mixture was stirred for 20 min at room temperature. After the addition of saturated ammonium chloride, the aqueous phase was extracted with ethyl acetate. The organic fractions were washed with brine, dried over sodium sulfate and concentrated in vacuo. Purification by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:6) yielded the **11** as a yellow oil (133 mg, 63%).

Compound **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.65 (s, 2H), 6.72 (d, 1H, J = 8.8 Hz), 6.30 (br s, 1H), 6.21 (d, 1H, J = 6.5 Hz), 3.76 (s, 3H), 3.24 (septet, 1H, J = 6.9 Hz), 3.17 (s, 3H), 2.15 (s, 6H), 1.12 (d, 6H, J = 6.9 Hz).

5.2.8. Synthesis of (*Z*)-5-[4-[*N*-(3-isopropyl-4-methoxyphenyl)-*N*-methylamino]-3,5-dimethylphenylmethylene]-thiazolidine-2,4-dione (12). To a solution of **11** (133 mg, 0.402 mmol) in dry ethanol (11 mL) under argon, piperidine (50 μL, 0.453 mmol) and 2,4-thiazolidinedione (**5**, 53.1 mg, 0.453 mmol) were added at room temperature. The reaction mixture was refluxed for 20 h, and the solvent was concentrated in vacuo. After the addition of water, the aqueous phase was extracted with ethyl acetate. The organic fractions were washed with brine, dried over sodium sulfate and concentrated in vacuo. Purification by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:3) yielded the **12** as a brown oil (122 mg, 74%).

Compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (br s, 1H), 7.83 (s,1H), 7.27 (s, 2H), 6.72 (d, 1H, J = 8.8 Hz), 6.32 (s, 1H), 6.20 (d, 1H, J = 8.8 Hz), 3.76 (s, 3H), 3.24 (septet, 1H, J = 6.9 Hz), 3.16 (s, 3H), 2.13 (s, 6H), 1.13 (d, 6H, J = 6.9 Hz).

5.2.9. Synthesis of 5-[4-[*N*-(3-isopropyl-4-methoxyphenyl)-*N*-methylamino]-3,5-dimethylphenylmethyl]thiazolidine-2,4-dione (13). To a rapidly stirred mixture of **12** (33.9 mg, 82.6 μmol) in THF (360 μL) and 1M NaOH (90.0 μL) at room temperature, $CoCl_2$–DMG complex solution (18.0 μL, made from 11.6 mg of cobalt chloride, 125 mg of dimethylglyoxime and 2.5 mL DMF) was added. After 30 min, sodium borohydride (18.0 mg, 0.476 mmol) in water (0.5 mL) was added and the mixture was stirred at 35 °C for 9 h. After the addition of water and aqueous HCl to the reaction mixture at 0 °C, the aqueous phase was extracted with ethyl acetate. The organic fractions were washed with brine, dried over sodium sulfate and concentrated in vacuo. Purification by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:3) yielded the **13** as a brown oil (25.2 mg, 74%).

Compound **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (br s, 1H), 6.97 (s, 2H), 6.71 (d, 1H, J = 8.8 Hz), 6.25 (s, 1H), 6.15 (d, 1H, J = 7.1 Hz), 4.56 (dd, 1H, J = 10.4 Hz, 3.8 Hz), 3.75 (s, 3H), 3.55 (dd, 1H, J = 13.9 Hz, 3.8 Hz), 3.23 (septet, 1H, J = 6.9 Hz), 3.14 (s, 3H), 3.03 (dd, 1H, J = 14.0 Hz, 10.4 Hz), 2.06 (s, 6H), 1.12 (d, 6H, J = 6.9H).

5.2.10. Synthesis of 4-[*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]-*N*-methylamino]-3,5-dimethylbenzonitrile (14a). Compound **14a** was prepared from **9d** (197 mg, 0.606 mmol) and iodomethane (250 μL, 4.02 mmol) according to the procedure described for **10** in yield 72% (147 mg, brown oil).

Compound **14a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 2H), 6.91 (d, 1H, J = 8.8 Hz), 6.25 (s, 1 H), 6.15 (d, 1H, J = 6.9 Hz), 5.09 (s, 2H), 3.49 (s, 3H), 3.26 (septet, 1H, J = 6.9 Hz), 3.14 (s, 3H), 2.10 (s, 6H), 1.14 (d, 6H, J = 6.9 Hz).

5.2.11. Synthesis of 4-[*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]-*N*-methylamino]-3,5-dimethylbenzaldehyde (15a). Compound **15a** was prepared from **14a** (227 mg, 0.670 mmol) according to the procedure described for **11** in yield 60% (147 mg, yellow oil).

Compound **15a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.65 (s, 2H), 6.91 (d, 1H, J = 8.8 Hz), 6.27 (s, 1H), 6.18 (d, 1H, J = 6.6 Hz), 5.09 (s, 2H), 3.49 (s, 3H), 3.26 (septet, 1H, J = 6.9 Hz), 3.17 (s, 3H), 2.15 (s, 6H), 1.13 (d, 6H, J = 6.9 Hz).

5.2.12. Synthesis of (*Z*)-5-[4-[*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]-*N*-methylamino]-3,5-dimethylphenylmethylene]thiazolidine-2,4-dione (16a). Compound **16a** was prepared from **15a** (137 mg, 0.401 mmol) and 2,4-thiazolidinedione (**5**, 55.3 mg, 0.472 mmol) according to the procedure described for **12** in yield 94% (165 mg, orange solid).

Compound **16a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.26 (s, 2H), 6.91 (d, 1H, J = 8.8 Hz), 6.29 (s, 1H), 6.16 (m, 1H), 5.09 (s, 2H), 3.49 (s, 3H), 3.27 (septet, 1H, J = 6.9 Hz), 3.16 (s, 3H), 2.13 (s, 6H), 1.14 (d, 6H, J = 6.9 Hz).

5.2.13. Synthesis of 5-[4-[*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]-*N*-methylamino]-3,5-dimethylphenylmethyl]thiazolidine-2,4-dione (17a). Compound **17a** was prepared from **16a** (165 mg, 0.375 mmol) according to the procedure described for **13** in yield 86% (143 mg, white solid).

Compound **17a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 6.97 (s, 2H), 6.89 (d, 1 H, J = 8.9 Hz), 6.23 (br s, 1H,), 6.11 (br, 1H,), 5.07 (s, 2H), 4.56 (dd, 1H, J = 10.2 Hz, 3.8 Hz), 3.54 (dd, 1H, J = 13.8 Hz, 3.8 Hz), 3.49 (s, 3H), 3.25 (septet, 1H, J = 7.0 Hz), 3.13 (s, 3 H), 3.05 (dd, 1H, J = 14.0 Hz, 10.3 Hz), 2.06 (s, 6H), 1.13 (d, 6H, J = 6.9 Hz).

5.2.14. Synthesis of 5-[4-[*N*-(4-hydroxy-3-isopropylphenyl)-*N*-methylamino]-3,5-dimethylphenylmethyl]thiazolidine-2,4-dione (3a). To a stirred solution of **17a** (94.7 mg, 0.214 mmol) in methanol (21 mL) and dichloromethane (1.0 mL), 5 M HCl (4.0 mL) was added and stirred at room temperature for 9 h. Then, the reaction mixture was concentrated in vacuo. After the addition of water, the aqueous phase was extracted with ethyl acetate. The organic fractions were washed with brine, dried over sodium sulfate and concentrated in vacuo. Purification by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:2) yielded the **3a** as a white amorphous solid (79.9 mg, 94%).

Compound **3a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.01 (s, 2H), 6.57 (d, 1H, J = 8.6 Hz), 6.16 (s, 1 H), 6.04 (d, 1H, J = 7.3 Hz), 4.74 (dd, 1H, J = 9.5 Hz, 4.2 Hz), 3.43 (dd, 1H, J = 13.9 Hz, 4.1 Hz), 3.17 (septet, 1H, J = 6.9 Hz), 3.10 (s, 3H), 3.06 (dd, 1H, J = 14.1 Hz, 9.7 Hz), 2.03 (s, 6H), 1.07 (d, 6H, J = 6.9 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 177.6, 173.6, 146.1, 145.5, 143.6, 139.4, 137.0, 136.3, 130.8, 130.7, 117.2, 110.0, 109.8, 54.7, 38.9, 37.7, 28.2, 23.1, 18.2; HRMS (ESI) calcd for $C_{22}H_{26}N_2O_3SNa$ ($M+Na^+$) 421.1566; found 421.1566.

5.2.15. Synthesis of 4-[*N*-(cyclopropylmethyl)-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylbenzonitrile (14b). Compound **14b** was prepared from **9d** (142 mg, 0.437 mmol) and cyclopropylmethyl bromide (250 μL, 2.58 mmol) according to the procedure described for **10** in yield 61% (102 mg, colourless oil).

Compound **14b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 2H), 6.90 (d, 1H, J = 8.9 Hz), 6.29 (d, 1H, J = 2.8 Hz), 6.19 (dd, 1H, J = 8.9 Hz, 2.9 Hz), 5.08 (s, 2H), 3.49 (s, 3H), 3.33 (d, 2H, J = 6.7 Hz), 3.26 (septet, 1H, J = 6.9 Hz), 2.16 (s, 6H), 1.13 (d, 6H, J = 6.9 Hz), 1.11–1.09 (m, 1H), 0.48–0.44 (m, 2H), 0.05–0.02 (m, 2H).

5.2.16. Synthesis of 4-[*N*-(cyclopropylmethyl)-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylbenzaldehyde (15b). Compound **15b** was prepared from **14b** (89.8 mg, 0.237 mmol) according to the procedure described for **11** in yield 89% (77.5 mg, yellow oil).

Compound **15b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.65 (s, 2H), 6.90 (d, 1H, J = 8.9 Hz), 6.32 (d, 1H, J = 2.8 Hz), 6.23 (dd, 1H, J = 8.8 Hz, 2.8 Hz), 5.08 (s, 2H), 3.49 (s, 3H), 3.36 (d, 2H, J = 6.7 Hz), 3.26 (septet, 1H, J = 6.9 Hz), 2.21 (s, 6H), 1.2–1.1 (m, 1H), 1.40 (d, 6H, J = 6.9 Hz), 0.5–0.4 (m, 2H), 0.1–0.0 (m, 2H).

5.2.17. Synthesis of (*Z*)-5-[4-[*N*-(cyclopropylmethyl)-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylphenylmethylene]thiazolidine-2,4-dione (16b). Compound **16b** was prepared from **15b** (68.5 mg, 0.186 mmol) and 2,4-thiazolidinedione (**5**, 33.6 mg, 0.287 mmol) according to the procedure described for **12** in yield 86% (65.9 mg, orange solid).

Compound **16b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (br s, 1H), 7.81 (s, 1H), 7.27 (s, 2H), 6.89 (d, 1H, J = 8.8 Hz), 6.34 (d, 1 H, J = 2.8 Hz), 6.21 (dd, 1H, J = 8.8 Hz, 2.7 Hz), 5.08 (s, 2H), 3.49 (s, 3H), 3.34 (d, 2H, J = 6.6 Hz), 3.26 (septet, 1H, J = 6.9 Hz), 2.18 (s, 6H), 1.2–1.1 (m, 1H), 1.15 (d, 6H, J = 6.9 Hz), 0.5–0.4 (m, 2H), 0.1–0.0 (m, 2H).

5.2.18. Synthesis of 5-[4-[*N*-(cyclopropylmethyl)-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylphenylmethyl]thiazolidine-2,4-dione (17b). Compound **17b** was prepared from **16b** (53.8 mg, 0.112 mg) according

to the procedure described for **13** in yield 89% (48.0 mg, white solid).

Compound **17b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 6.97 (s, 2H), 6.87 (d, 1H, J = 8.9 Hz), 6.27 (d, 1H, J = 2.7 Hz), 6.16 (dd, 1H, J = 8.5 Hz, 2.5 Hz), 5.08 (s, 2H), 4.56 (dd, 1H, J = 10.2 Hz, 4.1 Hz), 3.54 (dd, 1H, J = 14.0 Hz, 10.2 Hz), 3.49 (s, 3H), 3.32 (d, 2 H, J = 6.6 Hz), 3.25 (septet, 1H, J = 6.9 Hz), 3.05 (dd, 1H, J = 13.9 Hz, 10.2 Hz), 2.11 (s, 6H), 1.2–1.1 (m, 1H), 1.13 (d, 6H, J = 6.9 Hz), 0.5–0.4 (m, 2H), 0.1–0.0 (m, 2H).

5.2.19. Synthesis of 5-[4-[*N*-(cyclopropylmethyl)-*N*-(4-hydroxy-3-isopropylphenyl)amino]-3,5-dimethylphenylmethyl]thiazolidine-2,4-dione (3b). Compound **3b** was prepared from **17b** (48.0 mg, 99.5 mmol) according to the procedure described for **3a** in yield 91% (44.0 mg, white amorphous solid).

Compound **3b**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.02 (s, 2H), 6.56 (d, 1H, J = 8.7 Hz), 6.23 (d, 1H, J = 2.7 Hz), 6.10 (dd, 1H, J = 8.6 Hz, 2.8 Hz), 4.75 (dd, 1H, J = 9.2 Hz, 4.1 Hz), 3.42 (dd, 1H, J = 13.9 Hz, 9.1 Hz), 3.31 (d, 2H, J = 6.0 Hz), 3.18 (septet, 1H, J = 6.9 Hz), 3.10 (dd, 1H, J = 13.9 Hz, 9.2 Hz), 2.09 (s, 6H), 1.2–1.0 (m, 1H), 1.08 (d, 6H, J = 6.8 Hz), 0.5-0.4 (m, 2H), 0.1–0.0 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.5, 173.5, 146.1, 144.6, 143.2, 139.8, 139.8, 137.0, 136.0, 130.9, 130.8, 117.2, 110.4, 110.1, 57.1, 54.6, 38.8, 23.2, 18.7, 14.3, 11.1, 4.6; HRMS (ESI) calcd for $C_{25}H_{29}N_2O_3S$ ($M-H^+$) 437.1904; found 437.1911.

5.2.20. Synthesis of 4-[*N*-*n*-hexyl-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylbenzonitrile (14c). Compound **14c** was prepared from **9d** (142 mg, 0.437 mmol) and *n*-hexyl bromide (300 μL, 2.14 mmol) according to the procedure described for **10** in yield 25% (73.2 mg, colourless oil).

Compound **14c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 2H), 6.88 (d, 1H, J = 8.9 Hz), 6.22 (d, 1H, J = 2.9 Hz), 6.11 (dd, 1H, J = 8.8 Hz, 3.0 Hz), 5.08 (s, 2H), 3.49 (s, 3H), 3.5–3.4 (m, 2H), 3.25 (septet, 1H, J = 6.9 Hz), 2.12 (s, 6H), 1.7–1.6 (m, 2H), 1.4–1.3 (m, 6H), 1.12 (d, 6H, J = 6.9 Hz), 0.89 (t, 3H, J = 6.9 Hz).

5.2.21. Synthesis of 4-[*N*-*n*-hexyl-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylbenzaldehyde (15c). Compound **15c** was prepared from **14c** (73.2 mg, 0.179 mmol) according to the procedure described for **11** in yield 92% (67.5 mg, yellow oil).

Compound **15c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.63 (s, 2H), 6.88 (d, 1H, J = 8.9 Hz), 6.24 (d, 1H, J = 2.8 Hz), 6.15 (dd, 1H, J = 8.8 Hz, 2.0 Hz), 5.08 (s, 2H), 3.49 (s, 3H), 3.5–3.4 (m, 2H), 3.25 (septet, 1H, J = 6.9 Hz), 2.17 (s, 6H), 1.7-1.6 (m, 2H), 1.4–1.2 (m, 6H), 1.12 (d, 6H, J = 6.9 Hz), 0.89 (t, 3H, J = 6.9 Hz).

5.2.22. Synthesis of (*Z*)-5-[4-[*N*-*n*-hexyl-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylphenylmethylene]thiazolidine-2,4-dione (16c). Compound **16c** was prepared from **15c** (67.5 mg, 0.164 mmol) and 2,4-thiazolidinedione (**5**, 24.2 mg, 0.207 mmol) according to the procedure described for **12** in yield 89% (74.6 mg, orange solid).

Compound **16c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 7.81 (s, 1H), 7.27 (s, 2H), 6.88 (d, 1H, J = 8.9 Hz), 6.26 (d, 1H, J = 2.8 Hz), 6.13 (dd, 1H, J = 8.9 Hz, 2.9 Hz), 5.08 (s, 2H), 3.49 (s, 3H), 3.5–3.4 (m, 2H), 3.25 (septet, 1H, J = 6.9 Hz), 2.14 (s, 6H), 1.7–1.6 (m, 2H), 1.4–1.2 (m, 6H), 1.13 (d, 6H, J = 6.9 Hz), 0.89 (t, 3H, J = 7.0 Hz).

5.2.23. Synthesis of 5-[4-[*N*-*n*-hexyl-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylphenylmethyl]thiazolidine-2,4-dione (17c). Compound **17c** was prepared from **16c** (74.6 mg, 0.146 mmol) according to the procedure described for **13** in yield 84% (63.2 mg, white solid).

Compound **17c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (br s, 1H), 7.05 (s, 2H), 6.86 (d, 1H, J = 8.9 Hz), 6.19 (br s, 1H), 6.08 (dd, 1H, J = 8.8 Hz, 2.7 Hz), 5.07 (s, 2H), 4.56 (dd, 1H, J = 10.3 Hz, 3.8 Hz), 3.54 (dd, 1H, J = 14.1 Hz, 3.9 Hz), 3.53 (s, 3H), 3.5–3.4 (m, 2 H), 3.24 (septet, 1H, J = 6.9 Hz), 3.05 (dd, 1H, J = 14.0 Hz, 10.4 Hz), 2.07 (s, 6H), 1.62 (br m, 2H), 1.31 (br m, 6H), 1.12 (d, 6H, J = 6.9 Hz), 0.89 (t, 3H, J = 2.5 Hz).

5.2.24. Synthesis of 5-[4-[*N*-*n*-hexyl-*N*-(4-hydroxy-3-isopropylphenyl)amino]-3,5-dimethylphenylmethyl]thiazolidine-2,4-dione (3c). Compound **3c** was prepared from **17c** (63.2 mg, 0.123 mmol) according to the procedure described for **3a** in yield 88% (47.7 mg, white amorphous solid).

Compound **3c**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.01 (s, 2H), 6.54 (d, 1H, J = 8.7 Hz), 6.16 (d, 1H, J = 2.6 Hz), 5.99 (dd, 1H, J = 8.6 Hz, 2.7 Hz), 4.72 (dd, 1H, J = 9.5 Hz, 4.1 Hz), 3.5–3.3 (m, 3H), 3.17 (septet, 1 H, J = 6.9 Hz), 3.05 (dd, 1H, J = 14.0 Hz, 9.6 Hz), 2.04 (s, 6H), 1.7–1.5 (m, 2H), 1.4–1.2 (m, 6H), 1.07 (d, 6H, J = 6.8 Hz), 0.9–0.8 (m, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.4, 173.4, 146.0, 144.7, 143.0, 139.7, 136.9, 136.1, 130.8, 117.2, 110.4, 110.2, 54.6, 52.8, 38.9, 32.9, 29.5, 28.1, 28.1, 23.7, 23.2, 18.8, 14.4; HRMS (ESI) calcd for $C_{27}H_{35}N_2O_3S$ ($M-H^+$) 467.2374; found 467.2375.

5.2.25. Synthesis of 4-[*N*-benzyl-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylbenzonitrile (14d). Compound **14d** was prepared from **9d** (217 mg, 0.669 mmol) and benzyl chloride (274 μL, 2.38 mmol) according to the procedure described for **10** in yield 59% (164 mg, colourless oil).

Compound **14d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 2H), 7.3-7.2 (m, 5H), 6.86 (d, 1H, J = 8.9 Hz), 6.35 (d, 1H, J = 3.0 Hz), 6.21 (dd, 1H, J = 8.9 Hz, 3.1 Hz), 5.08 (s, 2H), 4.67 (s, 2H), 3.48 (s, 3H), 3.23 (septet, 1H, J = 6.9 Hz), 2.10 (s, 6H), 1.06 (d, 6H, J = 6.9 Hz).

5.2.26. Synthesis of 4-[*N*-benzyl-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylbenzaldehyde (15d). Compound **15d** was prepared from **14d** (164 mg,

0.396 mmol) according to the procedure described for **11** in yield 95% (156 mg, yellow oil).

Compound **15d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.63 (s, 2H), 7.4–7.2 (m, 5H), 6.85 (d, 1H, J = 8.9 Hz), 6.37 (d, 1H, J = 2.9 Hz), 6.23 (dd, 1H, J = 8.8 Hz, 2.9 Hz), 5.07 (s, 2H), 4.70 (s, 2H), 3.48 (s, 3H), 3.22 (septet, 1H, J = 6.9 Hz), 2.15 (s, 6H), 1.05 (d, 6H, J = 6.9 Hz).

5.2.27. Synthesis of (*Z*)-5-[4-[*N*-benzyl-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylphenylmethylene]thiazolidine-2,4-dione (16d). Compound **16d** was prepared from **15d** (156 mg, 0.374 mmol) and 2,4-thiazolidinedione (**5**, 49.2 mg, 0.420 mmol) according to the procedure described for **12** in quant (214 mg, orange solid).

Compound **16d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.80 (s, 1H), 7.4–7.2 (m, 7H), 6.85 (d, 1H, J = 8.9 Hz), 6.38 (d, 1H, J = 2.9 Hz), 6.22 (dd, 1H, J = 9.1 Hz, 3.1 Hz), 5.07 (s, 2H), 4.69 (s, 2H), 3.48 (s, 3H), 3.26 (septet, 1H, J = 7.0 Hz), 2.13 (s, 6H), 1.06 (d, 6H, J = 6.9 Hz).

5.2.28. Synthesis of 5-[4-[*N*-benzyl-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylphenylmethyl]thiazolidine-2,4-dione (17d). Compound **17d** was prepared from **16d** (193 mg, 0.374 mg) according to the procedure described for **13** in yield 87% (169 mg, yellow solid).

Compound **17d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (br s, 1H), 7.4–7.2 (m, 5H), 7.05 (s, 2H), 6.83 (d, 1H, J = 8.9 Hz), 6.31 (d, 1H, J = 3.0 Hz), 6.18 (dd, 1H, J = 8.6 Hz, 2.8 Hz), 5.06 (s, 2H), 4.67 (s, 2H), 4.55 (dd, 1H, J = 10.1 Hz, 2.9 Hz), 3.52 (dd, 1H, J = 14.0 Hz, 4.0 Hz), 3.48 (s, 3H), 3.22 (septet, 1H, J = 6.7 Hz), 3.05 (dd, 1H, J = 14.2 Hz, 10.4 Hz), 2.06 (s, 6H), 1.05 (d, 6H, J = 6.9 Hz).

5.2.29. Synthesis of 5-[4-[*N*-benzyl-*N*-(4-hydroxy-3-isopropylphenyl)amino]-3,5-dimethylphenylmethyl]thiazolidine-2,4-dione (3d). Compound **3d** was prepared from **17d** (169 mg, 0.327 mmol) according to the procedure described for **3a** in yield 77% (112 mg, white amorphous solid).

Compound **3d**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.28 (d, 2H, J = 7.5 Hz), 7.22 (t, 2H, J = 7.7 Hz), 7.16 (t, 1H, J = 7.2 Hz), 6.97 (s, 2H), 6.52 (d, 1 H, J = 8.7 Hz), 6.27 (d, 1H, J = 2.8 Hz), 6.09 (dd, 1H, J = 8.7 Hz, 2.9 Hz), 4.69 (dd, 1H, J = 9.3 Hz, 4.2 Hz), 4.62 (s, 2H), 3.38 (dd, 1H, J = 14.0 Hz, 4.1 Hz), 3.14 (septet, 1H, J = 6.9 Hz), 3.05 (dd, 1H, J = 14.0 Hz, 9.4 Hz), 2.01 (s, 6H), 1.00 (d, 6H, J = 6.9 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 177.3, 173.4, 146.6, 145.6, 143.2, 140.8, 139.6, 136.7, 136.2, 131.1, 131.1, 129.1, 129.0, 127.7, 116.9, 112.0, 111.7, 56.6, 54.5, 38.8, 28.0, 23.1, 19.2; HRMS (ESI) calcd for $C_{28}H_{29}N_2O_3S$ ($M-H^+$) 473.1904; found 473.1893.

5.2.30. Synthesis of 4-[*N*-isobutyl-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylbenzonitrile (14e). Compound **14e** was prepared from **9d** (201 mg, 0.618 mmol) and isobutyl bromide (200 μL, 1.85 mmol) according to the procedure described for **10** in yield 41% (95.2 mg, pale yellow oil).

Compound **14e**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 2H), 6.86 (d, 1H, J = 8.9 Hz), 6.27 (d, 1H, J = 3.0 Hz), 6.10 (dd, 1H, J = 8.9 Hz, 3.0 Hz), 5.08 (s, 2H), 3.48 (s, 3H), 3.28 (d, 2H, J = 6.4 Hz), 3.25 (septet, 1H, J = 6.9 Hz), 2.14 (s, 6H), 1.96 (heptet, 1H, J = 6.6 Hz), 1.12 (d, 6H, J = 6.9 Hz), 0.94 (d, 6H, J = 6.7 Hz).

5.2.31. Synthesis of 4-[*N*-isobutyl-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylbenzaldehyde (15e). Compound **15e** was prepared from **14e** (95.2 mg, 0.250 mmol) according to the procedure described for **11** in yield 91% (87.0 mg, yellow oil).

Compound **15e**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.65 (s, 2H), 6.86 (d, 1H, J = 8.9 Hz), 6.29 (d, 1H, J = 3.0 Hz), 6.13 (dd, 1H, J = 8.9 Hz, 3.1 Hz), 5.08 (s, 2H), 3.48 (s, 3H), 3.32 (d, 2H, J = 6.5 Hz), 3.25 (septet, 1H, J = 6.9 Hz), 2.19 (s, 6H), 1.99 (septet, 1H, J = 6.6 Hz), 1.12 (d, 6H, J = 6.9 Hz), 0.94 (d, 6H, J = 6.7 Hz).

5.2.32. Synthesis of (*Z*)-5-[4-[*N*-isobutyl-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylphenylmethylene]thiazolidine-2,4-dione (16e). Compound **16e** was prepared from **15e** (87.0 mg, 0.227 mmol) and 2,4-thiazolidinedione (**5**, 32.6 mg, 0.278 mmol) according to the procedure described for **12** in yield 89% (97.4 mg, yellow solid).

Compound **16e**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.81 (s, 1H), 7.27 (s, 2H), 6.85 (d, 1H, J = 8.9 Hz), 6.32 (d, 1H, J = 3.0 Hz), 6.11 (dd, 1H, J = 8.9 Hz, 3.1 Hz), 5.08 (s, 2H), 3.49 (s, 3H), 3.30 (d, 2H, J = 6.5 Hz), 3.27 (septet, 1H, J = 6.9 Hz), 2.16 (s, 6 H), 1.98 (septet, 1H, J = 6.6 Hz), 1.13 (d, 6H, J = 6.9 Hz), 0.95 (d, 6H, J = 6.7 Hz).

5.2.33. Synthesis of 5-[4-[*N*-isobutyl-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylphenylmethyl]thiazolidine-2,4-dione (17e). Compound **17e** was prepared from **16e** (97.4 mg, 0.202 mg) according to the procedure described for **13** in yield 72% (70.5 mg, pale yellow solid).

Compound **17e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (br s, 1H), 6.98 (s, 2H), 6.84 (d, 1H, J = 8.9 Hz), 6.25 (d, 1H, J = 2.9 Hz), 6.07 (dd, 1H, J = 9.0 Hz, 3.0 Hz), 5.07 (s, 2H), 4.56 (dd, 1H, J = 10.4 Hz, 3.9 Hz), 5.07 (s, 2H), 4.56 (dd, 1H, J = 10.4 Hz, 3.9 Hz), 3.55 (dd, 1 H, J = 14.1 Hz, 4.1 Hz), 3.48 (s, 3H), 3.25 (d, 2H, J = 6.8 Hz), 3.24 (septet, 1H, J = 6.7 Hz), 3.04 (dd, 1H, J = 13.9 Hz, 10.3 Hz), 2.09 (s, 6H), 1.96 (septet, 1H, J = 6.9 Hz), 1.12 (d, 6H, J = 6.9 Hz), 0.96 (d, 6H, J = 6.7 Hz).

5.2.34. Synthesis of 5-[4-[*N*-(4-hydroxy-3-isopropylphenyl)-*N*-isobutylamino]-3,5-dimethylphenylmethyl]thiazolidine-2,4-dione (3e). Compound **3e** was prepared from **17e** (70.5 mg, 0.146 mmol) according to the procedure

described for **3a** in yield 80% (51.3 mg, pale yellow amorphous solid).

Compound **3e**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.02 (s, 2H), 6.53 (d, 1H, J = 8.7 Hz), 6.20 (d, 1H, J = 2.8 Hz), 6.01 (dd, 1H, J = 8.7 Hz, 2.9 Hz), 4.71 (dd, 1H, J = 9.4 Hz, 4.1 Hz), 3.42 (dd, 1H, J = 14.0 Hz, 4.1 Hz), 3.25 (d, 1H, J = 6.5 Hz), 3.17 (septet, 1H, J = 6.9 Hz), 3.06 (dd, 1H, J = 14.0 Hz, 9.4 Hz), 2.06 (s, 6H), 1.92 (septet, 1H, J = 6.6 Hz), 1.07 (d, 6H, J = 6.9 Hz), 0.94 (d, 6H, J = 6.7 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 177.4, 173.4, 146.2, 145.4, 143.6, 139.3, 136.7, 135.9, 131.1, 131.0, 117.0, 110.9, 110.7, 61.7, 54.6, 38.9, 30.1, 28.9, 23.2, 21.7, 19.0; HRMS (ESI) calcd for $C_{25}H_{31}N_2O_3S_1$ ($M-H^+$) 439.2050; found 439.2058.

5.2.35. Synthesis of 4-[*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]-*N*-(3-methyl-2-butenyl)amino]-3,5-dimethylbenzonitrile (14f). Compound **14f** was prepared from **9d** (203 mg, 0.627 mmol) and prenyl bromide (220 μL, 1.87 mmol) according to the procedure described for **10** in yield 80% (198 mg, pale yellow oil).

Compound **14f**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 2H), 6.88 (d, 1H, J = 8.9 Hz), 6.27 (d, 1H, J = 2.4 Hz), 6.13 (dd, 1H, J = 8.8 Hz, 2.6 Hz), 5.4–5.3 (m, 1H), 4.05 (d, 2H, J = 6.3 Hz), 3.48 (s, 3H), 3.25 (septet, 1H, J = 6.9 Hz), 2.13 (s, 6H), 1.70 (br m, 3H), 1.62 (br s, 3H), 1.12 (d, 6H, J = 6.9 Hz).

5.2.36. Synthesis of 4-[*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]-*N*-(3-methyl-2-butenyl)amino]-3,5-dimethylbenzaldehyde (15f). Compound **15f** was prepared from **14f** (198 mg, 0.504 mmol) according to the procedure described for **11** in yield 90% (179 mg, yellow oil).

Compound **15f**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.63 (s, 2H), 6.87 (d, 1H, J = 8.9 Hz), 6.29 (d, 1H, J = 2.0 Hz), 6.16 (dd, 1H, J = 8.6 Hz, 2.1 Hz), 5.4–5.3 (m, 1H), 5.08 (s, 2H), 4.08 (d, 2H, J = 6.3 Hz), 3.49 (s, 3H), 3.25 (septet, 1H, J = 6.9 Hz), 2.18 (s, 6H), 1.70 (s, 3H), 1.62 (s, 3H), 1.05 (d, 6H, J = 6.9 Hz).

5.2.37. Synthesis of (*Z*)-5-[4-[*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]-*N*-(3-methyl-2-butenyl)amino]-3,5-dimethylphenylmethylene]thiazolidine-2,4-dione (16f). Compound **16f** was prepared from **15f** (179 mg, 0.452 mmol) and 2,4-thiazolidinedione (**5**, 60.5 mg, 0.517 mmol) according to the procedure described for **12** in yield 77% (173 mg, orange solid).

Compound **16f**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.81 (s, 1H), 7.26 (s, 2H), 6.87 (d, 1H, J = 8.9 Hz), 6.31 (d, 1H, J = 3.1 Hz), 6.14 (dd, 1H, J = 9.0 Hz, 3.1 Hz), 5.4–5.3 (m, 1H), 5.08 (s, 2H), 4.07 (d, 2H, J = 6.2 Hz), 3.49 (s, 3H), 3.25 (septet, 1H, J = 6.9 Hz), 2.15 (s, 6H), 1.70 (br m, 3H), 1.64 (s, 3H), 1.11 (d, 6H, J = 6.9 Hz).

5.2.38. Synthesis of 5-[4-[*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]-*N*-(3-methyl-2-butenyl)amino]-3,5-dimethylphenylmethyl]thiazolidine-2,4-dione (17f). Compound **17f** was prepared from **16f** (173 mg, 0.350 mg) according to the procedure described for **13** in yield 70% (122 mg, pale yellow solid).

Compound **17f**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 7.05 (s, 2H), 6.85 (d, 1H, J = 8.8 Hz), 6.25 (br s, 1H), 6.10 (d, 1H, J = 7.2 Hz), 5.4–5.3 (m, 1 H), 4.56 (dd, 1H, J = 10.2 Hz, 3.9 Hz), 4.04 (d, 2H, J = 6.3 Hz), 3.53 (dd, 1H, J = 14.1 Hz, 4.2 Hz), 3.48 (s, 3H), 3.24 (septet, 1H, J = 6.8 Hz), 2.08 (s, 6H), 1.69 (br s, 3H), 1.62 (br s, 3H), 1.11 (d, 6H, J = 6.9 Hz).

5.2.39. Synthesis of 5-[4-[*N*-(4-hydroxy-3-isopropylphenyl)-*N*-(3-methyl-2-butenyl)amino]-3,5-dimethylphenylmethyl]thiazolidine-2,4-dione (3f). Compound **3f** was prepared from **17f** (122 mg, 0.245 mmol) according to the procedure described for **3a** in yield 55% (61.1 mg, orange amorphous solid).

Compound **3f**: ^{1}H NMR (500 MHz, CD_3OD) δ 6.99 (s, 2H), 6.53 (d, 1H, J = 8.7 Hz), 6.21 (d, 1H, J = 2.7 Hz), 6.00 (dd, 1H, J = 8.6 Hz, 2.8 Hz), 5.4–5.3 (m, 1H), 4.71 (dd, 1H, J = 9.3 Hz, 4.2 Hz), 4.02 (d, 2H, J = 6.4 Hz), 3.40 (dd, 1H, J = 13.9 Hz, 4.1 Hz), 3.17 (septet, 1H, J = 6.9 Hz), 3.06 (dd, 1H, J = 14.0 Hz, 9.3 Hz), 2.05 (s, 6H), 1.67 (s, 3H), 1.58 (s, 3H), 1.07 (d, 6H, J = 6.7 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 177.4, 173.4, 146.1, 145.0, 143.1, 139.7, 136.9, 136.0, 134.5, 130.8, 123.5, 117.2, 110.8, 110.6, 54.6, 50.1, 38.8, 29.1, 25.9, 23.2, 18.8, 17.9; HRMS (ESI) calcd for $C_{26}H_{31}N_2O_3S_1$ ($M-H^+$) 451.2050; found 451.2060.

5.2.40. Synthesis of 4-[*N*-(cyclohexylmethyl)-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylbenzonitrile (14g). Compound **14g** was prepared from **9d** (200 mg, 0.616 mmol) and cyclohexylmethyl bromide (260 μL, 1.88 mmol) according to the procedure described for **10** in yield 69% (180 mg, orange oil).

Compound **14g**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 2H), 6.86 (d, 1H, J = 8.9 Hz), 6.24 (d, 1H, J = 2.8 Hz), 6.09 (dd, 1H, J = 8.9 Hz, 2.8 Hz), 5.08 (s, 2H), 3.48 (s, 3H), 3.25 (septet, 1H, J = 7.0 Hz), 2.13 (s, 6H), 1.8–1.7 (m, 4H), 1.7–1.6 (m, 2H), 1.3–1.1 (m, 3H), 1.12 (d, 6H, J = 6.9 Hz), 1.0–0.9 (m, 2H).

5.2.41. Synthesis of 4-[*N*-(cyclohexylmethyl)-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylbenzaldehyde (15g). Compound **15g** was prepared from **14g** (180 mg, 0.427 mmol) according to the procedure described for **11** in yield 90% (162 mg, yellow oil).

Compound **15g**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.65 (s, 2H), 6.87 (d, 1H, J = 8.9 Hz), 6.26 (d, 1H, J = 3.0 Hz), 6.13 (dd, 1H, J = 8.8 Hz, 3.0 Hz), 5.08 (s, 2H), 3.49 (s, 3H), 3.32 (d, 2H, J = 6.2 Hz), 3.25 (septet, 1H, J = 6.9 Hz), 2.18 (s, 6H), 1.8–1.6 (m, 7H), 1.3–1.1 (m, 2H), 1.12 (d, 6H, J = 6.9 Hz), 1.0–0.9 (m, 2H).

5.2.42. Synthesis of (*Z*)-5-[4-[*N*-(cyclohexylmethyl)-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylphenylmethylene]thiazolidine-2,4-dione (16g). Compound **16g** was prepared from **15g** (162 mg,

0.382 mmol) and 2,4-thiazolidinedione (**5**, 49.9 mg, 0.426 mmol) according to the procedure described for **12** in yield 83% (167 mg, yellow solid).

Compound **16g**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.81 (s, 1H), 7.27 (s, 2H), 6.86 (d, 1H, J = 8.9 Hz), 6.28 (d, 1H, J = 2.9 Hz), 6.11 (dd, 1H, J = 8.9 Hz, 3.0 Hz), 5.08 (s, 2H), 3.49 (s, 3H), 3.30 (d, 2H, J = 6.2 Hz), 3.26 (septet, 1H, J = 6.9 Hz), 2.15 (s, 6H), 1.9–1.6 (m, 6H), 1.3–1.1 (m, 3H), 1.13 (d, 6H, J = 6.9 Hz), 1.0–0.9 (m, 2H).

5.2.43. Synthesis of 5-[4-[*N*-(cyclohexylmethyl)-*N*-[3-isopropyl-4-(methoxymethoxy)phenyl]amino]-3,5-dimethylphenylmethyl]thiazolidine-2,4-dione (17g). Compound **17g** was prepared from **16g** (167 mg, 0.319 mg) according to the procedure described for **13** in yield 87% (146 mg, yellow solid).

Compound **17g**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (br s, 1H), 6.98 (s, 2H), 6.84 (d, 1H, J = 8.9 Hz), 6.22 (d, 1H, J = 3.0 Hz), 6.07 (dd, 1H, J = 8.9 Hz, 3.0 Hz), 5.07 (s, 2H), 4.57 (dd, 1H, J = 10.3 Hz, 3.8 Hz), 3.55 (dd, 1H, J = 13.9 Hz, 3.7 Hz), 3.48 (s, 3H), 3.26 (d, 2 H, J = 6.4 Hz), 3.24 (septet, 1H, J = 6.8 Hz), 3.04 (dd, 1H, J = 14.0 Hz, 10.4 Hz), 2.08 (s, 6H), 1.9–1.5 (m, 6H), 1.3–1.1 (m, 3H).

5.2.44. Synthesis of 5-[4-[*N*-(cyclohexylmethyl)-*N*-(4-hydroxy-3-isopropylphenyl)amino]-3,5-dimethylphenylmethyl]-thiazolidine-2,4-dione (3g). Compound **3g** was prepared from **17g** (146 mg, 0.278 mmol) according to the procedure described for **3a** in yield 52% (69.9 mg, pale yellow amorphous solid).

Compound **3g**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.02 (s, 2H), 6.52 (d, 1H, J = 8.7 Hz), 6.00 (dd, 1H, J = 11.7 Hz, 3.0 Hz), 4.73 (dd, 1H, J = 9.4 Hz, 4.1 Hz), 3.43 (dd, 1H, J = 14.0 Hz, 4.1 Hz), 3.26 (d, 2H, J = 6.2 Hz), 3.15 (septet, 1H, J = 6.9 Hz), 3.07 (dd, 1H, J = 14.0 Hz, 9.4 Hz), 2.05 (s, 6H), 1.9–1.7 (m, 2H), 1.7–1.5 (m, 4H), 1.07 (d, 6H, J = 6.9 Hz), 1.1–0.9 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.5, 173.5, 146.2, 145.5, 143.7, 139.3, 136.8, 135.9, 131.1, 131.0, 117.0, 110.9, 110.7, 60.5, 54.6, 40.0, 38.9, 33.4, 28.1, 27.6, 27.4, 23.2, 18.9; HRMS (ESI) calcd for $C_{28}H_{35}N_2O_3S_1$ ($M-H^+$) 479.2363; found 479.2372.

5.3. Transcriptional activation assay

Transient transactivation assays were carried out using COS-1 cells transfected with pCMX-hTRα1 or pCDNA-hTRβ1 and $(TREpal)_3$-TKLUC. The COS-1 cells were obtained from the Japanese Cancer Research Resources Bank (JCRB) and were maintained in Dulbecco's modified Eagle's medium (DMEM, Gibco), supplemented with 5% FBS (5% FBS/DMEM). The reporter plasmid, $(TREpal)_3$-TKLUC, contains three copies of the thyroid hormone-responsive palindromic element AGGTCA-TGACCT. For reporter gene assay, COS-1 cells were seeded in 24-well tissue culture plates at 8×10^4 cells per well with 5% FBS/DMEM. The cells were cultured at 37 °C in 5% CO_2 overnight and allowed to attach to the plates. Then, the medium was exchanged for 0.4 mL of serum-free DMEM and transfection was performed by use of the transfection reagent Lipofectamine 2000 (Invitrogen) according to the manufacturer's instructions. For each well, cells were transfected with 100 ng of receptor-expression plasmid, 200 ng of $(TREpal)_3$-TKLUC, 100 ng of the reference plasmid pCMVβ (Clontech) and carrier plasmid pUC18, to adjust the total DNA amount to 800 ng DMEM (0.1 mL) containing transfection reagent–DNA complex was added to each well. After 4–5 h of culture at 37 °C in 5% CO_2, 0.5 mL DMEM with 10% charcoal dextran-treated FBS (Hyclone) and test compounds were added to cells. Each test compound was added as an EtOH solution (final 0.5% EtOH). After an additional 40 h of incubation, the cells were harvested, and luciferase assay was performed with the Luciferase Assay System (Toyo Ink Mfg. Co., Ltd.). The luciferase activities were normalized to β-galactosidase activities. Assay was done in triplicate under each condition.

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