Thiazolidinediones with Thyroid Hormone Receptor Agonistic Activity

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Several thiazolidinedione derivatives (3—7) were designed and synthesized as candidate thyromimetic drugs. Among them, the dihydrogenated compounds, such as 5-2-[[4-(3-*tert*-butyl-4-hydroxyphenyl)oxy-3,5-diiodophenyl]ethyl]-2,4-thiazolidinedione (6b) and its 3-isopropyl analog (7b), exhibited potent thyroid hormone receptor α1 (TRα1) activation activity.

Key words thyroid hormone; nuclear receptor; thiazolidinedione

Thyroid hormones, 3,3′,5-triiodothyronine (T_3, **1**, Fig. 1) and 3,3′,5,5′-tetraiodothyronine (T_4, **2**), regulate various physiological processes including energy metabolism, the cardiovascular system, and lipid metabolism.[1] Natural and synthetic thyroid hormones[2,3] have therapeutic potential for the treatment of hypercholesterolemia, obesity and cardiac arrhythmia. However, they have significant side effects owing to their pleiotropic thyroid hormone activities, and the development of novel thyromimetics is needed for clinical use. Most of the biological actions of thyroid hormones are mediated by the specific thyroid hormone receptors (TRs),[4] which are the ligand-inducible transcription factors belonging to the nuclear receptor superfamily,[5] as well as by retinoid receptors (retinoic acid receptors, RARs, and retinoid X receptors, RXRs), vitamin D_3 receptors and peroxisome proliferator-activated receptors (PPARs). The ligands-binding domains of TRs possess high homology with those of RARs. Ligands of both nuclear receptors have a terminal polar carboxyl group as an essential structural factor, which interacts electrostatically with the amino acid moieties of the receptors. This model is supported by recent studies on the crystal structures of the liganded TR and RAR ligand-binding domains.[6,7]

Previously, we designed and synthesized novel retinoid receptor ligands bearing a thiazolidinedione moiety instead of the carboxyl group (Fig. 1),[8,9] based on a consideration of the structures of various ligands of nuclear receptor PPARs, i. e., some thiazolidinedione derivatives with antidiabetic activity are ligands of PPARγ,[10] which can also bind compounds having a terminal carboxyl group such as 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2, an endogenous ligand candidate,[11] and some non-steroidal anti-inflammatory drugs.[12] The potent activity of retinoidal thiazolidinediones is significant, though the replacement of the carboxyl group of retinoids with functional groups generally considered as bioisosters, including aminosulfonyl, amidino and tetrazole, diminished the retinoidal activity.[13] The results led us to synthesize compounds having a thiazolidinedione moiety on a thyroid hormone skeleton as candidates for novel thyromimetic drugs.

Some of our designed compounds **3**—**7** are shown in Fig. 1. We synthesized two types of thiazolidinedione derivatives, i.e., benzylidene-type compounds such as **3a** and **6a**, having an olefinic bond on the thiazolidine ring, and hydrogenated derivatives (**3b**, **6b** and **7b**). Several compounds having different substituents *ortho* to the phenolic hydroxyl group were also synthesized. Synthetic routes to the triiodo derivatives **3a** and **3b**, and the tetraiodo derivative **4** are illustrated in Chart 1 as representative examples. Ethyl 4-hydroxy-3,5-diiodobenzoate (**8a**) was treated with bis(4-methoxyphenyl)iodonium bromide in the presence of copper and triethylamine to afford a diphenylether **9**. The ester group of **9** was converted to the aldehyde of **11**, which was reacted with 2,4-thiazolidinedione in the presence of titanium tetrachloride in pyridine to give **12** as a single condensed product.[8,9] Demethylation using boron tribromide, and subsequent iodination afforded **3a** or **4**, depending on the molar ratio of iodine. Since hydrogenation of the olefinic bond of **3a** was unsuccessful, the thiazolidinedione **3b** was prepared in a different manner, as illustrated in Chart 1.[14] A diphenylether **13**, prepared from 2,6-diiodo-4-nitrophenol (**8b**), was converted to the α-chloroester **14** by diazotization. Compound **14** was reacted with thiourea, followed by acid treatment to give the thiazolidinedione **15**, which was converted to **3b** in a manner similar to that used to transform **12** to **3a**.

The activity of the synthesized compounds was examined

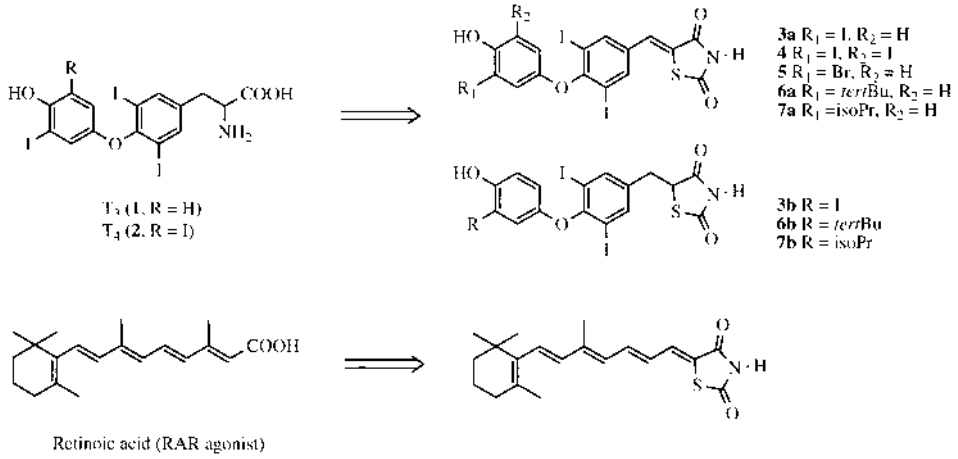

Fig. 1

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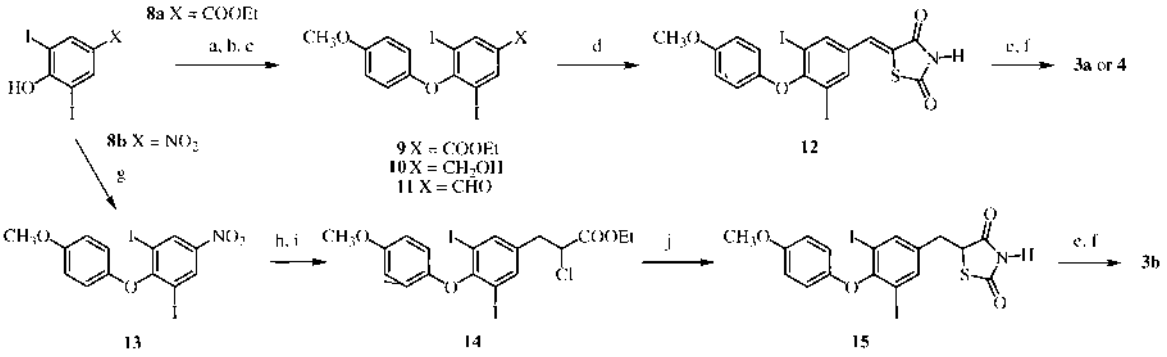

a) Bis(4-methoxyphenyl)iodonium bromide / Cu / Et_3N; b) DIBAL; c) PCC ; d) thiazolidinedione / $TiCl_4$ / pyridine; e) BBr_3; f) I_2 / KI / NH_4OH; g) Bis(4-methoxyphenyl)iodonium tetrafluoroborate / Cu / Et_3N; h) H_2 / Pt-C / AcOEt; i) $NaNO_2$ / HCl; ethyl acrylate / Cu_2O; j) thiourea; HCl / AcOH.

Chart 1

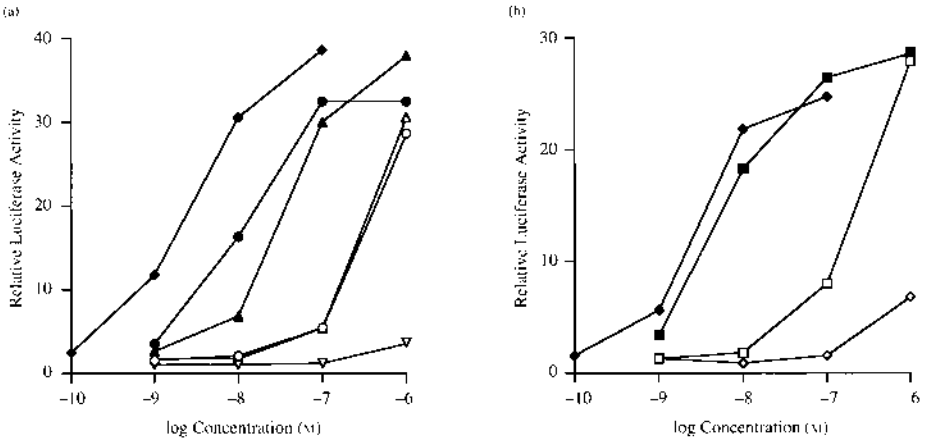

Fig. 2. Luciferase Assays in Cos-1 Cells Transiently Transfected with pCMX-hTRα1 and (TREpal)3-TKLUC

Vertical scale is the TR transactivation activity. The values were normalized to those of β-galactosidase activities, and are relative to that obtained when solvent alone was added, taken as 1. The horizontal scale is the molar concentration of the added compounds. Added compounds were T_3 (**1**, ◆), **3a** (△), **3b** (▲), **4** (▽), **5** (◇), **6a** (○), **6b** (●), **7a** (□) and **7b** (■).

by means of transient transactivation assay in COS-1 cells transfected with pCMX-hTRα1, prepared from pSV2-ear71, and (TREpal)3-TKLUC, using the Luciferase Assay System (Promega).[15] The luciferase activity was normalized to that of β-galactosidase obtained by transfecting with the reference plasmid pCMVβ (Clontech). The values relative to that obtained for solvent (DMSO or EtOH) alone, taken as 1 are shown in Fig. 2. Compound **3a**, a thiazolidinedione analog of T_3 (**1**), with an olefinic bond on the thiazolidine ring, exhibited TR activation activity at 10^{-6} M. Similarly, compounds **6a** and **7a**, having a *tert*-butyl or an isopropyl group, respectively, instead of the iodo group *ortho* to the phenolic hydroxyl group of **3a**, are weak TR agonists. However, the replacement of the iodo group of **3a** with a bromo group (**5**) or introduction of another iodo group (**4**) into the other *ortho* position to the phenolic hydroxyl group caused loss of activity. Since methylation of the phenolic hydroxyl group of **6a** or the imide nitrogen atom of **3a** also diminished the activity (data not shown), both acidic protons seem to be important for binding to and activating TR. These substituent effects are similar to those of thyromimetic compounds already known.[1,2]

In the case of retinoidal thiazolidinediones (RAR agonists), hydrogenation of the olefinic bond on the thiazolidine ring decreased the retinoidal agonistic activity.[16] Since thyroid hormones such as T_3 (**1**) have a carboxyl group attached to a saturated carbon atom, we synthesized the hydrogenated analogs of three selected compounds, **3a**, **6a** and **7a**. As shown in Fig. 2, all the dihydrogenated analogs were more potent than the corresponding unsaturated compounds by one or two orders of magnitude. Among them, compound **7b** is the most active, and its EC_{50} value of 7.9×10^{-9} M is similar to that of T_3 (**1**, 5.1×10^{-9} M).

In conclusion, we have designed and synthesized novel thyroid hormone receptor agonists with a thiazolidinedione moiety, by analogy with the structure–activity relationships of the ligands for other nuclear receptors, such as RARs and PPARs. Some of them exhibited potent TR agonistic activity equivalent to that of the natural thyroid hormone, T_3. Since the thyromimetic thiazolidinediones have a hybrid structure of TR and PPAR ligands, they may also modulate PPAR-related biological functions.

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