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Thyroid receptor ligands. Part 5: Novel bicyclic agonist ligands selective for the thyroid hormone receptor β

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Abstract—Based on the examination of the crystal structure of rat TRβ complexed with 3,5,3′-triiodo-L-thyronine (**2**) a novel TRβ-selective indole derivative **6b** was prepared and tested in vitro. This compound was found to be 14 times selective for TRβ over TRα in binding and its β-selectivity could be rationalized through the comparison of the X-ray crystallographic structures of **6b** complexed with TRα and TRβ.

Endogenous thyroid receptor hormones 3,5,3′,5′-tetraiodo-L-thyronine (T_4, **1**) and 3,5,3′-triiodo-L-thyronine (T_3, **2**) exert profound effects on growth, development, and homeostasis in mammals (Fig. 1).[1] Thyroid hormone receptor subtypes (TRα and TRβ) mediate differential functions, suggesting the possibility of developing selective thyromimetics that cause therapeutic increases in metabolic rate (anti-obesity effect) and lipid lowering without deleterious effects on the heart.[2] Our hypothesis is that selective TRβ activation can give such a profile.[3]

TRα and TRβ differ in a single amino acid residue in the hormone binding pocket (Ser-277 vs Asn-331, respectively). It has been proposed that this amino acid difference accounts for most of the observed selectivity for TRβ-binding in a series of phenyl acetic acid thyromimetics.[4] This amino acid residue as well as the α-alanine side chain of **2** is located in a highly flexible region of the receptor.[5] We reasoned that rigidification of the ligand carboxylic acid side chain through ring formation may lead to increased opportunities for subtype selectivity. In addition, the fused ring provides a rigid scaffold on which substituents could be introduced to more directly exploit this amino acid difference. We also decided to

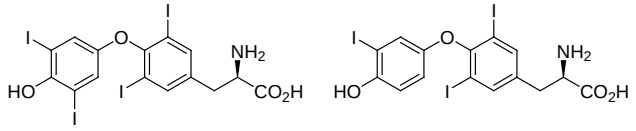

Figure 1. Chemical structures of L-T_4 and L-T_3.

replace the iodine atoms with alternative substituents since iodine is highly susceptible to reductive deiodination and furthermore hinders biaryl ether formation due to its large steric bulk. With regard to achieving a reasonable duration of action in vivo, replacing the iodine atoms with alternative substituents eliminates a potential route of metabolic deactivation via enzymatic deiodination.

An examination of the crystal structure[5] of rat $TR\alpha_1$ complexed with **2** (Fig. 2) reveals a significant unoccupied space in the binding cavity next to position-2 of the ligand. This suggests that a ring fusion between the benzylic carbon atom of the position-1 substituent and the position-2 of the aromatic ring would be sterically tolerated by the receptor.

Based on the observations above, we prepared a number of TR-analogues in which an additional ring has been fused to the inner ring of the TR ligand. As outlined below (Scheme 1), the first synthetic step involved

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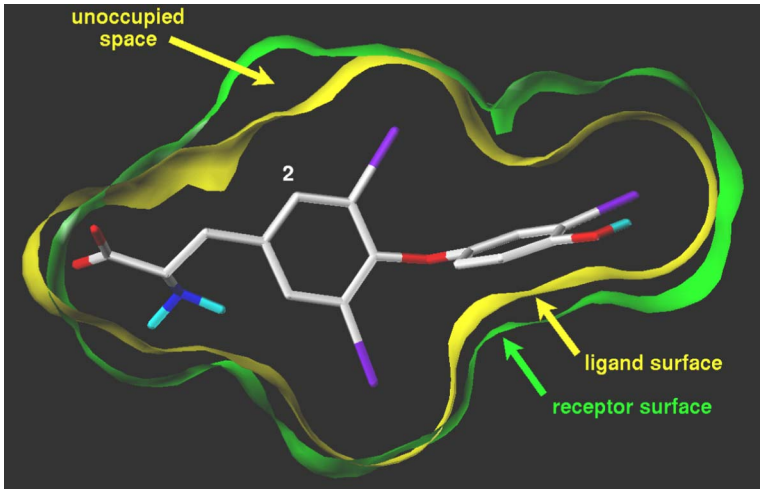
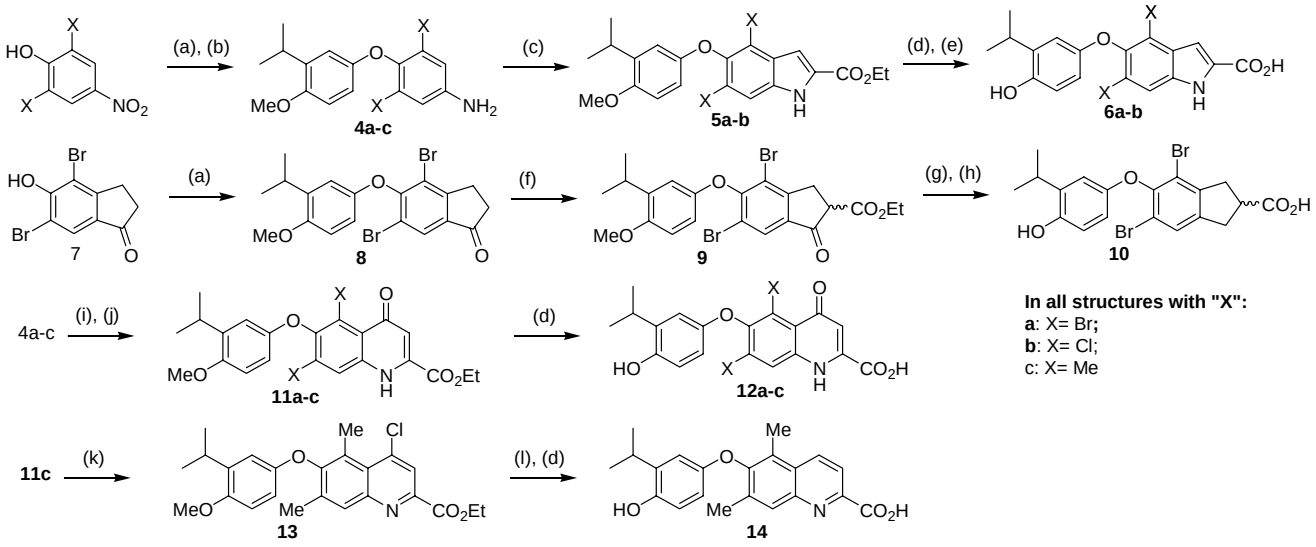


Figure 2. Comparison of the solvent accessible surface areas of thyroxine (**2**; yellow surface; ligand atom coloring scheme: white = carbon, blue = nitrogen, red = oxygen, purple = iodine, and light blue = hydrogen atoms) and the interior binding cavity of TRα (green surface) derived from the crystallographic structure of rat TRα complexed with thyroxine.[5] The solvent accessible surfaces are Z-clipped for the sake of clarity. The unoccupied space adjacent to position-2 of the ligand suggests that a ring fusion between the benzylic carbon atom of the position-1 substituent and the position-2 of the aromatic ring would be sterically tolerated by the receptor.



Scheme 1. Synthetic route for the preparation of the **6a**,**b**, **10**, **12a**–**c** and **14**. Reagents and conditions: (a) bis(3-isopropyl-4-methoxyphenyl)iodonium tetrafluoroborate, Et_3N, Cu; (b) $SnCl_2$; (c) (i) HCl; (ii) $NaNO_2$, $SnCl_2$, HCl; (iii) ethyl pyruvate, H_2SO_4, AcOH; (iv) PPA; (d) BBr_3, CH_2Cl_2; (e) NaOH, THF; (f) diethylcarbonate, NaH, C_6H_6; (g) triethylsilane, TFA; (h) BBr_3, CH_2Cl_2, −78 °C; (i) EtO_2CCCCO_2Et, MeOH; (j) PPA; (k) $POCl_3$; (l) H_2–Pd–C, KOH.

iodonium salt coupling[6] with the appropriate starting phenols **3a**–**c** and **7**, to obtain the corresponding biaryl ethers **4a**–**c** and **8** in good yield. Synthesis of the final target ligands 4,6-dibromo-**6a** and 4,6-dichloroindole **6b**[7] was accomplished via a modification of the Fisher Indole synthesis starting from the anilines **4a**,**b**. The indane-2-carboxylic acid **10** was prepared via direct 2-position carboxylation of the indanone **8**.[8] The 5,7-dibromo (**12a**), 5,7-dichloro- (**12b**), and 5,7-dimethyl-6-tetrahydroquinoline-2-carboxylic acids (**12c**) were all prepared from **4a**–**c** by reaction with ethynyldicarboxylic acid ethyl ester. The intermediate Schiff base was treated with PPA to give ring closure to intermediates **11a**–**c**. The 4-oxo substituent could be removed through treatment of **11c** with phosphorus chloride followed by reduction to give the quinoline-2-carboxylic acid **14**.

The results of a radioligand binding assay for the human $TR\alpha_1$ and $TR\beta_1$, as well as a reporter cell assay employing CHOK1-cells (Chinese hamster ovary cells) stably transfected with $hTR\alpha_1$ or $hTR\beta_1$ and an alkaline phosphatase reporter gene linked to a thyroid response element ($TRAF\alpha_1$ and $TRAF\beta_1$), are summarized in Table 1.[9] The endogenous hormone, **2**, binds to $TR\alpha_1$ and β_1 with an IC_{50} of 0.24 and 0.26 nM, respectively. Compared with **2**, the indole derivative **6a** binds with equal affinity for β_1, but 10 times lower for α_1, thus resulting in a normalized