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# Design and synthesis of novel 3-hydroxy-cyclobut-3-ene-1,2-dione derivatives as thyroid hormone receptor β (TR-β) selective ligands

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ABSTRACT

Design and synthesis of a novel 3-hydroxy-cyclobut-3-ene-1,2-dione derivatives are reported and their in vitro thyroid hormone receptor selectivity has been evaluated in the thyroid luciferase receptor assay. The 3-[3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)-phenylamino]-4-hydroxy-cyclobut-3-ene-1,2-dione **21** has shown selectivity towards thyroid hormone receptor β.



Thyroid hormones are important endocrine signalling hormones, which are involved in a number of important physiological processes such as lipid metabolism; control of energy expenditure and in the brain development.[1–4] Natural thyroid hormone, triiodothyronine ($T_3$) exhibits its physiological effect by acting on a thyroid hormone receptors (THR). It is an important endocrine signalling hormone essential for normal development, differentiation and maintenance of metabolic balance in mammals. The two major subtypes of THR are TR-α and TR-β. Further these two subtypes are classified as $\alpha_1$, $\alpha_2$ and $\beta_1$, $\beta_2$ isoforms.[5] The TR-$\alpha_1$ and TR-$\beta_1$ isoforms are ubiquitously expressed, although TR-$\alpha_1$ predominates in heart (70% of TRs), whereas TR-$\beta_1$ predominates in the liver (80% of TRs).[6] The activation of TR-$\alpha_1$ isoform mainly affects the heart rate and rhythm whereas, activation of TR-$\beta_1$ isoform is known to affect the liver and other tissues.[7,8]

$T_3$ is nonselective in binding towards both of the THR isoforms (TR-$\alpha_1$ and TR-$\beta_1$). Administration of $T_3$ lowers the plasma cholesterol, low-density lipoprotein (LDL) and triglyceride levels in animal models,[8,9] and in humans.[10–12] However, $T_3$ cannot be used therapeutically to treat hypercholesterolemia and obesity due to its cardiac side effects.[9,10] TR-$\beta_1$ agonist could lead to specific therapies for disorders such as obesity and hyperlipidaemia, while avoiding the cardiovascular and other toxicities of native thyroid hormone. Thus, the selectivity for the TR-$\beta_1$ over TR-$\alpha_1$ remains an important criterion in the development of THR ligands.

Axitirome (±)-*N*-[4-[3-(4-fluoro-α-hydroxybenzyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl] oxamic acid ethyl ester **1** (Fig. 1) has been extensively studied oxamic acid thyromimetics, which was progressed up to phase I.[13–16] However, it was discontinued in clinical trials in 1998 for unknown reasons.[17] Similarly 3,5-dichloro-4-[(4-hydroxy-3-isopropylphenoxy)phenyl]acetic acid **2** (KB-141, Fig. 1) was found to be promising due to its selectivity for TR-β subtype[18,19] and has been reviewed in detail for its biological properties.[20,21]

Replacement of biaryl ether linkage with a methylene linkage and phenoxy acetic acid led to a potent compound **3** (GC-1, Fig. 1). It has 10-fold TR-β selectivity in transactivation and lowers the serum cholesterol levels without affecting the heart rate.[22,23]

Hangeland et al. have reported compound **4** (Fig. 2) containing larger hydrophobic group replacing isopropyl group of KB-141 at position R, which demonstrated improved selectivity.[24] Similarly, substitution with aromatic hydrophobic group such as phenyl lead to more potent compound **5** (GC-24, Fig. 2) with higher affinity and stronger selectivity for the TR-β subtype.[25] Recently, compounds **6** and **7** containing 6-azauracil and 3′-carboxamide and 3′-sulfonamide linkage have been reported as potent and TR-β selective thyromimetics.[26] 4′-Amido derivatives **8** have also been described as TR-β selective (Fig. 3).[27]

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† ZRC communication # 241.

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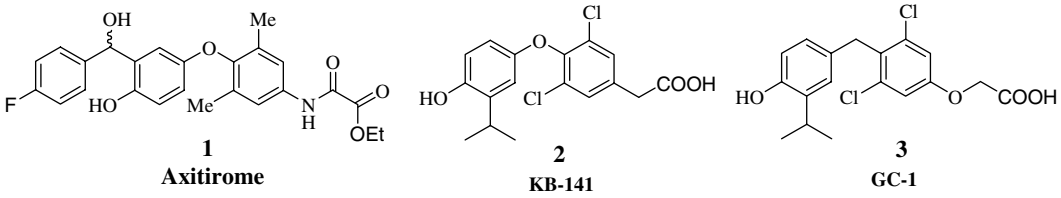



**Figure 1.**

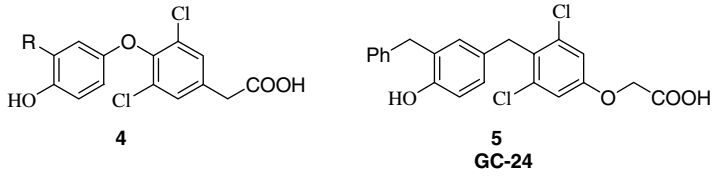



**Figure 2.**

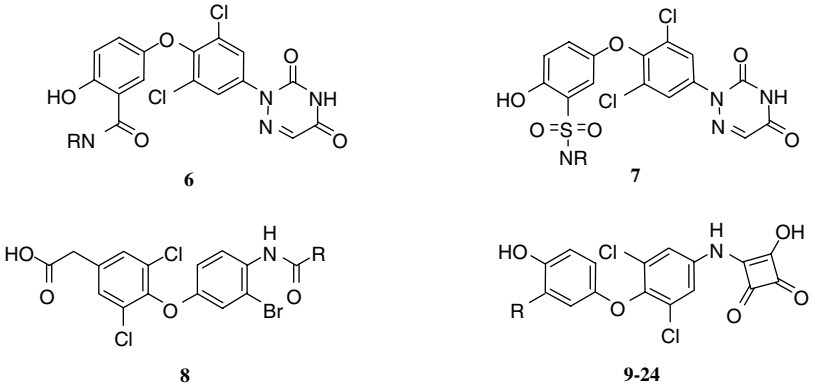



**Figure 3.**

The X-ray crystallographic structures of the ligand binding domains (LBD) of TR-$\alpha_1$ and TR-$\beta_1$ determined in complex with thyromimetics are accessible from Protein Data Bank (PDB).[18,24–26,28,29] The hormone binding pocket is very similar in both the receptors. These receptors differ only by one single amino acid residue, Asn331 in TR-β, which is substituted by Ser277 in TR-α. This results in a significantly different hydrogen bonding patterns between the acidic group of the ligands and the LBD of the two receptors and hence accounts for selectivity. In continuation of our thyroid hormone receptor research program,[32] we focused on modification of acidic moieties in the small molecules to find TRH agonist selective for β-type. Again, the flexibility in the hydrophobic aromatic pocket in TR-β is known to accommodate bulky groups such as benzyl and retain full agonistic activity.[24,25] The hydroxy-cyclobut-3-ene-1,2-dione derivatives **9–24** were designed and validated using molecular modeling.[33]

Molecular docking studies indicated that compounds **21** and **22** make similar interactions in the LBD of TR-α and TR-β as that of exhibited by the ligand 3,5-dichloro-4-[(4-hydroxy-3-isopropylphenoxy)phenyl]acetic acid KB-141 in the crystal structures (Fig. 4).[18]

On basis of favourable orientation and similar binding of designed compound to TR-β as that of KB-141 in molecular docking studies, the derivatives **9–24** comprising 3-hydroxy-cyclobut-3-ene-1,2-dione were synthesized.[34] The in vitro activities of the compounds **9–24** for TR-α and TR-β were evaluated with respect to $T_3$ in a thyroid luciferase receptor assay.[35]

The synthesis of compounds **9–24** has been outlined in Scheme 1. Phenol derivatives **25** were reacted with 1,2,3-trichloro-5-nitro benzene using sodium hydride to afford nitro substituted diaryl ether derivatives **26**. The nitro-diaryl ether derivatives **26** were subsequently reduced using tin chloride in acidic medium to get amino derivatives **27**. The demethylation of methoxy derivatives **27** was achieved using solution of boron tribromide to afford amine derivatives **28**. The resulting amine derivatives **28** were further reacted with 3,4-dihydroxy-3-cyclobutene-1,2-dione(squaric acid) to afford cyclobut-3-ene-1,2-dione derivatives **9–24**.

In vitro % TR-α and TR-β activities of 3-hydroxy-cyclobut-3-ene-1,2-dione derivatives **9–24** at different concentrations such as 0.001, 0.01 and 1 μM were evaluated with respect to $T_3$ (Table 1) keeping KB-141 as a positive control. The primary carboxamide derivatives **9–12** failed to show TR-α or TR-β activity as compared to potent TR-β selective compound **2** even at the concentration of 1 μM (Table 1). Following the unfavourable activity of compounds **9–12**, the primary carboxamide groups were replaced by secondary carboxamides, which resulted to the derivatives **13–16**. The *N*,*N*-dimethyl carboxamide derivative **13** exhibited mild activity at 1 μM concentration for both the TR-α and TR-β. The cyclopentyl carboxamide derivative **14** remained inactive at lower concen-

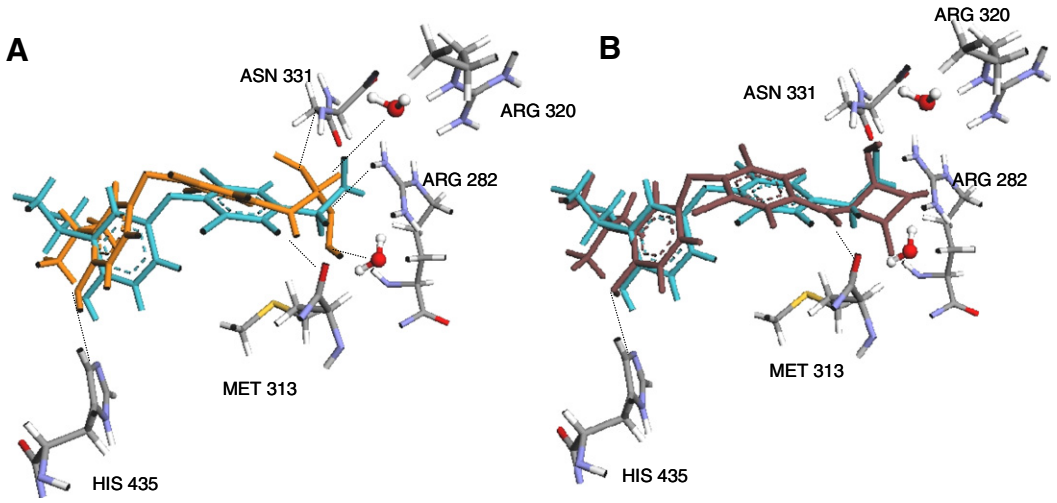
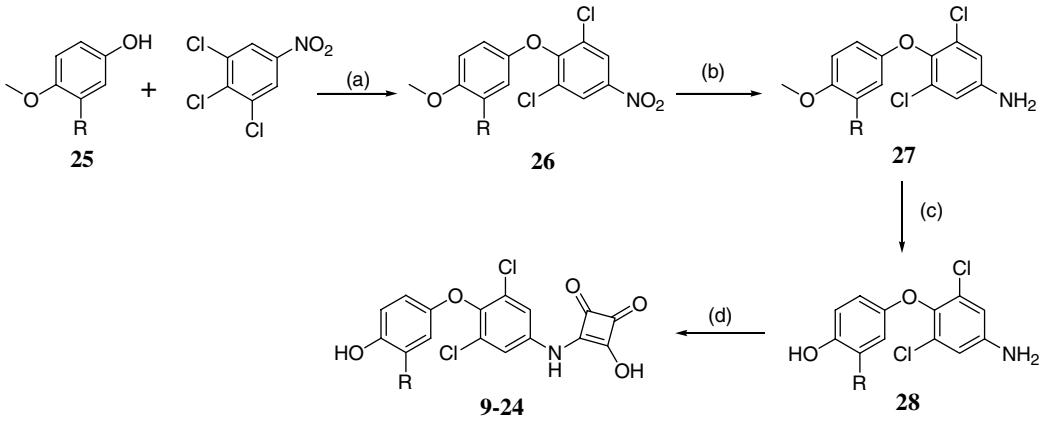



**Figure 4.** Docking of **21** and **22** in ligand binding pocket of TR-β including water molecules. Residues and ligands are shown as sticks. The docked conformers **21** and **22** are superimposed on compound **2** KB-141(shown in cyan as sticks). (A) The oxygen atoms in compound **21** (shown in orange) makes hydrogen bonding with the side chains of residues His435, Arg282, Asn331 and water molecules. The amide linkage makes hydrogen bond with the backbone of Met313 (B) Compound **22** shown in magenta makes similar interactions as that of shown by compound **21**.




**Scheme 1.** Reagents and conditions: (a) NaH, DMF, 120 °C, 3–4 h, 95%; (b) $SnCl_2{\cdot}2H_2O$, concd HCl, EtOH, 65–70 °C, 3 h, 95%; (c) 1 M $BBr_3$, $CH_2Cl_2$, 25 °C, 3 h, 20–50%; (d) $C_4H_2O_4$, $H_2O$, 100 °C, 4–6 h, 30–40%.

trations of 0.001 and 0.01 μM; however, the improved activity was seen at 1 μM concentration (50% for TR-α and 80% for TR-β), which is almost similar to compound **2** at the concentration of 0.001 μM. Changing the ring size of **14** from five- to six-membered, cyclohexyl carboxamide derivative **15** showed diminished activities for both TR-α and TR-β. The carboxamide with one more heteroatom, the morpholino derivative **16** remained inactive against thyroid receptor luciferase assay.

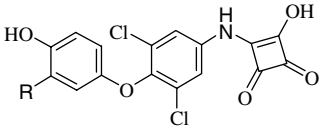
Due to the unfavourable in vitro TR-α and TR-β activities for primary and secondary carboxamide derivatives **9–16**, we evaluated some of the sulfonamide derivatives **17–19** in the same assay and compared with compound **2**. The cyclohexyl sulfonamide derivative **17** showed similar trend of inactivity as that of exhibited by its corresponding carboxamide derivative **10**. Interestingly, the secondary sulfonamide derivative **18** showed mild activity at 1 μM concentration; however, it remained inferior to the compound **2**. Similarly, the morpholino sulfonamide derivative **19** showed weak activities at 1 μM concentration for both TR-α and TR-β.

Furthermore, we tested unsubstituted analogue **20**, which did not show pronounce activities for TR-α and TR-β; however, the selectivity towards TR-β was noteworthy.

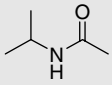
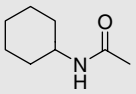
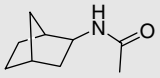
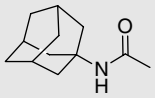
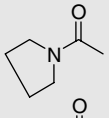
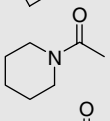
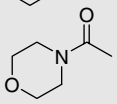
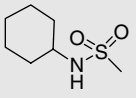
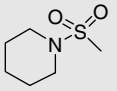
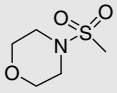
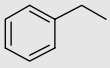
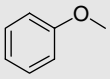
Contrary to carboxamide derivatives **9–16**, sulfonamide derivatives **17–19** and compound without amidic linkage **20**, the compounds substituted by isopropyl **21** and *tert*-butyl **22** gave the encouraging in vitro activity pattern for TR-α and TR-β at the concentration of 1 μM (Table 1). The *tert*-butyl derivative **22** was found to be equipotent to isopropyl derivative **21** (Table 1). Further, the benzyl derivative **23** and phenoxy derivative **24** were found to be inferior to the isopropyl derivative **21** and the *tert*-butyl derivatives **22**. Following the satisfactory in vitro selectivity of compounds **21** and **22**, the $EC_{50}$ values of compounds **21** and **22** were calculated for both TR-α and TR-β (Table 2). Both the compounds **21** and **22** exhibited nearly similar selectivities for TR-α and TR-β as that of shown by the compound **2**.

In summary, a rational structure activity relationship for 3-hydroxy-cyclobut-3-ene-1,2-dione compounds **9–24** as thyroid hormone receptor β culminated to compounds **21** and **22**, which exhibited similar selectivities for TR-α and TR-β as that of shown by the compound **2** (KB-141). The more elaborative SAR, lead optimization, in vitro, in vivo studies and pharmacokinetics in rodent models is in progress at our centre and will be published in future course of time.

**Table 1**
In vitro % activity of novel 3-hydroxy-cyclobut-3-ene-1,2-dione compounds **9–24** for TR-α and TR-β with respect to $T_3$



**9-24**

| Compound | R | Concn (μM) | % Activity for TR-α[a] | % Activity for TR-β[a] |
|---|---|---|---|---|
| **2** | KB-141 | 0.001 | 53.25 | 72.56 |
| | | 0.01 | 100.00 | 100.00 |
| | | 1 | 84.70 | 111.03 |
| **9** |  | 0.001 | 6.16 | 7.015 |
| | | 0.01 | 6.94 | 8.34 |
| | | 1 | 11.70 | 19.05 |
| **10** |  | 0.001 | 7.41 | 10.01 |
| | | 0.01 | 7.69 | 12.28 |
| | | 1 | 9.40 | 15.59 |
| **11** |  | 0.001 | 6.23 | 8.50 |
| | | 0.01 | 6.80 | 10.39 |
| | | 1 | 6.00 | 11.53 |
| **12** |  | 0.001 | 7.12 | 12.30 |
| | | 0.01 | 7.13 | 12.70 |
| | | 1 | 7.19 | 8.80 |
| **13** |  | 0.001 | 7.35 | 8.50 |
| | | 0.01 | 7.37 | 9.00 |
| | | 1 | 13.45 | 23.20 |
| **14** |  | 0.001 | 8.56 | 8.60 |
| | | 0.01 | 9.62 | 10.60 |
| | | 1 | 50.29 | 80.70 |
| **15** |  | 0.001 | 5.63 | 5.63 |
| | | 0.01 | 5.96 | 5.30 |
| | | 1 | 5.25 | 6.23 |
| **16** |  | 0.001 | 6.93 | 13.00 |
| | | 0.01 | 7.91 | 12.70 |
| | | 1 | 11.03 | 30.90 |
| **17** |  | 0.001 | 6.28 | 12.00 |
| | | 0.01 | 6.57 | 13.60 |
| | | 1 | 16.72 | 48.10 |
| **18** |  | 0.001 | 8.56 | 12.80 |
| | | 0.01 | 9.83 | 32.50 |
| | | 1 | 32.28 | 63.80 |
| **19** |  | 0.001 | 8.96 | 15.70 |
| | | 0.01 | 10.55 | 24.70 |
| | | 1 | 22.86 | 43.30 |
| **20** | H | 0.001 | 6.12 | 14.60 |
| | | 0.01 | 6.08 | 15.10 |
| | | 1 | 9.36 | 30.90 |
| **21** |  | 0.001 | 22.36 | 30.00 |
| | | 0.01 | 35.04 | 70.00 |
| | | 1 | 79.84 | 130.00 |
| **22** |  | 0.001 | 15.30 | 14.20 |
| | | 0.01 | 30.70 | 53.50 |
| | | 1 | 61.50 | 107.10 |
| **23** |  | 0.001 | 9.63 | 8.30 |
| | | 0.01 | 13.64 | 29.00 |
| | | 1 | 45.48 | 62.30 |
| **24** |  | 0.001 | 7.23 | 8.96 |
| | | 0.01 | 7.89 | 9.14 |
| | | 1 | 27.22 | 71.49 |

[a] The TRE-luciferase assay[35] has been used for the in vitro TR-α and TR-β activities and values are mean of duplicate measurements and expressed in nM. The variability of the measurements is on average of 25%.

**Table 2**
In vitro $EC_{50}$ for selected compounds **21** and **22** for TR-α, TR-β

| Compound | $EC_{50}$ TR-α[a] (nM) | $EC_{50}$ TR-β[a] (nM) | $EC_{50}$ TR-α/β |
|---|---|---|---|
| **2** | 4.5 | 1.12 | 4.01 |
| **21** | 222.00 | 70.00 | 3.00 |
| **22** | 1056.00 | 317.00 | 3.33 |

[a] $EC_{50}$ values are expressed as mean from the duplicate measurements and are expressed in nM. The variability of the measurements is on average of 25%.

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33. The X-ray crystallographic structure of the KB-141 (**2**) with TR-α (PDB Code: 1NAV) and TR-β (PDB Code: 1NAX) was selected for the docking study.[18] Docking was performed for compounds **9**–**24** using ArgusLab 4.0[30] in the presence of water molecules. Hydrogens and charges were added to the ligand and receptor using modules from DS Studio 2.0 (Accelrys, Inc.). The binding site was defined from the coordinates of the ligand in the PDB file. Argusdock exhaustive search docking engine was used, with grid resolution of 0.20 Å. Five hundred docking runs were used for each compound. Docking precision was set to 'high precision' and 'flexible ligand docking' mode was employed for each docking run. Docked conformers for each compound were ranked and scored using Ascore[31] implemented in ArgusLab. The interaction of the top ranked docked poses in the pocket were visualized using DS Visualizer 1.7 (Accelrys, Inc.).
34. Spectroscopic data for compounds **9–24**:
*Compound* **9**: 70% Yield; 96.1% purity by HPLC; mp 203–205 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 9.61 (s, 1H), 7.94 (s, 2H), 7.53 (d, $J$ = 2.76 Hz, 1H), 6.81 (d, $J$ = 9.0 Hz, 1H), 6.72 (d, $J$ = 9.03 Hz, 1H), 4.10–4.12 (m, 1H), 1.17 (d, $J$ = 6.57 Hz, 6H); ESI-MS: 449.0 $[M-H]^+$.
*Compound* **10**: 60% Yield; 97.7% purity by HPLC; mp 206–208 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 12.07 (s, 1H), 11.89 (s, 1H), 8.07 (s, 2H), 7.52 (s, 1H), 6.80–6.83 (m, 2H), 3.76–3.78 (br s, 1H), 1.56–1.80 (m, 6H), 1.30–1.32 (br s, 4H); ESI-MS: 488.8 $[M-H]^+$.
*Compound* **11**: 62% Yield; 96.5% purity by HPLC; mp 198–203 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.96 (s, 1H), 11.92 (s, 1H), 8.08 (s, 2H), 7.58 (d, $J$ = 2.7 Hz, 1H), 6.84 (d, $J$ = 9 Hz, 1H), 6.78 (d, $J$ = 3 Hz, 1H), 3.70–3.72 (br s, 1H), 2.24–2.26 (br s, 2H), 1.65–1.67 (m, 1H), 1.45–1.47 (m, 4H), 1.13–1.15 (m, 3H); ESI-MS: 500.0 $[M-H]^+$.
*Compound* **12**: 50% Yield; 97.9% purity by HPLC; mp 192–196 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.93 (s, 1H), 11.49 (s, 1H), 8.09 (s, 2H), 7.33 (s, 1H), 6.88 (s, 2H), 2.01–2.03 (br s, 9H), 1.62–1.64 (br s, 6H); ESI-MS: 541.0 $[M-H]^+$.
*Compound* **13**: 51% Yield; 97.1% purity by HPLC; mp 217–220 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 9.61 (s, 1H), 9.53 (s, 1H), 7.91 (s, 2H), 6.80 (d, $J$ = 8.91 Hz, 1H), 6.68–6.72 (dd, $J$ = 8.8 and 3.06 Hz, 1H), 6.45 (d, $J$ = 3.03 Hz, 1H), 2.71–2.79 (br s, 6H); ESI-MS: 435.0 $[M-H]^+$.
*Compound* **14**: 61% Yield; 96.9% purity by HPLC; mp >220 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 9.69 (s, 1H), 9.63 (s, 1H), 7.92 (s, 2H), 6.81 (d, $J$ = 8.91 Hz, 1H), 6.70–6.74 (dd, $J$ = 8.79 and 3 Hz, 1H), 6.51 (d, $J$ = 3 Hz,1H), 3.18–3.20 (br s, 4H), 1.77–1.79 (br s, 4H); ESI-MS: 461.1 $[M-H]^+$.
*Compound* **15**: 66% Yield; 97.1% purity by HPLC; mp 186–190 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.90 (s, 1H), 9.54 (s, 1H), 8.07 (s, 2H), 6.78 (d, $J$ = 8.49 Hz, 2H), 6.47 (s, 1H), 3.14–3.16 (br s, 4H), 1.43–1.53 (m, 6H); ESI-MS: 475.1 $[M-H]^+$.
*Compound* **16**: 64% Yield; 96.3% purity by HPLC; mp 210–214 °C; $^1$H NMR(300 MHz, DMSO-$d_6$): δ 9.65 (s, 1H), 9.63 (s, 1H), 7.92 (s, 2H), 6.80 (d, $J$ = 8.79 Hz, 1H), 6.70 (d, $J$ = 6.21 Hz, 1H), 6.52 (d, $J$ = 2.19 Hz, 1H), 3.53–3.55 (br s, 4H), 3.14–3.16 (br s, 4H); ESI-MS: 477.0 $[M-H]^+$.
*Compound* **17**: 50% Yield; 98.1% purity by HPLC; mp 182–184 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.92 (s, 1H), 8.09 (s, 2H), 7.21 (d, $J$ = 7.65 Hz, 1H), 7.06–7.10 (dd, $J$ = 8.7 and 3 Hz, 1H), 6.93 (d, $J$ = 3 Hz, 1H), 2.78–2.80 (br s, 1H), 1.53–1.56 (m, 4H), 1.02–1.18 (m, 6H); ESI-MS: 524.9 $[M-H]^+$.
*Compound* **18**: 87% Yield; 97.5% purity by HPLC; mp 189–193 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.94 (s, 1H), 10.43 (s, 1H), 8.10 (s, 2H), 6.94–7.07 (m, 3H), 3.03–3.05 (br s, 4H), 1.45-1.47 (br s, 6H); ESI-MS: 510.9 $[M-H]^+$.
*Compound* **19**: 60% Yield; 98.3% purity by HPLC; mp 196–199 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.95 (s, 1H), 10.58 (s, 1H), 8.09 (s, 2H), 6.95–7.09 (m, 3H), 3.55–3.57 (br s, 4H), 3.03–3.05 (br s, 4H); ESI-MS: 513.0 $[M-H]^+$.
*Compound* **20**: 65% Yield; 98.1% purity by HPLC; mp 205–208 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 9.71 (s, 1H), 9.06 (s, 1H), 7.81 (s, 2H), 6.53–6.62 (m, 4H); ESI-MS: 364.0 $[M-H]^+$.
*Compound* **21**: 41% Yield; 98.9% purity by HPLC; mp 210–213 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 9.63 (s, 1H), 8.99 (s, 1H), 7.90 (s, 2H), 6.62–6.65 (m, 2H), 6.25–6.29 (dd, $J$ = 8.67 and 3.03 Hz, 1H), 3.11–3.15 (m, 1H), 1.10 (d, $J$ = 6.9 Hz, 6H); ESI-MS: 406.0 $[M-H]^+$.
*Compound* **22**: 96% Yield; 99.1% purity by HPLC; mp 215–218 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 9.56 (s, 1H), 9.04 (s, 1H), 7.91 (s, 2H), 6.71 (d, $J$ = 3 Hz, 1H), 6.64 (d, $J$ = 8.7 Hz, 1H), 6.26–6.30 (dd, $J$ = 8.64 and 3.03 Hz, 1H), 1.29 (s, 9H); ESI-MS: 420.1 $[M-H]^+$.
*Compound* **23**: 81% Yield; 98.2% purity by HPLC; mp 219–221 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 9.58 (s, 1H), 9.14 (s, 1H), 7.89 (s, 2H), 7.10–7.26 (m, 5H), 6.69 (d, $J$ = 8.73 Hz, 1H), 6.58 (d, $J$ = 3.03 Hz, 1H), 6.34–6.38 (dd, $J$ = 8.64 and 3.09 Hz, 1H), 3.80 (s, 2H); ESI-MS: 454.1 $[M-H]^+$.
*Compound* **24**: 58% Yield;98.6% purity by HPLC; mp >222 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 9.61 (s, 1H), 9.27 (s, 1H), 7.89 (s, 2H), 7.27–7.32 (m, 2H), 6.98–7.03 (m, 1H), 6.81–6.88 (m, 3H), 6.42–6.48 (m, 2H); ESI-MS: 456.1 $[M-H]^+$.
35. *Thyroid receptor assay:* A luciferase receptor assay has been used to find the TR-α and TR-β selectivities of the compounds, where luciferase gene

expression is driven by a thyroid receptor binding element (TRE) upstream of the luciferase gene. Briefly $6 \times 10^4$ CV-1 cells were plated in each well of a 24-well cell culture plate. The cells were transfected 16 h after seeding with a plasmid bearing three copies of TRE cloned upstream of luciferase gene along with a plasmid expressing either the full length human thyroid receptor-α or -β isoform and a third plasmid expressing β-galactosidase. The transfection is carried out using polyfect reagent from Invitrogen, Inc. (Carlsbad, CA). The medium is replaced 6 h post transfection with fresh media having different concentrations of the agonist. The concentration of agonist is adjusted in such a way that the concentration of the solvent (DMSO) in each well is maintained at 1%. The plates are incubated at 37 °C for 16 h before lysing and assaying the luciferase activity using commercially available Glo-lysis kit from Promega and a standard luminometer. The β-galactosidase activity was measured by using the β-galactosidase assay kit from Promega and the absorbance was read at 415 nM.