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A new class of high affinity thyromimetics containing a phenyl-naphthylene core

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Abstract—High affinity thyromimetics containing a novel phenyl-naphthylene core are reported. The functionalized core is readily accessible via a Suzuki coupling protocol. Examples of this new class of TR ligands have sub-nanomolar binding affinities for the TRβ receptor and low to modest selectivity for TRβ. They also exhibit an SAR that diverges from other thyromimetics that are based on the diaryl ether core found in 3,5,3′-triiodothyronine.

Binding of the 3,5,3′-triiodothyronine (T3; **1** in Fig. 1) to the thyroid hormone receptor (TR) controls multiple physiological endpoints (e.g., heart rate, bone and muscle metabolism, cholesterol levels, and metabolic rate) through transcriptional control of various gene targets.[1] Levels of T3 in excess of normal physiologic amounts cause cardiac hypertrophy, tachycardia, bone and muscle wasting, and weight loss. Sub-physiological amounts produce bradycardia and weight gain. The amount of T3 needed to provide clinically relevant weight loss causes unwanted cardiac side effects, preventing its use for anti-obesity therapy.

The thyroid hormone receptor is encoded by two separate genes, TRα and TRβ. Each produces multiple splice variants, the predominant ones being $TR\alpha_1$ and $TR\beta_1$. $TR\alpha_1$ has been shown by tissue distribution data[2] and mouse knock-out studies[3] to be the dominant isoform in cardiac tissue, making it possible to separate unwanted cardiac side effects (e.g., cardiac hypertrophy and tachycardia) from beneficial effects by designing thyromimetics selective for $TR\beta_1$.[4]

X-ray crystal data of various thyromimetics bound to the TR ligand binding domain (LBD) show that the ligand is buried within the core of the LBD.[5] The ligand and protein contacts are tight, and binding of the ligand to the receptor induces conformational changes to the receptor surface that generate a co-factor binding site.[5] Formation of the co-factor binding site is critical for proper gene transcription control by the TR/ligand complex. In addition, these structures show conclusively that the bound conformation of the ligand has the 3′-group oriented away from the inner ring (i.e., in the distal position), confirming the outcome of earlier stereochemical and biological activity studies using thyroxin analogs.[6] While the association between the ligand and LBD is very tight, side-chain and backbone movements within the 3′-binding pocket of the LBD[9a,b] permit groups significantly larger than iodine to be appended onto the core structure at the 3′-position, leading to increased selectivity for TRβ while retaining full agonist activity.[9]

The vast majority of reported thyromimetics retain two features of the core structure of T3: a diphenyl ether and a 3,5-disubstituted inner ring, the two acting in concert to orient the phenyl rings in a skewed relationship. The skewed conformation is labeled 'ideal'[10] when the inner phenyl ring is orthogonal to the C–O–C plane ($\sigma = 90°$; Fig. 2A) and the outer ring is coplanar to the C–O–C plane ($\sigma' = 0°$; Fig. 2A). An analysis of in-house generated X-ray crystal structures for a variety of thyromimetics, including compound **4**,[8] complexed to either the TRα or TRβ LBD showed the average values for σ and σ' to be 79° and 47°, respectively (Fig. 2B). Thus, the receptor bound conformation of the ligand deviates from the ideal skewed conformation. Similar deviations were observed in X-ray crystal structures of T3, and

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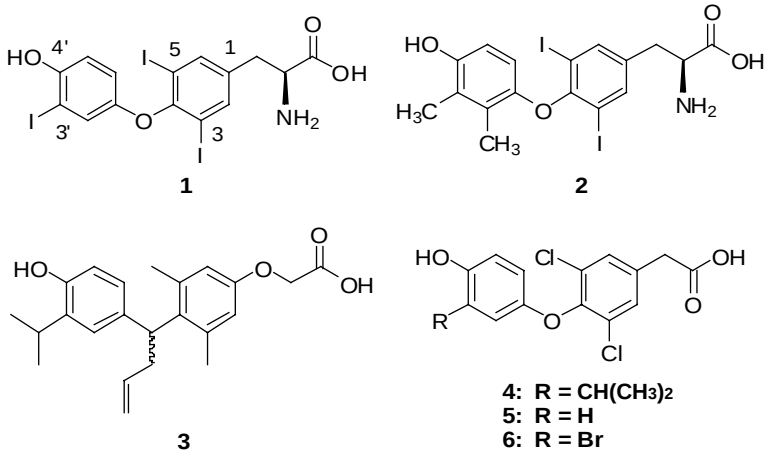


Figure 1. Structures of T3 (**1**), 2′,3′-substituted analogs of T3 from Jorgensen and Berteau (**2**),[6] carbon-linked analogs from Scanlan and co-workers (**3**),[7] and phenyl acetic acid analogs from Malm and co-workers (**4**).[8]

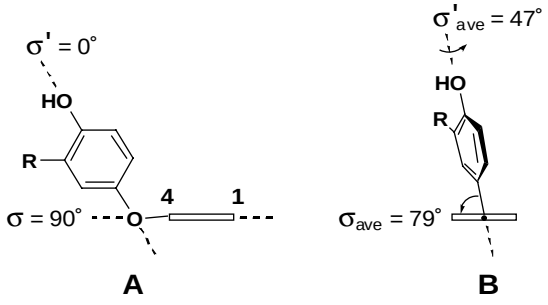


Figure 2. Two views of the conformational relationship between the phenyl rings of the diphenyl ether core of T3 and its analogs. (A) depicts a side view of an ideal skewed conformation where the outer ring is in the same plane as C–O–C and the inner ring is orthogonal to the C–O–C plane; (B) depicts a view of the diphenyl ether core looking down the C-1 → C-4 axis showing the deviation from the ideal skewed. Note that the outer ring has twisted such that, in this view, the 3′ group is positioned to the left and the outer ring has rotated counterclockwise.

closely related analogs, not complexed to the receptor LBD.[10]

To test if forcing the two phenyl rings to be orthogonal would lead to high affinity thyromimetics or would contribute to the selectivity for one TR isoform over the other, a novel phenyl-naphthylene core was designed (Fig. 3). The new core retained the essential relationship between the two phenyl rings, locked into position the distal conformational relationship of the 3′-substitutent to the inner phenyl ring, and enforced co-planarity of the outer ring with the C–O–C plane ($\sigma' = 0°$). The 2′-position of the outer phenyl ring was tied to the bridging carbon via a three carbon linker to form the second ring of the naphthylene moiety. By doing this, the new structure combined substitution patterns reported in two separate series: (1) analogs of T3 containing small alkyl substituents at the 2′- and 3′-positions[6] (**2** in Fig. 1), and (2) analogs of GC-1[11] containing substitution on the bridging methylene carbon linking the two phenyl rings[7] (**3** in Fig. 1). An analog of compound **3** containing a significantly larger group off the bridging carbon was reported to be a competitive antagonist in a transactivation assay, whereas compound **3** was reported to be a low-potency agonist.[7b]

The key carbon–carbon bond forming reaction used to construct the phenyl-naphthylene core was carried out using a Suzuki reaction (Scheme 1). The synthesis started from 6-methoxynaphth-1-ol (**7**),[12] which was converted to boronic ester **9** via triflate **8**.[13] The coupling partners of boronic ester **9** were obtained by conversion of methyl 2-(3,5-dichloro-4-hydroxy-phenyl)acetate (**10**)[8,9c] and 6-dichloro-4-nitrophenol (**11**) to their corresponding triflates **12** and **13**. Suzuki coupling of boronic ester **9** with triflate **12** required heating at 80 °C for 4 h to give compound **14**, albeit in low yield (ca. 9%). In contrast, coupling of ester **9** with triflate **13** gave compound **15** in good yield (69%) in 30 min at 80 °C. The higher yield obtained with triflate **13** was a key improvement in the synthesis of **15**, providing sufficient material to permit more extensive SAR studies than with **14**.

The first two examples of this new class of thyromimetic, compounds **16** and **17,** were synthesized from compound **14** (Scheme 2) and were modeled after compound **4**.[8] For comparison, two diaryl ether analogs of **16** and **17** were synthesized[14] (compounds **5**[15] and **6**, respectively, in Fig. 1). Compound **16** had modest affinity for TRα and TRβ, and was slightly selective for TRβ (Table 1). Its diaryl ether analog, compound **5**, had lower affinity for TRα and TRβ (2- and 4-fold, respectively), and was unselective. Compound **17**, which contained bromine at the 5′-position, had improved affinity for TRα and TRβ (15- and 42-fold, respectively) compared to **16**, and was slightly more selective for TRβ, reflecting a greater improvement in affinity for TRβ versus TRα. The improved potency was consistent with the 5′-substituent being located in the 3′-binding pocket of the LBD. In contrast to **5**, compound **6** was equipotent to **17** and had similar selectivity for TRβ. In addition, compound **17** was a full agonist with EC_{50} values of 57 nM (80% induction) for TRα and 40 nM (92% induction) for TRβ.[16]

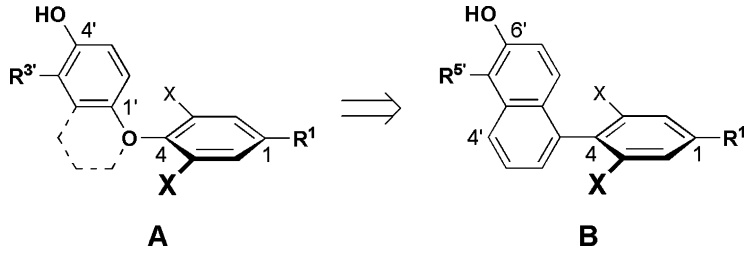
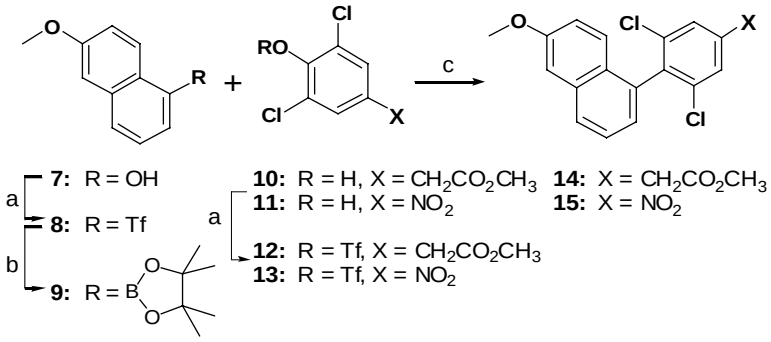
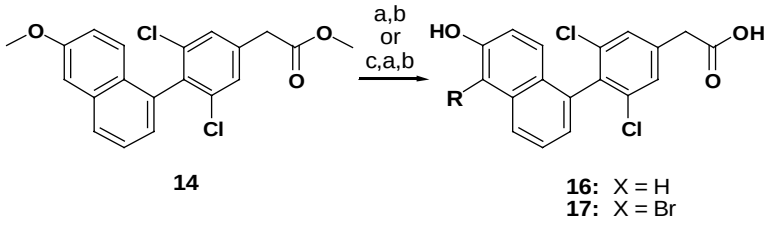


Figure 3. Schematic representation of the design of the phenyl-naphthylene core (B) as it relates to the traditional thyromimetic architecture (A). Note that the numbering of the naphthyl ring system differs from that of the outer ring of the diaryl ether core (e.g., the 3′ position of the diaryl ether core is equivalent to the 5′ position on the naphthylene ring).



Scheme 1. Synthesis of phenyl-naphthyl core structures **14** and **15**. Reagents and conditions: (a) Et_3N, triflic anhydride, CH_2Cl_2, −40 °C to −10 °C (99%); (b)[13] bis(pinacolato)diborane, anhyd potassium acetate, $PdCl_2$(dppf), 80 °C, 4 h (58%); (c) compound **14**: $Pd(PPh_3)_4$, K_2CO_3, toluene/acetone (1:1), 80 °C, 4 h (9%); compound **15**: $Pd(PPh_3)_4$, Na_2CO_3, DME/H_2O (3:1), 80 °C, 30 min (69%).



Scheme 2. Synthesis of compounds **16** and **17**. Reagents and conditions: (a) BBr_3, CH_2Cl_2, −78 °C, stirred at 0 °C for 90 min; (b) NaOH in CH_3OH, rt, 16 h (94% over two steps); (c)[22] 48% HBr, acetic acid, DMSO, rt, 16 h (97%).

Table 1. IC_{50} and selectivity data of phenyl-naphthylene thyromimetics and select analogs

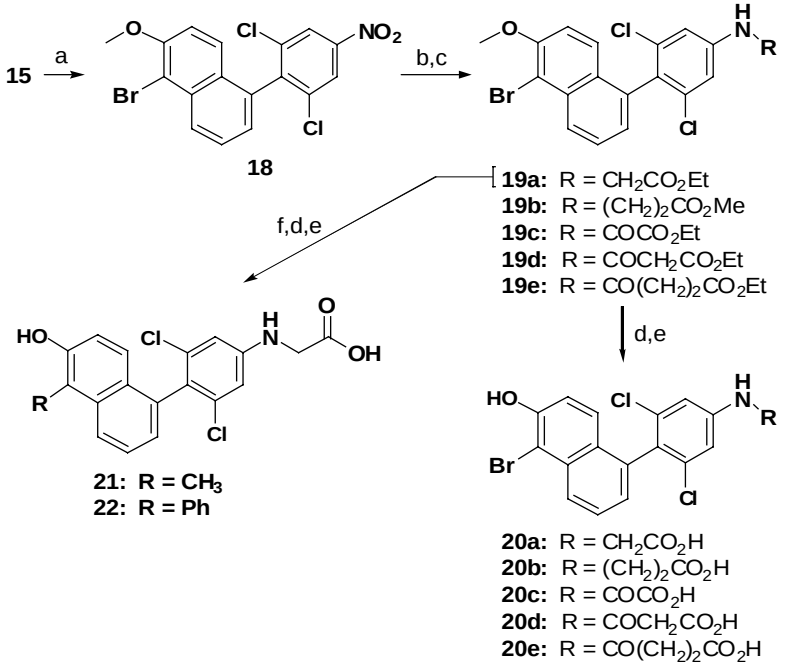
Compound	IC_{50}(nM)[a,b]		Sel[c]
	Tr-α	TR-β	
1	0.24	0.26	0.9
4	25	1.1	14
5	3605	2140	1
6	109	9	7
16	1538	545	2
17	101	13	5
20a	19	1.8	6
20b	13	1.8	4
20c	5.4	0.3	8
20d	4.3	0.3	9
20e	62	22	2
21	48	7.2	4
22	125	29	3
26	14	0.3	25

[a] Competitive binding affinities versus radioiodinated T3 using full-length cloned hTRα$_1$ and hTRβ$_1$.[8,17]

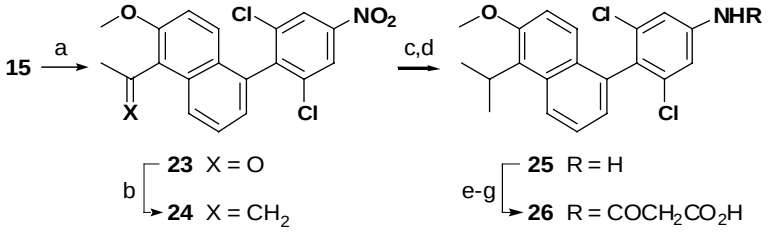
[b] IC_{50} values determined from a minimum of duplicate data. Values have an average variability of ±25%.

[c] Selectivity = (IC_{50} hTRα$_1$)/(IC_{50} hTRβ$_1$ × 1.7).[8,17]

Further SAR studies of the phenyl-naphthylene core were carried out starting from compound **15** owing to its greater synthetic flexibility and ready availability (Scheme 3). Modifications at C-1 were selected to increase affinity based, in part, on previously established SAR.[18] The rank ordering of C-1 side-chain affinities for TRβ was succinic acid (**20e**) < acetic acid (**17**) < 2-aminoacetic acid (**20a**) ≈ 3-aminopropanoic acid (**20b**) < oxalic acid (**20c**) ≈ malonic acid (**20d**), with the two most potent compounds having IC_{50} = 0.3 nM for TRβ. No significant change in isoform selectivity was observed for any of these analogs. Two analogs of compound **20a** were synthesized (**21** and **22** in Scheme 3) to assess the effect that changes to substituents at the 5′-position would have on binding affinity and agonist activity. As expected, the 5′-methyl analog **21** was slightly less potent than **20a** (2-fold) and was about equally selective for TRβ. This result is consistent with the 5′-position being located in a hydrophobic region of the TR LBD. The 5′-phenyl analog **22** was less potent for both TR isoforms and less selective for TRβ. Interestingly, compound **22** exhibited partial agonist



Scheme 3. Synthesis of compounds **20a**–**e**, **21**, and **22**. Reagents and conditions: (a) Br_2, CH_2Cl_2, rt, 3 h (89%); (b) iron powder, acetic acid containing 10% H_2O (v/v), rt, 16 h (89%); (c) compound **19a**: ethyl bromoacetate, K_2CO_3, acetonitrile, 80 °C, 16 h (85%); compound **19b**: methyl acrylate, acetic acid, 120 °C, 16 h (99% as a 1:1 mixture of methyl ester and free acid); compounds **19c**–**e**: $C_2H_5CO_2(CH_2)_nCOCl$ (n = 0–2), Et_3N, CH_2Cl_2, 0 °C to rt, 2 h; (d) BBr_3, CH_2Cl_2, −78 °C, stirred at 0 °C for 90 min; (e) NaOH in CH_3OH, rt, 16 h; (f) compound **21**:[19] $CH_3B(OH)_2$, $PdCl_2(dppf)$, K_3PO_4, 1,4-dioxane, 110 °C (sealed tube), 16 h (58%); compound **22**: $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME/H_2O (3:1), 80 °C, 30 min (45%).



Scheme 4. Synthesis of compound **26**. Reagents and conditions: (a)[20] acetic anhydride, $(CH_3)_2SBF_3$, CH_2Cl_2, −78 °C to rt, stirred at rt for 16 h (77%); (b)[21] Nysted reagent, $TiCl_4$, THF/CH_2Cl_2 (1:1), −78 °C to rt, stirred at rt for 16 h (27%); (c) iron powder, acetic acid containing 10% H_2O (v/v), rt, 16 h (99%); (d) PtO_2, H_2 (1 atm), EtOH, 2 h (97%); (e) $C_2H_5CO_2CH_2COCl$, Et_3N, CH_2Cl_2, 0 °C to rt, 2 h (91%); (f) BBr_3, CH_2Cl_2, −78 °C, stirred at 0 °C for 90 min; (g) NaOH in CH_3OH, rt, 16 h (80% over two steps).

activity for both TR isoforms (19% induction for TRα and 50% induction for TRβ).[16] Replacing the 5′-bromide of compound **20d** with an isopropyl group gave compound **26** (Scheme 4). This modification retained high affinity for both receptor isoforms and produced the most TRβ selective compound discovered in this series (25-fold for TRβ).

A proposed binding mode for **26** is shown in Figure 4 as an overlay with the X-ray structure for compound **4** complexed to TRβ.[8] The energy-minimized structure (Amber force field as implemented within Flo[23]) of **26** was found to adopt a favorable H-bonding distance between H435 and the pendant 6′-OH of 2.29 Å. The model suggests a unique deep pocket interaction between C-2′, C-3′, and C-4′ of the naphthylene moiety and residues L341 and F272 of the receptor LBD. In addition, the dihedral angle between the phenyl and naphthyl ring systems found in the bound model of **26** was 113°, while fully relaxed ring system preferred 91° (in vacuo, SAM1D[24]). The energy cost to assume the 113° rotamer is estimated to be 2–3 kcal/mol, which should be easily accommodated by minor reorganization of the hydrophobic residue side chains surrounding the naphthyl system (i.e., F272, I276, L341, and L346).

The binding data indicate that the SAR of the phenyl-naphthylene series diverges from thyromimetics containing a diphenyl ether core. A comparison of compounds **5** and **16** suggests that, in the absence of a lipophilic group projecting into the 3′-binding pocket of the TR LBD, the phenyl-naphthylene core has a modestly higher affinity. Addition of a lipophilic bromide to C-3′ and C-5′ (i.e., compounds **6** and **17**, respectively) resulted in a greater increase of affinity for the diphenyl ether series (237-fold for TRβ) than for the phenyl-naphthylene

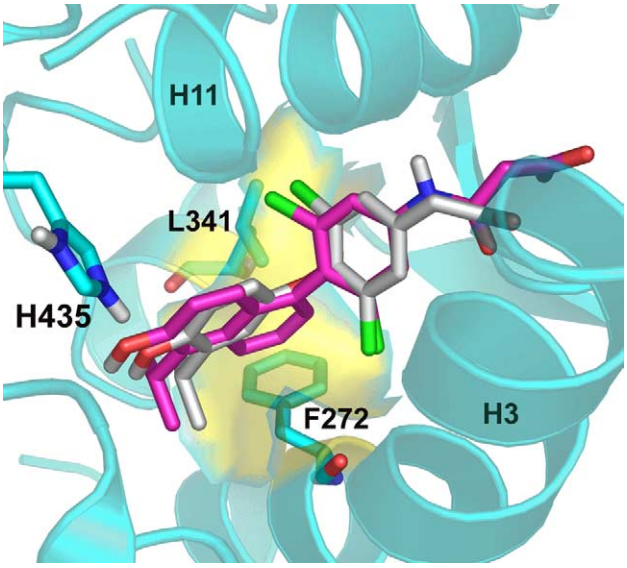


Figure 4. Overlay of compounds **4** (white) and **26** (magenta) within the ligand binding site of TRβ. The structure of **26** was modeled after the binding mode of **4** as found in the published X-ray structure[8] (Protein Data Bank entry 1NAX).

series (42-fold for TRβ). This suggests that the conformationally flexible diphenyl ether core is able to orient this group more optimally within the 3′-binding pocket of the LBD. This latter point is of consequence when considering the phenyl-naphthylene core, or its analogs, for further design of thyromimetics having either isoform selectivity or agonist versus antagonist properties. For example, analogs of compound **4**, containing a 3′-phenyl or substituted phenyl group, were selective for TRβ (up to 38-fold) and were full agonists for both isoforms.[9c] In contrast, compound **22**, which contains a 5′-phenyl group, is the *least* selective analog of the three closely related compounds (e.g., compounds **20a**, **21**, and **22**). Indeed, the most selective compound discovered (**26**; 25-fold for TRβ) contains a 3′-isopropyl group, which is not commonly thought to contribute to increased isoform selectivity.[8,9] Furthermore, the partial agonist activity exhibited by compound **22** suggests this position to be more sensitive to changes in steric bulk, both with respect to selectivity and agonist versus antagonist properties. Thus, this new class of thyromimetic may provide additional opportunities to discover TR ligands with improved separation of desired pharmacological outcome from unwanted cardiac side effects.

Acknowledgments

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