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Synthesis and Biological Activity of Novel Thyroid Hormone Analogues: 5′-Aryl Substituted GC-1 Derivatives

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Abstract—Compounds that selectively modulate thyroid hormone action by functioning as isoform-selective agonists or antagonists of the thyroid hormone receptors (TRs) might be useful for medical therapy. We have synthesized a high affinity TRβ-selective agonist ligand, **GC-1**,[1] and optimized the synthetic route to provide large quantities of the compound for animal testing.[2] In addition to an improvement in efficiency, the new synthetic route offers a chemical handle for selective modification of the thyronine skeleton to produce new derivatives. To explore the effect of **GC-1** core structure modifications on binding to TR isoforms and activation of transcription, we developed here an efficient and flexible route to a new series of 5′-substituted **GC-1** analogues. This route relies on ortho lithiation and in situ boration of the biarylmethane compound **1**, a key intermediate of the revised **GC-1** synthesis,[2] followed by Suzuki cross-coupling. Using this approach we prepared and tested eleven 5′-substituted **GC-1** analogues. Substitution at the 5′-position decreased binding affinity, but retained TRβ-selectivity for most of the compounds. Transactivation assays reveal that most of these compounds function as thyroid hormone agonists, but one compound (**GC-14**) antagonizes the response to thyroid hormone.

Introduction

Thyroid hormone, (T_3, Fig. 1), produced by deiodination of thyroxine (T_4, Fig. 1) in peripheral tissues and by the thyroid gland, exerts critical influences on the growth, development and metabolism of vertebrates.[3] Lack of T_3 in early human development results in growth disturbances and severe mental retardation;[4] later in life, T_3 plays an important role in metabolic balance.[5] In excess, thyroid hormones may cause weight loss, lowering of plasma lipid levels, tachycardia, atrial arrhythmias, and heart failure.

Essentially all known physiological actions of thyroid hormone are believed to occur through thyroid hormone receptors (TRs), which are members of the nuclear hormone receptor superfamily. Members of this superfamily are ligand-activated transcription regulators that control transcription of hormone-responsive genes.[6–8] Liganded and unliganded TRs bind at specific *cis*-acting thyroid hormone response elements (TREs), and may bind as monomers, homodimers, or heterodimers with other transcription factors such as the retinoid X receptor (RXR).[9] Like other nuclear receptors, the TRs have three structural domains; an N-terminal domain, a central DNA binding domain (DBD), and a C-terminal ligand binding domain (LBD). Crystal structures of the ligand-bound TR LBDs have been solved recently and reveal an internal binding mode for the ligand.[10–12]

There are two TR genes designated TRα and TRβ, located on different chromosomes (17 and 3, respectively, in humans). Alternative splicing from each gene generates at least four isoforms: $TR\alpha_1$, $TR\alpha_2$, $TR\beta_1$ and $TR\beta_2$.[9] The $TR\alpha_1$, $TR\alpha_2$, and $TR\beta_1$ isoforms are widely expressed with characteristic tissue distribution,[13–15] whereas $TR\beta_2$ expression is largely confined to the anterior pituitary.[16] Although thyroid hormone displays no selectivity in binding or activation of the TR isoforms, synthetic analogues have been developed that are TRβ-selective agonists.[17] The further development of

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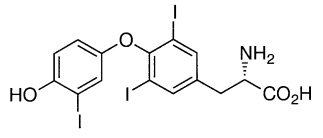
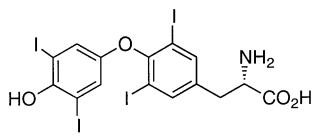


T3



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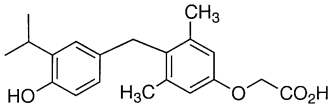
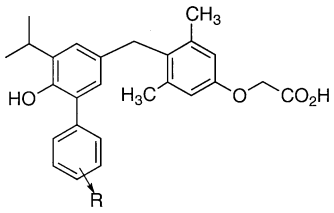


GC-1



5'-aryl substituted
GC-1 analogues

GC-13, R = H
GC-14, R = *p*-NO_2
GC-15, R = *p*-$NHCH_2COOH$
GC-16, R = *p*-NHCONHPh
GC-17, R = *p*-$NHCH_2CCCH_3$
GC-18, R = *p*-NH_2
GC-19, R = *m*-NO_2
GC-20, R = *o*-NO_2
GC-21, R = *p*-COOH
GC-22, R = *p*-$CONH_2$
GC-23, R = *p*-NHC(=NH)NH_2

Figure 1.

TR isoform-selective agonists and antagonists will provide useful pharmacological probes for studying thyroid hormone action, and may also provide new therapeutics for the treatment of metabolic disorders.

Compared to steroid ligands for nuclear receptors, T_3 analogue chemistry is relatively unexplored. Previous studies have focused on structure–activity relationships of the features of T_3,[18] as well as development of liver-specific thyroid hormone agonists for treatment of hypercholesterolemia.[19,20] There are, however, structural features of T_3 that present significant challenges to chemical synthesis, and thus limit analogue design. We initially designed and synthesized the high-affinity TRβ-selective thyroid hormone analogue, **GC-1** (Fig. 1), in an attempt to find a thyroid hormone scaffold that was more synthetically accessible than T_3.[1] **GC-1** differs from T_3 in three key respects: replacement of the ether bridge joining the two rings with methylene; replacement of the 3, 5, and 3′ iodine atoms with methyl (3,5) and isopropyl (3′); and replacement of 1-amino-propionic acid with oxyacetic acid. These changes produce an analogue with comparable dimensions to T_3 but significantly lower molecular weight.

Because the **GC-1** synthesis is well suited to generating analogues, we are using the scaffold to test the effects of substitution at various positions on the scaffold. We describe here the design and synthesis of a variety of 5′-aryl substituted **GC-1** derivatives (Fig. 1), and the receptor-binding and transactivation properties of these compounds. These analogues all bind TRs and most retain agonist activity with TRβ selectivity. However, one compound (**GC-14**) was found to have TRβ-selective antagonist activity.

Results and Discussion

Rationale and design

Our interest in probing the substituent effects at the 5′ position of **GC-1** was based on a crystallographic analyses that suggested this would be a good position to introduce a large extension that would result in a ligand with T_3 antagonist activity.[21] Our recently solved structure of the TRβ LBD bound to **GC-1**[12] reveals that the 5′ position of the ligand is adjacent to the loop between helices 11 and 12, and substituents at this position would not be accommodated by the ligand binding cavity. In analogy to the raloxifene and tamoxifen-bound estrogen receptor structures,[22,23] a large substituent at this position may perturb the packing of helix 12 and formation of the coactivator binding surface, resulting in abolishment of transciptional activity from the liganded TR.

We have recently optimized our original synthesis of **GC-1** using methoxymethyl (MOM) and triisopropylsilyl (TiPS) substituents as phenolic protecting groups.[2]

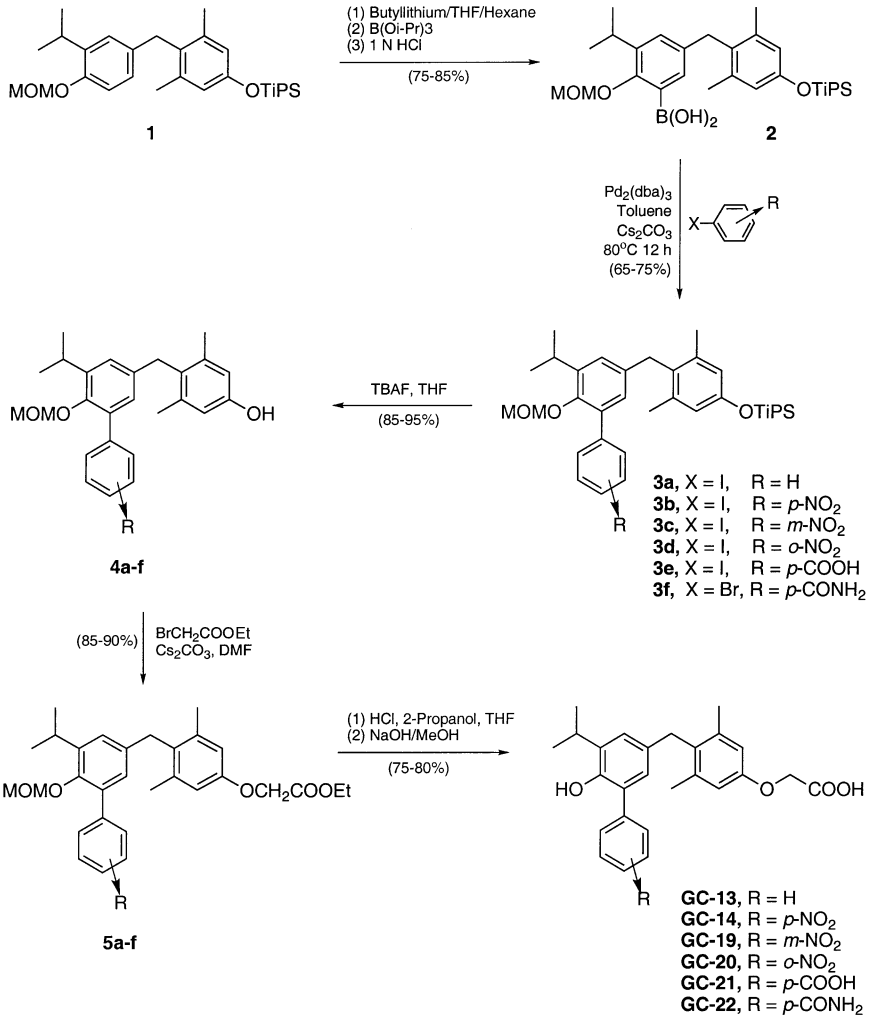
The new route allowed us to prepare multigram quantities of **GC-1** and offered a chemical handle for selective modification of the thyronine skeleton to produce new derivatives. Thus, this synthetic route was adopted for the synthesis of a new series of 5′-aryl **GC-1** analogues, and the chemistry used is outlined in Scheme 1.

Chemical synthesis

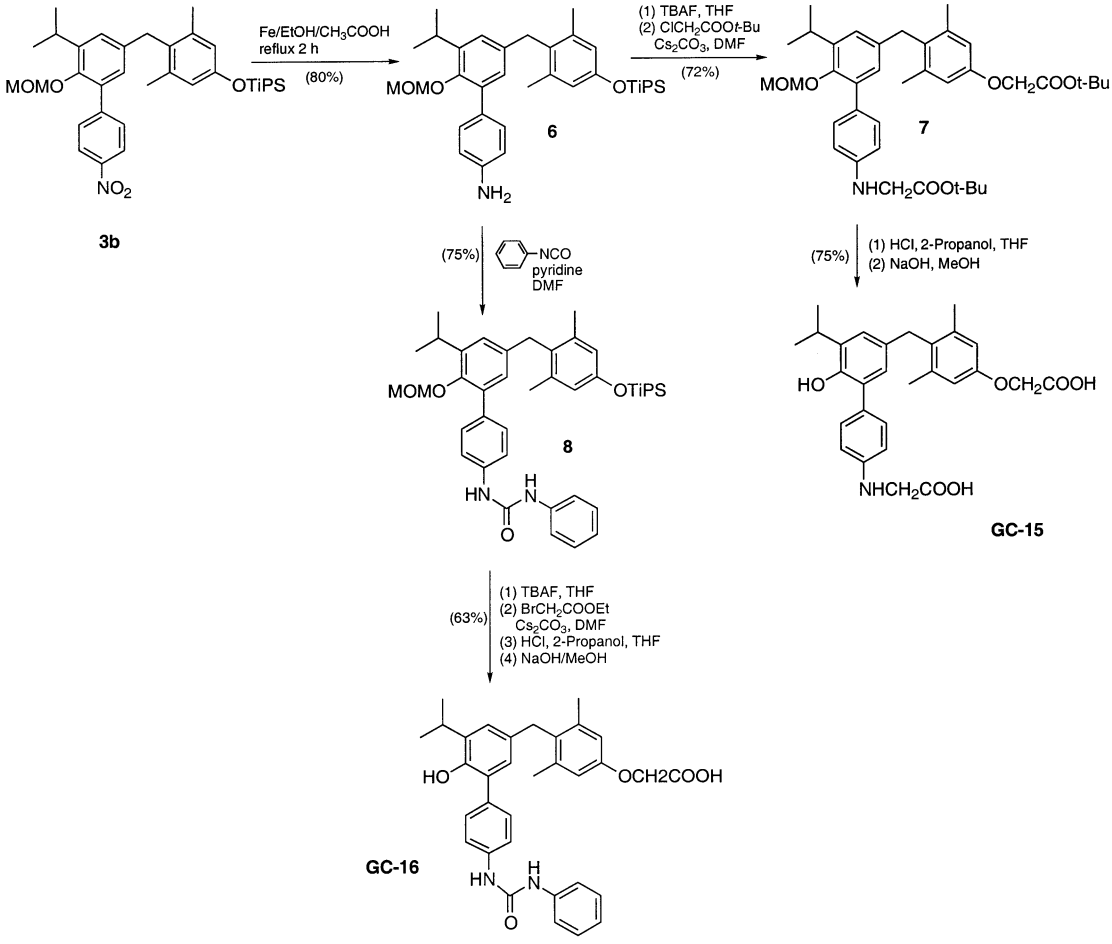
Compounds **GC-13**, **GC-14**, **GC-19**, **GC-20**, **GC-21**, and **GC-22** were prepared as described in Scheme 1. *Ortho* metalation and in situ boration[24] of the biarylmethane compound **1**, which was a key intermediate in the revised synthesis of **GC-1**,[2] using *n*-butyllithium as the base and triisopropylborate as the electrophile, in a 2:1 THF/hexanes solvent mixture, generates the boronic acid **2**. Suzuki coupling of **2** with a variety of aryl halides produced a series of 5′-aryl analogues **3a**–**3f**. The lithiation directed by the MOM group turned out to be a difficult step; the rate of lithiation was affected greatly by the polarity of the solvent. The best conditions we found were using a 2:1 THF/hexanes as the reaction solvent. Under these conditions the lithiation and subsequent boration proceeded in good overall yield. The subsequent Suzuki cross-coupling reaction with a variety of aryl iodides was straightforward and provided the desired cross-coupled products in good yield.

De-silylation of **3a**–**3f** with tetrabutylammonium fluoride generated the phenols **4a**–**4f**, which were then mono-alkylated using bromoethylacetate to give the mono-ester **5a**–**5f**. The desired 5′-aryl substituted thyronine analogues, **GC-13**, **GC-14**, **GC-19**, **GC-20**, **GC-21** and **GC-22** were obtained from the corresponding ester by removal of the methoxymethyl phenolic protecting group under acidic conditions, followed by basic saponification of the ethyl esters.

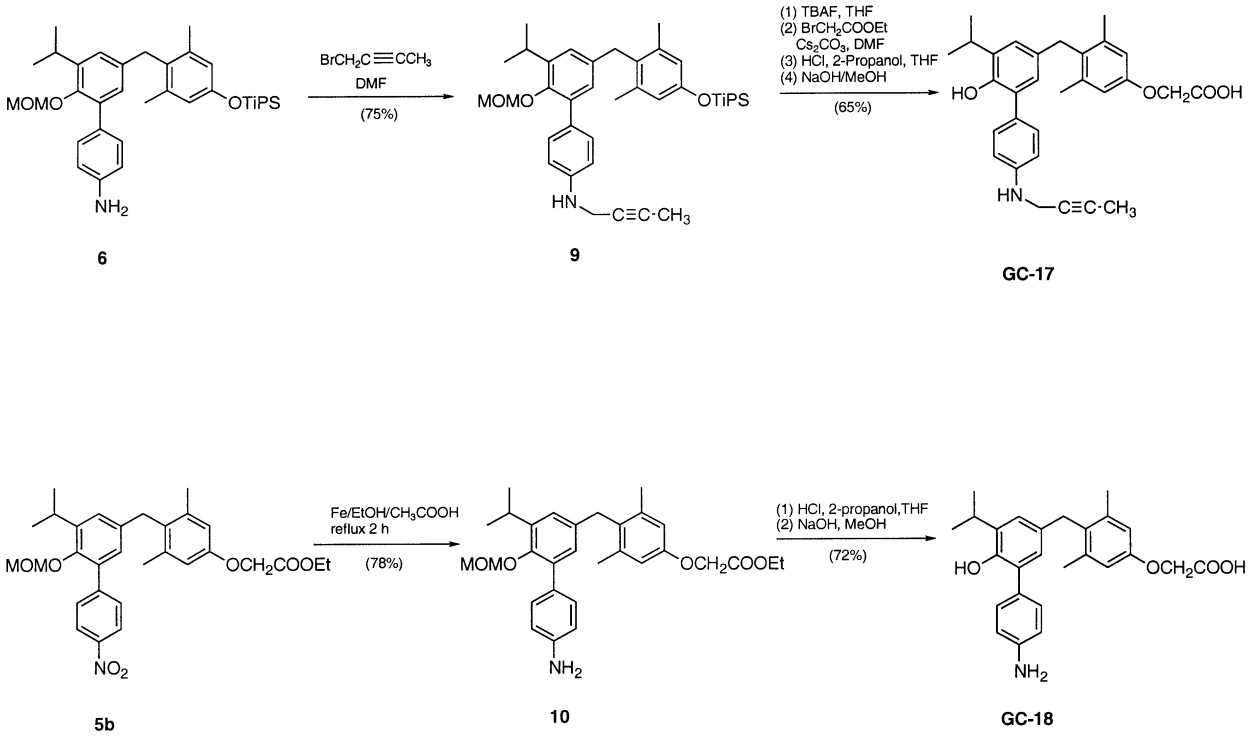
The 4′-carboxymethyl-amino analogue, **GC-15** and the urea analogue **GC-16** were prepared from the intermediate compound **3b** as shown in Scheme 2. The nitro group reduction of **3b** by iron/acetic acid led to the aniline **6**. Selective removal of the triisopropylsilyl phenolic protecting group of **6** followed by alkylation generated the bis-ester **7**, which after removal of the methoxymethyl phenolic protecting group was subjected to alkaline hydrolysis to yield **GC-15**. Reaction of **6** with phenylisocyanate generated the phenyl urea derivative **8**, which was elaborated to **GC-16** as described above.



Scheme 1. Synthetic route used for the preparation of 5′-aryl substituted **GC-1** analogues: **GC-13**, **GC-14**, **GC-19**, **GC-20**, **GC-21** and **GC-22**.



Scheme 2. Synthesis of **GC-15** and **GC-16**.



Scheme 3. Synthesis of **GC-17** and **GC-18**.

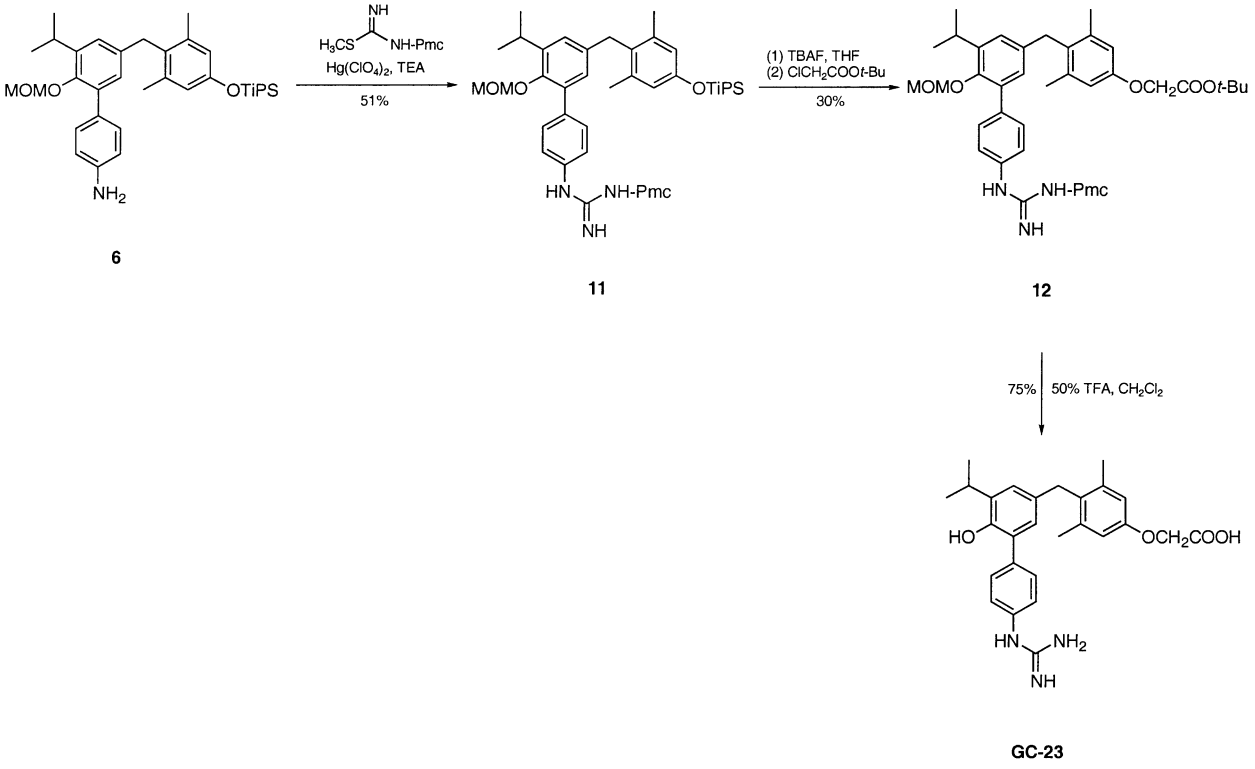
Analogues **GC-17** and **GC-18** were prepared as outlined in Scheme 3. *N*-alkylation of **6** with 1-bromo-2-butyne afforded the acetylene derivative **9**, which was elaborated to the final compound **GC-17** as described above. Nitro group reduction of **5b** gave aniline **10**, which was elaborated to **GC-18** as described above.

The guanidine derivative **GC-23** was prepared as outlined in Scheme 4. Guanylation of **6** with Pmc-*S*-methylisothiourea in the presence of triethylamine and $Hg(ClO_4)_2$ in refluxing THF led to the corresponding Pmc-protected guanidine **11**.[25] De-silylation of **11** followed by alkylation with *tert*-butylchloroacetate gave compound **12**, which upon acidic hydrolysis provided **GC-23**.

Receptor binding and transactivation properties

The human TRα and TRβ binding affinities for the 5′-aryl substituted **GC-1** analogues **GC-13**–**GC-23** are shown in Table 1. As a comparison, the parent compound **GC-1** was also tested. Binding affinity was measured with an in vitro radioligand-displacement assay, where recombinant human $TR\alpha_1$ and $TR\beta_1$ were analyzed independently using a fixed concentration of $[^{125}I]T_3$ in the presence of a range of concentrations of each analogue. In general, substitution at the 5′-position results in a decreased binding affinity for both TRα and TRβ compared to the parent compound **GC-1**. The parent compound has a K_D of 0.10 nM for TRβ whereas all of the 5′-substituted compounds bind TRβ with at least a two orders of magnitude reduced affinity. Although binding is impaired, the TRβ selectivity of **GC-1** is retained by most of the 5′-substituted compounds. This result is consistent with structural data,[12] which suggests the molecular determinant of selectivity is located on the oxyacetic acid side chain at the opposite end of the thyronine core structure.

To examine the transcriptional transactivation properties of the compounds, HeLa cells were co-transfected with an expression plasmid for $TR\beta_1$ or $TR\alpha_1$, together with a TRE-driven luciferase reporter plasmid, and luciferase expression was determined at different concentrations of added ligand. All of the compounds tested, except **GC-14**, were found to be full or nearly full agonists of $TR\beta_1$ activation and the EC_{50} values for each compound are shown in Table 1. Two of the compounds that had reasonably high affinity for $TR\alpha_1$ (**GC-13**, **GC-17**) were found to be full agonists of $TR\alpha_1$, but retained activation selectivity for $TR\beta_1$ (Table 1). The majority of the compounds were not tested in the $TR\alpha_1$ activation assay because their relatively poor affinity and potency for $TR\alpha_1$ made it difficult to obtain complete dose–response curves. The compound **GC-14** displayed weak partial agonism of reporter activation with both $TR\beta_1$ and $TR\alpha_1$; the maximum activation by **GC-14** was approximately 20 and 35% compared to **GC-1** for $TR\beta_1$ and $TR\alpha_1$, respectively (Table 1). We next tested whether **GC-14** could competitively block $TR\beta_1$ activation by T_3 in a dose-dependent manner and found that **GC-14** did indeed antagonize the activation of 1 nM

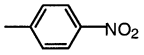
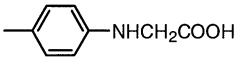
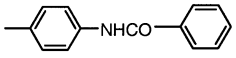
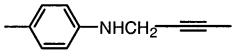
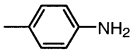
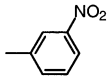
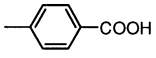
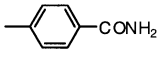
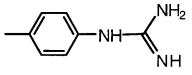


Scheme 4. Synthesis of **GC-23**.

T_3 down to the maximum level of activation observed with **GC-14** alone (Table 1 and Fig. 2). Under these conditions, the IC_{50} value of this antagonism by **GC-14** was 700 nM (Table 1). A similar competition experiment was performed with **GC-14** and TRα_1, and the IC_{50} value of T_3 antagonism was 5000 nM (Table 1), further demonstrating the TRβ selectivity of the compound.

The structure–activity relationship (SAR) data provided in Table 1 suggests that the partial agonism/antagonism of **GC-14** is not related to the size of the para-substituent appended to the 5-phenyl. For example, **GC-16** and **GC-17** bear significantly larger phenyl substituents than the nitro of **GC-14** and they are both agonists with tighter binding affinity to TRβ than **GC-14**. Moreover, the data indicate that the para position of the nitro group in **GC-14** is critical; the meta and ortho analogues (**GC19** and **GC-20**) are agonists and the ortho analogue **GC-20** is one of the more potent agonists within this series. The data further indicate that for this series of

Table 1. 5′-Aryl substituted GC-1 analogues TRβ_1 and TRα_1 binding affinities and transcriptional activity

	R	KD±SE (nM)[a]		% TRβ_1 activation[b]	TRβ_1 EC_{50} (IC_{50})[d] (nM)	% TRα_1 activation[f]	TRα_1 EC_{50} (IC_{50}) (nM)
		hTRβ_1	hTRα_1				
GC-1	H	0.1±0.02	1.8±0.2	100	7	100	45
GC-13		30±13	170±10	99	240	99	900
GC-14		35±12	200±60	18	680[e]	35	5000[e]
GC-15		23±3	140±15	72	750	n.d.	n.d.
GC-16		45±20	140±15	86	900	n.d.	n.d.
GC-17		12±8	42±8	79	650	100	4000
GC-18		21±5	150±80	100	550	n.d.	n.d.
GC-19		230±30	680±380	100	1120	n.d.	n.d.
GC-20		22±10	170±120	100	660	n.d.	n.d.
GC-21		16±2	120±10	100	630	n.d.	n.d.
GC-22		38±6	200±10	43[c]	550	n.d.	n.d.
GC-23		320±20	2300±300	57[c]	4950	n.d.	n.d.

[a]The K_D and standard error (SE) values were calculated by fitting the competition data to the equations of Swillens[27] and using the Graph-Pad Prism computer program.
[b]HeLa cells were co-transfected with a TRβ_1 expression vector and a TRE-luciferase reporter plasmid. Luciferase activity is expressed as a percent of the TRβ_1 response with 10^{-9} M T_3.
[c]Compound **GC-22** and **GC-23** tested in competition experiments with T_3 (10^{-9}M) were not able to antagonize T_3 activation in a dose-dependent manner.
[d]The EC_{50} value is the concentration of ligand required for half-maximun activation, whereas the IC_{50} value is the concentration of ligand required for half-maximun inhibition. EC_{50} values of transcriptional activation were determined graphically from dose response curves. IC_{50} values were determined graphically from dose-response curves obtained in competition experiments. In these experiments a fixed concentration of T_3 (10^{-9} M) was added to the cells along with a range of concentrations of the selected compound. See experimental for more details.
[e]These are IC_{50} values on TRβ_1 and TRα_1 respectively.
[f]HeLa cells were co-transfected with a TRα_1 expression vector and a TRE-luciferase reporter plasmid. Luciferase activity is expressed as a percent of the TRα_1 response with 10^{-9} M T_3.

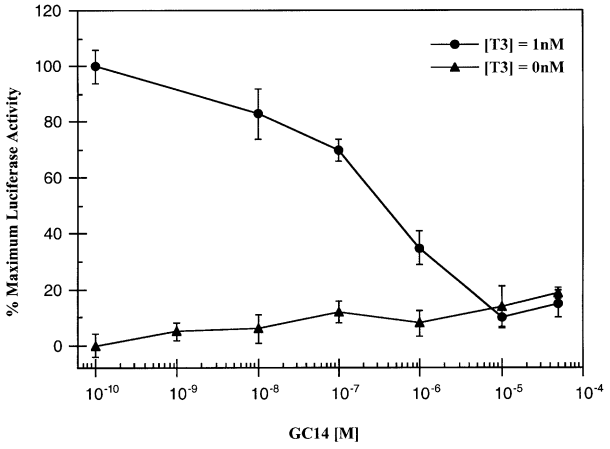


Figure 2. Transcription activation profile for **GC-14** with TRβ. Human uterine cervix cancer (HeLa) cells were trasfected with 0.5 mg of the TRβ expression vector and 10 mg of the DR4-Luciferase reporter gene and were treated with indicated concentrations of **GC-14** alone (triangle) or **GC-14** in the presence of 10^{-9} M T_3 (circle) for 24 h. Values are the mean ± SD for three separate experiments, and are expressed as a percent of the TRβ response with 10-9 M T3 , which is set at 100%.

compounds, the electronic properties of the **GC-14** nitro group are also critical as the isosteric carboxylate (**GC-21**), carboxyamide (**GC-22**), and guanidinium (**GC-23**) analogues all function as agonists. The SAR data presently in hand suggest a very restrictive set of structural criteria for antagonism within this series mandating an absolute requirement for a nitro group in a particular position on the 5′-phenyl ring.

Conclusions

We have prepared a new series of 5′-substituted thyroid hormone analogues using the TRβ-selective thyromimetic **GC-1** as the core element. These compounds were designed to not completely fit into the ligand binding cavity of the TR, and therefore to perturb potentially agonist-induced structure of the TR. All of the compounds within the series show reduced binding affinity for TRs compared to **GC-1**, yet like **GC-1**, they bind TRβ in preference to TRα. Surprisingly, all of the compounds in the series function as T_3 agonists in a TRE-driven reporter gene assay with the exception of one compound, **GC-14**. **GC-14** shows weak partial agonist activity by itself, and in competition experiments with T_3, it is able to antagonize T_3 activation of $TR\alpha_1$ and $TR\beta_1$ in a dose-dependent manner. **GC-14** antagonizes the T_3 response more potently with $TR\beta_1$ than with $TR\alpha_1$ indicating that the TRβ selectivity of the parent compound **GC-1** is retained in **GC-14**. The available SAR data indicates that the antagonistic property of **GC-14** is dictated by the nitro group attached to the 5′-phenyl extension, and that the size, position, and electronic properties of this nitro group are all essential for the observed activity.

Experimental

General

Proton and carbon-13 nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on either General Electric QE 300 (300 MHz) or Varian Unity 400 MHz spectrometers, using $CDCl_3$ or MeOD as solvent. Chemical shifts were reported as parts per million downfield from an internal tetramethylsilane standard ($\delta = 0.0$ for 1H) or from solvent references. NMR coupling constants are reported in Hertz. ^{13}C NMR were determined using ^{13}C pulse sequence parameters. High-resolution mass spectrometry was performed by the National Bio-Organic, Biomedical Mass Spectrometry Resource at UCSF. Flash chromatography on crude products was performed using 230–400 mesh silica gel (Aldrich Chemical Co.). Purity of compounds was determined by TLC using commercial silica gel plates (Alltech, AlugramR Sil G/UV 254) and by ^{1}H NMR and HRMS.

Glassware was oven- or flame-dried prior to use. Methylene Chloride (anhydrous), tetrahydrofuran (anydrous) and reagents were purchased from Aldrich Chemical Co. and used without further purification. Reactions were performed under Argon inert atmosphere.

Thyroid hormone receptor ligand binding assays

Full-length $hTR\alpha_1$ and $hTR\beta_1$ were produced using the TNT coupled reticulocyte lysate system (Promega). The ligand binding domains of $hTR\alpha_1$ and $hTR\beta_1$ were expressed in *Escherichia coli* and purified to greater than 95% homogeneity as described previously.[26] Competition ligand binding affinities were determined using 1nM [^{125}I]T_3 in gel filtration binding assays as described.[26] The K_D and standard error (SE) values were calculated by fitting the competition data to the equations of Swillens[27] and using the Graph-Pad Prism computer program (GraphPad Software, Inc.).

Transcriptional activation assay

Human uterine cervix cancer (HeLa) cells were mantained in culture and transfected as described previously.[28,29] Briefly, cells were collected and resuspended in Dulbecco's PBS (0.5 mL/transfection) containing 0.1% dextrose, 10 mg/mL bioprene, and mixed with 0.5 μg of the appropriate TR expression vector and 10 μg of the reporter plasmid. The TR expression vector contained either the full length human $TR\beta_1$ or human $TR\alpha_1$ under the control of the cytomegalovirus promoter, $CMVTR\beta_1$ and $CMVTR\alpha_1$, respectively. The reporter plasmid contained a synthetic TR response element (DR-4) containing two copies of a direct repeat spaced by four nucleotides (AGGTCA-cagg-AGGTCA) cloned immediately upstream of a minimal (−32/+45) thymidine kinase (tk) promoter linked to luciferase coding sequence. Cells (0.8×10^7) were electroporated using a Bio-Rad gene pulser at 350V and 960 microfarads, pooled in growth medium (DME H-21 with 10% charcoal-treated, hormone stripped, newborn bovine serum), and plated in 6-well dishes. Compounds

were added to the cell culture media as ethanol solutions so as to yield a final ethanol concentration of 0.1%. After incubation for 24 h at 37 °C cells were detached with 1 mL of calcium-magnesium-free PBS, 1 mM EDTA, pre-warmed at 37 °C, and transferred to 1.5 mL Eppendorf tubes. Cells were pelleted by centrifugation in a microfuge for 1 min at room temperature. The supernatants were aspirated and the pellets were lysed by addition of 120 μL of Tris–Cl 0.25 M pH 7.6, 0.1% Triton. After resuspension by vortexing for 5–10 s, the lysates were pelleted by centrifugation in a microfuge for 5 min at rt. Cellular lysates (100 μL) were then assayed for luciferase activity as previously described.[30]

Chemistry

{5′-[2,6-Dimethyl-4-(triisopropyl-silanyloxy)-benzyl]-3-isopropyl-2-methoxymethoxy-phenyl}-boronic acid (2). A solution of **1** (0.5 g, 1.06 mmol) in 5 mL of a 2:1 mixture of dry tetrahydrofuran/hexanes was treated under an inert atmosphere with 2.0 equiv of *n*-butyllithium in hexane and the mixture was stirred 2 h at rt to give a cloudy white suspension. Triisopropyl borate (0.3 mL, 1.2 mmol) was added and the mixture was stirred 1 h at room temperature. The reaction mixture was quenched by pouring into 1 N HCl aq, extracted with ethyl acetate, dried and filtered. The crude boronic acid **2** was used in subsequent Suzuki coupling reactions without further purification.

General procedure for Suzuki coupling of aryl iodines (3a–f)

A stirred mixture of the appropriate aryl iodine (1.0 mmol), $Pd_2(dba)_3.CHCl_3$ (34.7 mg, 0.03 mmol) in toluene (25 mL) under argon was successively treated with the phenyl boronic acid **2** (565.0 mg, 1.1 mmol), dissolved in a minimun volume of EtOH, and 2 M Cs_2CO_3 (1.1 mL). The resulting mixture was heated at reflux for 8 h, cooled, subjected to filtration. The filtrate was evaporated to dryness in vacuo and the residue was treated with satd NaCl solution. The resulting mixture was extracted with CH_2Cl_2, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel.

Triisopropil-[4-(5-isopropyl-6-methoxymethoxy-biphenyl-3ylmethyl)-3,5-dimethyl-phenoxy]-silane (3a). The coupling of iodobenzene with phenylboronic acid was effected using the general procedure to afford 382 mg (70%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1 (d, 18H, J = 6.9 Hz), 1.16 (d, 6H, J = 6.9 Hz), 1.23 (m, 3H), 2.20 (s, 6H), 3.24 (s, 3H), 3.39 (heptet, 1H, J = 6.9Hz), 3.95 (s, 2H), 4.49 (s, 2H), 6.59 (s, 2H), 6.78 (s, 1H), 6.99 (s, 1H), 7.22 (m, 1H), 7.32 (m, 2H), 7.48 (d, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.2, 152.6, 138.4, 137.3, 136.6, 135.5, 135.3, 129.0, 127.4, 126.1, 125.5, 122.4, 118.3, 101.3, 50.2, 28.9, 24.7, 22.4, 15.3, 14.8, 12.2.

Triisopropil-[4-(5-isopropyl-6-methoxymethoxy-4-nitro-biphenyl-3ylmethyl)-3,5-dimethyl-phenoxy]-silane (3b). The coupling of 4-iodonitrobenzene with phenylboronic acid was effected using the general procedure to afford 370 mg (68%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1 (d, 18H, J = 6.9 Hz), 1.16 (d, 6H, J = 6.9 Hz), 1.23 (m, 3H), 2.20 (s, 6H), 3.18 (s, 3H), 3.37 (heptet, 1H, J = 6.9 Hz), 3.96 (s, 2H), 4.52 (s, 2H), 6.61 (s, 2H), 6.71 (s, 1H), 6.98 (s, 1H), 7.63 (d, 2H, J = 8.7 Hz), 8.22 (d, 2H, J = 8.7 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.2, 152.6,147.3, 142.7, 138.4, 137.3, 135.5, 135.3, 128.3, 126.1, 125.5, 124.1, 122.4, 118.3, 101.3, 50.2, 28.9, 24.7, 22.4, 15.3, 14.8, 12.1.

Triisopropil-[4-(5-isopropyl-6-methoxymethoxy-3′-nitro-biphenyl-3ylmethyl)-3,5-dimethyl-phenoxy]-silane (3c). The coupling of 3-iodonitrobenzene with phenylboronic acid was effected using the general procedure to afford 380 mg (65%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1 (d, 18H, J = 6.9 Hz), 1.18 (d, 6H, J = 6.9 Hz), 1.24 (m, 3H), 2.19 (s, 6H), 3.18 (s, 3H), 3.36 (heptet, 1H, J = 6.9 Hz), 3.97 (s, 2H), 4.53 (s, 2H), 6.61 (s, 2H), 6.74 (s, 1H), 6.94 (s, 1H), 7.52 (t, 1H, J = 8.0 Hz), 7.77 (d, 1H, J = 8.0 Hz), 8.15 (d, 1H, J = 8.0), 8.37 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.2, 152.6,148.9, 138.4, 137.5, 137.3, 135.5, 135.3, 133.5, 129.9, 126.1, 125.5, 122.5, 122.4, 118.3, 101.3, 50.2, 28.9, 24.7, 22.4, 15.3, 14.8, 12.2.

Triisopropil-[4-(5-isopropyl-6-methoxymethoxy-2′-nitro-biphenyl-3ylmethyl)-3,5-dimethyl-phenoxy]-silane (3d). The coupling of 2-iodonitrobenzene with phenylboronic acid was effected using the general procedure to afford 435 mg (75%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1 (d, 18H, J = 6.9 Hz), 1.16 (d, 6H, J = 6.9 Hz), 1.23 (m, 3H), 2.18 (s, 6H), 3.0 8 (s, 3H), 3.27 (heptet, 1H, J = 6.9 Hz), 3.95 (s, 2H), 4.51 (s, 2H), 6.60 (s, 2H), 6.63 (s, 1H), 6.97 (s, 1H), 7.40 (d, 1H, J = 7.6 Hz), 7.43 (m, 1H), 7.56 (m, 1H), 7.90 (d, 1H, J = 8.0); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.2, 152.6, 147.3, 138.4, 137.3, 135.5, 135.3, 135.1, 131.7, 128.3, 126.1, 124.1, 122.4, 118.3, 101.3, 50.2, 28.9, 24.7, 22.4, 15.3, 14.8, 12.2.

5′-[2,6-Dimethyl-4-(triisopropyl-silanyloxy)-benzyl]-3′-isopropyl-2′-methoxymethoxy-biphenyl-4-carboxylic acid (3e). The coupling of 4-iodobenzoic acid with phenylboronic acid was effected using the general procedure to afford 390 mg (71%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1 (d, 18H, J = 6.9 Hz), 1.16 (d, 6H, J = 6.9 Hz), 1.23 (m, 3H), 2.21 (s, 6H), 3.19 (s, 3H), 3.39 (heptet, 1H, J = 6.9 Hz), 3.97 (s, 2H), 4.53 (s, 2H), 6.61 (s, 2H), 6.76 (s, 1H), 6.94 (s, 1H), 7.60 (d, 2H, J = 8.0 Hz), 8.12 (d, 2H, J = 8.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.0, 156.2, 152.6, 141.8, 138.4, 137.3, 135.5, 135.3, 130.6, 129.5, 127.3, 126.1, 122.4, 118.3, 101.3, 50.2, 28.9, 24.7, 22.4, 15.3, 14.8, 12.0.

5′-(2,6-Dimethyl-4-(triisopropyl-silanyloxy)-benzyl)-3′-isopropyl-2′-methoxymethoxy-biphenyl-4-carboxylic acid amide (3f). The coupling of 4-bromobenzamide with the phenyl boronic acid **6** was effected using the general procedure with 3.0 mol% $Pd_2(dba)_3.CHCl_3$ and 2 M Cs_2CO_3 to afford 200 mg (70%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1 (d,

18H, $J=6.9$ Hz), 1.18 (d, 6H, $J=6.9$ Hz), 1.25 (m, 3H), 2.18 (s, 6H), 3.20 (s, 3H), 3.39 (heptet, 1H, $J=6.9$ Hz), 3.95 (s, 2H), 4.50 (s, 2H), 6.60 (s, 2H), 6.74 (s, 1H), 6.92 (s, 1H), 7.55 (d, 2H, $J=8.0$ Hz), 7.81 (d, 2H, $J=8.0$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.7, 156.2, 152.6, 140.8, 138.4, 137.3, 135.5, 135.3, 132.6, 127.8, 127.5, 126.1, 122.4, 118.3, 101.3, 50.2, 28.9, 24.7, 22.4, 15.3, 14.8, 12.2.

4-[5-Isopropyl-6-methoxymethoxy-biphenyl-3-ylmethyl)-3,5-dimethyl-phenol (4a). Compound **3a** (137 mg, 0.25 mmol) and Bu_4NF (0.315 mL, 1.0 M in THF) were combined in a round bottom flask. Deprotection was determined to be nearly instantaneous by TLC. The reaction mixture was diluted with ethyl acetate (25 mL) and washed with water (2×25 mL) and brine (30 mL), dried, and concentrated. The crude product was purified by flash column chromatography (80:20 hexane/ethyl acetate) to yield **4a** (90.0 mg, 0.24 mmol, 95%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, 6H, $J=6.9$ Hz), 2.20 (s, 6H), 3.25 (s, 3H), 3.44 (heptet, 1H, $J=6.9$ Hz), 3.95 (s, 2H), 4.50 (s, 2H), 6.53 (s, 2H), 6.75 (s, 1H), 6.94 (s, 1H), 7.28 (m, 1H), 7.37 (m, 2H), 7.48 (d, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.2, 154.6, 138.9, 137.0, 136.6, 135.5, 135.3, 129.0, 127.4, 126.1, 125.5, 122.4, 113.9, 101.3, 50.2, 28.9, 24.7, 22.4, 15.3.

4-[5-Isopropyl-6-methoxymethoxy-4′-nitro-biphenyl-3-ylmethyl)-3,5-dimethyl-phenol (4b). Compound **3b** (150 mg, 0.25 mmol) and Bu_4NF (0.315 mL, 1.0 M in THF) were combined in a round bottom flask. Deprotection was determined to be nearly instantaneous by TLC. The reaction mixture was diluted with ethyl acetate (25 mL) and washed with water (2×25 mL) and brine (30 mL), dried, and concentrated. The crude product was purified by flash column chromatography (80:20 hexane/ethyl acetate) to yield **4b** (100.0 mg, 0.23 mmol, 95%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, 6H, $J=6.9$ Hz), 2.20 (s, 6H), 3.19 (s, 3H), 3.37 (heptet, 1H, $J=6.9$ Hz), 3.96 (s, 2H), 4.53 (s, 2H), 6.55 (s, 2H), 6.70 (s, 1H), 7.03 (s, 1H), 7.63 (d, 2H, $J=8.7$ Hz), 8.22 (d, 2H, $J=8.7$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.2, 154.6, 147.3, 142.7, 138.9, 137.0, 135.5, 135.3, 128.3, 126.1, 125.5, 124.1, 122.4, 113.9, 101.3, 50.2, 28.9, 24.7, 22.4, 15.3.

4-[5-Isopropyl-6-methoxymethoxy-3′-nitro-biphenyl-3-ylmethyl)-3,5-dimethyl-phenol (4c). Compound **3c** (150 mg, 0.25 mmol) and Bu_4NF (0.315 mL, 1.0 M in THF) were combined in a round bottom flask. Deprotection was determined to be nearly instantaneous by TLC. The reaction mixture was diluted with ethyl acetate (25 mL) and washed with water (2×25 mL) and brine (30 mL), dried, and concentrated. The crude product was purified by flash column chromatography (80:20 hexane/ethyl acetate) to yield **4c** (100.0 mg, 0.22 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, 6H, $J=6.9$ Hz), 2.21 (s, 6H), 3.16 (s, 3H), 3.38 (heptet, 1H, $J=6.9$ Hz), 3.97 (s, 2H), 4.53 (s, 2H), 6.56 (s, 2H), 6.73 (s, 1H), 6.99 (s, 1H), 7.54 (t, 1H, $J=8.0$ Hz), 7.78 (d, 1H, $J=7.6$ Hz), 8.15 (d, 1H, $J=8.0$), 8.36 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.2, 154.6, 148.9, 138.9, 137.5, 137.0, 135.5, 135.3, 133.5, 129.9, 126.1, 125.5, 122.5, 122.4, 113.9, 101.3, 50.2, 28.9, 24.7, 22.4, 15.3.

4-[5-Isopropyl-6-methoxymethoxy-2′-nitro-biphenyl-3-ylmethyl)-3,5-dimethyl-phenol (4d). Compound **3d** (150 mg, 0.25 mmol) and Bu_4NF (0.315 mL, 1.0 M in THF) were combined in a round bottom flask. Deprotection was determined to be nearly instantaneous by TLC. The reaction mixture was diluted with ethyl acetate (25 mL) and washed with water (2×25 mL) and brine (30 mL), dried, and concentrated. The crude product was purified by flash column chromatography (80:20 hexane/ethyl acetate) to yield **4d** (95.0 mg, 0.20 mmol, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, 6H, $J=6.9$ Hz), 2.20 (s, 6H), 3.11 (s, 3H), 3.32 (heptet, 1H, $J=6.9$ Hz), 3.95 (s, 2H), 4.52 (s, 2H), 6.56 (s, 2H), 6.63 (s, 1H), 6.97 (s, 1H), 7.41 (d, 1H, $J=7.6$ Hz), 7.45 (m, 1H), 7.56 (m, 1H), 7.92 (d, 1H, $J=8.0$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.2, 154.6, 147.3, 138.9, 137.0, 135.5, 135.3, 135.1, 131.7, 128.3, 126.1, 124.1, 122.4, 113.9, 101.3, 50.2, 28.9, 24.7, 22.4, 15.3.

5′ -(4-Hydroxy-2,6-dimethyl-benzyl)-3′-isopropyl-2′-methoxymethoxy-biphenyl-4-carboxylic acid (4e). Compound **3e** (148 mg, 0.25 mmol) and Bu_4NF (0.315 mL, 1.0 M in THF) were combined in a round bottom flask. Deprotection was determined to be nearly instantaneous by TLC. The reaction mixture was diluted with ethyl acetate (25 mL) and washed with water (2×25 mL) and brine (30 mL), dried, and concentrated. The crude product was purified by flash column chromatography (80:20 hexane/ethyl acetate) to yield **4e** (96.0 mg, 0.22 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, 6H, $J=6.9$ Hz), 2.19 (s, 6H), 3.18 (s, 3H), 3.40 (heptet, 1H, $J=6.9$ Hz), 3.95 (s, 2H), 4.51 (s, 2H), 6.56 (s, 2H), 6.71 (s, 1H), 6.99 (s, 1H), 7.54 (d, 2H, $J=8.0$ Hz), 8.09 (d, 2H, $J=8.0$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.0, 156.2, 154.6, 141.8, 138.9, 137.0, 135.5, 135.3, 130.6, 129.5, 127.3, 126.1, 122.4, 113.9, 101.3, 50.2, 28.9, 24.7, 22.4, 15.3.

5′-(4-Hydroxy-2,6-dimethyl-benzyl)-3′-isopropyl-2′-methoxymethoxy-biphenyl-4-carboxylic acid amide (4f). Compound **3f** (150 mg, 0.25 mmol) and Bu_4NF (0.315 mL, 1.0 M in THF) were combined in a round bottom flask. Deprotection was determined to be nearly instantaneous by TLC. The reaction mixture was diluted with ethyl acetate (25 mL) and washed with water (2×25 mL) and brine (30 mL), dried, and concentrated. The crude product was purified by flash column chromatography (80:20 hexane/ethyl acetate) to yield **4f** (98.0 mg, 0.22 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, 6H, $J=6.9$ Hz), 2.19 (s, 6H), 3.20 (s, 3H), 3.40 (heptet, 1H, $J=6.9$ Hz), 3.93 (s, 2H), 4.50 (s, 2H), 6.56 (s, 2H), 6.70 (s, 1H), 6.99 (s, 1H), 7.55 (d, 2H, $J=8.0$ Hz), 7.81 (d, 2H, $J=8.0$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.7, 156.2, 154.6, 140.8, 138.9, 137.0, 135.5, 135.3, 132.6, 127.8, 127.5, 126.1, 122.4, 113.9, 101.3, 50.2, 28.9, 24.7, 22.4, 15.3.

[4-(5-Isopropyl-6-methoxymethoxy-biphenyl-3-ylmethyl)-3,5-dimethyl-phenoxy]-acetic acid ethyl ester (5a). To cesium carbonate (334.0 mg, 1.02 mmol) and **4a** (80.0 mg, 0.20 mmol) in 5 mL of DMF was added ethylbromoacetate (0.023 mL, 0.20 mmol). The reaction mixture was stirred for 30 min at room temperature,

poured into 15 mL of cold 1 N HCl, and extracted with ethyl acetate (3 10 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 100 mg of crude, which was purified using flash column chromatography (silica gel, 90:10 hexane/ethyl acetate) to yield **5a** (88.0 mg, 0.19 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, 6H, J = 6.9 Hz), 1.29 (t, 3H, J = 7.2 Hz), 2.20 (s, 6H), 3.25 (s, 3H), 3.44 (heptet, 1H, J = 6.9 Hz), 3.95 (s, 2H), 4.27 (q, 2H, J = 7.2 Hz), 4.50 (s, 2H), 4.61 (s, 2H), 6.60 (s, 2H), 6.72 (s, 1H), 6.93 (s, 1H), 7.29 (m, 1H), 7.35 (m, 2H), 7.46 (d, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.3.6, 156.2, 138.5, 136.7, 136.6, 135.5, 135.3, 129.0, 127.4, 126.1, 125.5, 122.4, 112.3, 101.3, 75.6, 59.5, 50.2, 28.9, 24.7, 22.4, 15.3, 13.6.

[4-(5-Isopropyl-6-methoxymethoxy-4′-nitro-biphenyl-3-ylmethyl)-3,5-dimethyl-phenoxy]-acetic acid ethyl ester (5b). To cesium carbonate (334.0 mg, 1.02 mmol) and 4b (90 mg, 0.20 mmol) in 5 mL of DMF was added ethylbromoacetate (0.023 mL, 0.20 mmol). The reaction mixture was stirred for 30 min at rt, poured into 15 mL of cold 1 N HCl, and extracted with ethyl acetate (3×10 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 100 mg of crude, which was purified using flash column chromatography (silica gel, 90:10 hexane/ethyl acetate) to yield **5b** (98.0 mg, 0.19 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, 6H, J = 6.9 Hz), 1.29 (t, 3H, J = 7.2 Hz), 2.23 (s, 6H), 3.19 (s, 3H), 3.39 (heptet, 1H, J = 6.9 Hz), 3.98 (s, 2H), 4.27 (q, 2H, J = 7.2 Hz), 4.53(s, 2H), 4.61 (s, 2H), 6.64 (s, 2H), 6.67 (s, 1H), 7.02 (s, 1H), 7.63 (d, 2H, J = 8.7 Hz), 8.23 (d, 2H, J = 8.7 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.3, 156.2, 147.3, 142.7, 138.5, 136.7, 135.5, 135.3, 128.3, 126.1, 125.5, 124.1, 122.4, 112.3, 101.3, 75.6, 59.5, 50.2, 28.9, 24.7, 22.4, 15.3, 13.6.

5-Isopropyl-6-methoxymethoxy-3′-nitro-biphenyl-3-ylmethyl)-3,5-dimethyl-phenoxy]-acetic acid ethyl ester (5c). To cesium carbonate (334.0 mg, 1.02 mmol) and **4c** (90 mg, 0.20 mmol) in 5 mL of DMF was added ethylbromoacetate (0.023 mL, 0.20 mmol). The reaction mixture was stirred for 30 min at room temperature, poured into 15 mL of cold 1 N HCl, and extracted with ethyl acetate (3×10 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 100 mg of crude, which was purified using flash column chromatography (silica gel, 90:10 hexane/ethyl acetate) to yield **5c** (93.0 mg, 0.18 mmol, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, 6H, J = 6.9 Hz), 1.29 (t, 3H, J = 7.2 Hz), 2.23 (s, 6H), 3.16 (s, 3H), 3.38 (heptet, 1H, J = 6.9 Hz), 3.98 (s, 2H), 4.27 (q, 2H, J = 7.2 Hz), 4.49 (s, 2H), 4.53 (s, 2H), 6.62 (s, 2H), 6.73 (s, 1H), 6.98 (s, 1H), 7.54 (t, 1H, J = 8.0 Hz), 7.78 (d, 1H, J = 7.6 Hz), 8.14 (d, 1H, J = 8.0) 8.36 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.3, 156.2, 148.9, 138.5, 137.5, 136.7, 135.5, 135.3, 133.5, 129.9, 126.1, 125.5, 122.5, 122.4, 112.3, 101.3, 75.6, 59.5, 50.2, 28.9, 24.7, 22.4, 15.3, 13.6.

5-Isopropyl-6-methoxymethoxy-2′-nitro-biphenyl-3-ylmethyl)-3,5-dimethyl-phenoxy]-acetic acid ethyl ester (5d). To cesium carbonate (334.0 mg, 1.02 mmol) and **4d** (90 mg, 0.20 mmol) in 5 mL of DMF was added ethylbromoacetate (0.023 mL, 0.20 mmol). The reaction mixture was stirred for 30 min at room temperature, poured into 15 mL of cold 1 N HCl, and extracted with ethyl acetate (3×10 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 100 mg of crude, which was purified using flash column chromatography (silica gel, 90:10 hexane/ethyl acetate) to yield 5d (98.0 mg, 0.19 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, 6H, J = 6.9 Hz), 1.27 (t, 3H, J = 7.2 Hz), 2.20 (s, 6H), 3.08 (s, 3H), 3.29 (heptet, 1H, J = 6.9 Hz), 3.97 (s, 2H), 4.13 (q, 2H, J = 7.2 Hz), 4.52 (s, 2H), 4.59 (s, 2H), 6.57 (s, 2H), 6.60 (s, 1H), 7.01 (s, 1H), 7.41 (d, 1H, J = 7.6 Hz), 7.44 (m, 1H), 7.58 (m, 1H), 7.90 (d, 1H, J = 8.0); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.3, 156.2, 147.3, 138.5, 136.7, 135.5, 135.3, 135.1, 128.3, 126.1, 125.5, 122.4, 112.3, 101.3, 75.6, 59.5, 50.2, 28.9, 24.7, 22.4, 15.3, 13.6.

5′-(4-Ethoxycarbonylmethoxy-2,6-dimethyl-benzyl)-3′-isopropyl-2-methoxymethoxy-biphenyl-4-carboxylic acid (5e). To cesium carbonate (334.0 mg, 1.02 mmol) and **4e** (87.0 mg, 0.20 mmol) in 5 mL of DMF was added ethylbromoacetate (0.023 mL, 0.20 mmol). The reaction mixture was stirred for 30 min at rt, poured into 15 mL of cold 1 N HCl, and extracted with ethylacetate (3 10 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 100 mg of crude, which was purified using flash column chromatography (silica gel, 90:10 hexane/ethyl acetate) to yield **5e** (95.0 mg, 0.19 mmol, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, 6H, J = 6.9 Hz), 1.27 (t, 3H, J = 7.2 Hz), 2.22(s, 6H), 3.19 (s, 3H), 3.40 (heptet, 1H, J = 6.9 Hz), 3.96 (s, 2H), 4.26 (q, 2H, J = 7.2 Hz), 4.49 (s, 2H), 4.74 (s, 2H), 6.61 (s, 2H), 6.72 (s, 1H), 6.95 (s, 1H), 7.54 (d, 2H, J = 8.0 Hz), 8.08 (d, 2H, J = 8.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.0, 171.0, 159.3, 156.2, 141.8, 138.5, 136.7, 135.5, 135.3, 130.6, 129.5, 127.3, 126.1, 122.4, 112.3, 101.3, 75.6, 59.5, 50.2, 28.9, 24.7, 22.4, 15.3, 13.6.

[4-(4′-Carbamoyl-5-isopropyl-6-methoxymethoxy-biphenyl-3-ylmethyl)-3,5-dimethyl-phenoxy]-acetic acid ethyl ester (5f). To cesium carbonate (335.6 mg, 1.03 mmol) and **4f** (90 mg, 0.21 mmol) in 5 mL of DMF was added ethylbromoacetate (0.024 mL, 0.21 mmol). The reaction mixture was stirred for 30 min at room temperature, poured into 15 mL of cold 1 N HCl, and extracted with ethyl acetate (3×10 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 110 mg of crude, which was purified using flash column chromatography (silica gel, 90:10 hexane/ethyl acetate) to yield **5f** (95.0 mg, 0.19 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, 6H, J = 6.9 Hz), 1.28 (t, 3H, J = 7.2 Hz), 2.22 (s, 6H), 3.19 (s, 3H), 3.40 (heptet, 1H, J = 6.9 Hz), 3.97 (s, 2H), 4.25 (q, 2H, J = 7.2 Hz), 4.49 (s, 2H), 4.74 (s, 2H), 6.61 (s, 2H), 6.71 (s, 1H), 6.95 (s, 1H), 7.55 (d, 2H, J = 8.4 Hz), 7.82 (d, 2H, J = 8.4 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.7, 171.0, 159.3, 156.2, 140.8, 138.5, 136.7, 135.5, 135.3, 132.6, 127.8, 127.5, 126.1, 122.4, 112.3, 101.3,75.6, 59.5 50.2, 28.9, 24.7, 22.4, 15.3, 13.6.

[4-(6-Hydroxy-5-isopropyl-biphenyl-3-ylmethyl)-3,5-dimethyl-phenoxy]-acetic acid (GC-13). To the ester **5a**

(72.0 mg, 0.15 mmol) in 4 mL of a 50% (v/v) mixture of *i*-PrOH and THF was added 0.2 mL of 1 N HCl. The reaction mixture was stirred for 2 h at rt, diluted with 5 mL of water and extracted with ethyl acetate (2×25 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 60 mg of the corresponding *O*-methoxymethyl deprotected phenol, which was used directly in the following step. To the above phenol (5 0.0 mg, 0.11 mmol) in 4 mL of methanol was added 2.6 mL of 1 N NaOH. The reaction mixture was stirred for 1 h at rt, acidified with 3 mL of 2 N HCl, and extracted with ethyl acetate (2×25 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to give **GC-13** (40.0 mg, 0.099 mmol, 78%). ^{1}H NMR (300 MHz, CD_3OD) δ 1.18 (d, 6H, J=6.9 Hz), 2.22 (s, 6H), 3.32 (heptet, 1H, J=6.9 Hz), 3.92 (s, 2H), 4.37 (s, 2H), 6.57 (s, 1H), 6.65(s, 2H), 6.87 (s, 1H), 7.28 (m, 1H), 7.35 (m, 2H), 7.42 (d, 2H); ^{13}C NMR (300 MHz, CD_3OD) δ 159.3.6, 151.5, 138.5, 136.7, 136.6, 135.8, 136.9, 129.0, 127.4, 126.1, 125.5, 122.4, 112.3, 77.8, 28.9, 24.7, 22.1, 15.3. HR-MS calcd for $C_{26}H_{28}O_4$: 404.1988. Found: 404.2000.

[4-(6-Hydroxy-5-isopropyl-4′-nitro-biphenyl-3-ylmethyl)-3,5-dimethyl-phenoxy]-acetic acid (GC-14). To the ester **5b** (75.0 mg, 0.14 mmol) in 4 mL of a 50% (v/v) mixture of *i*-PrOH and THF was added 0.2 mL of 1 N HCl. The reaction mixture was stirred for 2 h at rt, diluted with 5 mL of water and extracted with ethyl acetate (2 25 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 65 mg of the corresponding *O*-methoxymethyl deprotected phenol, which was used directly in the following step. To the above phenol (5 0.0 mg, 0.10 mmol) in 4 mL of methanol was added 2.6 mL of 1 N NaOH. The reaction mixture was stirred for 1 h at rt, acidified with 3 mL of 2 N HCl, and extracted with ethyl acetate (2×25 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to give **GC-14** (33.0 mg, 0.075 mmol, 75%). ^{1}H NMR (300 MHz, CD_3OD) δ 1.19 (d, 6H, J=6.9 Hz), 2.21 (s, 6H), 3.31 (heptet, 1H, J=6.9 Hz), 3.94 (s, 2H), 4.36 (s, 2H), 6.63 (s, 1H), 6.65 (s, 2H), 6.95 (s, 1H), 7.62 (d, 2H, J=8.7 Hz), 8.21 (d, 2H, J=8.7 Hz); ^{13}C NMR (300 MHz, CD_3OD) δ 159.3, 151.5, 147.3, 142.7, 138.5, 136.9, 136.7, 135.8, 128.3, 126.5, 125.9, 124.1, 124.0, 112.3, 77.8, 28.9, 24.7, 22.1, 15.3. HR-MS calcd for $C_{26}H_{27}NO_6$: 449.1838. Found: 449.1844.

[4-(6-Hydroxy-5-isopropyl-3′-nitro-biphenyl-3-ylmethyl)-3,5-dimethyl-phenoxy]-acetic acid (GC-19). To the ester **5c** (75 mg, 0.14 mmol) in 4 mL of a 50% (v/v) mixture of *i*-PrOH and THF was added 0.2 mL of 1 N HCl. The reaction mixture was stirred for 2 h at rt, diluted with 5 mL of water and extracted with ethyl acetate (2×25 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 60 mg of the corresponding *O*-methoxymethyl deprotected phenol, which was used directly in the following step. To the above phenol (5 0.0 mg, 0.10 mmol) in 4 mL of methanol was added 2.6 mL of 1 N NaOH. The reaction mixture was stirred for 1 h at rt, acidified with 3 mL of 2 N HCl, and extracted with ethyl acetate (2 25 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to give **GC-19** (36.0 mg, 0.082 mmol, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, 6H, J=6.9 Hz), 2.25 (s, 6H), 3.18 (heptet, 1H, J=6.9 Hz), 3.96 (s, 2H), 4.65 (s, 2H), 6.62 (s, 1H), 6.65 (s, 2H), 6.95 (s, 1H), 7.59 (t, 1H, J=8.0 Hz), 7.74 (d, 1H, J=7.6 Hz), 8.19 (d, 1H, J=8.0), 8.29 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.3, 151.5, 148.9, 138.5, 137.5, 136.9, 136.7, 135.8, 133.5, 129.9, 126.5, 125.9, 122.5, 122.4, 112.3, 77.8, 28.9, 24.7, 22.1, 15.3. HR-MS calcd for $C_{26}H_{27}NO_6$: 449.1838. Found: 449.1848.

[4-(6-Hydroxy-5-isopropyl-2′-nitro-biphenyl-3-ylmethyl)-3,5-dimethyl-phenoxy]-acetic acid (GC-20). To the ester **5d** (75 mg, 0.14 mmol) in 4 mL of a 50% (v/v) mixture of *i*-PrOH and THF was added 0.2 mL of 1 N HCl. The reaction mixture was stirred for 2 h at rt, diluted with 5 mL of water and extracted with ethyl acetate (2 25 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 62 mg of the corresponding *O*-methoxymethyl deprotected phenol, which was used directly in the following step. To the above phenol (5 2.0 mg, 0.104 mmol) in 4 mL of methanol was added 2.6 mL of 1 N NaOH. The reaction mixture was stirred for 1 h at rt, acidified with 3 mL of 2 N HCl, and extracted with ethyl acetate (2×25 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to give **GC-20** (34.0 mg, 0.077 mmol, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, 6H, J=6.9 Hz), 2.23 (s, 6H), 3.11 (heptet, 1H, J=6.9 Hz), 3.94 (s, 2H), 4.65 (s, 2H), 6.49 (s, 1H), 6.63 (s, 2H), 6.95 (s, 1H), 7.36 (d, 1H, J=7.6 Hz), 7.48 (m, 1H), 7.60 (m, 1H), 7.91 (d, 1H, J=8.0); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.3, 151.5, 147.3, 138.5, 136.9, 136.7, 135.8, 135.1, 131.7, 128.3, 126.5, 125.9, 124.0, 124.1, 112.3, 77.8, 28.9, 24.7, 22.1, 15.3. HR-MS calcd for $C_{26}H_{27}NO_6$: 449.1838. Found: 449.1839.

5′-(4-Carboxymethoxy-2,6-dimethyl-benzyl)-2′-hydroxy-3′-isopropyl-biphenyl-4-carboxylic acid (GC-21). To the ester **5e** (83.0 mg, 0.16 mmol) in 5 mL of a 50% (v/v) mixture of *i*-PrOH and THF was added 0.3 mL of 1 N HCl. The reaction mixture was stirred for 2 h at rt, diluted with 7 mL of water and extracted with ethyl acetate (3×25 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 70 mg of the corresponding *O*-methoxymethyl deprotected phenol, which was used directly in the following step. To the above phenol (65.0 mg, 0.14 mmol) in 4 mL of methanol was added 2.6 mL of 1 N NaOH. The reaction mixture was stirred for 1 h at rt, acidified with 3 mL of 2 N HCl, and extracted with ethyl acetate (2×25 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to give **GC-21** (51.0 mg, 0.11 mmol, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, 6H, J=6.9 Hz), 2.23 (s, 6H), 3.20 (heptet, 1H, J=6.9 Hz), 3.96 (s, 2H), 4.69 (s, 2H), 6.63 (s, 1H), 6.76 (s, 2H), 6.99 (s, 1H), 7.53 (d, 2H, J=8.0 Hz), 8.18 (d, 2H, J=8.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.0, 172.0, 159.3, 151.5, 141.8, 138.5, 136.9, 136.7, 135.8, 130.6, 129.5, 127.3, 126.5, 124.0, 112.3, 77.8, 28.9, 24.7, 22.1, 15.3. HR-MS calcd for $C_{27}H_{28}O_6$: 448.1885. Found: 448.1889.

[4-(4′-Carbamoyl-6-hydroxy-5-isopropyl-biphenyl-3-ylmethyl)-3,5-dimethyl-phenoxy]-acetic acid (GC-22). To the ester **5f** (80.0 mg, 0.14 mmol) in 4 mL of a 50% (v/v) mixture of *i*-PrOH and THF was added 0.2 mL of 1 N HCl. The reaction mixture was stirred for 2 h at rt, diluted with 5 mL of water and extracted with ethyl acetate (2×25 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 65 mg of the corresponding *O*-methoxymethyl deprotected phenol, which was used directly in the following step. To the above phenol (53.0 mg, 0.10 mmol) in 4 mL of methanol was added 2.6 mL of 1 N NaOH. The reaction mixture was stirred for 1 h at rt, acidified with 3 mL of 2 N HCl, and extracted with ethyl acetate (2×25 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to give **GC-22** (34.0 mg, 0.075 mmol, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, 6H, J = 6.9 Hz), 2.23 (s, 6H), 3.25 (heptet, 1H, J = 6.9 Hz), 3.94 (s, 2H), 4.35 (s, 2H), 6.60 (s, 1H), 6.65 (s, 2H), 6.90 (s, 1H), 7.49 (d, 2H, J = 8.4 Hz), 7.88 (d, 2H, J = 8.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.0, 169.7, 159.3, 151.5, 140.0, 138.5, 136.9, 136.7, 135.8, 132.6, 127.8, 127.5, 126.5, 124.0, 112.3, 77.8, 28.9, 24.7, 22.1, 15.3. HR-MS calcd for $C_{27}H_{29}NO_5$: 447.2025. Found: 447.2037.

5′-[2,6-Dimethyl-4-(triisopropyl-silanyloxy)-benzyl]-3′-isopropyl-2′-methoxymethoxy-biphenyl-4-ylamine (6). To a 50 mL round-bottomed flask equipped with stirrer and reflux condenser was added: compound **3b** (150 mg, 0.25 mmol), iron power (49 mg, 0.87 mmol), glacial acetic acid (0.104 mL, 1.74 mmol), and absolute ethanol (3 mL). The mixture was stirred and refluxed for 2 h under argon and was then added to water (25 mL). The water layer was extracted with chloroform (4×25 mL). The combined organic portions were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give **6** (112 mg, 0.20 mmol, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1 (d, 18 H, J = 6.9 Hz), 1.19 (d, 6H, J = 6.9 Hz), 1.25 (m, 3H), 2.19 (s, 6H), 3.17 (s, 3H), 3.35 (heptet, 1H, J = 6.9 Hz), 3.90 (s, 2H), 4.53 (s, 2H), 6.58 (s, 2H), 6.61 (s, 1H), 6.74 (d, 2H, J = 8.4 Hz), 6.81 (s, 1H), 7.15 (d, 2H, J = 8.4 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 153.9, 149.5, 145.2, 142.0, 138.1, 137.9, 136.3, 134.5, 130.3, 129.9, 129.7, 127.5, 124.3, 119.4, 114.9, 99.2, 76.4, 57.3, 33.9, 26.4, 23.7, 20.4, 18.0, 12.7.

5′-(4-*tert*-Butoxycarbonylmethoxy-2,6-dimethyl-benzyl)-3′-isopropyl-2′-methoxymethoxy-biphenyl-4-ylamino]-acetic acid *tert*-butyl ester (7). Compound **6** (85 mg, 0.15 mmol) and Bu_4NF (0.190 mL, 1.0 M in THF) were combined in a round bottom flask. Deprotection was determined to be nearly instantaneous by TLC. The reaction mixture was diluted with ethyl acetate (25 mL) and washed with water (2×25 mL) and brine (30 mL), dried, and concentrated. The crude product was purified by flash column chromatography (80:20 hexane/ethyl acetate) to yield 52 mg, (0.12 mmol, 80%) of 4-(4′-Amino-5-isopropyl-6-methoxymethoxy-biphenyl-3 - ylmethyl)-3,5-dimethyl-phenol. To the above phenol (40 mg, 0.092 mmol) and cesium carbonate (150 mg, 0.46 mmol) in 3 mL of DMF was added *tert*-butyl-chloroacetate (27.86 mg, 0.185 mmol). The reaction mixture was stirred for 30 min at rt, poured into 15 mL of cold 1 N HCl, and extracted with ethyl acetate (3×10 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 50 mg of crude, which was purified using flash column chromatography (silica gel, 90:20 hexane/ethyl acetate) to yield **7** (45 mg, 0.075 mmol 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, 6H, J = 6.9 Hz), 1.41 (s, 9H), 1.48 (s, 9H), 2.22 (s, 6H), 3.38 (s, 3H), 3.57 (heptet, 1H, J = 6.9 Hz), 3.86 (s, 2H), 3.93 (s, 2H), 4.49 (s, 2H), 4.54 (s, 2H), 6.60 (s, 2H), 6.66 (d, 2H, J = 8.7 Hz), 6.70 (s, 1H), 6.85 (s, 1H), 7.30 (d, 2H, J = 8.7 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.3, 156.2, 142.4, 138.5, 136.7, 135.5, 135.3, 128.2, 126.1, 125.5, 125.0, 122.4, 112.8, 112.3, 101.3, 76.2, 73.2, 72.9, 55.5, 50.2, 28.9, 29.0, 24.7, 22.4, 15.3.

{4-[4′-(Carboxymethyl-amino)-6-hydroxy-5-isopropyl-biphenyl-3-ylmethyl]-3,5-dimethyl-phenoxy}-acetic acid (GC-15). To the ester **7** (40 mg, 0.06 mmol) in 2 mL of a 50% (v/v) mixture of *i*-PrOH and THF was added 0.2 mL of 1 N HCl. The reaction mixture was stirred for 2 h at rt, diluted with 3 mL of water and extracted with ethyl acetate (2×15 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 30 mg of the corresponding *O*-methoxymethyl deprotected phenol, which was used directly in the following step. To the above phenol (25 mg, 0.04 mmol) in 2 mL of methanol was added 1.3 mL of 1 N NaOH. The reaction mixture was stirred for 1 h at rt, acidified with 1.5 mL of 2 N HCl, and extracted with ethyl acetate (2×25 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to give **GC-15** (15 mg. 0.03 mmol, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, 6H, J = 6.9 Hz), 2.22 (s, 6H), 3.44 (heptet, 1H, J = 6.9 Hz), 3.92 (s, 2H), 3.98 (s, 2H), 4.60 (s, 2H), 6.65 (s, 2H), 6.68 (s, 1H), 6.84 (d, 2H, J = 8.4 Hz), 6.90 (s, 1H), 7.31 (d, 2H, J = 8.4 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.3, 151.5, 142.4, 138.5, 136.9, 136.7, 135.8, 128.2, 126.5, 125.9, 125.0, 124.0, 112.8, 112.3, 77.8, 57.1, 28.9, 24.7, 22.1, 15.3. HR-MS calcd for $C_{28}H_{31}NO_6$: 477.2151. Found: 477.2142.

1-{5′-[2,6-Dimethyl-4-(triisopropyl-silanyloxy)-benzyl]-3′-isopropyl-2′-methoxymethoxy-biphenyl-4-yl}-3-phenyl-urea (8). To the amine **6** (60 mg, 0.105 mmol) and pyridine (2.65 mg, 0.03 mmol) in 2 mL of DMF was added phenyl isocianate (14.5 mg, 0.105 mmol). The reaction mixture was stirred for 3 h at rt, poured into 5 mL of water, and extracted with ether (3×10 mL). The combined organic portions were washed with brine (20 mL), dried ($MgSO_4$), and evaporated to yield 70 mg of crude, which was purified using flash column chromatography (silica gel, 90:20 hexane/ethyl acetate) to yield **8** (55 mg, 0.079 mmol, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, 18 H, J = 6.9 Hz), 1.17 (d, 6H, J = 6.9 Hz), 1.25 (m, 3H), 2.18 (s, 6H), 3.26 (s, 3H), 3.37 (heptet, 1H, J = 6.9 Hz), 3.94 (s, 2H), 4.51 (s, 2H), 6.6 (s, 2H), 6.74 (s, 1H), 6.8 (s, 1H), 7.00 (m, 1H), 7.3–7.5 (m, 8H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.2, 152.6, 152.2, 138.4, 138.2, 137.3, 137.1, 135.5, 135.3, 128.7, 127.6, 126.1, 125.5, 124.1, 122.4, 120.9, 120.4, 118.3, 101.3, 50.2, 28.9, 24.7, 22.4, 15.3, 14.8, 2.2.

{4-[6-Hydroxy-5-isopropyl-4′-(3-phenyl-ureido)-biphenyl-3-ylmethyl]-3,5-dimethyl-phenoxy}-acetic acid (GC-16). The above *N*,*N*-diphenylurea analogue **8** (50 mg, 0.072 mmol) was converted by the procedure described in the synthesis of **GC-14**, starting from compound **3b**, to give **GC-16** (24 mg, 0.045 mmol, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, 6H, J = 6.9 Hz), 2.21 (s, 6H), 3.30 (heptet, 1H, J = 6.9 Hz), 3.92 (s, 2H), 4.36 (s, 2H), 6.56 (s, 1H), 6.65 (s, 2H), 6.85 (s, 1H), 7.01 (m, 1H), 7.27–7.32 (m, 4H), 7.41–7.44 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.3, 152.2, 151.5, 138.5, 138.2, 137.1, 136.7, 136.9, 135.8, 128.7, 127.6, 126.5, 125.5, 124.0, 124.1, 120.9, 120.4, 112.3, 77.8, 28.9, 24.7, 22.1, 15.3. HR-MS calcd for $C_{33}H_{34}N_2O_5$: 538.2468. Found: 538.2488.

But-2-ynyl-{5′-[2,6-dimethyl-4-(trisopropyl-silanyloxy)-benzyl]-3′-isopropyl-2′-methoxymethoxy-biphenyl-4-yl}-amine (9). To the amine **6** (70 mg, 0.12 mmol) and cesium carbonate (mg, 0.3 mmol) in 3 mL of DMF was added 1-bromo-2-butyne (0.013 mL, 0.15 mmol). The reaction mixture was stirred for 1 h at rt, poured into 10 mL of cold 1 N HCl, and extracted with ethyl acetate (3×10 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 80 mg of crude, which was purified using flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to yield **9** (55 mg, 0.09 mmol, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (d, 18H, J = 6.9 Hz), 1.18 (d, 6H, J = 6.9 Hz), 1.25 (m, 3H), 1.81 (s, 3H), 2.18 (s, 6H), 3.27 (s, 3H), 3.42 (heptet, 1H, J = 6.9 Hz), 3. 88 (s, 2H), 3.93 (s, 2H), 4.53 (s, 2H), 6.65 (d, 2H, J = 4.8 Hz), 6.74 (s, 1H), 6.81 (s, 1H), 7.30 (d, 2H, J = 4.8 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.2, 152.6, 142.4, 138.4, 137.3, 135.5, 135.3, 128.2, 126.1, 125.5, 125.0, 122.4, 118.3, 112.8, 101.3, 76.8, 50.2, 38.8, 28.9, 24.7, 22.4, 15.3, 14.8, 2.2, 1.2.

[4-(4′-But-2-ynylamino-6-hydroxy-5-isopropyl-biphenyl-3-ylmethyl)-3,5-dimethyl-phenoxy]-acetic acid (GC-17). The above amine (50 mg, 0.08 mmol) was converted by the procedure described in the synthesis of **GC-14**, starting from compound **3b**, to give **GC-17** (25 mg, 0.05 mmol, 65%).^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, 6H, J = 6.9 Hz), 1.81 (s, 3H), 2.24 (s, 6H), 3.27 (heptet, 1H, J = 6.9 Hz), 3. 89 (s, 2H), 3.92 (s, 2H), 4.63 (s, 2H), 6.55 (s, 1H), 6.62 (s, 2H), 6.72 (d, 2H, J = 4.8 Hz), 6.87 (s, 1H), 7.20 (d, 2H, J = 4.8 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.3, 151.5, 142.4, 138.5, 136.9, 136.7, 135.8, 128.2, 126.5, 125.9, 125.0, 124.0, 112.8, 112.3, 77.8, 76.8, 38.8, 28.9, 24.7, 22.1, 15.3, 1.2. HR-MS calcd for $C_{30}H_{33}NO_4$: 471.2410. Found: 471.2421.

[4-(4′-Amino-5-isopropyl-6-methxymethoxy-biphenyl-3-yl-methyl)-3,5-dimethyl-phenoxy]-acetic acid ethyl ester (10). To a 50 mL round-bottomed flask equipped with stirrer and reflux condenser was added: compound **5b** (75 mg, 0.14 mmol), iron power (27.4 mg, 0.49 mmol), glacial acetic acid (1.0 mmol), and 5 mL of absolute ethanol. The mixture was stirred and refluxed for 2 h under argon and was then added to water (25 mL). The water layer was extracted with chloroform (4×25 mL). The combined organic portions were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give **10** (55 mg, 0.11 mmol, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, 6H, J = 6.9 Hz), 1.27 (t, 3H, J = 6.8 Hz), 2.23 (s, 6H), 3.28 (s, 3H), 3.40 (heptet, 1H, J = 6.9 Hz), 3.94 (s, 2H), 4.25 (q, 2H, J = 6.8 Hz), 4.52 (s, 2H), 4.59 (s, 2H), 6.55 (s, 1H), 6.62 (s, 2H), 6.70 (d, 2H, J = 8.4 Hz), 6.85 (s, 1H), 7.21 (d, 2H, J = 8.4 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.3, 156.2, 145.6, 138.5, 136.7, 135.5, 135.3, 128.2, 126.6, 126.1, 125.5, 122.4, 115.6, 112.3, 101.3, 75.6, 59.5, 50.2, 28.9, 24.7, 22.4, 15.3.

[4-(4′-Amino-6-hydroxy-5-isopropyl-biphenyl-3-ylmethyl)-3,5-dimethyl-phenoxy]-acetic acid (GC-18). To the ester **10** (50 mg, 0.1 mmol) in 4 mL of a 50% (v/v) mixture of *i*-PrOH and THF was added 0.2 mL of 1 N HCl. The reaction mixture was stirred for 2 h at rt, diluted with 5 mL of water and extracted with ethyl acetate (2×25 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 45 mg of the corresponding *O*-methoxymethyl deprotected phenol, which was used directely in the following step. To the above phenol (40 mg, 0.09 mmol) in 4 mL of methanol was added 2.6 mL of 1 N NaOH. The reaction mixture was stirred for 1 h at rt, acidified with 3 mL of 2 N HCl, and extracted with ethyl acetate (2×25 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to give **GC-18** (31.0 mg, 0.072 mmol,72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, 6H, J = 6.9 Hz), 2.23 (s, 6H), 3.40 (heptet, 1H, J = 6.9 Hz), 3.94 (s, 2H), 4.52 (s, 2H), 6.55 (s, 1H), 6.62 (s, 2H), 6.70 (d, 2H, J = 8.4 Hz), 6.85 (s, 1H), 7.21 (d, 2H, J = 8.4 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.3, 151.5, 145.6, 138.5, 136.9, 136.7, 135.8, 128.2, 126.6, 126.3, 125.9, 124.0, 115.6, 112.3, 77.8, 28.9, 24.7, 22.1, 15.3. HR-MS calcd for $C_{26}H_{29}NO_4$: 419.2132. Found: 419.2146.

***N*-{5′-[2,6-Dimethyl-4-(triisopropyl-silanyloxy)-benzyl]-3′-isopropyl-2′-methoxy methoxy-biphenyl-4-yl}-*N*-(2,2,5,7,8-pentamethyl-chroman-6-yl)-guanidine (11).** Compound **6** (260 mg, 0.46 mmol) and Pmc-*S*-methyl-isothiourea (214 mg, 0.60 mmol) were dissolved in anhydrous THF (20 mL). TEA (0.13 mL, 0.93 mmol) and $Hg(ClO_4)_2$ (200 mg, 0.51 mmol) were added and the mixture was refluxed overnight. An additional 100 mg (0.7 equiv) of Pmc-*S*-methylisothiourea was added and refluxing continued for another 4 h. The mixture was concentrated in vacuo and the remaining residue was dissolved in ethyl acetate (75 mL), filtered through Celite, which was washed with ethyl acetate (3×50 mL). The combined filtrate was washed with H_2O, satd $NaHCO_3$, and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to yield a yellow foam. The foam was chromatographed on silica gel (3:1 to 2:1 gradient hexane/ethyl acetate) to yield the desired product (206 mg, 51%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.1 (d, 18H, J = 6.9 Hz), 1.21 (d, 6H, J = 6.9 Hz), 1.25 (m, 3H), 1.31 (s, 6H), 1.82 (t, 2H, J = 6.8 Hz), 2.13 (s, 3H), 2.18 (s, 6H), 2.62 (s, 3H), 2.64 (s, 3H), 2.65 (t, 2H, J = 6.8 Hz), 3.23 (s, 3H), 3.39 (heptet, 1H, J = 6.9 Hz), 3.95 (s, 2H), 4.51 (s, 2H), 6.60 (s, 2H), 6.65 (s, 1H), 6.94 (s, 1H), 7.21 (d, 2H, J = 8.4 Hz), 7.51 (d, 2H, J = 8.4 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.4, 153.9, 149.6, 142.4, 138.7, 138.0, 136.5, 135.7, 135.2, 134.1, 133.4, 132.8, 130.9, 129.4, 127.3, 125.7, 124.8, 124.2, 119.5, 118.0, 99.56, 73.7, 57.2, 33.9, 32.8, 26.7, 26.4, 23.7, 21.4, 20.4, 18.5, 17.9, 17.4, 12.6, 12.1.

(4-{5-Isopropyl-6-methoxymethoxy-4′-[*N*-(2,2,5,7,8-pentamethyl-chroman-6-yl)-guanidino]-biphenyl-3-ylmethyl}-3,5-dimethyl-phenoxy)-acetic acid *tert*-butyl ester (12). Compound **11** (195 mg, 0.22 mmol) and Bu_4NF (0.28 mL, 1.0 M in THF) were combined in a round bottom flask. The reaction was allowed to stir at rt for 10 min. It was then diluted with ether (25 mL) and washed with water (2×25 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated to yield orange foam. The crude product was purified by flash column chromatography (2:1 hexane/ethyl acetate) to yield 153 mg (96%) of the desired phenol product, which was used directly in the following step. To the above phenol (145.0 mg, 0.20 mmol) and cesium carbonate (335.0 mg,1.00 mmol) in 5 mL DMF, was added *tert*-butylchloroacetate (0.036 mL, 0.25 mmol). The reaction mixture was stirred for 30 min at rt, poured into 10 mL of cold 1 N HCl, and extracted with ethyl acetate (3×10 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 100 mg of crude, which was purified using flash column chromatography (silica gel, 4:1 hexane/ethyl acetate) to yield **12** (50.0 mg, 0.06 mmol, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, 6H, J=6.9 Hz), 1.31 (s, 6H), 1.48 (s, 9H), 1.81 (t, 2H, J=6.8 Hz), 2.12 (s, 3H), 2.21 (s, 6H), 2.60 (s, 3H), 2.62 (s, 3H), 2.65 (t, 2H, J=6.8 Hz), 3.22 (s, 3H), 3.39 (heptet, 1H, J=6.9 Hz), 3.95 (s, 2H), 4.48 (s, 2H), 4.50 (s, 2H), 6.61 (s, 2H), 6.64 (s, 1H), 6.95 (s, 1H), 7.25 (d, 2H, J=8.4 Hz), 7.47 (d, 2H, J=8.4 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.3, 153.9, 149.5, 142.3, 138.4, 137.6, 136.5, 135.7, 135.1, 134.8, 133.7, 132.7, 130.4, 128.7, 127.1, 125.7, 124.2, 123.7, 118.0, 114.9, 99.4, 75.6, 73.7, 59.5, 57.2, 33.9, 32.7, 26.7, 26.4, 23.7, 21.4, 20.3, 18.5, 17.5, 14.1, 13.6, 12.1.

[4-(4′-Guanidino-6-hydroxy-5-isopropyl-biphenyl-3-ylmethyl)-3,5-dimethyl-phenoxy]-acetic acid (GC-23). To the ester **12** (32.0 mg, 0.04 mmol) dissolved in CH_2Cl_2 (3 mL) was added TFA (3 mL). The reaction was stirred at rt for 1 h. The reaction mixture was then diluted with ethyl acetate (25 mL) and washed with satd $NaHCO_3$ (5×15 mL), water, and brine. The combined organic portions were dried ($MgSO_4$) and evaporated. The crude product was purified by preparative TLC (4:1:1 ethyl acetate/hexane/MeOH) to yield the desired product **GC-23** (20.0 mg, 0.03 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, 6H, J=6.9 Hz), 2.20 (s, 6H), 2.60 (s, 3H), 3.22 (s, 3H), 3.33 (heptet, 1H, J=6.9 Hz), 3.93 (s, 2H), 4.40 (s, 2H), 6.44 (s, 1H), 6.62 (s, 2H), 7.01 (s, 1H), 7.22 (d, 2H, J=8.0 Hz), 7.44 (d, 2H, J=8.0 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 157.3, 151.5, 145.6, 139.8, 138.6, 137.1, 133.7, 131.7, 130.4, 128.9, 126.1, 124.2, 114.8, 99.4, 77.6, 28.9, 24.7, 22.1, 15.6. HR-MS calcd for $C_{27}H_{31}N_3O_4$: 461.2315. Found: 461. 2333.

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