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Small Molecule Inhibitors of Retinoic Acid 4-Hydroxylase (CYP26): Synthesis and Biological Evaluation of Imidazole Methyl 3-(4-(aryl-2-ylamino)phenyl)propanoates

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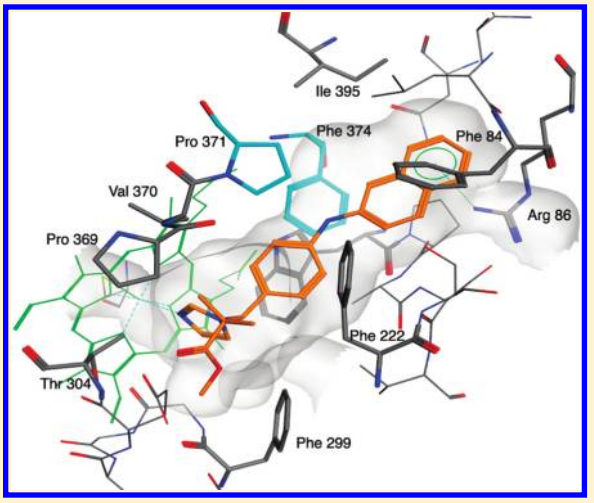
Supporting Information

ABSTRACT: The synthesis and potent inhibitory activity of novel imidazole methyl 3-(4-(aryl-2-ylamino)phenyl)propanoates in a MCF-7 CYP26A1 microsomal assay is described. The induction of CYP26A1 mRNA was used to evaluate the ability of the compounds to enhance the biological effects of all-*trans* retinoic acid (ATRA) in a retinoid-responsive neuroblastoma cell line. The most promising inhibitor, 3-imidazol-1-yl-2-methyl-3-[4-(naphthalen-2-ylamino)-phenyl]-propionic acid methyl ester (**20**), with an IC_{50} of 3 nM (compared with liarozole IC_{50} of 540 nM and R116010 IC_{50} of 10 nM) was further evaluated for CYP selectivity using a panel of CYP enzymes, mutagenicity (Ames screen), and hepatic stability.



INTRODUCTION

Retinoic acid (RA), the main biologically active derivative of vitamin A or retinol, regulates cell growth and differentiation. As a key signaling molecule, its intracellular concentrations are regulated by negative feedback controls tightly coupled to requirements for signaling in relation to cell differentiation and morphogenesis. RA exists in several isomeric forms, all-*trans* retinoic acid (ATRA), 13-*cis*-retinoic acid (13cisRA), and to a lesser extent 9-*cis*-retinoic acid (9cisRA). The endogenous metabolism of ATRA occurs primarily via oxidation,[1,2] with C-4 hydroxylation of the cyclohexenyl ring leading to formation of 4-hydroxy-ATRA, the most prominent metabolite. A number of cytochrome P450 enzymes, primarily CYPs 2C8, 3A4 and 2C9, can perform this oxidation but their contribution to RA metabolism may be relatively minor due to their high K_m values. The main route of RA catabolism, likely to represent the main negative feedback control of intracellular RA concentrations, is via a family of RA-inducible P450s, P450RAI or CYP26. The induction of CYP26 has been reported in a wide range of cells and tissues after RA treatment and RA-treated cells transfected with full-length CYP26 accumulate polar metabolites at an increased rate.[3−7]

The CYP26 family consists of CYP26A1, CYP26B1, and CYP26C1 for which ATRA is the preferred substrate leading to 4-hydroxylation. CYP26C1 can also recognize and metabolize 9cisRA.[6−8] While the induction of CYP26 in response to RA represents an important negative feedback loop controlling ATRA concentrations and limiting biological action within cells, this also has the potential to reduce the therapeutic efficacy of ATRA. Furthermore, ATRA deficiency is associated with diseases such as acne, psoriasis and ichthyosis, and with the progression of some cancers. Clearly, developing strategies to block both endogenous and pharmacologically induced ATRA metabolism and limit negative feedback control could have a substantial clinical impact. Knockdown of CYP26 expression using silencing RNA *in vitro* inhibits ATRA metabolism, emphasizing the role played by CYP26[9] and the potential for the development of RA metabolism blocking agents (RAMBAs) specifically targeting CYP26 for clinical use in cancer and other diseases.

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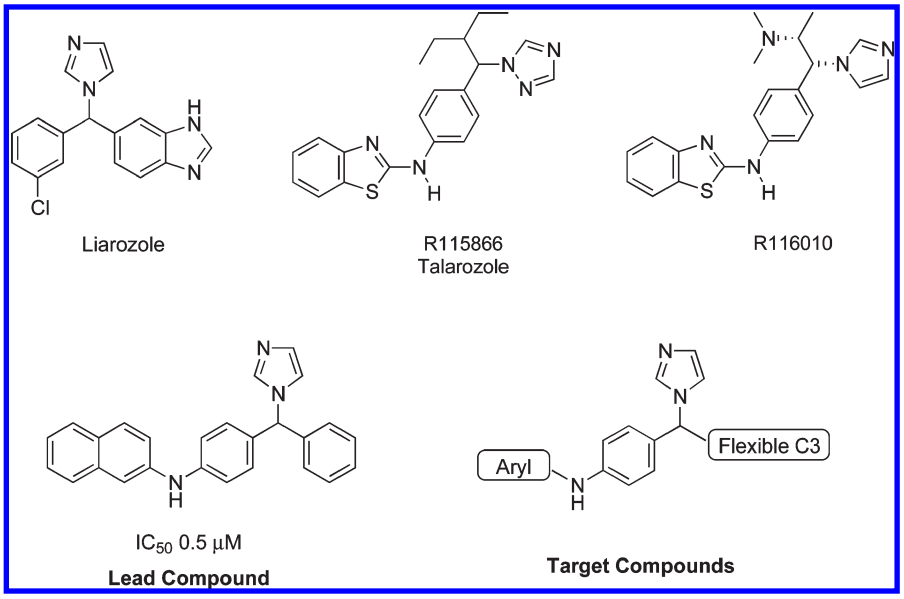

Figure 1. Retinoic acid metabolism blocking agents (RAMBAs) and target compounds.

A directly measurable consequence of RAMBA administration is a rise in plasma ATRA concentration, which is commonly used as a measure of the *in vivo* effectiveness of RAMBAs.[10] The most promising RAMBA described to date is the Janssen imidazole, liarozole (Figure 1),[11] which has been evaluated clinically in prostate cancer. While clinical results were initially promising, liarozole in this context has been discontinued owing to adverse side effects, which have been attributed to a lack of CYP isoform specificity.[12,13] Second generation Janssen compounds, the benzothiazolamines R115866 (talarozole)[14] and R116010[15] (Figure 1), are potent and selective inhibitors of retinoic acid metabolism. Talarozole increases endogenous tissue RA levels in rats after a single oral dose,[15] and recent data indicate that talarozole is beneficial in the treatment of acne and psoriasis,[16,17] while R116010 inhibits ATRA metabolism in neuroblastoma both *in vitro* and *in vivo*.[3,9]

We have recently developed a series of novel 4-[(imidazol-1-yl and triazol-1-yl)(phenyl)methyl]arylamines, with the most potent CYP26 inhibitor being a naphthyl derivative with an IC_{50} of 0.5 μM (Figure 1).[18] The research presented here describes the further development of this lead inhibitor, investigating the effect of substituting the phenyl ring with a flexible C3 chain combined with the biaryl groups (Figure 1) on biological activity.

RESULTS

Chemistry. Methyl 3-hydroxy-2,2-dimethyl-3-(4-nitrophenyl)-propanoate (**3**) was prepared by the Mukaiyama aldol condensation of 4-nitrobenzaldehyde (**1**) and trimethylsilyl ketene acetal (**2**) as described by Hagiwara et al.[19] Catalytic hydrogenation of **3** gave the amine (**4**) in good yield as the key intermediate for the synthesis of the aryl derivatives (Scheme 1).

The N-arylation using the Suzuki reaction followed described methodology[20,21] employing a stoichiometric amount of copper and a tertiary amine base, pyridine in this reaction series. By this method, reaction with the appropriate aryl boronic acid gave the *N*-aryl products (**5**−**11**) in good yields. The coupled products were confirmed by the presence of an NH singlet peak at approximately δ_H 5.59 in ^{1}H NMR (Scheme 1).

The isothiocyanate (**12**) was obtained by reaction of amine (**4**) with thiophosgene in a mixture of dichloromethane, ice, and water, overnight at 0 °C, then the thiophosgene residue and the hydrochloric acid formed during the reaction were removed by washing the organic layer thoroughly with water and sodium bicarbonate. The product was obtained in high yield and was pure enough for use in the next step.

Cyclization of the isocyanate (**12**) to form the benzoxazole (**13**) and benzothiazole (**14**) was achieved by reaction with 2-aminophenol and 2-aminothiophenol, in the presence of mercury oxide and catalytic sulfur (Scheme 1).[22] Introduction of the imidazole to give the required products **15**−**21** and **23** and **24** involved reaction with carbonyldiimidazole (CDI) and imidazole following described methodology,[18,23] with subsequent purification by column chromatography (Scheme 1). The 6-hydroxy-2-naphthyl product (**22**) was obtained by demethylation of the corresponding 6-methoxy-2-naphthyl imidazole compound (**21**) (Scheme 1)

Methyl 3-(4-aminophenyl)-3-hydroxy-2-methylpropanoate (**25**) was prepared by reduction of methyl 2-(hydroxy(4-nitrophenyl)methyl)acrylate as a mixture of *anti* and *syn* diastereoisomers according to the literature procedure.[24] N-Arylation using the Suzuki reaction with either phenyl or 2-naphthyl boronic acid, as previously described, gave the *N*-phenyl (**26** and **27**) and *N*-naphthyl products (**28** and **29**) in good yields. Separation of the diastereoisomers was achieved by flash column chromatography with the *anti* and *syn* forms obtained in a ratio of 2:1. The preference for *anti* over *syn* is consistent with previous studies,[24,25] which determined that the most preferable conformation is where the aryl substituent occupies the inside position and the carbon−oxygen bond is parallel to the π bond. This reduces any destabilizing interaction between the aryl substituent and the carboxyl group, and in the case of free alcohols this arrangement allows the delivery of hydrogen from the same face of the hydroxyl group and leads to the preferential formation of the *anti* product (Figure 2). The relative stereochemistry (C2/C3) was also confirmed by ^{1}H NMR and ^{13}C NMR, with the vicinal coupling (J) for *syn* diastereoisomer varying between 3.8−5.5 Hz and 8.8 Hz for the *anti* isomer, again this was in agreement with previously published studies.[25]

Steric hindrance around C3 would be expected to direct substitution of the alcohol with imidazole mainly through a

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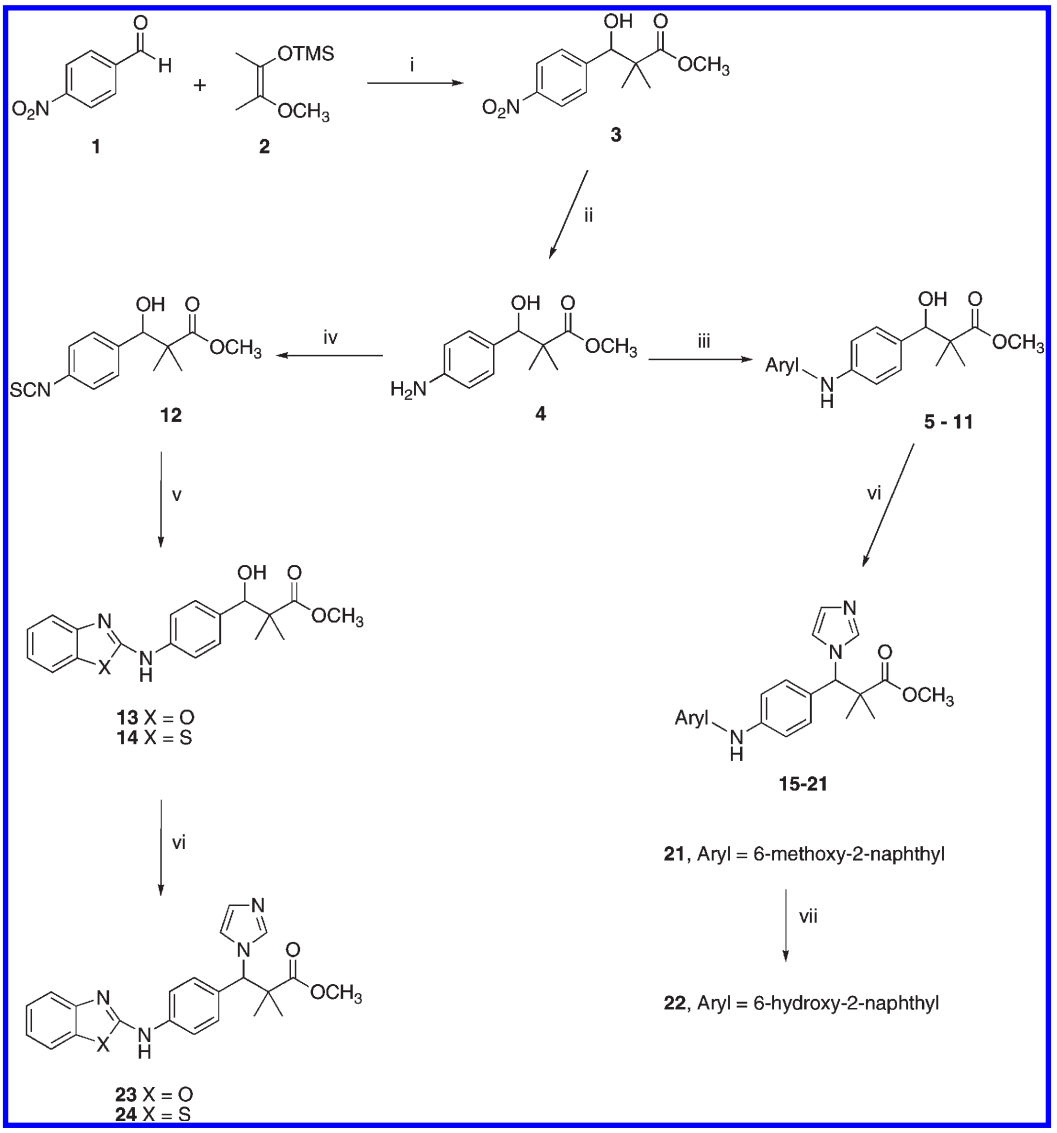
Scheme 1[a]



[a] Reagents and conditions: (i) Pyridine-*N*-oxide, LiCl, DMF, 18 h; (ii) H_2, Pd/C, EtOH, 30 min; (iii) aryl boronic acid, CuOAc, pyridine, 4 Å molecular sieves, CH_2Cl_2, rt, 2 days; (iv) $CSCl_2$, CH_2Cl_2, H_2O, 18 h, 0 °C; (v) (a) 2-aminophenol or 2-aminothiophenol, EtOH, o/n, rt, then (b) HgO, S, reflux, 2 h; (vi) 1,1′-carbonyldiimidazole, imidazole, CH_3CN, reflux, 2 h; (vii) *n*-Bu_4NI, CH_2Cl_2, BCl_3, −78 °C, 5 min then 20 °C, 1 h.

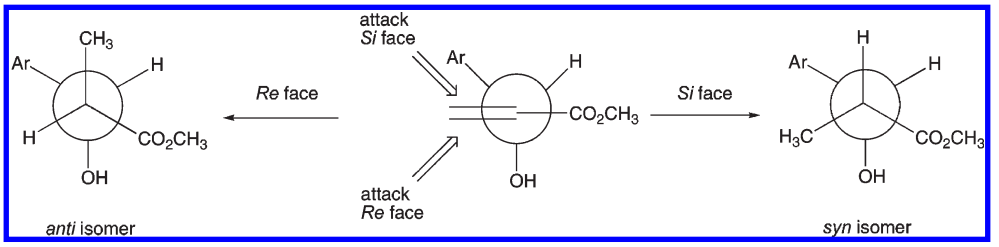


Figure 2. Stereochemical conformation of *anti* (**26**, **28**) and *syn* (**27**, **29**) isomers.

S_N1 mechanism, and it was found that reaction of each isomer (**26**−**29**) with CDI and imidazole gave only one major product with retention of configuration for each reaction (**30**−**33**) with only a trace of minor racemized product observed.

^{1}H NMR was employed to assign *anti* or *syn* conformation, in agreement with the hydroxy products (**26**−**29**), where a smaller C2/C3 coupling was noted for the *syn* products compared with the *anti* products (relative to dihedral angle), a *J* value of 0 Hz was observed for the *syn* imidazole products (**31**, **33**) and a *J* value of 11.3 Hz was observed for the *anti* imidazole products (**30**, **32**). Based on these observations, we tentatively assigned the *anti* and *syn* conformations (Scheme 2).

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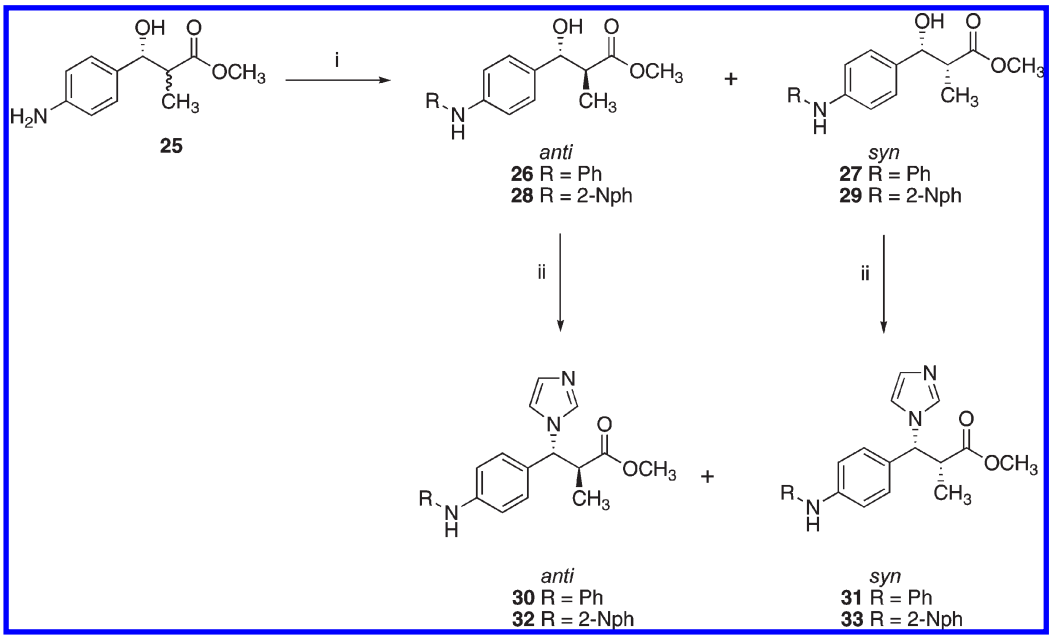
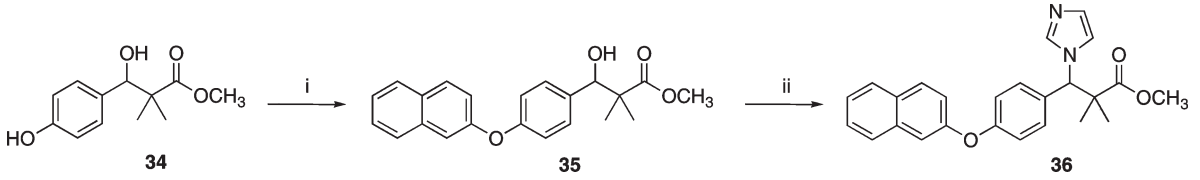
Scheme 2[a]



[a] Reagents and conditions: (i) Aryl boronic acid, CuOAc, pyridine, 4 Å molecular sieves, CH_2Cl_2, rt, 2 days; (ii) 1,1′-carbonyldiimidazole, imidazole, CH_3CN, reflux, 2 h.

Scheme 3[a]



[a] Reagents and conditions: (i) $Cu(OAc)_2$, 2-naphthylboronic acid, 4 Å sieves, CH_2Cl_2, Et_3N, rt, 19 h; (ii) 1,1′-carbonyldiimidazole, imidazole, CH_3CN, reflux, 2 h.

To investigate the importance of the *N*-aryl linker the NH was replaced with an *O*- and CH_2-aryl linker. The *O*-aryl-linked derivative (**35**) was prepared by copper-promoted arylation of (**34**)[26] with 2-naphthylboronic acid,[27,28] employing $Cu(OAc)_2$ as the copper source and triethylamine as the base, in a modest yield of 40%. The final step involved reaction of (**35**) with excess carbonyldiimidazole (CDI) and excess imidazole as previously described, to give the *O*-aryl-linked imidazole product (**36**) as a white solid (Scheme 3).

The first step in the preparation of the CH_2-aryl-linked derivative (**42**) involved Suzuki coupling of 2-bromomethylnaphthalene (**37**) and 4-formyl-phenylboronic acid (**38**), resulting in 4-naphthalen-2-ylmethyl-benzaldehyde (**39**) in 77% yield. Aldol Mukaiyama reaction of the aldehyde (**39**) with methyl trimethylsilyl dimethylketene acetal catalyzed by pyridine-*N*-oxide as a Lewis base catalyst[18,25] gave the TMS-protected intermediate methyl 2,2-dimethyl-3-(4-(naphthalen-2-ylmethyl)phenyl)-3-(trimethylsilyloxy)propanoate (**40**) in 33% yield, which on treatment with acidic resin gave the required alcohol methyl 3-hydroxy-2,2-dimethyl-3-(4-(naphthalen-2-ylmethyl)phenyl)propanoate (**41**) in 91% yield. Subsequent introduction of the imidazole using the standard procedure gave the CH_2-aryl-linked imidazole product (**42**) (Scheme 4).

Enzyme Inhibition. The imidazole derivatives were evaluated for their retinoic acid metabolism (CYP26) inhibitory activity with a cell-free microsomal assay[18,29] using radiolabeled [11,12-^{3}H]all-*trans*-retinoic acid as the substrate. Liarozole (a nonselective CYP26 inhibitor[11,12]) and R116010[15] were included in all experiments as comparative standards. With the exception of the bulky biphenyl (**17**), 2-ethoxy-1-naphthyl (**19**), and benzothiazole (**24**) aryl substitutents (IC_{50} = 250, 125, and 100 nM, respectively), all the aryl substitutents on the left-hand side of the molecule were well tolerated with IC_{50} values ranging from 3 to 10 nM, which was better than or comparable to the potent standard R116010 (IC_{50} = 10 nM) (Table 1).

Replacement of the 2,2-dimethylpropanoate side chain of either the phenyl (**15**) or 2-naphthyl (**20**) imidazole products with 2-methylpropanoate resulted in a moderate reduction in activity for the phenyl products (**30** and **31**, IC_{50} = 40 and 26 nM) and a more notable reduction for the 2-naphthyl products (**32** and **33**, IC_{50} = 140 and 50 nM) compared with their 2,2-dimethyl counterparts (**15** and **20**, respectively) (Table 2).

Replacement of the N-linker of the 2-naphthyl imidazole product (**20**, IC_{50} = 3 nM) with either an −O− (**36**) or $-CH_2-$ (**42**) linker resulted in a substantial loss in activity (IC_{50} > 1 μM) (Table 3).

Enhancement of Retinoic Acid Effects. The induction of CYP26A1 mRNA was used to evaluate the ability of the

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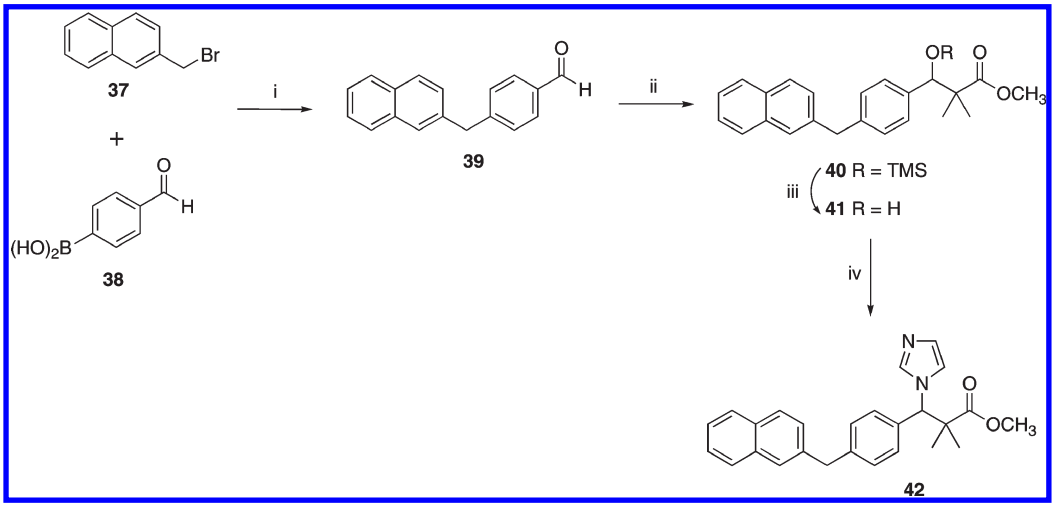
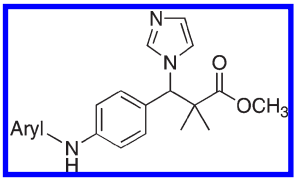
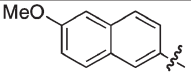
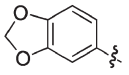
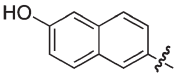
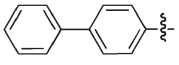
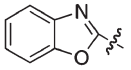
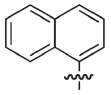
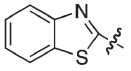
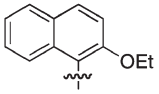
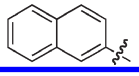
Scheme 4[a]



[a] Reagents and conditions: (i) $Pd(PPh_3)_4$, toluene, sat. aq. $NaHCO_3$, reflux, 20 h; (ii) trimethylsilyl ketene acetal (**2**), pyridine-*N*-oxide, LiCl, DMF, 18 h; (iii) resin (H^+), MeOH, 30 min; (iv) 1,1′-carbonyldiimidazole, imidazole, CH_3CN, reflux, 2 h.

Table 1. IC_{50} Values for Different Aryl Substituents[a]



Compd	Aryl	CYP26 IC_{50} (nM)	Compd	Aryl	CYP26 IC_{50} (nM)
15		10	21		8
16		8	22		3
17		250	23		10
18		6	24		100
19		125	Liarozole	-	540
20		3	R116010	-	10

[a] IC_{50} values are derived from the best fit of a four-point dose−response curve. The coefficient of variation of IC_{50} values for compound **20** ($n = 8$ repeat experiments) was ±15.5%.

compounds to enhance the biological effects of ATRA in a retinoid-responsive neuroblastoma cell line. Compounds with a microsomal CYP26 inhibitory $IC_{50} \leq 50$ nM were selected and analyzed in comparison to liarozole and R116010. None of these CYP26 inhibitors induced CYP26A1 mRNA when used alone. Liarozole or R116010 at a concentration of 1 μM co-incubated with 0.1 μM ATRA induced CYP26A1 mRNA 2.3- and 4.7-fold, respectively, compared with 0.1 μM ATRA alone; this level of induction in response to R116010 was comparable to treatment of cells with a 10-fold higher concentration of ATRA (1 μM) (Figure 3). Co-incubation of 0.1 μM ATRA in combination with 1 μM compounds **15**, **16**, **18**, **22**, **23**, **30**, and **33** for 72 h also substantially increased expression of CYP26A1 compared with 0.1 μM ATRA alone. Under these conditions, the 2-naphthyl

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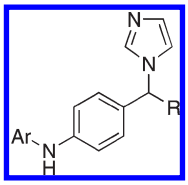
Table 2. Effect of C2 (R) Substituent on IC_{50} for the 2-Naphthyl Imidazole Derivatives



compd	R	aryl	CYP26 IC_{50} (nM)[a]
15	$C(CH_3)_2CO_2CH_3$	Ph	10
30	*anti*-$CH(CH_3)CO_2CH_3$	Ph	40
31	*syn*-$CH(CH_3)CO_2CH_3$	Ph	26
20	$C(CH_3)_2CO_2CH_3$	2-Nph	3
32	*anti*-$CH(CH_3)CO_2CH_3$	2-Nph	140
33	*syn*-$CH(CH_3)CO_2CH_3$	2-Nph	50
liarozole			540
R116010			10

[a] IC_{50} values are derived from the best fit of a four-point dose−response curve. The coefficient of variation of IC_{50} values for compound **20** ($n = 8$ repeat experiments) was ±15.5%.

imidazole product **20** enhanced the expression of CYP26A1 mRNA by 5.8-fold, whereas the methoxy 2-naphthyl imidazole **21** was the least active (Figure 3).

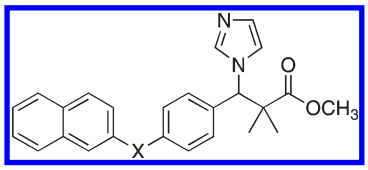
Selectivity. The 1-naphthyl (**18**), 2-naphthyl (**20**), benzoxazole (**23**), and benzothiazole (**24**) derivatives were evaluated for their inhibitory activity against a panel of P450 isoforms expressed in human liver microsomes (Table 4). The 1-naphthyl (**18**) and benzoxazole (**23**) derivatives were highly active against CYP3A4, and the bezothiazole derivative (**24**) was highly active against CYPs 2C9 and 2C19 at concentrations of 0.4 μM. At this concentration, the 2-naphthyl derivative (**20**) was either inactive or displayed borderline percent inhibition against the CYP panel.

To determine the selectivity of the 2-naphthyl imidazole (**20**) in comparison with R116010, IC_{50} assays against P450 isoforms expressed in human liver microsomes were performed. Micromolar concentrations of compound **20** or R116010 were needed to inhibit CYPs 1A2, 2C9, and 2C19. Furthermore, compound **20** and R116010 were ≥200-fold and ≥400-fold more potent against CYP26, respectively, compared with CYPs 1A2, 2C9, 2C19, and 2D6; however, both R116010 and **20** inhibited CYP3A4 with submicromolar activity, with **20** demonstrating greater potency (Table 5).

Mutagenicity and Microsomal Stability. Since the 2-naphthyl imidazole (**20**) had the greatest activity in the cell-free and whole-cell assays and is a likely candidate for further development, mutagenic potential and microsomal stability were evaluated. An Ames screen[30] was performed (Sequani Ltd.) using two strains of *Salmonella typhimurium*, TA98 and TA100, in the presence and absence of S-9 mix. Compound **20** showed no mutagenic potential under the conditions of these tests. Compound **20** also exhibited a low clearance rate (Cyprotex $t_{1/2}$ = 5 h, 1 min) in human liver microsomes, indicating minimal phase I metabolism.[31]

Molecular Modeling. We have performed a series of molecular docking and molecular dynamic (MD) simulations to investigate the possible binding mode for this series of compounds. Results obtained for **20** showed a similar binding to the one observed for a series of inhibitors we have reported recently.[18]

Table 3. IC_{50} Values for Varying Aryl Linker (X)



compd	X	CYP26 IC_{50}[a]
20	NH	3 nM
36	O	>1 μM
42	CH_2	>1 μM
liarozole		540 nM
R116010		10 nM

[a] IC_{50} values are derived from the best fit of a four-point dose−response curve. The coefficient of variation of IC_{50} values for compound **20** ($n = 8$ repeat experiments) was ±15.5%.

In particular, the imidazole ring is coordinating the heme iron and the phenylamino-naphthyl moiety is placed in a hydrophobic channel formed by Phe84, Trp112, Phe222, Pro371, Phe374, and Ile395 (Figure 4). An extra arene−cation interaction is also observed during the MD simulation between the naphthyl group and Arg86. Furthermore, the two methyl groups in the ester side chain are also establishing a series of nonpolar interactions with Phe299, Thr304, Pro369, and Val370. The reduced contact of the mono methyl analogues **32** and **33** with these residues could justify the reduction in activity observed for these compounds.

Interestingly, from Figure 4 it is also possible that in the binding channel around Phe84 and Arg86 there might not be enough space to accommodate bulkier aromatic groups like the diphenyl moiety of compound **17**. On the other hand, there appears to be a small pocket between Pro371 and Phe374. Indeed, docking results obtained for compound **18** showed that the 1-naphthyl moiety could bind to this area efficiently (Figure 5).

DISCUSSION

Evaluation of CYP26 inhibitory activity revealed that with the exception of the bulky substituents, the aryl substituents displayed potent activity, which was better than or equal to the potent standard R116010. Subsequent modifications of the phenyl (**15**) or 2-naphthyl (**20**) imidazole products did not significantly increase activity in this assay. Compounds with biochemical CYP26 inhibitory IC_{50} values ≤50 nM also enhanced the biological activity of exogenous ATRA, as evidenced by a 3.9−5.8-fold increase in CYP26A1 induction compared with ATRA alone. The 2-naphthyl imidazole (**20**) was the most potent; however, all compounds demonstrated an activity comparable to that of R116010, and the range of differences between compounds was much smaller than that observed in the microsomal CYP26 inhibition assay. Furthermore, the order of activity for these inhibitors at a concentration of 1 μM did not correlate with their biochemical CYP26 inhibitory IC_{50} values; compound **21** had an IC_{50} value of 8 nM, which was between 5- and 6-fold higher than inhibitors **30** and **33**; however, **21** was clearly the least effective at increasing ATRA-induced CYP26A1 expression. The reasons for this are not clear, though may relate to reduced cellular uptake.

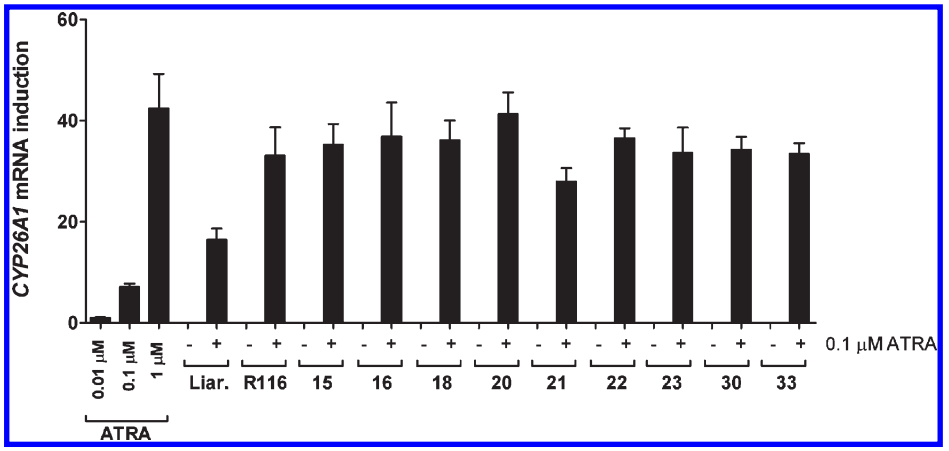


Figure 3. Real-time PCR analysis of CYP26A1 mRNA expression after treatment with ATRA in combination with liarozole (Liar.), R116010 (R116), **15**, **16**, **18**, **20**, **21**, **22**, **23**, **30**, and **33**. SH-SY5Y cells were treated with ATRA alone (0.01−1 μM) or with ATRA (0.1 μM) in combination with inhibitor (1 μM) for 72 h. Total RNA was isolated, reverse transcribed, and subjected to real-time PCR using TaqMan probes for CYP26A1 and β-actin. Values are normalized for β-actin levels and expressed as fold increase relative to CYP26A1 expression in SH-SY5Y cells treated with 0.01 μM ATRA. Data are mean values ± SD (n = 6).

Table 4. Percent Inhibition Data against CYP Panel at 0.4 μM

Compound	1A2	3A4	2C9	2C19	2D6
18	15	75	48	49	53
20	21	60	41	11	25
23	31	84	45	13	55
24	38	46	87	91	11

Inactive | Border line | Highly active

Table 5. CYP IC_{50} (μM) Profile of Lead Compound 20 and R116010

compd	1A2	2C9	2C19	3A4	2D6	26
20	1.2	8.0	1.5	<0.1	0.6	0.003
R116010	8.3	11.0	5.9	0.35	3.9	0.01

The CYP26 induction assay is a sensitive method to assess the ability of physiological concentrations of ATRA to induce gene expression. Since this assay is dependent on the cellular permeability or uptake of inhibitors, it is useful for highlighting compounds unsuitable for cellular analysis but may be unable to discriminate between highly active CYP26 inhibitors without additional data on relative cellular permeabilities and intracellular stability. Thus, further functional analysis, such as ease of entry into cells and cellular stability, as well as studies in relevant animal models,[9,14] will be necessary to select compounds for *in vivo* efficacy studies.

Direct comparison of CYP selectivity profiles for compound **20** and R116010 revealed decreased activity compared with CYP26 against CYPs 1A2, 2C9, 2C19, and 2D6. However, both compounds exhibited activity against the known ATRA hydroxylase CYP3A4, with IC_{50} values of <0.1 μM for compound **20** and 0.35 μM for R116010. Over 90% of drug oxidation can be attributed to the following CYPs: 1A2 (4%), 2A6 (2%), 2C9 (10%), 2C19 (2%), 2E1 (2%), 2D6 (30%), and 3A4 (50%).[32] CYP3A4 is the major metabolizer and is able to oxidize a broad range of small and large molecular substrates, which makes CYP selectivity vs CYP3A4 challenging. Modifications of the lead compound **20** are required to try to address the CYP3A4 liability and will be the subject of further research.

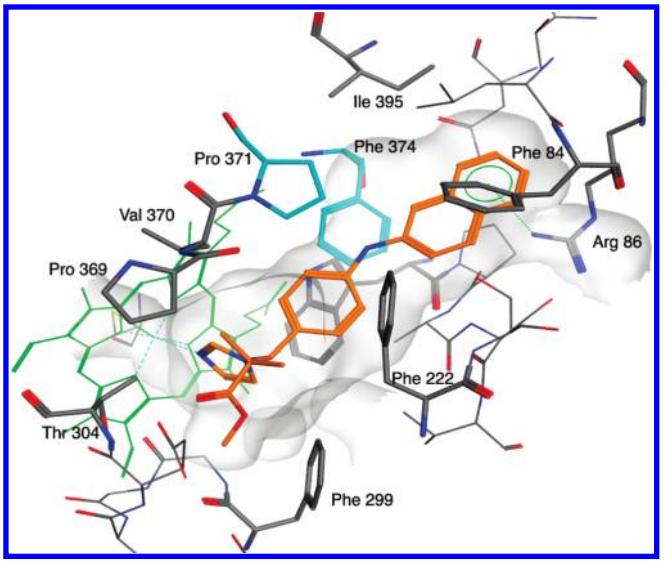


Figure 4. Predicted binding of compound **20**.

With a view to clinical development, while CYP3A4 inhibition may impact systemic use of compound **20**, this is likely to be less of an issue for topical administration in combination with ATRA. Furthermore, good stability in human liver microsomes and absence of mutagenic potential in an Ames assay suggest compound **20** is an appropriate candidate for further evaluation and development for use in the treatment of dermatological diseases.

EXPERIMENTAL SECTION

General Procedures. [11,12-^{3}H]All-*trans*-retinoic acid (37 MBq/mL) and Ultima Flo M scintillation fluid were purchased from Perkin-Elmer (U.K.). Acetic acid and ammonium acetate were obtained from Fisher Scientific (U.K.). All solvents used for chromatography were HPLC grade from Fisher Scientific (U.K.).

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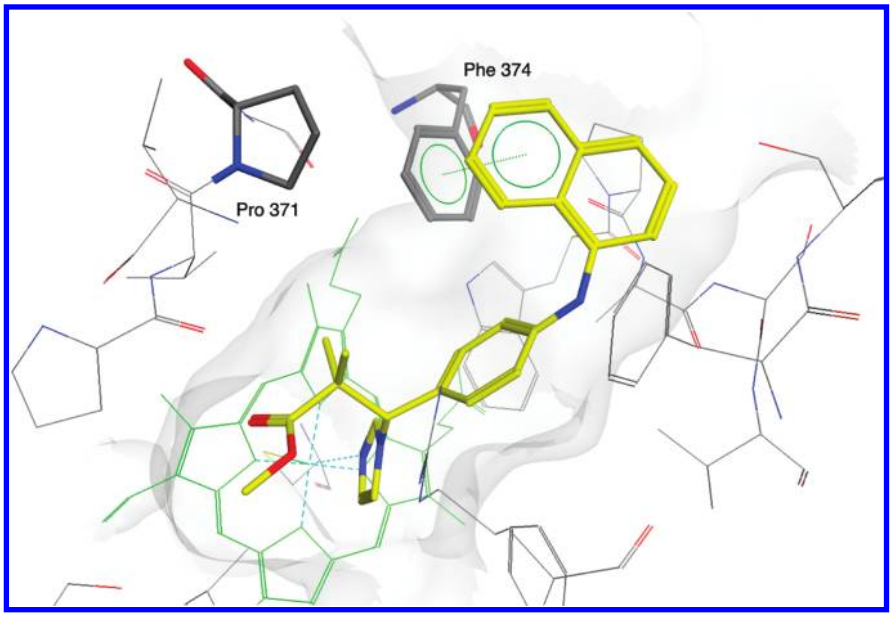

Figure 5. Predicted binding mode of compound **18**.

^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance DPX500 spectrometer operating at 500 and 125 MHz, with Me_4Si as internal standard. Mass spectra were determined by the EPSRC mass spectrometry center (Swansea, U.K.). Microanalyses were determined by Medac Ltd. (Surrey, U.K.). Flash column chromatography was performed with silica gel 60 (230−400 mesh) (Merck), and TLC was carried out on precoated silica plates (kiesel gel 60 F_{254}, BDH). Compounds were visualized by illumination under UV light (254 nm) or by the use of vanillin stain followed by charring on a hot plate. Melting points were determined on an electrothermal instrument and are uncorrected. All solvents were dried prior to use as described by the handbook Purification of Laboratory Chemicals[33] and stored over 4 Å molecular sieves, under nitrogen. All compounds were more than 95% pure.

The numbering of compounds for ^{1}H and ^{13}C NMR is provided in the Supporting Information.

Cell Culture and Retinoid Treatment. SH-SY5Y or MCF-7 cells were cultured at 37 °C in RPMI 1640 medium containing fetal calf serum (10%) and L-glutamine (2 mM) in a humidified atmosphere of 5% CO_2 in air. ATRA was dissolved in dimethyl sulfoxide and added to the culture medium as described by Armstrong et al.[9] Liarozole, R116010, and imidazole derivatives were dissolved in ethanol and diluted in cell culture medium. The final concentration of ethanol in all experiments never exceeded 0.8%.

Microsomal CYP26 Inhibition Assay. MCF-7 cells were pretreated for 24 h with 1 μM RA to induce CYP26 expression. Microsomes were prepared as described by Han and Choi.[29] Briefly, cells were homogenized in buffer A (10 mM Tris, pH 7.4, 1 mM EDTA, 0.5 M sucrose, and Complete protease inhibitor cocktail (Roche, U.K.)) using a Dounce homogenizer and diluted with an equal volume of Tris/EDTA, and the diluted homogenate was laid over a volume of buffer A equal to the original volume. Microsomes were then isolated by differential centrifugation (9000*g*, 10 min, 4 °C; 100 000*g*, 60 min, 4 °C). The microsomal pellet was suspended in buffer B (10 mM Tris, pH 7.4, 1 mM EDTA, 0.25 M sucrose, Complete protease inhibitor cocktail) and stored at −70 °C. Cytochrome *c* reductase activity was calculated at 5−15 U cyt *c*/μg protein, using the cytochrome *c* reductase (NADPH) kit (Sigma) according to the manufacturer's instructions. For ATRA metabolism, 50 μg of microsomal protein was incubated in assay buffer (50 mM Tris, pH 7.4, 150 mM KCl, 10 mM $MgCl_2$, 0.02% w/v BSA, 2 mM NADPH, 10 nM ATRA, 0.1 μCi ^{3}H ATRA) in amber eppendorfs in the absence or presence of CYP26 inhibitor (1−1000 nM) in a final volume of 200 μL for 1 h at 37 °C with shaking. The reaction was quenched with acetonitrile, mixed, and then centrifuged (18 000*g*, 5 min, 4 °C). Resolution of retinoids was performed with a Luna C18(2) column (3 μm, 50 mm × 2 mm) using a Waters 2690 separations module and subsequent Radiomatic series 500TR flow scintillation analyzer (Packard Biosciences), with Empower 2 chromatography data software and Flow-ONE software, respectively, for data acquisition. ^{3}H ATRA and ^{3}H metabolites were separated by gradient reversed-phase chromatography, using mobile phase A (50% acetonitrile, 50% (0.2%) acetic acid, w/w) and mobile phase B (acetonitrile, 0.1% acetic acid, w/w). A flow rate of 0.3 mL/min was used with linear gradients employed between the specified times as follows: 0, 100% A; 5 min, 100% A; 5.5 min, 40% A, 60% B; 12 min, 40% A, 60% B; 12.5 min, 20% A, 80% B; 17.5 min, 20% A, 80% B; 18 min, 100% A; 25 min, 100% A. Scintillant flow rate was 1 mL/min. CYP26 inhibition was calculated as the percentage ^{3}H ATRA metabolite peak area formation (activity ^{3}H metabolite(s)/total activity) compared with metabolite formation in the absence of inhibitor. IC_{50} values were calculated by nonlinear regression analysis in SigmaPlot (Systat Software Inc., USA) using an inhibition curve constructed from a minimum of four data points. Compound **20** was used as a standard in every assay.

Real-Time PCR for CYP26A1 Expression. RNA was isolated using an RNeasy Kit (Qiagen, Crawley, U.K.) and reverse-transcribed, and real-time PCR was performed on 20 ng of cDNA using TaqMan gene expression products for human CYP26A1 in combination with the TaqMan Universal PCR master mix (Applied Biosystems, Warrington, U.K.) on a GeneAmp 5700 Sequence Detection System as described previously.[9]

Chemistry. *3-(4-Aminophenyl)-3-hydroxy-2,2-propionic Acid Methyl Ester (**4**).* Pd/C catalyst (100 mg) was added to a solution of **3**[26] (1 g, 3.95 mmol) dissolved in EtOH (20 mL), and then the reaction was stirred under a H_2 atmosphere. After 30 min, the mixture was filtered through Celite, and the solvent was removed under reduced pressure.The oil formed was extracted with CH_2Cl_2 (100 mL), washed with H_2O (2 × 50 mL) and dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The product was obtained without further purification to give 3-(4-aminophenyl)-3-hydroxy-2,2-dimethylpropionic acid methyl ester (**4**) as a yellow solid. Yield, 0.87 g (87%); mp 130−132 °C; TLC (petroleum ether/EtOAc 2:1, R_f = 0.31). ^{1}H NMR (DMSO-d_6): δ 0.90 (s, 3H, H-4), 1.02 (s, 3H, H-5), 3.58 (s, 3H, H-1), 4.65 (s, 1H, OH), 4.93 (s, 2H, NH_2), 5.17 (s, 1H, H-6), 6.50 (d, J = 7.9 Hz, 2H, H-3′, H-5′), 6.92

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(d, J = 7.8 Hz, 2H, H-2′, H-6′). ^{13}C NMR (DMSO-d_6): δ 18.52 (CH_3, C-4), 19.41 (CH_3, C-5), 47.88 (C, C-3), 51.30 (CH_3, C-1), 76.82 (CH, C-6), 112.84 (CH, C-3′, C-5′), 128.01 (CH, C-2′, C-6′), 128.67 (C, C-1′), 147.61 (C, C-4′), 176.76 (C, C-2). Anal. C, H, N.

General Method: Suzuki Coupling. To the appropriate aryl boronic acid (4.0 mmol), 3-(4-aminophenyl)-3-hydroxy-2,2-dimethylpropionic acid methyl ester (**4**) (2.2 mmol), anhydrous Cu(II)$(OAc)_2$ (3.0 mmol), pyridine (4.0 mmol), and 250 mg of activated 4 Å molecular sieves under an atmosphere of air was added CH_2Cl_2 (15 mL), and the reaction was stirred under air atmosphere at ambient temperature for 2 days. The product was isolated by direct flash column chromatography of the crude reaction mixture (petroleum ether−EtOAc 70:30 v/v).

*3-Hydroxy-2,2-dimethyl-3-[4-(naphthalen-2-ylamino)-phenyl]-propionic Acid Methyl Ester (**10**).* Prepared from reaction of 2-naphthylboronic acid and (**4**) in 82% yield as a yellow-brown oil. TLC (2:1 petroleum ether/EtOAc, R_f = 0.59). ^{1}H NMR ($CDCl_3$): δ 1.18 (s, 3H, H-4), 1.22 (s, 3H, H-5), 3.15 (s, 1H, OH), 3.76 (s, 3H, H-1), 4.90 (s, 1H, H-6), 5.98 (s, 1H, NH), 7.13 (d, J = 7.5 Hz, 2H, H-3′, H-5′), 7.23 (s, 1H, H-2″), 7.26 (d, J = 8.5 Hz, 2H, H-2′, H-6′), 7.33 (t, J = 7.2 Hz, 1H, H-6″), 7.44 (m, 2H, H-5″, H-10″), 7.67 (*d*, J= 8.2 Hz, 1H, H-4″), 7.77 (d, J = 8.3 Hz, 2H, H-7″, H-9″). ^{13}C NMR ($CDCl_3$): δ 19.18 (CH_3, C-4), 23.05 (CH_3, C-5), 47.91 (C, C-3), 52.10 (CH_3, C-1), 78.52 (CH, C-6), 111.80 (CH, C-2″), 117.27 (CH, C-3′ C-5′, C-10″), 120.11 (CH, C-6″), 123.56 (CH, C-4″), 126.51 (CH, C-5″), 127.75 (CH, C-7″), 128.73 (CH, C-9″), 129.19 (CH, C-2′, C-6′), 129.25 (C, C-8″), 132.79 (C, C-1′), 134.63 (C, C-3″), 140.71 (C, C-4′), 142.60 (C, C-1″), 178.30 (C, C-2). EI-HRMS $(M + Na)^+$ found 372.1568, calculated for $C_{22}H_{23}NO_3$ 372.1570.

Compounds **5**, **6**, **7**, **8**, **9**, **11**, **26**, **27**, **28**, and **29** were prepared by this general method, details of which are provided in Supporting Information.

*3-Hydroxy-3-(4-isothiocyanatophenyl)-2,2-dimethylpropionic Acid Methyl Ester (**12**).* To a solution of 3-(4-aminophenyl)-3-hydroxy-2,2-dimethylpropionic acid methyl ester (**4**, 2.3 g, 10.3 mmol) in CH_2Cl_2 (20 mL) was added a mixture of ice (2 g) and H_2O (1 mL) and subsequently dropwise with vigorous stirring thiophosgene (0.92 mL, 12.07 mmol). The mixture was stirred for 2 h at 0 °C and kept overnight in a refrigerator. The organic layer was separated and extracted successively with H_2O (2 × 50 mL), 10% $NaHCO_3$ aq. (50 mL), and H_2O again (50 mL), dried ($MgSO_4$), and evaporated to obtain the pure product 3-hydroxy-3-(4-isothiocyanatophenyl)-2,2-dimethylpropionic acid methyl ester (**12**) as a yellow oil. Yield, 1.94 g (71%); TLC (petroleum ether/EtOAc 2:1, R_f = 0.57). ^{1}H NMR ($CDCl_3$): δ 1.01 (s, 1H, H-4), 1.04 (s, 1H, H-5), 3.21 (s, 1H, OH), 3.67 (s, 3H, H-1), 4.81 (s, 1H, H-6), 7.10 (d, J = 7.2 Hz, 2H, H-3′, H-5′), 7.21 (d, J = 7.4 Hz, 2H, H-2′, H-6′). ^{13}C NMR ($CDCl_3$): δ 19.15 (CH_3, C-4), 22.79 (CH_3, C-5), 47.71 (C, C-3), 52.22 (CH, C-6), 77.95 (CH, C-1), 125.07 (CH, C-3′, C-5′), 128.84 (CH, C-2′, C-6′), 130.63 (C, C-4′), 135.61 (C, C-1′), 139.38 (C, C-7′), 177.93 (C, C-2). EI-HRMS $(M)^+$ found 265.0768, calculated for $C_{23}H_{15}NO_3S$ 265.0767.

*3-[4-(Benzooxazol-2-ylamino)-phenyl]-3-hydroxy-2,2-dimethylpropionic Acid Methyl Ester (**13**).* 2-Aminophenol (0.33 g, 3.02 mmol) was added to a solution of (**12**) (0.8 g, 3.02 mmol) in absolute EtOH (10 mL). The mixture was then stirred overnight at room temperature. Then HgO (1.3 g, 6.0 mmol) and S (20 mg, 0.62 mmol) were added, and the reaction mixture was refluxed at 85 °C for 2 h then filtered through Celite. The solvent was evaporated *in vacuo* to give an oil, which was purified by column chromatography (petroleum ether−EtOAc 100:0 v/v increasing to 70:30 v/v) to give 3-[4-(benzooxazol-2-ylamino)-phenyl]-3-hydroxy-2,2-dimethylpropionic acid methyl ester (**13**) as a yellow solid. Yield, 0.89 g (87%); mp 164−166 °C; TLC (petroleum ether/EtOAc 1:1, R_f = 0.59). ^{1}H NMR (DMSO-d_6): δ 0.95 (s, 3H, H-4), 1.07 (s, 3H, H-5), 3.62 (s, 3H, H-1), 4.81 (s, 1H, H-6), 5.49 (s, 1H, OH), 7.13 (t, J = 7.7 Hz, 1H, H-3′), 7.22 (t, J = 7.6 Hz, 1H, H-5′), 7.28 (d, J = 8.2 Hz, 2H, H-2′, H-6′), 7.47 (m, 2H, H-4″, H-5″), 7.70 (d, J = 8.2 Hz, 2H, H-3″, H-6″), 10.59 (s, 1H, NH). ^{13}C NMR: (DMSO-d_6): δ 19.59 (CH_3, C-4), 21.38 (CH_3, C-5), 47.84 (C, C-3), 51.44 (CH, C-1), 76.46 (CH, C-6), 108.89 (CH, C-6″), 116.53 (CH, C-3′, C-5′), 121.57 (CH, C-3″), 123.95 (CH, C-4″, C-5″), 127.99 (CH, C-2′, C-6′), 135.46 (C, C-1′), 137.64 (C, C-2″), 142.43 (C, C-4′), 146.99 (C, C-7″), 157.99 (C, C-1″), 176.49 (C, C-2). Anal. C, H, N.

*3-[4-(Benzothiazol-2-ylamino)-phenyl]-3-hydroxy-2,2-dimethylpropionic Acid Methyl Ester (**14**).* 2-Aminothiophenol (0.32 mL, 2.99 mmol) was added to a solution of (**12**) (0.8 g, 3.02 mmol) in absolute EtOH (10 mL). The mixture was then stirred overnight at room temperature. Then HgO (1.3 g, 6.0 mmol) and S (20 mg, 0.62 mmol) were added, and the reaction mixture was refluxed at 85 °C for 2 h then filtered through Celite. The solvent was evaporated *in vacuo* to give an oil, which was purified by column chromatography (petroleum ether−EtOAc 100:0 v/v increasing to 70:30 v/v) to give 3-[4-(benzothiazol-2-ylamino)-phenyl]-3-hydroxy-2,2-dimethyl-propionic acid methyl ester (**14**) as a yellow solid. Yield, 0.9 g (84%); mp 156−158 °C; TLC (petroleum ether/EtOAc 1:1, R_f = 0.51). ^{1}H NMR (DMSO-d_6): δ 0.95 (s, 3H, H-4), 1.07 (s, 3H, H-5), 3.63 (s, 3H, H-1), 4.82 (s, 1H, H-6), 5.51 (s, 1H, OH), 7.16 (t, J = 7.4 Hz, 1H, Ar), 7.27 (d, J = 8.0 Hz, 2H, H-2′, H-6′), 7.33 (t, J = 7.5 Hz, 1H, Ar), 7.60 (d, J = 7.9 Hz, 1H, C-6″), 7.73 (d, J = 8.0 Hz, 2H, H-4″, H-5″), 7.80 (d, J = 7.7 Hz, 1H, C-3″), 10.48 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 19.52 (CH_3, C-4), 21.48 (CH_3, C-5), 47.84 (C, C-3), 51.45 (CH, C-1), 76.50 (CH, C-6), 116.78 (CH, C-3′, C-5′), 119.13 (CH, C-3″), 120.99 (CH, C-6″), 122.18 (CH, C-4″), 125.82 (CH, C-5″), 128.02 (CH, C-2′, C-6′), 129.96 (C, C-7″), 135.36 (C, C-1′), 139.59 (C, C-4′), 152.11 (C, C-2″), 161.55 (C, C-1″), 176.51 (C, C-2). Anal. C, H, N.

General Method: Conversion of Alcohols to Imidazoles. To a solution of alcohol (**5**−**11**, **13**, **14**, **26**−**29**, **35**, or **41**) (1.5 mmol) in anhydrous CH_3CN (20 mL) was added imidazole (4.5 mmol) and CDI (2.25 mmol). The mixture was then heated under reflux for 2 h. The reaction mixture was allowed to cool and then extracted with EtOAc (150 mL) and H_2O (3 × 100 mL). The organic layer was dried with $MgSO_4$, filtered, and reduced *in vacuo*. The product was purified by filtration and washing or flash column chromatography.

*3-Imidazol-1-yl-2,2-dimethyl-3-(4-phenylaminophenyl)-propionic Acid Methyl Ester (**15**).* Prepared by the reaction of **5** with CDI and imidazole. Purified by column chromatography (EtOAc) and obtained in 44% yield as a colorless oil. TLC (EtOAc, R_f = 0.38). ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 3H, H-4), 1.31 (s, 3H, H-5), 3.63 (s, 3H, H-1), 5.52 (s, 1H, NH), 6.37 (s, 1H, H-6), 6.97 (m, 4H, H-3′, H-5′, H-4″, H-3‴), 7.05 (s, 1H, H-2‴), 7.09 (d, J = 6.8 Hz, 2H, H-2″, H-6″), 7.14 (d, J = 7.9 Hz, 2H, H-2′, H-6′), 7.27 (*t*, J= 6.9 Hz, 2H, H-3″, H-5″), 7.61 (s, 1H, H-1‴). ^{13}C NMR ($CDCl_3$): δ 22.90 (CH_3, C-4), 23.45 (CH_3, C-5), 47.68 (C, C-3), 52.38 (CH, C-1), 67.55 (CH, C-6), 116.78 (CH, C-3′, C-5′), 118.66 (CH, C-2″, C-6″), 119.57 (CH, C-4″), 121.61 (CH, C-2‴), 127.86 (C, C-1′), 128.85 (CH, C-3‴), 129.56 (CH, C-3″, C-5″), 129.89 (CH, C-2′, C-6′), 137.97 (CH, C-1‴), 142.36 (C, C-4′), 143.75 (C, C-1″), 176.27 (C, C-2). EI-HRMS $(M + H)^+$ found 350.1862, calculated for $C_{21}H_{23}N_3O_2$ 350.1863.

*3-[4-(Benzo[1,3]dioxol-5-ylamino)-phenyl]-3-imidazol-1-yl-2,2-dimethyl-propionic Acid Methyl Ester (**16**).* Prepared by the reaction of **6** with CDI and imidazole. Purified by column chromatography (CH_2Cl_2−MeOH 100:0 v/v increasing to 97:3 v/v) and obtained as a brown oil in 41% yield. (97:3 CH_2Cl_2/MeOH, R_f = 0.43). ^{1}H NMR ($CDCl_3$): δ 1.21 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 3.62 (s, 3H, CH_3-ester), 5.49 (s, 1H, H-NH), 5.83 (s, 1H, CH), 5.91 (s, 2H, H−CH_2), 6.53 (d, J = 7.2 Hz, 1H, Ar), 6.66 (d, J = 2.2 Hz, 1H, Ar), 6.71 (d, J = 7.9 Hz, 1H, Ar), 6.80 (d, J = 7.8 Hz, 2H, Ar), 6.94−7.12 (m, 4H, Ar), 7.61 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 21.84 (CH, CH_3), 23.45 (CH, CH_3), 47.66 (C, C-3), 52.35 (CH, CH_3-ester), 60.37 (C, CH_2), 67.57 (CH, CH), 101.15 (C, Ar), 103.26 (CH, Ar), 108.55 (CH, Ar), 113.88 (CH, Ar), 115.13 (CH, Ar), 125.70 (C, Ar), 129.58 (CH, Ar), 136.34 (C, Ar), 143.36 (C, Ar), 145.15 (C, Ar), 148.24 (C, Ar), 176.26 (C, CO). EI-HRMS $(M + H)^+$ found 394.1754, calculated for $C_{22}H_{24}N_3O_4$ 394.1748.

*3-[4-(Biphenyl-4-ylamino)-phenyl]-3-imidazol-1-yl-2,2-dimethyl-propionic Acid Methyl Ester (**17**).* Prepared by the reaction of **7** with CDI and imidazole. After 2 h reflux, the resulting precipitate was filtered and the precipitate was washed with H_2O (10 mL) and hot CH_3CN (10 mL) to give the product as a white solid in 59% yield without further purification. Mp 200−202 °C; TLC (EtOAc, R_f = 0.43). ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 6H, H-4, H-5), 3.71 (s, 3H, H-1), 5.51 (s, 1H, H-6), 5.92 (s, 1H, NH), 7.07 (m, 4H, Ar), 7.14 (m, 4H, Ar), 7.32 (m, 1H, H-10″), 7.45 (m, 2H, Ar), 7.53 (d, J = 8.0 Hz, 2H, H-3″, H-5″), 7.61 (d, J = 7.9 Hz, 2H, H-8″, H-12″), 7.68 (s, 1H, H-1‴). ^{13}C NMR ($CDCl_3$): δ 23.00 (CH_3, C-4), 23.39 (CH_3, C-5), 47.68 (C, C-3), 52.40 (CH_3, C-1), 67.50 (CH, C-6), 116.82 (CH, C-3′, C-5′), 118.73 (CH, C-2″, C-6″, C-2‴), 126.59 (CH, C-8″, C-12″, C-3‴), 126.77 (CH, C-10″), 128.04 (CH, C-3″, C-5″), 128.46 (C, C-4″), 128.77 (CH, C-9″, C-11″), 129.05 (CH, C-1‴), 129.64 (CH, C-2′, C-6′), 134.61 (C, C-1′), 140.69 (C, C-7″), 141.57 (C, C-4′), 143.30 (C, C-1″), 176.25 (C, C-2). Anal. C, H, N.

*3-Imidazol-1-yl-2,2-dimethyl-3-[4-(naphthalen-1-ylamino)-phenyl]-propionic Acid Methyl Ester (**18**).* Prepared by the reaction of **8** with CDI and imidazole. Column chromatography (CH_2Cl_2 - MeOH 100:0 v/v increasing to 97:3 v/v) gave this product in 52% yield as a pale yellow oil. TLC (97:3 CH_2Cl_2/MeOH, R_f = 0.61). ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 6H, H-4, H-5), 3.65 (s, 3H, H-1), 5.51 (s, 1H, H-6), 6.11 (s, 1H, H-NH), 6.89 (d, J = 8.0 Hz, 2H, H-3′, H-5′), 7.03 (s, 1H, H-3‴), 7.09 (s, 1H, H-2‴), 7.14 (d, J = 8.1 Hz, 2H, H-2′, H-6′), 7.41 (m, 2H, H-2″, H-3″), 7.48 (m, 2H, H-4″, H-7″), 7.61 (m, 2H, H-8″, H-1‴), 7.88 (d, J = 8.0 Hz, 1H, H-6″), 8.12 (d, J = 8.2 Hz, 1H, H-9″). ^{13}C NMR ($CDCl_3$): δ 22.92 (CH_3, C-4), 23.42 (CH_3, C-5), 47.72 (C, C-3), 52.37 (CH_3, C-1), 67.57 (CH, C-6), 116.13 (CH, C-2″), 117.56 (CH, C-3′, C-5′), 121.97 (CH, C-4″), 123.96 (CH, C-9″), 125.89 (CH, C-2‴), 125.94 (CH, C-8″), 126.23 (CH, C-7″), 127.59 (CH, C-3‴), 128.33 (CH, C-3″, C-6″), 128.56 (C, C-10″), 128.95 (C, C-1′), 129.90 (CH, C-2′, C-6″, C-1‴), 134.74 (C, C-5″), 137.85 (C, C-4′), 145.34 (C, C-1″), 176.28 (C, C-2). Anal. C, H, N.

*3-[4-(2-Ethoxy-naphthalen-1-ylamino)-phenyl]-3-imidazol-1-yl-2,2-dimethyl-propionic Acid Methyl Ester (**19**).* Prepared by the reaction of **9** with CDI and imidazole. Purified by column chromatography (CH_2Cl_2−MeOH 100:0 v/v increasing to 97:3 v/v) and obtained as a brown oil in 38% yield (97:3 CH_2Cl_2/MeOH, R_f = 0.64). ^{1}H NMR ($CDCl_3$): δ 1.21 (s, 3H, H-4), 1.25 (s, 3H, H-5), 1.36 (t, J = 7.6 Hz, 3H, H-2‴), 3.66 (s, 3H, H-1), 4.16 (q, J = 7.5 Hz, 2H, H-1‴), 5.51 (s, 1H, H-6), 5.96 (s, 1H, NH), 6.62 (d, J = 7.8 Hz, 2H, H-3′, H-5′), 7.03 (d, J = 8.0 Hz, 2H, H-2′, H-6′), 7.08 (d, J = 2.2 Hz, 1H, Ar), 7.32−7.38 (m, 4H, Ar), 7.72 (d, J = 8.2 Hz, 1H, Ar), 7.81−7.86 (m, 3H, H-6″, H-9″, H-1‴). ^{13}C NMR ($CDCl_3$): 15.10 (CH_3, OEt), 22.59 (CH3, C-4), 23.81 (CH3, C-5), 47.67 (C, C-3), 52.42 (CH, C-1), 65.13 (CH_2 OEt), 68.29 (CH, C-6), 114.90 (CH, C-3′, C-5′), 115.09 (CH, C-3″), 123.44 (CH, C-9″, C-2‴), 123.90 (CH, C-4″), 124.03 (C, C-1″, C-10″), 125.76 (CH, C-7″, C-3‴), 126.27 (CH, C-8″), 126.36 (CH, C-6″), 129.31 (CH, C-2′, C-6′, C-1‴), 129.42 (C, C-5″), 130.68 (C, C-1′), 147.47 (C, C-4′), 150.24 (C, C-2″), 176.17 (C, C-2). EI-HRMS $(M + H)^+$ found 444.2280, calculated for $C_{27}H_{30}N_3O_3$ 444.2282.

*3-Imidazol-1-yl-2-methyl-3-[4-(naphthalen-2-ylamino)-phenyl]-propionic Acid Methyl Ester (**20**).* Prepared by the reaction of **10** with CDI and imidazole. Column chromatography (CH_2Cl_2 - MeOH 100:0 v/v increasing to 97:3 v/v) gave this product in 54% yield as a light brown solid. Mp 190−192 °C; TLC (97:3 CH_2Cl_2/MeOH, R_f = 0.61). ^{1}H NMR (DMSO-d_6): δ 1.21 (s, 6H, H-4, H-5), 3.55 (s, 3H, H-1), 5.58 (s, 1H, H-6), 6.91 (s, 1H, H-2″), 7.17 (d, J = 8.0 Hz, 2H, H-3′, H-5′), 7.28 (m, 2H, H-6″, H-10″), 7.38 (m, 3H, H-2′, H-6′, H-5″), 7.44 (s, 1H, H-3‴), 7.50 (s, 1H, H-2‴), 7.71 (d, J = 8.2 Hz, 1H, H-4″), 7.77 (m, 2H, H-7″, H-9″), 7.83 (s, 1H, H-1‴), 8.51 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 22.70 (CH_3, C-4), 22.90 (CH_3, C-5), 47.34 (C, C-3), 51.92 (CH_3, C-1), 66.73 (CH, C-6), 109.84 (CH, C-2″), 112.84 (CH, C-10″), 116.20 (CH, C-3′, C-5′), 120.10 (CH, C-6″. C-2‴), 122.98 (CH, C-4″), 126.23 (CH, C-5″, C-7″), 127.37 (CH, C-9″), 127.96 (C, C-8″), 128.00 (CH, C-3‴), 128.10 (C, C-1′), 128.82 (CH, C-1‴), 129.79 (CH, C-2′, C-6′), 134.29 (C, C-3″), 140.68 (C, C-4′), 142.99 (C, C-1″), 175.31 (C, C-2). Anal. C, H, N.

*3-Imidazol-1-yl-3-[4-(6-methoxy-naphthalen-2-ylamino)-phenyl]-2,2-dimethyl-propionic Acid Methyl Ester (**21**).* Prepared by the reaction of **11** with CDI and imidazole. After 2 h reflux, the resulting precipitate was filtered and washed with H_2O (10 mL) and hot CH_3CN (10 mL) to give the product as a white solid in 68% yield without further purification. Mp 220−222 °C; TLC (97:3 CH_2Cl_2/MeOH, R_f = 0.64). ^{1}H NMR (DMSO-d_6): δ 1.22 (s, 6H, H-4, H-5), 3.57 (s, 3H, H-1), 3.89 (s, 3H, OCH_3), 5.60 (s, 1H, H-6), 6.85 (s, 1H, Ar), 7.18 (m, 3H, Ar), 7.20 (s, 1H, H-3‴), 7.24 (d, J = 7.8 Hz, 1H, Ar), 7.29 (d, J = 7.7 Hz, 2H, H-2′, H-6′), 7.41 (s, 1H, H-2‴), 7.45 (s, 1H, H-1‴), 7.61 (d, J = 8.2 Hz, 1H, H-4″), 7.69 (d, J = 8.3 Hz, 1H, H-9″), 7.82 (s, 1H, H-2″), 8.33 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 22.69 (CH_3, C-4), 22.91 (CH_3, C-5), 47.35 (C, C-3), 51.91 (CH_3, C-1), 55.06 (CH_3, OCH_3), 66.75 (CH, C-6), 106.08 (CH, C-7″), 111.59 (CH, C-2″), 112.59 (CH, C-2‴), 115.37 (CH, C-3′, C-5′, C-10″), 118.60 (CH, C-4″), 119.73 (CH, C-3‴), 120.94 (CH, C-5″), 127.25 (CH, C-1‴), 127.67 (C, C-8″), 127.86 (CH, C-9″), 128.08 (CH, C-2′, C-6′), 129.45 (C, C-1′), 129.78 (C, C-3″), 138.53 (C, C-4′), 143.65 (C, C-1″), 155.54 (C, C-6″), 175.32 (C, C-2). Anal. C, H, N.

*3-[4-(Benzooxazol-2-ylamino)-phenyl]-3-imidazol-1-yl-2,2-dimethylpropionic Acid Methyl Ester (**23**).* Prepared by the reaction of **13** with CDI and imidazole. Column chromatography (EtOAc) gave this product in 47% yield as a white solid. Mp 158−160 °C; TLC (EtOAc, R_f = 0.28). ^{1}H NMR (DMSO-d_6): δ 1.21 (s, 6H, H-4, H-5), 3.57 (s, 3H, H-1), 5.62 (s, 1H, H-6), 6.91 (s, 1H, H-3‴), 7.14 (t, J = 7.7 Hz, 1H, H-4″), 7.23 (t, J = 7.6 Hz, 1H, H-5″), 7.48 (m, 5H, H-3′, H-5′, H-3″, H-6″, H-2‴), 7.75 (d, J = 8.1 Hz, 2H, H-2′, H-6′), 7.84 (s, 1H, H-1‴), 10.71 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 22.78 (CH_3, C-4, C-5), 47.30 (C, C-3), 51.97 (CH_3, C-1), 66.62 (CH, C-6), 108.99 (CH, C-6″), 116.64 (CH, C-2‴), 117.20 (CH, C-3′, C-5′, −3″), 121.77 (CH, C-3‴), 124.03 (CH, C-4″, C-5″), 128.15 (CH, C-1‴), 129.55 (CH, C-2′, C-6′), 130.34 (C, C-1′), 138.47 (C, C-2″), 142.26 (C, C-4′), 146.97 (C, C-7″), 157.79 (C, C-1″), 175.20 (C, C-2). EI-HRMS $(M + H)^+$ found 391.1761, calculated for $C_{22}H_{22}N_4O_3$ 391.1765.

*3-[4-(Benzothiazol-2-ylamino)-phenyl]-3-imidazol-1-yl-2,2-dimethyl-propionic Acid Methyl Ester (**24**).* Prepared by the reaction of **14** with CDI and imidazole. Column chromatography (CH_2Cl_2/MeOH 100:0 increasing to 95:5 v/v) gave this product in 44% yield as a yellow oil. TLC (CH_2Cl_2/MeOH 95:5, R_f = 0.46). ^{1}H NMR (DMSO-d_6): δ 1.22 (s, 6H, H-4, H-5), 3.61 (s, 3H, H-1), 5.62 (s, 1H, H-6), 6.85 (s, 1H, H-3‴), 7.09 (m, 3H, H-4″, H-6″, H-2‴), 7.34 (t, J = 7.6 Hz, 1H, H-5″), 7.46 (d, J = 8.2 Hz, 2H, H-3′, H-5′), 7.61 (d, J = 7.9 Hz, 1H, H-3″), 7.78 (d, J = 8.1 Hz, 1H, H-2′), 7.81 (d, J = 7.9 Hz, 1H, H-6′), 7.85 (s, 1H, H-1‴), 10.59 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 22.91 (CH_3, C-4), 23.53 (CH_3, C-5), 47.56 (C, C-3), 52.50 (CH_3, C-1), 67.63 (CH, C-6), 118.49 (CH, C-3′, C-5′), 119.76 (CH, C-3″), 120.73 (CH, C-6″, C-2‴), 122.66 (CH, C-4″), 126.08 (CH, C-5″, C-3‴), 128.66 (CH, C-1‴), 129.35 (CH, C-2′, C-6′), 130.25 (C, C-7″), 130.58 (C, C-1′), 140.54 (C, C-4′), 151.71 (C, C-2″), 162.54 (C, C-1″), 176.15 (C, C-2). EI-HRMS $(M + H)^+$ found 407.1535, calculated for $C_{22}H_{22}N_4O_2S$ 407.1536.

*Methyl anti-3-(1H-1-Imidazolyl)-3-[4-(phenylamino)phenyl]-2-methyl-propanoate (**30**).* Prepared by the reaction of **26** with CDI and imidazole. Purified by column chromatography (CH_2Cl_2−MeOH 100:0 v/v increasing to 97:3 v/v) and obtained in 65% yield as a brown solid. Mp 218−222 °C; TLC (9:1 CH_2Cl_2/MeOH, R_f = 0.4). ^{1}H NMR ($CDCl_3$): δ 1.11 (d, 3H, J = 6.9 Hz, CH-C$\underline{H}_3$), 3.33−3.39 (m, 1H, C$\underline{H}$-CH_3), 3.52 (s, 3H, OCH_3), 5.18 (d, 1H, J = 11.3 Hz, C$\underline{H}$-imidazole), 7.79 (s, 1H, NH), 6.87−6.95 (m, 1H, H-4″), 6.97−7.01 (m, 4H, H-3′, H-5′, H-2″, H-6″), 7.04−7.07 (m, 2H, H-2′, H-6′), 7.20−7.24 (m, 2H, H-3″, H-5″), 7.20−7.24 (m, 2H, H-2‴, H-3‴), 7.57 (s, 1H, H-1‴). ^{13}C

NMR ($CDCl_3$): δ 15.98 (CH_3, C-4), 44.95 (CH, C-2), 52.07 (CH_3, C-1), 63.98 (CH, C-3), 116.78 (CH, C-4″), 118.91 (CH, C-3′, C-5′, C-2″, C-6″), 121.89 (CH, imid), 128.22 (C, C-1′), 128.49 (CH, C-2′, C-6′, C-3″, C-5″), 129.54 (CH, C-3‴), 142.51 (C, C-4′), 144.28 (C, C-1″), 174.54 (C, C-1). Anal. C, H, N.

*Methyl syn-3-(1H-1-Imidazolyl)-3-[4-(phenylamino) phenyl]-2-methyl-propanoate (**31**).* Prepared by the reaction of **27** with CDI and imidazole. Purified by column chromatography (CH_2Cl_2−MeOH 100:0 v/v increasing to 97:3 v/v) and obtained in 57% yield as an oily product. TLC (9:1 CH_2Cl_2/MeOH, R_f = 0.52). ^{1}H NMR ($CDCl_3$): δ 1.15 (d, 3H, *J* = 2.8 Hz, CH-C$\underline{H}_3$), 3.33−3.43 (m, 1H, C$\underline{H}$-CH_3), 3.59 (s, 3H, OCH_3), 5.22 (d, 1H, *J* = 11.3 Hz, C$\underline{H}$-imidazole), 6.25 (s, 1H, NH), 6.96−6.99 (m, 1H, H-4″), 7.01−7.05 (m, 4H, H-3′, H-5′, H-2″, H-6″), 7.07−7.11 (m, 2H, H-2′, H-6′), 7.15−7.20 (m, 2H, H-3″, H-5″), 7.25−7.33 (m, 2H, H-5″, H-6″), 7.61 (s, 1H, H-3‴). ^{13}C NMR ($CDCl_3$): δ 16.02 (CH_3, C-4), 44.99 (CH, C-2), 52.11 (CH_3, C-1), 63.98 (CH, C-3), 116.90 (CH, C-4″), 119.39 (CH, C-3′, C-5′, C-2″, C-6″), 122.18 (CH,imid), 124.76 (C, C-1′), 128.55 (CH, C-2′, C-6′, C-3″, C-5″), 129.92 (CH, C-imid‴), 142.28 (C, C-4′), 144.15 (C, C-1″), 174.52 (C, C-1). EI-HRMS $(M + H)^+$ found 336.1709, calculated for $C_{20}H_{21}N_3O_2$ 336.1707.

*Methyl anti-3-(1H-1-Imidazolyl)-3-[4-(2-naphthylamino)phenyl]-2-methylpropanoate (**32**).* Prepared by the reaction of **28** with CDI and imidazole. Purified by column chromatography (CH_2Cl_2−MeOH 100:0 v/v increasing to 97:3 v/v) and obtained in 61% yield as a brown solid. Mp 131−133 °C; TLC (9:1 CH_2Cl_2/MeOH, R_f = 0.62). ^{1}H NMR ($CDCl_3$): δ 1.09 (d, 3H, *J* = 7.0 Hz, CH-C$\underline{H}_3$), 3.29−3.37 (m, 1H, C$\underline{H}$-CH_3), 3.52 (s, 3H, O−CH_3), 5.16 (d, 1H, *J* = 11.3 Hz, C$\underline{H}$-imidazole), 5.96 (s, 1H, NH), 6.95−7.04 (m, 2H, H-1″, imid), 7.12−7.18 (m, 2H, H-3′, H-5′), 7.24−7.27 (m, 3H, H-2′, H-6′, H-3″), 7.32−7.36 (m, 1H, H-4″), 7.38−7.39 (m, 2H, H-7″, H-8″), 7.53 (s, 1H, imid), 7.59 (d, 1H, *J* = 8.2 Hz, imid), 7.67−7.69 (m, 2H, H-6″, H-9″). ^{13}C NMR ($CDCl_3$): δ 16.04 (CH_3, C-4), 44.99 (CH, C-2), 52.23 (CH_3, C-1), 64.00 (CH, C-3), 113.16 (CH, C-1″, imid), 117.52 (CH, C-3′, C-5′, C-3″), 120.47 (CH, C-7″), 123.96 (CH, C-9″), 126.61 (CH, C-8″), 127.68 (CH, C-6″), 128.66 (CH, C-4″, imid), 129.16 (C, C-5″), 129.32 (CH, C-2′, C-6′, C-3‴), 129.60 (C, C-1′), 134.50 (C, C-10″), 139.81.54 (C, C-4′), 143.84 (C, C-2″), 174.47 (C, C-1). EI-HRMS $(M + H)^+$ found 386.1858, calculated for $C_{24}H_{23}N_3O_2$ 386.1863.

*Methyl syn-3-(1H-1-Imidazolyl)-3-[4-(2-naphthylamino)phenyl]-2-methylpropanoate (**33**).* Prepared by the reaction of **29** with CDI and imidazole. Purified by column chromatography (CH_2Cl_2−MeOH 100:0 v/v increasing to 97:3 v/v) and obtained in 57% yield as an oily product. TLC (9:1 CH_2Cl_2/MeOH, R_f = 0.66). ^{1}H NMR ($CDCl_3$): δ 1.08 (d, 3H, *J* = 7.0 Hz, CH-C$\underline{H}_3$), 3.29−3.37 (m, 1H, C$\underline{H}$-CH_3), 3.52 (s, 3H, O−CH_3), 4.47 (d, 1H, *J* = 11.3 Hz, C$\underline{H}$-imidazole), 5.90 (s, 1H, NH), 6.94−7.05 (m, 2H, H-1″, imid), 7.13−7.19 (m, 2H, H-3′, H-5′), 7.24−7.27 (m, 3H, H-2′, H-6′, H-3″), 7.33−7.36 (m, 1H, H-4″), 7.39−7.41 (m, 2H, H-7″, H-8″), 7.52 (s, 1H, imid), 7.60 (d, 1H, J = 8.15 Hz, imid), 7.67−7.70 (m, 2H, H-6″, H-9″). ^{13}C NMR ($CDCl_3$): δ 16.05 (CH_3, C-4), 44.99 (CH, C-2), 52.24 (CH_3, C-1‴), 63.99 (CH, C-3), 113.19 (CH, C-1″, imid), 117.52 (CH, C-3′, C-5′, C-3″), 120.47 (CH, C-7″), 123.98 (CH, C-9″), 126.61 (CH, C-8″), 127.68 (CH, C-6″), 128.66 (CH, C-4″, imid), 129.16 (C, C-5″), 129.32 (CH, C-2′, C-6′, imid), 129.60 (C, C-1′), 134.50 (C, C-10″), 139.81.54 (C, C-4′), 143.84 (C, C-2″), 174.47 (C, C-1). EI-HRMS $(M + H)^+$ found 386.1862, calculated for $C_{24}H_{23}N_3O_2$ 386.1863.

*Methyl 3-(1H-Imidazol-1-yl)-2,3-dimethyl-3-((4-naphthalene-2-yloxy)phenyl)propanoate (**36**).* Prepared by the reaction of **35** with CDI and imidazole. Purified by column chromatography (CH_2Cl_2−MeOH 100:0 increasing to 80:20 v/v, then EtOAc−MeOH 80:20 v/v) and obtained in 16% yield as a white solid. Mp 124−126 °C; TLC (9:1 CH_2Cl_2/MeOH, R_f = 0.1). ^{1}H NMR (DMSO-d_6): δ 1.16 (s, 3, CH_3), 1.27 (s, 3, CH_3), 3.64 (s, 3H, OCH_3), 6.18 (s, 1H, CH), 7.10 (m, 3H, Ar), 7.30 (dd, J = 2.5, 8.9 Hz, 1H, Ar), 7.49 (m, 5H, Ar), 7.68 (s, 1H, Ar), 7.84 (d, J = 8.0 Hz, 1H, Npth), 7.93 (d, J = 8.0 Hz, 1H, Npth), 7.98 (d, J = 8.9 Hz, 1H, Npth), 8.39 (s, 1H, imid). ^{13}C NMR (DMSO-d_6): δ 19.7 (CH_3), 21.9 (CH_3), 46.7 (C, C$\underline{Me}_2$), 52.2 (CH, C$\underline{H}$OH), 82.3 (CH_3, OCH_3), 130.2, 129.3, 127.7, 127.1, 126.7, 125.0, 120.0, 117.8, 117.5, and 114.7 (14 × CH, Ar), 157.2, 153.6, 147.3, 133.9, and 130.0 (5 × C, Ar), 174.8 (C═O). ES^+-LRMS *m*/*z*: 401 $(M + H)^+$, 369 $(M - OCH_3)^+$, 333 $(M -$ imidazole $C_3H_3N_2)^+$. EI-HRMS $(M + H)^+$ found 401.1857, calculated for $C_{25}H_{24}N_2O_3$ 401.1860.

*3-Imidazol-1-yl-2,2-dimethyl-3-(4-naphthalen-2-ylmethyl-phenyl)-propionic Acid Methyl Ester (**42**).* Prepared by the reaction of **41** with CDI and imidazole. Purified by column chromatography (CH_2Cl_2−MeOH 100:0 increasing to 97:3 v/v) and obtained in 70% yield as a white solid. Mp 126−128 °C; TLC (9:1 CH_2Cl_2/MeOH, R_f = 0.33). ^{1}H NMR (DMSO-d_6): δ 1.09 (s, 3H, H−CH_3), 1.24 (s, 3H, H−CH_3), 3.62 (s, 3H, H−CH_3-ester), 4.11 (s, 2H, H−CH_2), 6.12 (s, 1H, H−CH), 7.08 (s, 1H, Ar), 7.27 (d, *J* = 7.4 Hz, 2H, Ar), 7.33 (d, *J* = 7.6 Hz, 2H, Ar), 7.38 (d, *J* = 8.4 Hz, 1H, Ar), 7.45−7.50 (m, 2H, Ar), 7.62 (s, 1H, Ar), 7.74 (s, 1H, Ar), 7.81−7.86 (m, 3H, Ar), 8.31 (s, 1H, Ar). ^{13}C NMR (DMSO-d_6): δ 19.69 (CH, CH_3), 21.80 (CH, CH_3), 40.80 (C, CH_2), 46.65 (C, C-3), 52.13 (CH, CH_3-ester), 82.61 (C, CH), 117.47 (CH, Ar), 125.41 (CH, Ar), 126.08 (CH, Ar), 126.71 (CH, Ar), 127.34 (CH, Ar), 127.45 (CH, Ar), 127.55 (CH, Ar), 127.98 (CH, Ar), 128.45 (CH, Ar), 130.57 (CH, Ar), 131.60 (CH, Ar), 132.84 (C, Ar), 133.14 (C, Ar), 138.41 (C, Ar), 141.68 (C, Ar), 147.24 (CH, Ar), 174.74 (C, CO). EI-HRMS $(M + H)^+$ found 399.2067, calculated for $C_{26}H_{26}N_2O_2$ 399.2067.

*3-[4-(6-Hydroxy-naphthalen-2-ylamino)-phenyl]-3-imidazol-1-yl-2,2-dimethyl-propionic Acid Methyl Ester (**22**).* 3-Hydroxy-3-[4-(6-methoxy-naphthalen-2-ylamino)-phenyl]-2,2-dimethyl-propionic acid methyl ester (**21**) (0.1 g, 0.23 mmol) and *n*-Bu_4NI (0.11 g, 0.3 mmol) were stirred in dry CH_2Cl_2 (10 mL) at −78 °C under N_2. A solution of BCl_3 (0.6 mL, 1.0 M in CH_2Cl_2, 2.5 mmol) was added over 2 min. After 5 min, the reaction solution was allowed to warm to 20 °C and was stirred for 1 h. The reaction solution was quenched with ice and H_2O, stirred for 30 min then diluted with sat. aq. $NaHCO_3$ solution (25 mL), and extracted with CH_2Cl_2 (50 mL). The organic layer was dried ($MgSO_4$), filtered, and reduced *in vacuo*. Purification by flash column chromatography (CH_2Cl_2/MeOH 100:0 increasing to 95:5) gave 3-[4-(6-hydroxy-naphthalen-2-ylamino)-phenyl]-3-imidazol-1-yl-2,2-dimethyl-propionic acid methyl ester (**22**) as a yellow oil. Yield 0.047 g (49%). TLC (97:3 CH_2Cl_2/MeOH, R_f = 0.59). ^{1}H NMR ($CDCl_3$): δ 1.27 (s, 3H, H-4), 1.30 (s, 3H, H-5), 3.65 (s, 3H, H-1), 5.57 (s, 1H, H-6), 6.01 (s, 1H, H-NH), 7.04 (d, *J* = 7.8 Hz, 2H, Ar), 7.11 (s, 1H, H-3‴), 7.20 (m, 3H, Ar), 7.26 (d, *J* = 7.6 Hz, 1H, Ar), 7.33 (d, *J* = 7.5 Hz, 2H, H-2′ H-6′), 7.41 (s, 1H, H-2‴), 7.50 (d, *J* = 8.0 Hz, 1H, H-4″), 7.62 (s, 1H, H-1‴), 7.69 (d, *J* = 8.2 Hz, 1H, H-9″), 7.73 (s, 1H, H-2″), 7.91 (s, 1H, H−OH). ^{13}C NMR ($CDCl_3$): δ 22.67 (CH_3, C-4), 22.93 (CH_3, C-5), 47.35 (C, C-3), 51.84 (CH_3, C-1), 66.88 (CH, C-6), 104.88 (CH, C-7″), 110.87 (CH, C-2″), 112.44 (CH, C-2‴), 116.06 (CH, C-3′ C-5′ C-10″), 118.62 (CH, C-4″), 119.71 (CH, C-3‴), 121.22 (CH, C-5″), 127.15 (CH, C-1‴), 127.68 (C, C-8″), 128.01 (CH, C-9″), 128.09 (CH, C-2′ C-6′, 129.44 (C, C-1′), 130.15 (C, C-3″), 136.13 (C, C-4′), 141.28 (C, C-1″), 148.91 (C, C-6″), 175.55 (C, C-2). EI-HRMS $(M + H)^+$ found 416.1970, calculated for $C_{25}H_{25}N_3O_3$ 416.1969.

*Methyl 3-Hydroxy-2,2-dimethyl-3-(4-(naphthalene-2-yloxy)phenyl)propanoate (**35**).* To a mixture of **34**[26] (1.3 g, 5.8 mmol), $Cu(OAc)_2$ (1.16 g, 6.4 mmol), 2-naphthylboronic acid (2.0 g, 11.6 mmol), and powdered activated 4 Å molecular sieves (7.5 g) was added CH_2Cl_2 (40 mL) followed by Et_3N (4.0 mL, 29.0 mmol), and the reaction mixture was stirred vigorously at room temperature for 19 h. The reaction mixture was filtered through Celite, and the residue was washed with CH_2Cl_2. The filtrate was washed with 1 M aqueous HCl (100 mL), which was back-extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a brown syrup. Purification by flash column

chromatography (petroleum ether−EtOAc 80:20) gave the required product as a white solid. Yield 0.82 g (40%); mp 80−82 °C; TLC (2:1 petroleum ether/EtOAc, R_f = 0.51). ^{1}H NMR ($CDCl_3$): δ 1.05 (s, 3, CH_3), 1.09 (s, 3, CH_3), 3.07 (d, J = 4.2 Hz, 1H, CHOH), 3.65 (s, 3H, OCH_3), 4.82 (d, J = 4.2 Hz, 1H, CHOH), 6.94 (d, J = 8.7 Hz, 2H, Ph), 7.17 (m, 1H, Npth), 7.21 (d, J = 8.6 Hz, 2H, Ph), 7.22 (m, 1H, Npth), 7.34 (m, 2H, Npth), 7.61 (d, J = 8.2 Hz, 1H, Npth), 7.73 (d, J = 7.8 Hz, 1H, Npth), 7.74 (d, J = 8.9 Hz, 1H, Npth). ^{13}C NMR ($CDCl_3$): δ 19.2 (CH_3), 23.0 (CH_3), 47.8 (C, CMe_2), 52.1 (CH, CHOH), 78.3 (CH_3, OCH_3), 129.9, 129.1, 127.8, 127.1, 126.6, 124.8, 120.0, 118.3, and 114.3 (11 × CH, Ar), 156.8, 154.9, 135.0, 134.3, and 130.2 (5 × C, Ar), 178.2 (C=O). Anal. C, H.

*4-Naphthalen-2-ylmethyl-benzaldehyde (**39**).* A solution of 2-bromomethylnaphthalene (**37**) (2.0 g, 9.05 mmol) in anhydrous toluene (20 mL) was treated with $Pd(PPh_3)_4$ (1.0 g, 0.9 mmol). The mixture was then purged with N_2 and stirred for 30 min. 4-Formyl-phenylboronic acid (**38**) (2.0 g, 13.6 mmol) was then added followed by sat. aq. Na_2CO_3 (8 mL), and the reaction mixture was purged again with N_2 and refluxed for 20 h. The solvent was then evaporated *in vacuo*, and the residue was dissolved in CH_2Cl_2 (100 mL), extracted with H_2O (2 × 50 mL), and dried ($MgSO_4$). The organic layer was evaporated to dryness under reduced pressure, and the residue was purified by flash column chromatography (petroleum ether−EtOAc 90:10 v/v increasing to 80:20 v/v) to give the product[34] as a yellow syrup in 1.72 g (77%) yield. TLC (3:1 petroleum ether/EtOAc, R_f = 0.57). ^{1}H NMR ($CDCl_3$): δ 4.12 (s, 2H, CH_2), 7.19 (dd, J = 1.7, 8.4 Hz, 1H, Ar), 7.29 (d, J = 8.0 Hz, 2H, Ar), 7.36 (m, 2H, Ar), 7.54 (s, 1H, Ar), 7.69 (m, 5H, Ar), 9.88 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$); δ 42.3 (CH_2), 130.1, 129.7, 128.4, 127.7, 127.6, 127.4, 126.2, and 125.7 (11 × CH), 148.3, 137.2, 134.8, 133.6, and 132.2 (5 × C), 191.9 (C, CHO).

*Methyl 2,2-Dimethyl-3-(4-(naphthalen-2-ylmethyl)phenyl)-3-(trimethylsilyloxy) Propanoate (**40**).* To a stirred solution of pyridine-*N*-oxide (22 mg, 0.235 mmol) and LiCl (20 mg, 0.47 mmol) in anhydrous DMF (2 mL) was added a solution of 4-(naphthalen-2-ylmethyl)benzaldehyde (**39**)[35] (0.58 g, 2.35 mmol) in anhydrous DMF (5 mL) followed by methyl trimethylsilyl dimethylketene acetal (1.9 mL, 0.42 mmol), and the reaction was stirred at room temperature for 72 h. The reaction flask was cooled in ice and 1 M aqueous HCl (25 mL) added slowly to quench the reaction. The product was extracted into EtOAc (2 × 50 mL), and then the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a dark yellow syrup. Purification by flash column chromatography (petroleum ether−EtOAc 4:1 v/v) gave the TMS protected compound as a white waxy solid in a yield of 0.323 g (33%). TLC (2:1 petroleum ether/EtOAc, R_f = 0.87). ^{1}H NMR ($CDCl_3$): δ 0.00 (s, 9H, $Si(CH_3)_3$), 1.03 (s, 3, CH_3), 1.16 (s, 3, CH_3), 3.71 (s, 3H, OCH_3), 4.17 (s, 2H, CH_2), 4.99 (s, 1H, CH), 7.18 (m, 2H, Ar), 7.23 (m, 2H, Ar), 7.36 (dd, J = 1.6, 8.4 Hz, 1H, Ar), 7.48 (ddd, J = 1.5, 6.9, 8.4 Hz, 2H, Ar), 7.65 (s, 1H, Ar), 7.83 (m, 3H, Ar). ^{13}C NMR ($CDCl_3$): δ 0.00 (CH_3, TMS), 19.1 (CH_3), 21.8 (CH_3), 41.8 (CH_2), 49.1 (C), 51.6 (CH), 79.0 (CH_3, OCH_3), 128.1, 128.0, 127.9, 127.7, 127.6, 127.55, 127.1, 126.0, and 125.4 (11 × CH, Ar), 140.0, 138.7, 138.6, 133.6, and 132.1 (5 × C, Ar), 177.4 (C=O).

*Methyl 3-Hydroxy-2,2-dimethyl-3-(4-(naphthalen-2-ylmethyl)phenyl)-propanoate (**41**).* The TMS-protected product (**40**, 0.32 g, 0.76 mmol) was dissolved in MeOH (15 mL) and treated with Dowex 50W (H^+) (1.20 g) [Dowex 50W was washed with 10% aqueous HCl (20 mL), MeOH (20 mL), CH_2Cl_2 (20 mL) and another 10% aqueous HCl (20 mL) prior to use] for 30 min. The Dowex resin was removed by filtration, and the MeOH was evaporated *in vacuo*. The resulting yellow syrup was dissolved in EtOAc (75 mL), washed with saturated aqueous $NaHCO_3$ (40 mL) and H_2O (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give the required product (**41**) as a pale yellow syrup that became a waxy solid on standing. Yield 0.24 g (91%); mp 91−92 °C; TLC (2:1 petroleum ether/EtOAc, R_f = 0.56). ^{1}H NMR ($CDCl_3$): δ 1.03 (s, 3, CH_3), 1.06 (s, 3, CH_3), 2.93 (d, J = 4.0 Hz, 1H, OH), 3.63 (s, 3H, OCH_3), 4.05 (s, 2H, CH_2), 4.79 (d, J = 3.6 Hz, 1H, CH), 7.10 (m, 2H, Ar), 7.16 (m, 2H, Ar), 7.22 (dd, J = 1.7, 8.5 Hz, 1H, Ar), 7.35 (ddd, J = 1.5, 6.9, 8.3 Hz, 2H, Ar), 7.54 (s, 1H, Ar), 7.70 (m, 3H, Ar). ^{13}C NMR ($CDCl_3$): δ 19.1 (CH_3), 23.1 (CH_3), 41.8 (CH_2), 47.7 (C), 52.1 (CH), 78.6 (CH_3, OCH_3), 128.5, 128.1, 127.8, 127.6, 127.55, 127.1, 126.0, and 125.4 (11 × CH, Ar), 140.5, 138.5, 137.9, 133.6, and 132.1 (5 × C, Ar), 178.2 (C=O). Anal. C, H.

Molecular Modeling. All molecular modeling studies were performed on a MacPro dual 2.66 GHz Xeon running Ubuntu 9. Ligand structures were built in MOE[36] minimized using the MMFF94x forcefield until a rmsd gradient of 0.05 kcal mol^{-1} Å^{-1} was reached. Docking simulations were performed using PLANTS[37] (aco_ants 20; aco_evap 0.15; aco_sigma 5.0), with ligands docked within the active site of the CYP26A1 homology model,[38] and the results were visualized in MOE. Molecular dynamics simulations were performed with GROMACS[39,40] and the Gromos96 force field in a NPT environment. Individual ligand/protein complexes obtained from the docking results were soaked in a triclinic water box and minimized using a steepest descent algorithm to remove unfavorable van der Waals contacts. The system was then equilibrated via a 100 ps MD simulation at 300 K with restrained ligand/protein complex atoms. Finally, a 5 ns simulation was performed at 300 K with a time step of 2 fs and hydrogen atoms constrained with a LINCS algorithm. Visualization of the dynamics trajectories was performed with the VMD software package, version 1.8.3.[41]

■ ASSOCIATED CONTENT

Supporting Information. The numbering of compounds for ^{1}H and ^{13}C NMR characterization and synthetic details and full spectroscopic data for compounds **5**, **6**, **7**, **8**, **9**, **11**, **26**, **27**, **28**, and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS

ATRA, all-*trans*-retinoic acid; RA, retinoic acid; RAMBAs, retinoic acid metabolism blocking agents

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