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Inhibitors of Lipoprotein(a) Assembly

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Abstract—Compounds of the general structure **A** and **B** were investigated for their activity as lipoprotein(a), [Lp(a)], assembly (coupling) inhibitors. SAR around the amino acid derivatives (structure **A**) gave compound **14-6** as a potent coupling inhibitor. Oral dosing of compound **14-6** to Lp(a) transgenic mice and cymologous monkeys resulted in a $>30\%$ decrease in plasma Lp(a) levels after 1–2 weeks of treatment at 100 mg/kg/day.

Introduction

Current therapies for the treatment and prevention of premature atherosclerotic vascular disease (i.e., coronary heart disease and stroke) are changes in diet, exercise and administration of lipid lowering agents. However, there still remains a significant number of patients who do not benefit from the latter protective measures.[1] This suggests the presence of additional risk factors that are not modified by existing therapies. One of these additional risk factors may be lipoprotein(a), [Lp(a)], for which there is no suitable treatment.[1] Some epidemiological studies have demonstrated that plasma Lp(a) levels >20–30 mg/dL is an independent risk factor for the development of premature atherosclerotic vascular disease.[1] Consistent with the latter findings, Lp(a) accumulates in the arterial wall at a concentration proportional to its plasma concentration.[2] Furthermore, recent studies using transgenic rabbits have directly demonstrated that Lp(a) is atherosclerotic.[3]

Lp(a) consists of two particles, apolipoprotein(a), [apo(a)], and apolipoproteinB-100, (apoB-100), of low density lipoprotein (LDL).[1] Apo(a) is highly related to plasminogen. However, unlike plasminogen, apo(a) contains multiple and variable amounts of the kringleIV domain.[4] Both apo(a) and apoB-100 are synthesized predominantly by the liver and coupled through a single disulfide bond to form Lp(a). The coupling reaction is thought to occur extracellularly.[1] Unlike LDL, plasma Lp(a) levels are genetically determined and unaffected by diet, exercise and commonly used lipid lowering agents.[4] A suitable treatment for elevated plasma Lp(a) would have great potential in treating those that do not respond to current therapies.

Previous studies have demonstrated that inhibition of the apo(a)/apoB-100 coupling reaction may be a potential means of lowering Lp(a).[5,6] Therefore, it was our goal to develop compounds which would reduce plasma Lp(a) levels by blocking the disulfide bond formation between apo(a)/apoB-100. Our efforts were directed at two series of compounds, the amino acid (general structure A) and the sulfonamide (general structure B) derivatives. The sulfonamide series gave a flat SAR and

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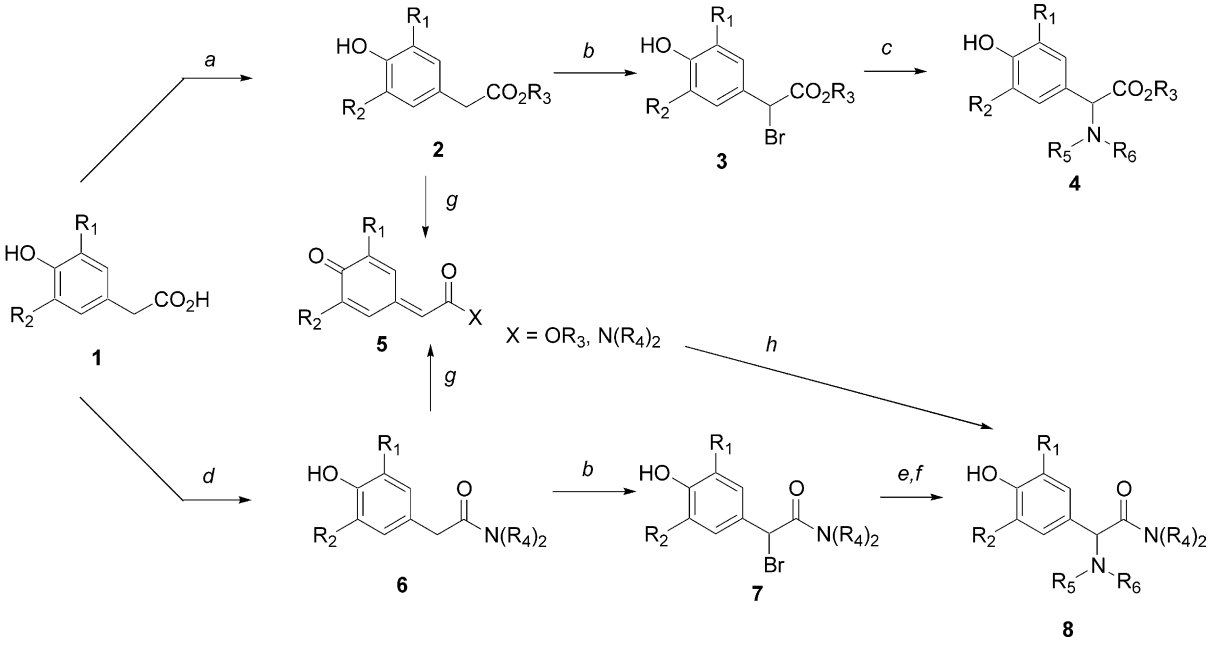
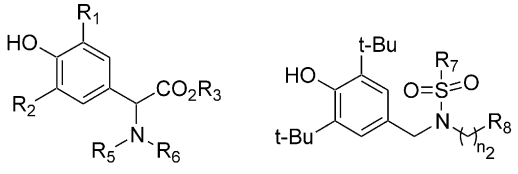


Scheme 1. (a) H_2SO_4, R_3OH; Note: when $R_3 = t$-Bu, H_2SO_4, isobutylene, aq KOH, Et_2O, dioxane; (b) NBS, cat $(PhCO)_2O_2$, CCl_4; (c) NHR_5R_6, Et_3N, THF; (d) $(COCl)_2$, cat DMF; $NH(R_4)_2$, Et_3N, CH_2Cl_2 or HOBt, DCC, $NH(R_4)_2$, CH_2Cl_2; (e) NH_2R_5, Et_3N, THF; (f) R_6CHO, $NaHB(OAc)_3$, DCE; (g) KOH, $K_3Fe(CN)_6$, C_6H_6, H_2O; (h) NHR_5R_6, THF.

was inactive in vivo so most of our efforts focused on the amino acid derivatives. Compound **14-6**, an amino acid derivative, was taken forward for in vivo studies. In Lp(a) transgenic mice, plasma Lp(a) levels were decreased 21±3.2% after a single week of dosing and 30.7±3.2% after 2 weeks of oral dosing. Due to the efficacy of compound **14-6** in the Lp(a) transgenic mice, it was administered to cynomolgus monkeys. After 1 week of treatment (100 mg/kg/day), monkey plasma Lp(a) levels were decreased 34.7±5.6%. In this paper we discuss the chemistry, SAR and biological activity of these compounds.



14-6(A): R_1, R_2 = tBu; R_3 = Et; R_5, R_6 = CH_2-3-pyridyl

Chemistry

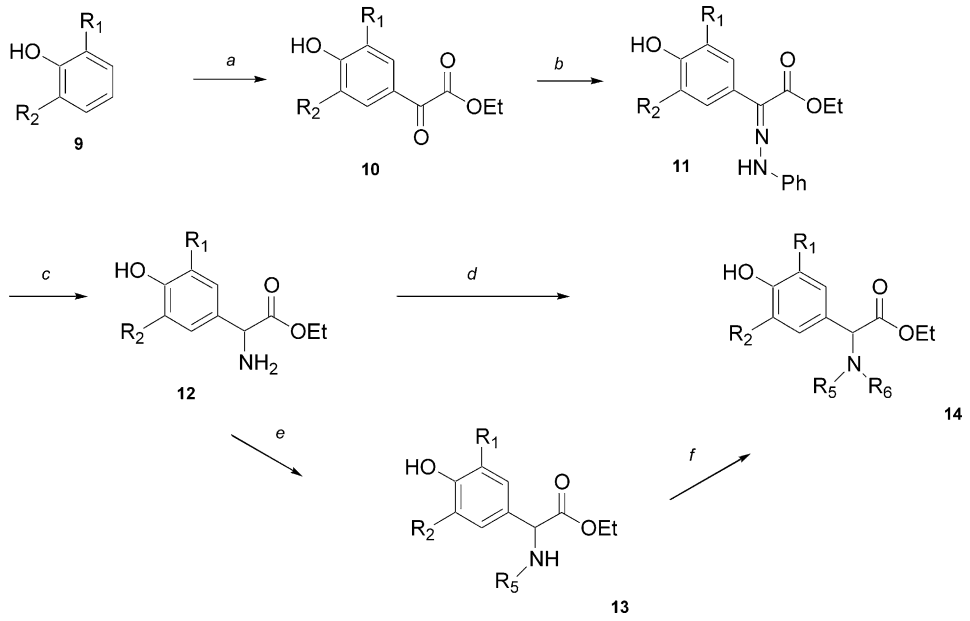
Amino acid derivatives

All amino acid derivatives were prepared according to Scheme 1 or 2. The ester analogues (Scheme 1) were prepared by Fischer esterification of a 4-hydroxyphenyl acetic acid derivative (**1**), followed by bromination (**3**) with *N*-bromosuccinimide (NBS) and displacement by the appropriate amine to give the desired product (**4**). The amide analogues were also prepared according to Scheme 1. Amide (**6**) was made from carboxylic acid (**1**) via the acid chloride or using HOBt and DCC as coupling reagents. The amide (**6**) was either brominated with NBS (**7**) followed by displacement with an amine to give the final compound (**8**) or oxidized to the quinone methine (**5**) and then coupled with an amine to give **8**. If the amine was not commercially available (Scheme 1, step e), it was prepared using reductive amination conditions with the appropriate amine and aldehyde. Quinone derivatives (**5**) were obtained by oxidizing the ester (**2**) or amide (**6**) with potassium ferricyanide (III).

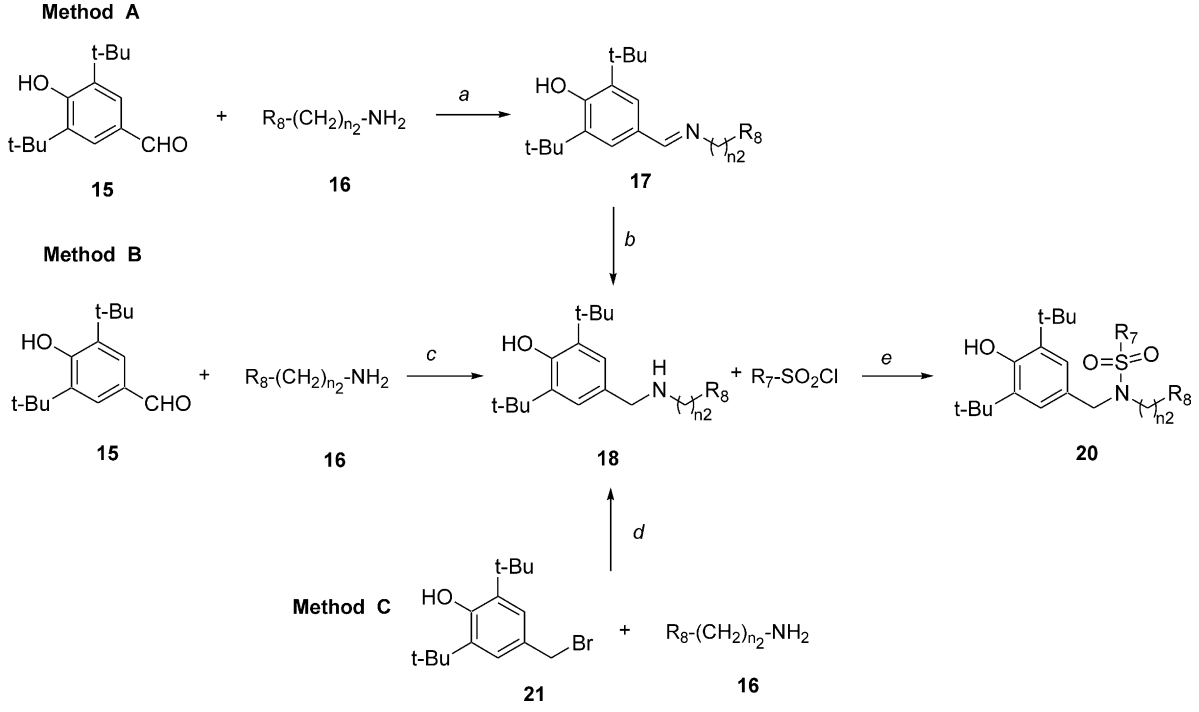
In Scheme 2, the desired compounds were made by a Friedel–Craft acylation of the appropriate 2,6-disubstituted phenol (**9**) with ethyl oxalyl chloride, followed by condensation with phenylhydrazine (**11**) and reduction to the amine (**12**) with 10% palladium on carbon. This amine (**12**) was subjected to reductive amination conditions in 1,2-dichloroethane (DCE) to obtain secondary and tertiary amines (**13**, **14**).

Sulfonamides

All sulfonamides were prepared as shown in Scheme 3, except **24** and **27**. For compounds in Table 9, the penultimate amine (**18**) [2,6-di-*tert*-butyl-4-(pyridin-3-ylaminomethyl)phenol] was prepared according to Scheme 3, method A by refluxing 3-aminopyridine (**16**) with 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**15**) in toluene and catalytic amounts of *p*-toluenesulfonic acid (PTSA) to form the corresponding imine (**17**). This imine (**17**) was reduced by catalytic hydrogenation using Raney nickel in a methanol/THF solution at room temperature. Amine (**18**) was coupled with various sulfonyl chlorides (**19**) by heating in pyridine at 60 °C with catalytic amounts of 4-dimethylaminopyridine (4-DMAP) to obtain the desired product (**20**).



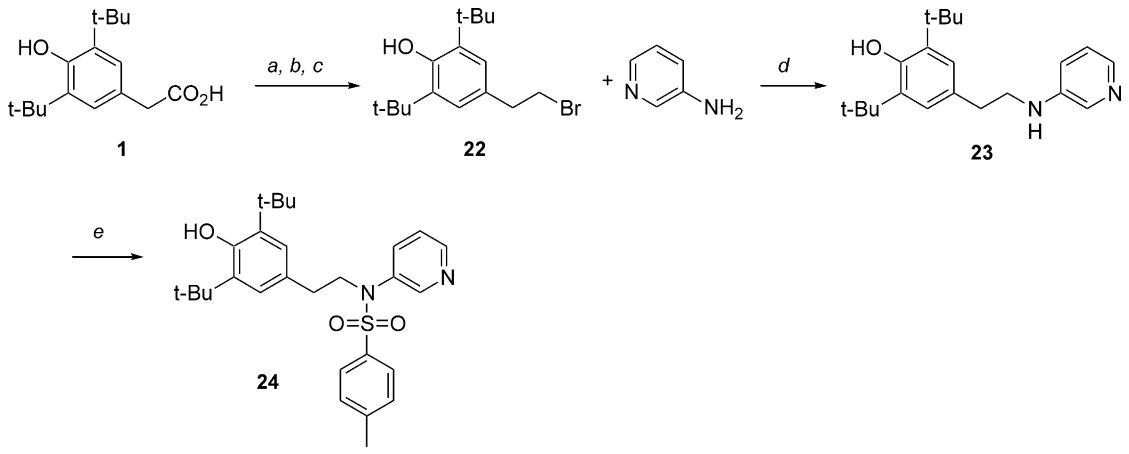
Scheme 2. (a) $AlCl_3$, ethyloxalyl chloride, CH_2Cl_2; (b) $PhNHNH_2$, EtOH; (c) H_2, 10% Pd/C, 1.5:1 THF/EtOH; (d) 2 equiv R_5CHO, $NaB(OAc)_3H$, DCE: (e) equiv R_5CHO, $NaB(OAc)_3H$, DCE; (f) 1 equiv R_6CHO, $NaB(OAc)_3H$, DCE.



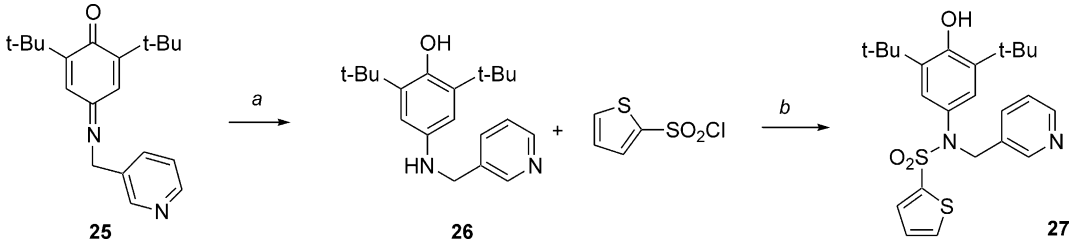
Scheme 3. (a) Cat PTSA, $PhCH_3$; (b) RaNi, THF/MeOH or 20%Pt/C, MeOH, AcOH; (c) $NaB(OAc)_3H$, DCE; (d) K_2CO_3, CH_3CN; (e) cat. 4-DMAP, pyridine.

For compounds in Table 10, 4-toluenesulfonyl chloride was coupled with various amines (**18**) to form the sulfonamides (**20**). Three methods (A, B, C) were used to make amines (**18**). Only imine (**17**) formation was observed with heterocyclic amines under reductive amination conditions. For this reason, amines containing heterocycles were subjected to condensation/reduction conditions (Scheme 3, method A). For aniline and substituted anilines, reductive amination conditions gave the desired penultimate amine, **18** (Scheme 3, method B). In one case, nucleophilic displacement was utilized (Scheme 3, method C).

For compounds in Table 11, the penultimate amine (**18**) was prepared as shown in Scheme 3, method A, unless otherwise noted, then coupled with various sulfonyl chlorides (**19**) to give the sulfonamides, **20**. To prepare compound **24** (Scheme 4), 3,5-di-*tert*-butyl-4-hydroxyphenylacetic acid was converted to the acid chloride, reduced with lithium aluminum hydride (LAH), brominated with phophorus tribromide and coupled with 3-aminopyridine in refluxing toluene to give amine **23**. This was coupled with 4-toluenesulfonyl chloride to give sulfonamide, **24**. Compound **27** (Scheme 5) was prepared from 2,6-di-*tert*-butyl-1,4-benzoquinone and 3-



Scheme 4. (a) $(COCl)_2$, cat DMF; (b) LAH, Et_2O; (c) PBr_3, Et_2O; (d) Et_3N, Kl, $PhCH_3$; (e) TsCl, cat 4-DMAP, pyridine.



Scheme 5. (a) $NaB(OAc)_3H$, AcOH, DCE; (b) pyridine, DCE.

aminopyridine as described by Reiker and Kessler[7] to form imine, **26**, which was subsequently reduced with sodium triacetoxyborohydride and coupled with 2-thiophenesulfonyl chloride to give the desired product, **27**.

Biological Methods

The Lp(a) biochemical coupling assay, LpABC, consists of incubating recombinant apo(a), [r-apo(a)], with apoB-100 of LDL. Lp(a) generated from the latter reaction is analyzed by a previously described ELISA.[8] The source of r-apo(a) is conditioned media from human 293 cells permanently expressing a human 17-kringle IV apo(a) cDNA expression construct.[9] Conditioned media from HepG2 cells is used as a source of LDL. To analyze the influence of compounds on the Lp(a) coupling reaction, 45 μL of conditioned media from the 293 cells is added to a 0.5 μL test tube followed by the addition of 10 μL of compound at concentrations ranging from 0.03 to 50 μM and 45 μL of HepG2 conditioned media (LDL source). The mixture is incubated at 37 °C for 30 min and Lp(a) measured by ELISA as described above. Optical density at $\lambda_{450\ nm}$ (OD_{450}) from the Lp(a) ELISA plates is used as a direct measure of the amount of Lp(a) generated by the coupling of r-apo(a) and apoB-100.

The Lp(a) cellular assay, LpA3, uses HepG2 cells permanently transfected with the apo(a) cDNA construct described above. The expressed r-apo(a) couples to the endogenously made apoB-100 from the HepG2 cells to form Lp(a). In the assay, compounds are incubated with the cells for 8 h. Lp(a) is measured in the culture media by ELISA as described above. The cell-based LpA3 assay is used to test the activity of the compounds in a more physiological setting than LpABC (e.g., presence of plasma proteins). Compounds active in the cellular assay (LpA3) but not the biochemical assay (LpABC) (i.e., those that are not coupling inhibitors) could affect any other aspect of apo(a) and/or apoB-100 synthesis.

In vivo studies

For in vivo testing, Lp(a) transgenic mice, generated essentially as described,[10] and cynomolgus monkeys[11] were used. Mice were dosed by oral gavage with the compound delivered in a solution consisting of carboxy methlycellulose and 0.3% Tween-20. Monkeys were dosed by placing the compound in their meal. Animals were bled and plasma Lp(a) levels were determined on a COBAS MIRA Plus (Roche) chemistry system using Wako reagents.

Results and Discussion

Amino acid derivatives—in vitro data

The first structure–activity relationship (SAR) studied was replacements of the 3,5-di-*tert*-butyl-4-phenol moiety. Table 1 shows that all replacements for the *tert*-butyl groups were detrimental to the activity in the biochemical (LpABC) assay. For this reason, the 3,5-di-*tert*-butyl-4-phenol moiety was retained.

The structure of the compounds may suggest that they work as antioxidants. While this may be one possible

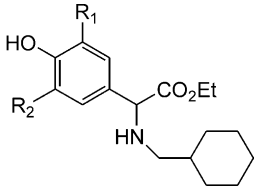
mechanism, it is not the only one, as shown by several lines of evidence. If the compounds worked as antioxidants, derivatives without the *tert*-butyl groups should still be active. Our results show that any changes to the *tert*-butyl groups gave inactive compounds (Table 1). The activity changed as the substitution on the amine was varied, both from primary to secondary to tertiary (Table 6) and also among the different tertiary amines (Tables 3 and 6). This shows that the substitution on the amine also contributed to the activity.

Several quinone methine derivatives (**5**) were synthesized and are shown in Table 2. These quinone methine derivatives (**5**) were some of the potent analogues in the biochemical (LpABC) assay.

Tables 3 and 4 summarize SAR on secondary amines. Table 3 highlights secondary amines containing alkyl, cycloalkyl, benzyl and substituted benzyl amines. In the biochemical (LpABC) assay, alkyl and cycloalkylamines showed moderate activity with cyclohexyl derivatives being the more potent of these compounds (**4-6**, **13-1**). Most of the benzyl and substituted benzyl compounds were inactive in the biochemical (LpABC) assay. Of the ones that exhibited activity, only moderate (10–50 μM) activity was observed. Table 4 displays secondary amines with various aromatic and heteroaromatic groups and carbamates. It was observed that bulky substituents on the amine were inactive [(**13-45**–**13-48,** except compound **13-44** (21.99 μM)],as well as carbamates (**13-49**, **13-50**). The phenethyl amine (**13**–**43**) and furyl amine (**13-55**) exhibited moderate activity while the pyridyl amine (**13-51**) and methyl pyridyl amines (**13-9**, **13-10**, **13-12**) were the most active of the secondary amines.

Compounds containing tertiary amines are summarized in Table 5. It was found that in the biochemical (LpABC) assay, compounds with alkyl groups gave submicromolar activity, although little change was observed in in vitro potency among the different alkyl groups (**4-2**, **4-4**, **4-7**–**4-9**). Tertiary amines with a benzyl group exhibited only moderate activity or were inactive (**14-2**, **14-13**, **14-14**), the most potent compound containing a methylene-2-pyridine moiety (**14-5**). It was

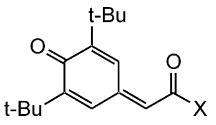
Table 1. Effect of R_1, R_2 on in vitro activity



Compd	R_1	R_2	LpABC IC_{50} (μM)	LpA3 IC_{50} (μM)
13-1	*t*-Bu	*t*-Bu	6.52	ia
13-2	*t*-Bu	Me	ia	NA
13-3[a]	*t*-Bu	H	ia	ia
13-4	H	H	ia	ia
13-5	Cl	Cl	ia	ia
13-6	Ph	Ph	60.18	ia
13-7	s-Bu	s-Bu	67.39	35.2

ia, inactive (no dose–responsive curve was obtained up to 100 μM); NA, not available; $p < 0.05$.
[a]HCl salt.

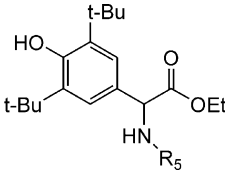
Table 2. In vitro activity of quinone methine derivatives



Compd	X	LpABC IC_{50} (μM)	LpA3 IC_{50} (μM)
5-1	O-*n*-Bu	0.30	0.9
5-2	N(*n*-Bu)$_2$	0.38	NA
5-3	OMe	1.03	3.80

NA, not available.

Table 3. Effect of R_5 on in vitro activity



Compd	R_5	LpABC IC_{50} (μM)	LpA3 IC_{50} (μM)
4-1	Me	19.04	16
4-5	Et	10.89	13
4-2	*n*-Bu	11.22	40
4-6	Cyclohexyl	4.16	49
13-1	CH_2-cyclohexyl	6.52	ia
13-13	CH_2-cyclopropyl	12.17	25
13-8	Bn	10.27	ia
13-14[a]	3-(OH)Bn	ia	ia
13-15[a]	4-(OH)Bn	29.18	ia
13-16[a]	2-(OMe)Bn	54.30	ia
13-17[a]	4-(OMe)Bn	29.63	ia
13-18[a]	4-(OBn)Bn	ia	ia
13-19[a]	2-(CF_3)Bn	33.41	ia
13-20[a]	3-(CF_3)Bn	53.94	ia
13-21[a]	2-(Cl)Bn	43.40	ia
13-22	3-(Cl)Bn	12.48	ia
13-23[a]	4-(Cl)Bn	ia	ia
13-24[a]	2-(F)Bn	50.16	ia
13-25[a]	3-(NO_2)Bn	46.68	ia
13-26[a]	4-(NO_2)Bn	ia	ia
13-27[a]	4-(NH_2)Bn	ia	ia
13-28[a]	4-(NMe_2)Bn	53.99	ia
13-29[a]	4-(NBu_2)Bn	ia	ia
13-30[a]	4-(CN)Bn	ia	ia
13-31[a]	2-(Me)Bn	ia	ia
13-32[a]	3-(Me)Bn	ia	ia
13-33[a]	2,4-(diCl)Bn	47.94	ia
13-34[a]	3,4-(diCl)Bn	ia	ia
13-35[a]	3,5-(diCl)Bn	ia	ia
13-36[a]	3-(Me)-4-(OMe)Bn	ia	ia
13-37[a]	4-(OH)-3-(OMe)Bn	14.98	ia
13-38[a]	4-(OH)-3-(OEt)Bn	59.08	ia
13-39	3,4,5-(OMe)Bn	10.26	4.6
13-40	3-(OH)-4,5-(OMe)Bn	10.59	9.3
13-41	3,5-(di-*t*-Bu)-4-(OH)Bn	ia	ia
13-42[a]	3,5-(diCl)-2-(OH)Bn	15.87	ia

ia, inactive (no dose–response curve was obtained up to 100 μM); $p < 0.05$.
[a]Parallel synthesis.

found that the di(methylene-2-pyridine) moiety gave submicromolar activity (**14-3**). In general, tertiary amines substituted with two pyridyl groups were more active than those with only one pyridyl group (**14-3**, **14-4**, **14-6**, **14-7** vs **14-5**, **14-13**, **14-14**, **14-9**). Enantiomic separation for compound **14-6** di(methylene-3-pyridine) was performed and the activities of the two enantiomers were comparable. For this reason, only the racemates were synthesized in further studies.

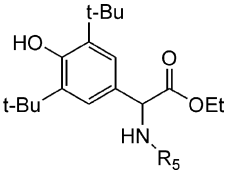
Table 6 compares the activities of primary, secondary and tertiary amines. It was found that in the biochemical (LpABC) assay, the primary amine was inactive (**12**) and that tertiary amines were, in general, more potent than secondary amines (**4-1** vs **4-2**, **4-3** vs **4-4**, **13-8** vs **14-2**, etc.).

SAR studies on the ester (R_3) are summarized in Table 7. It was possible that the ethyl ester would be metabolized in vivo and a more hindered ester, such as the *tert*-butyl ester, or an amide, would prevent such metabolism. The carboxylic acid was found to be inactive (**13-11**). In general, in the biochemical (LpABC) assay, ester modification of compounds containing a tertiary amine resulted in little change in activity (**4-12**, **4-14**–**4-16**), although the ethyl ester was always the most active. For compounds containing secondary amines, changing the ethyl ester to a bulkier group, such as the *tert*-butyl ester, resulted in decreased activity (**13-1** vs **4-19**, **13-10** vs **4-20**, **4-21**).

Table 8 outlines SAR around compounds containing either an amide or an ester. Replacing the ester with an amide had little effect on in vitro potency in the biochemical (LpABC) assay, regardless of the substituents on the amino portion of the molecule (**4-2** vs **8-1**–**8-3**, **14-6** vs **8-4** through **8-6**, **4-17** vs **8-7**–**8-10**). Based on this data, the amide was considered a suitable replacement for the ethyl ester.

In general, the activity decreased in the cell-based assay (LpA3) compared to the biochemical assay (LpABC). This may be attributed to one of two reasons. In the cellular assay (LpA3), the compound could have been bound to other cellular components or possibly metabolized into less active or inactive metabolites. It should be noted that, in most cases, the rank order of potency was similar in the two assays. In some cases, the compounds are more active in the cellular (LpA3) assay compared to the biochemical (LpABC) assay (**4-1**, **4-15**, **4-20**, **13-7**, **13-39**, **13-52**, **12**). This may be due to possible formation of more active metabolites.

Table 4. Effect of R_5 on in vitro activity



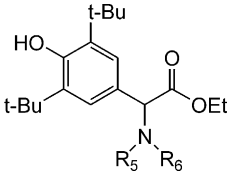
Compd	R_5	LpABC IC_{50}(μM)	LpA3 IC_{50}(μM)
13-43	$(CH_2)_2Ph$	8.54	64.4
13-44[a]	$CH_2CH(Ph)_2$	21.99	ia
13-45[a]	CH_2-4-diphenyl ether	ia	ia
13-46[a]	CH_2-1-naphthyl	ia	ia
13-47[a]	CH_2-1-(4-OMe)naphthyl	ia	ia
13-48[a]	CH_2-2-anthracene	ia	ia
13-49	CO_2Bn	ia	ia
13-50	CO_2t-Bu	ia	ia
13-51	3-Pyridyl	3.05	7.60
13-52	CO-3-pyridyl	ia	44
13-9	CH_2-2-pyridyl	6.48	9.10
13-10	CH_2-3-pyridyl	5.90	20
13-12	CH_2-4-pyridyl	7.27	25.4
13-53	CH_2-2-thiophene	20.21	65.6
13-54[a]	CH_2-3-thiophene	34.47	ia
13-55[a]	CH_2-3-furan	9.37	22

ia, inactive (no dose-response curve was obtained up to 100 μM); $p < 0.05$.
[a]Parallel synthesis.

Sulfonamides—in vitro data

Table 9 outlines SAR studies done on R_7, the sulfonamide portion of the molecule. Little variation in activity in the biochemical (LpABC) assay was observed among the different substitution patterns—from small alkyl groups (**20-1**) to aromatic and heteroaromatic groups (**20-2**, **20-3**, **20-19**, **20-20**, **20-21**) to electron donating and withdrawing groups (**20-7**, **20-4**, **20-9**). Changing the position of substituents on the phenyl ring (**20-4**, **20-5**, **20-6**, **20-9**, **20-10**) resulted in minor changes in in vitro

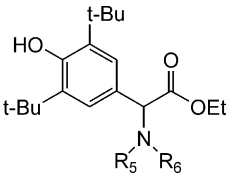
Table 5. Effect of R_5, R_6 on in vitro activity



Compd	R_5	R_6	LpABC IC_{50} (μM)	LpA3 IC_{50} (μM)
4-2	Me	Me	0.40	1.40
4-7	Me	*n*-Bu	0.65	1.40
4-8[a]	Me	*n*-Oct	1.48	NA
4-9[a]	Me	$(CH_2)_2$-NMe_2	0.95	NA
4-4[a]	*n*-Bu	*n*-Bu	0.63	2.40
4-10	$-(CH_2)_4-$		1.58	2.70
4-11	$-(CH_2)_5-$		0.53	1.80
4-12	$-(CH_2)_2O(CH_2)_2-$		0.80	1.30
4-13	$-(CH_2)_2NMe(CH_2)_2-$		1.65	2.50
14-2	Bn	Bn	ia	NA
14-5	CH_2-2-pyridyl	Bn	3.20	NA
14-13	CH_2-3-pyridyl	Bn	ia	NA
14-14	CH_2-4-pyridyl	Bn	20	NA
14-3	CH_2-2-pyridyl	CH_2-2-pyridyl	0.55	NA
14-6	CH_2-3-pyridyl	CH_2-3-pyridyl	1.30	3.90
14-12	CH_2-4-pyridyl	CH_2-4-pyridyl	2.32	NA
14-4	CH_2-2-pyridyl	CH_2-3-pyridyl	0.85	NA
14-7	CH_2-3-pyridyl	CH_2-4-pyridyl	2.88	NA
14-8	CH_2-3-pyridyl	CH_2-cyclohexyl	1.48	3.70
14-9	CH_2-2-thiophene	CH_2-3-pyridyl	20.26	NA
14-10	CH_2-3-thiophene	CH_2-3-pyridyl	8.08	NA
14-11	CH_2-2-furyl	CH_2-3-pyridyl	3.91	NA
14-1	CH_2-cyclohexyl	SO_2Me	2.14	20

ia, inactive (no dose-response curve was obtained up to 100 μM); NA, not available; $p < 0.05$.
[a]HCl salt.

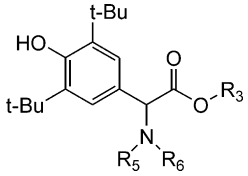
Table 6. Effect of R_5, R_6 on in vitro activity



Compd	R_5	R_6	LpABC IC_{50} (μM)	LpA3 IC_{50} (μM)
12	H	H	ia	46
4-1	Me	H	19.04	16
4-2	Me	Me	0.40	1.40
4-3	*n*-Bu	H	11.22	40
4-4[a]	*n*-Bu	*n*-Bu	0.63	2.40
13-1	CH_2-cyclohexyl	H	6.52	ia
14-1	CH_2-cyclohexyl	SO_2Me	2.14	20
13-8	Bn	H	10.27	ia
14-2	Bn	Bn	ia	NA
13-9	CH_2-2-pyridyl	H	6.48	9.10
14-3	CH_2-2-pyridyl	CH_2-2-pyridyl	0.55	NA
14-4	CH_2-2-pyridyl	CH_2-3-pyridyl	0.85	NA
14-5	CH_2-2-pyridyl	Bn	3.20	NA
13-10	CH_2-3-pyridyl	H	5.90	20
14-6	CH_2-3-pyridyl	CH_2-3-pyridyl	1.30	3.90
14-7	CH_2-3-pyridyl	CH_2-4-pyridyl	2.88	NA
14-8	CH_2-3-pyridyl	CH_2-cyclohexyl	1.48	3.70
14-9	CH_2-3-pyridyl	CH_2-2-thiophene	20.26	NA
14-10	CH_2-3-pyridyl	CH_2-3-thiophene	8.08	NA
14-11	CH_2-3-pyridyl	CH_2-2-furyl	3.91	NA
13-12	CH_2-4-pyridyl	H	7.27	25.40
14-12	CH_2-4-pyridyl	CH_2-4-pyridyl	2.32	NA

ia, inactive (no dose-response curve was obtained up to 100 μM); NA, not available, $p < 0.05$.
[a]HCl salt.

Table 7. Effect of ester modification (R_3) on in vitro activity

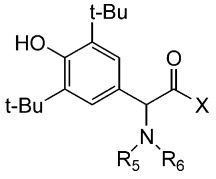


Compd	R_3	R_5	R_6	LpABC IC_{50} (μM)	LpA3 IC_{50} (μM)
4-14	Me	$-(CH_2)_2O(CH_2)_2-$		1.79	1.95
4-12	Et	$-(CH_2)_2O(CH_2)_2-$		0.80	1.30
4-15	*n*-Bu	$-(CH_2)_2O(CH_2)_2-$		1.18	0.50
4-2	Et	Me	Me	0.40	1.40
4-16	*n*-Bu	Me	Me	0.41	0.60
4-17	*t*-Bu	Me	Me	0.84	1.98
14-6	Et	CH_2-3-pyr	CH_2-3-pyr	1.30	3.90
14-15	*t*-Bu	CH_2-3-py	CH_2-3-pyr	2.10	NA
14-1	Et	CH_2-cyclohexyl	SO_2Me	2.14	20
14-16	*t*-Bu	CH_2-cyclohexyl	SO_2Me	ia	NA
4-18	Me	CH_2-cyclohexyl	H	10.83	54.7
13-1	Et	CH_2-cyclohexyl	H	4.16	49.2
4-19	*t*-Bu	CH_2-cyclohexyl	H	9.04	NA
13-11	H	CH_2-3-pyr	H	ia	ia
13-10	Et	CH_2-3-pyr	H	5.90	20
4-20	*i*-Pr	CH_2-3-pyr	H	24.67	9.60
4-21	*t*-Bu	CH_2-3-pyr	H	20.61	NA

ia, inactive (no dose–response curve was obtained up to 100 μM); NA, not available; $p < 0.05$.

activity. However, when the para substituent on the phenyl group changed from methyl to ethyl, *n*-propyl, or *tert*-butyl, the activity decreased more than two fold (**20-12**, **20-13**, **20-14**, **20-15**). Bulky substituents on the sulfonamide portion were detrimental to activity as shown by the decrease in activity with the naphthyl group (**20-18**). Extending the chain length more than

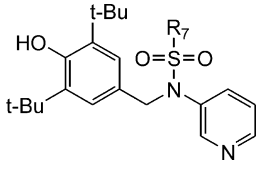
Table 8. In vitro activity comparison of amides and esters



Compd	$R_5 = R_6$	X	LpABC IC_{50} (μM)	LpA3 IC_{50} (μM)
4-2	Me	OEt	0.40	1.40
8-1[a]	Me	$N(Me)_2$	1.49	NA
8-2[a]	Me	$N(n\text{-}Bu)_2$	1.03	NA
8-3[a]	Me	NMe(*n*-Bu)	1.48	NA
14-6	CH_2-3-pyridyl	OEt	1.30	3.90
8-4	CH_2-3-pyridyl	$N(Me)_2$	0.98	NA
8-5	CH_2-3-pyridyl	$N(Et)_2$	1.08	NA
8-6[a]	CH_2-3-pyridyl	$N(n\text{-}Bu)_2$	0.50	NA
4-17	$-(CH_2)_2O(CH_2)_2-$	OEt	0.80	1.30
8-7	$-(CH_2)_2O(CH_2)_2-$	$N(Me)_2$	1.59	10.98
8-8	$-(CH_2)_2O(CH_2)_2-$	$N(Et)_2$	1.17	5
8-9[a]	$-(CH_2)_2O(CH_2)_2-$	$N(n\text{-}Bu)_2$	0.74	NA
8-10[a]	$-(CH_2)_2O(CH_2)_2-$	NMe(*n*-Bu)	1.55	NA

NA, not available; $p < 0.05$.
[a]HCl salt.

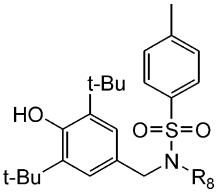
Table 9. Effect of R_7 on in vitro potency



Compd	R_7	LpABC IC_{50}(μM)	LpA3 IC_{50} (μM)
20-1	Me	5.58	41.2
20-2	Ph	4.12	16.2
20-3	CH_2Ph	3.49	NA
20-4	2-(Br)Ph	2.43	12
20-5	3-(Br)Ph	2.76	11.13
20-6	4-(Br)Ph	3.16	NA
20-7	4-(OMe)Ph	3.70	5.80
20-8	4-(F)Ph	2.6	7.50
20-9	4-(NO_2)Ph	2.6	9.4
20-10	3-(NO_2)Ph	4	7.4
20-11	4-(NH_2)Ph	4.78	16.3
20-12	4-(Me)Ph	2.38	6.9
20-13	4-(Et)Ph	8.6	7.7
20-14	4-(*n*-Pr)Ph	7.6	10
20-15	4-(*t*-Bu)Ph	11.8	23.6
20-16	4-(Acetamido)Ph	3.5	12.5
20-17	CH=CHPh	16.84	NA
20-18	2-Naphthyl	7.07	13
20-19	2-Thiophene	2.64	8.9
20-20	2-Thiophene-5-pyrid-2-yl	1.66	24.3
20-21	2-Acetamido-4-(Me)thiazole	2.3	ia

ia, inactive (no dose–response curve was obtained up to 100 μM); NA = not available; $p < 0.05$.

Table 10. Effect of R_8 on in vitro potency



Compd	R_8	LpABC IC_{50} (μM)	LpA3 IC_{50} (μM)
20-22	Cyclohexyl	ia	ia
20-23	Ph	ia	ia
20-24	3-(Cl)Ph	ia	ia
20-25	3,5-(diCl)Ph	27.86	ia
20-26	3-(NO_2)Ph	ia	ia
20-27	4-(OMe)Ph	ia	ia
20-28	2-Pyridyl	ia	ia
20-12	3-Pyridyl	2.38	6.9
20-29	4-Pyridyl	ia	NA
20-30	2-(Cl)-3-pyridyl	1.63	7.6
20-31	6-(Cl)-3-pyridyl	5	39.1
20-32	2-(OMe)-3-pyridyl	24.2	ia
20-33	2,6-(diMe)-3-pyridyl	77.91	8.5
20-34	6-(OEt)-2-benzothiazole	ia	ia

ia, inactive (no dose–response curve was obtained up to 100 μM); NA, not available; $p < 0.05$.

one carbon between the aromatic and sulfonyl group resulted in a significant drop in activity (**20-17**).

Maintaining one of the better substitution patterns in both the biochemical (LpABC) and cellular assays (LpA3) for R_7 (4-tolyl), the SAR for R_8 was investigated. The results are displayed in Table 10. It was found that 3-pyridine (**20-12**) was most desirable for in vitro activity in the biochemical (LpABC) assay. Electron withdrawing substituents to the 3-pyridine ring were tolerated (**20-30**, **20-31**) while electron donating substituents led to a significant drop in activity (**20-32**, **20-33**). Moving the nitrogen of the pyridine ring to either an ortho or para position resulted in inactive compounds (**20-28**, **20-29**). Replacement of the pyridine ring with a phenyl ring, either substituted or unsubstituted, saturated system or other heterocycle, also gave inactive compounds (**20-22**, **20-23**, **20-24**, **20-26**, **20-34**).

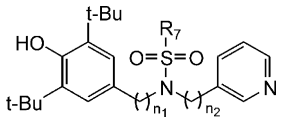
Table 11 summarizes studies done on the methylene linkers, n_1 and n_2. The optimal compounds had $n_1 = 1$ and $n_2 = 0$ (**20-19**, **20-18**, **20-12**). All other permutations resulted in inactive compounds. (**20-35**, **20-36**, **20-37**, **24-1**, **27-1**).

Again, compounds were less active in the cellular assay (LpA3) compared to the biochemical assay (LpABC). This may be due to the reasons discussed previously for the amino acid derivatives.

In vivo data

Base on the in vitro results, compounds from both the amino acid derivatives (**4-2, 4-17**, **14-6**) and the sulfonamides (**20-19**) were taken forward for in vivo studies

Table 11. Effect of chain length (n_1, n_2) on in vitro activity



Compd	R_7	n_1	n_2	LpABC IC_{50}(μM)	LpA3 IC_{50}(μM)
20-19	2-Thiophene	1	0	2.64	8.9
20-35	2-Thiophene	1	1	ia	53.8
27-1[a,c]	2-Thiophene	0	1	ia	ia
20-18	2-Naphthyl	1	0	7.07	13
20-36	2-Naphthyl	0	1	ia	ia
20-12	4-Tolyl	1	0	2.38	7.50
20-37	4-Tolyl	1	1	ia	ia
24-1[b]	4-Tolyl	2	1	ia	NA

ia, inactive (no dose–response curve was obtained up to 100 μM); NA, not available; $p < 0.05$.
[a]Scheme 5.
[b]Scheme 4.
[c]HCl salt.

in Lp(a) transgenic mice. The mice were dosed at a concentration of 100 mg/kg/day for 2 weeks. At the end of each week of dosing, the mice were bled 2 h after dosing and plasma Lp(a) levels were measured.

Compounds **4-2**, **4-17** and **20-19** were not active in Lp(a) transgenic mice after 1 week of dosing. Compound **14-6** showed a $21 \pm 3.2\%$ decrease in plasma Lp(a) levels after 1 week and a $30.7 \pm 3.2\%$ decrease after 2 weeks in a group of five animals.

Compound **14-6** was tested in monkeys at a dose of 100 mg/kg/day. After one week of treatment with **14-6**, monkey plasma Lp(a) levels were decreased $34.7 \pm 5.6\%$ ($n = 7$). All seven monkeys tested responded to treatment.

Conclusion

We have identified a potent Lp(a) coupling inhibitor, **14-6**, that was effective in lowering plasma Lp(a) levels in Lp(a) transgenic mice and in monkeys. Further in vivo studies are ongoing in our laboratory.

Experimental

All melting points were recorded on a Thomas Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian INOVA 400 MHz spectrometer. Positive and negative ion atmospheric pressure chemical ionization (APCI) mass spectra were obtained on a Micromass Platform LC mass spectrometer. Silica gel TLC was performed on silica gel 60 F_{254} precoated sheets and column chromatography on silica gel 60 (70–230 mesh). Elemental analyses were performed by Quantitative Technologies, Inc., NJ, USA.

Esters (**2**) were obtained by Fischer esterification except for the *tert*-butyl ester.

Procedure for 3,5-di-*tert*-butyl-4-hydroxyphenyl acetic acid *tert*-butyl ester (2). To a solution of concentrated H_2SO_4 (30 mL) in 300 mL dioxane under nitrogen was added 3,5-di-*tert*-butyl-4-hydroxyphenyl acetic acid (29.76 g, 113 mmol) followed by isobutylene (300 mL). The cold mixture was sealed and stirred at room temperature for 4 days and poured into a rapidly stirred mixture of 85% potassium hydroxide (75 g), water, ice and ether. The organic layer was separated, washed with brine and evaporated at reduced pressure to give a yellow oil (23.02 g, 64%). MS *m/z* 320.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.43 (s, 18H) 1.45 (s, 9H) 3.43 (s, 2H) 5.11 (s, 1H) 7.06 (s, 2H).

General procedure for synthesis of 2-phenylacetamides (6)

Method 1. The carboxylic acid, **1**, was converted to the acid chloride using excess oxalyl chloride and a catalytic amount of DMF at room temperature. The solvent was removed in vacuo, redissolved in THF and the appropriate amine (excess) was added. The reaction was stirred at room temperature until all the starting material was consumed. The solvent was removed in vacuo and the solid was triturated to obtain the desired product.

Method 2. Carboxylic acid, **1**, *N*-hydroxybenzotriazole (1.07 equiv) and dicyclohexylcarbodiimide (1.07 equiv) in CH_2Cl_2 was stirred for 5 min and then treated with the appropriate amine (1.1 equiv). The mixture was stirred at room temperature for 24 h then filtered. The organic solution was washed with water and brine. The organic phase was dried ($MgSO_4$) and solvent removed in vacuo. The pure product was obtained by column chromatography.

General procedure for synthesis of 2-bromo acetates and acetamides (3, 7)

To a solution of **2** or **6** in CCl_4 was added *N*-bromosuccinimide (1.5 equiv) and a catalytic amount of benzoyl peroxide. The reaction was heated to 60 °C for 18 h. The solvent was removed in vacuo. The residue was dissolved in EtOAc, washed with water and brine, dried ($MgSO_4$) and the solvent removed in vacuo to give the crude product as an orange oil which was taken on to the next step without further purification.

General procedure for oxidation of 2-phenylacetates (2) or 2- phenylacetamides (6) to quinone methine derivatives (5)

To a 1:1 mixture of benzene/water was added **2** or **6**, KOH (9 equiv) and potassium ferricyanide (III) (2 equiv). The reaction was heated at 40 °C for 3–18 h. The reaction was cooled, the layers were separated and the organic layer was washed with water and brine, dried ($MgSO_4$) and the solvent removed in vacuo to give the product.

General procedure for synthesis of 2-aminoacetamides (8)

Method 1. To the quinone methine (**5**, 1 equiv) in THF was added a solution of amine (2 equiv) in THF. The solution was stirred at room temperature for 18 h. The solution was then concentrated in vacuo and the residue dissolved in CH_2Cl_2. It was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The product was obtained by column chromatography ($MeOH/CH_2Cl_2$). The amino acid was dissolved in ether and treated with 4 N HCl in dioxane (4 mL) and stirred for 1 h. The resultant hydrochloride salt was collected by filtration.

Method 2. To a solution of compound **7** (1 equiv) in THF was added the amine (1 equiv) and Et_3N (1 equiv). The reaction was stirred at room temperature for 18 h. The solvent was removed in vacuo. The residue was dissolved in EtOAc, washed with water and brine, dried ($MgSO_4$) and concentrated. The intermediate was obtained by column chromatography.

To this intermediate (1 equiv) in 1,2-dichloroethane was added the appropriate aldehyde (1.05 equiv) and sodium triacetoxyborohydride (2 equiv). The reaction was heated to 50 °C for 1 h. Water was added and the organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The desired product was obtained by column chromatography.

Amino-(3,5-di-*tert*-butyl-4-hydroxy-phenyl)-acetic acid ethyl ester (12). Aluminum chloride (24 g, 180 mmol) was added to a solution of ethyloxalyl chloride (24.6 g, 180 mmol) in CH_2Cl_2 (350 mL) and then cooled to 0 °C. The mixture then treated, dropwise over 15 min, with 2,6-di-*tert*-butyl phenol, **9**, (30.9 g, 150 mmol) in CH_2Cl_2 (125 mL). The mixture was stirred cold for 1 h and then warmed to room temperature and stirred an additional h. The solution was cooled to 0 °C and quenched with water. The organic phase was separated and washed with 1 N HCl and brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give the ketoester, **10**, as an oil, 44.6 g (97%). The ketoester, **10**, (44.6 g, 146 mmol) and phenylhydrazine (20.5 g, 190 mmol) were dissolved in 150 mL ethanol. The mixture was heated to reflux for 18 h. The solution was cooled to room temperature and the hydrazone, **11**, allowed to precipitate. The solid was collected by filtration and washed twice with ethanol. The resultant hydrazone, **11**, was dried at 65 °C for 3 h at reduced pressure to give, 41.5 g (72%). The hydrazone, **11**, (19.6 g, 49.4 mmol) was dissolved in a mix of ethanol (100 mL) and THF (150 mL). This solution was treated with 10% Pd/C and subjected to hydrogen gas for 14 h. The mixture was filtered and the solvents removed in vacuo to give a white solid. The solid was recrystallized from hexanes to give a white crystalline solid (**12**, 12.7 g, 84%, 58% overall). MS *m/z* 308.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H), 1.39 (s, 18H), 4.07–4.21 (m, 2H), 4.47 (s, 1H), 5.17 (s, 1H), 7.11 (s, 2H). Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.10; H, 9.53; N, 4.46.

General procedure for the synthesis of amino acid derivatives (4, 13, 14)

Method 1 (compound 4). To a solution of bromide, **3**, in THF was added the appropriate amine (excess). The reaction was stirred at room temperature until all start-

ing material was consumed. The reaction mixture was concentrated in vacuo, dissolved in EtOAc, washed with brine, dried ($MgSO_4$) and concentrated. The pure product was obtained by column chromatography.

Method 2 (compounds 13). To a solution of **12** in 1,2-dichloroethane was added the appropriate aldehyde (4 equiv) and sodium triacetoxyborohydride (4 equiv). The reaction was stirred at room temperature until all starting material was consumed. The reaction was concentrated in vacuo. The residue was dissolved in EtOAc, washed with water and brine, dried ($MgSO_4$) and the solvent removed in vacuo. The pure product was obtained by column chromatography. This procedure was followed for all compounds made by parallel synthesis.

Method 3 (compounds 14). To a solution of **4** ($R_6 = H$), **12**, or **13** in 1,2-dichloroethane was added the appropriate aldehyde (1.05–2.1 equiv) and sodium triacetoxyborohydride (1.4–3.0 equiv). The reaction was stirred at room temperature until all starting material was consumed. The reaction was concentrated in vacuo. The residue was dissolved in EtOAc, washed with water and brine, dried ($MgSO_4$) and concentrated. The pure product was obtained by column chromatography.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)methylaminoacetic acid ethyl ester (4-1). MS *m/z* 322.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H), 1.42 (s, 18H), 2.42 (s, 3H), 4.12–4.29 (m, 3H), 5.19 (s, 1H), 7.14 (s, 2H). Calcd for $C_{19}H_{31}NO_3$: C, 70.99; H, 9.72; N, 4.36. Found: C, 71.05; H, 9.72; N, 4.21.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)dimethylaminoacetic acid ethyl ester (4-2). MS *m/z* 336.3 $(M-H)^+$; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3H), 1.42 (s, 18H), 2.1–2.4 (br. s, 6H), 3.7–3.8 (m, 1H), 4.10–4.30 (m, 2H), 5.22 (s, 1H), 7.19 (s, 2H). Calcd for $C_{20}H_{33}NO_3$: C, 71.60; H, 9.91; N, 4.17. Found: C, 71.05; H, 9.72; N, 4.21.

Butylamino(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (4-3). MS *m/z* 364.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H), 1.24 (t, 3H), 1.25–1.60 (m, 4H), 1.42 (s, 18H), 2.50–2.65 (m, 2H), 4.08–4.25 (m, 2H), 4.26 (s, 1H), 5.19 (s, 1H), 7.15 (s, 2H). Calcd for $C_{22}H_{37}NO_3$: C, 72.68; H, 10.26; N, 3.85. Found: C, 72.83; H, 10.10; N, 3.76.

Dibutylamino(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester, hydrochloride (4-4). MS *m/z* 420.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.60–0.70 (m, 3H), 0.85–0.95 (m, 3H), 1.10–1.18 (m, 3H), 1.25–1.70 (m, 8H), 1.35 (s, 18H), 2.8–3.5 (m, 4H), 4.2–4.3 (m, 2H), 5.20 (d, 1H), 7.28 (s, 2H), 7.51 (s, 1H). Calcd for $C_{26}H_{45}NO_3 \cdot HCl$: C, 68.47; H, 10.17; N, 3.07. Found: C, 68.50; H, 10.25; N, 2.91.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)ethylaminoacetic acid ethyl ester (4-5). MS *m/z* 336.2 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 0.98 (t, 3H), 1.12 (t, 3H), 1.34 (s, 18H), 2.10–2.50 (m, 2H), 4.0–4.15 (m, 2H), 4.20 (s, 1H), 6.91 (s, 1H), 7.07 (s, 2H). Calcd for $C_{20}H_{33}NO_3$: C, 71.60; H, 9.91; N, 4.17. Found: C, 71.91; H, 9.99; N, 4.11.

Cyclohexylamino(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (4-6). MS *m/z* 390.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.12–1.90 (m, 13H), 1.42 (s, 18H), 2.31–2.39 (m, 1H), 4.07–4.26 (m, 2H), 4.39 (s, 1H), 5.16 (s, 1H), 5.29 (s, 1H), 7.14 (s, 2H). Calcd for $C_{24}H_{39}NO_3$: C, 73.99; H, 10.09; N, 3.60. Found: C, 73.71; H, 9.87; N, 3.49.

(Butylmethylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl) acetic acid ethyl ester (4-7). MS *m/z* 378.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.82 (t, 3H), 1.20–1.45 (m, 4H), 1.24 (s, 3H), 1.42 (s, 18H), 2.25 (s, 3H), 2.20–2.50 (m, 2H), 4.07 (s, 1H), 4.10–4.25 (m, 2H), 5.18 (s, 1H), 7.18 (s, 2H). Calcd for $C_{23}H_{39}NO_3$: C, 73.17; H, 10.41; N, 3.71. Found: C, 73.20; H, 10.07; N, 3.82.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(methyloctylamino)acetic acid ethyl ester, hydrochloride (4-8). MS *m/z* 434.4 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 0.78–0.86 (m, 6H), 1.35 (s, 18H), 2.20–2.85 (m, 3H), 2.80–3.40 (m, 2H), 4.22 (q, 2H), 5.20–5.40 (m, 1H), 7.24 (s, 2H), 7.47–7.49 (m, 1H), 10.3–10.7 (m, 1H). Calcd for $C_{27}H_{47}NO_3 \cdot HCl\ 0.25H_2O$: C, 68.32; H, 10.30; N, 2.95; Cl, 7.47. Found: C, 68.35; H, 10.42; N, 2.70; Cl, 6.90.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-[(2-dimethylaminoethyl)methylamino]acetic acid ethyl ester, hydrochloride (4-9). MS *m/z* 393.4 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 1.14 (t, 3H), 1.36 (s, 18H), 2.40–2.80 (m, 9H), 3.30–3.60 (m, 4H), 4.18–4.26 (m, 2H), 5.30 (s, 1H), 7.25 (s, 2H), 7.41 (s, 1H). Calcd for $C_{23}H_{40}N_2O_3 \cdot 2.0HCl \cdot 2.0H_2O$: C, 55.08; H, 9.25; N, 5.59; Cl, 14.14. Found: C, 55.23; H, 9.22; N, 5.31; Cl, 13.49.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)pyrrolidin-1-yl-acetic acid ethyl ester (4-10). MS *m/z* 362.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.22 (t, 3H), 1.43 (s, 18H), 1.75–1.85 (m, 4H), 2.40–2.60 (m, 4H), 3.81 (s, 1H), 4.18-4.27 (m, 2H), 5.19 (s, 1H), 7.21 (s, 2H). Calcd for $C_{22}H_{35}NO_3$: C, 73.09; H, 9.76; N, 3.87. Found: C, 73.25; H, 9.71; N, 3.70.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)piperidin-1-yl-acetic acid ethyl ester (4-11). MS *m/z* 376.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.22 (t, 3H), 1.43 (s, 18H), 1.50–1.70 (m, 6H), 2.25–2.45 (m, 4H), 3.88 (s, 1H), 4.1–4.3 (m, 2H), 5.18 (s, 1H), 7.17 (s, 2H). Calcd for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73. Found: C, 73.27; H, 9.57; N, 3.90.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)morpholin-4-yl-acetic acid ethyl ester (4-12). MS *m/z* 378.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.22 (t, 3H), 1.43 (s, 18H), 2.40–2.55 (m, 4H), 3.65–3.80 (m, 4H), 3.88 (s, 1H), 4.1-4.3 (m, 2H), 5.21 (s, 1H), 7.18 (s, 2H). Calcd for $C_{22}H_{35}NO_4$: C, 69.99; H, 9.34; N, 3.71. Found: C, 69.94; H, 9.23; N, 3.61.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(4-methylpiperazin-1-yl)acetic acid ethyl ester (4-13). MS *m/z* 391.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.21 (t, 3H), 1.41 (s, 18H), 2.29 (s, 3H), 2.40–2.60 (m, 8H), 3.92 (s, 1H), 4.1–4.25 (m, 2H), 5.19 (s, 1H), 7.16 (s, 2H). Calcd for

$C_{23}H_{38}N_2O_3 \cdot 0.25$ EtOAc: C, 69.81; H, 9.70; N, 6.79. Found: C, 69.54; H, 9.67; N, 7.18.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)morpholin-4-yl-acetic acid methyl ester (4-14). MS *m/z* 364.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.42 (s, 18H), 2.30–2.55 (m, 4H), 3.60–3.80 (m, 4H), 3.69 (s, 3H), 3.89 (s, 1H), 5.23 (s, 1H), 7.26 (s, 2H). Calcd for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15; N, 3.85. Found: C, 69.51; H, 9.18; N, 3.80.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)morpholin-4-yl-acetic acid butyl ester (4-15). MS *m/z* 406.3 $(M+H)^+$; 'p^1H NMR ($CDCl_3$) δ 0.84 (t, 3H), 1.20–1.30 (m, 2H), 1.42 (s, 18H), 1.50–1.65 (m, 2H), 2.40–2.55 (m, 4H), 3.65–3.80 (m, 4H), 3.86 (s, 1H), 4.05–4.15 (m, 2H), 5.20 (s, 1H), 7.18 (s, 2H). Calcd for $C_{24}H_{39}NO_4 \cdot 0.167 \cdot H_2O$: C, 70.48; H, 9.63; N, 3.43. Found: C, 70.47; H, 9.69; N, 3.33.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)dimethylaminoacetic acid butyl ester (4-16). MS *m/z* 364.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.84 (t, 3H), 1.20-1.35 (m, 2H), 1.42 (s, 18H), 1.50–1.65 (m, 2H), 2.2–2.3 (m, 6H), 3.7–3.8 (br.s, 1H), 4.05–4.20 (m, 2H), 5.21 (s, 1H), 7.18 (s, 2H). Calcd for $C_{22}H_{37}NO_3$: C, 72.68; H, 10.26; N, 3.85. Found: C, 72.78; H, 10.07; N, 3.79.

***N*,*N*-dimethylamino(3,5-di-*tert*-butyl-4-hydroxyphenyl) acetic acid *tert*-butyl ester (4-17).** Mp 74−76 °C; MS *m/z* 364.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.42 (s, 18H) 2.24 (s, 6H) 3.68 (s, 1H) 5.17 (s, 1H) 7.16 (s, 2H). Calcd for $C_{22}H_{37}NO_3 \cdot 0.33H_2O$: C, 71.44; H, 10.19; N, 3.79. Found: C, 71.45; H, 9.82; N, 3.49.

(Cyclohexylmethylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid methyl ester (4-18). MS *m/z* 390.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.80–1.0 (m, 2H), 1.10–1.80 (m, 9H), 1.43 (s, 18H), 2.40–2.55 (m, 2H), 3.74 (s, 3H), 5.26 (s, 1H), 7.16 (s, 2H). Calcd for $C_{24}H_{39}NO_3$: C, 73.99; H, 10.09; N, 3.60. Found: C, 74.19; H, 10.30; N, 3.38.

(Cyclohexylmethylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid *tert*-butyl ester (4-19, Method 1). Mp 75–77 °C; MS *m/z* 432.5 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.8–1.0 (m, 2H) 1.10–1.30 (m, 3H) 1.42 (d, 27H) 1.6–1.85 (m, 6H) 2.40 (m, 2H) 4.10 (s, 1H) 5.13 (s, 1H) 7.13 (s, 2H). Calcd for $C_{27}H_{45}NO_3$: C, 75.13; H, 10.51; N, 3.24. Found: C, 75.15; H, 10.53; N, 3.24.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-[(pyridin-3-ylmethyl)amino]acetic acid isopropyl ester (4-20). MS *m/z* 413.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.12 (d, 3H), 1.22 (d, 3H), 1.38 (s, 18H), 3.68–3.79 (m, 2H), 4.19 (s, 1H), 5.01–5.05 (m, 1H), 5.16 (s, 1H), 7.08 (s, 2H), 7.21–7.23 (m, 2H), 7.66–7.69 (m, 1H), 8.46–8.52 (m, 2H). Calcd for $C_{25}H_{36}N_2O_3$: C, 72.78; H, 8.80; N, 6.79. Found: C, 72.61; H, 8.88; N, 6.45.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-[(pyridin-3-ylmethyl)amino]acetic acid *tert*-butyl ester (4-21). Mp 116–118 °C; MS *m/z* 427.4 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.42 (d, 27H) 3.78 (q, 2H) 4.15 (s, 1H) 5.17 (s, 1H) 7.11 (s, 2H) 7.26 (m, 1H) 7.75 (m, 1H) 8.55 (dd, 1H) 8.56 (d, 1H). Calcd for $C_{26}H_{38}N_2O_3 \cdot 0.167H_2O$: C, 72.62; H, 8.92; N, 6.52. Found: C, 72.73; H, 8.99; N, 6.36.

(3,5-Di-*tert*-butyl-4-oxo-cyclohexa-2,5-dienylidene)acetic acid butyl ester (5-1). MS *m/z* 319.3 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H), 1.27 (s, 9H), 1.30 (s, 9H), 1.36–1.48 (m, 2H), 1.63–1.70 (m, 2H), 4.2 (t, 2H), 6.15 (s, 1H), 6.78 (m, 1H), 8.27 (m, 1H). Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.50; H, 9.86.

***N*,*N*-Dibutyl-2-(3,5-di-*tert*-butyl-4-oxo-cyclohexa-2,5-dienylidene)acetamide (5-2).** MS *m/z* 374.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.93–1.0 (m, 6H), 1.27 (s, 9H), 1.29 (s, 9H), 1.20–1.65 (m, 8H), 3.25–3.35 (m, 2H), 3.4-3.5 (m, 2H), 6.49 (s, 1H), 6.82 (m, 1H), 7.48 (m, 1H). Calcd for $C_{24}H_{39}NO_2$: C, 77.16; H, 10.52; N, 3.75. Found: C, 77.52; H, 10.73; N, 3.74.

(3,5-Di-*tert*-butyl-4-oxo-cyclohexa-2,5-dienylidene)acetic acid methyl ester (5-3). MS *m/z* 277.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.27 (s, 9H), 1.29 (s, 9H), 3.80 (s, 3H), 6.13 (s, 1H), 6.77 (m, 1H), 8.29 (m, 1H). Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.55; H, 8.77.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-dimethylamino-*N*,*N*-dimethyl-acetamide, hydrochloride (8-1, Method 1). MS *m/z* 335.2 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 1.35 (s, 18H), 2.33–2.35 (m, 3H), 2.81–2.82 (m, 3H), 2.86–2.88 (m, 6H), 5.54 (d, 1H), 7.27 (s, 2H), 7.43 (s, 1H), 10.0 (s, 1H). Calcd for $C_{20}H_{34}N_2O_2 \cdot HCl$: C, 64.76; H, 9.51; N, 7.55; Cl, 9.56. Found: C, 64.43; H, 9.82; N, 7.27; Cl, 9.46.

***N*,*N*-Dibutyl-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-dimethylamino-acetamide, hydrochloride (8-2, Method 1).** MS *m/z* 419.4 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ 0.7–0.95 (m, 6H), 1.00–1.50 (m, 8H), 1.34 (s, 18H), 2.36–2.38 (m, 3H), 2.80–2.82 (m, 3H), 3.00–3.50 (m, 4H), 5.40–5.47 (m, 1H), 7.25 (s, 2H), 7.44 (s, 1H), 9.9 (s, 1H). Calcd for $C_{26}H_{46}N_2O_2 \cdot HCl$: C, 68.62; H, 10.41; N, 6.16; Cl, 7.79. Found: C, 68.76; H, 10.68; N, 6.06; Cl, 7.79.

***N*-Butyl-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-methyl-2-morpholin-4-yl-acetamide, hydrochloride (8-3, Method 1).** MS *m/z* 419.4 $(M+H)^+$ ^1H NMR (DMSO-d_6) δ 0.61–1.15 (m, 7H), 1.35 (s, 18H), 2.80 (d, 3H), 2.9–3.1 (m, 2H), 3.15–3.40 (m, 2H), 3.65–4.0 (m, 6H), 5.60–5.67 (m, 1H), 7.29 (s, 2H), 7.43–7.45 (m, 1H), 10.35 (s, 1H). Calcd for $C_{25}H_{42}N_2O_3 \cdot HCl \cdot 0.6H_2O$: C, 64.45; H, 9.56; N, 6.01; Cl, 7.61. Found: C, 64.85; H, 9.75; N, 5.83; Cl, 7.50.

2-(Bis-pyridin-3-ylmethylamino)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*,*N*-dimethylacetamide (8-4, Method 1). MS *m/z* 489.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.40 (s, 18H), 2.55 (s, 3H), 3.03 (s, 3H), 3.80–4.02 (m, 4H), 4.58 (s, 1H), 5.21 (s, 1H), 7.05 (s, 2H), 7.20–7.26 (m, 2H), 7.59–7.62 (m, 2H), 8.45–8.48 (m, 4H). Calcd for $C_{30}H_{40}N_4O_2$: C, 73.74; H, 8.25; N, 11.46. Found: C, 72.82; H, 8.32; N, 11.21.

2-(Bis-pyridin-3-ylmethylamino)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*,*N*-diethylacetamide (8-5, Method 2). Mp 159–160 °C; MS *m/z* 517.3 $(M+H)^+$; ^1H NMR

($CDCl_3$) δ 0.64–0.69 (t, 3H) 1.19–1.23 (t, 3H) 1.41 (s, 18H) 2.69–3.06 (m, 3H) 3.80–4.04 (m, 5H) 4.53 (s, 1H) 5.20 (s, 1H) 7.09 (s, 2H) 7.20 (m, 2H) 7.61 (d, 2H) 8.44 (dd, 2H) 8.52 (d, 2H). Calcd for $C_{32}H_{44}N_4O_2$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.26; H, 8.32; N, 10.86.

2-(Bis-pyridin-3-ylmethylamino)-*N*,*N*-dibutyl-2-(3,5-di-*tert*-butyl-4-hydroxy-phenyl)-acetamide, hydrochloride (8-6, Method 1). MS *m*/*z* 573.5 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 0.60–0.95 (m, 9H), 1.00–1.60 (m, 9H), 1.29 (s, 18H), 2.78–2.95 (m, 3H), 3.50–3.60 (m, 1H), 4.05–4.12 (m, 1H), 4.88 (s, 1H), 7.01 (s, 2H), 7.81–7.86 (m, 2H), 8.34–8.36 (m, 2H), 8.66–8.73 (m, 4H). Calcd for $C_{36}H_{52}N_4O_2 \cdot 2.5HCl \cdot 0.7H_2O$: C, 63.94; H, 8.33; N, 8.29; Cl, 13.11. Found: C, 63.76; H, 8.48; N, 7.97; Cl, 12.72.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*N*,*N*-dimethyl-2-morpholin-4-yl-acetamide (8-7, Method 1). MS *m*/*z* 377.3 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.42 (s, 18H), 2.4–2.6 (m, 4H), 2.92 (s, 3H), 2.99 (s, 3H), 3.65–3.80 (m, 4H), 4.1–4.18 (m, 1H), 5.2 (s, 1H), 7.14 (s, 2H). Calcd for $C_{22}H_{36}N_2O_3 \cdot 0.15H_2O$: C, 69.67; H, 9.65; N, 7.34. Found: C, 69.59; H, 9.71; N, 7.32.

2-(3,5-Di-*tert*-butyl-4-hydroxy-phenyl)-*N*,*N*-diethyl-2-morpholin-4-yl-acetamide (8-8, Method 1). MS *m*/*z* 405.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.91–1.14 (m, 3H), 1.05–1.14 (m, 3H), 1.41 (s, 18H), 2.4–2.65 (m, 4H), 3.10–3.60 (m, 4H), 3.65–3.80 (m, 4H), 4.10–4.15 (m, 1H), 5.20 (s, 1H), 7.25 (s, 2H). Calcd for $C_{24}H_{40}N_2O_3$: C, 71.25; H, 9.97; N, 6.92. Found: C, 70.97; H, 9.79; N, 6.82.

***N*,*N*-Dibutyl-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-morpholin-4-yl-acetamide, hydrochloride (8-9, Method 1).** MS *m*/*z* 461.5 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 0.70-0.85 (m, 6H), 0.97–1.50 (m, 8H), 1.35 (s, 18H), 2.97–3.10 (m, 5H), 3.40–3.55 (m, 3H), 3.68–4.0 (m, 4H), 5.5–5.55 (m, 1H), 7.27 (s, 2H), 7.46 (s, 1H), 10.25 (s, 1H). Calcd for $C_{28}H_{48}N_2O_3 \cdot HCl$: C, 67.65; H, 9.93; N, 5.63; Cl, 7.13. Found: C, 67.27; H, 10.04; N, 5.50; Cl, 7.06.

***N*-Butyl-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-dimethylamino-*N*-methyl-acetamide, hydrochloride (8-10, Method 1).** MS *m*/*z* 377.3 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 0.85–1.1 (m, 7H), 1.35 (s, 18H), 2.34–2.37 (m, 3H), 2.77–2.83 (m, 6H), 2.95–3.10 (m, 1H), 3.65–3.75 (m, 1H), 5.40–5.55 (m, 1H), 7.24 (s, 2H), 7.39–7.41 (m, 1H), 9.95 (s, 1H). Calcd for $C_{23}H_{40}N_2O_2 \cdot HCl$: C, 66.88; H, 10.01; N, 6.78; Cl, 8.58. Found: C, 66.90; H, 10.21; N, 6.63; Cl, 8.24.

(Cyclohexylmethylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (13-1). MS *m*/*z* 404.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.8–1.8 (m, 14H), 1.38 (s, 18H), 2.35 (dd, 2H), 4.02–4.11 (m, 2H), 4.18 (s, 1H), 5.13 (s, 1H), 7.11 (s, 2H). Calcd for $C_{25}H_{41}NO_3$: C, 74.40; H, 10.24; N, 3.47. Found: C, 74.42; H, 10.44; N, 3.39.

(3-*tert*-Butyl-4-hydroxy-5-methylphenyl)-(cyclohexylmethylamino)acetic acid ethyl ester (13-2). MS *m*/*z* 362.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.8–1.0 (m, 2H), 1.1-1.35 (m, 2H), 1.23 (t, 3H), 1.40 (s, 9H), 1.45–1.82 (m, 8H), 2.23 (s, 3H), 2.41–2.44 (m, 2H), 4.05–4.28 (m, 2H), 4.30–4.55 (br.s., 1H), 4.81 (s, 1H), 7.04 (s, 1H), 7.13 (s, 1H). Calcd for $C_{22}H_{35}NO_3$: C, 73.09; H, 9.76; N, 3.87. Found: C, 72.73; H, 9.49; N, 4.06.

(3-*tert*-Butyl-4-hydroxyphenyl)-(cyclohexylmethylamino)acetic acid ethyl ester, hydrochloride (13-3). MS *m*/*z* 348.2 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 0.75–0.88 (m, 2H), 1.05–1.20 (m, 6H), 1.28 (s, 9H), 1.5–1.75 (m, 6H), 2.45–2.65 (m, 2H), 4.1–4.2 (m, 2H), 5.05 (s, 1H), 6.83 (d, 1H), 7.10 (d, 1H), 7.25 (s, 1H), 9.3 (s, 1H), 9.45 (s, 1H), 9.93 (s, 1H). Calcd for $C_{21}H_{33}NO_3 \cdot HCl$: C, 65.69; H, 8.93; N, 3.65; Cl, 9.23. Found: C, 65.82; H, 9.10; N, 3.40; Cl, 8.90.

(Cyclohexylmethylamino)-(4-hydroxyphenyl)acetic acid ethyl ester (13-4). MS *m*/*z* 292.1 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 0.7–0.92 (m, 2H), 1.0–1.18 (m, 6H), 1.20–1.35 (m, 1H), 1.55–1.70 (m, 5H), 2.09–2.21 (m, 3H), 3.91–4.06 (m, 2H), 4.07–4.11 (m, 1H), 6.64 (d, 2H), 7.09 (d, 2H), 9.35 (s, 1H). Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.12; H, 8.76; N, 4.71.

(Cyclohexylmethylamino)-(3,5-dichloro-4-hydroxyphenyl) acetic acid ethyl ester (13-5). MS *m*/*z* 360.0 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 0.70–0.90 (m, 2H), 1.0–1.75 (m, 14H), 2.2 (dd, 2H), 3.96–4.15 (m, 2H), 4.24 (s, 1H), 7.36 (s, 2H). Calcd for $C_{17}H_{23}Cl_2NO_3$: C, 56.67; H, 6.43; N, 3.89; Cl, 19.68. Found: C, 56.76; H, 6.28; N, 3.79; Cl, 19.60.

(Cyclohexylmethylamino)-(2′-hydroxy-[1,1′;3′,1″]terphenyl-5′-yl)acetic acid ethyl ester (13-6). MS *m*/*z* 444.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.8–1.0 (m, 2H), 1.1–1.35 (m, 3H), 1.25 (t, 3H), 1.40–1.60 (m, 1H), 1.6–1.82 (m, 5H), 2.38–2.50 (m, 2H), 4.1–4.30 (m, 2H), 4.34 (s, 1H), 5.42 (s, 1H), 7.29–7.56 (m, 12H). Calcd for $C_{29}H_{33}NO_3 \cdot 0.25H_2O$: C, 77.73; H, 7.54; N, 3.12. Found: C, 77.75; H, 7.63; N, 2.95.

(Cyclohexylmethylamino)-(3,5-di-*s*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (13-7). MS *m*/*z* 404.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.75–0.9 (m, 8H), 1.0–1.20 (m, 12H), 1.5–1.70 (m, 7H), 1.70–1.85 (m, 3H), 2.5–2.62 (m, 2H), 2.90–3.05 (m, 2H), 4.23 (q, 2H), 4.85–4.92 (m, 1H), 7.06–7.08 (m, 2H), 8.85 (s, 1H), 10.9 (s, 1H); HPLC: 94%, C18 column, 1:1 CH_3CN/H_2O, λ = 254 nm.

Benzylamino(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (13-8). 66356x16c PD 189107; mp 95 °C; MS *m*/*z* 398.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H) 1.42 (s, 18H) 3.70–3.80 (q, 2H) 4.10–4.25 (m, 2H) 4.27 (s, 1H) 5.19 (s, 1H) 7.14 (s, 2H) 7.20–7.40 (m, 5H). Calcd for $C_{25}H_{35}NO_3$: C, 75.53; H, 8.87; N, 3.52. Found: C, 75.36; H, 8.78; N, 3.41.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-[(pyridin-2-ylmethyl)amino]acetic acid ethyl ester (13-9). MS *m*/*z* 399.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.21 (t, 3H), 1.38 (s, 18H), 3.79–3.91 (m, 2H), 4.06–4.22 (m, 2H), 4.30 (s, 1H), 5.15 (s, 1H), 7.07–7.12 (m, 3H), 7.28–7.30 (m, 1H), 7.56–7.61 (m, 1H), 8.5–8.52 (m, 1H). Calcd for

$C_{24}H_{34}N_2O_3$: C, 72.33; H, 8.60; N, 7.03. Found: C, 72.50; H, 8.66; N, 6.92.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-[(pyridin-3-ylmethyl) amino]acetic acid ethyl ester (13-10). MS *m/z* 399.3 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H) 1.41 (s, 18H) 3.75 (q, 2H) 4.10–4.25 (m, 2H) 4.25 (s, 1H) 5.10 (s, 1H) 7.10 (s, 2H) 7.20–7.25 (m, 1H) 7.70 (m, 1H) 8.50–8.60 (m, 2H). Calcd for $C_{24}H_{34}N_2O_3$: C, 72.33; H, 8.60; N, 7.03. Found: C, 72.39; H, 8.50; N, 6.83.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-[(pyridin-3-ylmethyl) amino]acetic acid, hydrochloride (13-11). Compound **13-10** was hydrolyzed with aqueous sodium hydroxide. MS *m/z* 371.2 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 1.31 (t, 18H), 3.80–3.85 (m, 2H), 4.14 (s, 1H), 6.99 (s, 1H), 7.05 (s, 2H), 7.30–7.35 (m, 1H), 7.70–7.78 (m, 1H), 8.46 (s, 2H). Calcd for $C_{22}H_{30}N_2O_3 \cdot 0.7HCl$: C, 66.73; H, 7.81; N, 7.07. Found: C, 67.06; H, 7.77; N, 7.34.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-[(pyridin-4-ylmethyl) amino]acetic acid ethyl ester (13-12). MS *m/z* 400.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H), 1.38 (s, 18H), 3.66–3.78 (m, 2H), 4.10–4.19 (m, 2H), 4.20 (s, 1H), 5.22 (s, 1H), 7.09 (s, 1H), 7.22–7.25 (m, 1H), 8.49–8.51 (m, 1H). Calcd for $C_{24}H_{34}N_2O_3$: C, 72.33; H, 8.60; N, 7.03. Found: C, 72.43; H, 8.60; N, 6.95.

(Cyclopropylmethylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (13-13). MS *m/z* 362.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 0.0–0.09 (m, 2H), 0.37–0.45 (m, 2H), 0.87–0.97 (m, 1H), 1.16 (t, 3H), 1.35 (s, 18H), 2.28–2.46 (m, 2H), 4.02–4.19 (m, 2H), 4.26 (s, 1H), 5.11 (s, 1H), 7.08 (s, 2H). Calcd for $C_{22}H_{35}NO_3$: C, 73.09; H, 9.76; N, 3.87. Found: C, 72.87; H, 9.79; N, 3.83.

(3-Chloro-benzylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (13-22). MS *m/z* 432.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H), 1.39 (s, 18H), 3.68–3.71 (m, 2H), 4.10–4.21 (m, 2H), 4.22 (s, 1H), 5.19 (s, 1H), 7.10 (s, 2H), 7.20–7.22 (m, 3H), 7.31 (s, 1H). Calcd for $C_{25}H_{34}ClNO_3$: C, 69.51; H, 7.93; N, 3.24. Found: C, 69.55; H, 8.13; N, 3.31.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(3,4,5-trimethoxybenzylamino)acetic acid ethyl ester (13-39). MS *m/z* 488.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.18–1.22 (m, 3H), 1.39 (s, 18H), 3.62–3.72 (m, 2H), 3.80–3.82 (s, 9H), 4.05–4.22 (m, 2H), 4.24 (s, 1H), 5.16 (s, 1H), 6.54 (s, 2H), 7.11 (s, 2H). Calcd for $C_{28}H_{41}NO_6$: C, 68.97; H, 8.47; N, 2.87. Found: C, 68.96; H, 8.45; N, 2.80.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(3-hydroxy-4,5-dimethoxybenzylamino)-acetic acid ethyl ester (13-40). MS *m/z* 474.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3H), 1.42 (s, 18H), 3.60–3.71 (m, 2H), 3.84 (s, 3H), 3.88 (s, 3H), 4.08–4.25 (m, 2H), 4.27 (s, 1H), 5.19 (s, 1H), 5.68–5.80 (m, 1H), 6.51–6.54 (d, 2H), 7.14 (s, 2H). Calcd for $C_{27}H_{39}NO_6$: C, 68.47; H, 8.30; N, 2.96. Found: C, 68.37; H, 8.33; N, 2.89.

(3,5-Di-*tert*-butyl-4-hydroxy-benzylamino)-(3,5-di-*tert*-butyl-4-hydroxy-phenyl)acetic acid ethyl ester (13-41). Mp 110–112 °C; MS *m/z* 526.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H) 1.41 (d, 36H) 3.60 (q, 2H) 4.00–4.20 (m, 2H) 4.25 (s, 1H) 5.05 (s, 1H) 5.15 (s, 1H) 7.05 (s, 2H) 7.10 (s, 2H). Calcd for $C_{33}H_{51}NO_4 \cdot H_2O$: C, 72.89; H, 9.75; N, 2.57. Found: C, 72.71; H, 9.82; N, 2.36.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-phenethylaminoacetic acid ethyl ester (13-43). MS *m/z* 412.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.21 (t, 3H), 1.41 (s, 18H), 2.77–2.92 (m, 4H), 4.05–4.23 (m, 2H), 4.30 (s, 1H), 5.19 (s, 1H), 7.26 (s, 2H), 7.28–7.31 (m, 5H). Calcd for $C_{26}H_{37}NO_3$: C, 75.87; H, 9.06; N, 3.40. Found: C, 75.86; H, 8.81; N, 3.28.

Benzyloxycarbonylamino(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (13-49). Compound **13-49** was synthesized by reacting compound **12** with benzylchloroformate; MS *m/z* 442.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3H), 1.41 (s, 18H), 4.1–4.3 (m, 3H), 5.12 (m, 2H), 5.25–5.29 (m, 1H), 5.6–5.65 (m, 1H), 7.13 (s, 2H), 7.26–7.40 (m, 5H). Calcd for $C_{26}H_{35}NO_5$: C, 70.72; H, 7.99; N, 3.17. Found: C, 70.83; H, 8.03; N, 3.20.

***tert*-Butoxycarbonylamino-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-acetic acid ethyl ester (13-50).** Compound **13-50** was synthesized by reacting compound 12 with *tert*-butylchloroformate; MS *m/z* 406.2 $(M-H)^-$; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3H), 1.41 (s, 18H), 1.44 (s, 9H), 4.1–4.3 (m, 2H), 5.15–5.22 (m, 2H), 5.30–5.40 (m, 1H), 7.12 (s, 2H). Calcd for $C_{23}H_{37}NO_5$: C, 67.78; H, 9.15; N, 3.44. Found: C, 67.69; H, 8.99; N, 3.34.

(3,5-Di-*tert*-butyl-4-hydroxy-phenyl)-[(pyridine-3-carbonyl)-amino]-acetic acid ethyl ester (13-52). Compound **13-52** was made by reacting compound **12** with nicotinyl chloride. MS *m/z* 413.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3H), 1.39 (s, 18H), 4.16–4.27 (m, 2H), 5.27 (s, 1H), 5.64 (d, 1H), 6.92–6.94 (m, 1H), 7.17 (s, 2H), 7.34–7.38 (m, 1H), 8.08–8.11 (m, 1H), 8.69–8.70 (m, 1H), 9.00 (s, 1H). Calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82; N, 6.79. Found: C, 69.68; H, 7.93; N, 7.02.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-[(thiophen-2-ylmethyl)amino]acetic acid ethyl ester (13-53). MS *m/z* 404.1 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.17 (t, 3H), 1.36 (s, 18H), 3.91 (s, 2H), 4.0–4.20 (m, 2H), 4.29 (s, 1H), 5.14 (s, 1H), 6.88–6.89 (m, 2H), 7.08 (s, 2H), 7.16–7.18 (m, 1H). Calcd for $C_{23}H_{33}NO_3S$: C, 68.45; H, 8.24; N, 3.47. Found: C, 68.49; H, 8.04; N, 3.39.

The following compounds were synthesized using the parallel synthesis method (compounds **13**).

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(3-hydroxybenzylamino)acetic acid ethyl ester (13-14). MS *m/z* 414.4 $(M+H)^+$; HPLC purity = 88%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(4-hydroxybenzylamino)acetic acid ethyl ester (13-15). MS *m/z* 414.4 $(M+H)^+$; HPLC purity = 91%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(2-methoxybenzylamino)acetic acid ethyl ester (13-16). MS *m/z* 428.4 $(M+H)^+$; HPLC purity = 93%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(4-methoxybenzylamino)acetic acid ethyl ester (13-17). MS *m/z* 428.4 $(M+H)^+$; HPLC purity = 86%.

(4-Benzyloxy-benzylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (13-18). MS *m/z* 504.4 $(M+H)^+$; HPLC purity = 89%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(2-trifluoromethylbenzylamino)acetic acid ethyl ester (13-19). MS *m/z* 466.3 $(M+H)^+$; HPLC purity = 76%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(3-trifluoromethylbenzylamino)acetic acid ethyl ester (13-20). MS *m/z* 466.3 $(M+H)^+$; HPLC purity = 88%.

(2-Chloro-benzylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (13-21). MS *m/z* 432.3 $(M+H)^+$; HPLC purity = 89%

(4-Chloro-benzylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (13-23). MS *m/z* 432.3 $(M+H)^+$; HPLC purity = 95%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(2-fluoro-benzylamino)acetic acid ethyl ester (13-24). MS *m/z* 416.4 $(M+H)^+$; HPLC purity = 76%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(3-nitro-benzylamino)acetic acid ethyl ester (13-25). MS *m/z* 443.3 $(M+H)^+$; HPLC purity = 83%

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(4-nitro-benzylamino)acetic acid ethyl ester (13-26). MS *m/z* 443.3 $(M+H)^+$; HPLC purity = 78%

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(4-dimethylamino-benzylamino)acetic acid ethyl ester (13-28). MS *m/z* 441.4 $(M+H)^+$; HPLC purity = 81%.

(4-Dibutylamino-benzylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (13-29). MS *m/z* 525.4 $(M+H)^+$; HPLC purity = 86%.

(4-Cyano-benzylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (13-30). MS *m/z* 423.4 $(M+H)^+$; HPLC purity = 87%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(2-methyl-benzylamino)acetic acid ethyl ester (13-31). MS *m/z* 412.4 $(M+H)^+$; HPLC purity = 84%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(3-methyl-benzylamino)acetic acid ethyl ester (13-32). MS *m/z* 412.4 $(M+H)^+$; HPLC purity = 89%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(2,4-dichloro-benzylamino)acetic acid ethyl ester (13-33). MS *m/z* 466.3 $(M+H)^+$; HPLC purity = 87%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(3,4-dichloro-benzylamino)acetic acid ethyl ester (13-34). MS *m/z* 466.3 $(M+H)^+$; HPLC purity = 94%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(3,5-dichlorobenzylamino)acetic acid ethyl ester (13-35). MS *m/z* 466.3 $(M+H)^+$; HPLC purity = 92%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(4-methoxy-3-methylbenzylamino)-acetic acid ethyl ester (13–36). MS *m/z* 442.4 $(M+H)^+$; HPLC purity = 87%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(4-hydroxy-3-methoxybenzylamino)-acetic acid ethyl ester (13-37). MS *m/z* 444.4 $(M+H)^+$; HPLC purity = 93%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(3-ethoxy-4-hydroxybenzylamino)acetic acid ethyl ester (13-38). MS *m/z* 458.4 $(M+H)^+$; HPLC purity = 97%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(3,5-dichloro-2-hydroxybenzylamino)-acetic acid ethyl ester (13-42). MS *m/z* 482.3 $(M+H)^+$; HPLC purity = 91%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(2,2-diphenylethylamino)acetic acid ethyl ester (13-44). MS *m/z* 488.4 $(M+H)^+$; HPLC purity = 84%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(4-phenoxybenzylamino)-acetic acid ethyl ester (13-45). MS *m/z* 490.4 $(M+H)^+$; HPLC purity = 79%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-[(naphthalen-1-ylmethyl)amino]acetic acid ethyl ester (13-46). MS *m/z* 448.4 $(M+H)^+$; HPLC purity = 88%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-[(4-methoxynaphthalen-1-ylmethyl)amino]acetic acid ethyl ester (13-47). MS *m/z* 478.4 $(M+H)^+$; HPLC purity = 92%.

[(Anthracen-9-ylmethyl)amino]-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (13-48). MS *m/z* 498.4 $(M+H)^+$; HPLC purity = 96%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-[(thiophen-3-ylmethyl)amino]acetic acid ethyl ester (13-54). MS *m/z* 404.3 $(M+H)^+$; HPLC purity = 100%.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-[(furan-3-ylmethyl)amino]acetic acid ethyl ester (13-55). MS *m/z* 388.4 $(M+H)^+$; HPLC purity = 73%.

(Cyclohexylmethylmethanesulfonylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (14-1, Method 3). Compound **14-1** was synthesized by reacting compound **13-1** with methanesulfonyl chloride; MS *m/z* 480.2 $(M-H)^-$; ^{1}H NMR ($CDCl_3$) δ 0.4–0.9 (m, 6H), 1.1–1.19 (m, 1H), 1.25 (t, 3H), 1.38 (s, 18H), 1.4–1.55 (m, 4H), 2.87 (s, 3H), 3.03 (d, 2H), 4.13–4.35 (m, 2H), 5.29 (s, 1H), 5.67 (s, 1H), 7.02 (s, 2H). Calcd for $C_{26}H_{43}NO_5S$: C, 64.83; H, 9.00; N, 2.88. Found: C, 64.93; H, 8.92; N, 2.88.

Dibenzylamino(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (14-2, Method 3). Mp 101–102 °C; MS *m/z* 488.3 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H) 1.40 (s, 18H) 3.75 (q, 4H) 4.25 (q, 2H) 4.50 (s, 1H) 5.15

(s, 1H) 7.10–7.40 (m, 12H). Calcd for $C_{32}H_{41}NO_3$: C, 78.81; H, 8.47; N, 2.87. Found: C, 78.91; H, 8.68; N, 2.81.

(Bis-pyridin-2-ylmethylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (14-3, Method 3). MS m/z 490.3 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H) 1.40 (s, 18H) 3.90–4.10 (q, 4H) 4.25 (q, 2H) 4.60 (s, 1H) 5.20 (s, 1H) 7.10 (m, 2H) 7.19 (s, 2H) 7.50 (d, 2H) 7.60 (m, 2H) 8.45 (m, 2H). Calcd for $C_{30}H_{39}N_3O_3$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.28; H, 8.07; N, 8.31.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(pyridin-2-ylmethyl-pyridin-3-ylmethylamino)acetic acid ethyl ester (14-4, Method 3). Mp 102–103°C. MS m/z 490.4 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H) 1.41 (s, 18H) 3.80–4.00 (m, 4H) 4.25 (q, 2H) 4.52 (s, 1H) 5.20 (s, 1H) 7.05–7.20 (m, 2H) 7.40 (d, 1H) 7.60 (m, 2H) 8.40 (m, 2H) 8.50 (d, 1H). Calcd for $C_{30}H_{39}N_3O_3$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.44; H, 8.00; N, 8.46.

(Benzyl-pyridin-2-ylmethylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (14-5, Method 3). MS m/z 489.4 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H) 1.41 (s, 18H) 3.80–4.04 (m, 4H) 4.20–4.29 (q, 2H) 4.54 (s, 1H) 5.16 (s, 1H) 7.08–7.38 (m, 8H) 7.54–7.65 (m, 2H) 8.46 (m, 1H). Calcd for $C_{31}H_{40}N_2O_3{\cdot}0.25H_2O$: C, 75.43; H, 8.21; N, 5.68. Found: C, 75.51; H, 7.89; N, 5.51.

(Bis-pyridin-3-ylmethylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (14-6, Method 3). Mp 125–127 °C; MS m/z 490.4 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H) 1.41 (s, 18H) 3.77 (s, 4H) 4.25 (q, 2H) 4.46 (s, 1H) 5.23 (s, 1H) 7.09 (s, 2H) 7.20 (m, 2H) 7.60 (m, 2H) 8.45–8.50 (m, 4H). Calcd for $C_{30}H_{39}N_3O_3$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.32; H, 8.07; N, 8.43.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(pyridin-3-ylmethyl-pyridin-4-ylmethylamino)acetic acid ethyl ester (14-7, Method 3). MS m/z 490.4 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H) 1.41 (s, 18H) 3.77 (s, 4H) 4.26–4.29 (q, 2H) 4.46 (s, 1H) 5.22 (s, 1H) 7.09 (s, 2H) 7.20–7.23 (m, 3H) 7.61 (m, 1H) 8.47–8.53 (m, 4H). Calcd for $C_{30}H_{39}N_3O_3{\cdot}0.5H_2O$: C, 72.19; H, 8.02; N, 8.42. Found: C, 72.19; H, 8.09; N, 8.12.

(Cyclohexylmethylpyridin-3-ylmethylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (14-8, Method 3). MS m/z 495.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.45–0.90 (m, 3H), 1.00–1.40 (m, 7H), 1.41 (s, 18H), 1.50–1.85 (m, 4H), 2.28–2.51 (m, 2H), 3.63–3.83 (m, 2H), 4.21–4.30 (m, 2H), 4.57 (s, 1H), 5.17 (s, 1H), 7.11 (s, 2H), 7.16–7.21 (m, 1H), 7.56–7.59 (m, 1H), 8.43–8.47 (m, 2H). Calcd for $C_{31}H_{46}N_2O_3$: C, 75.26; H, 9.37; N, 5.66. Found: C, 75.03; H, 9.30; N, 5.50.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(pyridin-3-ylmethyl-thiophen-2-ylmethylamino)acetic acid ethyl ester (14-9, Method 3). Mp 141–142 °C; MS m/z 495.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H) 1.42 (s, 18H) 3.73–4.07 (m, 4H) 4.30 (q, 2H) 4.56 (s, 1H) 5.19 (s, 1H) 6.91 (m, 2H) 7.16 (s, 1H) 7.21–7.26 (m, 2H) 7.75 (m, 1H) 8.46 (dd, 1H) 8.57 (d, 1H). Calcd for $C_{29}H_{38}N_2O_3S{\cdot}0.167H_2O$: C, 69.92; H, 7.70; N, 5.63. Found: C, 69.91; H, 7.86; N, 5.51.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(pyridin-3-ylmethyl-thiophen-3-ylmethylamino)acetic acid ethyl ester (14-10, Method 3). Mp 148–150 °C. MS m/z 495.4 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H) 1.41 (s, 18H) 3.68–3.82 (m, 4H) 4.27 (q, 2H) 4.49 (s, 1H) 5.19 (s, 1H) 7.00 (dd, 1H) 7.12 (m, 3H) 7.18–7.27 (m, 2H) 7.61 (m, 1H) 8.45 (dd, 1H) 8.51 (d, 1H). Calcd for $C_{29}H_{38}N_2O_3S{\cdot}H_2O$: C, 67.88; H, 7.80; N, 5.46. Found: C, 67.79; H, 7.47; N, 5.35.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-(furan-2-ylmethyl-pyridin-3-ylmethylamino)acetic acid ethyl ester (14-11, Method 3). Mp 118–119 °C; MS m/z 479.4 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.29 (t, 3H) 1.41 (s, 18H) 3.66–3.80 (m, 4H) 4.25 (m, 2H) 4.46 (s, 1H) 5.19 (s, 1H) 6.14 (d, 1H) 6.30 (m, 1H) 7.20 (m, 3H) 7.38 (m, 1H) 7.71 (m, 1H) 8.45 (dd, 1H) 8.54 (d, 1H). Calcd for $C_{29}H_{38}N_2O_4$: C, 72.77; H, 8.00; N, 5.85. Found: C, 72.62; H, 8.10; N, 5.62.

(Bis-pyridin-4-ylmethylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (14-12, Method 3). Mp 90–92 °C. MS m/z 490.3 $(M+H)^+$; p^1H NMR ($CDCl_3$) δ 1.30 (t, 3H) 1.41 (s, 18H) 3.75 (t, 4H) 4.25 (q, 2H) 4.45 (s, 1H) 5.20 (s, 1H) 7.10 (d, 2H) 7.20 (s, 4H) 8.55 (d, 4H). Calcd for $C_{30}H_{39}N_3O_3{\cdot}0.33H_2O$: C, 72.75; H, 8.08; N, 8.48. Found: C, 72.60; H, 8.14; N, 8.13.

(Benzylpyridin-3-ylmethylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (14-13, Method 3). Mp 120–121 °C; MS m/z 489.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H) 1.41 (s, 18H) 3.75 (d, 2H) 3.78 (s, 2H) 4.27 (q, 2H) 4.49 (s, 1H) 5.18 (s, 1H) 7.11 (s, 2H) 7.18-7.33 (m, 6H) 7.60 (m, 1H) 8.45 (dd, 1H) 8.52 (d, 1H). Calcd for $C_{31}H_{40}N_2O_3$: C, 76.19; H, 8.25; N, 5.73. Found: C, 76.15; H, 8.31; N, 5.62.

(Benzylpyridin-4-ylmethylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid ethyl ester (14-14, Method 3). MS m/z 489.4 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H) 1.41 (s, 18H) 3.75 (s, 2H) 3.78 (s, 2H) 4.25 (q, 2H) 4.49 (s, 1H) 5.18 (s, 1H) 7.10 (s, 2H) 7.22–7.33 (m, 7H) 8.49 (dd, 2H). Calcd for $C_{31}H_{40}N_2O_3{\cdot}0.25H_2O$: C, 75.43; H, 8.21; N, 5.68. Found: C, 75.51; H, 8.27; N, 5.54.

(Bis-pyridin-3-ylmethylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid *tert*-butyl ester (14-15, Method 3). Mp 152–153 °C. MS m/z 518.4 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.42 (s, 18H) 1.54 (s, 9H) 3.78 (q, 4H) 4.35 (s, 1H) 5.19 (s, 1H) 7.12 (s, 2H) 7.20 (q, 2H) 7.59 (d, 2H) 8.47 (d, 2H) 8.51 (d, 2H). Calcd for $C_{32}H_{43}N_3O_3$: C, 74.24; H, 8.37; N, 8.12. Found: C, 74.32; H, 8.56; N, 7.98.

(Cyclohexylmethylmethanesulfonylamino)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic acid *tert*-butyl ester (14-16). Compound **14-16** was synthesized by reacting compound **4-21** and methanesulfonyl chloride; Mp

134–136 °C. MS *m/z* 508.3 $(M-H)^-$. ^1H NMR ($CDCl_3$) δ 0–1.2 (m, 11H) 1.42 (s, 18H) 1.49 (a, 9H) 2.89 (s, 3H) 3.10 (m, 2H) 5.30 (s, 1H) 5.57 (s, 1H) 7.07 (s, 2H). Calcd for $C_{28}H_{47}NO_5S$: C, 65.98; H, 9.29; N, 2.75. Found: C, 65.59; H, 8.97; N, 2.52.

Sulfonamides

Amine (18). Method A. A mixture of the appropriate aldehyde, **15** (1 equiv), amine, **16** (1.1 equiv), and catalytic *p*-toluenesulfonic acid in toluene was heated to reflux until the starting material was consumed and the product observed by mass spec. Water was removed via molecular sieves and a Dean-Stark trap. The molecular sieves were filtered off and the reaction evaporated at reduced pressure and the crude product (imine, **17**) was recrystallized from EtOAc. Imine, **17**, can be reduced to amine, **18**, with Raney nickel or with 20% Pt/C. The reaction was subjected to hydrogen gas and stirred at room temperature until all starting material was consumed and the product was observed by tlc. The catalyst was filtered off and the filtrate was removed in vacuo to obtain the product which was purified by column chromatography.

Method B (18). To a solution of the appropriate aldehyde, **15** (1 equiv), in 1,2-dichloroethane was added amine, **16** (1.08 equiv) and sodium triacetoxyborohydride (1.5 equiv). The reaction was stirred at room temperature for 18 h. The reaction was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The pure product was obtained by column chromatography.

Method C (18). A mixture of bromide, **21** (1 equiv), amine, **16** (10 equiv) and potassium carbonate (1 equiv) in acetonitrile was heated to 70 °C until all starting material was consumed and the product was observed by mass spec. The reaction was cooled and filtered. The filtrate was concentrated in vacuo, redissolved in EtOAc, washed with water and brine, and dried ($MgSO_4$) to give the final product.

General procedure for sulfonamide formation. To a solution of amine, **18**, in pyridine was added the appropriate sulfonyl chloride, **19**, and a catalytic amount of 4-dimethylaminopyridine. The reaction was heated to 60 °C for 18 h. The reaction was cooled and the solvent evaporated in vacuo. The residue was dissolved in EtOAc, washed with water (3X) and brine, dried ($MgSO_4$) and evaporated at reduced pressure. The pure product, **20**, was obtained by column chromatography.

Sulfonamides. Compounds **20-1** to **20-21** use amine **18** (R_1 = 3-pyridine, $n_2 = 0$) as starting material. This amine was synthesized as described in Scheme 3, method A.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-*N*-pyridin-3-ylmethanesulfonamide (20-1).** MS *m/z* 391.1 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.35 (s, 18H) 2.95 (s, 3H) 4.80 (s, 2H) 5.20 (s, 1H) 6.95 (s, 2H) 7.28 (t, 1H) 7.55 (m, 1H) 8.45 (d, 1H) 8.55 (dd, 1H). Calcd for $C_{21}H_{30}N_2O_3S \cdot H_2O$: C, 61.73; H, 7.83; N, 6.85. Found: C, 61.86; H, 7.26; N, 6.67.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-*N*-pyridin-3-ylbenzenesulfonamide (20-2).** Mp 143–145 °C; MS *m/z* 453.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.35 (s, 18H) 4.70 (s, 2H) 5.15 (s, 1H) 6.85 (s, 2H) 7.20 (m, 1H) 7.35 (d, 1H) 7.55 (t, 2H) 7.60 (t, 1H) 7.65 (d, 2H) 8.15 (d, 1H) 8.43 (dd, 1H). Calcd for $C_{26}H_{32}N_2O_3S$: C, 69.00; H, 7.13; N, 6.19. Found: C, 68.62; H, 6.86; N, 5.95.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-*N*-pyridin-3-ylbenzylsulfonamide (20-3).** Mp 139–140 °C. MS *m/z* 467.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.33 (s, 18H) 4.32 (s, 2H) 4.52 (s, 2H) 5.18 (s, 1H) 6.88 (s, 2H) 7.15 (m, 1H) 7.23 (m, 1H) 7.38 (s, 4H) 8.21 (d, 1H) 8.42 (dd, 1H). Calcd for $C_{27}H_{34}N_2O_3S$: C, 69.50; H, 7.34; N, 6.00. Found: C, 69.70; H, 7.43; N, 6.18.

2-Bromo-*N*-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-*N*-pyridin-3-ylbenzenesulfonamide (20-4). Mp 103–107 °C; MS *m/z* 533.1 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.34 (s, 18H) 4.91 (s, 2H) 5.17 (s, 1H) 6.93 (s, 2H) 7.16 (m, 1H) 7.33 (t, 2H) 7.43 (m, 1H) 7.76 (d, 1H) 7.92 (d, 1H) 8.27 (d, 1H) 8.40 (dd, 1H). Calcd for $C_{26}H_{31}N_2O_3SBr \cdot 0.33H_2O$: C, 58.04; H, 5.89; N, 5.21. Found: C, 58.12; H, 5.90; N, 4.74.

3-Bromo-*N*-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-*N*-pyridin-3-ylbenzenesulfonamide (20-5). Mp 129–131 °C; MS *m/z* 533.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.33 (s, 18H) 4.70 (s, 2H) 5.16 (s, 1H) 6.88 (s, 2H) 7.26 (m, 1H) 7.40 (t, 2H) 7.54 (d, 1H) 7.74 (d, 1H) 7.83 (t, 1H) 8.18 (d, 1H) 8.48 (dd, 1H). Calcd for $C_{26}H_{31}N_2O_3SBr \cdot 0.33H_2O$: C, 58.04; H, 5.89; N, 5.21. Found: C, 58.10; H, 5.71; N, 4.89.

4-Bromo-*N*-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-*N*-pyridin-3-ylbenzenesulfonamide (20-6). Mp 129–130 °C; MS *m/z* 533.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.32 (s, 18H) 4.67 (s, 2H) 5.14 (s, 1H) 6.87 (s, 2H) 7.20 (q, 1H) 7.33 (m, 1H) 7.50–7.65 (dd, 4H) 8.13 (d, 1H) 8.46 (dd, 1H). Calcd for $C_{26}H_{31}N_2O_3SBr$: C, 58.75; H, 5.88; N, 5.27. Found: C, 58.93; H, 5.83; N, 5.17.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-4-methoxy-*N*-pyridin-3-ylbenzenesulfonamide (20-7).** Mp 142–143 °C; MS *m/z* 483.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.32 (s, 18H) 3.88 (s, 3H) 4.66 (s, 2H) 5.12 (s, 1H) 6.88 (s, 2H) 6.95 (d, 2H) 7.20 (m, 1H) 7.39 (m, 1H) 7.60 (d, 2H) 8.13 (d, 1H) 8.42 (d, 1H). Calcd for $C_{27}H_{34}N_2O_4S$: C, 67.19; H, 7.10; N, 5.80. Found: C, 66.93; H, 7.18; N, 5.66.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-4-fluoro-*N*-pyridin-3-ylbenzenesulfonamide (20-8).** Mp 137–138 °C; MS *m/z* 471.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.32 (s, 18H) 4.67 (s, 2H) 5.14 (s, 1H) 6.88 (s, 2H) 7.20 (m, 3H) 7.37 (m, 1H) 7.66 (q, 2H) 8.13 (d, 1H) 8.45 (dd, 1H). Calcd for $C_{26}H_{31}N_2O_3SF$: C, 66.36; H, 6.64; N, 5.95. Found: C, 66.46; H, 6.54; N, 5.87.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-4-nitro-*N*-pyridin-3-ylbenzenesulfonamide (20-9).** Mp 157–158 °C; MS *m/z* 498.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.29 (s, 18H) 4.68

(s, 2H) 5.15 (s, 1H) 6.84 (s, 2H) 7.20 (s, 1H) 7.30 (d, 1H) 7.80 (d, 2H) 8.10 (s, 1H) 8.30 (d, 2H) 8.46 (d, 1H). Calcd for $C_{26}H_{31}N_3O_5S$: C, 62.76; H, 6.28; N, 8.44. Found: C, 62.85; H, 6.30; N, 8.25.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-3-nitro-*N*-pyridin-3-ylbenzenesulfonamide (20-10).** Mp 99–107 °C; MS *m/z* 498.1 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.32 (s, 18H) 4.74 (s, 2H) 5.17 (s, 1H) 6.89 (s, 2H) 7.26 (m, 1H) 7.33 (m, 1H) 7.71 (t, 1H) 7.91 (d, 1H) 8.13 (d, 1H) 8.50 (m, 3H). Calcd for $C_{26}H_{31}N_3O_5S{\cdot}0.33H_2O$: C, 61.95; H, 6.29; N, 8.33. Found: C, 62.11; H, 6.41; N, 8.21.

4-Amino-*N*-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-*N*-pyridin-3-ylbenzenesulfonamide (20-11). Compound **20-9** was stirred in acetic acid (2 mL) and zinc dust (7:1 w/w, zinc/compound) at room temperature. The reaction was complete after 1.5 h and filtered through Celite, rinsing with EtOAc. The filtrate was washed with saturated aqueous $NaHCO_3$, evaporated at reduced pressure and purified by column chromatography to obtain **20-11**.

Mp 169–170 °C; MS *m/z* 468.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.32 (s, 18H) 4.15 (s, 2H) 4.64 (s, 2H) 5.10 (s, 1H) 6.64 (d, 2H) 6.89 (s, 2H) 7.18 (m, 1H) 7.41 (d, 2H) 8.16 (s, 1H) 8.40 (s, 1H). Calcd for $C_{26}H_{33}N_3O_3S{\cdot}0.33H_2O$: C, 65.87; H, 7.11; N, 8.87. Found: C, 66.24; H, 7.12; N, 8.38.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-4-methyl-*N*-pyridin-3-ylbenzenesulfonamide (20-12).** Mp 129–130 °C; MS *m/z* 467.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.32 (s, 18H) 2.44 (s, 3H) 4.67 (s, 2H) 5.12 (s, 1H) 6.88 (s, 2H) 7.20 (q, 1H) 7.30 (d, 2H) 7.38 (m, 1H) 7.56 (d, 2H) 8.11 (d, 1H) 8.43 (dd, 1H). Calcd for $C_{27}H_{34}N_2O_3S$: C, 69.50; H, 7.34; N, 6.00. Found: C, 69.49; H, 7.43; N, 5.92.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-4-ethyl-*N*-pyridin-3-ylbenzeneulfonamide (20-13).** Mp 113–116 °C; MS *m/z* 481.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H) 1.32 (s, 18H) 2.73 (q, 2H) 4.68 (s, 2H) 5.13 (s, 1H) 6.88 (s, 2H) 7.26 (m, 2H) 7.35 (d, 2H) 7.59 (d, 2H) 8.14 (m, 1H) 8.44 (dd, 1H). Calcd for $C_{28}H_{36}N_2O_3S$: C, 69.97; H, 7.55; N, 5.83. Found: C, 70.21; H, 7.61; N, 5.78.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-4-propyl-*N*-pyridin-3-ylbenzenesulfonamide (20-14).** Mp 93–95 °C; MS *m/z* 495.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.96 (t, 3H) 1.32 (s, 18H) 1.67 (q, 2H) 2.67 (t, 2H) 4.67 (s, 2H) 5.12 (s, 1H) 6.91 (s, 2H) 7.20 (m, 1H) 7.29 (d, 2H) 7.38 (m, 1H) 7.58 (d, 2H) 8.13 (d, 1H) 8.44 (dd, 1H). Calcd for $C_{29}H_{38}N_2O_3S{\cdot}0.33H_2O$: C, 69.50; H, 7.72; N, 5.59. Found: C, 69.55; H, 7.76; N, 5.40.

4-*tert*-Butyl-*N*-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-*N*-pyridin-3-yl-benzenesulfonamide (20-15). Mp 155–156 °C; MS *m/z* 509.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.32 (s, 18H) 1.36 (s, 9H) 4.69 (s, 2H) 5.13 (s, 1H) 6.88 (s, 2H) 7.53 (dd, 4H) 8.18 (m, 1H) 8.44 (m, 1H). Calcd for $C_{30}H_{40}N_2O_3S$: C, 70.83; H, 7.93; N, 5.51. Found: C, 70.59; H, 7.91; N, 5.41.

***N*-{4-[(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-pyridin-3-yl-sulfamoyl]phenyl}acetamide (20-16).** Mp 163–165 °C; MS *m/z* 510.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.32 (s, 18H) 1.36 (s, 9H) 4.69 (s, 2H) 5.13 (s, 1H) 6.88 (s, 2H) 7.53 (dd, 4H) 8.18 (m, 1H) 8.44 (m, 1H); LCMS: 96.98%, retention time: 4.250 min, gradient: 60% CH_3CN/40% H_2O, column: Alltech Alltima C18 150×4.6 5μ.

2-Phenylethenesulfonic acid (3,5-di-*tert*-butyl-4-hydroxybenzyl)pyridin-3-ylamide (20-17). Mp 215–216 °C; MS *m/z* 479.3 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 1.23 (s, 18H) 4.77 (s, 2H) 6.86 (s, 1H) 6.89 (s, 2H) 7.35–7.60 (m, 5H) 7.74–7.80 (m, 3H) 8.40 (m, 2H). Calcd for $C_{28}H_{34}N_2O_3S{\cdot}0.167H_2O$: C, 69.76; H, 7.13; N, 5.81. Found: C, 69.38; H, 7.12; N, 5.79.

Naphthalene-2-sulfonic acid (3,5-di-*tert*-butyl-4-hydroxybenzyl)pyridin-3-ylamide (20-18). Mp 169–171 °C; MS *m/z* 503.2 $(M+H)^+$; 'p^1H NMR ($CDCl_3$) δ 1.30 (s, 18H) 4.74 (s, 2H) 5.13 (s, 1H) 6.89 (s, 2H) 7.22 (m, 1H) 7.41 (m, 1H) 7.65 (m, 3H) 7.97 (m, 3H) 8.17 (d, 1H) 8.27 (d, 1H) 8.44 (d, 1H). Calcd for $C_{30}H_{34}N_2O_3S$: C, 71.68; H, 6.82; N, 5.57. Found: C, 71.29; H, 6.74; N, 5.36.

Thiophene-2-sulfonic acid (3,5-di-*tert*-butyl-4-hydroxybenzyl)pyridin-3-ylamide (20-19). Mp 137–138 °C; MS *m/z* 459.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.33 (s, 18H) 4.73 (s, 2H) 5.15 (s, 1H) 6.91 (s, 2H) 7.12 (q, 1H) 7.22 (q, 1H) 7.40 (m, 1H) 7.43 (dd, 2H) 8.63 (dd, 1H) 8.20 (d, 1H) 8.47 (dd, 1H). Calcd for $C_{24}H_{30}N_2O_3S_2$: C, 62.85; H, 6.59; N, 6.11. Found: C, 63.17; H, 6.69; N, 6.01.

5-Pyridin-2-ylthiophene-2-sulfonic acid (3,5-di-*tert*-butyl-4-hydroxybenzyl)pyridin-3-ylamide (20-20). MS *m/z* 536.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.33 (s, 18H) 4.81 (s, 2H) 5.17 (s, 1H) 6.93 (s, 2H) 7.29 (m, 1H) 7.37 (d, 2H) 7.52 (d, 1H) 7.67 (m, 2H) 7.79 (m, 1H) 8.30 (d, 1H) 8.47 (dd, 1H) 8.61 (d, 1H). Calcd for $C_{29}H_{33}N_3O_3S_2{\cdot}1.5H_2O$: C, 61.84; H, 6.39; N, 7.46. Found: C, 61.95; H, 6.23; N, 6.87.

***N*-{5-[(3,5-Di-*tert*-butyl-4-hydroxybenzyl)pyridin-3-yl-sulfamoyl]-4-methylthiazol-2-yl}acetamide (20-21).** Mp 175–177 °C; MS *m/z* 531.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.33 (s, 18H) 2.17 (s, 3H) 2.27 (s, 3H) 4.81 (s, 2H) 5.15 (s, 1H) 6.93 (s, 2H) 7.29 (m, 1H) 7.56 (m, 1H) 8.34 (d, 1H) 8.47 (dd, 1H). Calcd for $C_{26}H_{34}N_4O_4S_2$: C, 58.84; H, 6.46; N, 10.56. Found: C, 59.11; H, 6.46; N, 10.42.

***N*-Cyclohexyl-*N*-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-4-methylbenzenesulfonamide (20-22).** Amine **18** (R_1 = cyclohexane, $n_2 = 0$) was synthesized as described for Scheme 3, Method C. Mp 175–177 °C; MS *m/z* 254.1 $(M-218)^+$; ^1H NMR ($CDCl_3$) δ 1.39 (s, 18H) 1.20–1.80 (m, 10H) 2.38 (s, 3H) 3.72 (m, 1H) 4.31 (s, 2H) 5.11 (s, 1H) 7.08 (s, 2H) 7.21 (d, 2H) 7.58 (d, 2H). Calcd for $C_{28}H_{41}NO_3S{\cdot}0.167H_2O$: C, 70.78; H, 8.71; N, 2.95. Found: C, 70.71; H, 8.49; N, 2.77.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-4-methyl-*N*-phenylbenzenesulfonamide (20-23).** Amine **18** ($R_1 = C_6H_5$, $n_2 = 0$) was synthesized as described for Scheme 3, Method B (MS, NMR); MS *m/z* 248.1 $(M-218)^+$; ^1H

NMR ($CDCl_3$) δ 1.25 (s, 18H) 2.36 (s, 3H) 4.57 (s, 2H) 5.01 (s, 1H) 6.81 (s, 2H) 6.86 (m, 2H) 7.14 (m, 3H) 7.21 (m, 2H) 7.49 (d, 2H). Calcd for $C_{28}H_{35}NO_3S$: C, 72.22; H, 7.58; N, 3.01. Found: C, 71.95; H, 7.56; N, 3.07.

***N*-(3-Chlorophenyl)-*N*-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-4-methylbenzenesulfonamide (20-24).** Amine **18** (R_1 = 3-Cl–C_6H_4, n_2 = 0) was synthesized as described for Scheme 3, method B (MS); Mp 105–107 °C; MS *m/z* 282.1 $(M-218)^+$; ^1H NMR ($CDCl_3$) δ 1.33 (s, 18H) 2.43 (s, 3H) 4.40 (s, 2H) 5.10 (s, 1H) 6.85 (s, 2H) 6.87 (m, 2H) 7.15 (m, 2H) 7.28 (d, 2H) 7.55 (d, 2H). Calcd for $C_{28}H_{34}NO_3SCl$: C, 67.25; H, 6.85; N, 2.80. Found: C, 67.16; H, 6.91; N, 2.69.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-*N*-(3,5-dichlorophenyl)-4-methylbenzenesulfonamide (20-25).** Amine **18** (R_1 = 3,5-diCl–C_6H_3, n_2 = 0) was synthesized as described for Scheme 3, method B (MS). Mp 143–145 °C; MS *m/z* 316.0 $(M-218)^+$; ^1H NMR ($CDCl_3$) δ 1.34 (s, 18H) 2.46 (s, 3H) 4.57 (s, 2H) 5.14 (s, 1H) 6.85 (m, 4H) 7.19 (t, 1H) 7.30 (d, 2H) 7.56 (d, 2H). Calcd for $C_{28}H_{33}NO_3SCl_2$: C, 62.91; H, 6.22; N, 2.62. Found: C, 62.91; H, 6.26; N, 2.46.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-4-methyl-*N*-(3-nitrophenyl)benzenesulfonamide (20-26).** Amine **18** (R_1 = 3-NO_2–C_6H_4, n_2 = 0) was synthesized as described for Scheme 3, Method B (MS).

Mp 128–130 °C; MS *m/z* 291.1 $(M-218)^-$; ^1H NMR ($CDCl_3$) δ 1.30 (s, 18H) 2.45 (s, 3H) 4.65 (s, 2H) 5.15 (s, 1H) 6.85 (s, 2H) 7.30 (d, 2H) 7.40 (m, 2H) 7.55 (d, 2H) 7.70 (m, 1H) 8.05 (m, 1H). Calcd for $C_{28}H_{34}N_2O_5S$: C, 65.86; H, 6.71; N, 5.49. Found: C, 65.83; H, 6.75; N, 5.32.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-*N*-(3-methoxyphenyl)-4-methylbenzenesulfonamide (20-27).** Amine **18** (R_1 = 3-OMe–C_6H_4, n_2 = 0) was synthesized as described for Scheme 3, method B. Mp 119–121 °C; MS *m/z* 278.1 $(M-218)^+$; ^1H NMR (CDCl3) δ 1.32 (s, 18H) 2.43 (s, 3H) 3.64 (s, 3H) 4.62 (s, 2H) 5.09 (s, 1H) 6.45 (m, 1H) 6.50 (m, 1H) 6.73 (m, 1H) 6.88 (s, 2H) 7.08 (t, 1H) 7.29 (s, 1H) 7.57 (d, 2H). Calcd for $C_{29}H_{37}NO_4S$: C, 70.27; H, 7.52; N, 2.83. Found: C, 70.11; H, 7.44; N, 2.66.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-4-methyl-*N*-pyridin-2-ylbenzenesulfonamide (20-28).** Amine **18** (R_1 = 2-pyridine, n_2 = 0) was synthesized as described for Scheme 3, Method A. Mp 117 °C; MS *m/z* 249.1 $(M-218)^+$; ^1H NMR ($CDCl_3$) δ 1.32 (s, 18H) 2.40 (s, 3H) 4.88 (s, 2H) 5.06 (s, 1H) 7.03 (s, 2H) 7.08 (m, 1H) 7.25 (d, 2H) 7.47 (q, 3H) 7.62 (m, 1H) 8.31 (dd, 1H). Calcd for $C_{27}H_{34}N_2O_3S$: C, 69.50; H, 7.34; N, 6.00. Found: C, 69.32; H, 7.26; N, 5.94.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-4-methyl-*N*-pyridin-4-ylbenzenesulfonamide (20-29).** Amine **18** (R_1 = 4-pyridine, n_2 = 0) was synthesized as described for Scheme 3, method A.

Mp 215 °C; MS *m/z* 467.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.40 (s, 18H) 2.36 (s, 3H) 4.91 (s, 2H) 5.38 (s, 1H) 6.95 (s, 2H) 7.07 (d, 2H) 7.23 (d, 2H) 7.42 (d, 2H) 7.85 (d, 2H). Calcd for $C_{27}H_{34}N_2O_3S$: C, 69.50; H, 7.34; N, 6.00. Found: C, 69.46; H, 7.24; N, 5.93.

***N*-(2-Chloropyridin-3-yl)-*N*-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-4-methylbenzenesulfonamide (20-30).** Amine **18** (R_1 = 2-Cl-3-pyridine, n_2 = 0) was synthesized as described for Scheme 3, Method A. Mp 117–119 °C; MS *m/z* 501.2 $(M+H)^+$ ^1H NMR ($CDCl_3$) δ 1.31 (s, 18H) 2.44 (s, 3H) 4.54–4.89 (dd, 2H) 5.14 (s, 1H) 6.86 (s, 2H) 7.07 (q, 1H) 7.28 (dd, 3H) 7.65 (d, 2H) 8.24 (dd, 1H). Calcd for $C_{27}H_{33}N_2O_3SCl$: C, 64.72; H, 6.64; N, 5.59. Found: C, 64.72; H, 6.68; N, 5.49.

***N*-(6-Chloropyridin-3-yl)-*N*-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-4-methylbenzenesulfonamide (20-31).** Amine **18** (R_1 = 6-chloro-3-pyridine, n_2 = 0) was synthesized as described for Scheme 3, Method A. Mp 152–153 °C; MS *m/z* 501.1 $(M+H)^+$ ^1H NMR ($CDCl_3$) δ 1.33 (s, 18H) 2.45 (s, 3H) 4.63 (s, 2H) 5.15 (s, 1H) 6.88 (s, 2H) 7.18 (d, 1H) 7.29 (m, 3H) 7.53 (d, 2H) 7.86 (d, 1H). Calcd for $C_{27}H_{33}N_2O_3SCl$: C, 64.72; H, 6.64; N, 5.59. Found: C, 65.03; H, 6.82; N, 5.42.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-*N*-(6-methoxypyridin-3-yl)-4-methylbenzenesulfonamide (20-32).** Amine **18** (R_1 = 6-OMe-3-pyridine, n_2 = 0) was synthesized as described for Scheme 3, Method A. Mp 127–129 °C; MS *m/z* 497.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.33 (s, 18H) 2.44 (s, 3H) 3.87 (s, 3H) 4.60 (s, 2H) 5.13 (s, 1H) 6.57 (d, 1H) 6.88 (s, 2H) 7.11 (dd, 1H) 7.30 (d, 2H) 7.56 (d, 2H) 7.62 (d, 1H). Calcd for $C_{28}H_{36}N_2O_4S$: C, 67.71; H, 7.31; N, 5.64. Found: C, 67.81; H, 7.35; N, 5.53.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-*N*-(2,6-dimethylpyridin-3-yl)-4-methylbenzenesulfonamide (20-33).** Amine **18** (R_1 = 2,6-diMe-3-pyridine, n_2 = 0) was synthesized as described for Scheme 3, Method A. Mp 147–148 °C; MS *m/z* 495.2 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.29 (s, 18H) 2.15 (s, 3H) 2.45 (d, 6H) 4.20–4.80 (dd, 2H) 5.14 (s, 1H) 6.76 (s, 2H) 6.81 (d, 2H) 7.29 (d, 2H) 7.60 (d, 2H). Calcd for $C_{29}H_{38}N_2O_3S$: C, 70.41; H, 7.74; N, 5.66. Found: C, 70.56; H, 7.80; N, 5.62.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-*N*-(6-ethoxybenzothiazol-2-yl)-4-methylbenzenesulfonamide (20-34).** Amine **18** (R_1 = 6-OEt-2-benzothiazole, n_2 = 0) was synthesized as described for Scheme 3, Method A. Mp 214–216 °C; MS *m/z* 567.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.29 (s, 18H) 1.38 (t, 3H) 2.37 (s, 3H) 4.00 (q, 2H) 5.16 (s, 1H) 5.22 (s, 2H) 6.87 (dd, 1H) 7.02 (s, 2H) 7.06 (d, 1H) 7.15 (d, 3H) 7.82 (d, 2H). Calcd for $C_{31}H_{38}N_2O_4S_2$: C, 65.69; H, 6.76; N, 4.94. Found: C, 65.63; H, 6.85; N, 4.77.

Thiophene-2-sulfonic acid (3,5-di-*tert*-butyl-4-hydroxybenzyl)-pyridin-3-ylmethylamide (20-35). Amine **18** (R_1 = 3-pyridine, n_2 = 1) was synthesized as described for Scheme 3, Method B. Mp 110–112 °C; MS *m/z* 473.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.33 (s, 18H) 4.27 (d,

4H) 5.19 (s, 1H) 6.85 (s, 2H) 7.13 (m, 2H) 7.57 (m, 3H) 8.16 (s, 1H) 8.42 (d, 1H). Calcd for $C_{25}H_{32}N_2O_3S_2$: C, 63.53; H, 6.82; N, 5.93. Found: C, 63.27; H, 6.86; N, 5.87.

Naphthalene-2-sulfonic acid (3,5-di-*tert*-butyl-4-hydroxybenzyl)-pyridin-3-ylmethylamide (20-36). Amine **18** (R_1 = 3-pyridine, n_2 = 1) was synthesized as described for Scheme 3, Method B. Mp 164–165 °C; MS *m*/*z* 517.2 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 1.16 (s, 18H) 4.24 (s, 2H) 4.32 (s, 2H) 5.74 (s, 1H) 6.73 (s, 2H) 7.13 (q, 1H) 7.40 (m, 1H) 7.68 (m, 2H) 7.87 (dd, 1H) 8.06 (m, 1H) 8.14 (m, 3H) 8.30 (m, 1H) 8.57 (s, 1H). Calcd for $C_{31}H_{36}N_2O_3S \cdot 0.33H_2O$: C, 71.16; H, 7.02; N, 5.36. Found: C, 71.41; H, 7.11; N, 5.32.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-4-methyl-*N*-pyridin-3-ylmethylbenzenesulfonamide (20-37).** Amine **18** (R_1 = 3-pyridine, n_2 = 1) was synthesized described for Scheme 3, Method B. Mp 164–166 °C; MS *m*/*z* 481.2 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 1.22 (s, 18H) 2.40 (s, 3H) 4.15 (s, 2H) 4.22 (s, 2H) 5.74 (s, 1H) 6.80 (s, 2H) 7.12 (q, 1H) 7.40 (m, 3H) 7.75 (d, 2H) 8.18 (d, 1H) 8.30 (dd, 1H). Calcd for $C_{28}H_{36}N_2O_3S{\cdot}1.25H_2O$: C, 66.71; H, 7.64; N, 5.56. Found: C, 66.81; H, 7.36; N, 5.45.

***N*-[2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-ethyl]-4-methyl-*N*-pyridin-3-ylbenzenesulfonamide (24-1).** 3,5-Di-*tert*-butyl-4-hydroxyphenyl acetic acid (**1**, 5.72 g, 22 mmol) was converted to the acid chloride in excess oxalyl chloride and a catalytic amount of DMF. The solvent was removed under vacuum and the residue redissolved in ether (100 mL) and treated with lithium aluminum hydride (1.15 g, 30 mmol) and stirred at room temperature for 18 h. The reaction was then heated to reflux for 2 h. The reaction was cooled, treated with Na_2SO_4 and filtered through Celite. The ether filtrate was washed with brine, dried ($MgSO_4$), concentrated in vacuo and the residue triturated with hexanes to obtain 3.80 g (70%) of 2-(3,5-di-*tert*-butyl-4-hydroxyphenethyl)alcohol.

To a solution of the alcohol (3.80 g, 15 mmol) in ether (25 mL) was added dropwise a solution of phosphorus tribromide (0.71 mL, 7.5 mmol) in 10 mL ether. The reaction was stirred at room temperature for 3 days. The reaction was concentrated in vacuo. The residue was dissolved in EtOAc, washed with saturated Na_2CO_3 and brine, dried ($MgSO_4$) and concentrated in vacuo. The pure product, **22**, was obtained by column chromatography (45%).

To a solution of the bromide (**22**, 2.11 g, 6.7 mmol) in 20 mL toluene was added 3-aminopyridine (0.65 g, 6.8 mmol) and Et_3N (0.96 mL, 6.8 mmol). The reaction was heated to reflux for one week. The solvent was removed in vacuo. The residue was partitioned between EtOAc and water. An insoluble tan solid was collected by filtration to give **23** in 45% yield. The general procedure for sulfonamides was followed to obtain **24-1** (R_1 = 3-pyridine, R_2 = 4-Me–C_6H_4, n_1 = 2, n_2 = 0). Yield: 22% mp 224–227 °C; MS *m*/*z* 481.2 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 18H) 2.35 (s, 3H) 3.02 (t, 2H) 4.30 (t, 2H) 5.19 (s, 1H) 6.67 (s, 2H) 6.99 (m, 1H) 7.19 (d, 3H) 7.88 (d, 3H) 8.31 (s, 1H). Calcd for $C_{28}H_{36}N_2O_3S{\cdot}0.33H_2O$: C, 69.04; H, 7.53; N, 5.75. Found: C, 68.64; H, 7.30; N, 5.66.

Thiophene-2-sulfonic acid (3,5-di-*tert*-butyl-4-hydroxyphenyl)-pyridin-3-ylmethylamide (27-1). A mixture of 2,6-di-*tert*-butyl-1,4-benzoquinone (2.2 g, 10 mmol) and 3-amino-methylpyridine (1.08 g, 10 mmol) and two drops acetic acid in 15 mL toluene was heated to reflux for 30 min. The solvent was removed in vacuo and the desired product (**25**) obtained by column chromatography.

To a solution of the imine (**25**, 2.0 g, 6.5 mmol) in 1,2-dichloroethane was added sodium triacetoxyborohydride (1.65 g, 7.8 mmol) and a catalytic amount of acetic acid. The reaction was stirred at room temperature for two h. The reaction was washed with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated in vacuo. The product, **26**, was purified by column chromatography.

Yield 1.6 g (80%). To a solution of the amine (**26**, 312 mg, 1 mmol) in 1,2-dichloroethane was added two drops of pyridine and 2-thiophenesulfonyl chloride (269 mg, 1.5 mmol). The mixture was stirred at room temperature for 18 h. The reaction was evaporated at reduced pressure. Trituration with hexanes resulted in a crystalline product (**27-1**).

Mp 135–140 °C; MS *m*/*z* 459.2 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 18H) 4.80 (s, 2H) 5.30 (s, 1H) 6.63 (s, 2H) 7.10 (q, 1H) 7.36 (dd, 1H) 7.65 (dd, 1H) 7.72 (m, 1H) 8.41 (d, 1H) 8.49 (s, 1H) 8.59 (d, 1H). Calcd for $C_{24}H_{30}N_2O_3S_2{\cdot}HCl{\cdot}0.83H_2O$: C, 56.45; H, 6.40; N, 5.49. Found: C, 56.24; H, 6.00; N, 5.20.

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